THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

The Total Synthesis of Natural Products

VOLUME 8

Edited by

John ApSimon

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and

Department of Chemistry
Carleton University, Ottawa



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Preface

The art and science of organic synthesis is alive and well! This volume presents chapters on the synthesis of a variety of natural products.

A long overdue treatment of tri- and tetracyclic diterpenes appears together with an equally important report on naturally occurring quinone synthesis. Recent interests in the biologically important polysaccharides necessitate a consideration of that class of compounds and a background paper on synthetic work to 1985 is provided. Finally a diversion from the traditional treatment of whole biosynthetic classes as synthetic targets provides an overview of strategies and methods derived for those natural products containing the spiroketal functional group.

The announcement of the award of the 1990 Nobel Prize in chemistry to a champion synthetic strategist, Professor E. J. Corey, attests to the scientific importance of organic molecular construction. This volume is dedicated to Professor Corey in honor of his multitudinous contributions to organic synthesis.

JOHN APSIMON

Ottawa, Canada
October 1991

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THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

The Total Synthesis of Natural Products, Volume 8
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The Total Synthesis of Tri- and Tetracyclic Diterpenes

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Department of Chemistry, Emory University, Atlanta, Georgia

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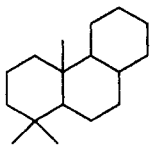
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INTRODUCTION

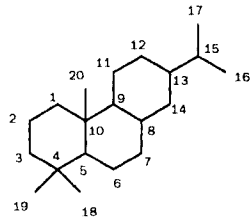
This review covers the synthesis of tri- and tetracarbocyclic diterpenes[1, 2] from the late 1930s until approximately 1987. Some synthetic work from 1988 and 1989 is included. In keeping with the title of the series, the syntheses reviewed here are largely *total* syntheses. Conversions of one natural product into another are, for the most part, not included. The decisions as to which partial syntheses to cover were made on an almost entirely arbitrary basis. Much excellent chemistry has emerged from partial syntheses and conversions, but the general principal has been that if the starting material appears to be more complex and/or more difficult to synthesize than the target molecule, the work is not included. In addition, the field of diterpene synthesis is marked by a myriad of excellent model studies. I have not included, however, preliminary or model study work except when directly applicable to a particular synthesis.

The chapter is organized broadly around skeletal types and these are given in Table 1. Within the general class of abietanes and pimaranes a further

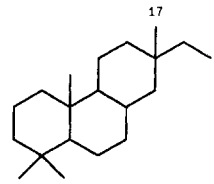
Table 1 Synthesized Diterpene Skeletal Types



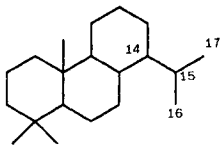
podocarpane



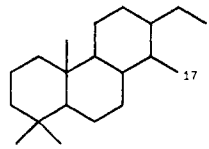
abietane



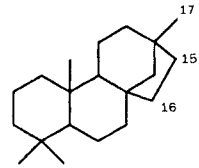
pimarane



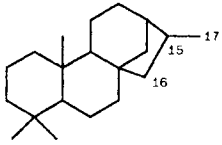
totarane



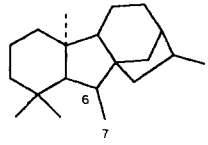
cassane



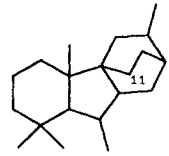
beyerane



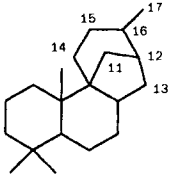
kaurane



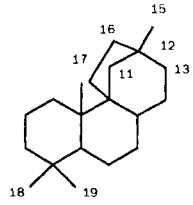
gibbane



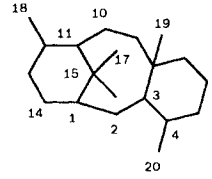
antheridane



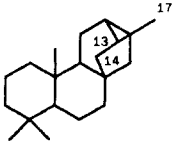
stemodane



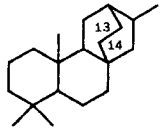
stemarane



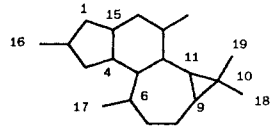
taxane



trachylobane

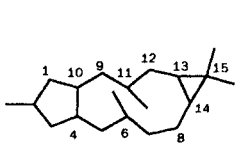


atisane

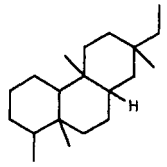


jatrophane

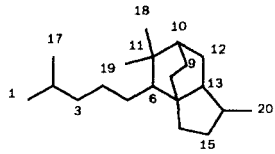
Table 1 Synthesized Diterpene Skeletal Types (*Continued*)



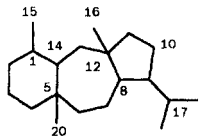
lathyrane



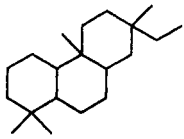
dolabrane



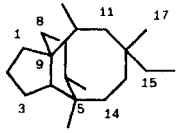
eremane



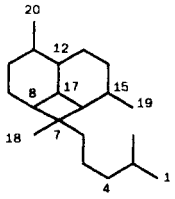
dolastane



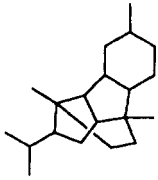
rosane



mutilane



decipiane



ryanodane

division along the lines of major functionality is also made. Abietane C-ring phenols, epoxides, and quinones, for example, are discussed separately from abietic and related acids. The biosynthesis of the diterpenes is not discussed in detail but the the origin of some of the compound types from geranylgeraniol pyrophosphate is outlined to illustrate the structural relationships between members of a general class of substances.

As noted in an earlier volume in this series, the proof of the synthesis review pudding is in the synthetic schemes, and I have attempted to make these as explicit as possible, both with regard to the number of structures in each scheme and in the way that they are presented graphically. In some cases the same molecule may be shown in different structural representations depending on how these may illustrate a particular synthesis. I have also repeated the structures of many of the starting materials and intermediates so that the reader will not have to search for structure **43** when it is used again

for the synthesis of molecule **277**. The discussions of the syntheses in contrast are brief, serving to illustrate some of the more critical points of stereochemistry or strategy or to serve simply as a guide to the structural road map. I apologize in this respect for being unable (and unwilling) to search out and use any additional synonyms for yield, produce, afford, provide, give, and lead to in describing the outcome of a particular transformation. The normal three- and four-letter codes for reagents are used throughout.

Finally, I would like to acknowledge the aid of several graduate students in chemistry at Emory University, in particular Guy Stone, Kevin Swiss, and William Hinkley, for their aid in searching out and gathering the relevant literature.

1. TRICYCLIC DITERPENES

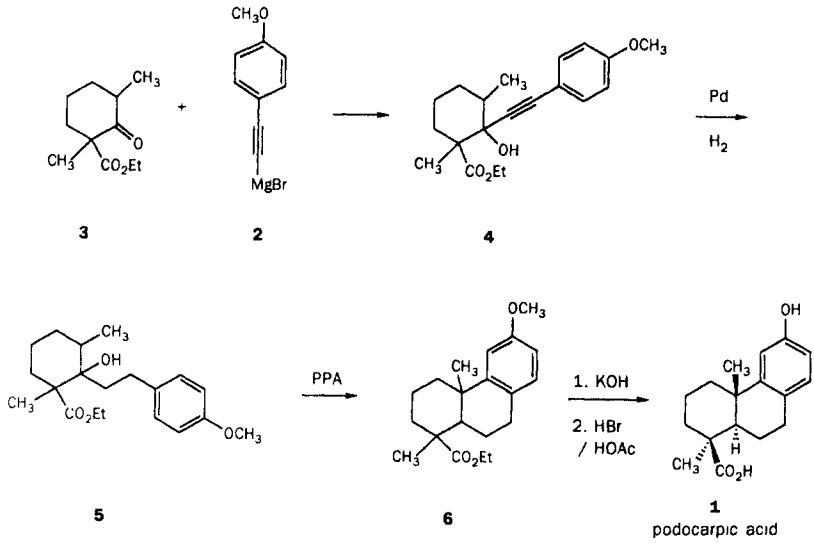
A. Abietanes and Pimaranes

(1) Resin Acids

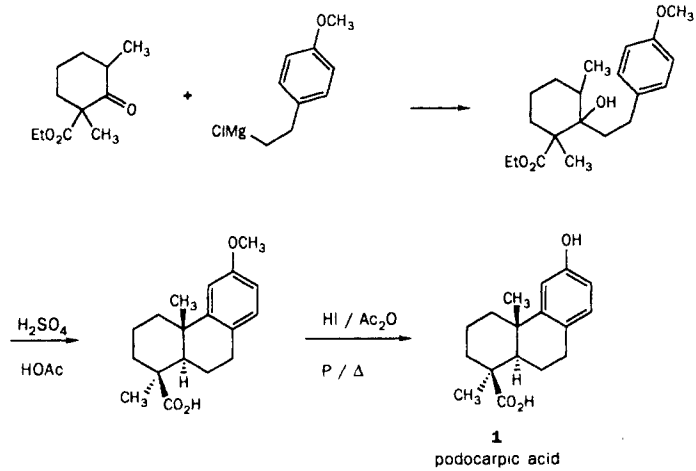
Podocarpic Acid

The first synthesis of podocarpic acid, **1**, in which the product was compared to the natural compound and its constitution verified was carried out by King, King, and Topliss[3] at Nottingham University (Scheme 1). The carbon skeleton is assembled by addition of Grignard reagent **2** to ketone **3**. Catalytic hydrogenation of the acetylene group of **4** affords **5**, which in turn is subjected to acid-catalyzed cyclization with polyphosphoric acid. The product of this unselective reaction is a mixture of several isomers from which **6** is isolated in 30% yield. Hydrolysis of the ester and ether groups of **6** by standard, if drastic, methods affords podocarpic acid. The King group also demonstrated that the compound prepared earlier but not identified by Haworth and Moore[4] (Scheme 2) at Sheffield was podocarpic acid.

The synthesis of podocarpic acid by Wenkert and Tahara[5,6] from Iowa State University (Scheme 3) is based on a Robinson annelation construction of the tricyclic system[7] from 1-methyl 2-naphthol and methyl ethynyl ketone. The highly unsaturated hydroxyketone **7** obtained in 26% yield is subjected to catalytic hydrogenation and acid-catalyzed dehydration to yield enone **8**. Lithium in ammonia affords the *trans*-fused saturated tricyclic ketone **9**. The latter, upon carbonation of the kinetically produced enolate mixture, yields the C-4 keto acid in near equal measure with its C-2 isomer. Both products are isolated as the derived methyl esters and **10**, the appropriate one for podocarpane synthesis, is carried forward. When methylation of **10** is carried

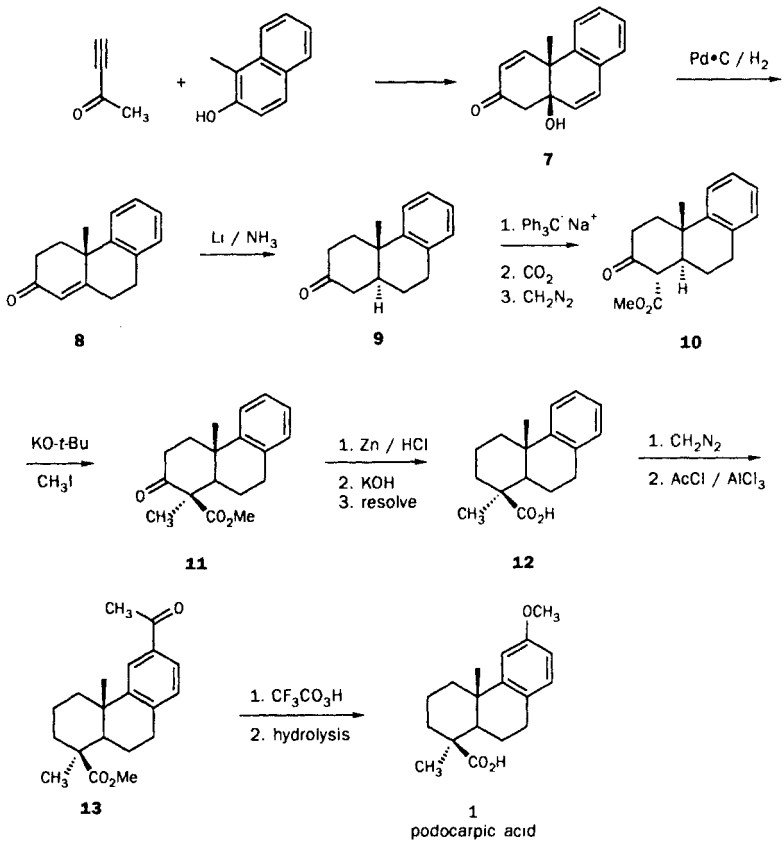


SCHEME 1. King's synthesis of podocarpic acid.



SCHEME 2. Podocarpic acid synthesis of Haworth and Moore.

out with *t*-butoxide and methyl iodide the reaction provides a mixture of products in the ratio of 2.4 to 1 with the desired podocarpane system **11** as the minor isomer. Clemmensen reduction of the ketone function gives desoxypodocarpic acid methyl ester and the derived acid is resolved via its



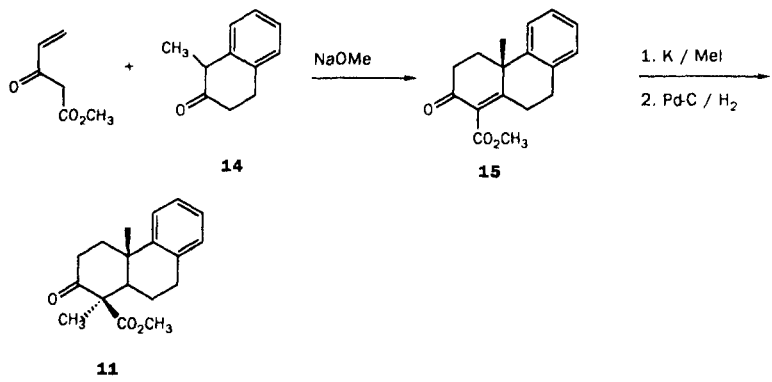
SCHEME 3. Wenkert first synthesis of podocarpic acid.

cinchonine salt to yield the natural series isomer (+)-desoxypodocarpic acid **12**.

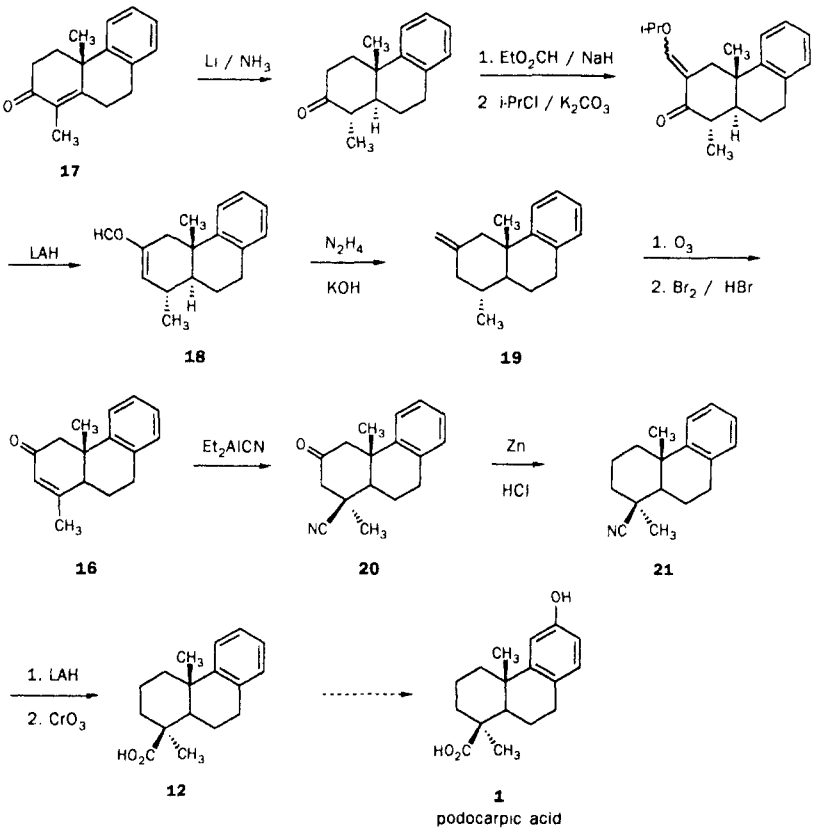
In previous work Wenkert and Jackson[8] showed that desoxypodocarpic acid can be reconverted to the natural product **1** by acetylation of the methyl ester of **12** to give **13** followed by Baeyer–Villiger (Emmons) oxidation and reductive cleavage of the C-4 axial ester group.

The second synthesis of podocarpic acid by Wenkert and co-workers[9] (Scheme 4) features an alternative preparation of keto ester **11** starting from β-tetralone **14**. Alkylation and reduction of Robinson annelation product **15** affords **11** in a more efficient fashion than the original synthetic scheme.

The synthesis of podocarpic acid by Meyer and Maheshwari[10] at the University of Arkansas (Scheme 5) differs from most other approaches to this molecule in the manner in which the stereochemistry at C-4 is introduced.



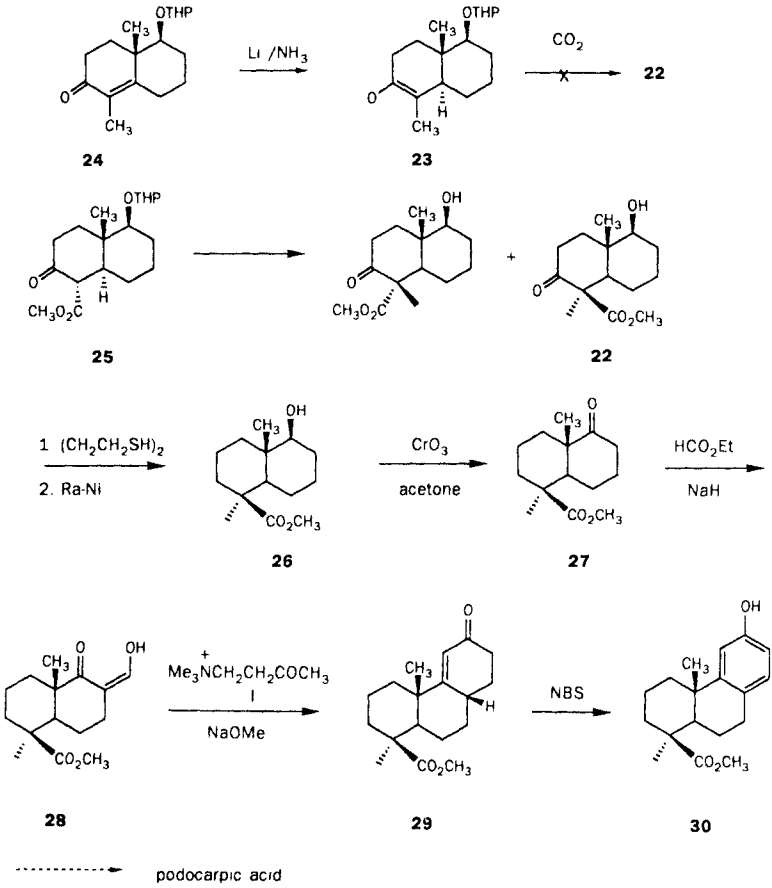
SCHEME 4. Wenkert's alternative synthesis of an intermediate for podocarpic acid.



SCHEME 5. Meyer's synthesis of podocarpic acid.

Rather than introducing a methyl or potential carboxyl group as an electrophile, a one-carbon unit is added by 1,4-nucleophilic addition to a tricyclic enone **16**. Starting from the standard Robinson annelation product **17**, the key intermediate **16** is prepared by an enone transposition sequence. The key step in the transposition is the Wolff–Kishner reduction of **18**, which gives the exocyclic olefin **19** rather than the endocyclic isomer. Addition of the Nagata reagent to enone **16** occurs in an axial sense to produce the podocarpic nitrile stereochemistry of **20**. Subsequent removal of the C-2 keto group to produce nitrile **21** and conversion of the nitrile function to a carboxylic acid one yields an intermediate, **12**, which had been carried through to podocarpic acid.[8]

The approach of Spencer and co-workers[11] at Dartmouth College to podocarpic acid (Scheme 6) is to construct an aromatic C-ring onto a



SCHEME 6. Synthesis of podocarpic acid methyl ester by Spencer.

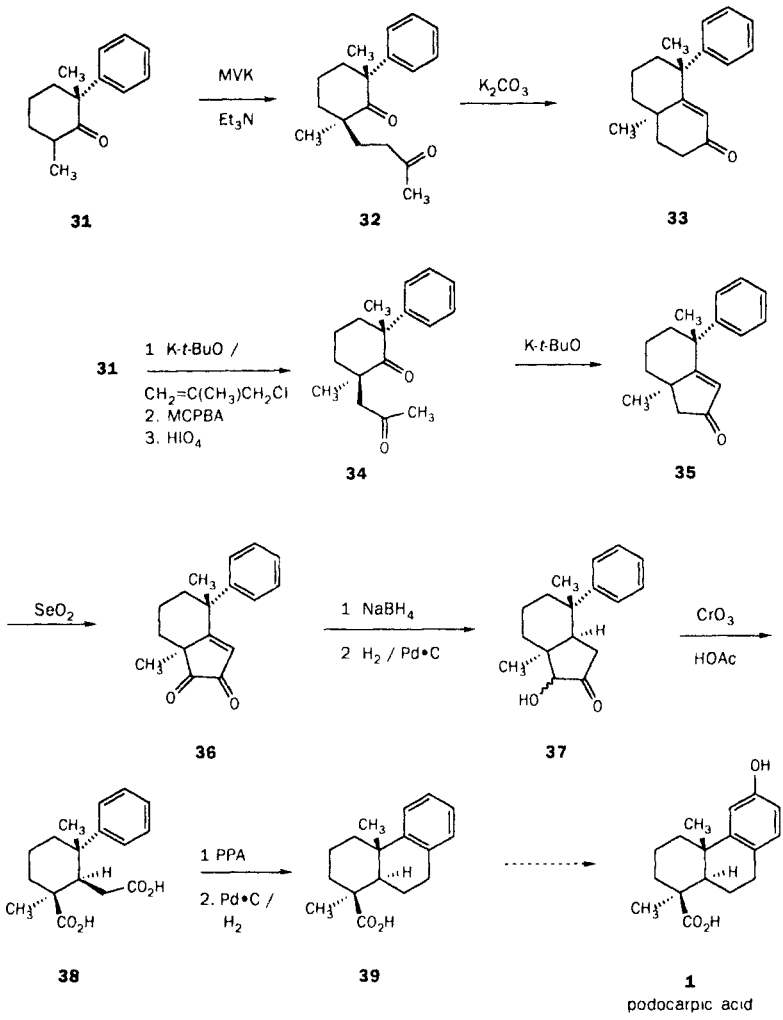
preexisting A/B system. The desired intermediate for the achievement of this plan is ketoester **22**. Initial attempts to produce **22** by carbonation of enolate **23** (generated by lithium–ammonia reduction of **24**) were unsuccessful. Instead **22** is prepared as the minor product from alkylation of saturated ketoester **25**.

To carry **22** forward it is converted into its ethylene thioketal derivative and the latter function is removed by Raney-nickel desulfurization to yield **26**. Oxidation yields **27**, which in turn is condensed with ethyl formate to yield the enolic keto aldehyde **28**. Robinson annelation affords unsaturated ketone **29**, which upon NBS oxidation provides podocarpic acid methyl ester, **30**.

Ireland and Giarrusso[12] at the University of Michigan carried out a synthesis of podocarpic acid (Scheme 7) employing the same general strategy used by Ireland and Kierstead[13, 14] for the synthesis of dehydroabietic acid, **68**. Thus a ring-A unit, **31**, bearing at one α position an aromatic group for ring-C and a methyl group for the angular substituent plus the potential C-4 methyl group at the other α carbon is alkylated first with methyl vinyl ketone to give **32**. In contrast to the epimeric substance used in the synthesis of dehydroabietic acid, the aldol cyclization of **32** to **33** is accompanied by a competing reverse Michael reaction to give substantial amounts of the starting material **31**. Since a 1,4-diketo system would not be subject to the reverse Michael process, **31** is alkylated instead with methallyl chloride and the methallyl group is oxidatively cleaved to yield **34**. The alkylation reaction occurs preferentially from the least-hindered face of the enolate, that is, away from the phenyl group yielding the podocarpic acid stereochemistry. Aldol condensation then produces the fused bicyclic enone **35**.

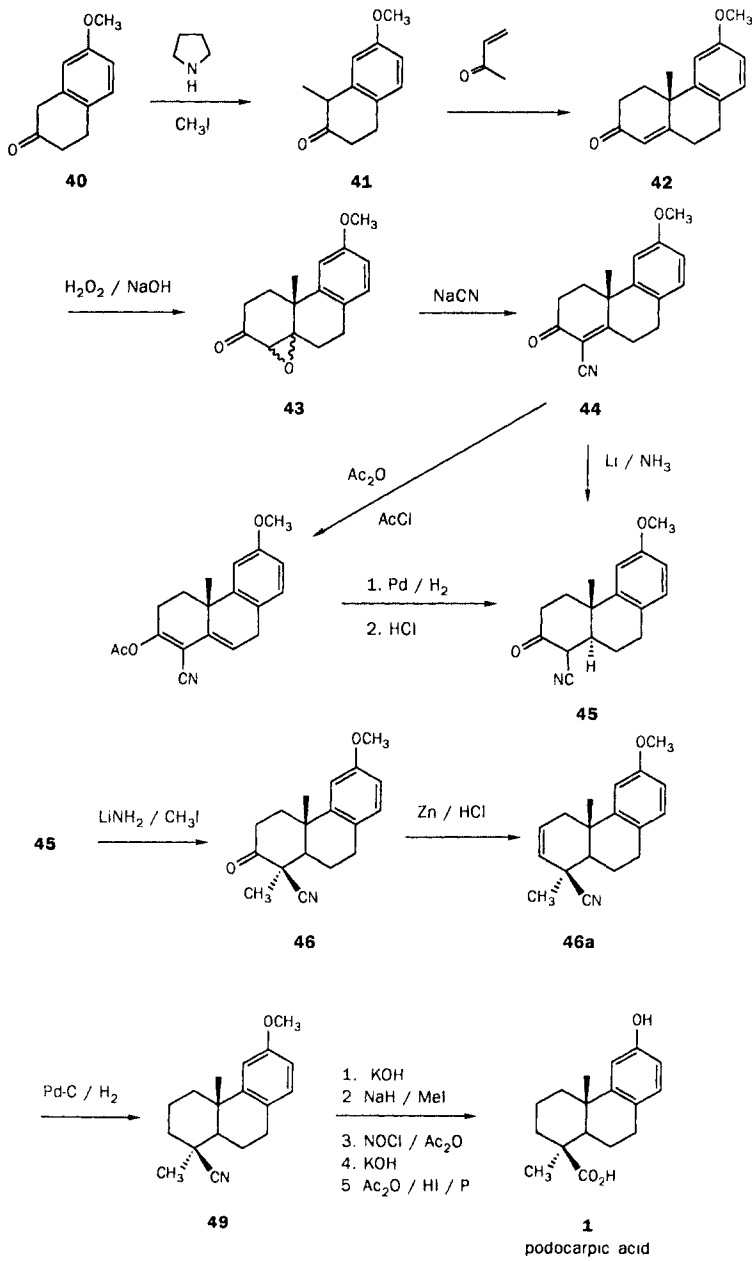
The stereochemistry of the eventual A/B ring junction is established by catalytic reduction after conversion of **35** to α-diketone **36**. Chemical reduction of **35** does not proceed with great stereoselectivity, but the catalytic process produces only the desired geometry. Oxidative cleavage of the five-membered ring of the reduction product **37** then affords a diacid, **38**, which upon cyclization and hydrogenolysis affords desoxypodocarpic acid, **39**. This compound is then carried through to the racemic natural product **1** using the method of Wenkert.[8]

The starting material for the synthesis (Scheme 8) of podocarpic acid by Kuehne and Nelson[15, 16] from the University of Vermont is 7-methoxy-β-tetralone, **40**. Methylation to afford **41** and Robinson annelation leading to tricyclic ketone **42** is followed by base-catalyzed epoxidation affording epoxy ketone **43**. Treatment of **43** with sodium cyanide proceeds via displacement and elimination to form the enone nitrile **44**. Two sequences are employed, both unfortunately going in low yield, to proceed to the saturated cyano-ketone **45**. In each case, however, the desired A/B *trans*-fused product is obtained.

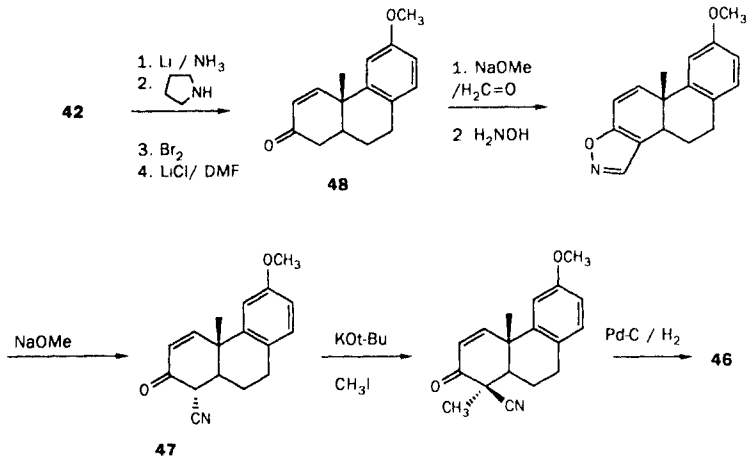


SCHEME 7. Ireland's synthesis of podocarpic acid.

Alkylation of **45** occurs *anti* to the angular methyl group to give **46** with the correct podocarpic acid stereochemistry. Another synthesis (Scheme 9) of this intermediate had been done earlier[15] by conversion of **42** to **47** via the $\Delta^{1,2}$-unsaturated ketone **48**. Alkylation of the unsaturated keto nitrile **47** also yields the podocarpic acid stereochemistry. The saturated alkylation product **46** of Scheme 8 is converted into olefin **46a**, thence to podocarponitrile methyl ether **49** by catalytic reduction. Methods which normally result in reduction



SCHEME 8. Kuehne's synthesis of podocarpic acid.

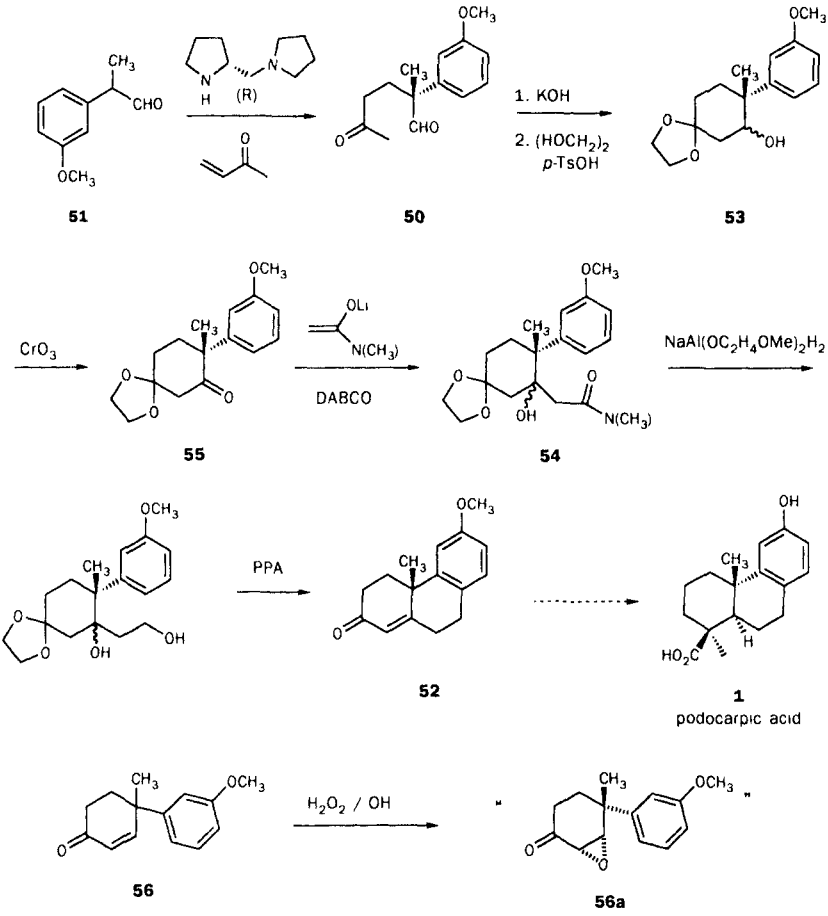


SCHEME 9. Kuehne's alternative synthesis of a podocarpic acid intermediate.

of a carbonyl group to a saturated carbon, for example, the Clemmenson reduction, when applied to ketone **46** yield the partial reduction product **46a**.

To obtain podocarpic acid methyl ether the nitrile, **49**, is subjected to a four-step sequence of partial hydrolysis, methylation, and nitrosation of the resulting amide and hydrolysis of the *N*-nitroso intermediate. Ether cleavage was carried out by the method of Haworth and Moore.[4]

For a chiral synthesis of podocarpic acid, Yamada and co-workers[17-19] at the University of Tokyo first carried out the preparation of keto-aldehyde **50** using (R)-pyrrolidonmethyl pyrrolidine as catalyst for the addition of aldehyde **51** to methyl vinyl ketone (Scheme 10). The product of this asymmetric synthesis, **50**, is chiral but the optical yield is only 42% e.e. For the synthesis of the target molecule only one other stereogenic center, C-5 with its α-disposed hydrogen, must be set. To do so the Yamada group converted **50** to enone **52**, a compound used by Welch[20] in his synthesis of racemic podocarpic acid. In the course of the conversion of **50** into **52** several of the intermediates contain chiral centers other than the one at C-10 established in the initial Michael addition. For example, **53** has a secondary hydroxyl at C-5 and **54**, produced by addition of the lithium enolate of dimethyl acetamide to **55**, has a tertiary hydroxyl and an acetamido chain at the same position. The chirality at C-5 of these compounds is lost in the course of the synthesis, but it is interesting to note that in every case the assignment of the relative configuration at C-5 is most probably incorrect.

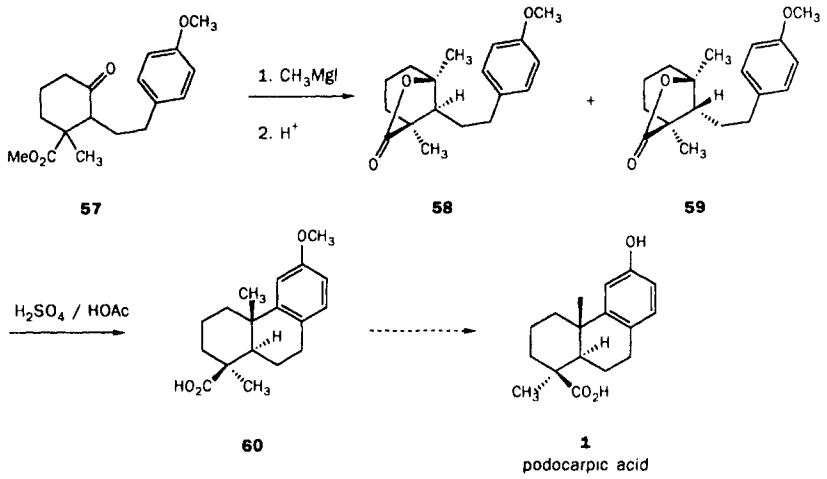


SCHEME 10. Yamada's synthesis of podocarpic acid.

For example, in one series of experiments[17] enone **56** is subjected to base-catalyzed epoxidation. On the basis of the difference in A-value[21] between a phenyl group and a methyl group, the major epoxide product is assigned the stereochemistry shown in **56a**, that is, axial attack of the epoxidizing agent has occurred from the side opposite to the "axial methyl group." In fact, a thorough conformational search[22] of **56** by use of molecular mechanics calculations[23] indicates that the major conformer of **56** (72%) is the one with an axial phenyl group! The minor conformer (28%) is the one with the methyl group in the axial position. Since it is unlikely that major differences in the rate of epoxidation would occur between these two conformers, the ratio of

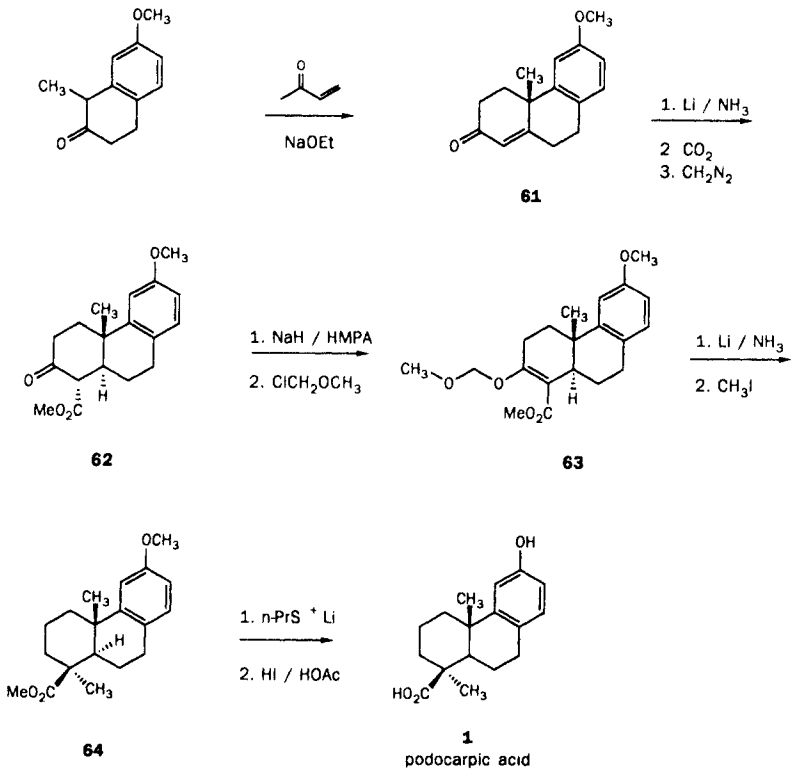
products ought to reflect the initial conformer populations. Indeed the products are obtained in the proportion of 3.5:1 (78–22%), but the assignment of stereochemistry appears to be reversed.

The Ghatak[24] synthesis of podocarpic acid (Scheme 11) from the Indian Association for the Cultivation of Science follows the pattern of the original King approach[3] but is more highly stereoselective. Starting from ketone **57** a mixture of lactones **58** and **59** is produced in a ratio of 9:1. When subjected to acid-catalyzed cyclization, this mixture affords podocarpic acid methyl ether **60** as the sole crystalline product in 41% yield. This material as noted has been carried forward to podocarpic acid.



SCHEME 11. Ghatak's synthesis of podocarpic acid.

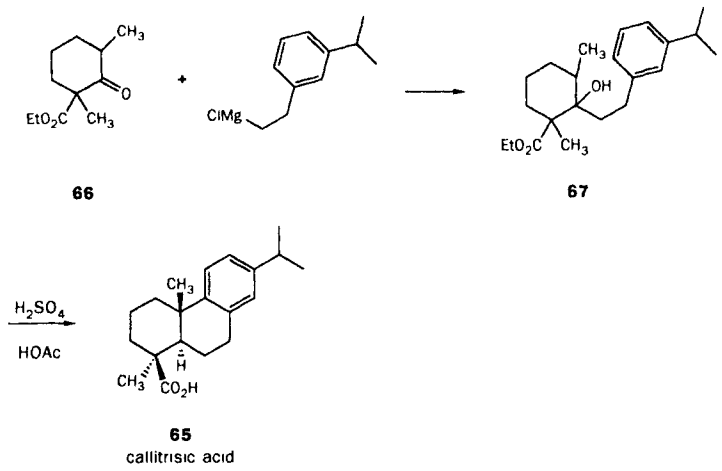
In the Welch[20–27] syntheses of podocarpic acid done at the University of Houston, the C-4 methyl group is introduced by alkylation of an exocyclic ester enolate (Scheme 12). This is in contrast to the more general use of the enolate of a C-3 keto group. In accord with the other syntheses in this domain, however, alkylation again occurs from the α face of the nucleophilic carbon. In the approach used by Welch, tricyclic enone **61**, produced by standard means, is converted through dissolving metal reduction, carbonation, and esterification to β-ketoester **62**. O-alkylation then provides enol ether **63**, which in a second lithium in ammonia reaction undergoes reduction, elimination, and then reduction again to provide the enolate ion of the C-4 ester group. Upon addition of methyl iodide, alkylation occurs principally from the least-hindered face of the anion and ester **64** is produced. Cleavage of both ester and ether functions yields podocarpic acid.



SCHEME 12. Welch's synthesis of podocarpic acid.

Callitrisic Acid and Alkylation Stereochemistry

The first synthesis of a resin acid, callitrisic acid, **65**, was carried out in 1939 by Haworth and Baker[28] (Scheme 13). The publication of the work was "desirable in view of the intention of Sterling and Bogert to enter the same field." The synthetic scheme is an extension of the "Bogert–Cook" route to phenanthrene derivatives.[29, 30] The substituted β-keto ester **66** is reacted with a substituted phenylethyl magnesium bromide to afford alcohol **67**. Following dehydration, acid-catalyzed cyclization provides one of the isomers of dehydroabietic acid in approximately 13% yield. At the time of publication this product could not be compared with naturally occurring material short of a resolution. Twenty-four years later, Sharma, Ghatak, and Dutta[31] demonstrated that the product obtained by Haworth and Baker is callitrisic acid, **65**.



66 67

65
callitrisic acid

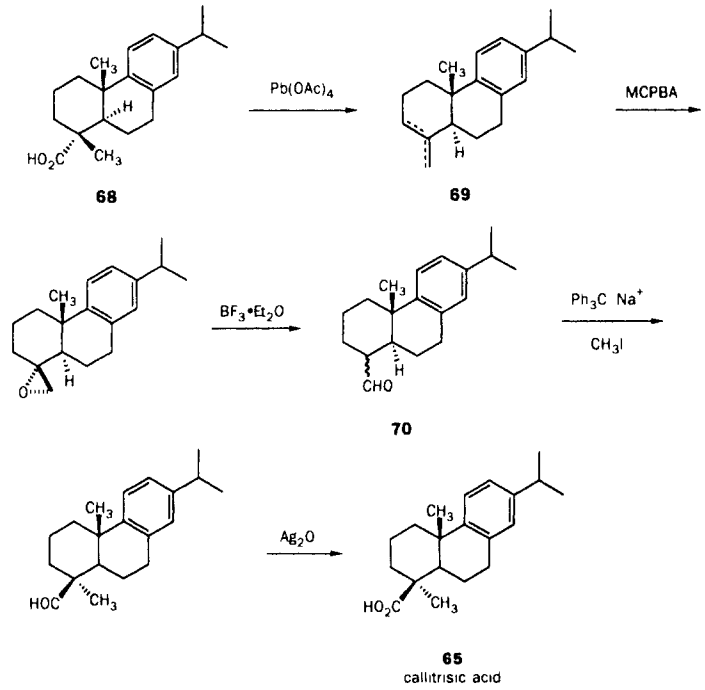
SCHEME 13. Haworth's synthesis of callitrisic acid.

A partial synthesis of callitrisic acid was carried out by Pelletier and Herald[31] (Scheme 14) by "inverting" C-4 of dehydroabietic acid. Thus the natural product, **68**, is oxidatively decarboxylated to yield a mixture of dienes from which the exomethylene compound **69** is isolated in moderate yield. Epoxidation, rearrangement to aldehyde **70**, methylation from the less-hindered α face, and final oxidation affords callitrisic acid, **65**.

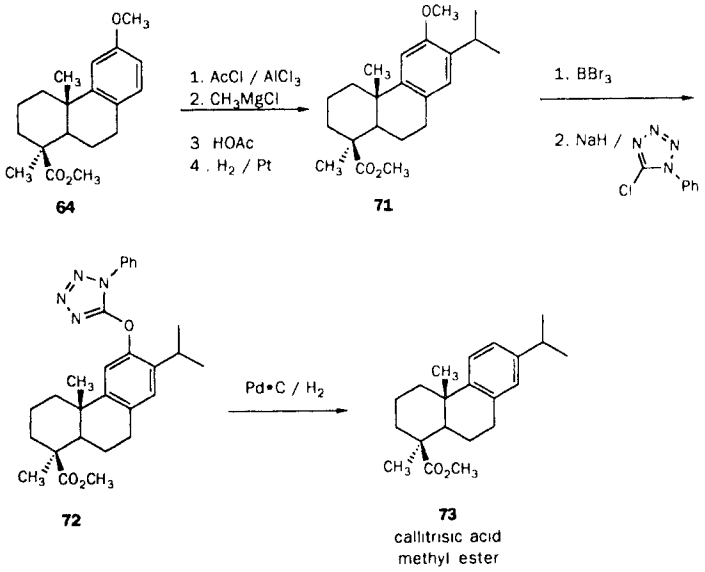
A partial synthesis was also carried out by Huffman[32] at Clemson University (Scheme 15). Following the procedure of Campbell and Todd,[33] *O*-methyl podocarpic acid methyl ester **64** is converted into the isopropyl-substituted ether **71**. Cleavage of the ether group is followed by formation of the phenyltetrazole derivative **72**. Hydrogenolysis provides **73**, the methyl ester of callitrisic acid.

In the Welch[26,27] synthesis of callitrisic acid a tricyclic intermediate **77** (Scheme 16) is constructed by a twofold annelation sequence starting from **74**. "Friedel–Crafts" acylation of **75** with concomitant cyclization affords **76**, and subsequent Robinson annelation affords **77**. By dissolving metal reduction and carbonation **77** is converted into the *trans*-fused keto ester **78**. As in the podocarpic acid synthesis, an enol ether, **79**, is prepared and further reduction again effects the loss of the C-3 oxygen with production of an ester enolate at C-4. Addition of methyl iodide to yield **80**, followed by demethylation of the ester group, affords callitrisic acid, **65**.

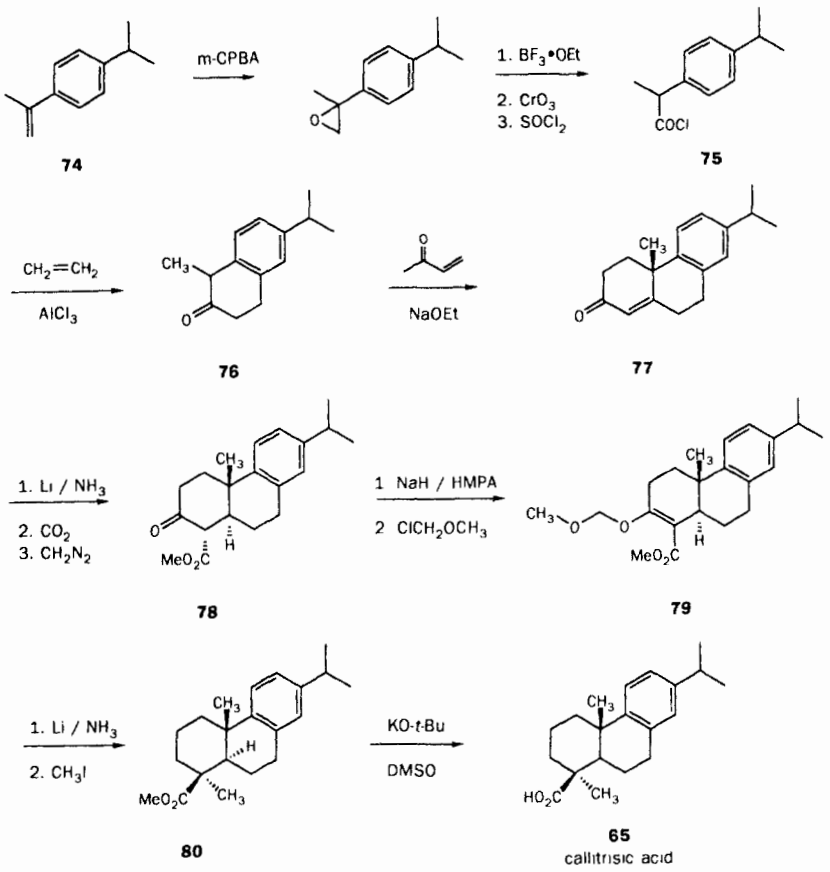
An alternative synthesis of callitrisic acid was carried out in a joint effort by Carman and co-workers[34] at Queensland and Mori and Matsui at Tokyo. Enone (Scheme 17) is prepared either by the method of Barltrop and Day,[35]



SCHEME 14. Partial synthesis of callitrisic acid by Pelletier.



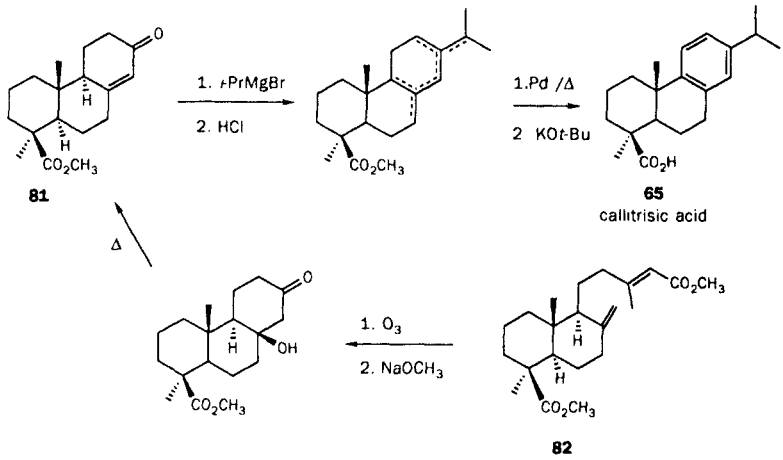
SCHEME 15. Huffman's formal synthesis of callitrisic acid.



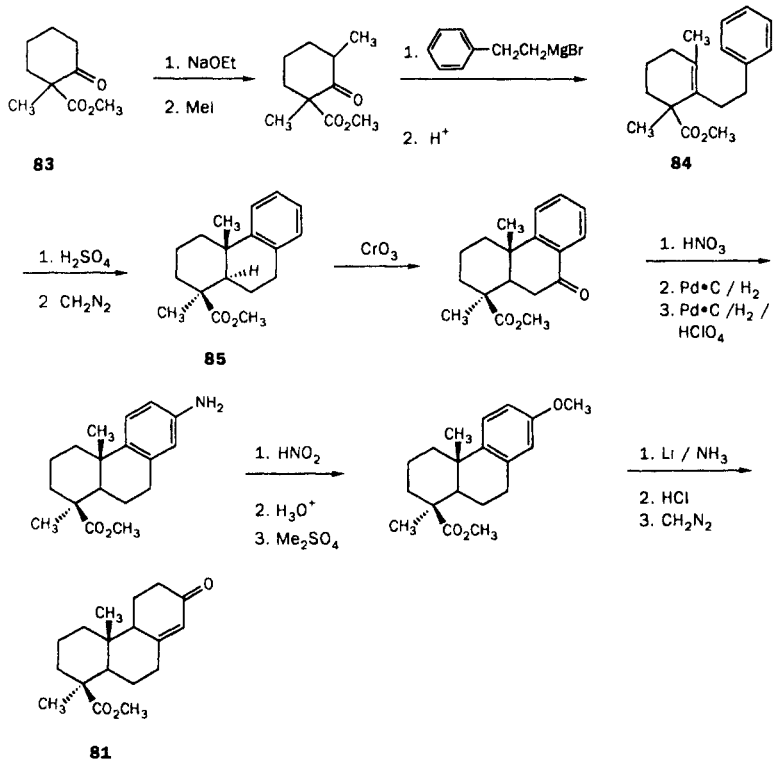
SCHEME 16. Welch's synthesis of callitrisic acid.

by the oxidation of dimethyl agathate **82** and subsequent aldol cyclization, or by a route[36] (Scheme 17a) starting from cyclohexanone carboxylate **83**. In this preparation of **81** the key cyclization reaction, **84** to **85**, which sets the A/B-ring fusion and the stereochemistry at C-4 as well occurs in low yield but the *trans*-fused product is the only one to be isolated. This cyclization was originally carried out by Haworth and Barker,[28] but the stereochemistry of the product was not determined. To carry **85** forward to callitrisic acid, **65**, the addition of an isopropyl Grignard reagent to the enone carbonyl is executed followed by dehydration and aromatization (Scheme 17).

It is appropriate with the results of the Welch syntheses of podocarpic and callitrisic acids to reflect on the stereochemistry of the alkylation of anions at



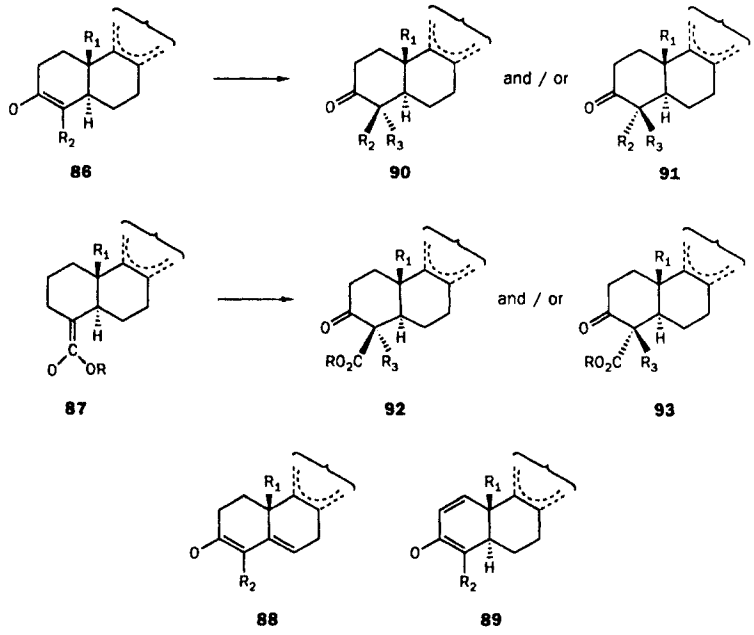
SCHEME 17. Carman and Mori's synthesis of callitrisic acid.



SCHEME 17a. Mori's Preparation of an intermediate for callitrisic acid.

C-4 of the tricyclic diterpene skeleton. This subject has been discussed frequently and an excellent recent review has been published by Evans.[37]

Three factors may be considered to be operative in determining the stereochemical outcome of the alkylation of enolates **86** and **87** (or the related dienolates **88** and **89**) to yield **90** and **91** or **92** and **93** (or the corresponding products from **88** and **89**).



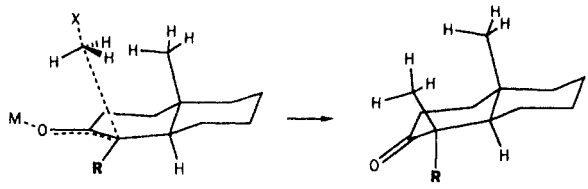
86 **90** **91**

87 **92** **93**

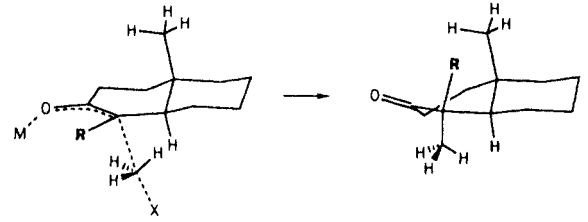
88 **89**

The first is a stereoelectronic effect which reflects maximum maintenance of overlap of the p-orbitals of the enolate system in the transition state. The second factor is the steric effect resulting from an interaction of the angular substituent at C-10 with the entering electrophile. The third is the possible reflection of product energies in the energy of the transition state by virtue of a late transition state.[38]

The work of House[39] on the alkylation of 4-tert-butylcyclohexanone suggests that the stereoelectronics are not critical in 6-membered-ring ketone alkylations. That is, alkylation is an exothermic process with an early transition state. As a consequence, reaction through either a chair-like conformation (**94** to **95**) or a twist-boat-like conformation (**96** to **97**) results in transition states of comparable energy (ignoring steric factors). Axial alkylation through a chair is not required.

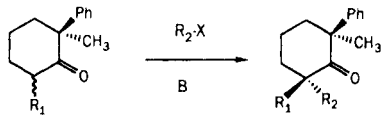


94 95



96 97

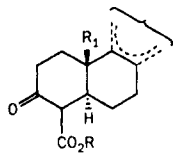
This conclusion was challenged by Ireland[12,40] on the basis of the alkylations of phenyl-substituted ketones of type **98**. However, Ireland's conclusions were based on an erroneous assignment of the configurations of the starting materials **98** and the preferred conformations of both **98** and the products, **99**. Starting materials and products in these cases prefer the phenyl groups *axial*[41] by a substantial amount (ca. 3 kcal/mole!) and the preferred mode of alkylation of **98** type compounds is through the twist-boat form (i.e., equatorial alkylation).



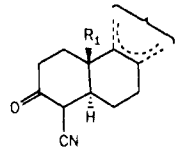
98 99

It is clear from the results of almost all of the alkylation reactions at C-3 of diterpene intermediates that stereoelectronics (with one exception) are not the controlling factor. Steric hindrance by the angular substituent appears to be the principal determinant of product stereochemistry. The one exception is the β-ketoester **100**. This system in general undergoes alkylation from the β face of the enolate and yields a product with the abietic acid stereochemistry.[6,42–44] The explanation often given is that the reactions of highly stabilized enolates are slow relative to simple enolates and thus occur

through late transition states; that is, the relative energies of the products are reflected in the transition state. In the case of **100**, however, that is not the case. Molecular modeling calculations (Table II) show that the podocarpic acid systems **101** and **102** are approximately 2 kcal/mol lower in energy than the corresponding abietic acid types **103** and **104**.



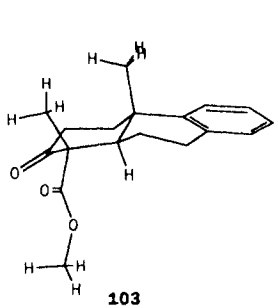
100



111

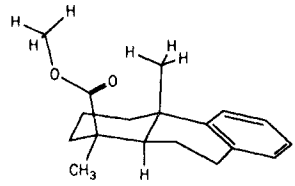
A better explanation for the alkylation stereochemistry of the β-ketoester enolate is that here stereoelectronics are dominant since this system is far more delocalized than a simple ketone enolate. As a consequence, overlap of

Table 2 Steric Energies of Podocarpic and Abietic Ester Systems



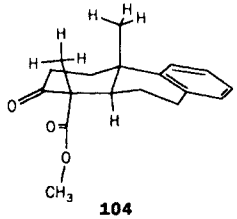
103

steric energy =38.86



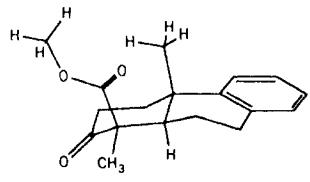
101

steric energy =36.94



104

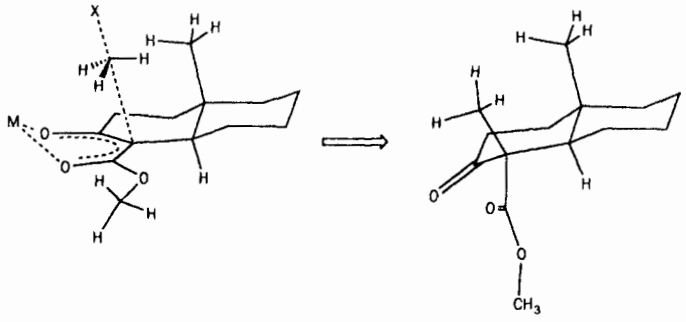
steric energy =41.99



102

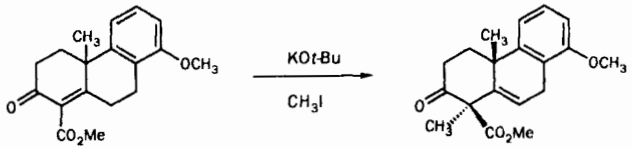
steric energy =39.34

the system is better maintained (**105** and **106**) when the transition state is more chair-like. "Axial" alkylation therefore is favored.

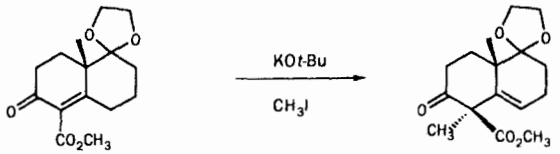


105 **106**

The stereoelectronic effect is readily lost, however, when additional conjugation is added to the enolate system. For example, enone esters **107** and **108** both yield the products of steric control of alkylation, **109** and **110**,[9,45] that is, methylation opposite to the angular substituents.



107 **109**



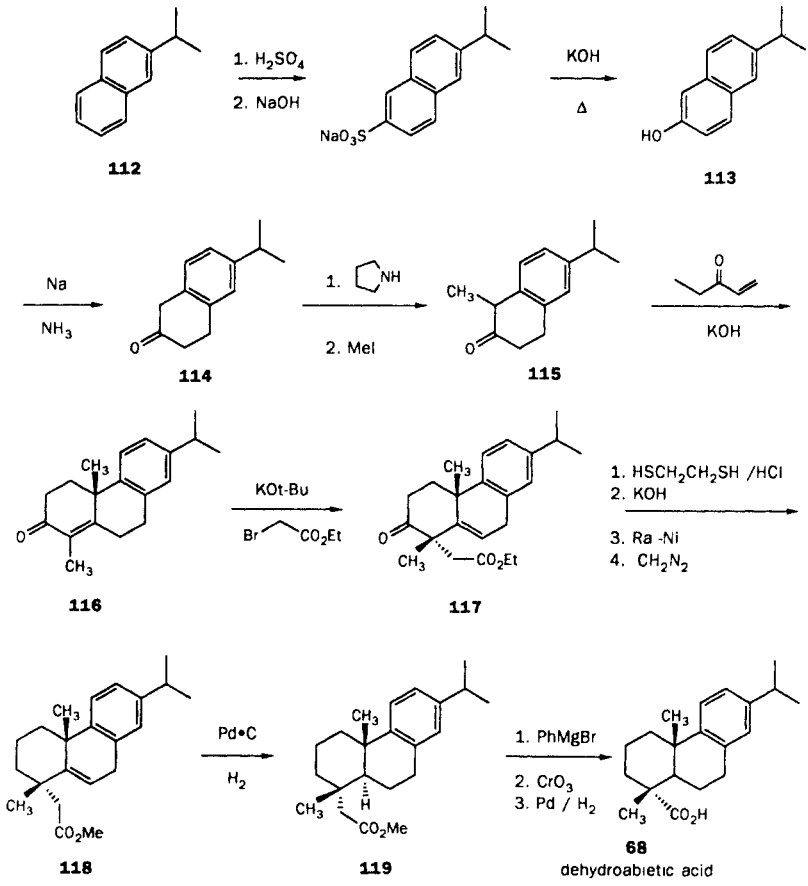
108 **110**

One last case that must be explained is that of the β-keto nitrile **111**. This "resonance stabilized" enolate gives the opposite result from the keto ester.[46] In unhindered cyclohexyl systems β-ketonitriles as well as β-keto esters are known to give more axial alkylation than do simple ketones.[16,46a] Nitrile groups, however, are also known to provide significant stabilization to anionic carbon centers through induction and indeed, the lithiate of 2,2-

dimethylcyclopropylcarbonitrile has been shown to have a tetrahedral anionic site with a carbon–lithium bond.[46b] Thus in the alkylation of **111**, steric hindrance appears to be the dominant factor again and the anion may readily be stabilized by both the keto and the nitrile groups without the necessity of coplanarity.

Dehydroabietic Acid

The first stereorational synthesis of a diterpene resin acid is the synthesis of dehydroabietic acid **68** by Stork and Schulenberg[47, 48] at Columbia University (Scheme 18). Starting from isopropylnapthalene, **112**, β-naphthol, **113**, is



SCHEME 18. Stork and Schulenberg's synthesis of dehydroabietic acid.

prepared by sulfonation followed by fusion with sodium hydroxide. Birch reduction then yields tetralone, **114**, which is alkylated to **115** in what was one of the first examples of the use of the enamine alkylation process. Subsequent Robinson annelation with ethyl vinyl ketone affords tricylic enone **116**. The alkylation of **116** with an electrophile of some steric demand results in stereoselective reaction from the α face to give keto ester **117**. A reduction sequence via olefin **118** leads to **119**. This homologue of dehydroabietic acid is converted into the natural product, **68**, by use of the Barbier–Wieland protocol.

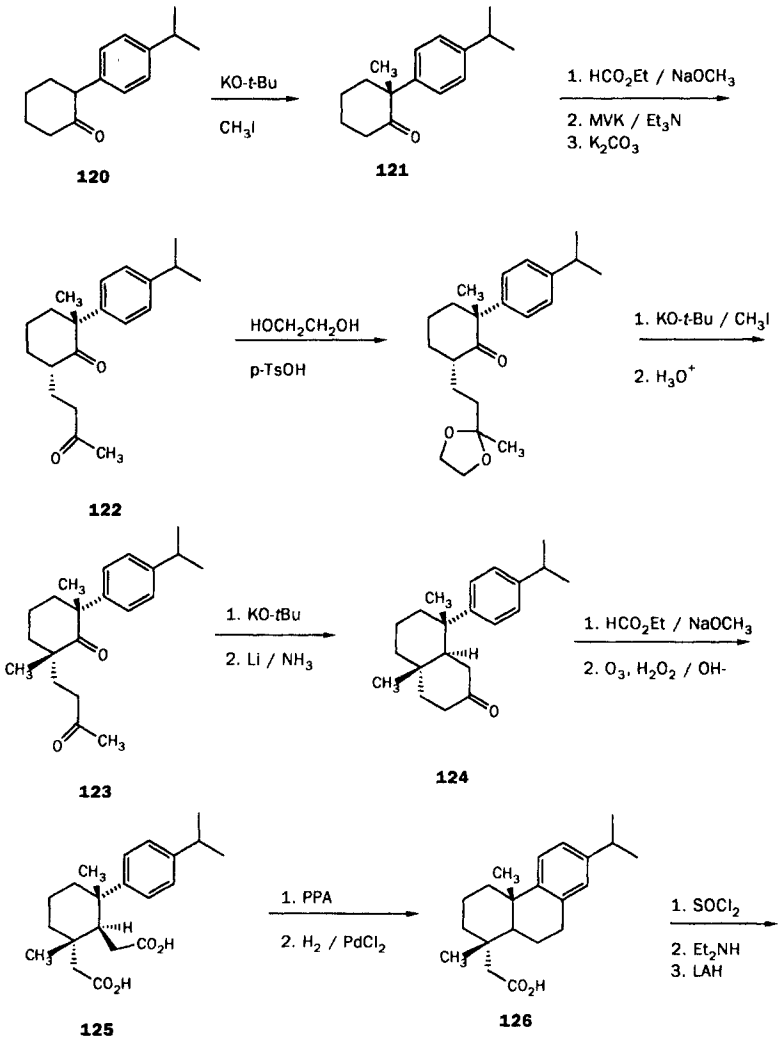
Ireland and co-workers,[12-14, 40, 49, 50, 51] first at Michigan and subsequently at the California Institute of Technology carried out an extensive series of experiments designed to elucidate the stereochemistry of the resin acids and to provide rational routes for their laboratory synthesis. The basic approach taken is to start with a bicyclic A-C system and to fuse to both these initial portions the elements of ring B. Thus arylcyclohexanone **120** is methylated to introduce the eventual angular substituent (Scheme 19) and this product, **121**, is added to methyl vinyl ketone to produce **122**. In light of recent findings,[52] however, the stereochemistry reported for **122** is almost certainly incorrect. The methyl group and the butanone side chain of **122** are most probably *cis* not *trans*, as described originally, since axial methyl is conformationally worse than axial phenyl when the two groups are geminally substituted.[53, 54]

Following protection of the side-chain carbonyl group a second methylation is carried out to produce, after deketalization, **123**. In this fashion the construction of the B-ring will be entirely intramolecular and the extreme hindrance at the cyclohexanone carbonyl carbon toward intermolecular reaction will not be an inhibiting factor in the creation of the tricyclic system.

Interestingly, the conformation of **123** is again not that assumed in the original discussion of this work. The molecule prefers by ca. 4 kcal/mole to exist as **124** (Scheme 19) with the phenyl ring and the butanone side chain in axial positions rather than as the diaxial–dimethyl conformer **125**. The reasons for this preference are twofold. First, as noted earlier, 2-methyl-2-phenylcyclohexanones in general prefer axial–phenyl conformations by as much as 3 kcal/mole and second, the axial–axial interaction of the flat, sterically anisotropic phenyl ring and the butanone chain is significantly less than that of two similarly disposed methyl groups. Nevertheless, the relative stereochemistry of **123** is as shown and the substance undergoes aldol cyclization in good yield. Reduction of the aldol product yields the *trans*-fused bicyclic ketone **124**, which in turn is subjected to formylation and oxidative ozonization to produce diacid **125**. Cyclization of **125** with polyphosphoric acid followed by hydrogenolysis of the C-7 keto group affords homo-dehydroabietic acid **126**. Following a route different than the

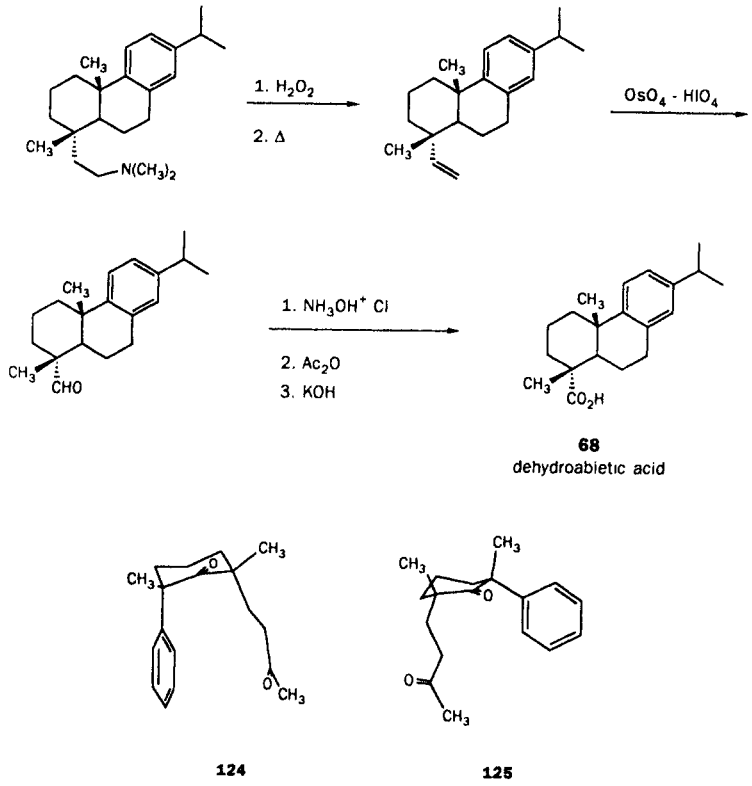
Barbier–Wieland approach of Stork, Ireland and Kierstead carry out the degradation of **126** to dehydroabietic acid **68**.

For the synthesis of methyl dehydroabietate, **127** (and by extension, dehydroabietic acid and abietic acid), Meyer and co-workers[55, 56] at the University of Arkansas employed the same strategy used in their syntheses of carnosic acid, ferruginol, and other aromatic ring-C oxygenated tricyclic



120 121 122 123 124 125 126

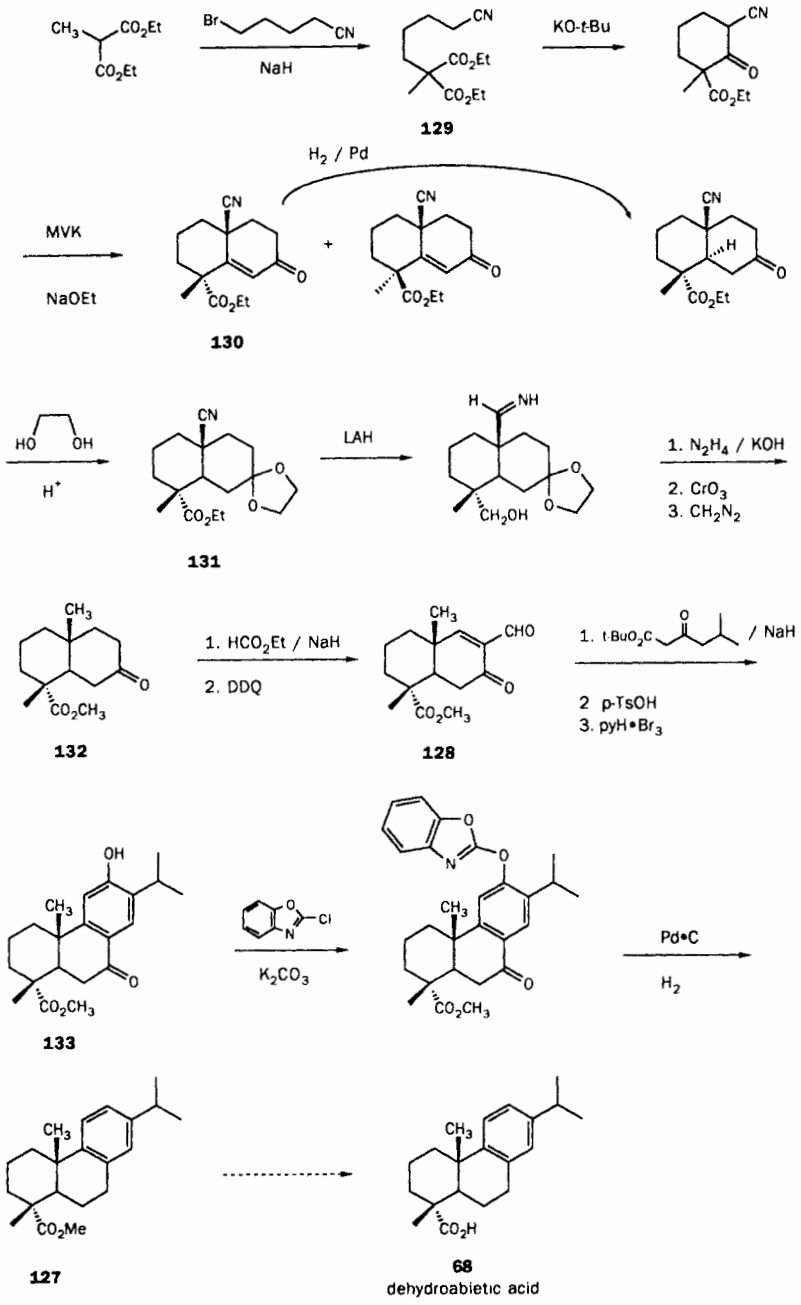
SCHEME 19. Ireland's synthesis of dehydroabietic acid.



SCHEME 19. Ireland's synthesis of dehydroabietic acid (*continued*).

diterpenes (Scheme 20). The general strategy is the preparation of an A–B bicyclic enal, for example, **128**, followed by a Robinson annelation approach—the addition of the C-ring by base-catalyzed Michael addition and aldol condensation. The route leads in all cases to an intermediate with a phenolic hydroxyl at C-12 and in the case of dehydroabietic acid synthesis this group must be removed. In addition, ring A must bear a carboxyl function with the appropriate stereochemistry.

To prepare the A–B portion of the molecule for the synthesis of dehydroabietic acid, cyanodiester **129** is converted by a Claisen condensation–Robinson annelation sequence to a mixture of bicyclic enones. As only **130** is potentially useful for the abietane series, the overall sequence lacks stereoselectivity. After ketone protection, a sequence of lithium aluminum hydride reduction followed by Wolff–Kishner reduction and restoration of the C-4 ester function, the angular cyano group of **131** is converted into the C-10 methyl group of **132**. Completion of the synthesis is accomplished by

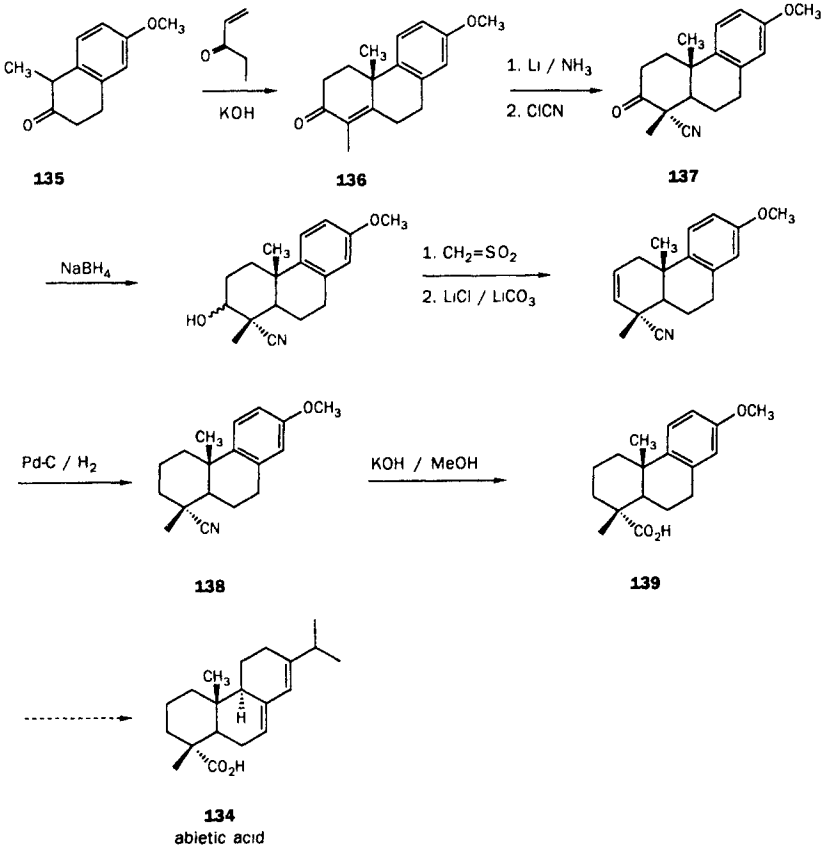


SCHEME 20. Meyer's synthesis of dehydroabietic acid.

preparation of ketoaldehyde **128**, Robinson annelation to produce **133**, and hydrogenolysis of both keto and phenolic oxygen functions to yield methyl dehydroabietate, **127**.

Abietic Acid

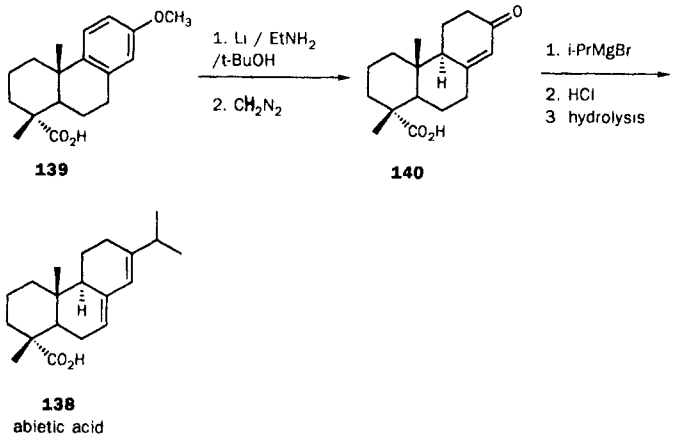
Kuehne and Nelson's syntheses of abietic and podocarpic acids helped to clarify the principal stereochemical modes of alkylation of 10-methyl *trans*-fused bi- and tricyclic ketones. Although the yields of alkylated products are not high in the cases that were examined, unique products were obtained in each case. Thus, as a general result, the alkylation of a 10-methyl substituted-



SCHEME 21. Abietic acid synthesis of Kuehne.

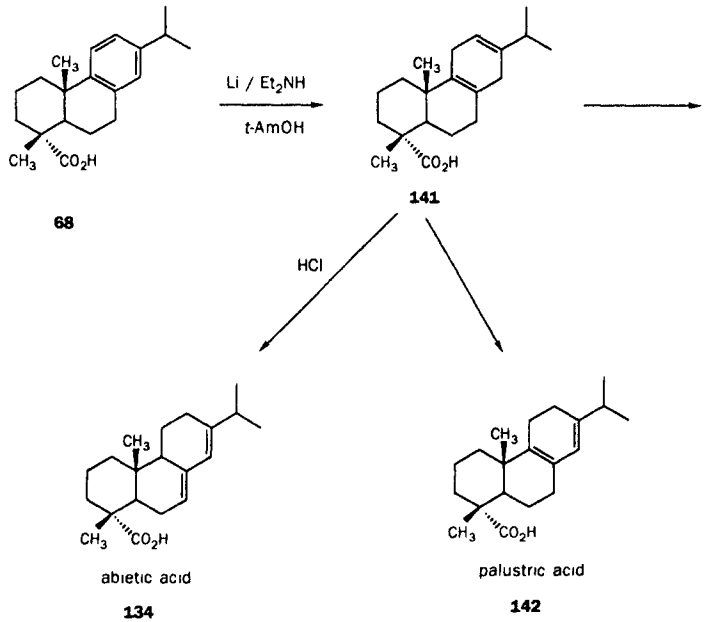
3-ketone occurs from the α-side; that is, away from the sterically hindering angular substituent.

For abietic acid **134** the synthesis[16] begins (Scheme 21) with the venerable 1-methyl-6-methoxy-β-tetralone **135** as starting material. Robinson annelation of **135** using ethyl vinyl ketone yields tricyclic enone **136**. When reduced with lithium in ammonia, **136** affords an enolate with trans geometry at the A/B-ring junction. Cyanation of this enolate then gives ketone **137**, reaction as already noted, occurring away from the angular group. Clemmenson reduction or desulfurization of the derived thioketal failing, the ketone group of **137** is removed by a three-step reduction, elimination, reduction sequence to give **138**. The remaining steps to a formal synthesis of abietic acid are straightforward. First is the hydrolysis of the cyano group to a carboxylic acid function, **138** to **139**. This acid (albeit in enantiospecific form) was converted by Burgstahler[57] into abietic acid. Thus, reduction of **139** to enone **140** (Scheme 22) is followed by reaction with isopropyl magnesium bromide and dehydration of the resulting alcohol to yield the methyl ester of abietic acid. Base-catalyzed hydrolysis of the ester affords the natural product **134**.



SCHEME 22. Burgstahler's formal synthesis of abietic acid.

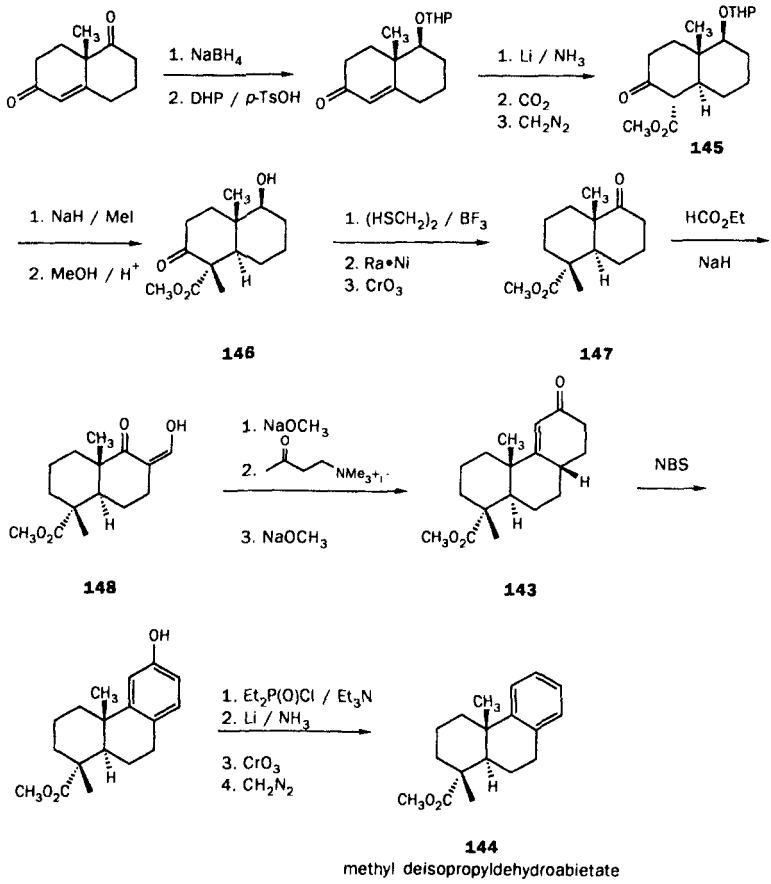
Subsequent to the Stork synthesis of the aromatic resin acid Burgstahler and Worden[58] from the University of Kansas showed that dehydroabietic acid, **68**, is converted (Scheme 23) by reduction with lithium in diethylamine into nonconjugated diene **141**. Acid-catalyzed isomerization of **141** affords abietic acid, **134**. When **141** is heated with base it isomerizes to palustric acid, **142**.



SCHEME 23. Burgsthaler's conversion of dehydroabietic acid to abietic and palustric acids.

Deisopropyldehydroabietic Acid

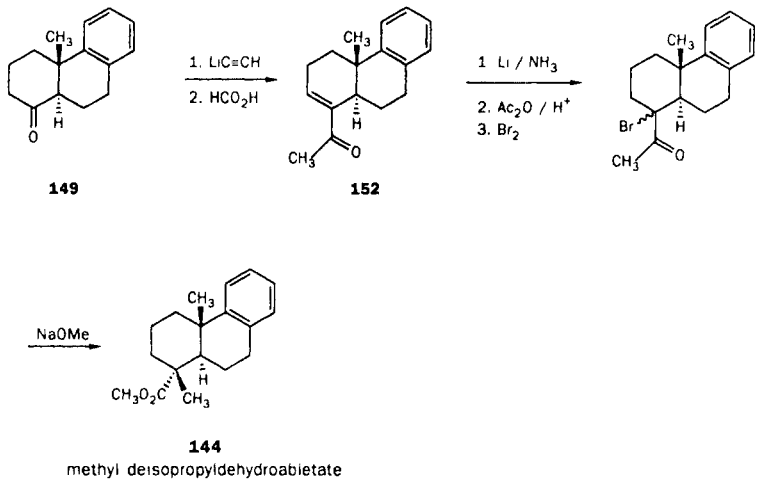
Tricyclic enone **143** was used by Spencer and co-workers[42] for the synthesis of both methyl deisopropyldehydroabietate **144** and methyl vinhaticoate (**11**, Scheme 80). While the deisopropyl compound is not a natural product it (and the corresponding "relay" derived from dehydroabietic acid) have been useful in diterpene synthesis. To obtain **143** (Scheme 24), the Wieland–Mischer ketone is reduced to a ketol and then protected as a tetrahydropyranyl ether. Reductive carbonation affords the *trans*-fused β-keto ester **145**. The methylation of **145** yields a 10:1 mixture of isomers with the predominant product having the expected abietic acid stereochemistry. Hydrolysis of the alkylation product gives ketol **146**. After removal of the C-3 keto group the third ring of **143** is added by first converting **147** into its hydroxymethylene derivative **148** and then Robinson annelation to yield **143**. Ring C is aromatized with *N*-bromosuccinimide and the phenol hydroxyl group is reductively eliminated followed by oxidative reformation of the 4-carbomethoxy group to produce the target molecule **144**.



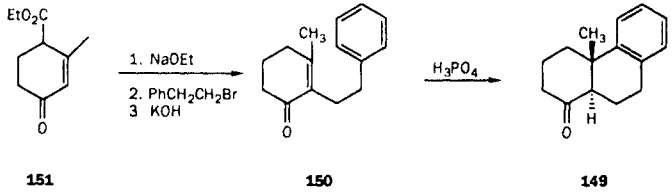
SCHEME 24. Spencer's synthesis of methyl deisopropyldehydroabietate.

An earlier synthesis (Scheme 25) of the deisopropyl compound **144** was carried out by Barltrop and Day[59] at Oxford University. *Trans*-fused ketone **149** is the starting material for this synthesis and was prepared previously (Scheme 26) by Stork and Burgstahler.[60] The synthesis of **149** is carried out by preparation of enone **150** from Hagemann's ester **151** and the cyclization is effected by phosphoric acid.

Ethynylation of **149** (Scheme 25) and subsequent hydrolysis provides enone **152**. Surprisingly, **152** alkylates exclusively on the methyl group, in contrast to the behavior of acetyl cyclohexenone. To introduce the C-4 methyl group, therefore, the enone double bond is reduced to give a saturated



SCHEME 25. Barltrop's synthesis of methyl deisopropyldehydroabietate.



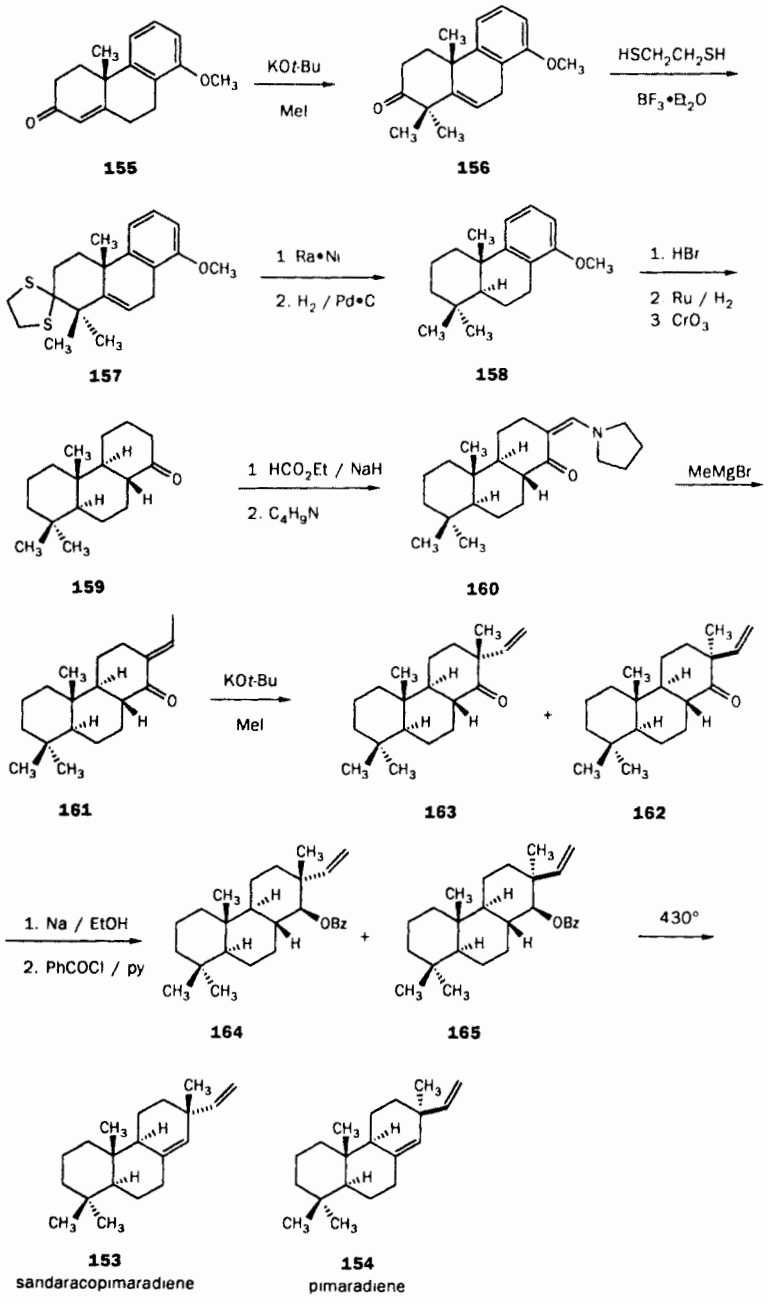
SCHEME 26. Stork's preparation of an intermediate for the synthesis of methyl deisopropyldehydroabietate.

ketone which in turn is converted into bromide **153**. Favorskii rearrangement of **153** affords a mixture of esters from which methyl deisopropyldehydroabietate is isolated.

(2) Sandaracopimaradiene and Pimaradiene

Sandaracopimaradiene, **153**, and pimaradiene, **154** (Scheme 27), were synthesized by Ireland and Schiess[50] as part of a program in the assignment of structure and stereochemistry to the pimarane hydrocarbons and the pimaric acids.

The starting material for the two dienes is the Cornforth–Robinson ketone **155**.[61] Typical for such enones, methylation of **155** occurs twice in the presence of *tert*-butoxide to give β,γ-unsaturated ketone **156**. The carbonyl



SCHEME 27. Ireland's synthesis of sandaracopimaradiene and pimaradiene.

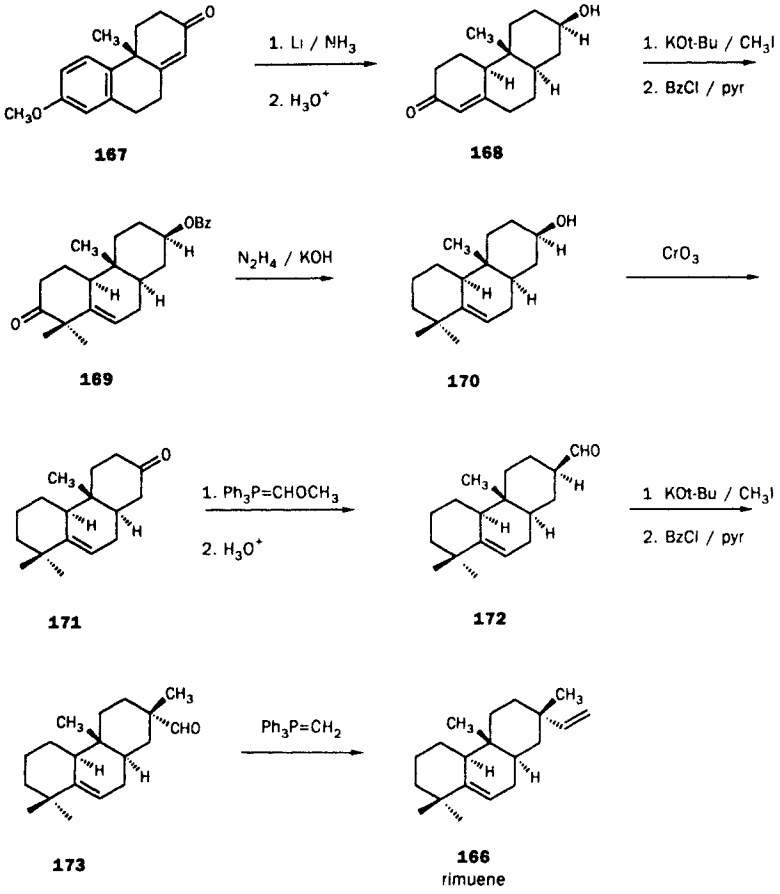
group is then removed by Raney nickel reduction of the derived thioketal **157** and hydrogenation affords tricyclic ether **158**. Reduction of the aromatic ring is effected on the corresponding phenol, obtained by hydrobromic acid cleavage of the methyl ether function, and oxidation of the hydrogenated product affords *trans-anti-trans*-ketone **159**.

To attach the side-chain substituents ketone **159** is transformed into its α-formyl derivative, thence to enamide **160**. Addition of a methyl Grignard reagent produces α,β-unsaturated ketone **161**. Two products are obtained when **161** is subjected to methylation; one, in low yield, is the equatorial methyl substance **162** and the other is the product of axial methylation **163**. The ketones are separated and carried through to dienes by thermodynamically controlled reduction to afford equatorial alcohols, followed by benzoylation to yield **164** and **165**. Since the benzoate group in both of these molecules is syn to the angular hydrogen at C-8, a thermal *cis* elimination is feasible. Thus, heating of **164** and **165** individually affords sandaracopimaradiene, **153**, and pimaradiene, **154**, respectively.

(3) Rimuene

Rimuene, **166**, is a rearranged pimaradiene in the biogenesis of which the C-10 methyl group has migrated to C-9 with concomitant 1,2-shifts of the C-5 and C-9 protons. The configurations at C-8, C-9, and C-10 are opposite to those found normally in the tricyclic diterpenes. The structure and stereochemistry of rimuene were a subject of some debate and several postulated structures were ruled out on the basis of synthetic work, in particular the synthesis of sandaracopimaradiene by the Ireland group. For the synthesis of rimuene, Ireland and Mander[62] choose the readily available tricyclic ketone **167** (Scheme 28) prepared from 1-methyl-6-methoxy β-tetralone and methyl vinyl ketone, but as a consequence of the position of the angular methyl group in rimuene they elected to use the aromatic ring of **167** as the source of ring-A of the diterpene rather than the more common application of this unit as the precursor to ring-C.

Lithium in ammonia reduction of **167** followed by methylation and benzoylation of the enone product **168** affords keto ester **169**. As a consequence of the dissolving metal reduction conditions the "backbone stereochemistry" of **169** is characteristically *trans-anti-trans*.[63] Wolff–Kishner reduction of **169** affords alcohol **170**, which is then oxidized to **171**. The carbonyl function of **171** is homologated through a Wittig reaction to aldehyde **172** and subsequent methylation affords **173**. Final Wittig methylenation of **173** provides racemic rimuene, **166**.



167 **168** **169** **170** **171** **172** **173**

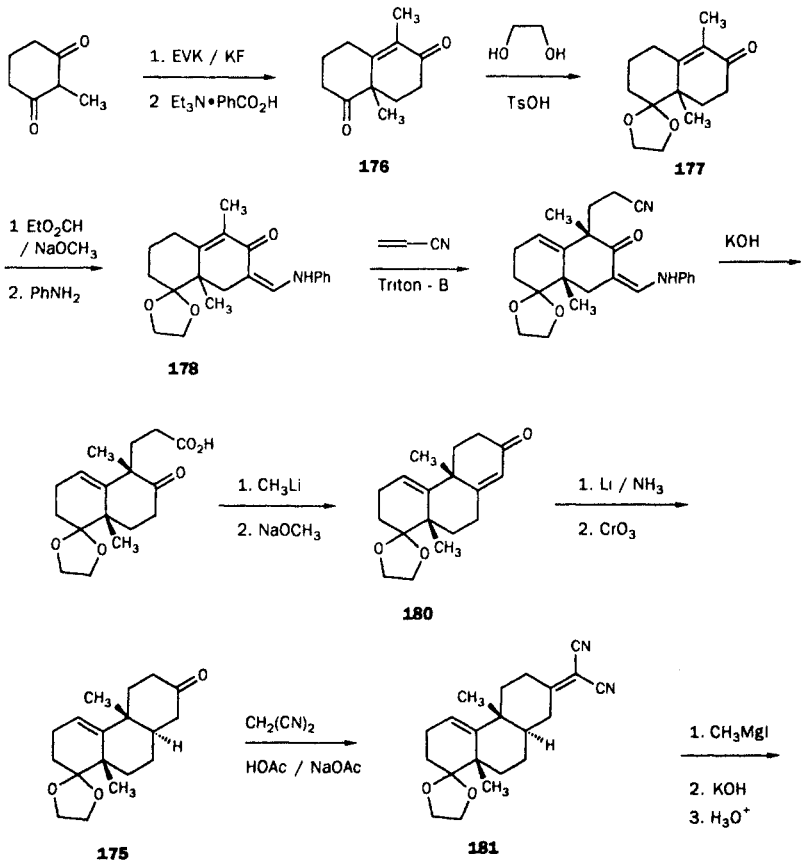
166
rimuene

SCHEME 28. Ireland's synthesis of rimuene.

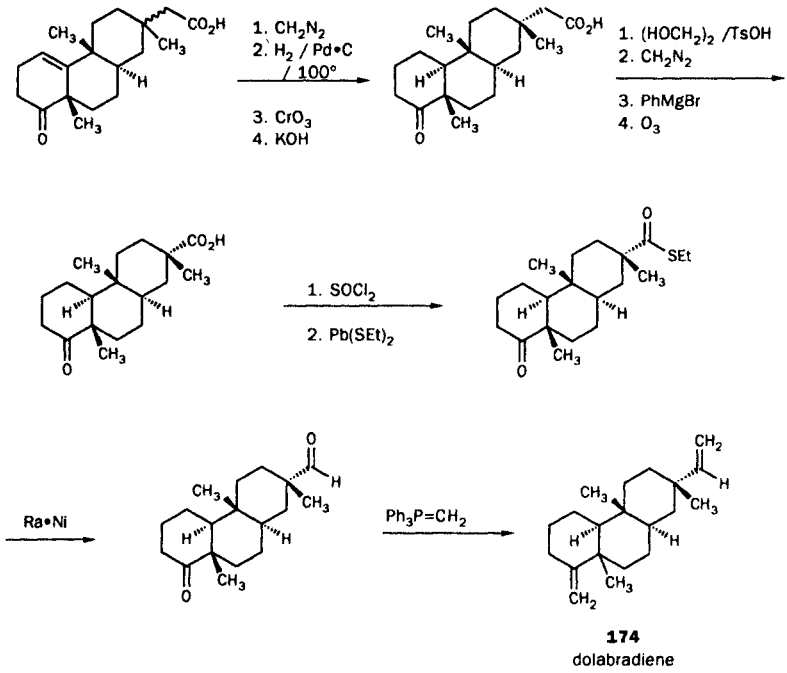
(4) Dolabradiene

Taking the backbone rearrangement of pimaradienes one step further than rimuene the structure of dolabradiene, **174** (Scheme 29), displays inverted stereochemistry at all of the ring-junction positions, and bears methyl groups at C-5 and C-9 rather than at C-4 and C-10. Thus, 1,2-shifts in the biosynthesis of this diene have resulted in the migration of every ring-junction group and in a structure analogous to the clerodanes of the bicyclic diterpene class.

The synthesis of dolabradiene **174** by Kitahara and co-workers[64] from Tohoku University is characterized by a reasonably efficient synthesis of a tricyclic intermediate **175** (Scheme 29). The starting material is **176**, the C-4 methyl equivalent of the Wieland–Mischer ketone. Direct Robinson annelation of **176** fails to occur in adequate yield and an alternative method for the addition of the third ring of dolabradiene is used. The sequence that is followed is adapted from the Woodward steroid synthesis.[65] First, the saturated ketone function of **176** is protected as a ketal, **177**. Next, to ensure that alkylation of the enone occurs only at the unsaturated α carbon the saturated α' position is protected as an enamide, **178**. "Cyanoethylation" from the less-hindered α face and hydrolysis then affords the β,γ-unsaturated ketonitrile **179**. The last stage of constructing the C-ring involves



SCHEME 29. Synthesis of dolabradiene by Kitahara.



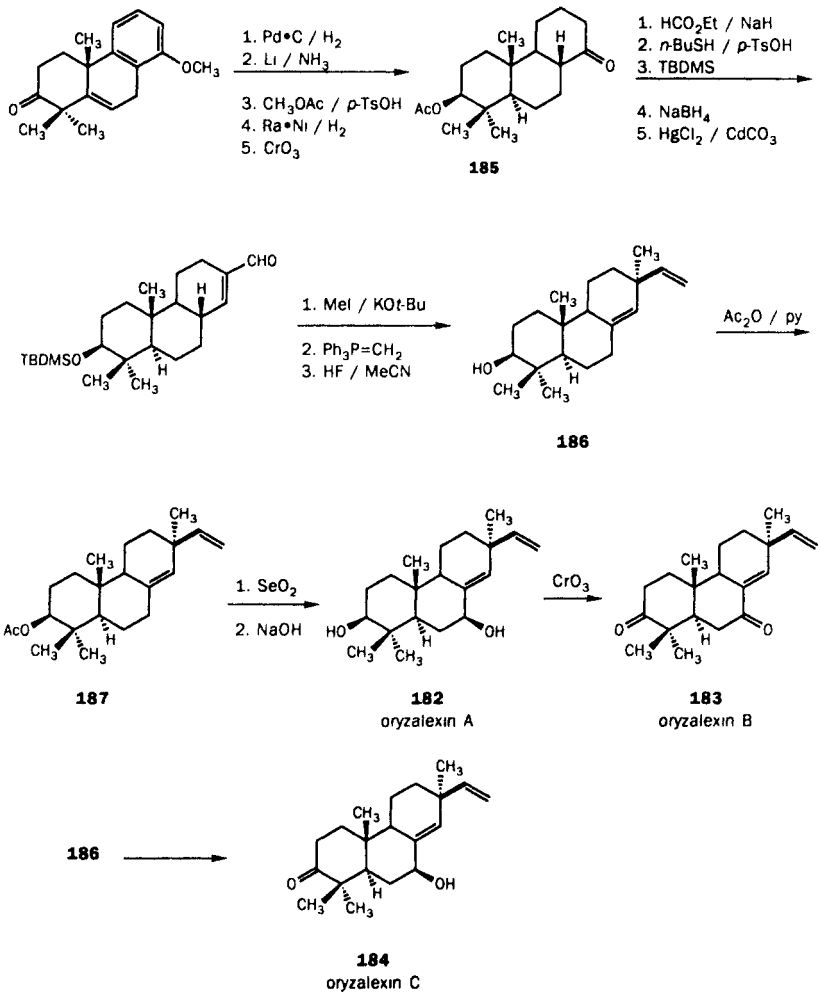
174
dolabradiene

SCHEME 29. Synthesis of dolabradiene by Kitahara (*continued*).

methyl–lithium addition to the ketone carbonyl and subsequent aldol closure. The product of this step, **180**, is reduced under dissolving metal conditions to provide **175**. The remainder of the synthesis involves a very lengthy sequence for the generation of the ring-C substituents and lacks stereoselectivity, the addition of methyl magnesium bromide to **181** producing both possible isomers at C-13.

(5) Oryzalexin A, B, and C

Three oryzalexins, A, **182**, B, **183**, and C, **184**, oxidized pimaradienes, (Scheme 30), were synthesized by Mori and Waku[66] from the University of Tokyo. The route is an adaptation of the synthetic approaches of Ireland and Turner to the tri- and tetracyclic diterpenes. Thus tricyclic ketone **185** is converted by a multistep sequence to alcohol **186** and acetate **187**. Selenium-dioxide and chromic-acid oxidations are used to prepare samples of the natural products.

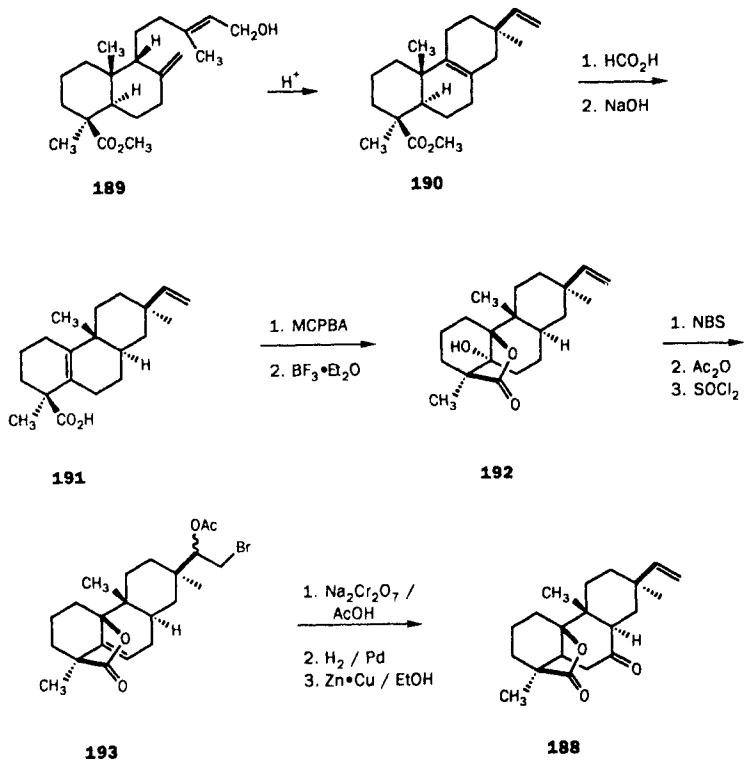


SCHEME 30. Mori's synthesis of the oryzalexins.

(6) Rosenonolactone

The carbon skeleton of rosenonolactone, **188**, is related to rimune. The configuration at C-13, however, is inverted in the roseane series. A partial synthesis of rosenonlactone designed along biogenetic lines was carried out by McCreadie, Overton, and Allison[67] at Glasgow.

The starting material for the synthesis, methyl isocuppressate, **189**, is cyclized to yield diene **190** and its C-13 epimer, as shown in Scheme 31. The

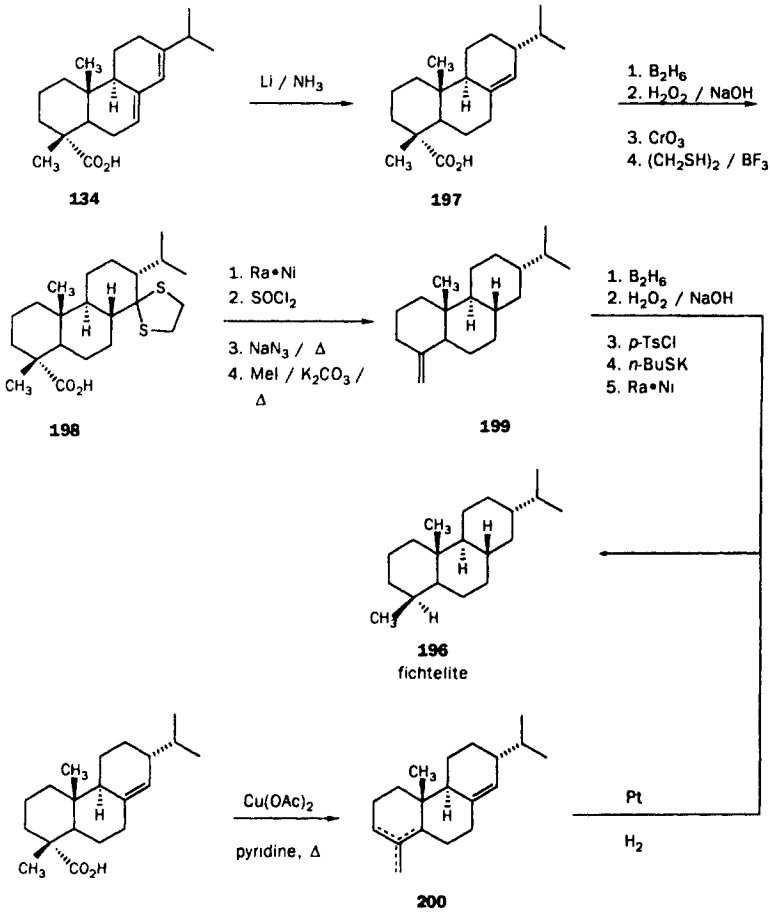


SCHEME 31. Overton's synthesis of rosenonolactone.

mixture is subjected to acid-catalyzed rearrangement to yield a rosadienoic acid **191** after separation of the material with the natural configuration and followed by hydrolysis. A relay compound is then used to complete the synthesis. Epoxidation and rearrangement affords lactone **192**. Following protection of the C-ring double bond, a dehydration is carried out to produce **193**. Allylic oxidation at C-7, reduction of the B-ring double bond, and reductive restoration of the exocyclic olefinic bond affords rosenonolactone, **188**.

(7) Fichtelite

Fichtelite, **196** (Scheme 32), is a naturally occurring C-20-*nor* decomposition product of abietic and related acids. Partial syntheses of the compound were carried out by Burgstahler and Marx[68] at Kansas and by Johnson and Jensen[69] at Stanford University. Both routes follow the same general route

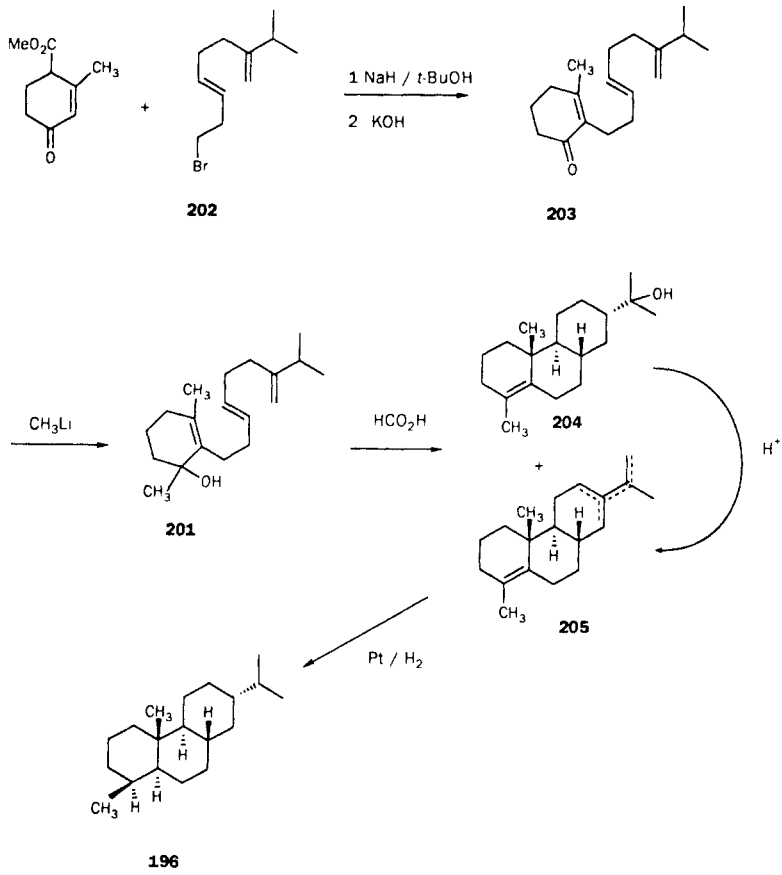


SCHEME 32. Syntheses of fichtelite by Burgstahler and Johnson.

with abietic acid, **134**, as the starting material. Birch reduction yields unsaturated acid **197**. In the Burgstahler work a lengthy sequence for the ultimate reduction of the C-ring double bond is carried out. Hydroboration of **197** from the β face is followed by oxidation and thioketal formation to provide **198**. Raney nickel reduction of **198** removes the thioketal unit and a Curtius degradation sequence is applied to the carboxyl group for the introduction of an exocyclic double bond in ring-A. The reduction of the double bond of **199** is then carried out in a lengthy but stereocontrolled fashion. Hydroboration occurs from the α face at C-4 and the resulting β-hydroxymethyl group is then carried through a reduction sequence to

afford fichtelite, **96**. In later work Johnson carries out an oxidative decarboxylation on abietic acid to yield a mixture of dienes, **200**. These are reduced directly to yield fichtelite as 50% of the product. Hydrogenation occurs from the β face at C-8 but from the α side at C-4.

A total synthesis of fichtelite using a biomimetic polyene cyclization approach to synthesis of the compound was also carried out by the Johnson group[70, 71] and is illustrated in Scheme 33. A triene, **201**, carrying a potential cationic center is constructed by first alkylating Hagemann's ester with bromodiene **202**. Following hydrolysis to **203** methyl lithium is added to the enone carbonyl to produce allylic alcohol **201**. Treatment of the alcohol with formic acid yields a mixture of a tertiary alcohol, **204**, and four olefins, **205**. The alcohol is convertible on treatment with acid to the mixture of alkenes.



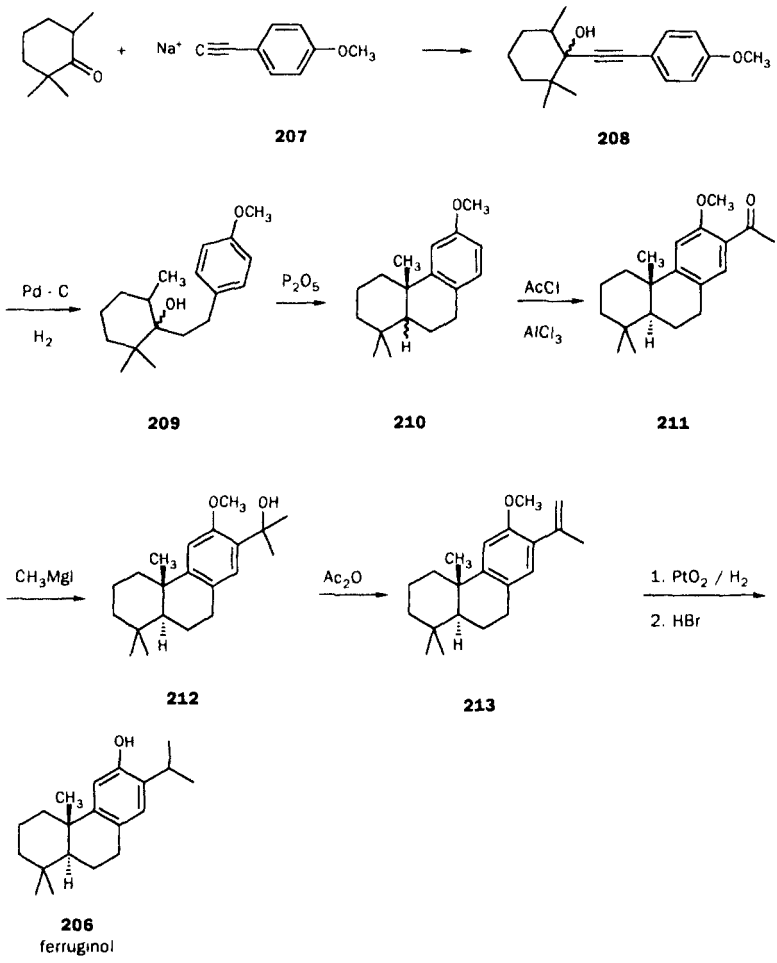
SCHEME 33. Johnson's biomimetic synthesis of fichtelite.

For the preparation of fichtelite, **196**, the alkene mixture is hydrogenated to yield the natural material.

(8) Phenols, Quinones, and Epoxides

Ferruginol, Sugiol, Xanthopterol, Hinokione, and Sempervirol

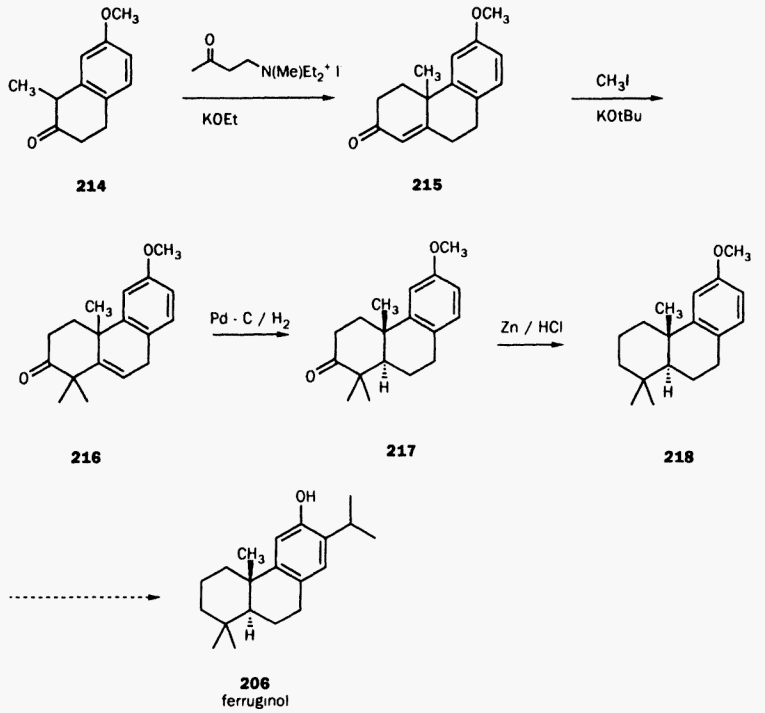
One of the first total syntheses of a tricyclic diterpene is that of ferruginol **206** (Scheme 34) by King, King, and Topliss.[72] The synthesis follows the same



SCHEME 34. King's synthesis of ferruginol.

general Bogert–Cook route for the construction of an octahydrophenanthrene system employed by Barltrop and Rogers for totarol. Thus, the addition of sodium acetylide **207** to 2,2,6-trimethylcyclohexanone affords acetylenic alcohol **208**. Reduction of the triple bond leads to **209** and this tertiary alcohol is caused to cyclize in the presence of phosphorous pentoxide to yield a mixture of the *cis* and *trans* isomers of **210**. In contrast to the *m*-methoxy systems used in this type of ring construction, the cyclization of **209** shows little selectivity. The mixture of aryl ether isomers is acylated in high yield and *trans*-isomer **211** is isolated after extensive purification. Reaction of **211** with methyl magnesium bromide affords **212**, which is in turn dehydrated to form the isopropenyl compound **213**. Saturation of the olefinic double bond and cleavage of the methyl ether group produces racemic ferruginol, **206**.

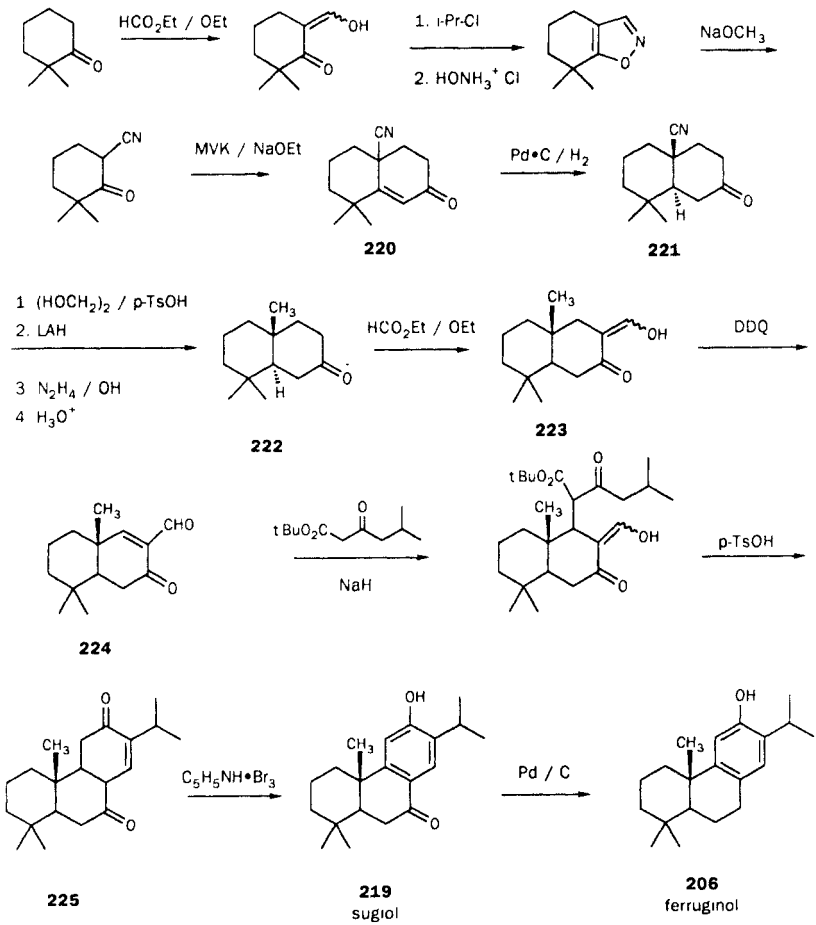
A stereoselective formal synthesis of ferruginol was carried out by Rao and Raman[73] (Scheme 35) using a Robinson annelation approach. Tetralone **214** is reacted with the Mannich base methiodide of methyl vinyl ketone to yield



SCHEME 35. Rao's synthesis of ferruginol.

the bicyclic enone **215**. On methylation, the latter affords the β,γ-unsaturated ketone **216**. Catalytic reduction leads to the *trans*-fused saturated ketone **217** as the sole product in close to quantitative yield. After removal of the keto group by Clemmensen reduction to give **218**, ferruginol is prepared following the route described by King.

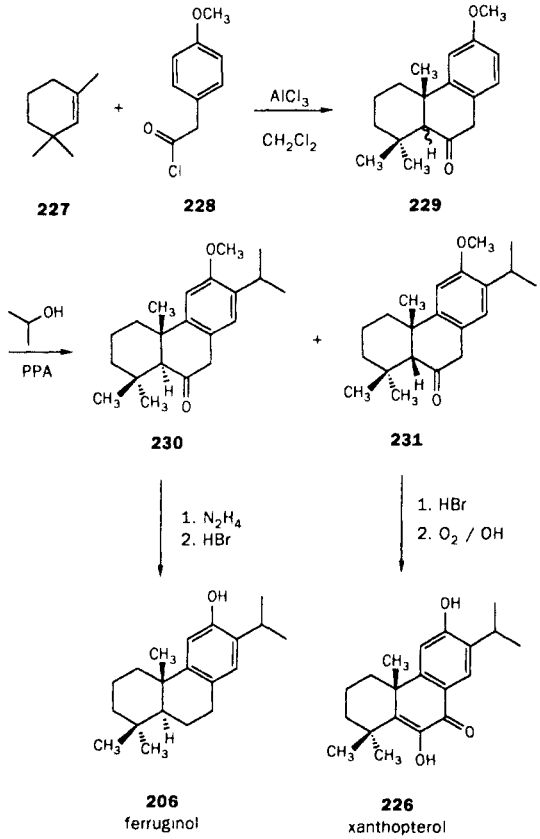
As noted for podocarpic acid, the approach of the Meyer group[74, 75] to the synthesis of tricyclic aromatic-C-ring diterpenes is based an A → AB → ABC construction of the ring system. For ferruginol, **206**, and the related ketone sugiol, **219**, the A-ring synthon is 2,2-dimethylcyclohexanone and angularly functionalized octalone **220** is constructed by a sequence involving Robinson



SCHEME 36. Meyer's synthesis of sugiol and ferruginol.

annelation (Scheme 36). Reduction of the enone double bond of **220** affords *trans*-fused **221**. The cyano group of this compound serves as the source of several other functionalities in the general Meyer approach and for sugiol and ferruginol it is converted by a reduction sequence to the methyl group of ketone **222**. Hydroxymethylation of **222** yields **223** which upon dehydrogenation with DDQ affords an unsaturated keto aldehyde **224**. Incorporation of the aromatic C-ring is then accomplished by Michael addition of a β-ketoester unit to **224** and subsequent acid-catalyzed aldol cyclization to give enedione **225**. Aromatization affords sugiol, **219**, and reductive deoxygenation of sugiol produces ferruginol, **206**.

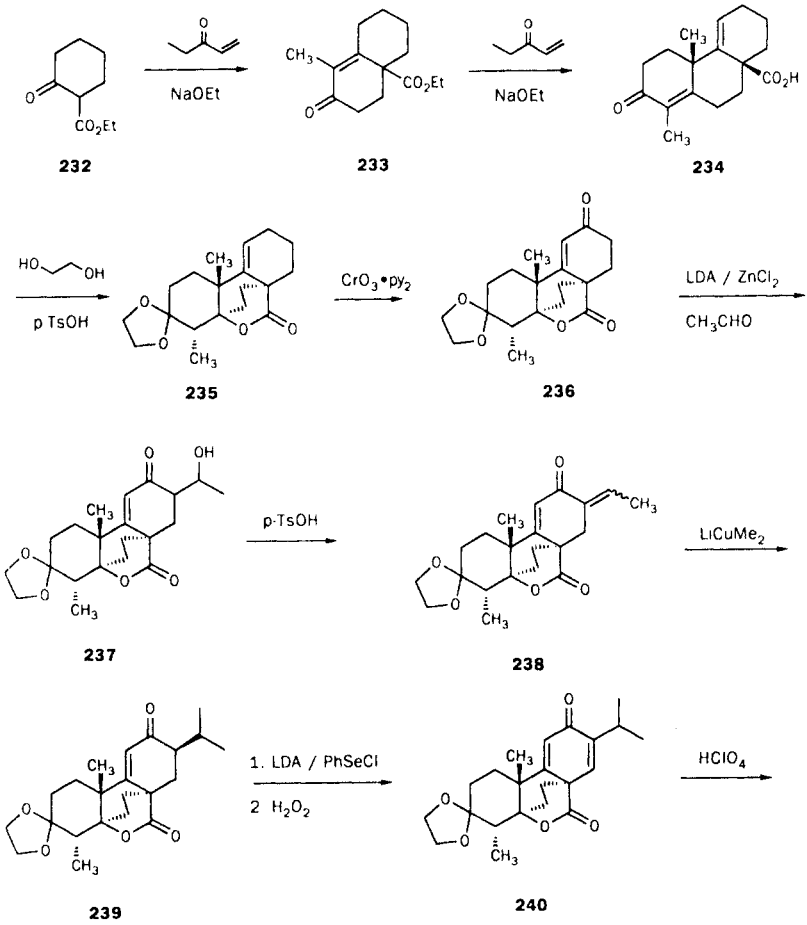
A simple and brief synthesis (Scheme 37) of ferruginol **206** and the related α-diketone xanthopterol, **226**, has been described by Wolinsky and associates[76] at Purdue University. The tricyclic system is assembled in one step by



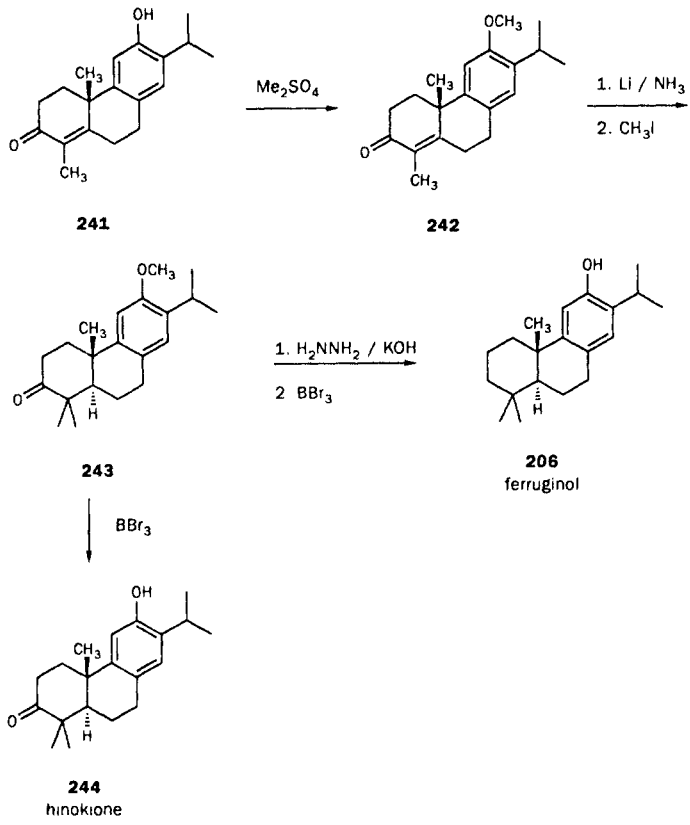
SCHEME 37. Wolinsky's synthesis of ferruginol and xanthopterol.

Friedel–Crafts cycloaddition of trimethylcyclohexene **227** and acid chloride **228**. The resulting product **229** is alkylated with isopropyl alcohol to yield a mixture of two ketones in the ratio of 2:3, *trans* to *cis*. The *trans* ketone **230** is converted to ferruginol, **206**, by demethylation and Wolff–Kishner reduction. For xanthopterol, **226**, the *cis* ketone **231** is also demethylated and then oxidized in the presence of base to yield the natural product.

In their synthesis of ferruginol (Scheme 38), Watt, Himmelsbach, and Snitman[77] from the University of Colorado build the tricyclic ring system by successive Michael additions employing ethyl vinyl ketone and cyclohexanone carboxylic ester **232**, first to give enone **233**, thence to **234**. The *syn*



SCHEME 38. Watt's synthesis of ferruginol and hinokione.



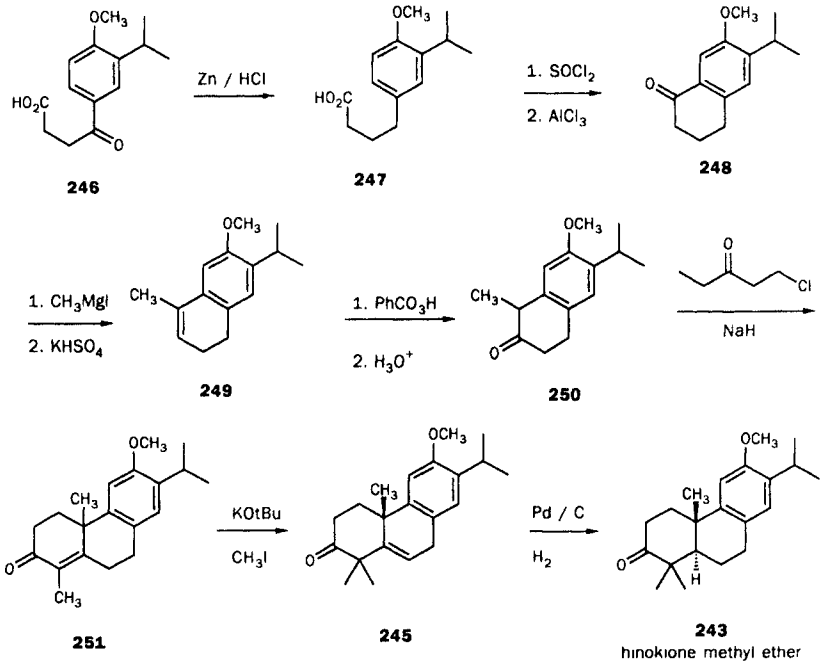
SCHEME 38. Watt's synthesis of ferruginol and hinokione (*continued*).

stereochemistry of the ring junction substituents of **234** results from Michael addition occurring *anti* to the carboethoxy group of **233**. Treatment of **234** with ethylene glycol and acid causes both ketalization and lactonization with the production of **235**. Both the ring-A carbonyl and the olefinic groups are thus protected. A second enone system is then introduced through allylic oxidation to yield **236** and chelation-controlled aldol condensation of **236** produces ketol **237**.

The Watt synthesis utilizes a novel aromatization reaction which is employed following addition of the C-ring substituent. To this end dehydration of **237** to **238** is followed by cuprate addition to yield the isopropyl-substituted enone **239**. This substance is further oxidized by means of a phenylselenenylation–deselelenylation sequence to form dienone **240**. The ring-A enone system is now unmasked with concomitant decarboxylative

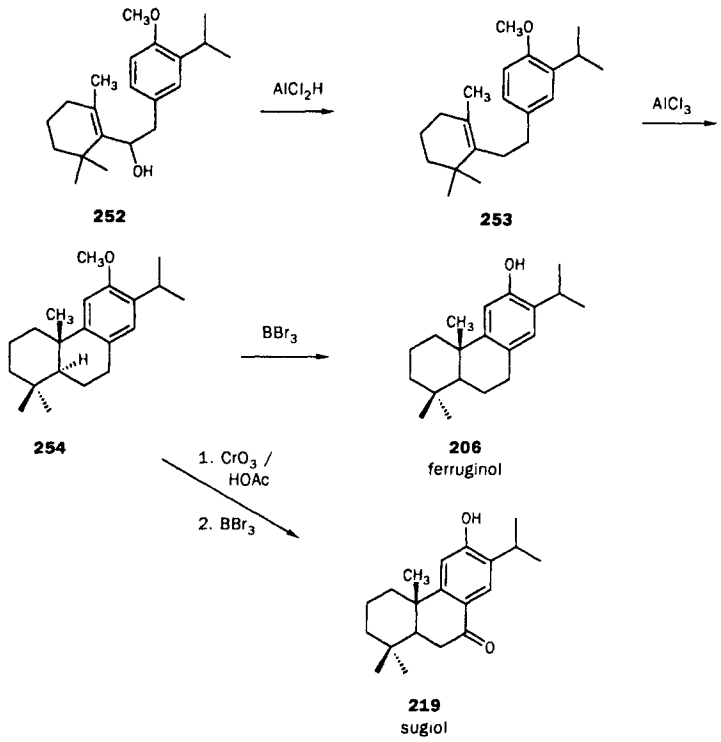
aromatization of ring-C, **240** to **241**. When **242**, the derived methyl ether, is subjected to the conditions of reductive methylation **243**, hinokione methyl ether, is formed. This compound is converted into ferruginol, **206** by Wolff–Kishner reduction and demethylation. Demethylation of **243** produces hinokione, **244**.

The first synthesis of hinokione methyl ether **243**, and by extension hinokione **244** as well was carried out by Chow.[78] His approach (Scheme 39) is based, as in many other dehydroabietane syntheses, on the establishment of the A/B-ring fusion stereochemistry by catalytic reduction of a ring-B olefin, **245**. To achieve this the reaction product, **246**, of succinic anhydride and *o*-methoxyisopropylbenzene is subjected to Clemmensen reduction to afford acid **247**, which in turn is subjected to Friedel–Crafts cyclization to produce **248**. Grignard addition and dehydration gives olefin **249**, which is then converted through the corresponding epoxide to ketone **250**. Robinson annelation, in this case effected with a β-chloroketone, affords the tricyclic enone **251** and base-mediated methylation leads to the key intermediate **245**. Typically, catalytic hydrogenation occurs from the α face of the double bond in such compounds to yield hinokione methyl ether, **243**.



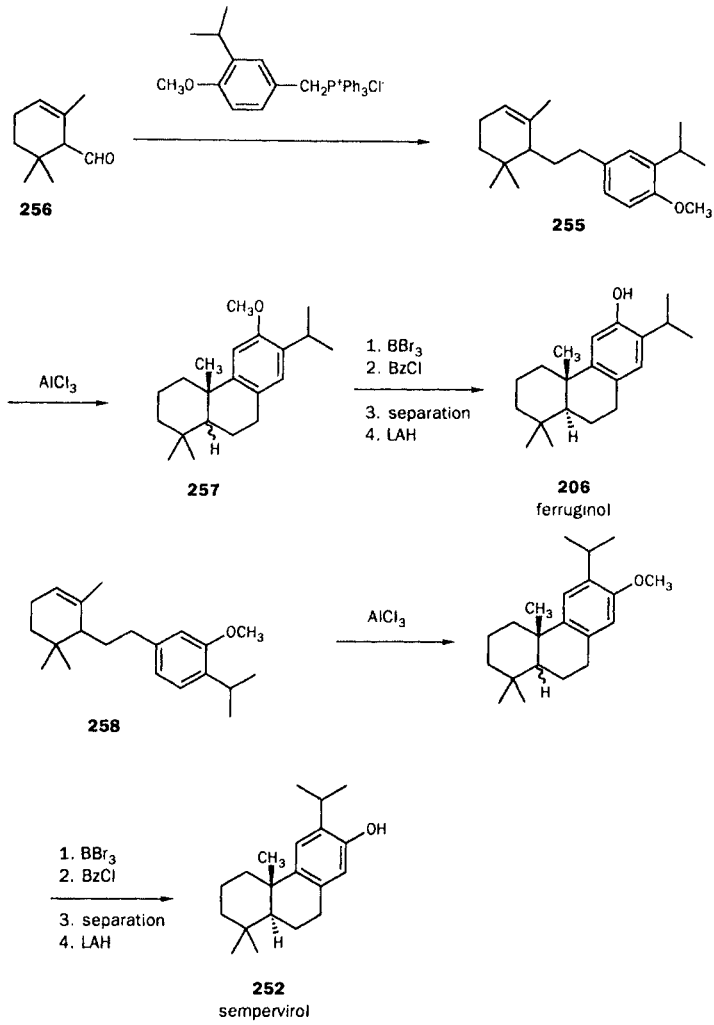
SCHEME 39. Chow's synthesis of hinokinone.

As part of a program in the synthesis of highly oxygenated tricyclic diterpenes Matsumoto and colleagues[79, 80] at Hiroshima prepared ferruginol, **206**, sugiol, **219**, and sempervirol, **252**. The route to ferruginol was carried out twice with minor variations in the nature of the precursor to the tricyclic system. In one synthesis (Scheme 40), alcohol **252** prepared from β-cyclocitral is reduced to alkene **253** and cyclization is effected to yield **254** after separation from its C-5 epimer. Cleavage of the methyl ether of **254** affords ferruginol, **206**, and oxidation followed by ether cleavage gives sugiol, **219**.



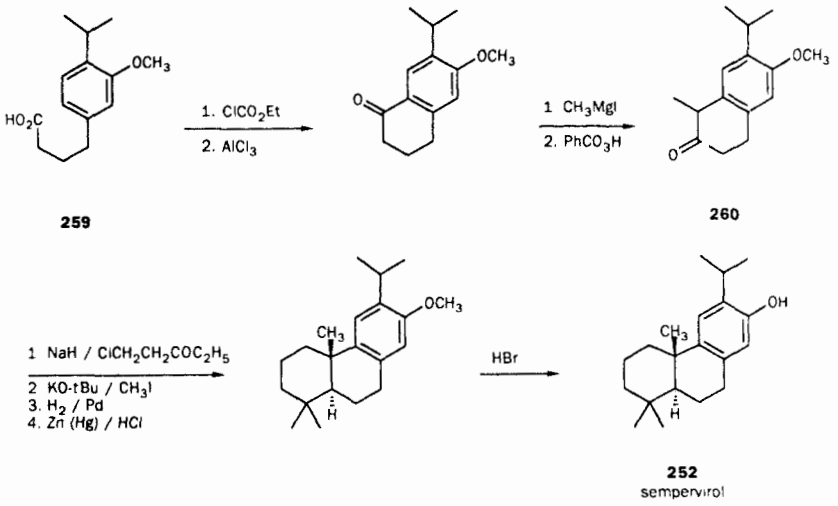
SCHEME 40. Synthesis of ferruginol and sugiol by Matsumoto.

In the second synthesis[80] (Scheme 41), Matsumoto and Usui prepared the cyclization substrate **255** by a Wittig sequence starting from α-cyclocitral, **256**. Treatment of **255** with aluminum chloride affords a 1:1 mixture of tricyclic products, **257**, from one of which ferruginol, **206**, may be prepared. In similar fashion substrate **258** is prepared and converted into sempervirol, **252**, a positional isomer of ferruginol.



SCHEME 41. Synthesis of ferruginol and sempervirol by Matsumoto.

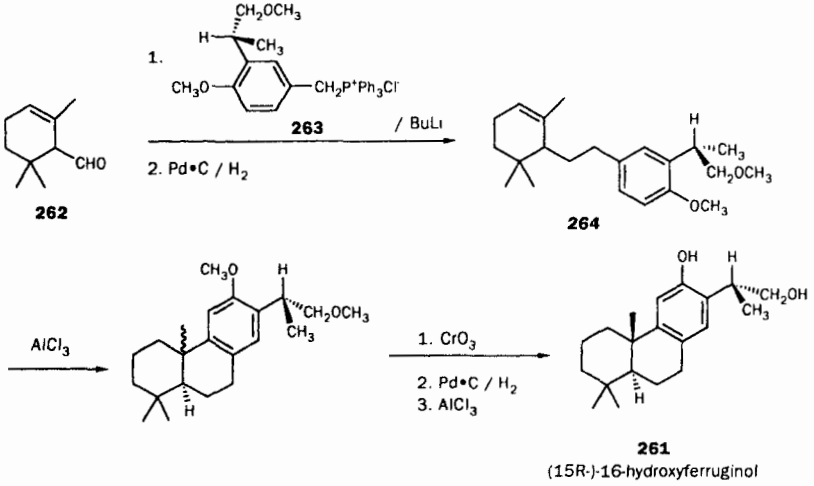
Sempervirol was prepared also (Scheme 42) by Caputo and Mangoni[81] from arylbutanoic acid **259** by standard annelation methods for the generation of an A/B-*trans*-fused abietane derivative. Cyclization of **259** followed by methylation and ketone transposition yields **260**. A sequence of Robinson annelation, methylation, reduction, and ether cleavage yields sempervirol, **252**.



SCHEME 42. Synthesis of sempervirol by Caputo.

16-Hydroxyferruginol

Following the same general route used for ferruginol, Matsumoto and coworkers[82] prepare 16-hydroxyferruginol **261** (Scheme 43) starting with the Wittig condensation of (R)-(−)-α-cyclocitral, **262**, and the "15-R" phosphonium salt **263**. The cyclization reaction of **264** provides both A/B-*trans* and

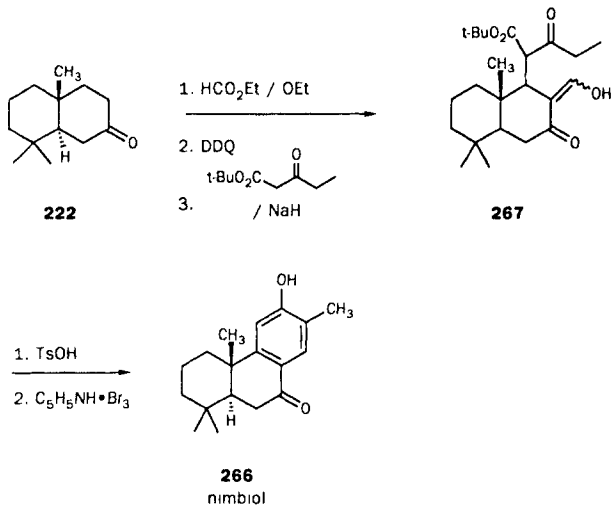


SCHEME 43. Synthesis of 16-hydroxyferruginol by Matsumoto.

A/B-*cis* isomers **265** in close to 1 : 1 proportions. To separate these, oxidation to the corresponding 9-keto compounds is necessary. Subsequent reduction and ether cleavage affords 16-hydroxyferruginol, **261**. The enantiomer of **261** was also carried through the synthetic scheme since the configuration of the natural product at C-15 was unknown until these syntheses were completed.

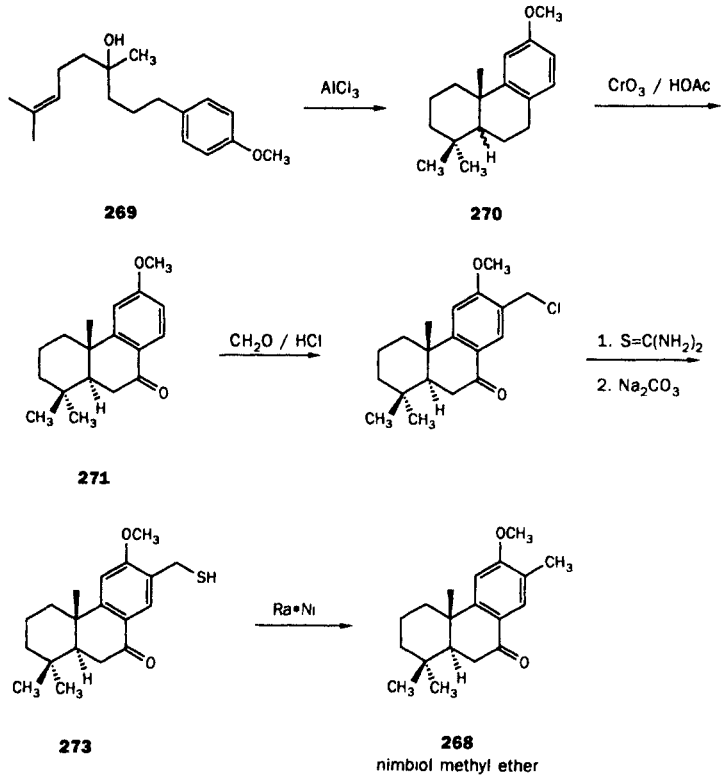
Nimbiol

For the synthesis of nimbiol **266** (Scheme 44), the Meyer group[75] again employed bicyclic intermediate **222**, used previously in the synthesis of sugiol and ferruginol. The *β*-ketoester component in the ring-C annelation sequence, however, carries only a methyl substituent here rather than the isopropyl group of the other two natural products. Following the Michael addition step yielding **267**, aldol cyclization and aromatization yields nimbiol, **266**, directly.



SCHEME 44. Meyer's synthesis of nimbiol.

A synthesis of nimbiol, as its methyl ether **268**, was carried out by Fétizon and Delobelle[83, 84] at the Ecole Polytechnique from olefinic alcohol **269** (Scheme 45). Cyclization affords a mixture of tricyclic ethers **270** which, after oxidation to the corresponding ketones, yield **271** on chromatographic separation. Attachment of the aryl methyl group is achieved by a sequence of chloromethylation to yield **272**, displacement of the benzyl halide by thiourea, and Raney nickel reduction of the thiol, **273**, obtained by hydrolysis of the thiourea product, to afford nimbiol methyl ether, **268**.

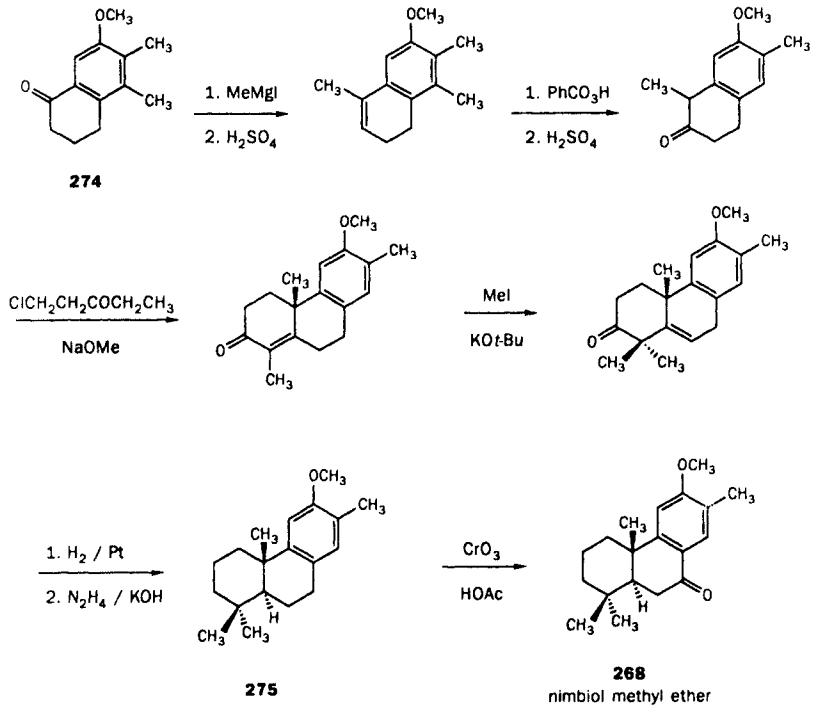


SCHEME 45. Fétizon's synthesis of nimbiol methyl ether.

The second of the original syntheses of nimbiol (Scheme 46) was accomplished by Dutta and Ramachandran.[85] Using Robinson annelation chemistry on β-tetralone **274** followed by the standard methylation–reduction sequences, they generate phenolic ether **275**. Oxidation of this material affords nimbiol methyl ether **268**.

Coleon U and V

The highly oxygenated diterpenes coleon-U, **276**, and coleon-V, **277**, were prepared from ferruginol, **206**, by Matsumoto.[86, 87] The synthesis (Scheme 47) is characterized by the variety of oxidation steps required for the introduction of an additional four oxygen functions.

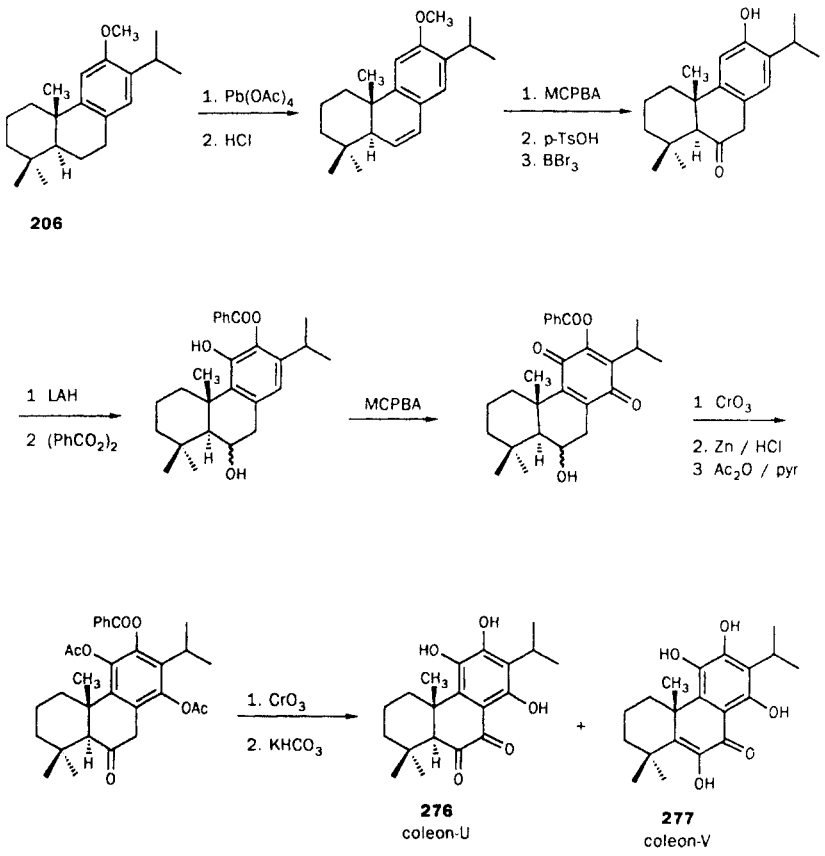


SCHEME 46. Dutta's synthesis of nimbiol methyl ether.

Carnosic Acid and Carnosol

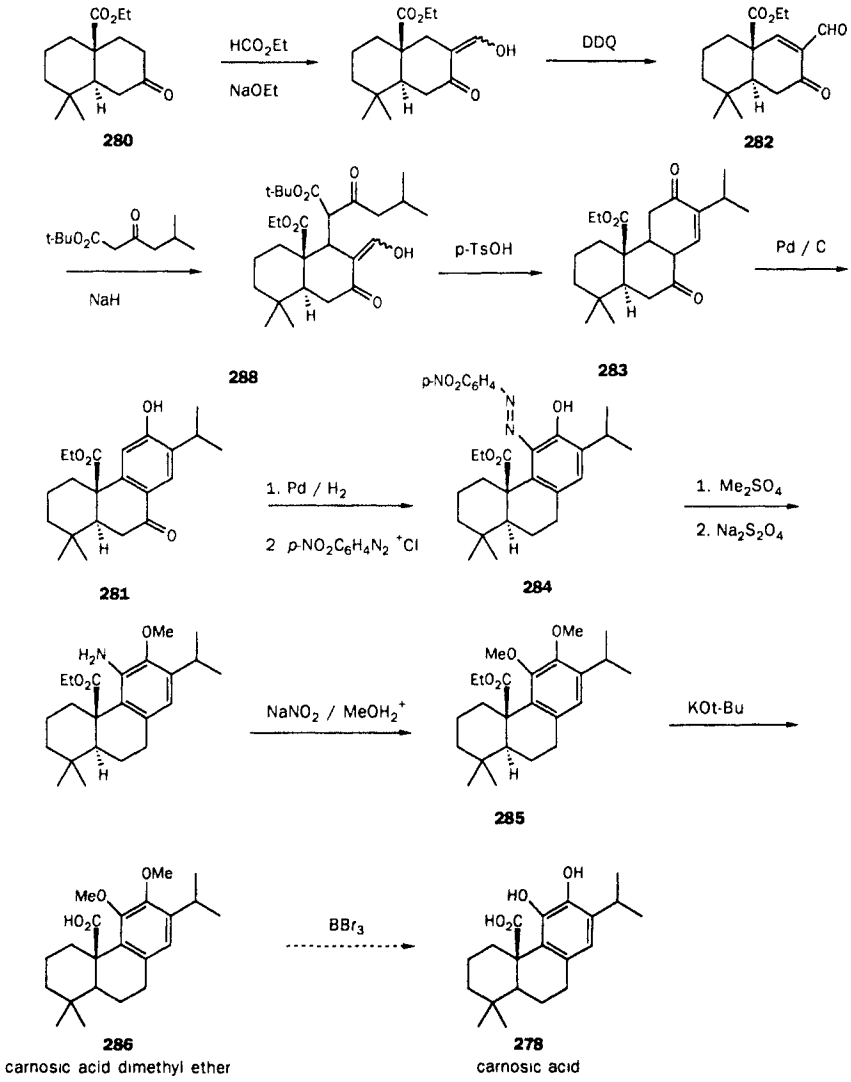
Two routes for the synthesis of carnosic acid **278** and carnosol **279** (as their methyl ethers) were employed by the Meyer group.[88–90] In the first synthesis (Scheme 48) of carnosic acid Meyer and Schindler[88] use the same approach employed for sugiol and ferruginol. Thus an A/B keto ester **280** is homologated to the tricyclic aromatic species **281** by conversion first into an unsaturated keto-aldehyde, **282**, followed by Robinson annelation to enedione **283**. This intermediate in turn is aromatized to **284** with palladium. To add the second phenolic hydroxyl of carnosic acid, the sodium salt of **281** is treated with a diazonium salt followed by cleavage of the diazo grouping of **284** and further diazotization of amine **285** to afford **286**. Finally, the angular ester group is hydrolyzed to yield a diether, **286**, previously transformed into the natural product.

For the second route to carnosic acid (Scheme 49) Meyer and coworkers[90] substitute β-keto sulfoxide **287** for the keto ester employed



SCHEME 47. Matsumoto's synthesis of coleon-U and coleon-V.

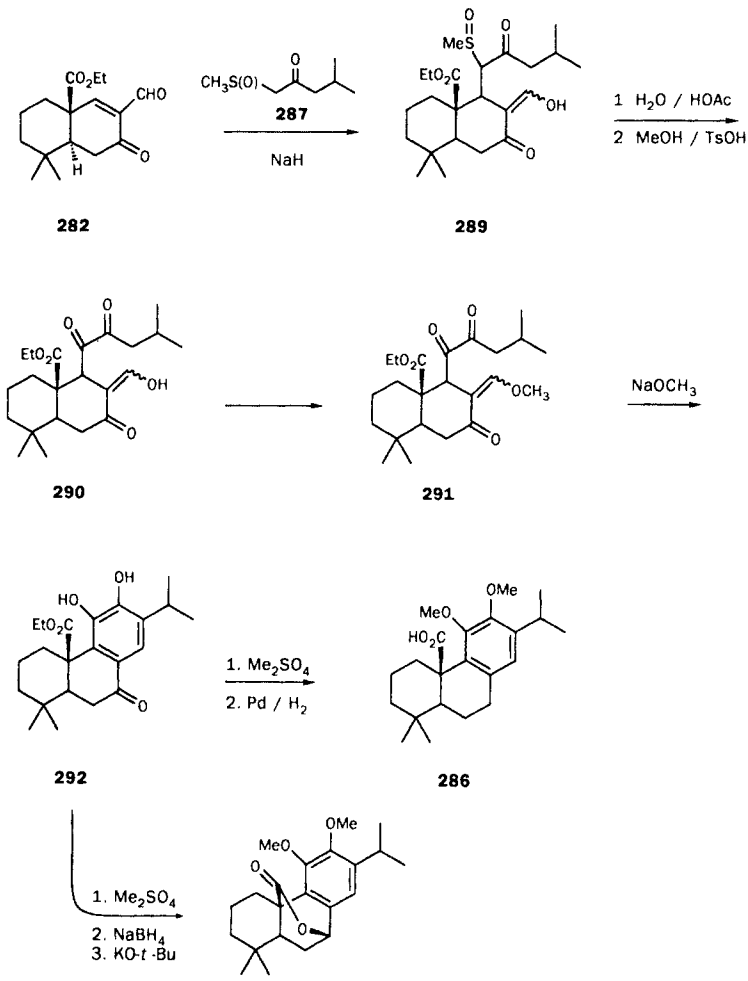
previously to add the elements of ring-C. The sulfoxide group in contrast to the ester function of **288** (Scheme 48) provides a ready source of the C-11 oxygen substituent of the target molecule. Thus Michael addition of **287** to enone **282** provides sulfoxide **289**. Pummerer rearrangement under mild acid conditions converts the sulfoxide group to a ketone function yielding a triketone **290**. Closure of the C-ring in this case is unsuccessful under acid conditions, but base-catalyzed cyclization to **291** occurs after the acidic proton of the hydroxymethylene group is replaced by conversion of **290** to enol ether **291**. Carnosic acid dimethyl ether **286** is formed from **292** by methylation and hydrogenolysis, and carnosol dimethyl ether **279** is prepared when catechol **292** is methylated, reduced to an alcohol with sodium borohydride, and then lactonized under basic conditions.



SCHEME 48. Meyer's synthesis of carnosic acid and carnosol dimethyl ethers.

Pisiferol, Pisiferal, and Pisiferin

Several members of the pisiferol family of diterpenes have been synthesized by Matsumoto and co-workers.[91–93] Pisiferol **293** itself has been prepared by two different routes. The first (Scheme 50)[91] is a route based on the

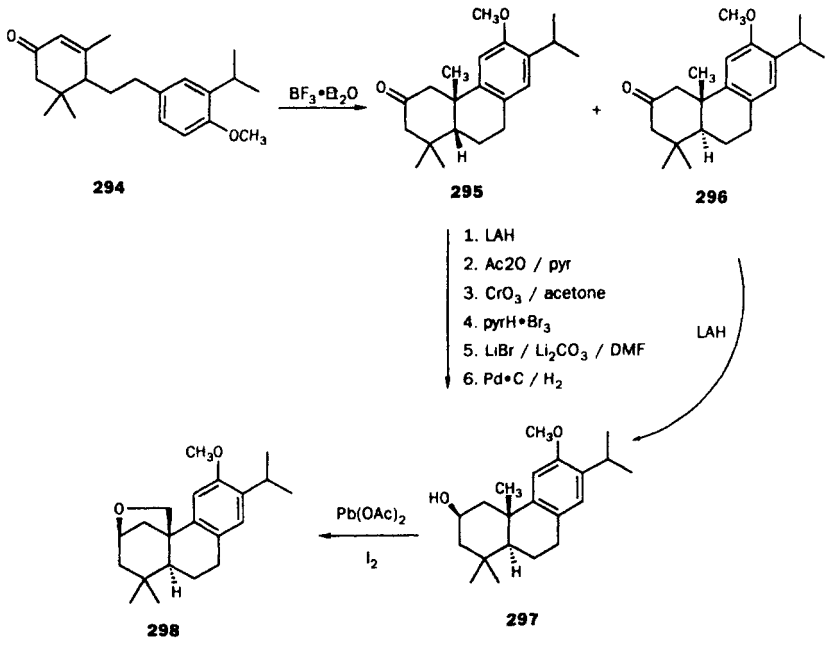


SCHEME 49. Meyer's second synthesis of carnosic acid and carnosol.

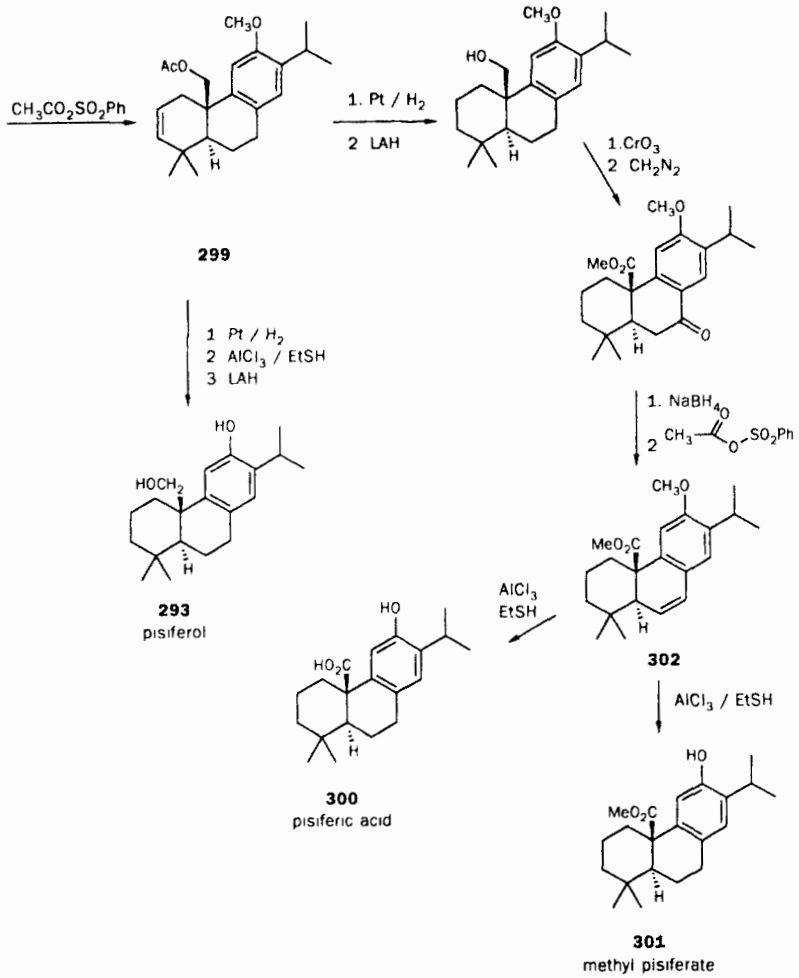
cyclization of enone **294** to yield the two tricyclic ketones **295** and **296** in a ratio of 1 to 1.75. As a consequence, a laborious sequence for isomerizing the ring junction of **295** is followed to produce axial alcohol **297**. The same alcohol is produced from **296** by hydride reduction, and in both cases the epimeric alcohol is also generated.

Introduction of the angular hydroxymethyl group of the target compound is achieved by a radical process to form **298** and the C-2 oxygen is removed by elimination to yield **299**. For pisiferol, **293**, the double bond of **299** is reduced, the aromatic ether is cleaved, and the acetate group is removed reductively. Acetate **299** is also converted to pisiferic acid, **300**, and methyl pisiferate, **301**, through a series of oxidations and reductions leading to **302**. Ether cleavage alone then yields the naturally occurring ester **301**, whereas cleavage of both alkyl-oxygen functions affords the acid **300**.

In the second Matsumoto synthesis[92] (Scheme 51) of pisiferol **293** a radical functionalization of the C-10 angular methyl group is used again. In this case however, the starting material **303** is converted by elimination to styrene **304**, followed by the introduction of a carbonyl at C-6. Reduction of the keto group of **305** yields the C-6 β-hydroxy compound **306** and this in turn is converted into tetrahydrofuran **307**. Elimination affords an olefin mixture, **308**, which upon catalytic reduction yields a mixture of *cis*- and *trans*-fused tricyclic products **309** and **310**. The *trans* isomer is subjected to Friedel–Crafts acetylation to give **311**, and Baeyer–Villiger oxidation followed by removal of the acetate function leads to pisiferol, **293**. Oxidation of pisiferol with Cr^{VI} leads to pisiferol, **312**.

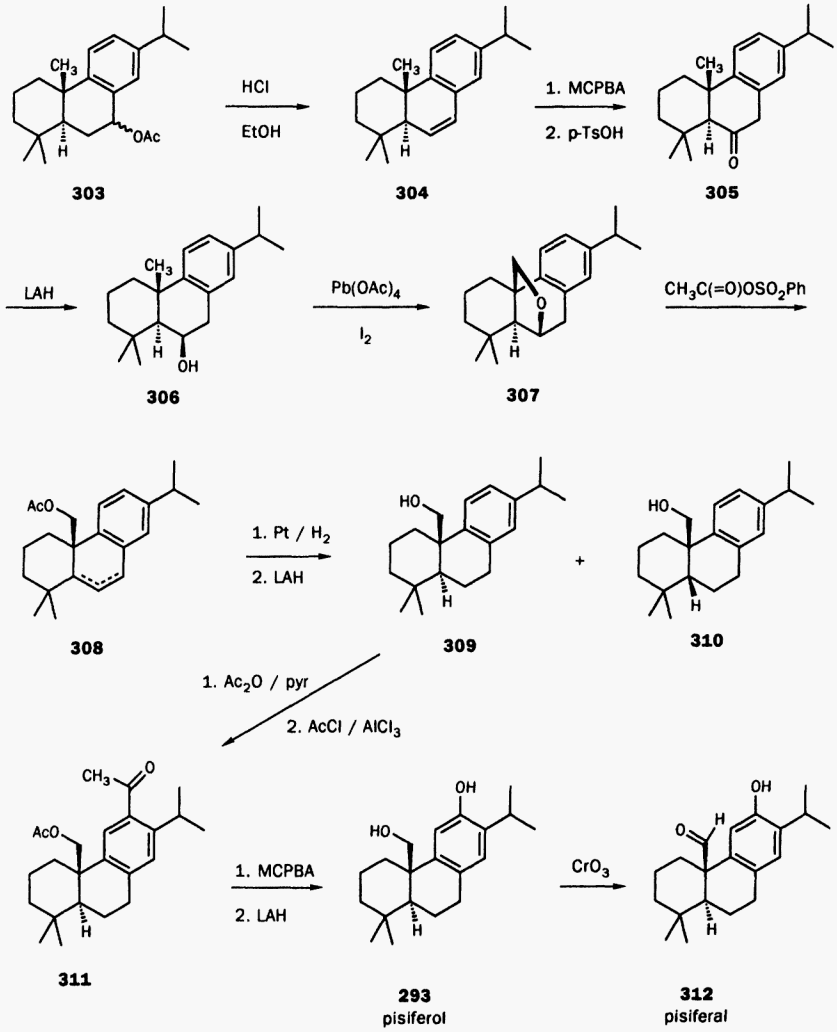


SCHEME 50. Matsumoto's synthesis of piseferol, pisiferic acid, and methyl pisiferate.



SCHEME 50. Matsumoto's synthesis of piseferol, pisiferic acid, and methyl pisiferate (*continued*).

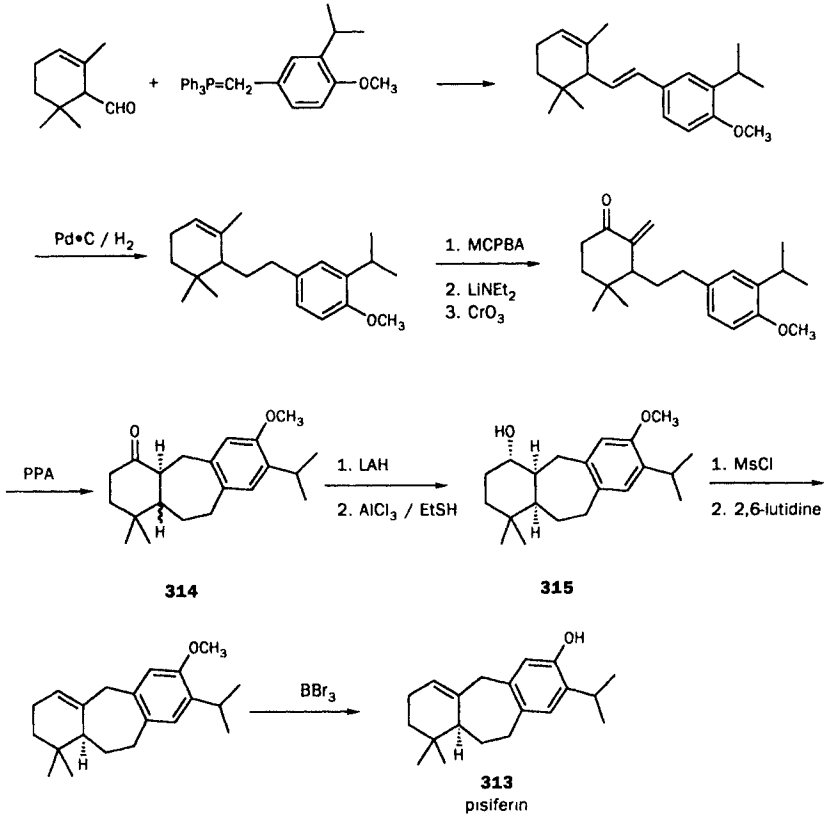
Accompanying the C-20 oxygenated compounds in *Chamaecyparis pisifera* is the rearranged diterpene hydrocarbon pisiferin, **313**. A synthesis of the substance has been carried out by the Matsumoto group,[93] as illustrated in Scheme 52. However, several of the steps lead to multiple products and the target molecule is only one of several possible outcomes of the synthetic plan. In the cyclization step for the formation of the 7-membered B-ring two isomers, **314**, are produced, of which only the *cis* isomer proves useful.



SCHEME 51. Matsumoto's synthesis of pisiferol and pisiferal.

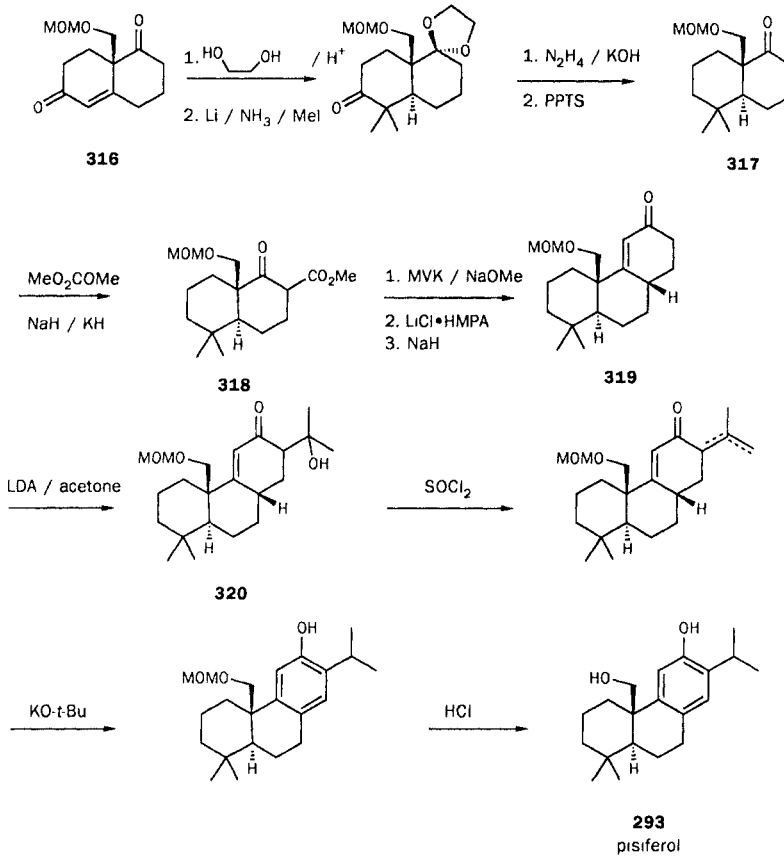
Reduction of this *cis* compound in turn yields two alcohols and again only one, **315**, leads onto the final product **313**. This is accomplished by treatment of **315** with mesyl chloride and lutidine, followed by reduction of the remaining aromatic mesylate group.

The synthesis of (+)-pisiferol by Uda, Tamai, and Hagiwara[94] at Tohoku University follows the route developed by Spencer[11, 95] for the diterpene



SCHEME 52. Matsumoto's synthesis of pisiferin.

resin acids. Starting from optically active Wieland–Mischer enedione analogue **316** (Scheme 53), the C-4 methyl groups are added and the C-3 carbonyl group removed in standard fashion to produce **317**. The acidity of the ring-B carbonyl group α position is enhanced by carbomethoxylation to give **318** and a subsequent Robinson annelation–decarbomethoxylation sequence affords tricyclic enone **319**. The isopropyl side chain is appended by aldol condensation of **319** with acetone affording **320**. Dehydration, and base-catalyzed aromatization then yields the methoxymethyl ether of pisiferol and the natural product **293** is achieved by hydrolysis. On a formal basis this synthesis also constitutes the preparation of other compounds of the series obtainable by simple redox transformations of pisiferol.

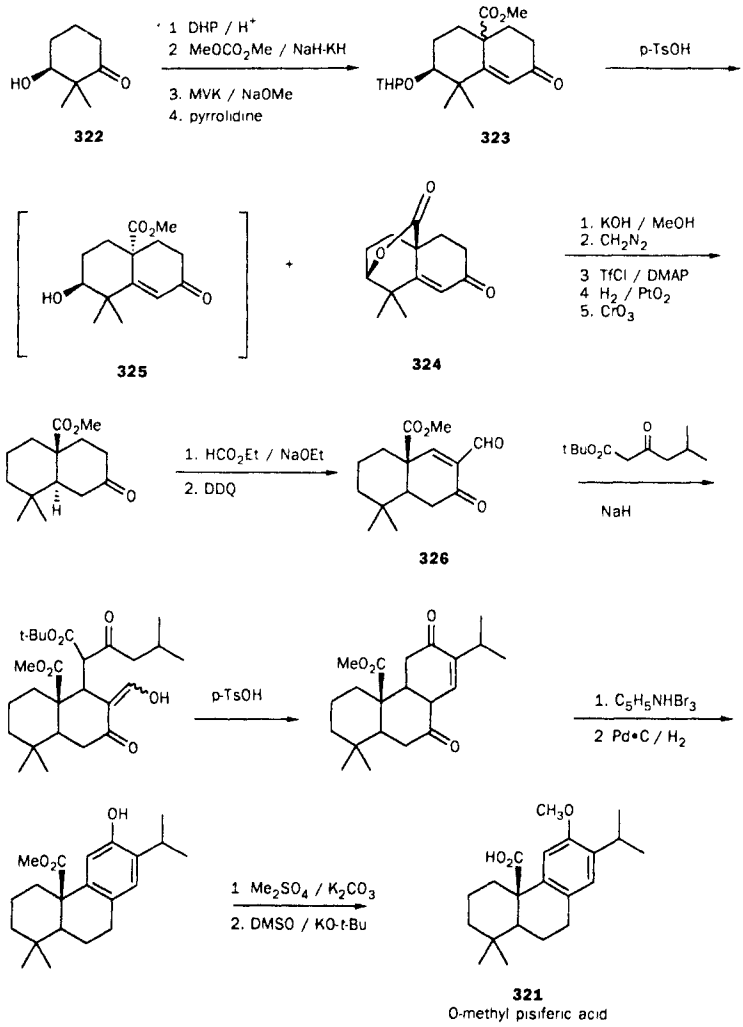


SCHEME 53. Uda's synthesis of pisiferol.

O-Methyl Pisiferic Acid

For the synthesis of *O*-methyl pisiferic acid **321** Mori and Mori[96] adopt the synthetic strategy developed by Meyer[97] for the construction of an A/B enone aldehyde system to which the C-ring is appended by Robinson annelation. The Mori synthesis (Scheme 54) is *enantiospecific*; that is, the starting material **322** is available in high optical purity and was carried through to both antipodes of the natural product.

To prepare the natural material, optically active **322** is obtained by enzymatic reduction of the corresponding diketone. Robinson annelation and hydrolysis of the THP ether group of **323** gives lactone **324** as the major



SCHEME 54. Synthesis of *O*-methylpisiferic acid by Mori.

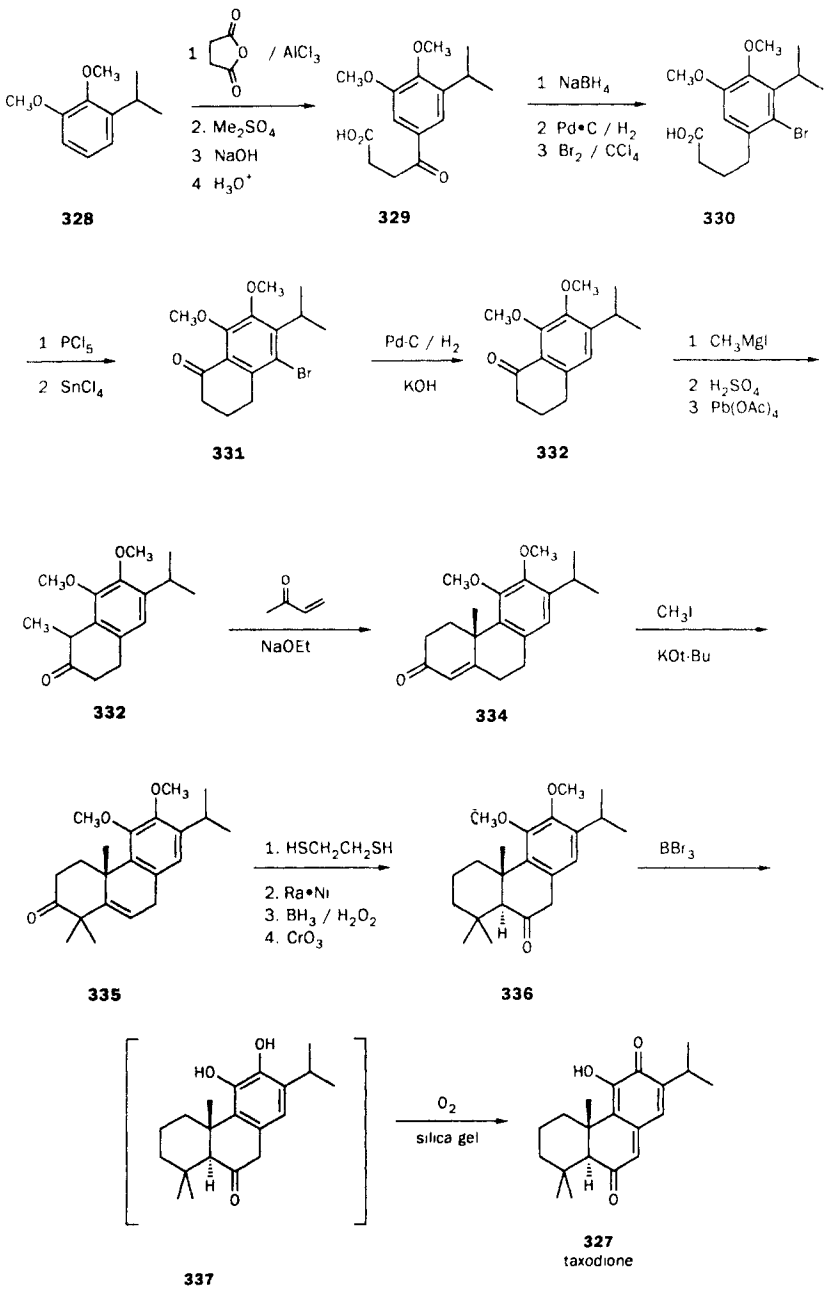
product. The lactone has the correct configuration at C-10 for pisiferic acid in contrast to the minor product, ester **325**. By a sequence involving removal of the C-3 hydroxy group and introduction of an enal system in ring-B by Meyer's methodology, lactone **324** is converted into **326**. Application of the Meyer protocol for construction of ring-C affords optically active *O*-methyl pisiferic acid, **321**.

Taxodione and Cryptojapanol

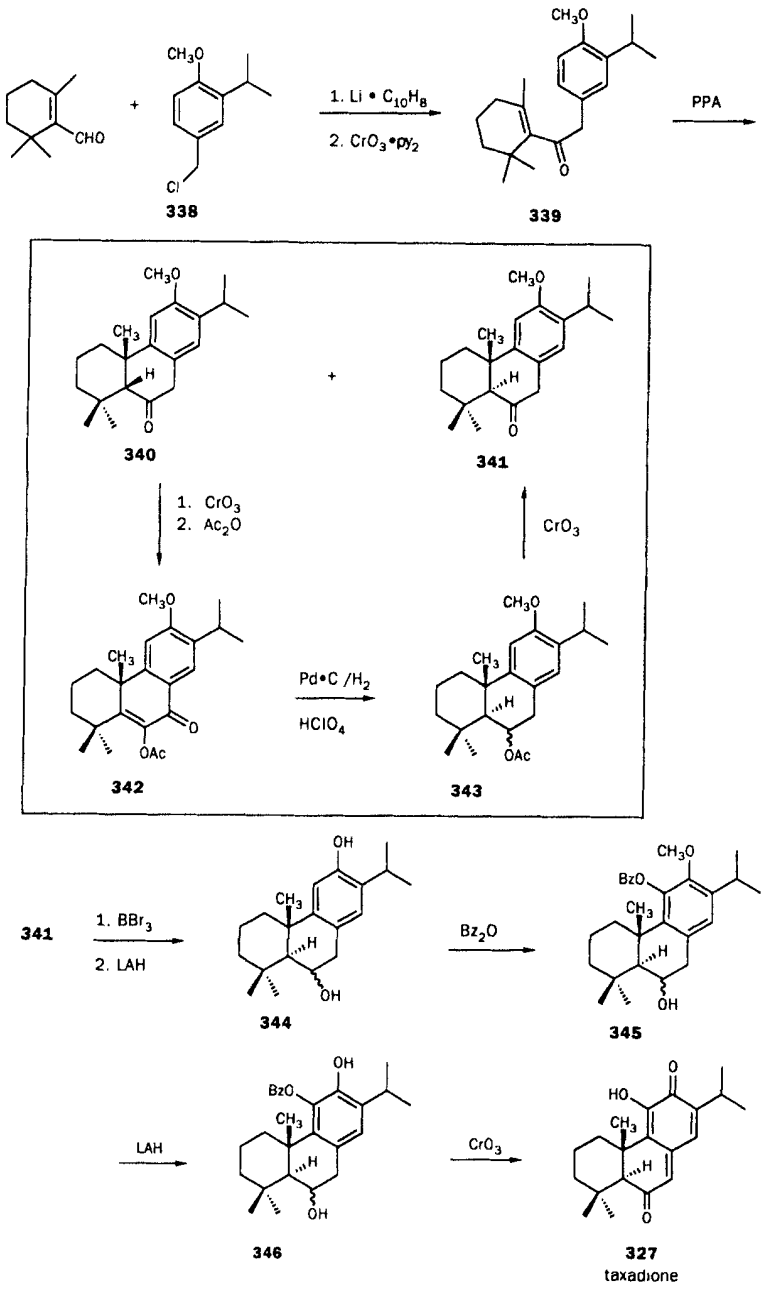
The first total synthesis (Scheme 55) of taxodione, **327**, by Matsumoto and co-workers[98] follows the same general pathway for the tricyclic system used by Chow in the synthesis of hinokione methyl ether. An aromatic ether, **328**, is reacted with succinic anhydride to form ketoacid **329**. The ketone carbonyl group is then removed by sequential reductions with borohydride and hydrogen and the position *ortho* to the isopropyl group is blocked with bromine producing carboxylic acid **330**. Without this last step subsequent cyclization gives the wrong tetralone isomer. With the bromine present, however, Friedel–Crafts cyclization of **330** affords bromoketone **331** and the bromine is then removed catalytically with the formation of **332**. Following Grignard addition of a methyl group to **332** the β-tetralone **333** is then formed by dehydration and oxidation. Standard Robinson annelation using methyl vinyl ketone gives tricycle **334** and methylation affords enone **335**. The C-3 keto group is removed and a new carbonyl group is introduced at C-6 by a hydroboration–oxidation sequence leading to **336**. The remaining steps are an application of the work of Kupchan[99] on the conversion of optically active **336** to taxodione. Thus, cleavage of the methyl ethers yields an unstable bisphenol, **337**, which on aerial oxidation in the presence of silica gel affords racemic taxodione, **327**.

A second synthesis (Scheme 56) of taxodione by Matsumoto and co-workers[100] features a simple and efficient construction of the tricyclic system based on the condensation of the lithiate of substituted benzyl chloride **338** with β-cyclocitral. The resulting alcohol is oxidized to ketone **339** and this in turn is subjected to acid-catalyzed cyclization. As is common for ring-C aromatic intermediates, however, the resulting product is largely the *cis*-fused tricyclic ketone **340** rather than the required *trans* compound **341**. As a consequence, a sequence for the interconversion of the two ketones is carried out. Ketone **340** is oxidized and acetylated to give enol acetate **342**. Reduction then affords the A/B *trans*-fused acetate **343** and hydrolysis and oxidation provides *trans* ketone **341**. For the conversion of **341** into taxodione the phenolic ether is cleaved and the keto group is reduced to produce **344**. Benzoyl peroxide oxidation introduces a C-11 benzoyloxy group and this product, **345**, is reduced to phenol **346**. Oxidation then yields taxodione **327**.

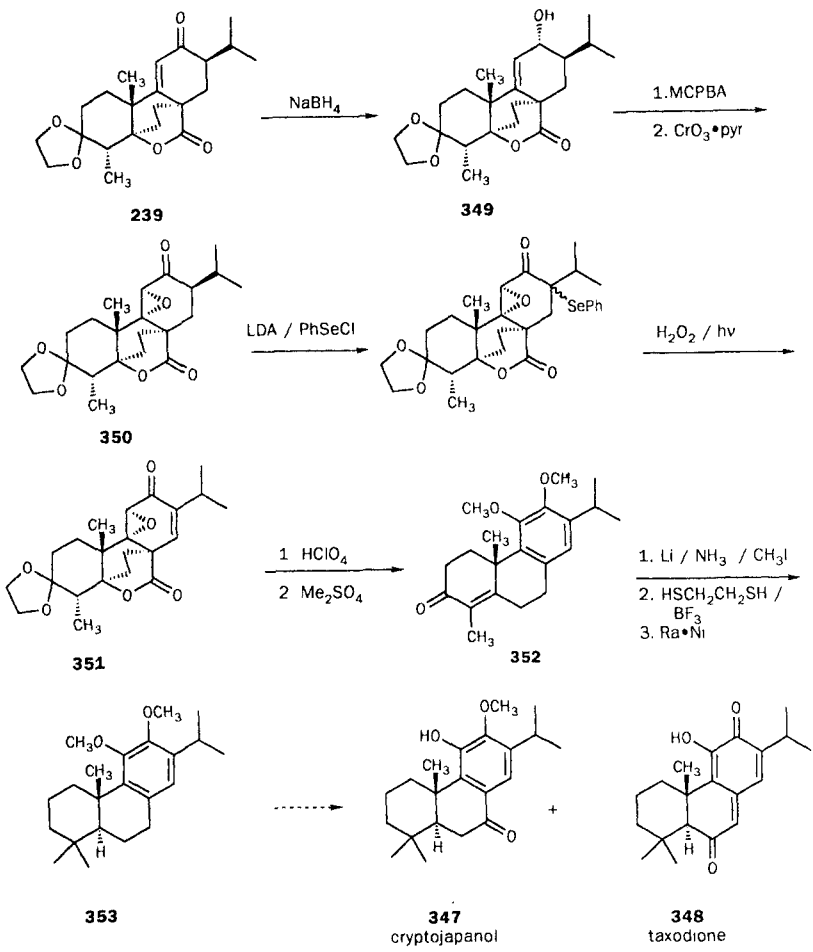
For the synthesis of cryptojapanol, **347**, and taxodione, **348** (Scheme 57) Watt and co-workers[101] employed ketone **239**, used previously for the synthesis of ferruginol. The key steps for taxodione and cryptojapanol are the introduction of an oxygen at C-11 and the generation of the aromatic C-ring by decarboxylative elimination. Thus, epoxidation of α-alcohol **349**, obtained as the principal isomer in the hydride reduction of **239**, followed by oxidation, yields **350**. Following conversion to enone **351**, a complex "unraveling"



SCHEME 55. Matsumoto's synthesis of taxodione.



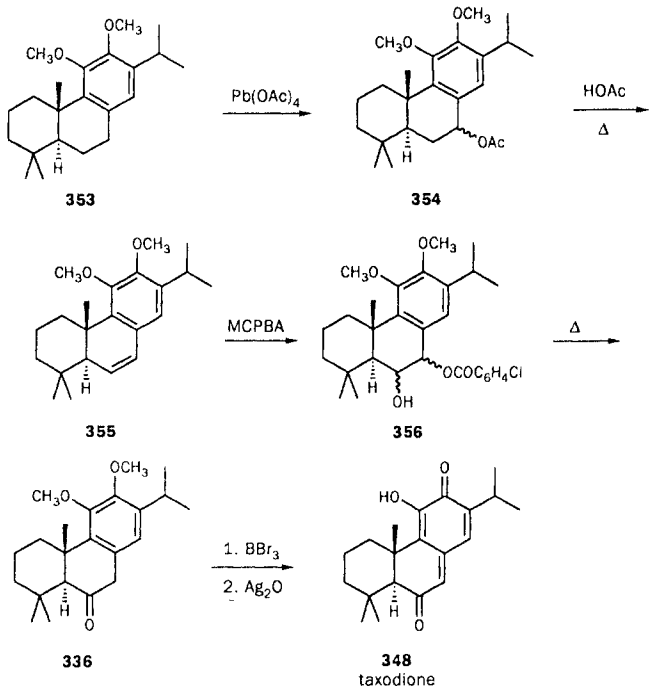
SCHEME 56. Matsumoto's second synthesis of taxodione.



SCHEME 57. Watt's synthesis of cryptojapanol and taxodione.

reaction is effected with acid. Hydrolysis of the ketal unit is followed by elimination of the carboxyl group, and decarboxylation coupled to opening of the epoxide group. Methylation of the emergent phenolic hydroxyl group yields **352** and C-methylation and reduction affords ether **353**. Conversion of this compound to cryptojapanol was carried out by Wenkert[102] and co-workers and to taxodione by Mori.

In the Mori conversion[103] of 11-methoxyferruginol methyl ether, **353**, to taxodione (Scheme 58) the first step is the introduction of an acetoxy group at C-7 by lead tetraacetate oxidation to yield a mixture of acetates, **354**. These

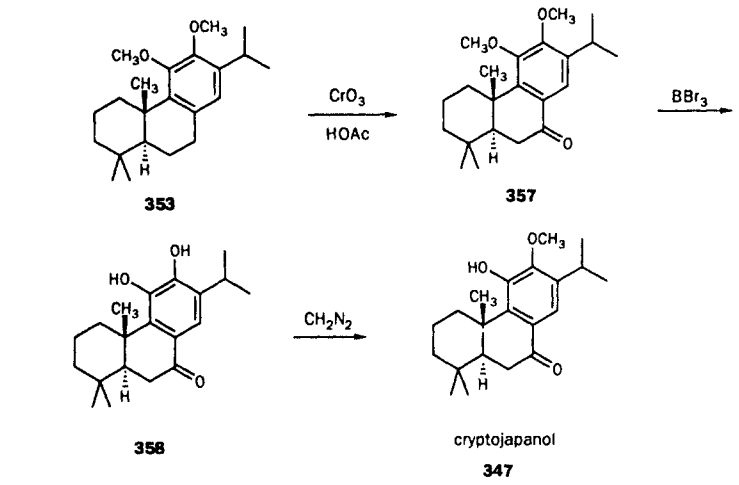


SCHEME 58. Mori's synthesis of taxodione.

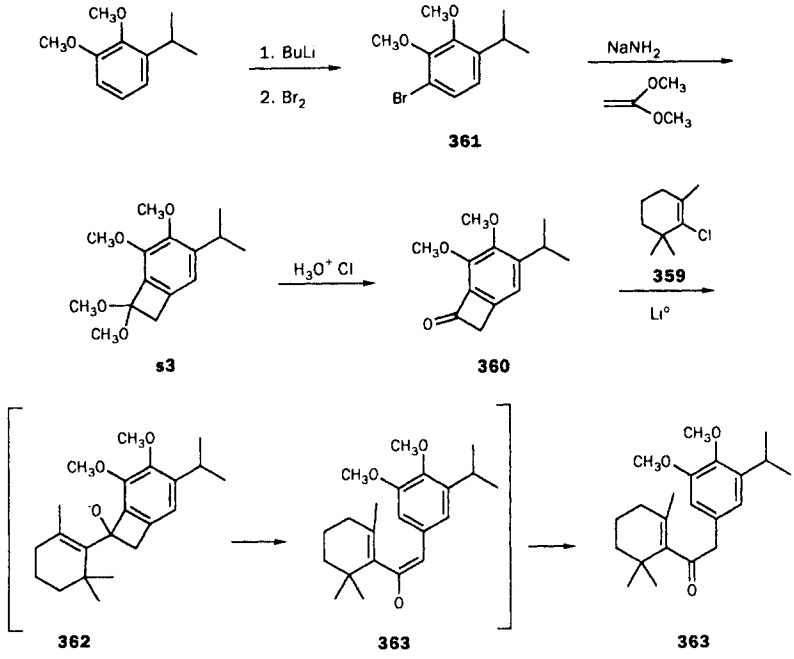
are subjected to elimination to form olefin **355**, which in turn is oxidized with peracid to provide a mixture of diol monoesters, **356**. A second, thermal, elimination leads to the same ketone, **336**, used in the Matsumoto synthesis of taxodione. In the Mori work **336** is demethylated and oxidized with silver oxide to provide taxodione, **348**.

For the conversion of **353** to cryptojapanol (Scheme 59), Wenkert and coworkers[102] oxidized the benzylic position with chromium trioxide to form ketone **357**. Demethylation to **358** is effected with boron tribromide and partial reetherification affords cryptojapanol, **347**.

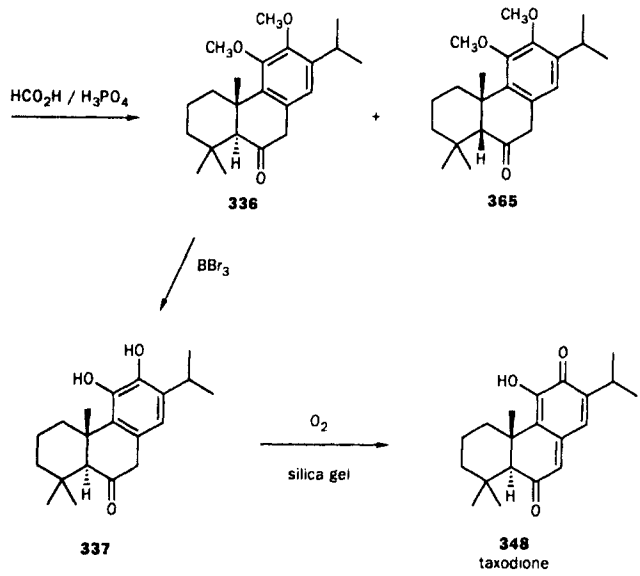
A synthesis of taxodione designed to produce the natural product in significant quantity was reported by Stevens and Bisacchi[104] from the University of California at Los Angeles. The key step in the process (Scheme 60) is the addition of the lithiate of chlorocyclohexene **359** to benzocyclobutanone **360**. The ketone is produced by addition of 1,1-dimethoxyethylene to the benzyne derived from bromocatechol **361**. In the critical addition step the initially formed cyclobutanol **362** opens in regioselective fashion, but the anion **363** fails to cyclize, undergoing a 1,3-proton shift to yield the enolate of



SCHEME 59. Wenkert's preparation of cryptojapanol.



SCHEME 60. Steven's synthesis of taxodione.

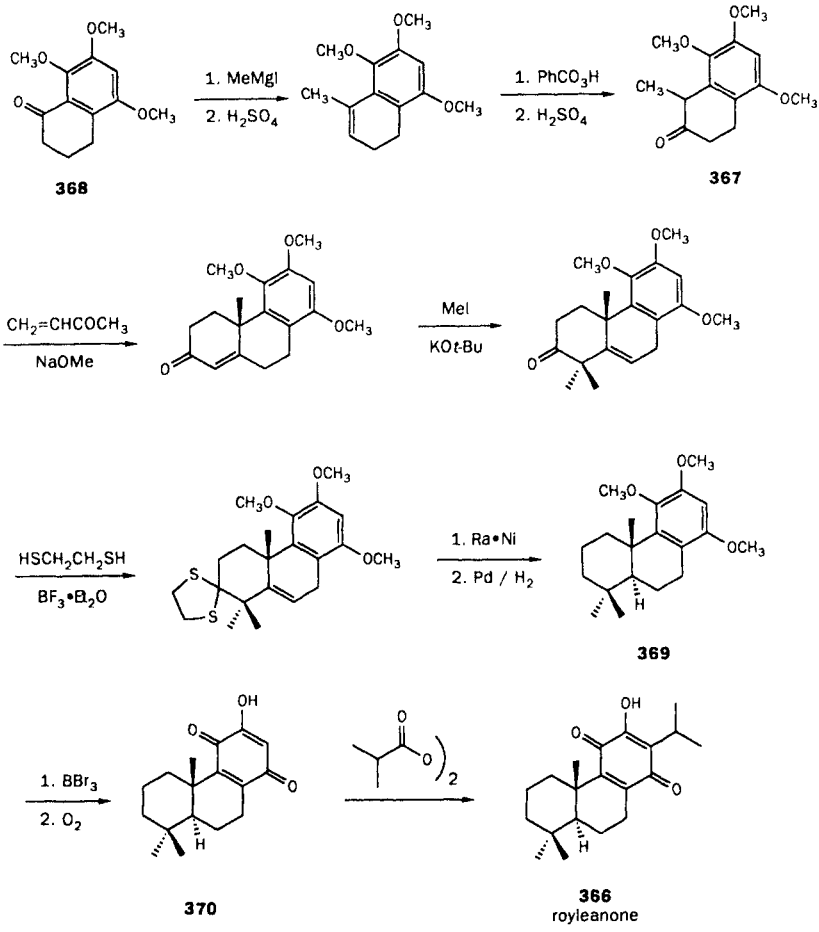


SCHEME 60. Steven's synthesis of taxodione (*continued*).

product **364**. With the failure of the desired anionic cyclization, enone **364** is treated with acid to effect cyclization. Unfortunately, as in the Matsumoto synthesis, both the *trans*- and *cis*-tricyclic ketones **336** and **365** are formed (in a ratio of 3:2) and in only a total yield of 66%. Considering the small differences in steric energy (ca. 0.5 kcal/mole by MM2 calculation) between *cis*- and *trans*-tricyclic ketones of this type it is not surprising that both isomers should be obtained under what are essentially equilibrium conditions. Nevertheless, *trans* ketone **336** is conveniently transformed according to the Matsumoto protocol into taxodione, **348**, by demethylation to **337** and aerial oxidation.

Royleanone

Royleanone, **366**, has been the product of several partial syntheses[100, 105, 106] starting from either abietic acid or podocarpic acid and three total syntheses. The first total synthesis (Scheme 61) by Matsumoto, Tachibana, and Fukui[107] features a straightforward construction of the tricyclic system using Robinson annelation chemistry. Thus β-tetralone **367** prepared from α-tetralone **368** by methyl magnesium iodide addition, dehydration, and epoxidation–rearrangement is condensed with methyl vinyl ketone. Sub-

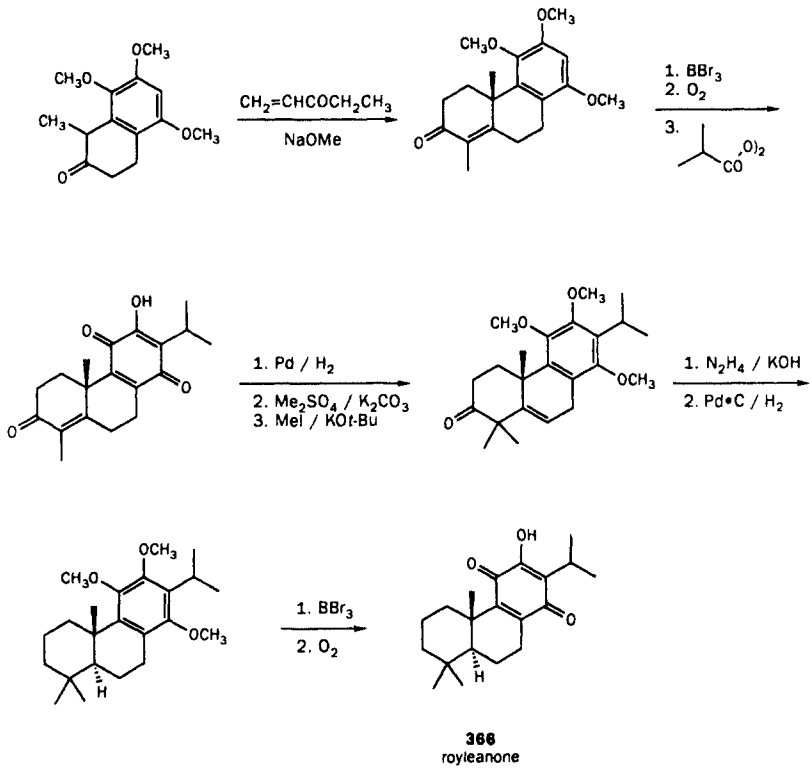


SCHEME 61. Matsumoto's synthesis of royleanone.

sequent methylation, thioketal formation, desulfurization, and reduction affords the *tris*-ether **369**. This intermediate lacks the isopropyl group of royleanone. To append the C_3-unit, cleavage of the ethers is first effected followed by oxidation to quinone **370**. Treatment of this substance with isobutyryl peroxide in a radical coupling process afforded royleanone, **366**.

A second synthesis from the Hiroshima laboratory is reported by Matsui.[108] It is a variation of the previous work and features an earlier introduction of the isopropyl group (Scheme 62).

A recent total synthesis has been completed by Liebeskind and Chidambaram[109] at Emory University employing a novel construction of the C-ring

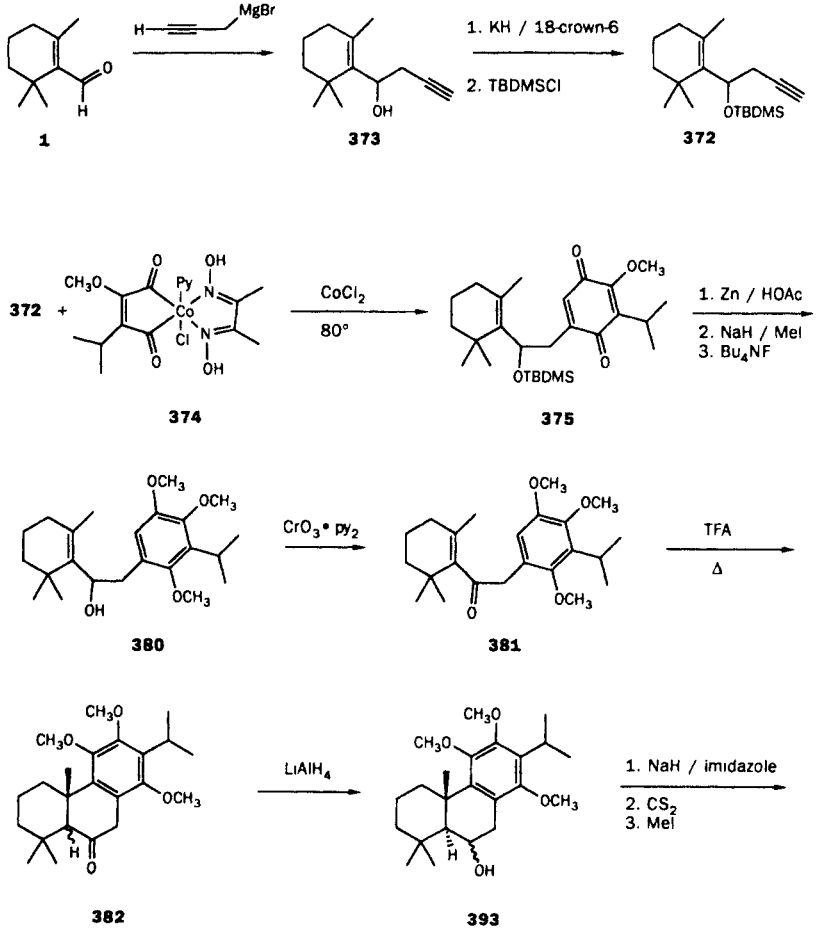


SCHEME 62. Matsui's synthesis of royleanone.

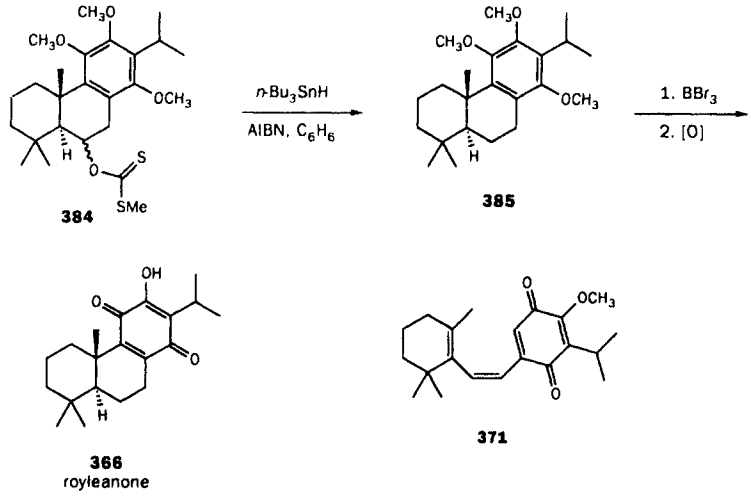
(Scheme 63). As in the Stevens synthesis of taxodione, the central ring of the abietane skeleton of royleanone was originally envisoned as arising from the electrocyclization reaction of an intermediate, **371**, bearing suitably functionalized A and C rings. The cyclization process fails to occur, however, and the alternative approach shown in Scheme 63 is followed. Intermediate alkynyl silyl ether **372** is prepared from β-cylocitral by Grignard addition to produce **373**, followed by protection of the hydroxyl group. The alkynyl unit **372** is then coupled with cobalt complex **374** to produce quinone **375**.

The cobalt complex **374** is prepared from squaric acid **376** (Scheme 64). Esterification of squaric acid with isopropanol is followed by conjugate addition of isopropyl magnesium bromide to provide a product, **377**, in which one alkoxy group has been replaced. After replacement of the second isopropoxy group by methoxy, **378**, the cobalt metallocycle **379** is prepared. Reaction of this species with dimethylglyoxime affords **374**.

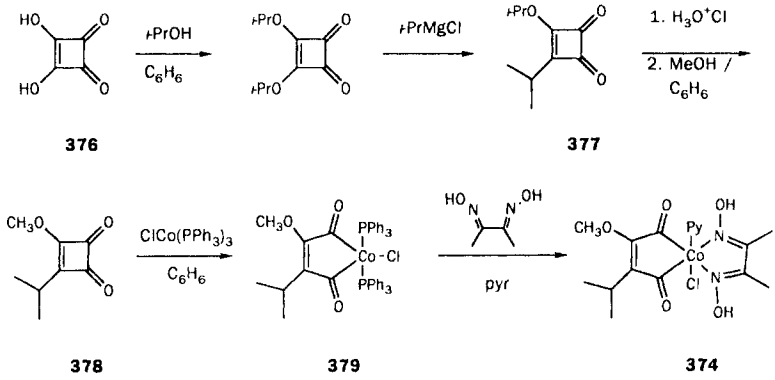
Following reductive aromatization of the newly formed quinone ring the siloxy group *exo* to ring-A is hydrolyzed and the resulting alcohol **380** is oxidized to the corresponding ketone **381**. Cyclization of this compound under acid conditions produces a mixture of epimeric tricyclic ketones **382** of which the desired A/B-*trans* system is the major and kinetic product (5:1). Following separation and reduction to **383**, the *trans*-isomer, as the derived xanthate **384**, is deoxygenated with tin hydride to give *tris*-ether **385**. Subsequent ether cleavage with boron bromide followed by aerial oxidation affords royleanone, **366**.



SCHEME 63. Liebeskind's synthesis of royleanone.



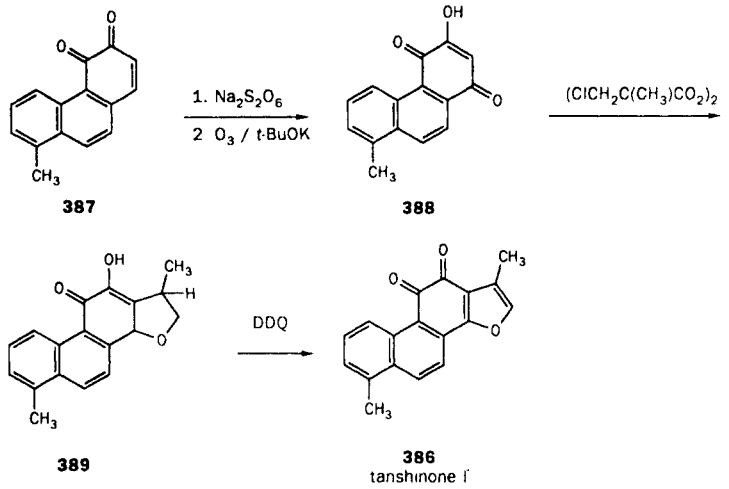
SCHEME 63. Liebeskind's synthesis of royleanone (*continued*).



SCHEME 64. Preparation of metallocycle for royleanone.

Tanshinones

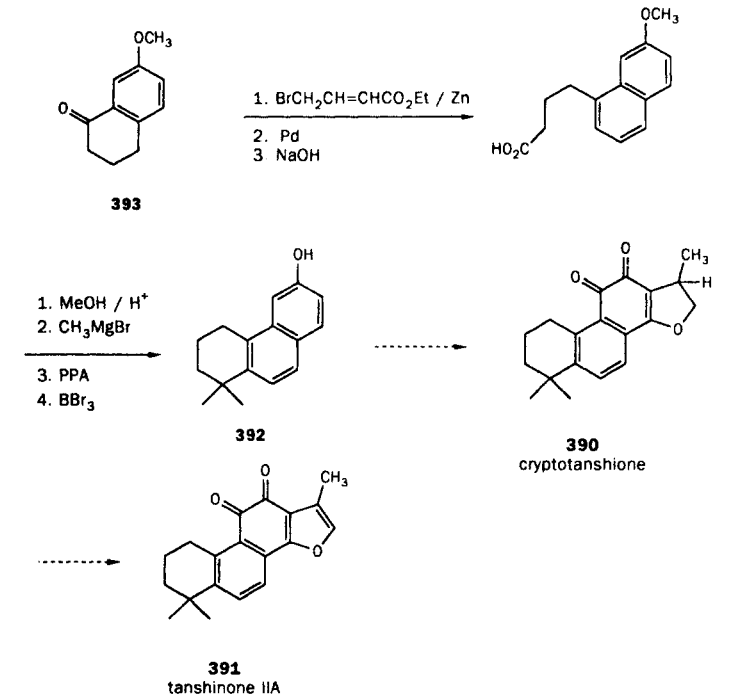
The first syntheses of the natural tanshinones C-18 *nor*-methyl and C-18,20 *bisnor*-methyl aromatic diterpenes from *Salvia miltiorrhiza* in which the usual abietane side chain is incorporated into a furan ring were carried out by Baillie and Thomson[110] at Aberdeen. For tanshinone I (Scheme 65), the fully aromatic *bisnor*-methyl compound, **386**, *o*-quinone **387** is oxidized to **388** and



387 **388** **389**

386
tanshinone I

SCHEME 65. Thomson's synthesis of tanshinone I.



393 **392** **390**
cryptotanshione

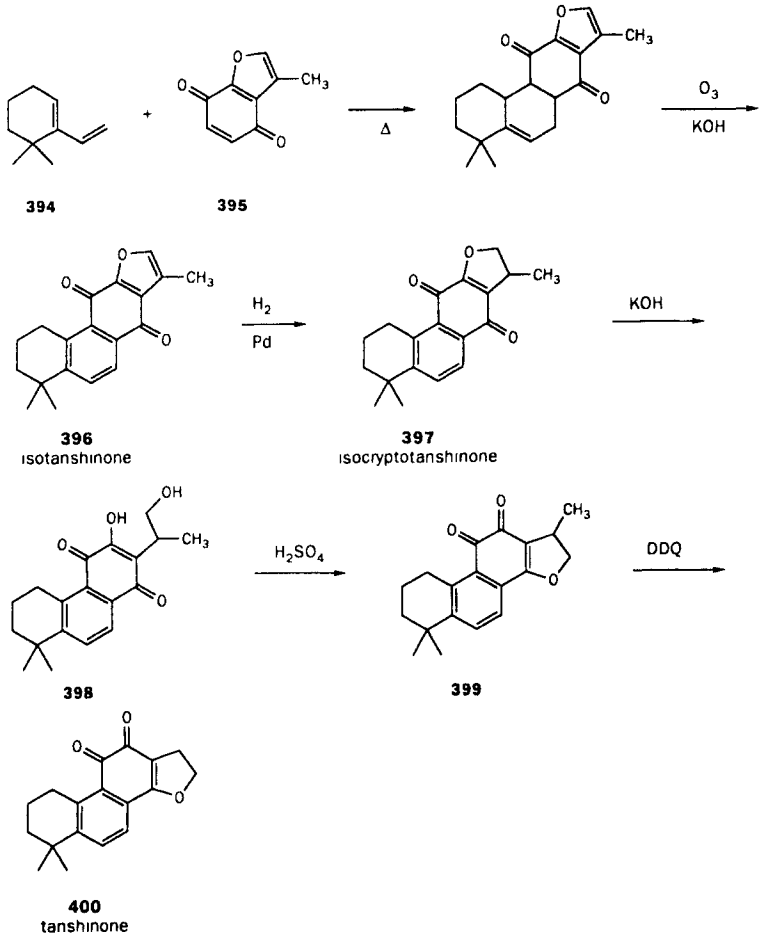
391
tanshinone IIA

SCHEME 66. Thomson's synthesis of cryptotanshinone and tanshinone IIA.

then coupled to the radical produced from β-chloroisobutyryl peroxide to yield **389**. Dehydrogenation affords tanshinone I, **386**.

For the synthesis (Scheme 66) of the less-oxidized tanshinones **390**, cryptotanshinone, and **391**, tanshinone IIA, tricyclic phenol **392** is prepared by standard aromatic substitution processes from α-tetralone **393**. The conversion of **392** into **390** and **391** is carried out as developed previously for tanshinone I.

The Kakisawa group at Tokyo Kyoiku have synthesized three of the tanshinones. The first synthesis[111] (Scheme 67) is based on a Diels–Alder

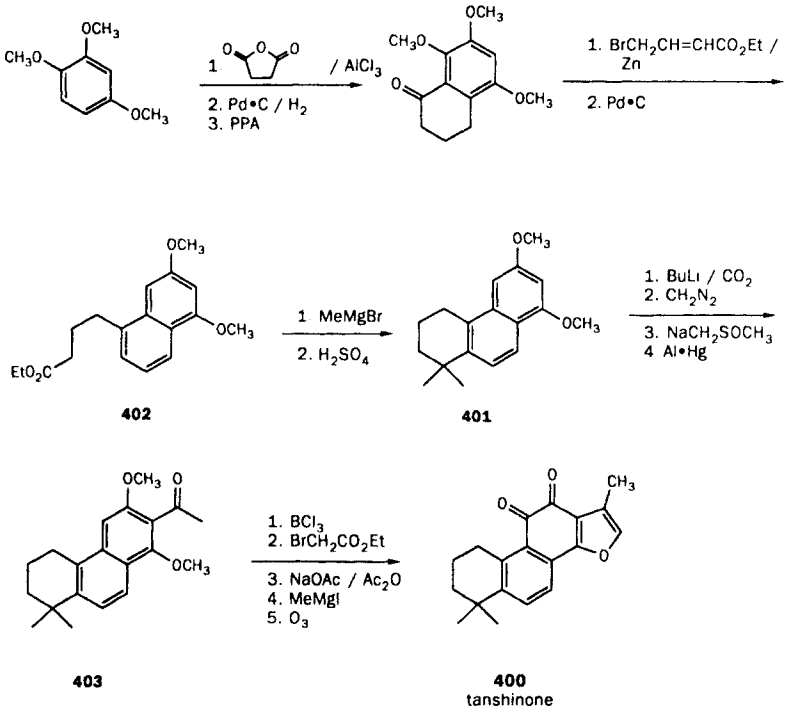


SCHEME 67. Kakisawa's synthesis of isotanshinone, isocryptotanshinone, and tanshinone.

reaction and is the model for the similar synthesis of miltirone executed by Knapp.

The components of the cycloaddition are the dimethylvinylcyclohexene **394** and quinone **395**. The adduct, formed in high yield, affords isotanshinone, **396**, when aromatized. When reduced catalytically **396** leads to isocryptotanshinone **397**. This substance, when treated with alkali, opens to form enol alcohol **398**. Reclosure under the influence of acid affords **399**, which when dehydrogenated gives tanshinone, **400**.

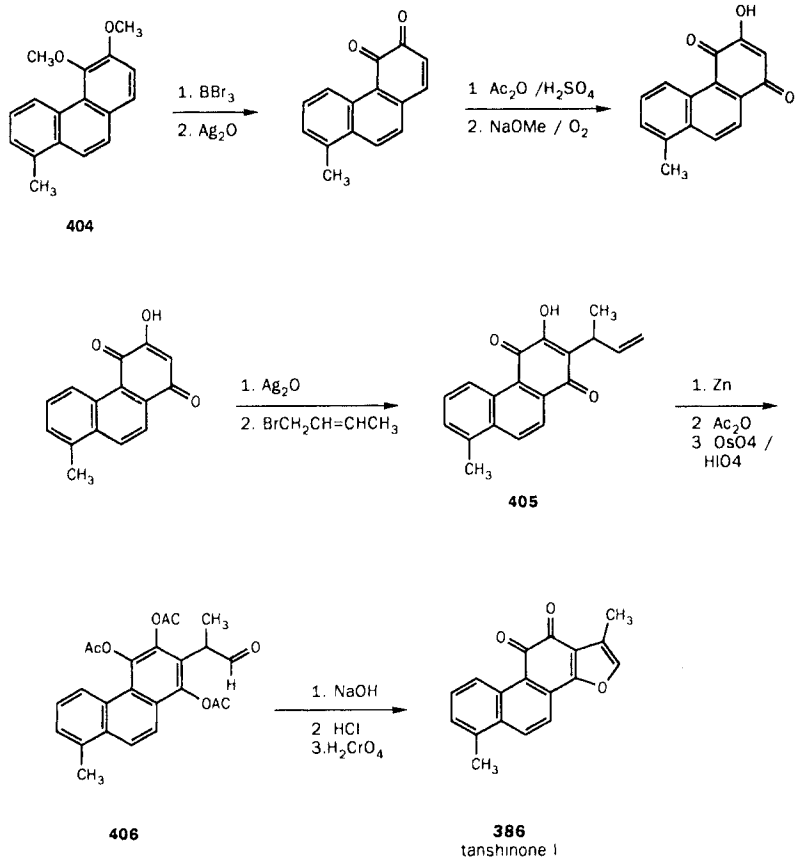
In earlier work (Scheme 68) Kakisawa, Tateishi, and Kusumi[111–113] carried out a different synthetic approach to the tanshinones. Here they built a tricyclic material **401** by standard aromatic substitution and cyclization chemistry. Interestingly, in the internal reduction–aromatization reaction leading to **402** one of the original methoxy groups is lost. The oxygen atom is readily restored in the last step, however. After attachment of the acetyl side chain in **403** the C-13 ether function is selectively cleaved and reetherified with bromoacetic ester and the product is subjected to an internal Perkin



SCHEME 68. Kakisawa's synthesis of tanshinone.

condensation. Final cleavage of the remaining methoxy group is followed by aerial oxidation to yield tanshinone, **400**.

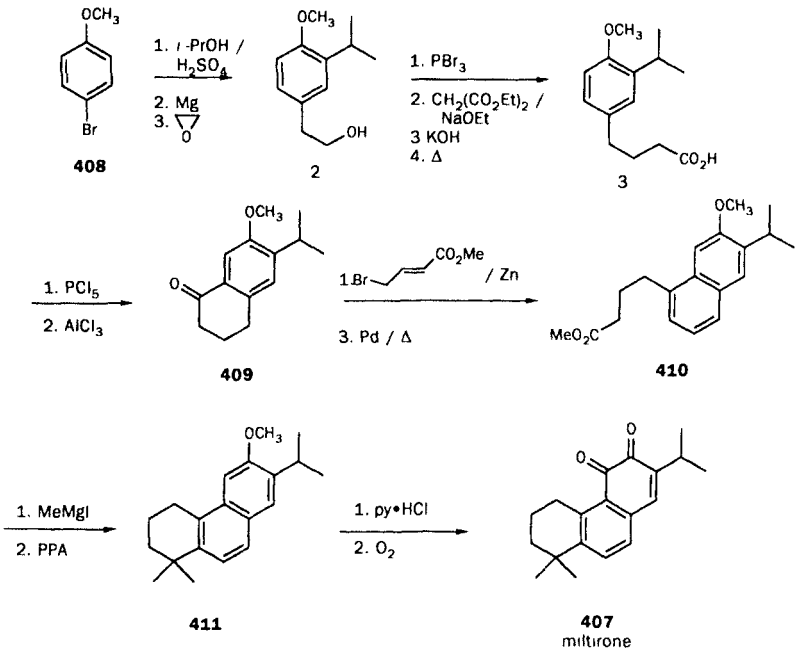
Tanshinone I, **386**, has also been synthesized by Huot and Brassard[114] at Laval University using an allylic rearrangement during alkylation for the construction of the furano portion of the molecule. Starting from tricyclic diether **404** (Scheme 69), an oxidation and alkylation sequence affords **405**. Following reduction and protection of the three oxygen functions, oxidation of the external double bond with periodate–osmium tetroxide leads to aldehyde **406**. Hydrolysis of the acetate esters, ring closure of the furan, and oxidation produces tanshinone I, **386**.



SCHEME 69. Synthesis of tanshinone I by Brassard.

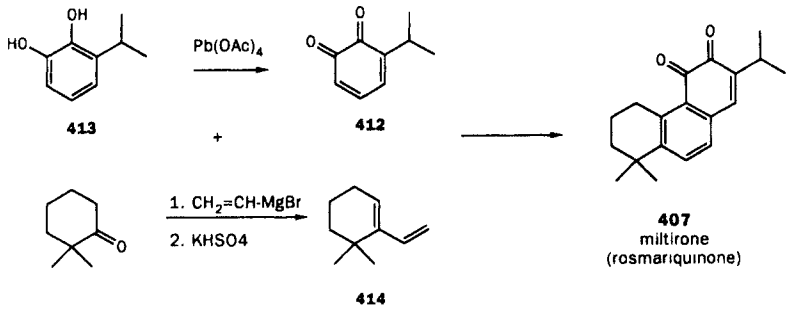
Miltirone (Rosmaraquinone)

Miltirone, **407**, another aromatic B-ring, C-20 *nor*-diterpene quinone was synthesized in straightforward fashion by Nasipuri and Mitra[115] from the Indian Institute of Science. Bromoanisole **408** (Scheme 70) is converted to α-tetralone **409** by a Grignard and Friedel–Crafts sequence and is then further annelated by addition of the Reformatsky reagent derived from γ-bromocrotonate and reduction to form **410**, followed by Grignard addition and acid-catalyzed cyclization. The product of these steps, **411**, is subjected to ether cleavage with pyridine hydrochloride followed by aerial oxidation to yield the target molecule **407**.



SCHEME 70. Synthesis of miltirone by Nasipuri

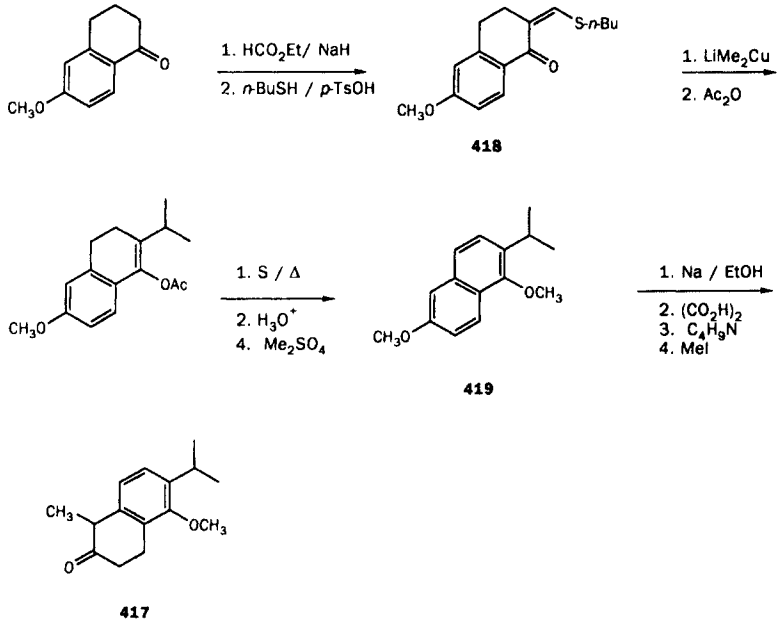
A very short synthesis of miltirone **407** (called rosmaraquinone) was reported by Knapp and Sharma[116] from Rutgers University. *o*-Quinone **412** (Scheme 71), prepared from the available catechol **413**, is heated with vinylcyclohexene **414** in refluxing ethanol. The reaction product is directly miltirone, **407**, the initial cycloadduct having suffered oxidation at the expense of the quinone starting material.



SCHEME 71. Knapp's synthesis of miltirone (rosmariquinone).

Triptolide and Triptonide

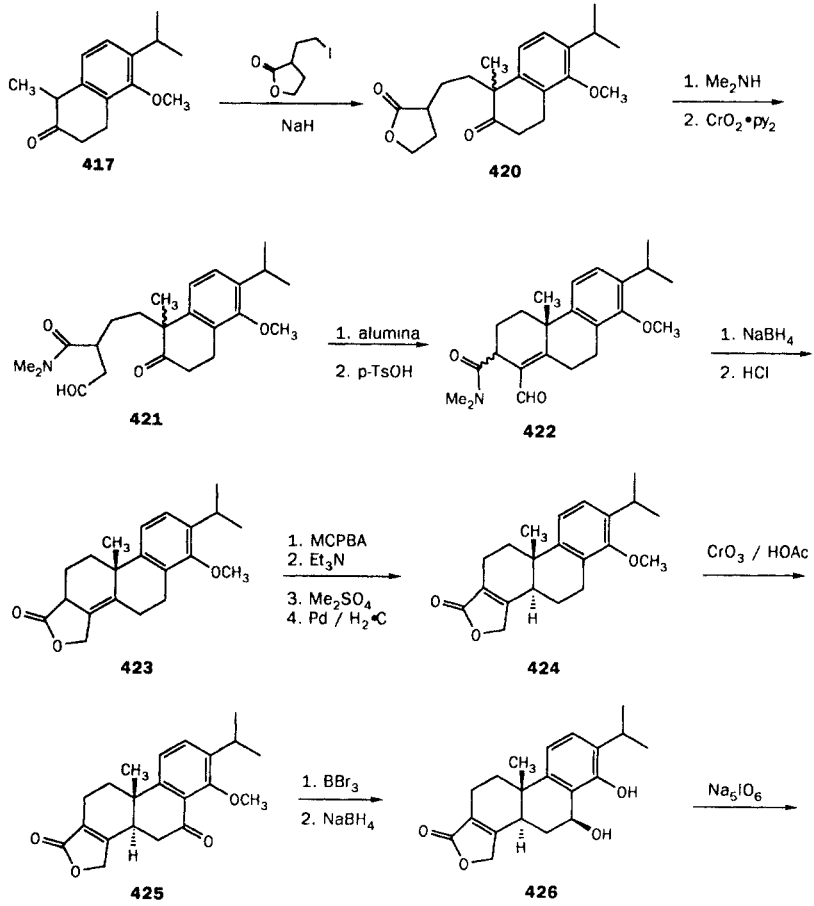
Triptolide, **415**, and triptonide, **416** (Scheme 73), are tri-epoxy abietane lactones. The cyctotoxic activity of triptolide has stimulated efforts to prepare these compounds synthetically. The first total synthesis was accomplished by Berchtold and co-workers[117–119] at the Massachusetts Institute of Technology.



SCHEME 72. Berchtold's preparation of an intermediate for triptolide.

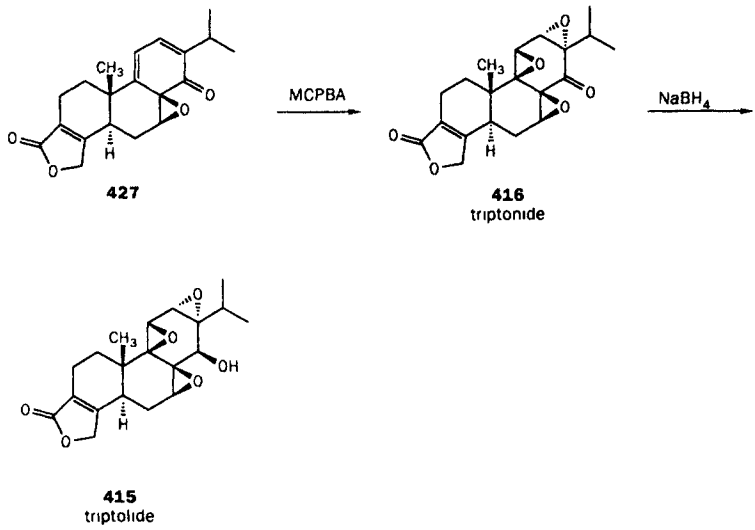
The starting point for the Berchtold synthesis (Scheme 72) is the bicyclic ketone **417** prepared from 6-methoxy α-tetralone. In this preparation the oxidation state of the two rings is "interchanged." After introduction of the isopropyl group through cuprate addition to **418**, aromatization affords naphthalene derivative **419**. The less electron-rich monosubstituted ring is then selectively reduced with sodium in alcohol and the resulting ketone as its pyrrolidine enamine is methylated to afford **417**.

The key problems in the synthesis are (1) the attachment of the A-ring unit, (2) the stereochemistry of the A/B fusion and the position of the ring-A double bond, and (3) the introduction of the myriad oxygen functions of rings B and



417 **420** **421** **422** **423** **424** **425** **426**

SCHEME 73. Berchtold's synthesis of triptolide.



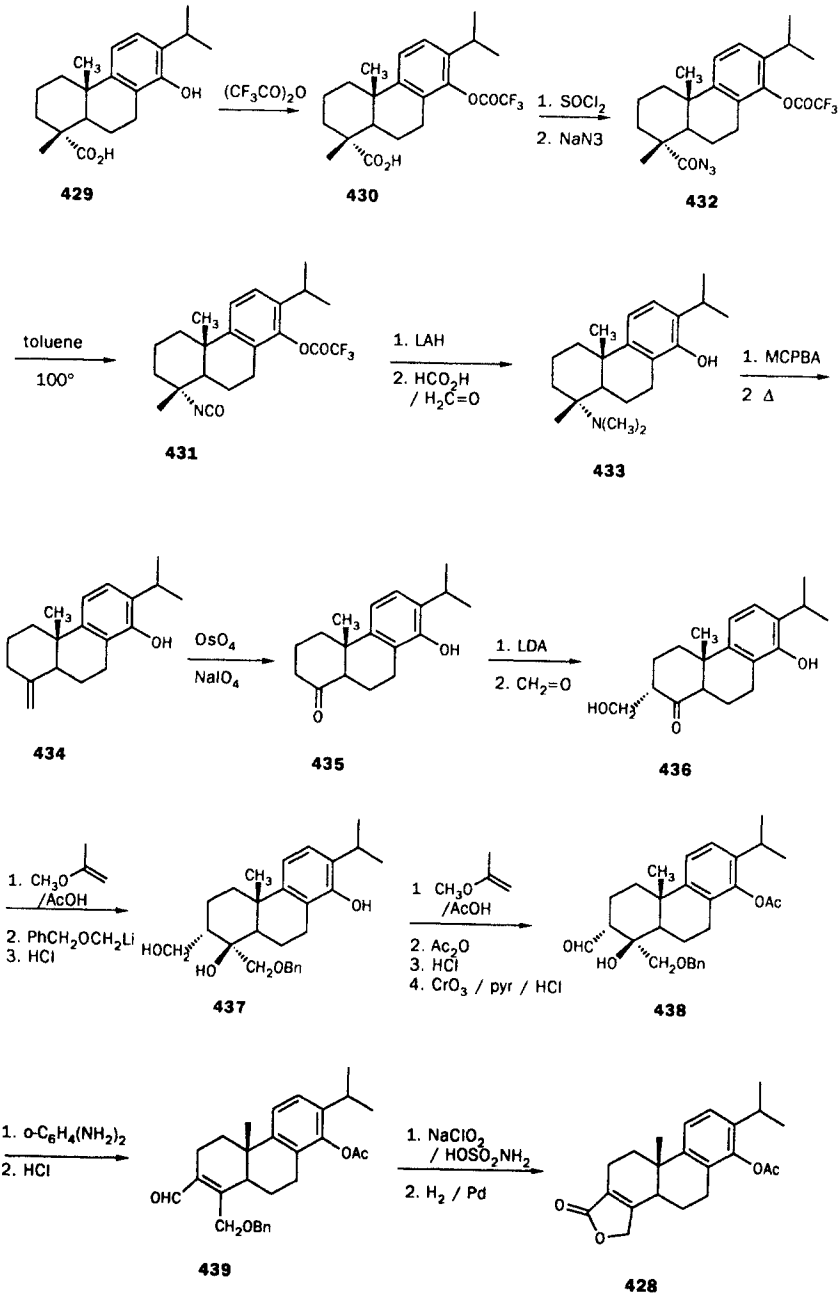
SCHEME 73. Berchtold's synthesis of triptolide (*continued*).

C. For completion of the first objective (Scheme 73), the elements of ring A are added to provide **420** by alkylation of **417** with 2-(iodoethyl)butyrolactone. Cleavage of the lactone ring of **420** with dimethyl amine and subsequent oxidation of the resulting primary alcohol affords aldehyde **421** as a mixture of epimers. Aldol cyclization is then carried out to give **422**, alumina being more effective in this reaction than the usual catalytic agents. When the aldehyde group is then reduced, β,γ-lactone **423** is formed as a single isomer.

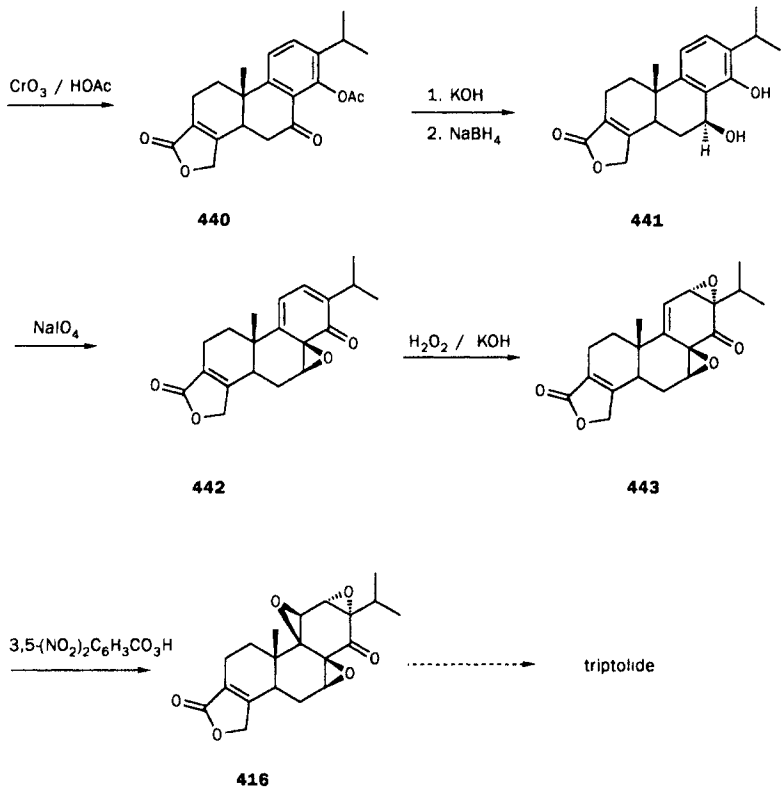
Direct methods for the equilibration of the double bond of **423** with concomitant introduction of the stereogenic center at C-5 lead to mixtures. As a consequence **423** is subjected to an epoxidation–elimination–reduction sequence to provide the C-5-α compound **424**. Benzylic oxidation is then carried out to introduce an oxygen atom in ring B, **425**, and the ether group of ring-C is cleaved, giving phenol **426**.

When **426** is oxidized with periodate epoxy dienone **427** is formed, which in turn is converted with MCPBA to triptonide **416** in modest yield. Reduction of the carbonyl group of triptonide affords a mixture of diastereoisomeric alcohols from which triptolide **415** is obtained by chromatographic separation.

Van Tamelen and co-workers[120–122] at Stanford University carried out three syntheses of triptonide, **416**, in each case employing a different route for preparation of the key tricyclic intermediate **428** (Scheme 74). In the first partial synthesis[122] they employed l-dehydroabietic acid as starting material.



SCHEME 74. Van Tamelen's first synthesis of triptolide.



SCHEME 74. Van Tamelen's first synthesis of triptolide (*continued*).

Conversion[123] of the "relay" to its 14-hydroxy derivative **429** is followed by formation of the trifluoroacetate ester **430**. By a series of operations at the ring-A carboxyl group the isocyanate **431** is prepared by Curtius rearrangement of the intermediate azide **432**. Reduction of the derived urethane and subsequent Clark–Eschweiler methylation affords tertiary amine **433**.

Oxidation followed by Cope elimination produces the exomethylene compound **434**, which in turn is oxidatively cleaved to ketone **435**.

In a long multistep sequence the butenolide unit of the triptonides is appended. Hydroxymethylation of **435** to yield **436** is followed by protection of the aliphatic hydroxyl group and addition of an α-benzyloxymethyl group at C-4 by nucleophilic addition to the carbonyl group. Acidic workup at the end of this sequence yields **437**. After reblocking of the ring-A diol group as an acetonide the phenolic hydroxyl is acetylated, the substituent at C-3 is again deblocked, and the resulting alcohol is converted to aldehyde **438**.

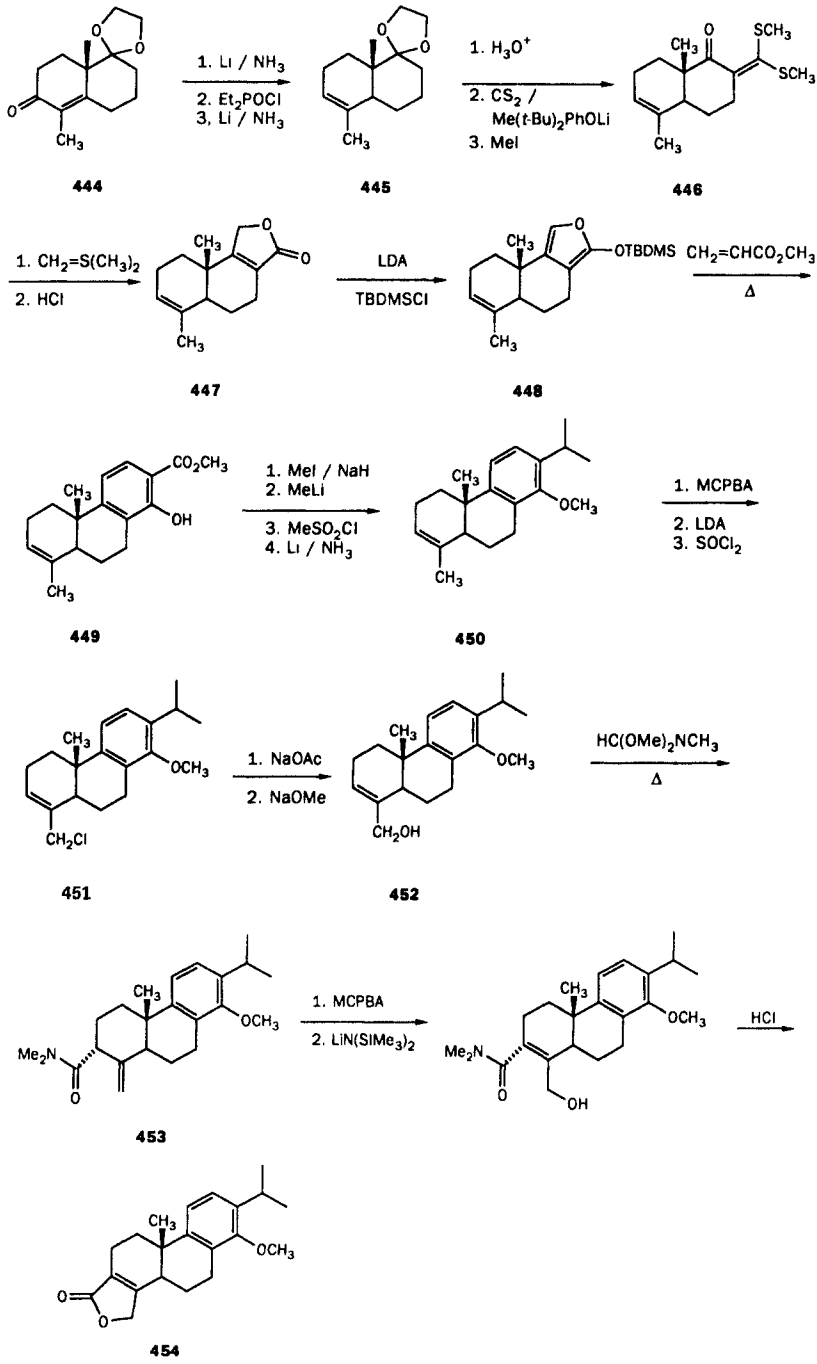
The latter is dehydrated in only 20% to **439**. Methods other than the one employed for this transformation apparently yielded significant quantities of the *cis* A/B isomer. The butenolide function is finally constructed by successive oxidation and debenzylation yielding **428**.

For introduction of the highly oxygenated functionality of the B/C rings of triptonide oxidation is first effected at the benzylic position of **428** to yield **440**. The latter is then subjected to hydrolysis of the C-14 acetate followed by borohydride reduction to give alcohol **441**. Oxidation leads to epoxy dienone **442**. Basic epoxidation (to give an unspecified mixture of isomers, **443**) is followed by peracid epoxidation affording triptonide **416**. Since **416** on borohydride reduction yields triptolide **415**, a formal synthesis of the latter is also achieved.

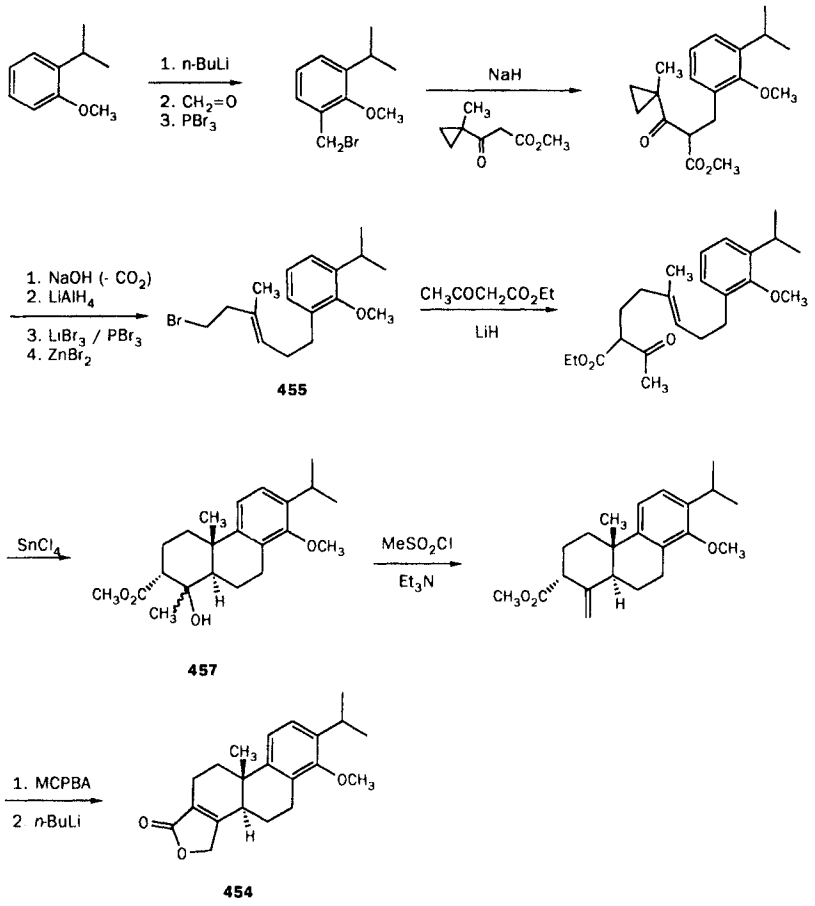
The second synthesis of triptonide and triptolide by the van Tamelen group (Scheme 75) is based on the use of the Kitahara enone acetal **444**[64] and constitutes a full total synthesis of the natural product. Similar to the approach of Spencer, Liebeskind, Meyers, and others, the aromatic C-ring of an abietane is constructed *de novo*, in this case from a furan. To accomplish this end enone **444** is first converted into olefin **445** by conjugate reduction, trapping of the intermediate enolate as a phosphate ester, and subsequent reductive cleavage of the C_3–oxygen bond. Following cleavage of the ketal function a dithioacetal unit is introduced by condensation with carbon disulfide to form **446**. Methylenation–epoxidation employing the Corey–Chaykofsky sulfonium methylide reagent[124] is followed by acid-catalyzed rearrangement and hydrolysis to lactone **447**. This substance is then converted into a furanol silyl ether derivative **448** which is caused to undergo Diels–Alder addition with methyl acrylate. The resultant salicylic ester product **449** is subjected to a multistep sequence to yield the abietane ether **450**.

Epoxidation and allylic "manipulation" of the double bond of ring-A of **450** yields, after displacement of chloride **451**, a C-4 hydroxymethyl intermediate, **452**. When the alcohol is heated with *N*-methylformamide dimethyl acetal the first formed orthoamide undergoes α-elimination followed by cyclopropanation and rearrangement to yield amide **453**. Epoxidation, base-catalyzed elimination, and hydrolysis then affords the previously prepared intermediate **454**.

The third synthesis of triptolide and triptonide (Scheme 76) by the van Tamelen group[121] features a "biomimetic" approach to the ring system. Bromide **455** is first prepared following the Julia methodology for the synthesis of *E*-trisubstituted olefins. After alkylation of acetoacetic ester with this halide yielding **456**, a cyclization is carried out directly with the β-ketoester to provide tricyclic alcohol **457**. Elimination of the derived mesylate affords an exocyclic olefin which is then converted by epoxidation and elimination to lactone **454**.



SCHEME 75. Van Tamelen's second synthesis of triptolide.

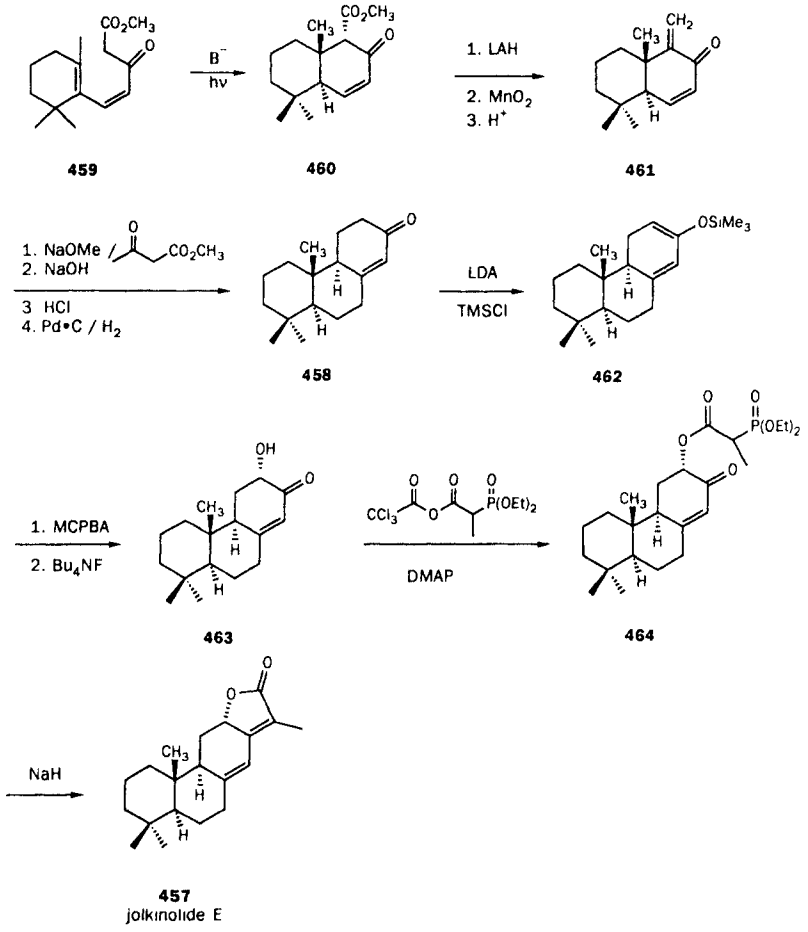


SCHEME 76. Van Tamelen's third synthesis of an intermediate for triptolide.

Jolkinolide A, B, and E

The jolkinolides A, B, and E (**455**, **456**, and **457**) are abietane lactones related to triptolide and triptonide. They have been synthesized by Isoe, Katsumura, and Kimura[125, 126] at Osaka University.

For the preparation of the key tricyclic intermediate **458** used in the syntheses of the jolkinolides, the Isoe group employs a sequence involving a photocyclization reaction rather than the usual Robinson annelation or cationic cyclization route starting from aromatic materials usually used for this enone. Thus β-ionone carboxylic ester **459** (Scheme 77), is photolyzed as its enolate and undergoes electrocyclization to provide β-ketoester **460**.

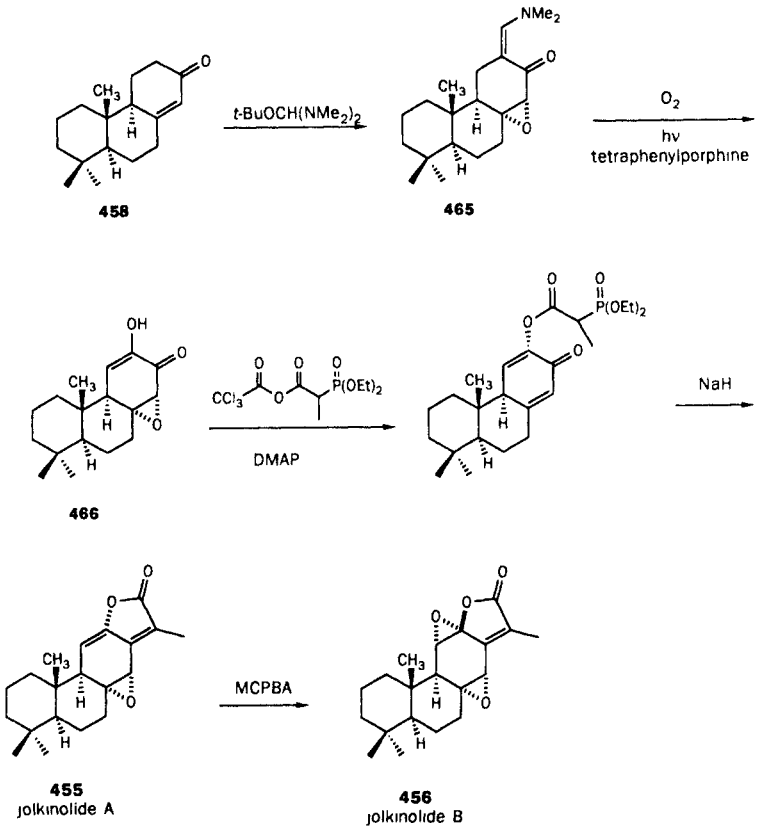


SCHEME 77. Synthesis of jolkinolide E by Isoe.

Reduction, allylic oxidation, and elimination yields methylene ketone **461**. Michael addition of acetoacetic ester to this enone and subsequent aldol condensation is followed by hydrolysis and decarboxylation and reduction of the B-ring double bond to yield tricyclic enone **458**.

For the synthesis of jolkinolide E,[126] **457**, the Rubottom epoxidation procedure[127] is applied to enol silyl ether **462** and the resulting alcohol, **463**, is esterified with a β-phosphonatoanhydride to afford **464**. Aldol (Wittig) condensation of **464** affords jolkinolide E, **457**.

For the preparation of the A and B compounds[125] (Scheme 78), intermediate **458** is epoxidized and then converted to the dimethylimino ketone



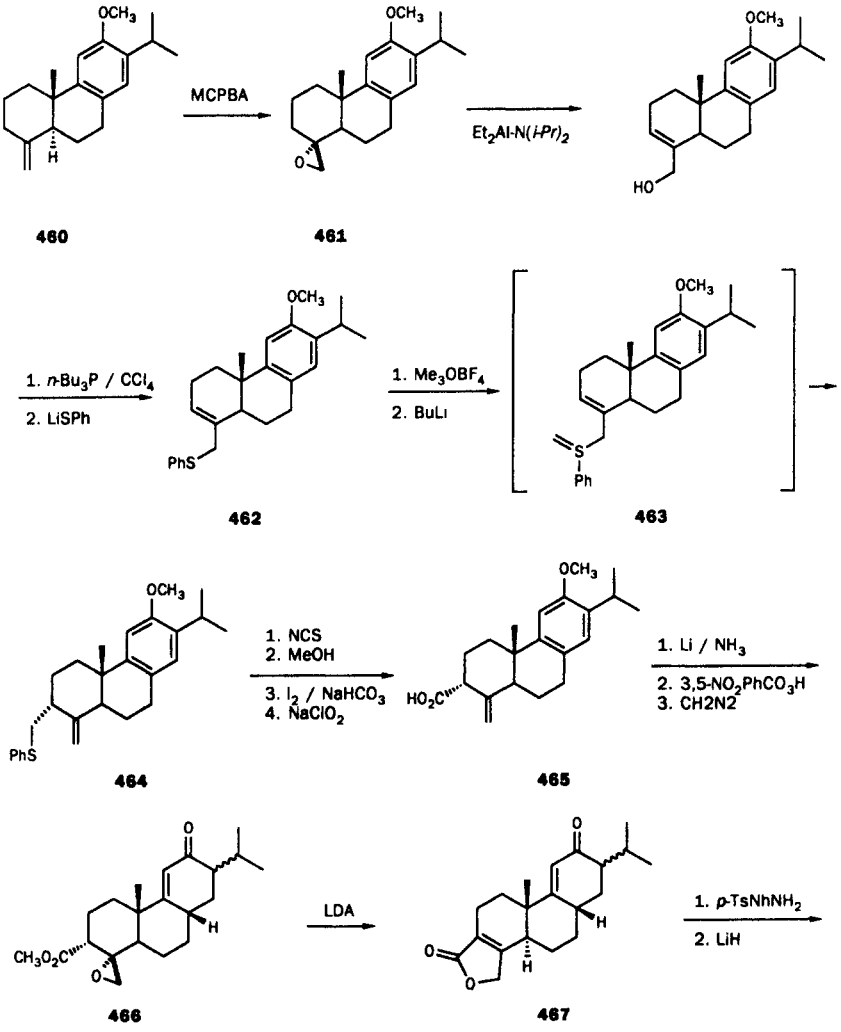
SCHEME 78. Isoe's synthesis of jolkinolide A and B.

465. The diosphenol **466** is then prepared by application of Wasserman's protocol for photochemical oxidation. Using the same methodology employed for jolkinolide E, the Isoe group transforms **466** first to jolkinolide A, **455**, and then by epoxidation to jolkinolide B, **456**.

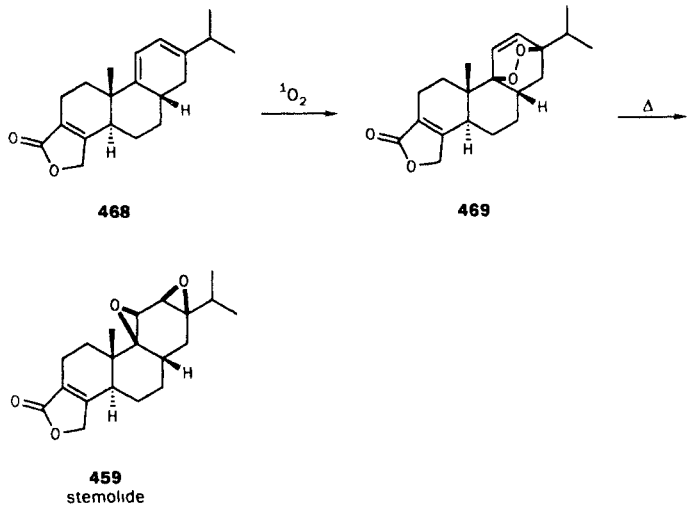
Stemolide

Van Tamelen and Taylor[128] also carried out a synthesis of a related diterpenoid epoxide, stemolide **459**. The principal problems to be solved in this case, as in the triptolide cases, are the creation of the A-ring lactone unit and the introduction of epoxide functionality into ring-C. However, stemolide is functionally simpler than triptolide and the epoxidation sequence is less problematic.

The starting material, alkene **460**, is derived again from dehydroabietic acid. Epoxidation of the exomethylene group followed by elimination yields allylic alcohol **461**. The hydroxyl group is replaced in a two-step sequence by a thiophenyl one to provide allylic sulfide **462**. When the sulfur atom is further methylated and then treated with base, an ylide is formed which spontaneously rearranges to **464**. The carbon now introduced at C-3 serves as the source of the eventual lactone carbonyl group and conversion of the



SCHEME 78a. Van Tamelen's synthesis of stemolide.



SCHEME 78a. Van Tamelen's synthesis of stemolide (*continued*).

sulfide to a carboxyl function is achieved by a four-step oxidation sequence affording **465**. Reduction of ring-C and hydrolysis to an enone is performed on **465** and the product is epoxidized and esterified to give enone ester **466**. Base treatment opens the epoxide and a lactone ring forms spontaneously with the formation of **467**.

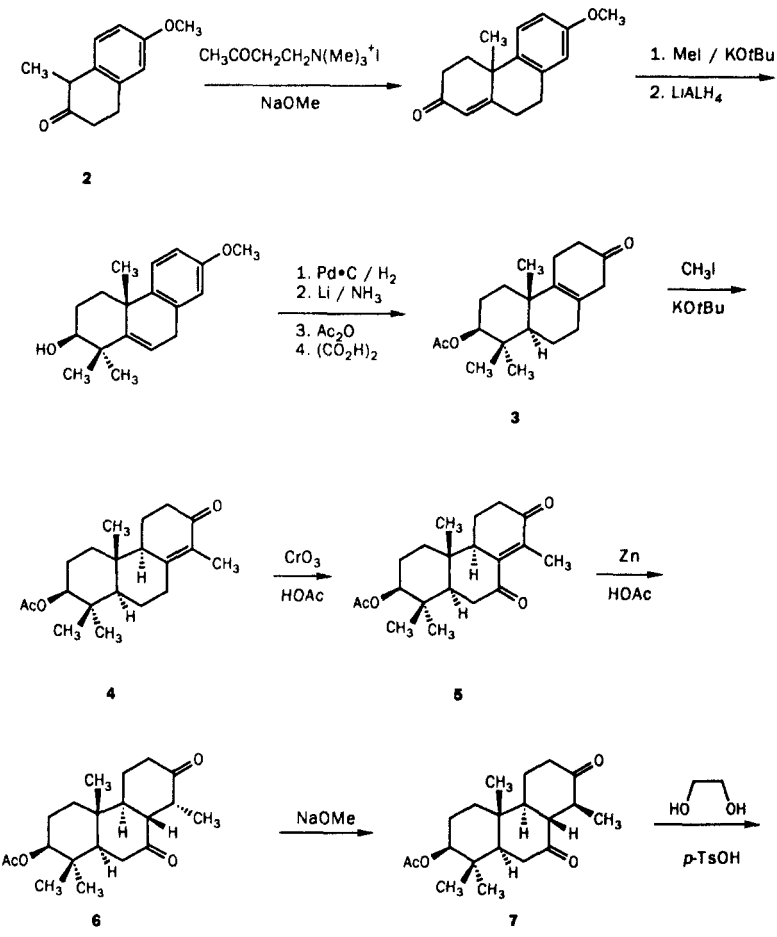
The diene **468** produced from enone **467** upon treatment with hydrazine and base is exposed to singlet oxygen affording *endo*-epoxide **469**. Heating of the peroxide effects final rearrangement to stemolide **459**.

B. Cassanes and Totaranes

(1) Cassane

Cassaic Acid

The synthesis of cassaic acid **1** (Scheme 79) by Turner and co-workers[129] from Rice University illustrates an important aspect of natural products total synthesis that, for the most part, is no longer current. At one time, prior to the availability of high-resolution NMR and X-ray crystallography, total synthesis was used frequently as the "ultimate" proof of structure. With respect to the constitution of cassaic acid the authors of this synthesis state, "In view of limited supplies of natural material for degradative work, a synthetic approach was undertaken." Nevertheless, even as this work was in progress



SCHEME 79. Turner's synthesis of cassaic acid.

an NMR study[130] was underway that settled the question of the structure and stereochemistry of cassaic acid without the need for large quantities of the natural material.

Despite the length of the synthesis, the low yields of some of the steps, and the need for a relay compound from the natural product, there are several novel features in the Turner synthesis. Starting from the methyl β-tetralone **2**[131] a β,γ-unsaturated enone acetate **3** is produced by a Robinson annelation, methylation, and reduction sequence. The monomethylation of this enone to produce the α,β-unsaturated enone **4** is entirely dependent on the position of the double bond. In contrast to the usual methylations of α,β-unsaturated

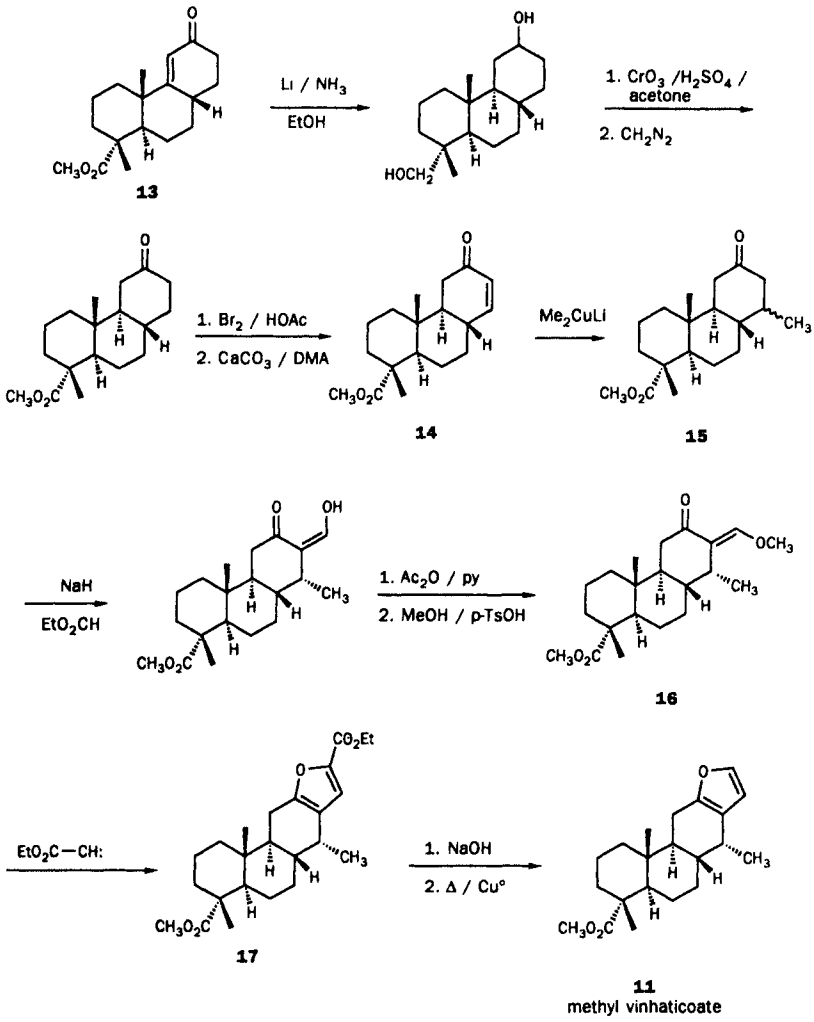
enones in the presence of *tert*-butoxide which yield dialkylated products, the use of the β,γ-unsaturated compound ensures that the starting material will be kinetically more acidic than the product. As a consequence, the product from the introduction of only one methyl group, **4**, is obtained. Unfortunately, at this point the one method which proved capable of producing diketone **5**, chromium trioxide in acetic acid oxidation, affords the compound in a yield of less than 10%. Thus, after reduction of **5** to **6** a resolution is carried out and the corresponding material obtained from degradation of cassaic acid is employed. Following epimerization of **6** to the more stable **7**, a four-step sequence yields ketol **8**. Of particular interest here is the fact that ketal **9** is epimerized to the natural configuration at C-13 on prolonged treatment with acid, **9** to **10**. Reformatsky addition of the side chain to **8** followed by oxidation, dehydration, and hydrolysis of the acetate and methyl ester groups yields cassaic acid, **1**.

Methyl Vinhaticoate

Methyl vinhaticoate, **11** (Scheme 80), and methyl vouacapenate, **12** (Scheme 81), are members of the cassane family of diterpenes in which the C-13 ethyl group is incorporated into a furan unit. The synthesis of methyl vinhaticoate from tricyclic enone **13** requires the introduction of a methyl group at the unactivated C-14 position. To accomplish this, Spencer and co-workers[42, 95] subjected **13** to an enone transposition sequence to afford **14**. The conjugate addition of lithium dimethylcuprate to **14** was expected to yield principally the desired axially substituted product, but instead a 1:1 mixture of this substance and its C-14 epimer, **15**, are obtained. Standard methods for the formation of furans failed with ketone **15**. As a consequence, a novel procedure was devised in which **15** is first converted to the α-methoxymethylene ketone **16** via a three-step sequence. When **16** is then heated with ethyl diazoacetate, cyclopropanation of the enol ether occurs, followed by rearrangement to afford diester **17**. Selective hydrolysis of the less-hindered ester, the aromatic group of **17**, gives a furan carboxylic acid which upon heating with copper affords the natural product **11**.

Methyl Vouacapenate

The same synthetic sequence[95] is also used to prepare methyl vouacapentae **12** starting from *O*-methyl podocarpic acid **18** (Scheme 81). As in the synthesis of methyl vinhaticoate, the addition of lithium dimethylcuprate to a cyclohexenone, in this case compound **19**, fails to show any stereoselectivity. Following separation of the desired addition product, however, application of the furan synthesis methodology developed previously leads to **12**.

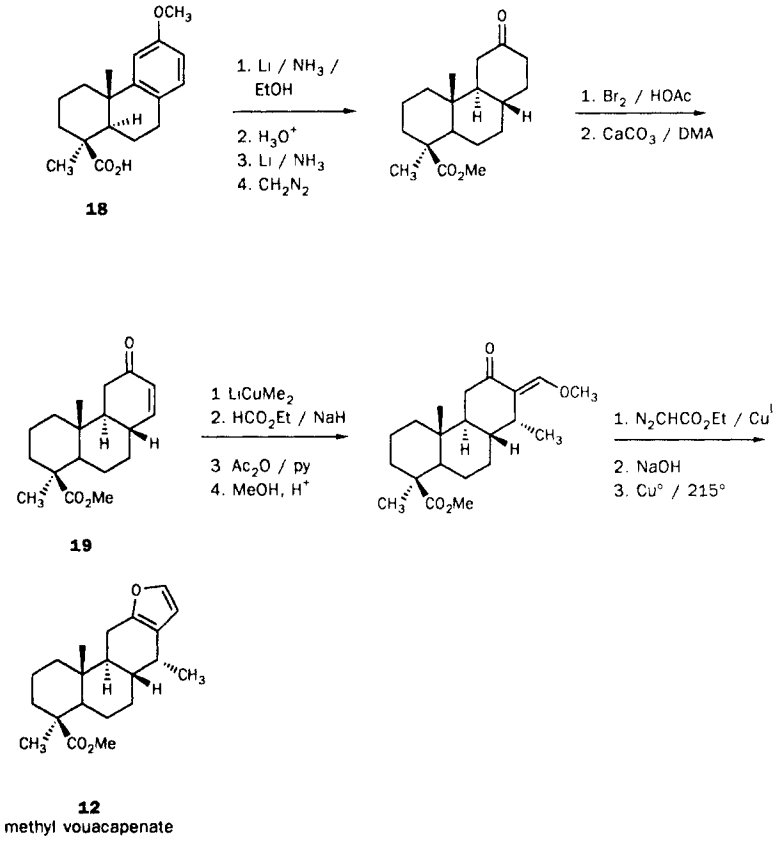


SCHEME 80. Spencer's synthesis of methyl vinhaticoate.

(2) Totarane

Totarol

The synthesis (Scheme 82) of totarol **20** by Barltrop and Rogers[132, 133] is based on the tricyclic aryl ether **21** as the key intermediate. This compound is also the principal intermediate in the syntheses of atisirene, phyllocladene,

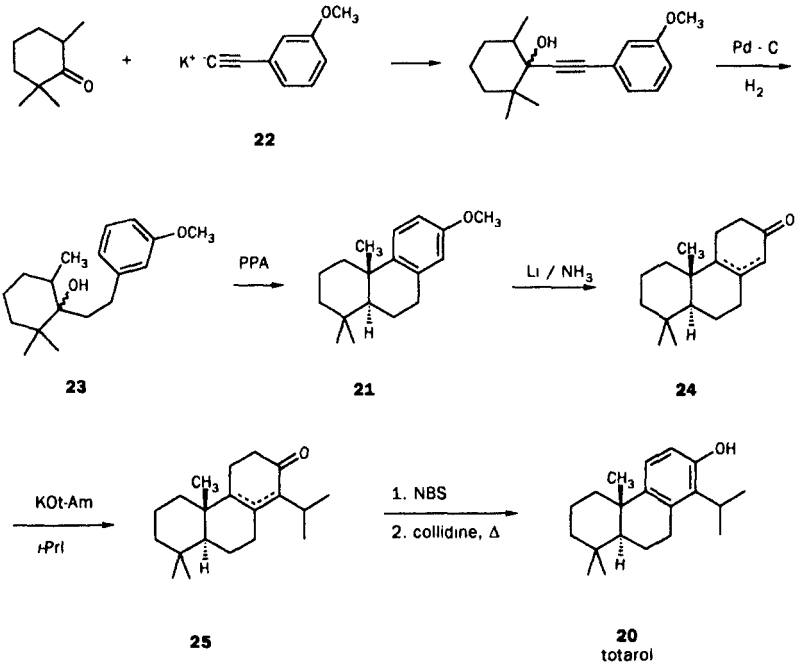


SCHEME 81. Spencer's synthesis of methyl vouacapenate.

and kaurene by Ireland and co-workers. To produce **21**, 2,2,6-trimethylcyclohexanone is reacted with the potassium acetylide **22**. The resulting acetylenic alcohol is reduced to **23**, which is then subjected to acid-catalyzed cyclization to form **21**. The *cis* isomer of **21** is not observed. Birch reduction of **21** results in a mixture of enones, **24**. The mixture is alkylated to form enones **25** and this mixture in turn is aromatized by a bromination–dehydrobromination step to yield totarol, **20**.

"16" (19)-Hydroxytotarol and Macrophyllic Acid

The totarol derivatives, "16"-hydroxytotarol (more properly called 19-hydroxytotarol) **26** and macrophyllic acid **27** were prepared by Day[134] at

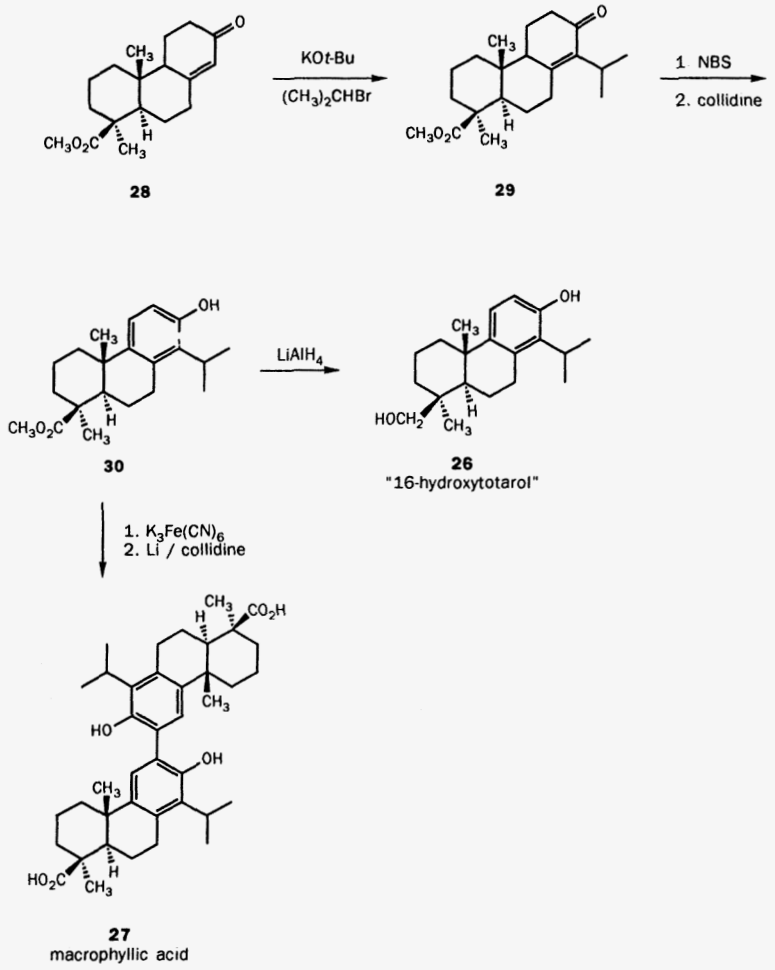


SCHEME 82. Barltrop's synthesis of totarol.

Oxford. The starting material (Scheme 83) is the enone ester **28**, used here as a relay from naturally occurring sources but having been synthesized previously by Barltrop and Day.[35] Alkylation of **28** with isopropyl iodide affords ketone **29**, which upon bromination–dehydrobromination affords the totarol carboxylic ester **30**. Reduction with lithium aluminium hydride yields the hydroxytotarol **26**, while oxidative coupling of **30** in the presence of ferricyanide affords a diester which is hydrolyzed to yield macrophyllic acid, **27**.

Dispermol, Dispermone, and Maytenoquinone

Three other naturally occurring totarane derivatives, dispermone, **31**, dispermol, **32**, and maytenoquinone, **33**, have been synthesized by Matsumoto and Usui.[135–137] Starting from α-cyclocitral (Scheme 84) the tricyclic skeleton is constructed by classical acid-catalyzed cyclization chemistry. Thus Wittig condensation of the aldehyde **34** with **35** followed by reduction gives the cyclization substrate **36**. This on treatment with Lewis acid gives tricyclic material but, not unexpectedly, the product is a mixture of roughly equal amounts of *cis*- and *trans*-**37**. Only the *trans*-isomer is useful for further

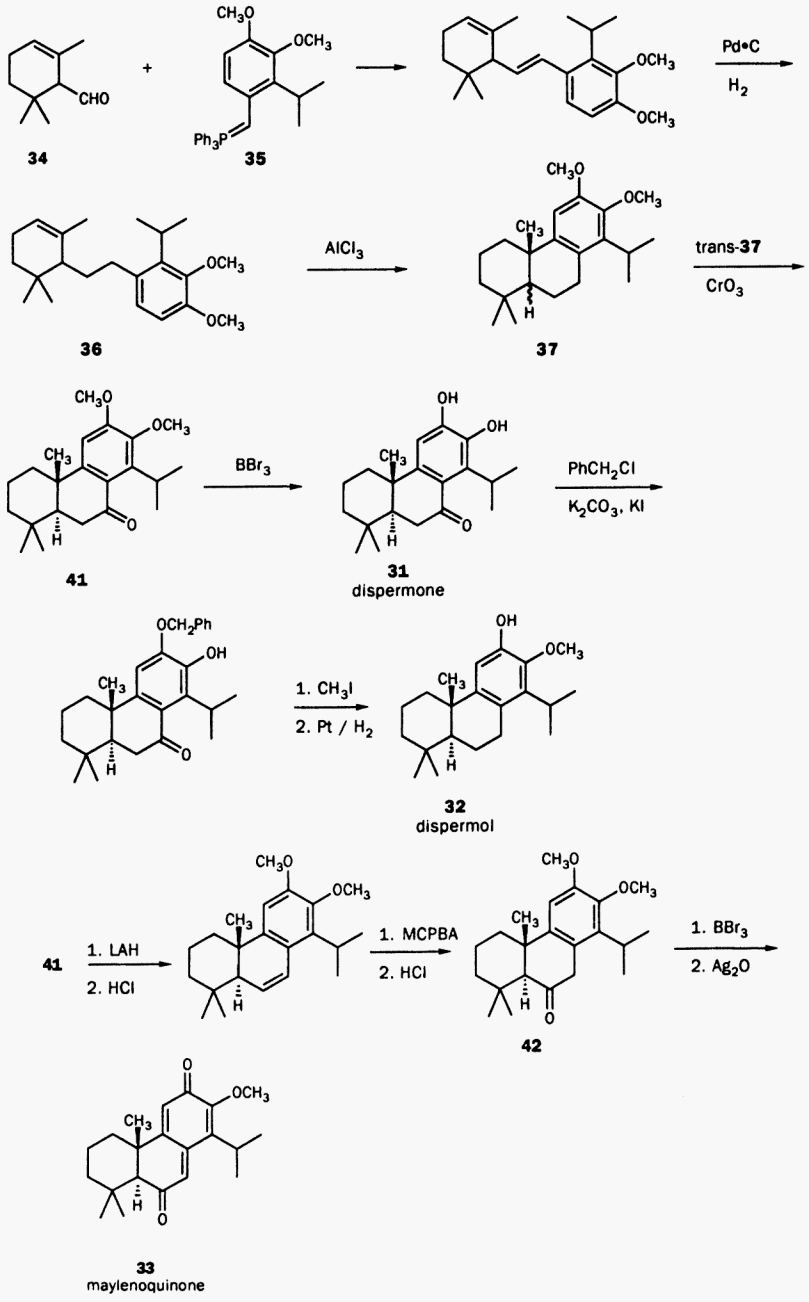


SCHEME 83. Day's synthesis of "16-hydroxytotarol" and macrophyllic acid.

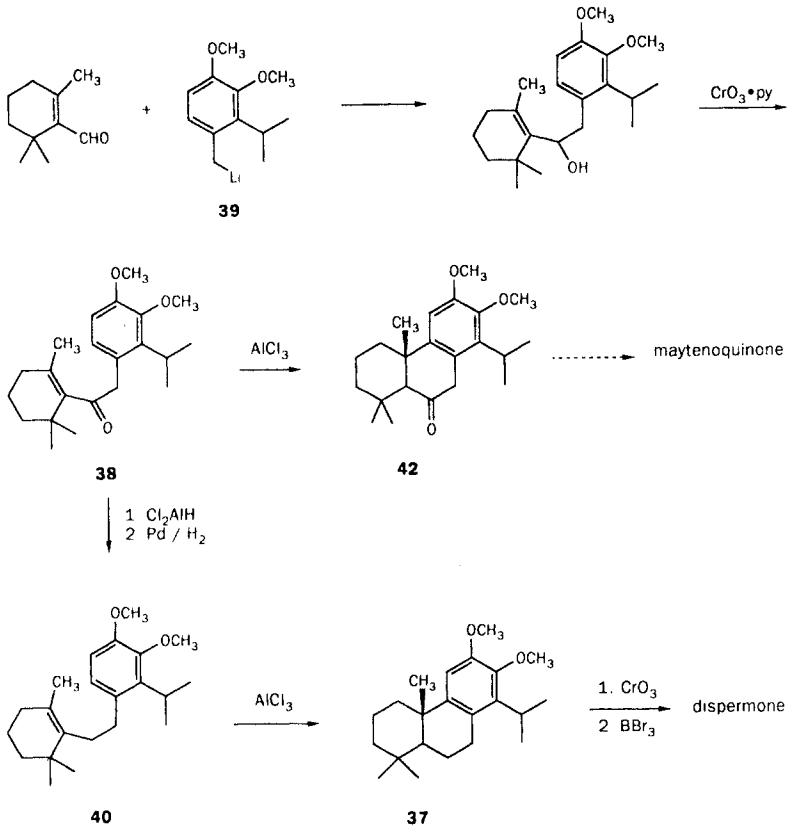
synthetic efforts and it is transformed via a standard oxidation and ether cleavage sequence to dispermone, **31**. In an earlier approach to these compounds, (Scheme 85) ketone **38** is prepared by the addition of benzyl lithium **39** to β-cyclocitral followed by oxidation. Hydrogenation of **38** to **40** followed by cyclization again affords tricyclic ether **37**.

Dispermone (Scheme 84) is selectively benzylated, methylated, and reduced to afford dispermol, **32**.

A third natural product, maytenoquinone, **33**, is prepared from ketone **41** (Scheme 84) by a sequence involving ketone transposition to **42** followed by



SCHEME 84. Matsumoto's synthesis of dispermol, dispermone, and maytenoquinone.

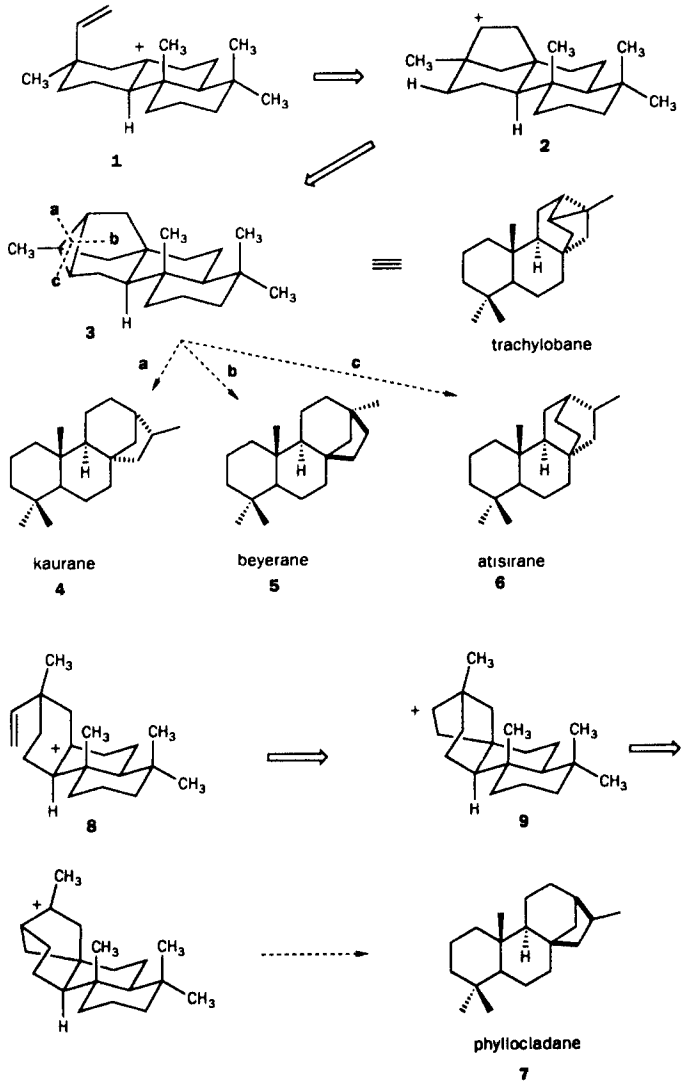


SCHEME 85. Matsumoto's first synthesis of dispermone and maytenoquinone.

ether cleavage. Quinone methide formation through oxidation with silver oxide affords maytenoquinone, **33**. In the earlier work[135] (Scheme 85), ketone **42** was generated as a mixture of isomers by cyclization of the bicyclic enone **38**.

2. TETRACYCLIC DITERPENES

The tetracyclic diterpene carbon skeletons of the kauranes, atisiranes, and beyeranes arise from the cyclization of an intermediate pimaranyl cation **1** (Scheme 86) to produce tetracyclic cation **2**. Closure of this species occurs by either formation of a protonated cyclopropropane or, as illustrated in



SCHEME 86. Structural relationships of tetracyclic diterpenes.

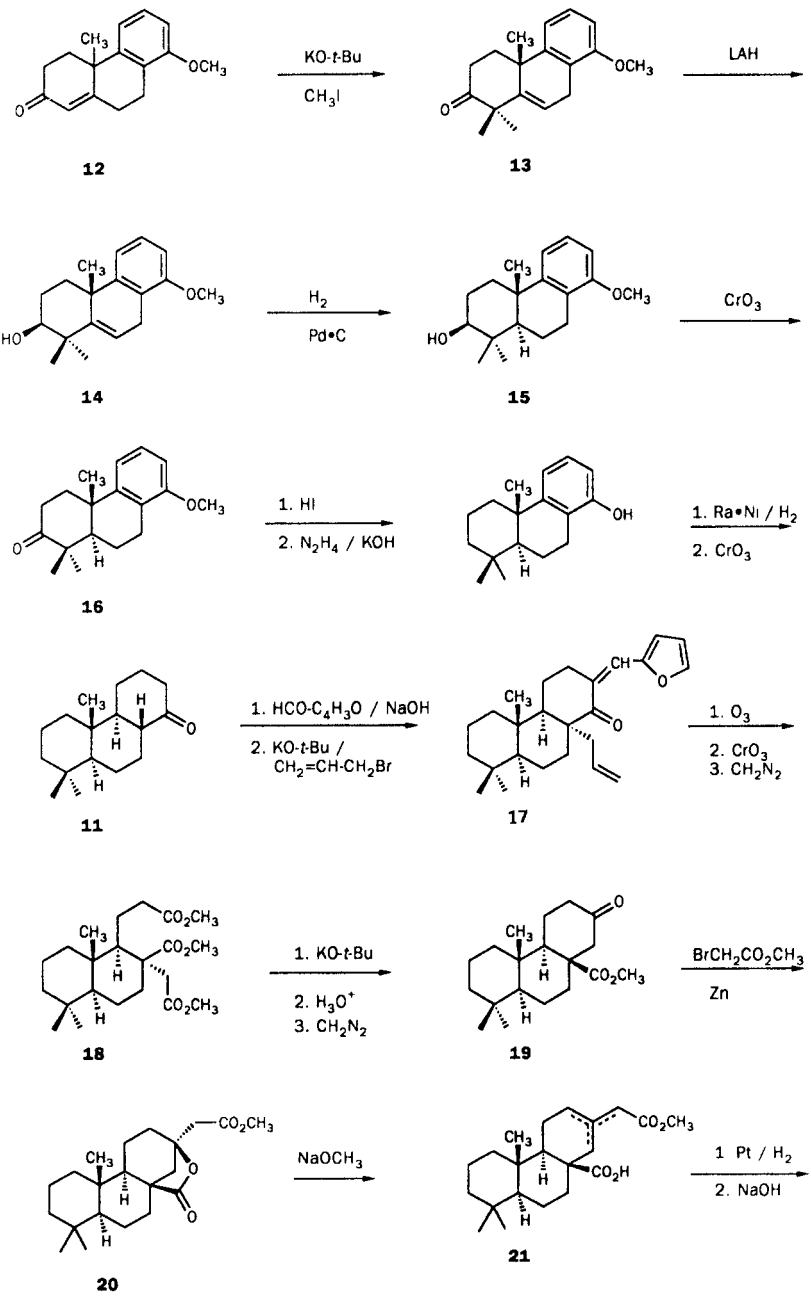
Scheme 86, by loss of a proton forming the pentacyclic hydrocarbon trachylobane **3**. The three possible cleavage modes of the cyclopropane ring then lead to kaurane **4** (path **a**), atisirane **5** (path **b**), or beyerane **6** (path **c**). Phyllocladane, **7** (a natural product skeletal type from the antipodes), results from a "down-under" cyclization of the intermediate cation **8** to form

tetracycle **9**. In contrast to kaurane, phyllocladane has a B/C *trans*-fusion rather than a *cis* one. The absolute stereochemistry among these diterpenes varies as well. Kaurene is known in both antipodal forms and the gibberellins are derived directly from the *ent*-kaurene isomer.

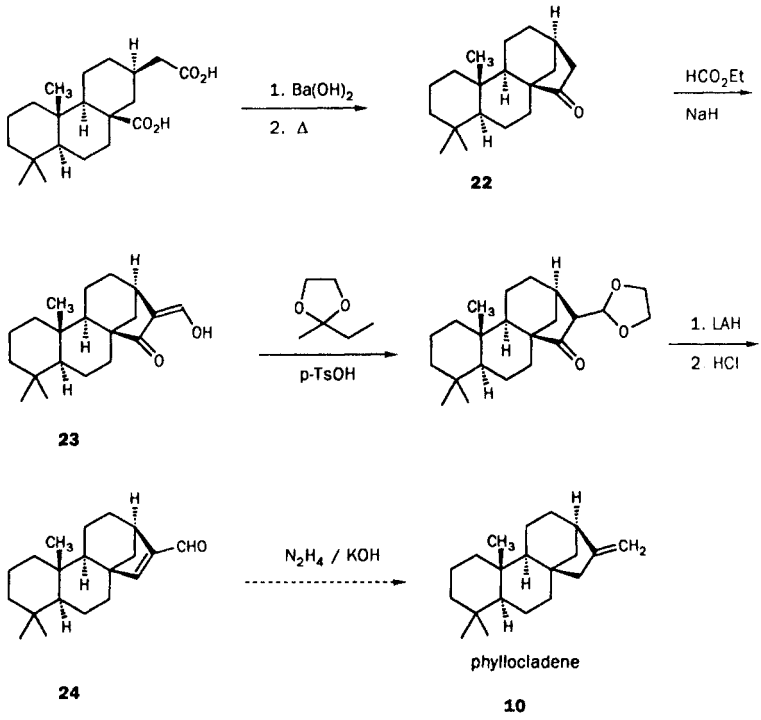
A. Phyllocladene

The first synthesis of phyllocladene, **10** (Scheme 87), by Turner and co-workers[138, 139] is a milestone in the history of stereorational diterpene synthesis. Much of the current understanding of the conformational and configurational stability relationships of perhydrophenanthrenes, analyzed by Johnson,[63] was set on a firm experimental footing by Turner. As for the synthesis of phyllocladene itself, it is based on the preparation of a key tricyclic ketone intermediate, **11**, starting from the Robinson–Cornforth ketone,[61] **12**, and following a route which has now become routine. Methylation produces **13**, the ketone function is reduced to an alcohol, **14**, the B-ring double bond is catalytically reduced to produce a *trans*-fused product, **15**, and the ring-A oxygen is removed by oxidation followed by Wolff–Kishner reduction. The product of this last step, **16**, gave poor results using the Birch reduction technology of the time and as a consequence catalytic reduction of the corresponding phenol followed by oxidation of the resulting alcohol is carried out affording **11**. The *trans-anti-trans* stereochemistry of this intermediate, now assumed, is proven by thorough ORD analysis of resolved material and comparison to other ketones of like stereochemistry.

To provide for the construction of the fourth ring an allyl chain is added through alkylation at C-8 of the furfuylidene derivative of **11**. The alkylation reaction, however, occurs from the less-hindered face to produce **17**. The allyl group is thus incorrectly disposed to yield the correct stereochemistry for ring-D of phyllocladene. As a consequence a sequence which interchanges the ring-C, position-14, and the angular group carbon atoms for the reformation of ring-C is carried out by ozonolysis–oxidation of **17** to yield **18** followed by Claisen condensation to form **19**. Synthetic **19** is then resolved and shown to be identical to a degradation product of natural phyllocladene. The relay material is then carried back to phyllocladene by a lengthy sequence. Reformatsky addition to **19** yields a lactone **20** which is then subjected to β-elimination. The resulting mixture of olefins **21** is hydrogenated stereoselectively and a Claisen condensation seves to form the D-ring providing ketone **22**. The remaining carbon atom is now added through a formylation reaction yielding hydroxymethylene ketone **23** and following protection of the aldehyde function the remaining carbonyl group is reduced. Acid hydrolysis of the intermediate alcohol affords aldehyde **24**. Conversion of this



SCHEME 87. Turner's synthesis of phyllocladene.

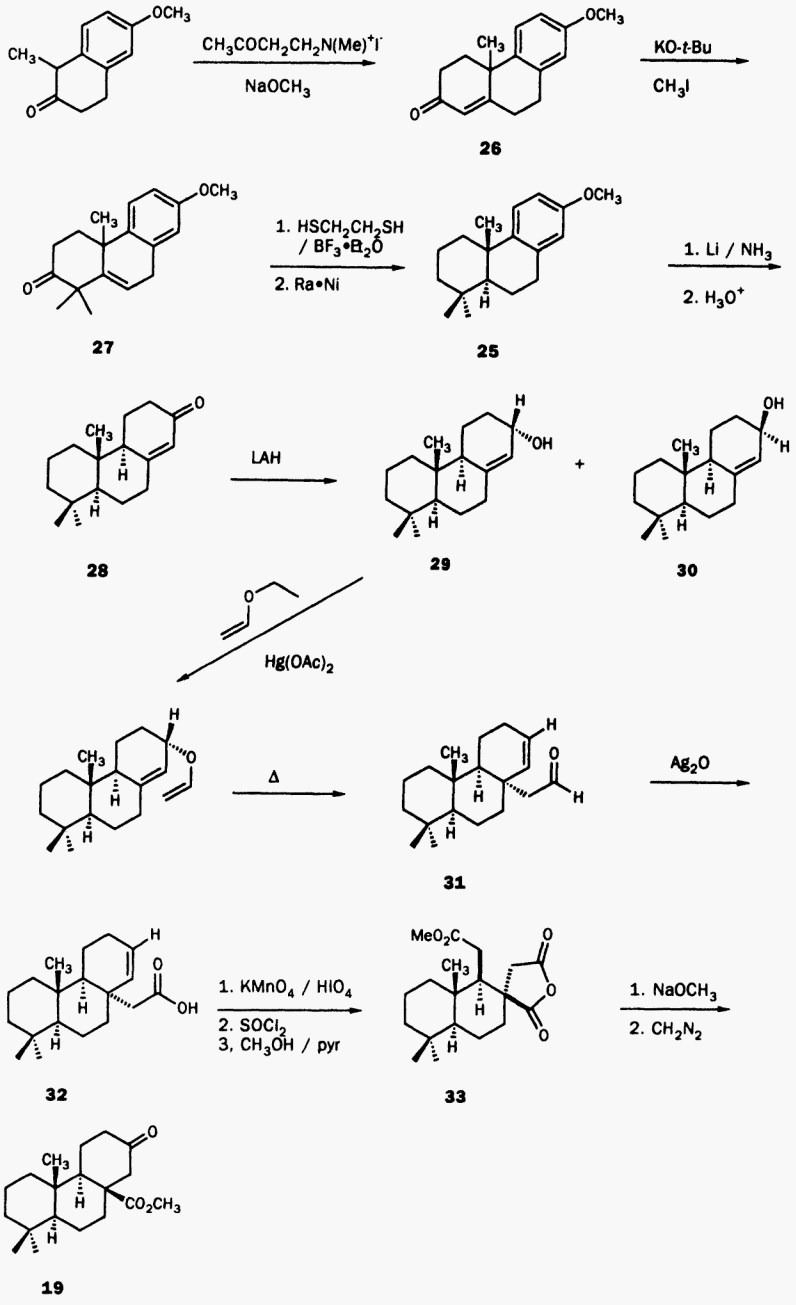


SCHEME 87. Turner's synthesis of phyllocladene (*continued*).

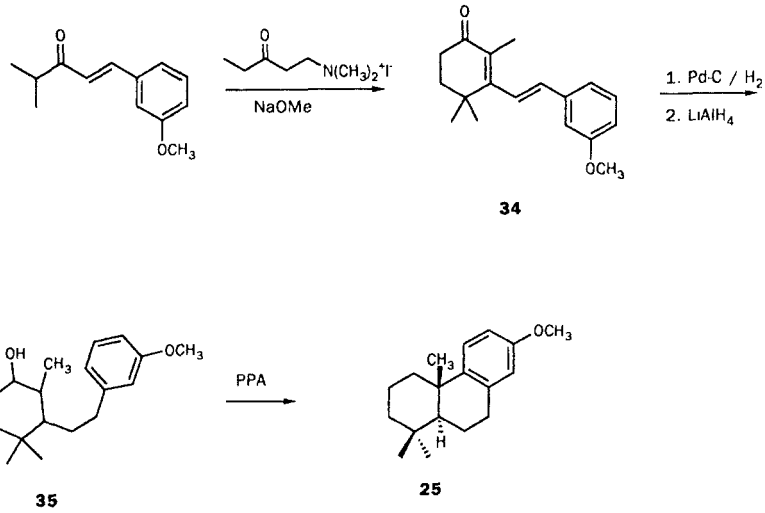
species to phyllocladene **10** under Wolff–Kishner conditions had been carried out by Briggs.[140]

A formal total synthesis of phyllocladene was carried out by Ireland and co-workers.[141, 142] Contemporaneous with Turner they prepared **25** (Scheme 89) in racemic form by a cationic cyclization route.[141] Subsequently they reported[142] a second and more efficient route (Scheme 88). In this one the often-employed enone **26** is methylated to produce **27** and a two-step reduction used to produce **25**. Following Birch reduction to form enone **28**, hydride reduction yields a mixture of alcohols **29** and **30** in a ratio of 4:1. The major product is submitted to a Claisen rearrangement sequence to produce aldehyde **31** and after oxidation to **32** the C-ring is cleaved as in the Turner approach to generate the correct stereochemistry for the angular substituent of **19**. Thus, after cleavage of the ring-C double bond and anhydride–ester formation, **33**, Claisen condensation generates the Turner intermediate **19**.

In the original Ireland route[141] (Scheme 89), enone **34** is reduced to secondary alcohol **35**. Treatment with polyphosphoric acid affords a low



SCHEME 88. Ireland's synthesis of phyllocladene.

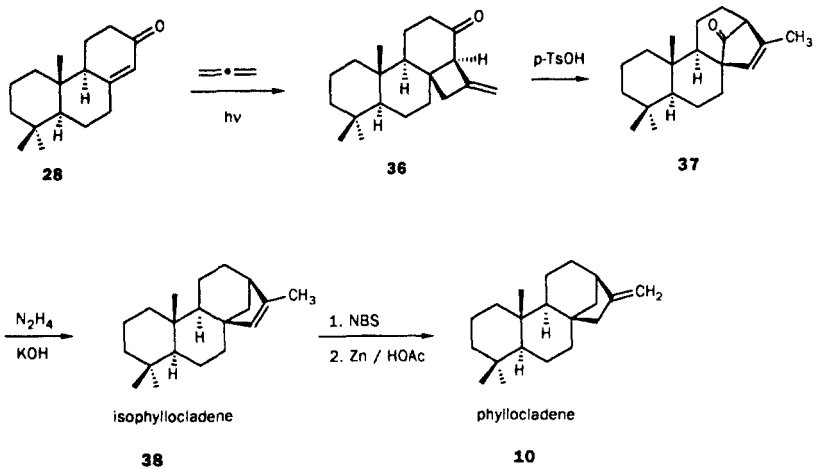


34 35 25

SCHEME 89. Alternative preparation of Ireland's intermediate for phyllocladene.

yield of **25**, accompanied by material assumed to have an A/B-*cis* configuration.

A brief synthesis of phyllocladene **10** was carried out by Fetizon, Duc, and Lazare.[143a] Starting from the frequently used tricyclic ketone **28** (in this case obtained in optically active form from manool) the "end game" (Scheme 90) is



28 36 37 38 10

SCHEME 90. Fétizon's synthesis of phyllocladene.

carried out by adding the elements of ring D in the stereo- and regioselective photochemical 2 + 2 cycloaddition of allene so frequently employed in the tetracyclic diterpene series to yield **36**. Acid-catalyzed rearrangement then affords **37**, which upon Wolff–Kishner reduction leads to isophyllocladene **38**. Though the yield of the rearrangement reaction is only 50%, the overall process is much more efficient than the longer sequences used in other syntheses. Phyllocladene, **10**, is produced by submitting **38** to an allylic bromination–reduction sequence.

Kende and Sanfillipo[144] at the University of Rochester reported a short synthesis (Scheme 91) of phyllocladene featuring a Pd(II)-mediated cycloalkenylation. The substrate for the key reaction is prepared starting from 2-allylcyclohexanone **39**. Successive Robinson annelations produce tricyclic enone **40**. Reductive methylation is used to introduce the C-4 *gem*-dimethyl group of **41** and Wolff–Kishner reduction yields diene **42**. This diene is selectively oxidized at the less-hindered allylic position producing ketone **43**, which is converted in turn into the cross-conjugated dienol silyl ether **44**. Cyclization mediated by palladium acetate forms tetracycle **45**. To complete the synthesis the enone functionality is subjected to dissolving metal-reduction conditions to yield the *trans-anti-trans*-fused ketone **46**, which upon a second Wolff–Kishner reduction yields phyllocladene, **10**.

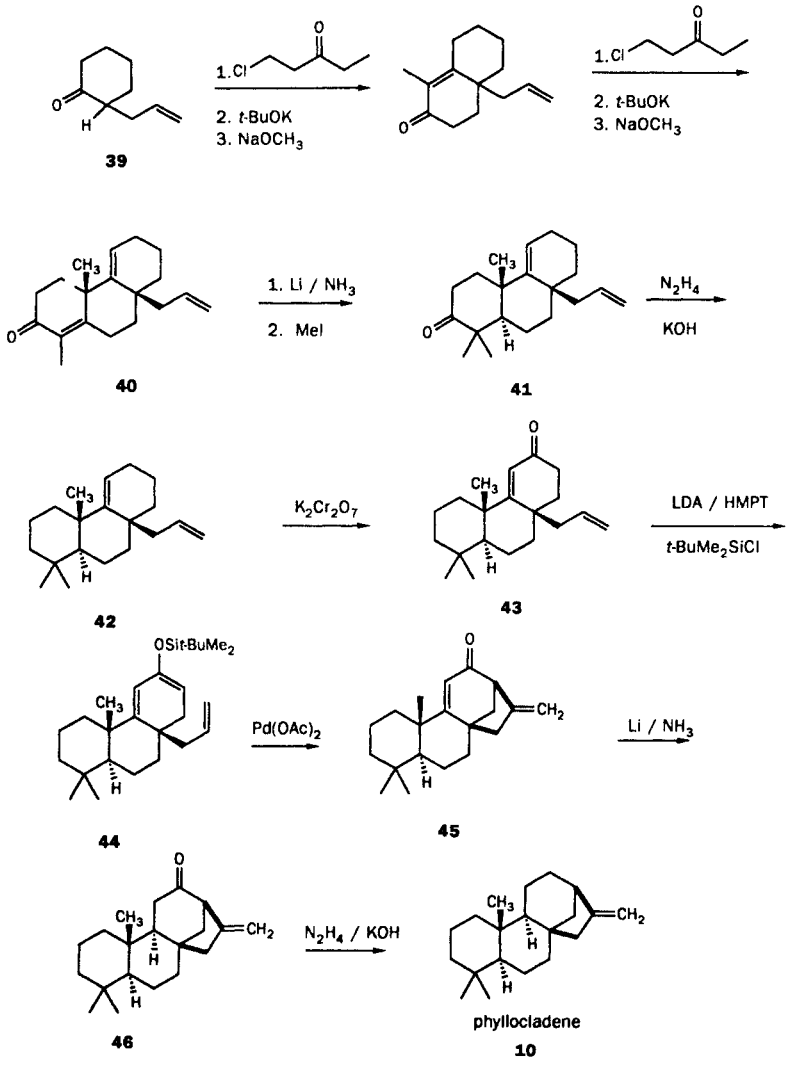
B. Kaurene

Aldehyde **31** (Scheme 89) is the key branch point for the synthesis of several diterpenes by Ireland and colleagues.[141, 142, 145, 146] For kaurene, **47** (Scheme 92), and atisirene, **48** (Scheme 96), it contains all of the necessary carbon atoms for construction of the fourth ring with the appropriate stereochemistry for the two-carbon side chain. By means of a ring closure and subsequent reopening in the opposite stereochemical sense, aldehyde **31** is also used for the synthesis of phyllocladene (Scheme 89).

For the synthesis of kaurene,[145] the aldehyde function of **31** is protected as an acetal **49**, which upon hydroboration–oxidation affords ketones **50** and **51** in a ratio of 1.6:1.

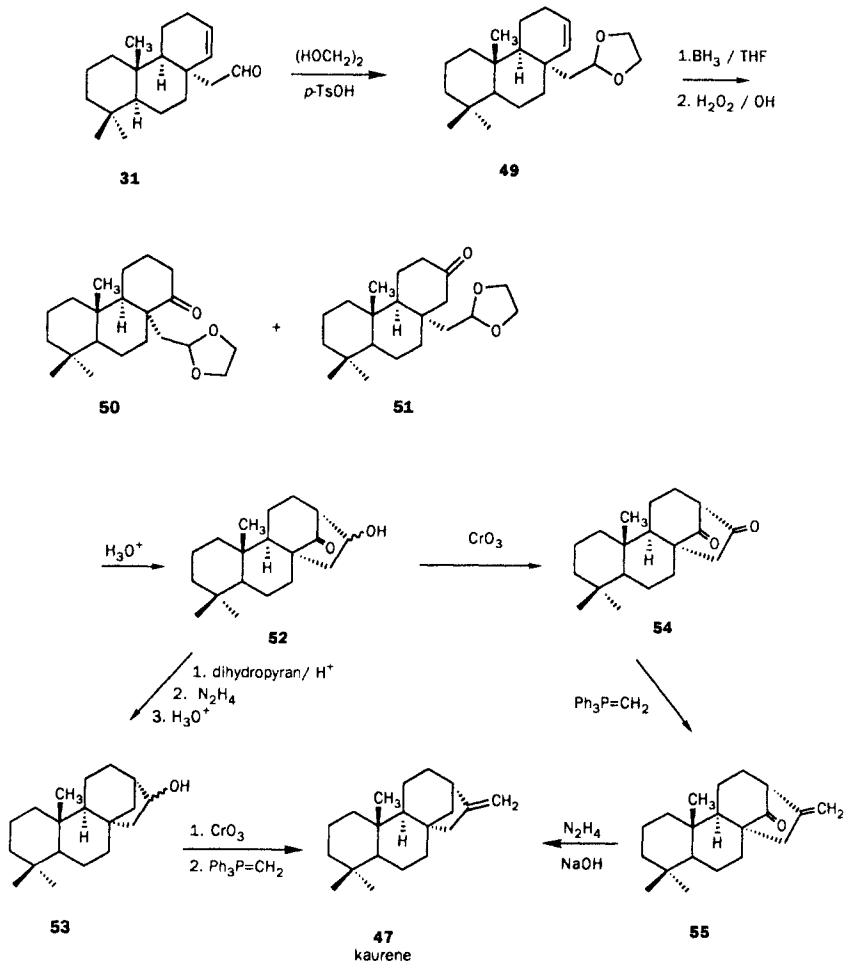
The placement of the carbonyl group of **50** at C-14 allows for closure of the kaurene skeleton by acid treatment of the ketoacetal system. The resulting aldol **52** is then converted to the natural product by two independent routes. In one the hydroxyl group is protected and the carbonyl is removed by Wolff–Kishner reduction. Hydrolysis of the protecting group restores the carbonyl function to yield **53** and Wittig methylenation affords kaurene, **47**.

In the alternative route dione **54** is produced from **52** and selectively methylenated to yield **55**. Reduction again gives kaurene, **47**.



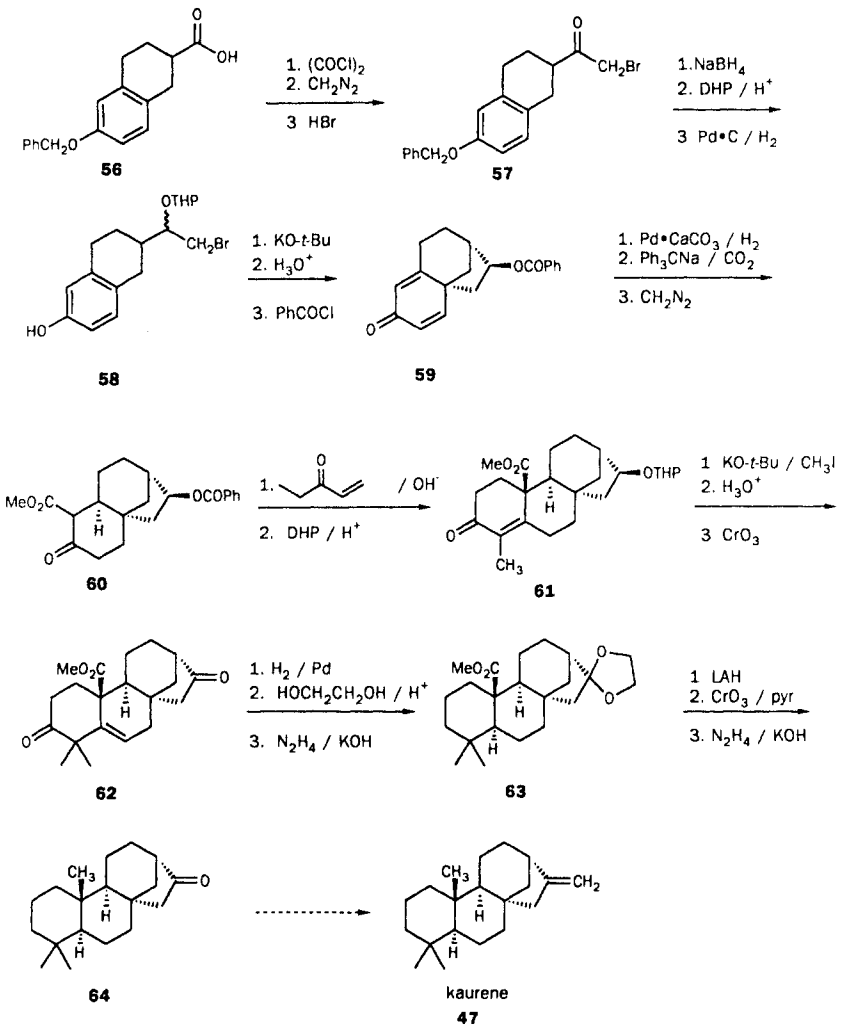
SCHEME 91. Phyllocladene synthesis by Kende and Sanfillipo.

A synthesis of kaurene (Scheme 93) by Masamune[147, 148] then at the University of Alberta employs an Ar_15 reaction for formation of the bridged-ring system. Acid **56** is converted into **57**, thence into a mixture of the protected bromohydrins **58**. When treated with base, one isomer undergoes cyclization to form dienone **59**. Following reduction the ketone is carboxylated regiospecifically and the product esterified to afford **60**. A



SCHEME 92. Ireland's synthesis of kaurene.

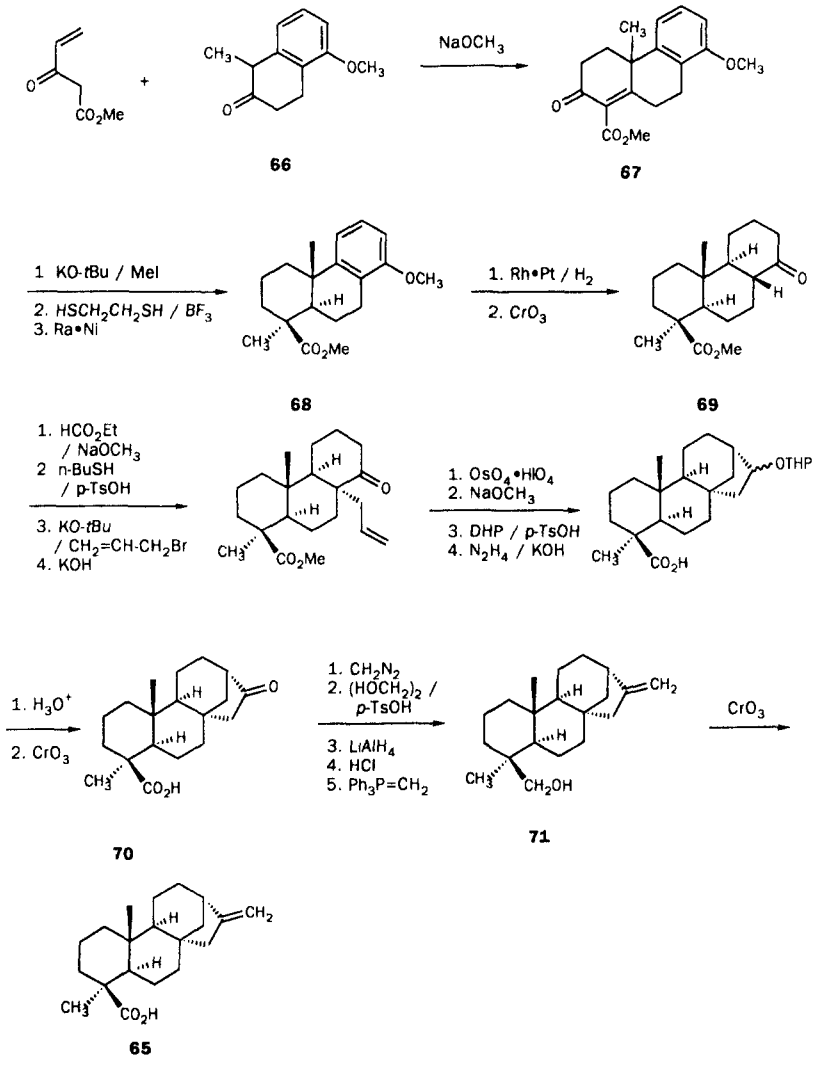
Robinson annelation sequence employing ethyl vinyl ketone yields tricyclic enone **61**. Following standard methylation, enedione **62** is obtained. Reduction, selective ketalization at the cyclopentanone carbonyl, and Wolff–Kishner reduction provides ester **63**. At this point a relay compound obtained by the degradation of veatchine is used to complete the synthesis, though no successful resolution of the synthetic material is accomplished. To achieve the kaurene synthesis the angular carbomethoxy group of optically active **63** is converted into a methyl group with the production of **64**, an intermediate employed by Ireland for the preparation of the natural product.



SCHEME 93. Masamune's synthesis of kaurene.

C. Kaurenoic Acid

The synthesis of kaurenoic acid **65** by Mori and Matsui[149, 150] (Scheme 94) follows the general approaches used previously by Wenkert and Ireland. Thus a tricyclic system is built by Robinson annelation of β-tetralone **66** to yield enone ester **67**. Alkylation followed by reduction of the double bond



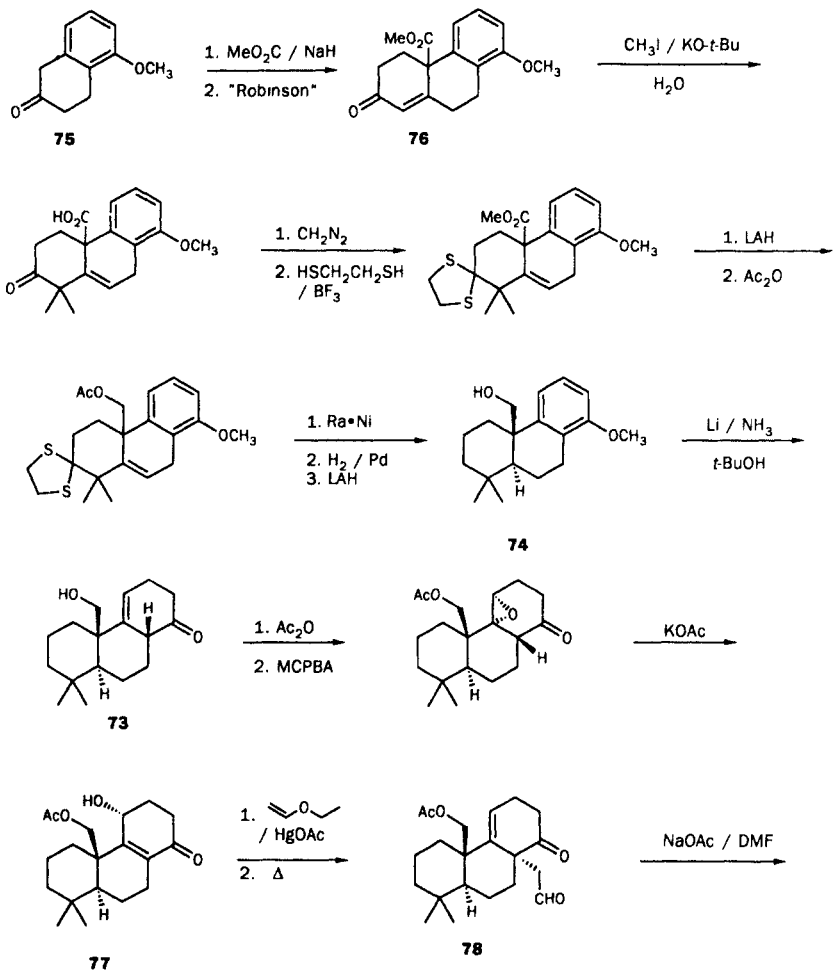
SCHEME 94. Mori and Matsui's synthesis of kaurenoic acid.

and the keto group yields ester **68**. Further reduction of the aromatic ring gives a saturated alcohol. The tricyclic ketone **69** is produced by Jones oxidation. The bicyclic C/D system is then built using the Ireland scheme by allylation of a protected ketone, cleavage of the allyl unit to give a keto aldehyde, aldol cyclization, Wolff–Kishner reduction, and oxidation resulting

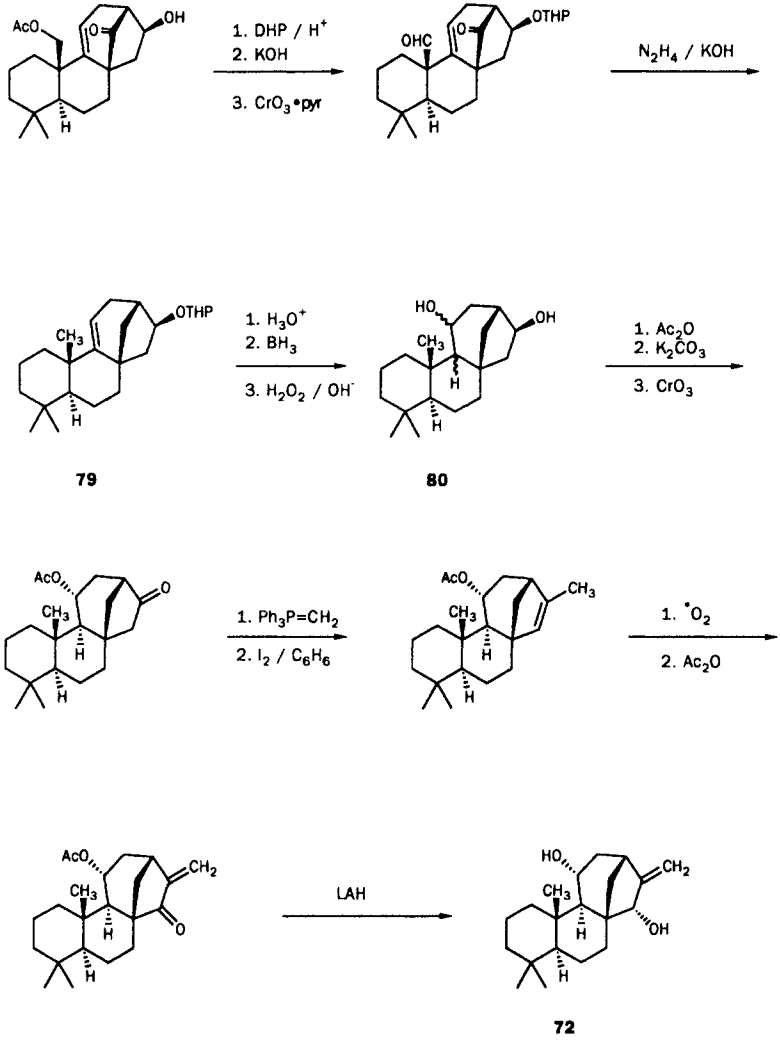
in ketone **70**. In earlier work this ester had been converted to kaureneol, **71**, and the alcohol was oxidized to kaurenoic acid **65**.

D. Kaurene-11,15-diol

In the synthesis of a kaurene-11,15-diol, **72** (Scheme 95), the key step is the regiocontrolled formation of a specific β,γ-unsaturated ketone **73** from Birch reduction of an anisole ring. Fujita and Ochiai[151] prepare methoxy alcohol



SCHEME 95. Fujita's synthesis of kaurenediol.



SCHEME 95. Fujita's synthesis of kaurenediol (*continued*).

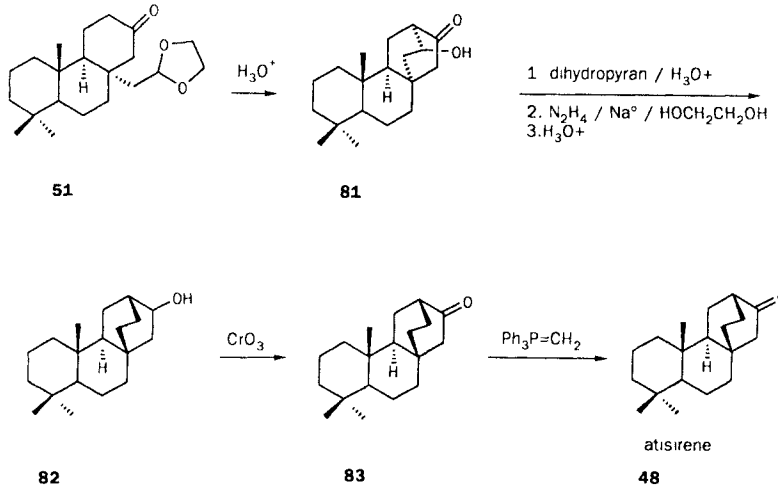
74 by standard Robinson annulation chemistry (employing *N*-piperidinobutan-3-one methiodide as the Michael acceptor) starting from 5-methoxy-β-tetralone **75**. Methylation of **76** is carried out in the presence of water, a procedure which inhibits overalkylation at C-2. The Birch reduction of **74** is controlled regiochemically by the presence of the angular hydroxymethyl group which serves as a specific protonating agent for the initially formed

radical anion. As a consequence, enone **73** is obtained in 62% yield accompanied by fully saturated products. Epoxidation and base-catalyzed elimination provides hydroxy enone **77**.

The two-carbon unit required for the five-membered D-ring is also annealed in selective fashion using the α-hydroxy group at C-11 of **77** as the directing species. The product of the Claisen rearrangement, **78**, is then carried forward to the natural product. As with many syntheses in this domain the construction of the basic tricyclic system with its appropriate stereochemistry is done in an efficient and selective fashion, but the "end game," the completion of the route, whether it be the introduction of ring-C substituents or the construction of ring D, suffers from excessive length and a lack of selectivity. Thus in the Fujita synthesis of this diol the transformation of **79** into **80** is an unselective reaction and the entire sequence is characterized by a large number of oxidations and reductions before **72** is achieved.

E. Atiserene

For atiserene, **48** (Scheme 96), the lesser product from the Claisen rearrangement–oxidation sequence used in the synthesis of kaurene, keto acetal **51**, was subjected by the Ireland group[141, 142, 146] to acid-catalyzed aldol cyclization. The product ketol **81** was then carried through the same "end-game" tactics used in the kaurene work. Thus **81** is first converted into alcohol **82** by removal of the ketone function. The remaining oxygen function

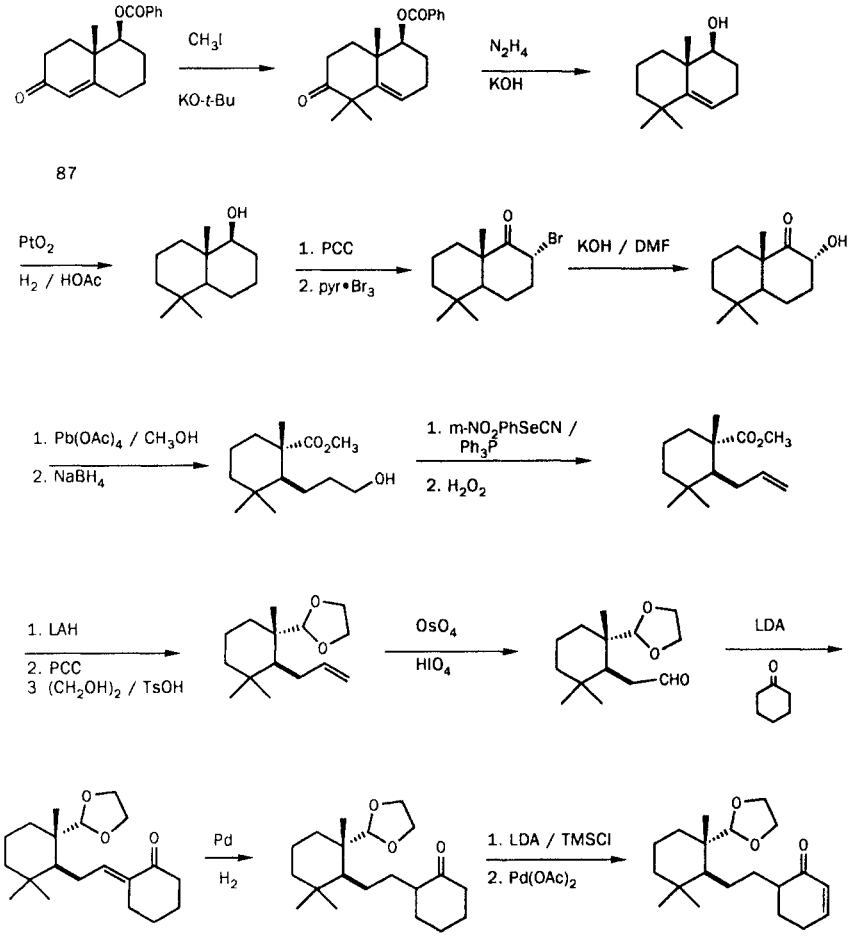


51 81 82 83 48

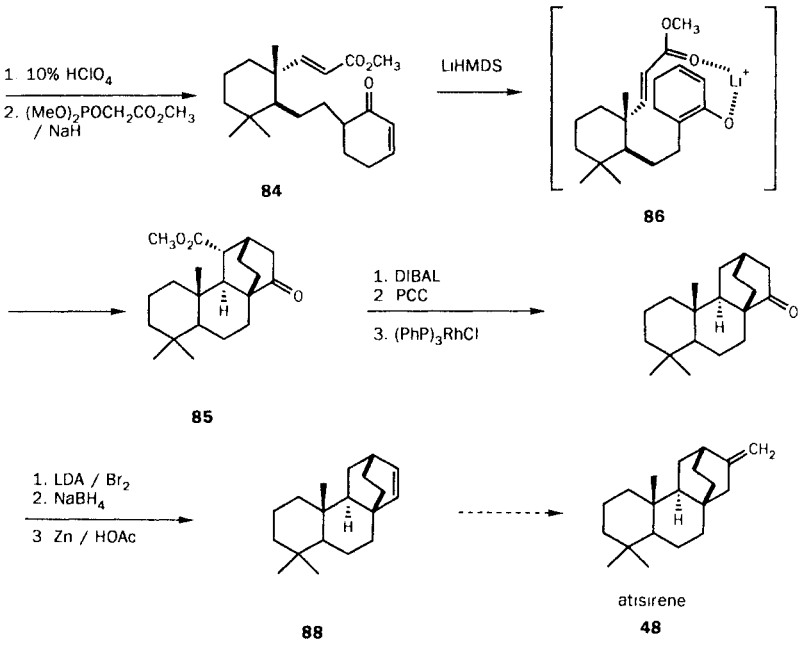
SCHEME 96. Ireland's synthesis of atisirene.

of **82** is then transformed into the exomethylene group of atiserene, **48**, by oxidation to ketone **83** and subsequent Wittig methylenation.

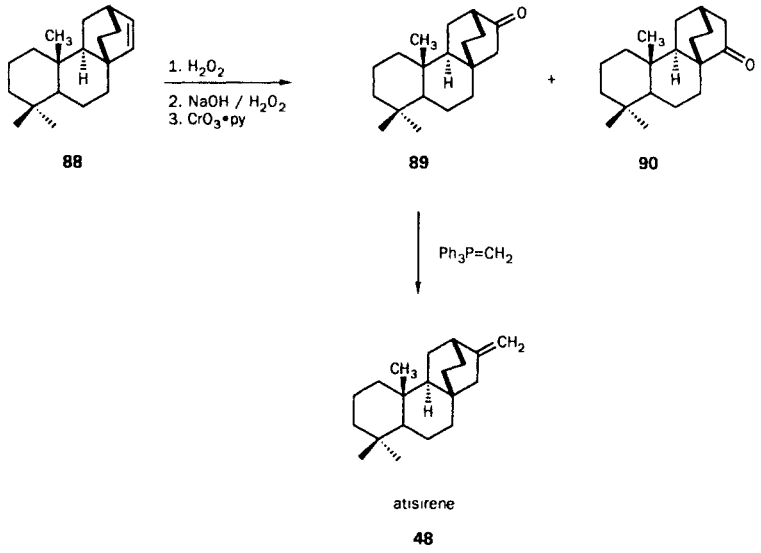
In the Fukumoto formal synthesis[152–154] of (+)-atiserene the bridged-ring system is constructed by a novel internal "double Michael" (intramolecular dienolate 2 + 4 cycloaddition) reaction (Scheme 97). Ketone **84** is converted to its lithium enolate and the latter undergoes cyclization to form **85**. The stereochemical result is attributed to a chelated lithium dienolate–ester complex **86**. Unfortunately, the route to **84** is long and requires the cleavage of the B-ring of the starting material (the optically active Wieland–Mischer ketone derivative **87**) only to reconstruct it in the double



SCHEME 97. Fukumoto's synthesis of atisirene.



SCHEME 97. Fukumoto's synthesis of atisirene (*continued*).

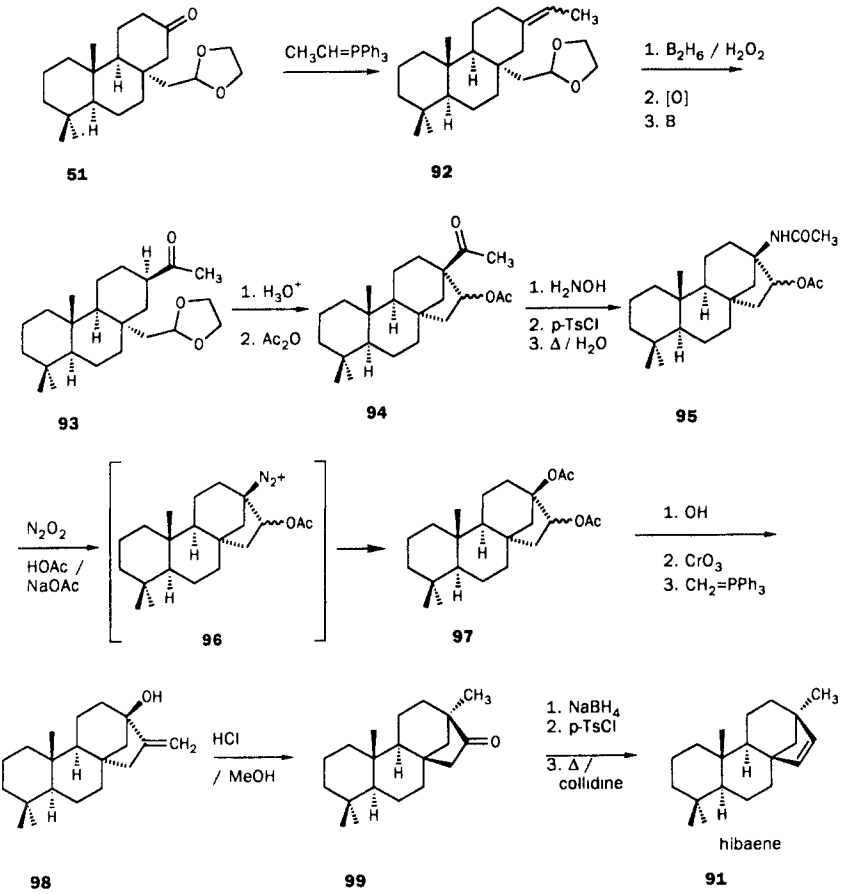


SCHEME 98. Zalkow's preparation of atisirene.

addition step. The synthesis concludes with the removal of the ester group of **85** by reductive deformylation of the derived aldehyde and conversion to olefin **88**. This substance has been converted into atiserene by Zalkow[155] (Scheme 98). Hydroboration and oxidation of **88** leads to a mixture of D-ring ketones, **89** and **90**, of which the atiserene precursor **89** is the major isomer. Wittig methylenation of **89** affords atiserene, **48**.

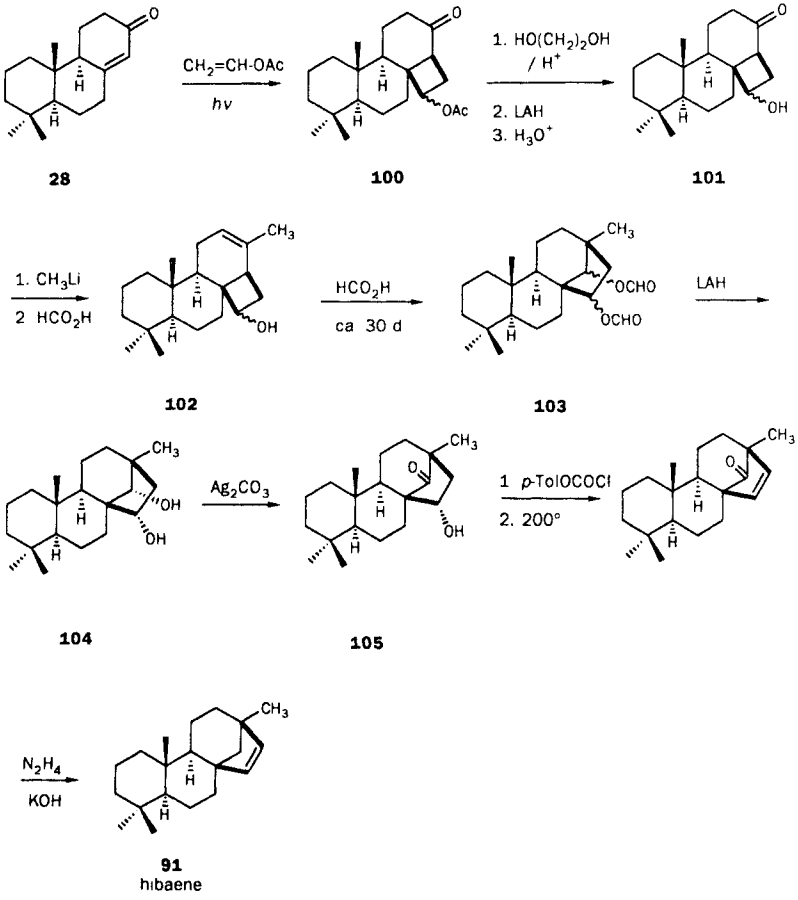
F. Hibaene

The fourth member of this general class of tetracyclic diterpenes to be synthesized by the Ireland group is hibaene, **91**. For the synthesis of this hydrocarbon (Scheme 99), Ireland and Mander[156] used the same ketoacetal,



SCHEME 99. Ireland's synthesis of hibaene.

51, employed for the synthesis of atiserene. To apply this compound to hibaene requires that the stereochemistry at C-8 be inverted and this is accomplished by rearrangement. Addition of an ethylidene Wittig reagent to **51** yields olefin **92**, which is then converted into methyl ketone **93**. Hydrolysis of the acetal function is accompanied by aldol cyclization and the product of this reaction is acetylated to give **94**. The introduction of an hydroxyl group at the bridgehead position is accomplished through a sequence involving Beckmann rearrangement to **95** and replacement of an intermediate diazonium intermediate **96** by acetate affording **97**. After conversion of the secondary acetate of **97** into the exomethylene group of intermediate **98**, the rearrangement from one 3.2.1 system into the other is effected with acid to yield ketone **99**. Last, borohydride reduction and elimination provides the natural product **91**.



SCHEME 100. Fétizon's synthesis of hibaene.

Using one enantiomer of Ireland's intermediate ketone, **28**, obtained from manool, Fetizon and co-workers[143b] synthesized hibaene **91** (Scheme 100) in a fashion similar to their route to phyllocladene. Thus photocycloaddition, in this case of vinyl acetate, affords a mixture of regio- and stereo-isomeric cyclobutyl acetates, two of which, **100**, bear the oxygen function at the position necessary for rearrangement to the hibaene skeleton. The ketone functions are next protected as the corresponding dioxolanes, the ketal acetates, are reduced to secondary alcohols, and hydrolysis then provides ketols **101**. Following methyl lithium addition and dehydration the olefin **102** is incubated with formic acid for the prolonged period of a month (August?) to yield bis-formates **103**. Diol **104**, produced by hydride reduction of one of the isomers is selectively oxidized with silver carbonate to ketol **105**, which in turn is subjected to thermolytic *cis*-elimination and Wolff–Kishner reduction to yield hibaene, **91**.

G. Stachenone

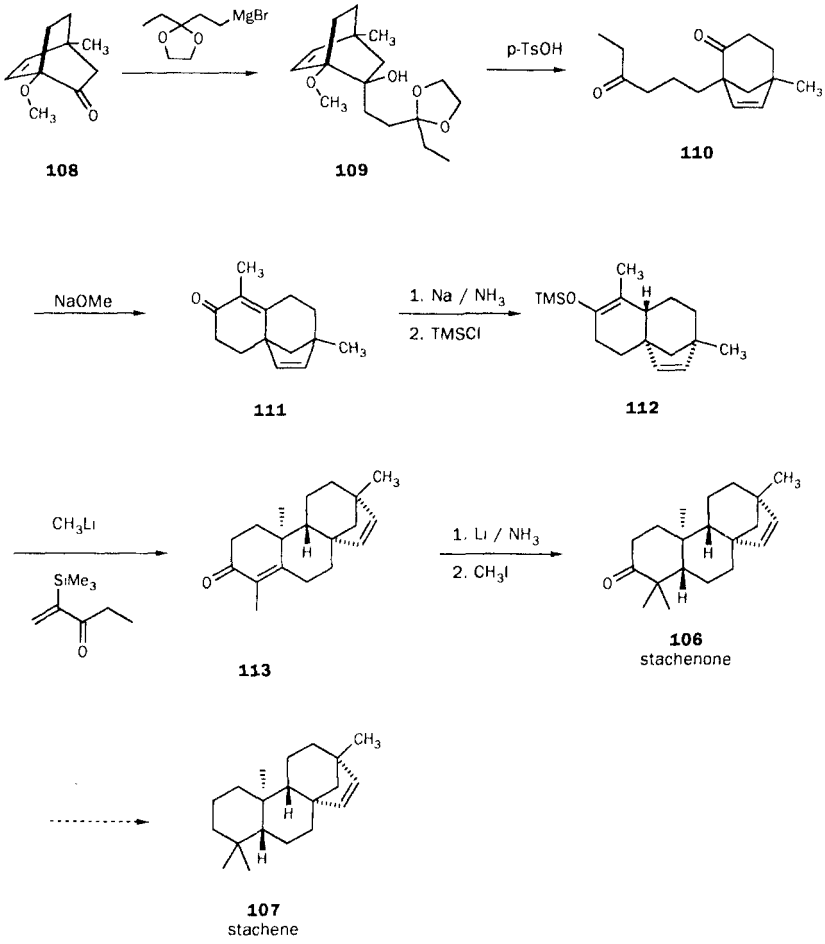
Stachenone **106** is derived from stachene, **107**, the naturally occurring enantiomer of (–) hibaene. The synthesis of **106** by Monti[157] differs from other syntheses in the kaurene–hibaene series in that it starts with the construction of a bridged bicyclic C/D ring unit and then proceeds with the addition of rings B and A.

The starting material **108** (Scheme 101) is the Diels–Alder derived bicyclic ketone of Evans[158] which is converted by Grignard addition to tertiary alcohol **109**. The alcohol is then rearranged in the presence of acid to afford diketone **110**, the ketal unit suffering hydrolysis during the course of the reaction. The diketone is then cyclized in the presence of base to afford **111**.

Lithium–ammonia reduction of **111** leads principally to the production of an A/B *trans*-fused system and it is isolated as enol ether **112**. Regeneration of an enolate from **112** with methyl lithium, Michael addition of a silyl enone, and aldol cyclization affords tetracyclic ketone **113** in 65% yield. Reductive alkylation of the latter then yields racemic stachenone, **106**. A formal total synthesis of stachene, **107**, is also achieved since the ketone had been previously converted to the parent hydrocarbon.[159]

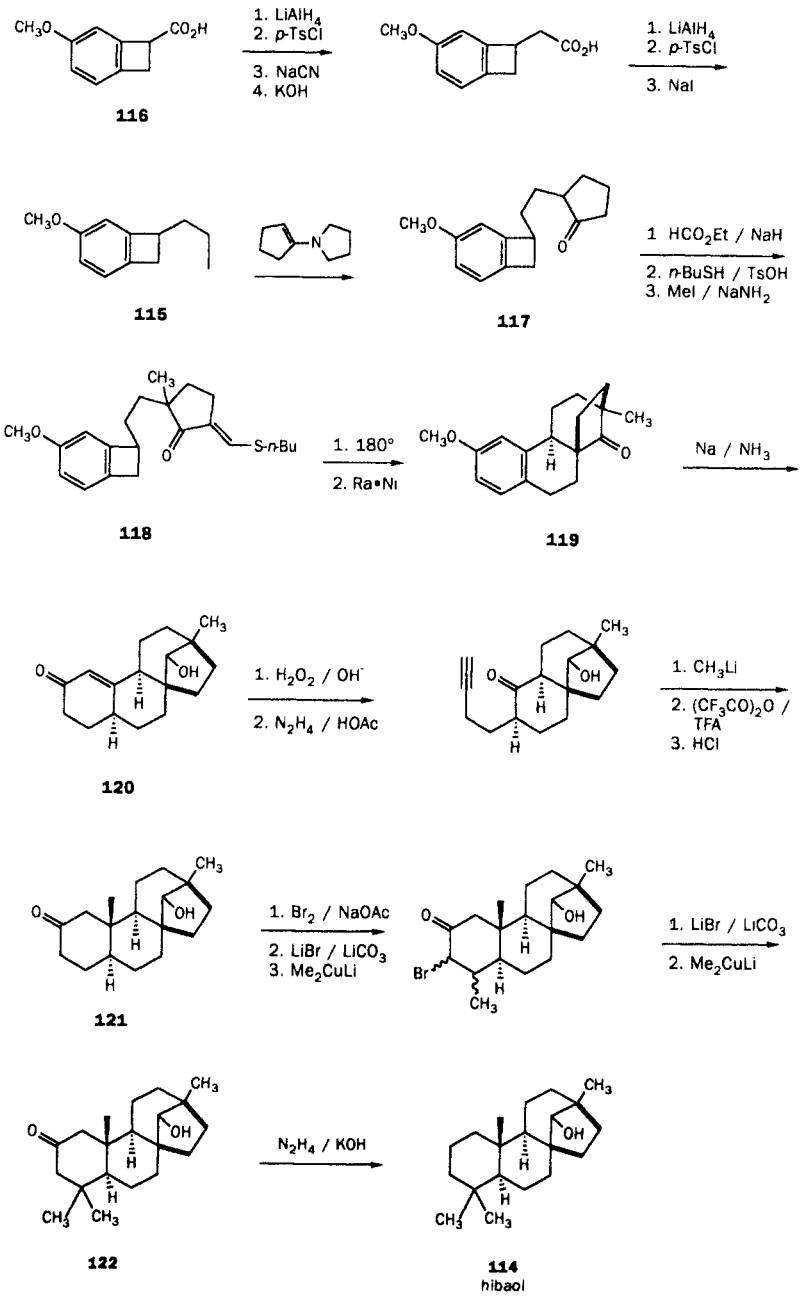
H. Hibaol

Kametani and co-workers[160] at Tokyo have employed their *o*-quinonedimethide cycloaddition methodology to a synthesis of hibaol, **114** (Scheme 102). Benzocyclobutenyl iodide, **115**, is prepared by homologation of **116** and



SCHEME 101. Synthesis of stachenone by Monti.

caused to react with the enamine of cyclopentanone to provide ketone **117**. A thiobutylmethylene group is added to one α position of the ketone function to provide both a blocking group and the dienophile portion of the intended intramolecular Diels–Alder reaction. After methylation at the α' position ketone **118** is obtained. The skeleton of the tetracyclic system is then created in a single step when **118** is heated to produce **119**. This very rapid and efficient construction of the ring system is followed, however, by a lengthy series of transformations required to place three methyl groups in a saturated ring-A. Since conjugate addition of a methyl group to the enone double bond of **120** would almost certainly result in the wrong stereochemistry at C-10, a



SCHEME 102. Kametani's synthesis of hibaol.

sequence involving Eschenmoser cleavage, methyl lithium addition, and reconstitution of the A-ring is required to produce an A/B-*trans* intermediate **121**. Since the carbonyl group of this substance is inappropriately placed for simple alkylation to yield the hibaol structure it is necessary to twice introduce a 3,4-double bond and add the two remaining methyl groups by cuprate addition. Removal of the keto function of **122** affords hibaol, **114**.

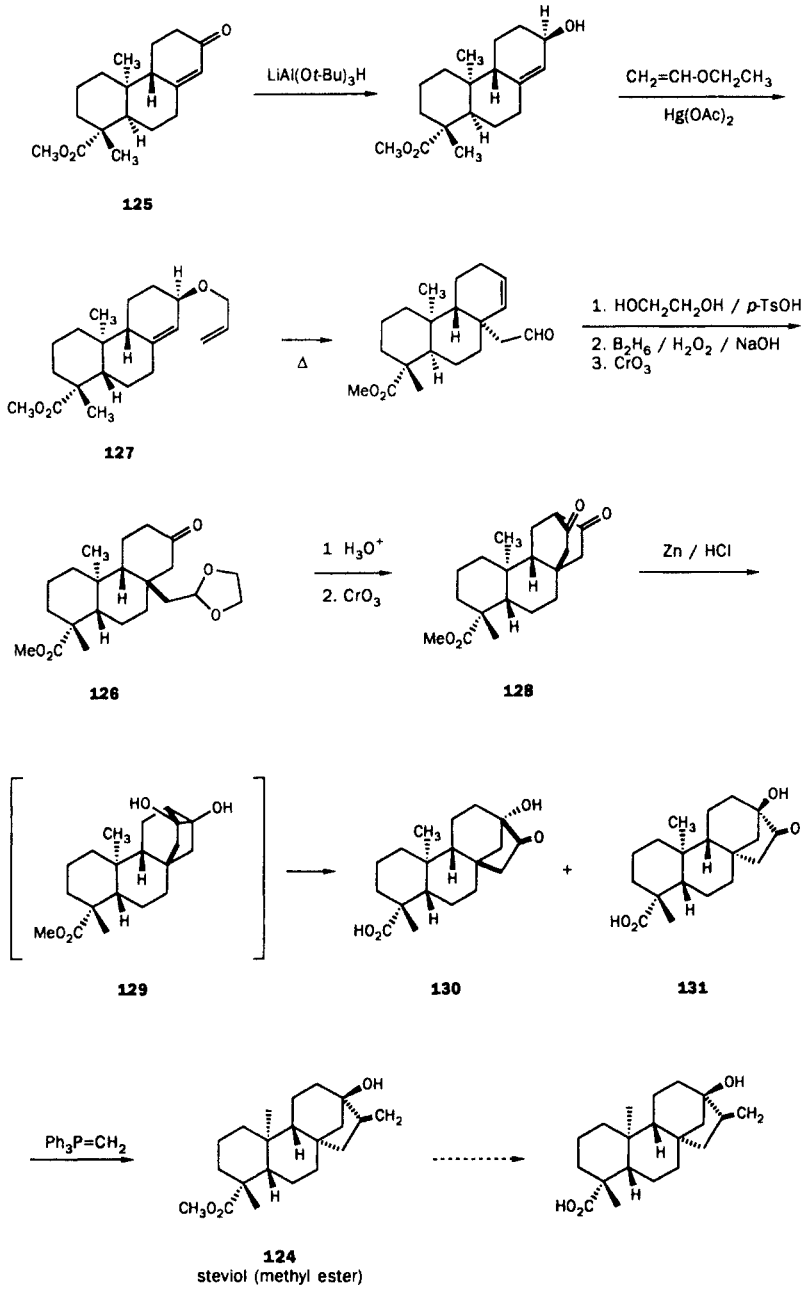
I. Steviol

Steviol, **123** (Scheme 103), has been of interest as a synthetic target principally for its similarity to several of the gibberellins. The C/D-ring system of steviol, a hydroxylated methylenebicyclo[3.2.1]octane, is identical to that of gibberellic acid, but the remainder of the molecule poses fewer synthetic problems than do the structures of the more complex gibberellin compounds.

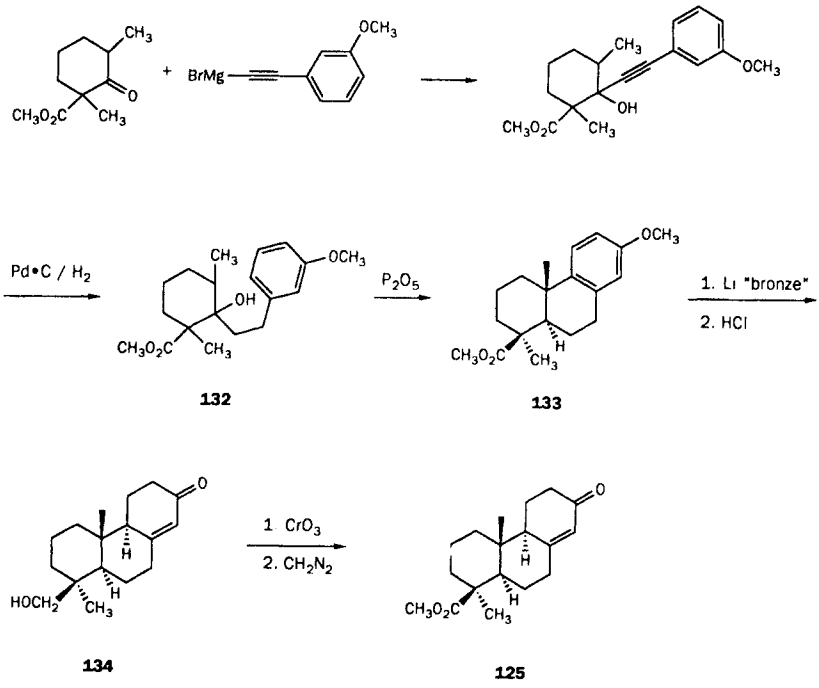
The first synthesis (Scheme 103) of steviol as its methyl ester **124** by Mori, Nakahara, and Matsui[36, 161, 162] employs the tricyclic enone ester **125** prepared by Barltrop and Day.[35] Following the approach used by the Ireland group, **125** is converted into keto-acetal **126** by Claisen rearrangement of vinyl enol ether **127**, followed by acetal formation and a hydroboration–oxidation sequence. The hydroboration reaction affords, after Jones oxidation, a mixture of C-12 and C-13 ketones in which the desired product **126** predominates in a ratio of 5:1. The acetal function of **126** is hydrolyzed and the resulting ketoaldehyde undergoes acid-catalyzed aldol condensation. Oxidation provides bridged bicyclic diketone **128**. Reductive closure of **128** is carried out with zinc and from the putative intermediate **129** a mixture of ketols **130** and **131** is obtained. Isomer **130** upon methylenation affords steviol methyl ester, **124**.

In the original preparation of enone **125** by Barltrop and Day[35] (Scheme 104), the critical cyclization reaction of **132** affords roughly equal measures of the "podocarpane" isomer **133** and its C-4 epimer. Following separation of the isomers the aromatic ring of **133** is reduced with lithium "bronze" in ammonia with concomitant reduction of the C-4 carbomethoxy group to a primary alcohol function. This product, **134**, upon oxidation and esterification yields **125**.

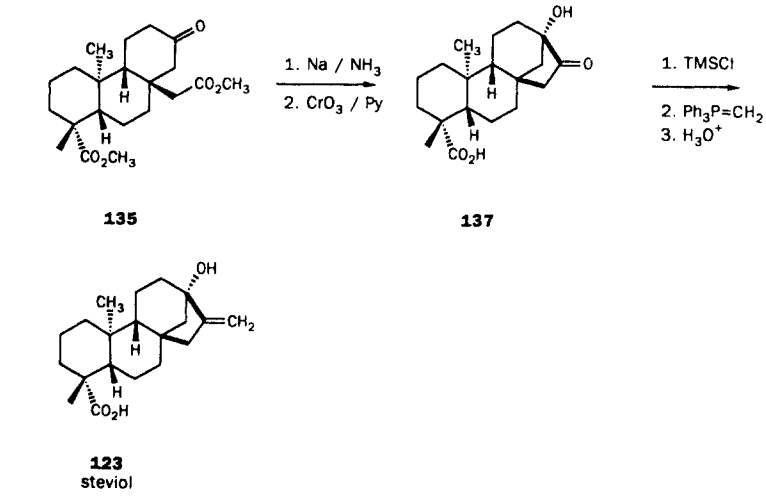
A formal synthesis of steviol **123** was carried out by Cook and Knox[163] using **135** as the starting material (Scheme 105). This keto ester was obtained by degradation of kaurenoic acid, but it had been prepared by oxidation of **136** by Mori and Matsui[161] (Scheme 106). To convert **135** to steviol it is treated with sodium in ammonia in an acyloin-like condensation. Among the products of this reduction is a dihydroxy acid which upon oxidation affords



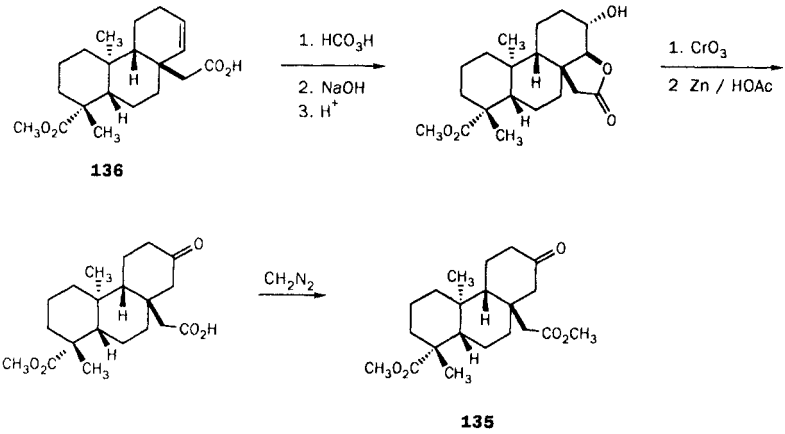
SCHEME 103. Mori's synthesis of steviol methyl ester.



SCHEME 104. Synthesis of the Barltrop–Day enone.



SCHEME 105. Cook's synthesis of steviol.



136

135

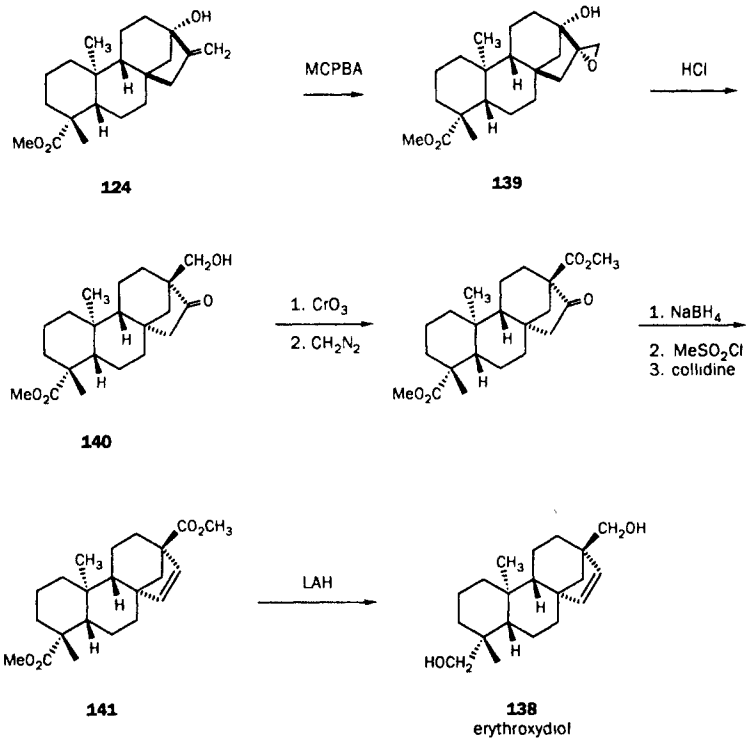
SCHEME 106. Mori's synthesis of an intermediate for steviol.

ketol **137**. Protection of the hydroxyl group as a silyl ether followed by Wittig methylenation and deprotection yields steviol, **123**.

Having synthesized steviol, Mori and co-workers[164] used the natural product as the starting material (Scheme 107) for the synthesis of erythroxydiol, **138**. Thus steviol methyl ester, **124**, is epoxidized and the product, **139**, is subjected to acid-catalyzed rearrangement to yield hydroxymethyl ketone **140**. Manipulation of the two oxygen functions affords a very low yield of ester **141**, which upon reduction yields erythroxydiol, **138**.

Using the Wiesner allene photocycloaddition protocol[165–169] for formation of the C/D ring system Ziegler and Kloek at Yale carried out a synthesis of steviol (Scheme 108). The Barltrop–Day acid **142**[35] is prepared by a new sequence starting from Hagemann's ester. The thermodynamically favored isomer of ketone **143**, the first tricyclic intermediate, has a *cis*-A/B fusion, but Wittig condensation of the ketone with methoxymethyltriphenyl phosphorane affords only the *trans*-fused product **144**. The *cis* isomer **143** is sufficiently slow to react that when the Wittig process is run under equilibrating conditions, only the minor *trans*-isomer of the ketone forms the product olefin, **144**. This effect has also been reported[170] by Huffman at Clemson in the synthesis of diterpene intermediates.

Following Wittig olefination to introduce a C-4 carbonyl group and oxidation to acid **145**, Birch reduction of the aromatic ring provides enone **142**. Removal of the C-ring oxygen under Wolff–Kishner conditions converts **142** into olefin **146a**. Ozonolysis and aldol recyclization through the derived enamine then affords cyclopentene carboxaldehyde **146b**. When the allene photocycloaddition reaction is applied to this enal, a methylene cyclobutene

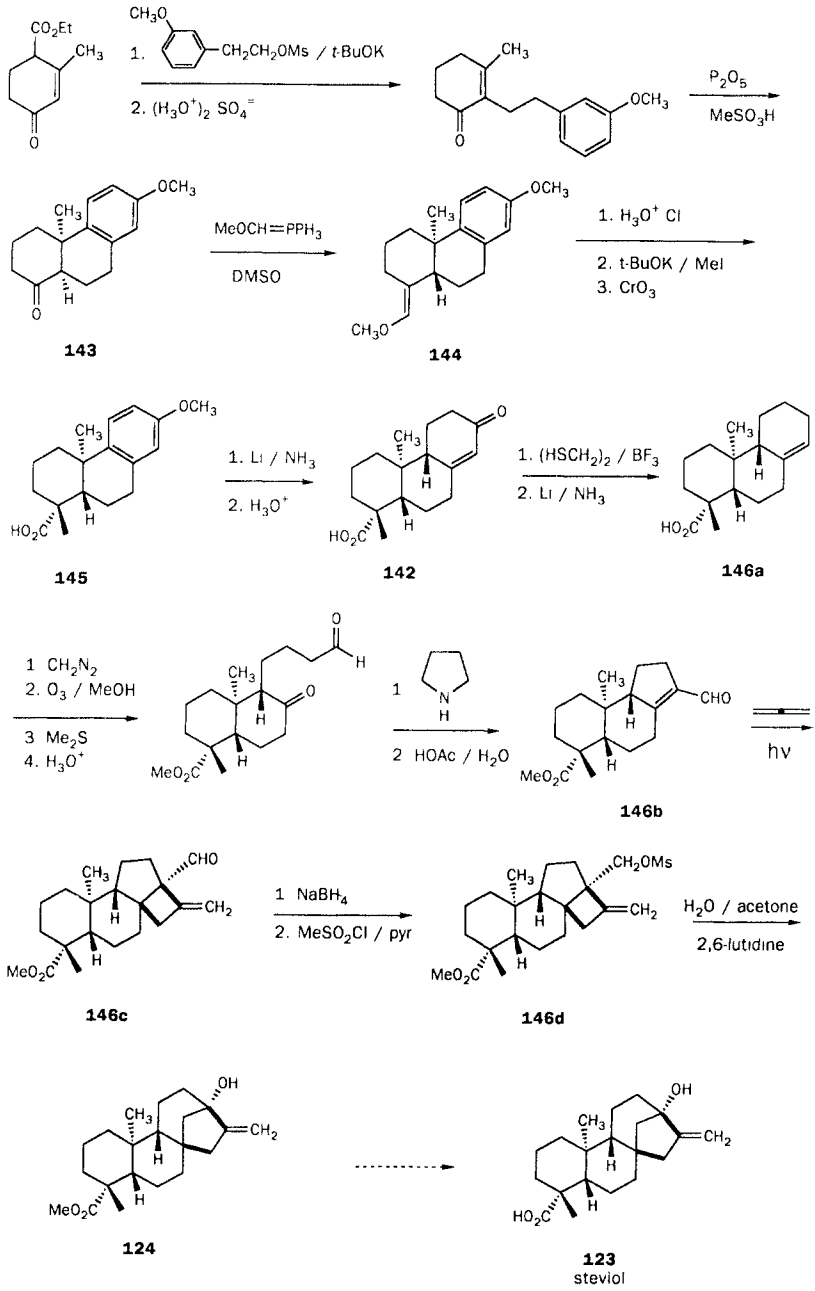


SCHEME 107. Mori's synthesis of erythroxydiol.

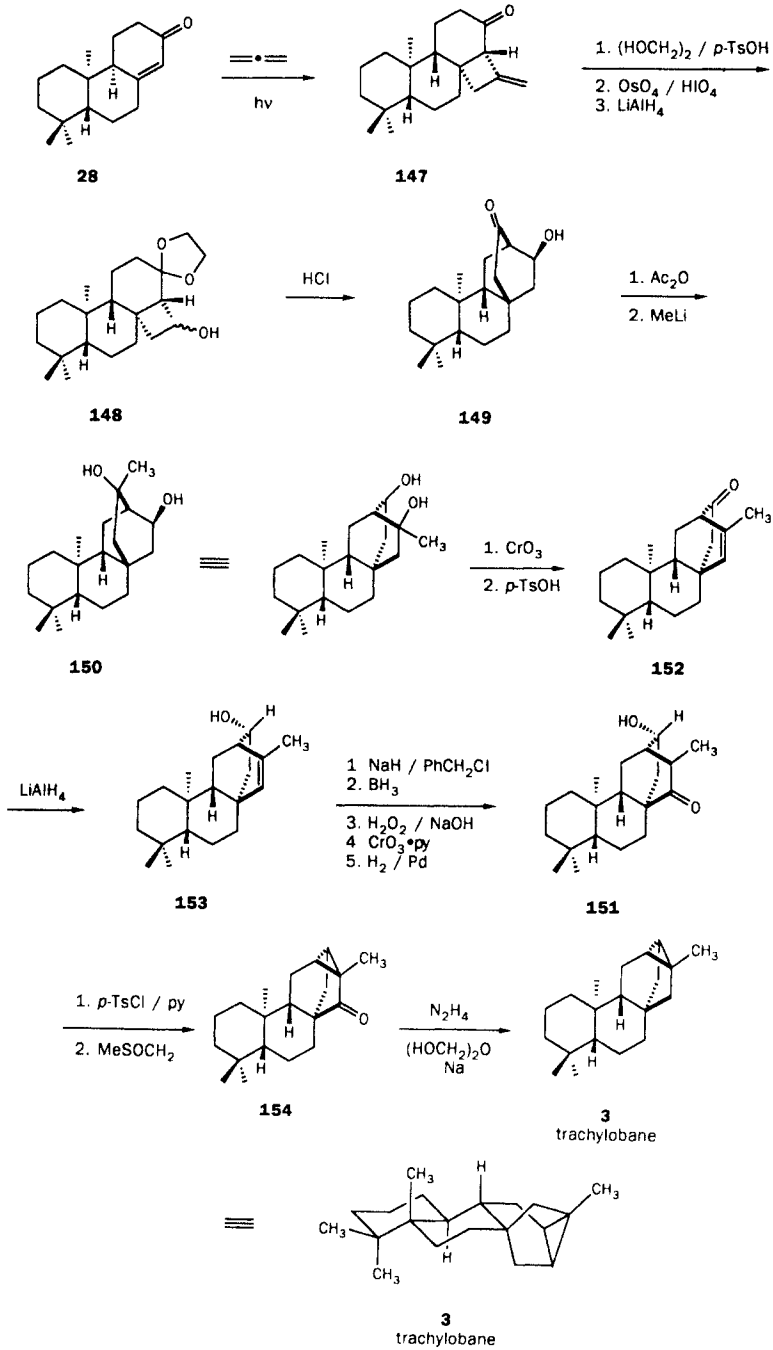
146c with the desired stereochemistry is obtained as the major product. The aldehyde group of **146c** is reduced, followed by conversion of the resulting hydroxy compound to mesylate **146d**. Solvolysis of the mesylate does yield steviol methyl ester, **124**, but unfortunately in only 3% yield.

J. Trachylobane

Trachylobane, **3**, for the purposes of this review an "honorary" tetracyclic diterpene, is the central compound in the structural relationship of kaurane, atisirane, beyerane, and their functionalized congeners. Trachylobane has been synthesized by Kelly and co-workers[171–173] at New Brunswick. Using an allene–enone photocycloaddition reaction[167] (Scheme 109), a reaction used effectively for members of the *stemodia* class of diterpenes by the Kelly group as well, they add allene to enone **28** to yield tetracyclic ketone **147**.



SCHEME 108. Ziegler's synthesis of steviol.

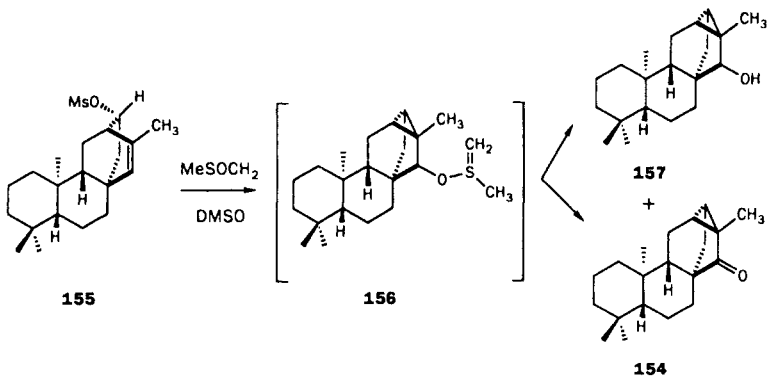


SCHEME 109. Kelly's synthesis of trachylobane.

(This reaction is also used by the Fétizon group in their synthesis of phyllocladene.)

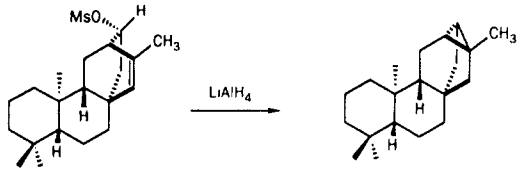
Following protection of the ketone carbonyl group, the exomethylene double bond of **147** is cleaved and the resulting ketone function is reduced. The alcohol product **148** is then subjected to acid-catalyzed hydrolysis and aldolization which provides a single 2.2.2-bicyclic hydroxyketone **149**. The design of the synthesis is to create the cyclopropyl group of trachylobane by internal alkylation. Thus, a methyl group is added to the ketone carbonyl group of the acetate of **149** to form diol **150** and the two oxygen functions are then manipulated through a sequence which leads to transposed ketol **151**. The key step in this process is the reduction of enone **152** to **153** in which both of the hydroxyl epimers are obtained. Derivatization of the ketol, **151**, obtained from the desired epimer **153** as a tosylate, followed by base-catalyzed internal alkylation yields pentacyclic ketone **154**. Modified Wolff–Kishner reduction provides the naturally-occurring hydrocarbon **3**.

The Kelly group has also carried out two modifications of the trachylobane synthesis. In one[172] (Scheme 110), the fifth ring is closed by solvolysis of mesylate **155** in the presence of "dimsyl" anion. A bifurcation of the reaction path along the lines of either Pummer rearrangement or Moffat oxidation occurs after the formation of an initial sulfinyl ester **156** to lead to a mixture of alcohol **157** and ketone **154**.



SCHEME 110. Kelly's first variation on the synthesis of trachylobane.

The third synthesis[171] (Scheme 111) differs from the others in that trachylobane, **3**, is formed directly from olefin–mesylate **155** by reduction with lithium aluminium hydride.



155 3
trachylobane

SCHEME 111. Kelly's second variation on the synthesis of trachylobane.

K. Gibberellins

The gibberellins are constituents of both fungi and of higher plants. They promote the growth of plants and were discovered in Japan in an investigation of the "baka-nae" (stupidly overgrown seedling) disease of rice attributed to the fungus *Gibberella fujikuroi*. In higher plants the gibberellins, particularly gibberellic acid, are normal growth factors. The remarkable effect of the gibberellins on plant growth has stimulated a great amount of activity in synthesis. An excellent review of gibberellin chemistry and synthesis has appeared recently.[174]

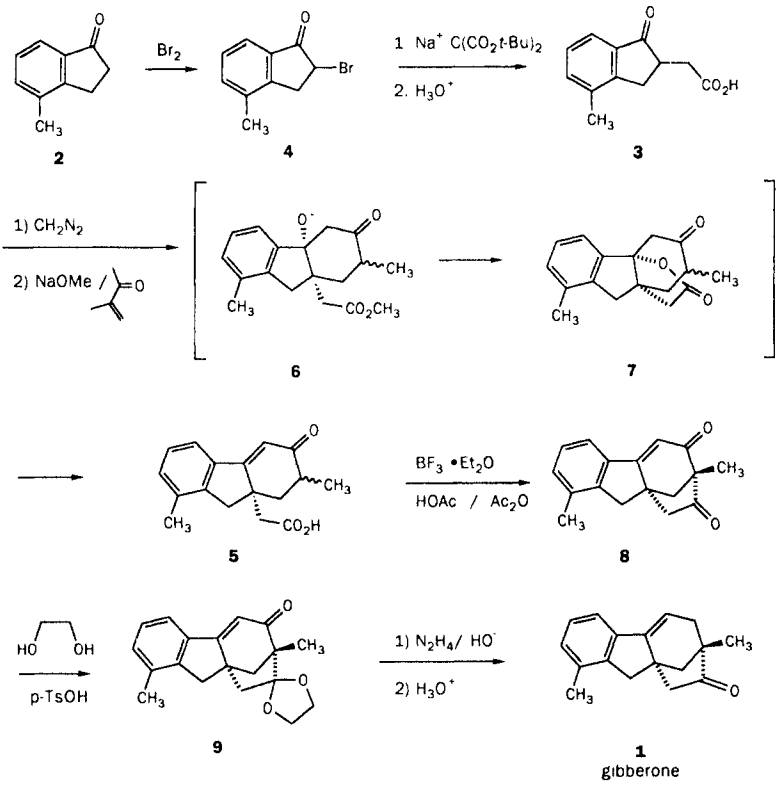
The earliest gibberellin compounds to be prepared by synthesis were degradation products. Because this work laid the foundation for much of the effort in the total synthesis of the natural product themselves, the syntheses of several of the degradation products are reviewed here.

(1) Degradation Products

Gibberone

One of the first syntheses of a tetracyclic degradation product of the gibberellins is the synthesis of gibberone **1** (Scheme 112) by Loewenthal and Kos[175, 176] in Haifa. The route used here for the construction of the C/D bridged ring system is also employed for the synthesis of several members of the gibbane class of natural products as well as for their degradation products.

The starting material, 4-methylindanone **2** is not readily converted to keto acid **3** by direct alkylation, but its α-bromo derivative **4** reacts readily with the sodium enolate of di-*tert*-butyl malonate. Hydrolysis and decarboxylation of the product yields keto acid **3**. Both the methyl and *t*-butyl esters of this acid react in a Michael addition fashion with methyl isopropenyl ketone to yield

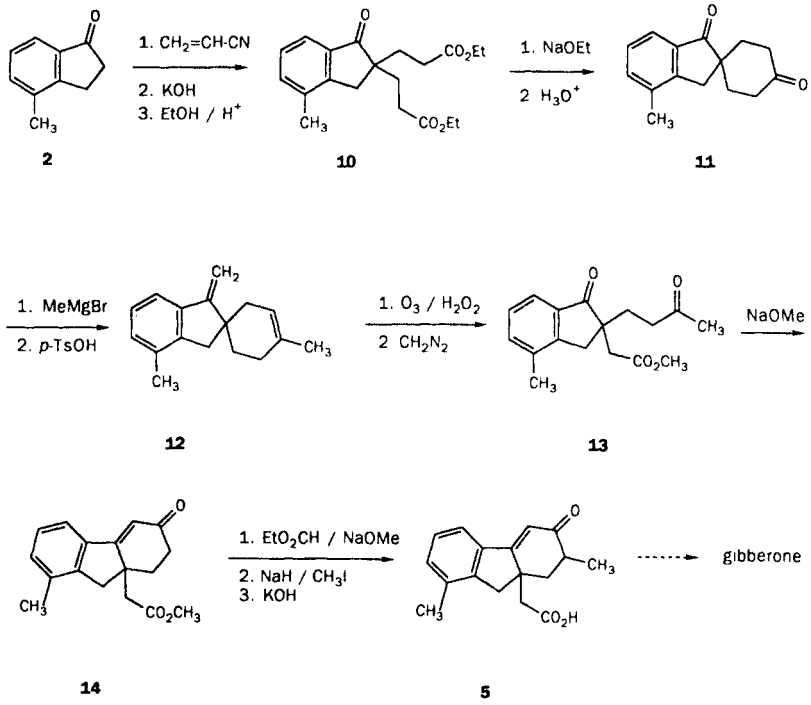


SCHEME 112. Loewenthal's synthesis of gibberone.

keto acid **5**; cleavage of the ester function having occurred during the annelation step. Presumably, the aldolate ion **6** formed on ring closure lactonizes to form **7**. The latter, in a mode similar to the events of the Stobbe condensation, undergoes β-elimination with the creation of a free carboxylate.

Lewis-acid-catalyzed Claisen condensation of **5** affords tetracyclic diketone **8** in high yield. This nonenolizable β-diketone is sensitive to hydrolytic conditions, but it can be converted in moderate yields to the monoketal **9**. Wolff–Kischner reduction of the remaining ketone function of **9** and subsequent hydrolysis yields racemic gibberone **1**.

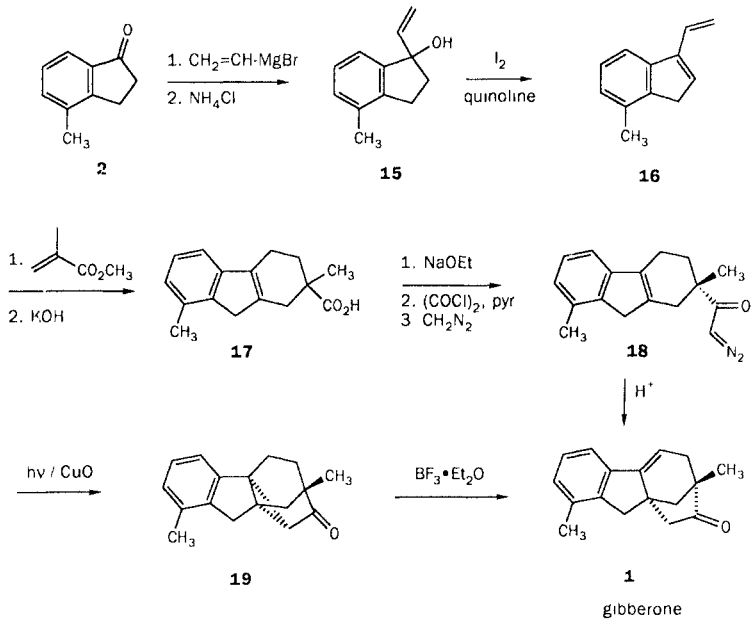
The synthesis of ketone **5** (Scheme 113) by Money, Raphael, Scott, and Young[177] from Glasgow also constitutes a synthesis of gibberone since this intermediate had been previously employed by Loewenthal in his preparation of the gibberellin degradation product.



SCHEME 113. Money's synthesis of an intermediate for gibberone.

In this case addition of indanone **2** to acrylonitrile affords a di- "cyanoethylated" product **10**. Esterification of the diacid obtained from hydrolysis of the nitrile affords diester **10**, and the latter is then cyclized to a β-keto ester, which upon acid-catalyzed hydrolysis yields diketone **11**. The six-membered ring of this intermediate is now to be cleaved to yield the carbon atoms of both rings C and D. To this effect methyl magnesium bromide is first added to both carbonyl groups of **11**, and the resulting ditertiary diol is dehydrated to yield diene **12**. Under the acid conditions of the dehydration, the favored product is as expected, the one having an endo double bond in the six-membered ring. Ozonolysis of **12** with oxidative workup and treatment with diazomethane then affords diketoester **13**. The latter is cyclized under aldol conditions to enone ester **14**. Methylation of **14** via the formyl derivative and subsequent hydrolysis then yields Loewenthal's keto acid **5**.

Ghatak[178] has reported a synthesis of gibberone (Scheme 114) which uses the Mander protocol[179] for building the bridged bicyclooctane C/D ring system onto a preexisting fluorene unit by diazocarbonyl addition. The

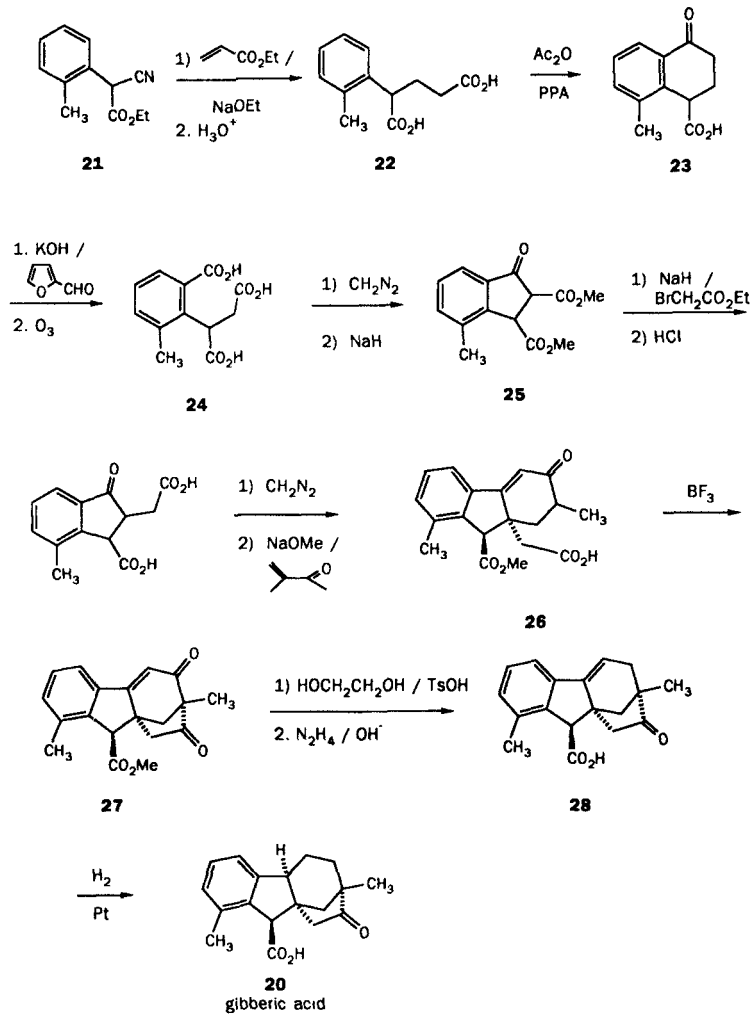


SCHEME 114. Ghatak's synthesis of gibberone.

methyl-substituted aromatic ketone **2** is reacted with vinyl magnesium bromide and the resulting benzylic alcohol, **15**, is dehydrated with iodine–quinoline to yield diene **16**. Diels–Alder addition of **16** to methyl methacrylate, catalyzed by dry HCl, leads to a mixture of adducts in low yield. The free acid **17**, isolated after separation of hydrolysis of the mixture, is then converted to diazoketone **18** following the usual sequence of preparing the acid chloride followed by reaction with diazomethane. Closure of the carbenoid obtained from **18** by exposure to light in the presence of CuO affords the pentacyclic ketone **19**. Treatment of the latter with boron fluoride–etherate gives gibberone, **1**. In a more efficient and alternative, procedure gibberone is produced directly from **18** by acid-catalyzed cyclization.

Gibberic Acid

For the synthesis of gibberic acid **20** (Scheme 115), Loewenthal and Malhotra[180] employed the cyano ester **21** as the starting material. Michael addition of **21** to ethyl acrylate produces a cyano diester which is hydrolyzed to diacid **22**. The latter under acid conditions cyclizes to **23**. Ozonolysis of the



SCHEME 115. Synthesis of gibberic acid by Lowenthal.

furfurylidiene derivative of **23** affords triacid **24** and Dieckmann cyclization of the derived ester now gives the A/B system of the target in the form of keto ester **25**. Following introduction of an acetic ester side chain by alkylation of **25**, the β-ester function is removed and ring C is added by Robinson annelation using methyl isopropenyl ketone as the acceptor species. The product of this sequence is the half-ester **26**, produced in the same fashion as

previously observed in Loewenthal and Kos synthesis of gibberone, and treatment of it with a Lewis acid effects cyclization to **27**.

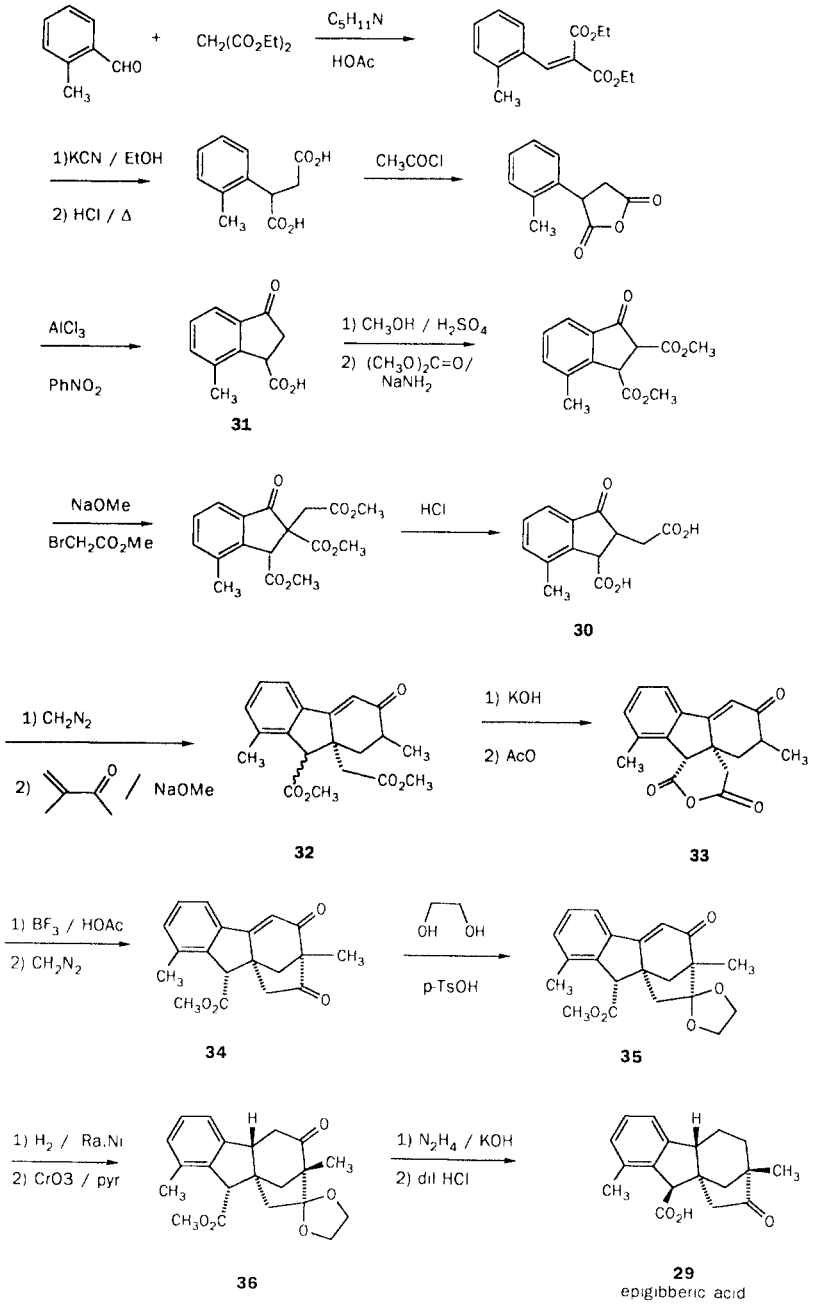
As also cited by Mori and co-workers,[181, 182] who also used this scheme for their synthesis of epigibberic acid, the catalytic reduction of a tetracyclic intermediate with a β-carboxylate function at C-6 results in the formation of the gibberic acid stereochemistry, that is, a B/C *cis*-ring fusion. Thus, this synthesis produces dehydrogibberic acid **28**, after monoketalization of **27**, followed by Huang–Minlon reduction and hydrogenation of **28** to yield gibberic acid **20**.

Epigibberric Acid

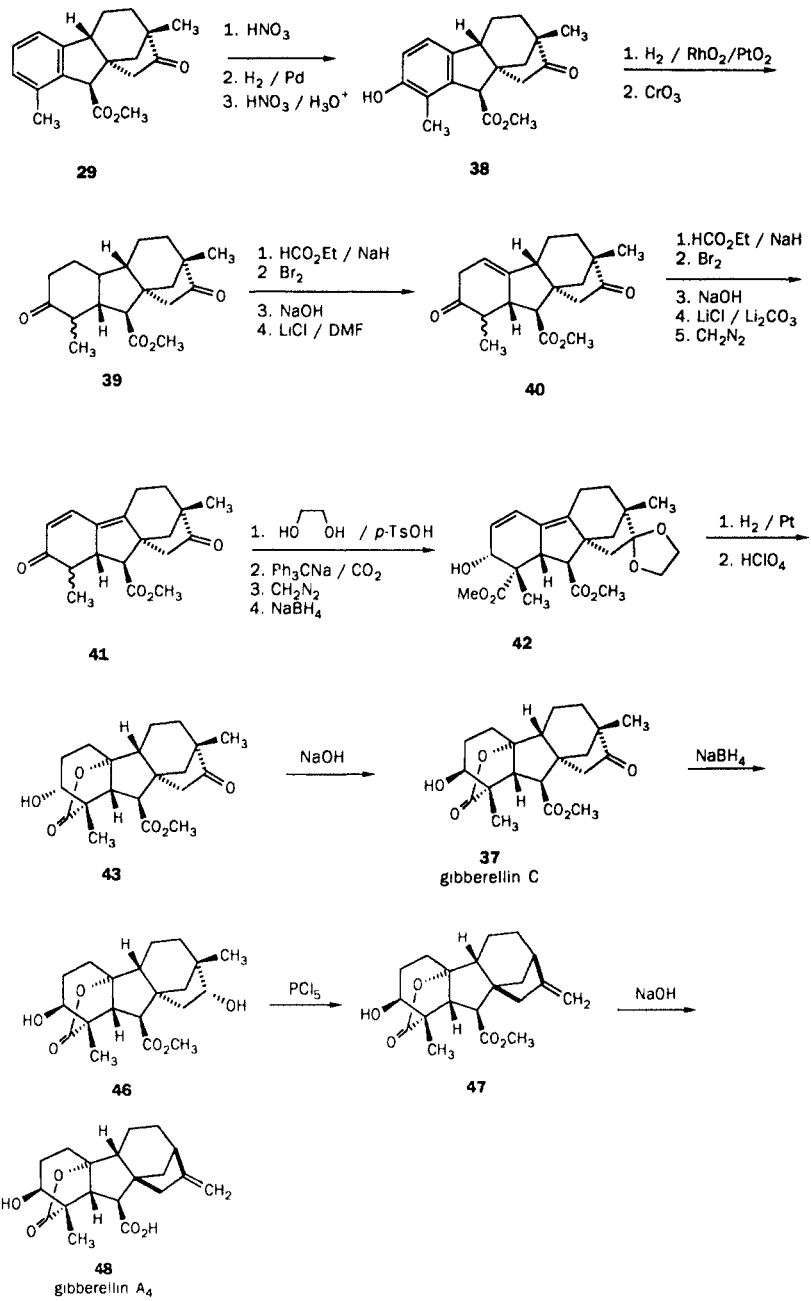
The synthesis of epigibberic acid **29** by the Mori group[181, 182] illustrated in Scheme 116 closely parallels the Loewenthal synthesis of gibberic acid in the manner in which the tricyclic "fluorene" unit is prepared. A bicyclic diacid, **30**, is constructed, in the Mori case from an indanone monocarboxylic acid **31** by standard alkylation chemistry. The diacid is esterified and caused to react with methyl isopropenyl ketone to give Robinson annelation product **32**. Hydrolysis of the ester functions of **32** and treatment with acetic anhydride then affords cyclic anhydride **33**. Acid-catalyzed internal Claisen condensation next affords a tetracyclic keto acid which upon esterification affords keto ester **34** with an α-oriented carboxyl at C-6. The more reactive cyclopentanone-saturated carbonyl group is then selectively ketalized and the product, **35**, is hydrogenated in the presence of Raney nickel to give an enone, **36** (after oxidation of an intermediate alcohol), which has a *trans* junction of the five membered B ring and the ketonic C ring. This result is in contrast to the reduction results achieved by Loewenthal in the synthesis of gibberic acid (*cis* ring junction), where the hydrogenation is carried out after removal of the C-ring carbonyl. In Mori work Wolff–Kishner reduction is carried out on **36** with concomitant epimerization and hydrolysis of the C-6 ester group substituent. Subsequent hydrolysis of the ketal affords epigibberic acid, **29**.

Gibberellins C and A_4

For gibberellin C, **37**, Mori and co-workers[183, 184] employed synthetic epigibberic acid, **29**, as starting material. The plan for the synthesis, shown in Scheme 117, is to functionalize the A ring with activation of the C-10 position as a prelude to formation of the lactone unit of the natural product. Ring A therefore is functionalized by nitration to give a 3-nitro compound as the major product. Replacement of the nitro function by hydroxyl is carried out by the classical diazotization procedure yielding phenol **38**. A multistep sequence designed to convert the saturated ketone function of **39** to the



SCHEME 116. Mori's synthesis of epigibberic acid.

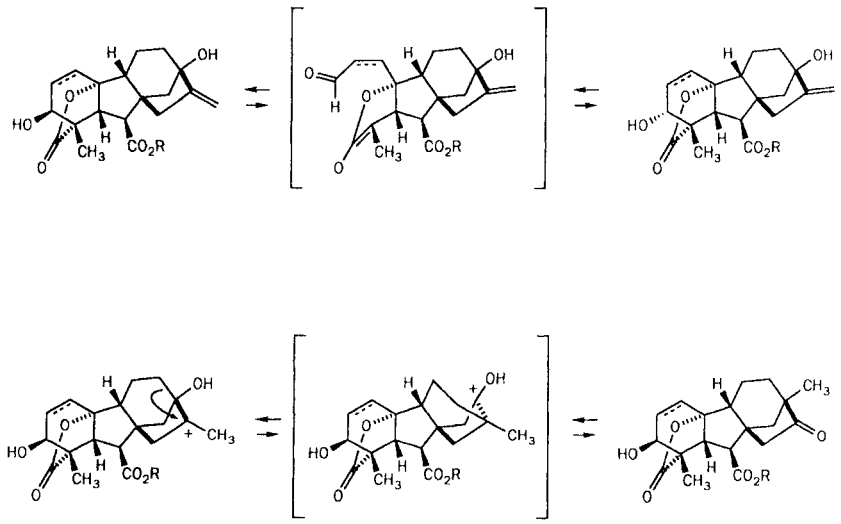


SCHEME 117. Mori's synthesis of gibberellins A and C.

corresponding α,β-unsaturated derivative yielded the β,γ-isomer **40** in very low overall yield instead. A second extended sequence is then used to introduce a second double bond and to give dienone **41**. The presence of the two double bonds now provides a reactive center at C-10 and provides a way for the selective formation of a dioxolane derivative of the five-membered ring ketone. Thus, treatment of **41** with ethylene glycol followed, by a three-step sequence of carboxylation, esterification, and ketone carbonyl reduction, provides hydroxy ester **42**.

The full functionalization of ring A with accompanying reprotonation at C-9 is accomplished by reduction of the $\Delta^{1,2}$-double bond of **42**, followed by treatment with acid. The resulting product, lactone **43**, is subjected to epimerization at the C-3 hydroxyl position.[185] This reaction (Scheme 118), well known in gibberellin chemistry,[174] involves the reversible dealdolization–realdolization of the ring-A hydroxy-lactone system, and although the equilibrium almost always favors the equatorially substituted α-hydroxy component (e.g., **44**), some of the material having the natural configuration **45** can be isolated. In this case, the equilibrium process provides gibberellin C methyl ester, **37**, as the minor component. Gibberellin C is obtained by hydrolysis.

When gibberellin C methyl ester is reduced to alcohol **46** and this product is treated with phosphorous pentachloride, the methyl ester, **47**, of gibberellin A_4 is produced. The rearrangement (Scheme 118) is again characteristic of



SCHEME 118. Gibberellin ring A epimerization and C/D rearrangement.

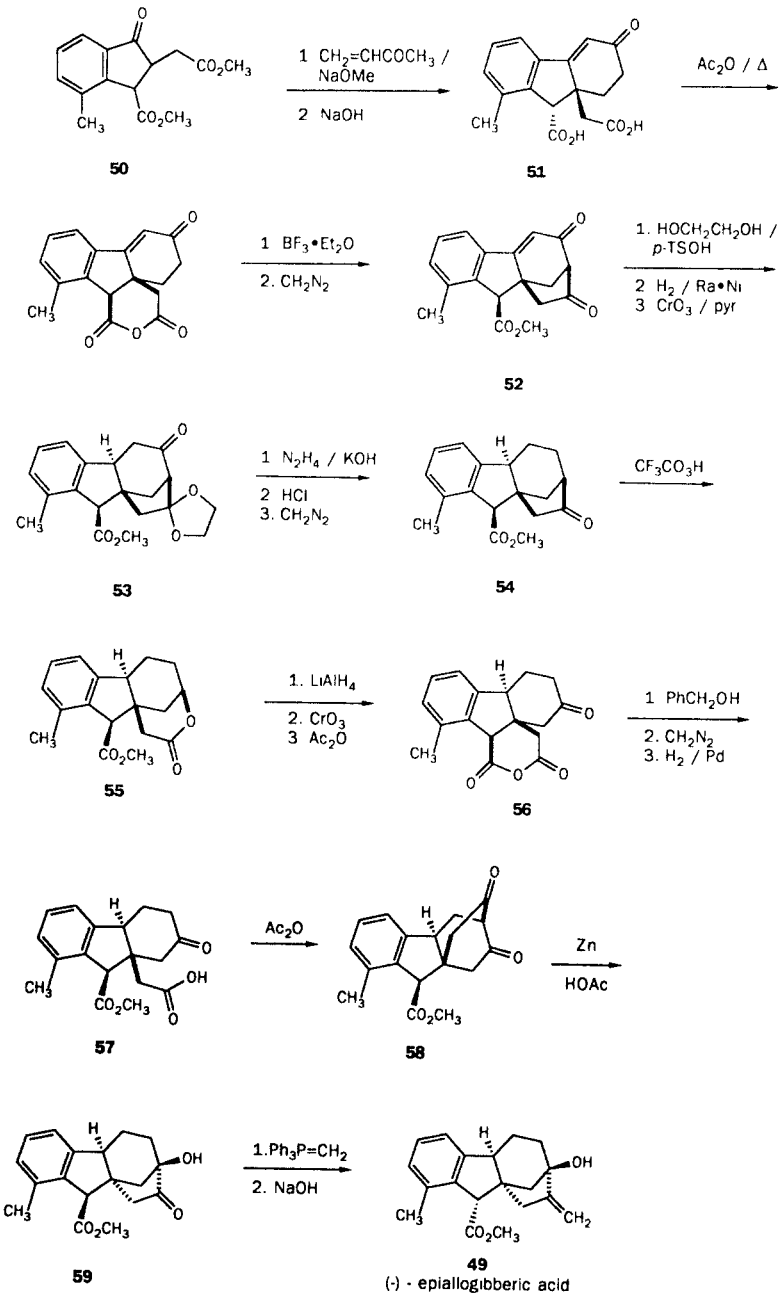
similarly substituted gibberellin and kaurene–hibaene derivatives, but occurs here in a yield of only 5%. The natural product, **48**, is obtained by hydrolysis accompanied by the C-3 hydroxyl epimer and produced again in extremely low yield.

Epiallogibberic Acid

For epiallogibberic acid, **49**, produced first as a degradation product but later isolated from *Gibberella fujikuori*, Mori[186] employs (Scheme 119) the same starting material, indanone **50**, used previously for epigibberic acid. Since the *allo* series of gibberellins retains the common C/D ring system with a hydroxyl group at the ring junction, the bicyclic ketone is condensed with methyl acrylate rather than with the methacrylate ester. The resulting enone **51** is conducted along the same path as used previously to produce tetracyclic diketone **52**. Differential ketal formation and catalytic reduction leads to ketone **53**, following oxidation of an intermediate alcohol function produced in the reduction step. The hydrogenation of the double bond in **52** takes place from the α face of the molecule away from the C-6 carboxyl group and the two-carbon bridge of the D ring.

Removal of the C-12 carbonyl is then effected by Wolff–Kishner reduction and the incidentally hydrolyzed carboxyl group is reesterified to afford tetracyclic ketone **54**. Baeyer–Villiger oxidation then gives lactone **55** which, in turn, as a *relay* substance obtained from gibberellic acid itself, is converted by reduction to a triol, reoxidation to a keto diacid, and acetic anhydride treatment to yield anhydride **56**. Selective cleavage of the anhydride is realized by reaction with benzyl alcohol at the less-hindered carboxyl group and the resulting half-acid is further esterified with diazomethane. Hydrogenolysis of the benzyl ester furnishes the alternative half-ester **57**, which upon treatment with acetic anhydride is condensed to produce bicyclic ketone **58**. The novel reductive rearrangement used by the Mori group in the kaurene series[36, 161, 162] is applied to **58** and the product is ketol **59**. The alternative, and more stable, ketol with the two-carbon ketonic bridge β-oriented is a minor product. Final conversion of **59** to epiallogibberic acid **49** is accomplished by Wittig methylenation, epimerization at C-6, and concomitant hydrolysis.

A peculiarity of the Mori synthesis raises the question of what actually constitutes a "formal" total synthesis. Normally, when a natural material is used as a source of a key intermediate in a synthesis, the reconversion of the "relay" to the natural material yields precisely that; the natural material. In the case of the synthesis of epiallogibberic acid, however, the relay material **55**, prepared from gibberellic acid, yields, as a consequence of the pinacol reduction of **58** and the opening of the intermediate diol, the *enantiomer* of the



SCHEME 119. Mori's synthesis of epiallogibberric acid.

natural product! Thus in a sense, and in contrast to a synthesis of a racemic material, this synthesis never returns to the natural product. Unless the final product is recycled through a degradation–resynthesis scheme, the natural material is never synthesized. In this work, however, the degradation product doesn't come from epiallogibberic acid!

As the outcome of extensive model studies a synthesis of epiallogibberic acid, **49** (Scheme 120), was carried out by House, Melilo, and Sauter[187, 188] at the Georgia Institute of Technology. The tricyclic A-B-C system is constructed through 4 + 2 cycloaddition of an indene carboxylic ester **60** and butadiene. The resulting tricyclic diester is hydrolyzed, caused to undergo iodolactonization, and dehalogenated with tin hydride to yield lactone **61**.

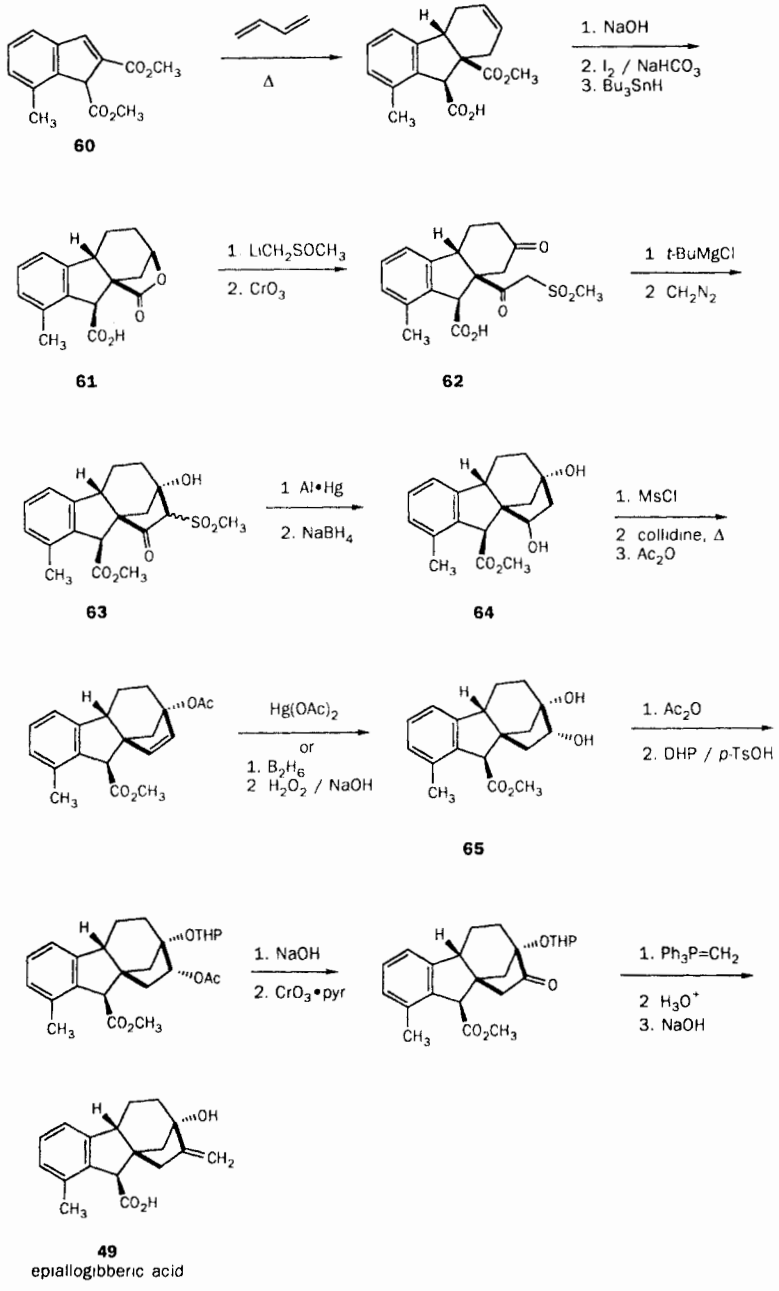
The House mode for the creation of the 3.2.1-bicyclo C/D ring system of the gibberellins is the aldol-type closure of a keto sulfone.[189, 190] To this end, lactone **61** is opened with methyl sulfinyl anion to give β-keto sulfone **62** and subsequent aldolization and esterification affords tetracycle **63**. The sulfone group is then reductively removed and the D-ring carbonyl group is reduced to give alcohol **64**. Next, the hydroxyl group is transposed one carbon atom by a sequence of elimination and hydroxylation affording diol **65**. Completion of the synthesis is realized through manipulation of the oxygen functions and a final methylenation and hydrolysis to give epiallogibberic acid, **49**.

(2) C_{20} Gibberellins

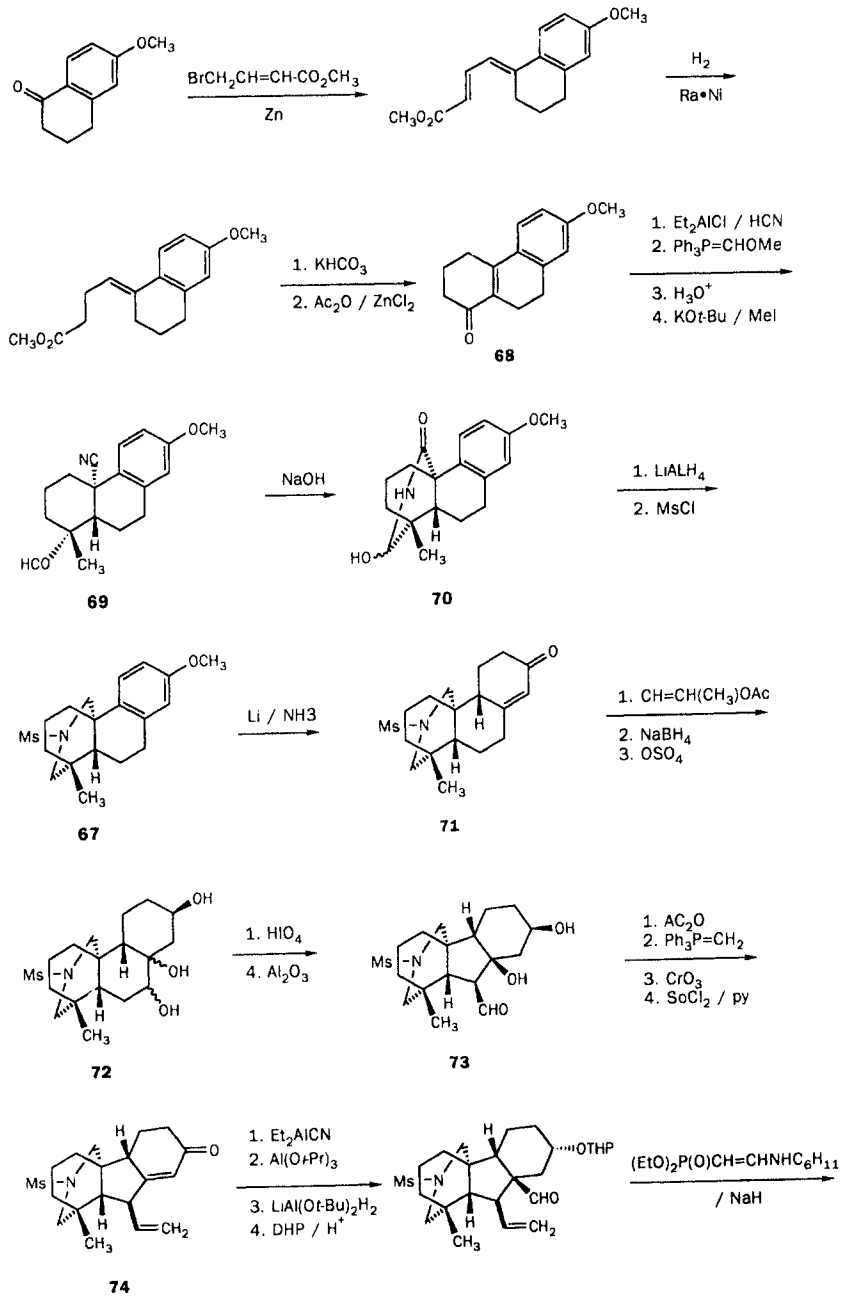
Gibberellin A_{15}

The first total synthesis (Scheme 121) of a naturally occurring gibberellin, a synthesis that proceeds from synthetic starting material to synthetic product, without relays or a complex natural product as the starting material, is the synthesis of gibberellin A_{15} **66** by Nagata and colleagues[191, 192] at the Shinogi Laboratory in Osaka. A monumental effort, it comprises some 43 steps in which a diterpenoid atisine-like "alkaloid" is first prepared, only to be degraded to the characteristic gibberellin A-ring lactone structure. Indeed, the starting material for the gibberellin A_{15} synthesis is the bridged piperidine derivative **67**, a key intermediate in the synthesis[192] of the diterpene alkaloids atisine, veatchine, and garryine.

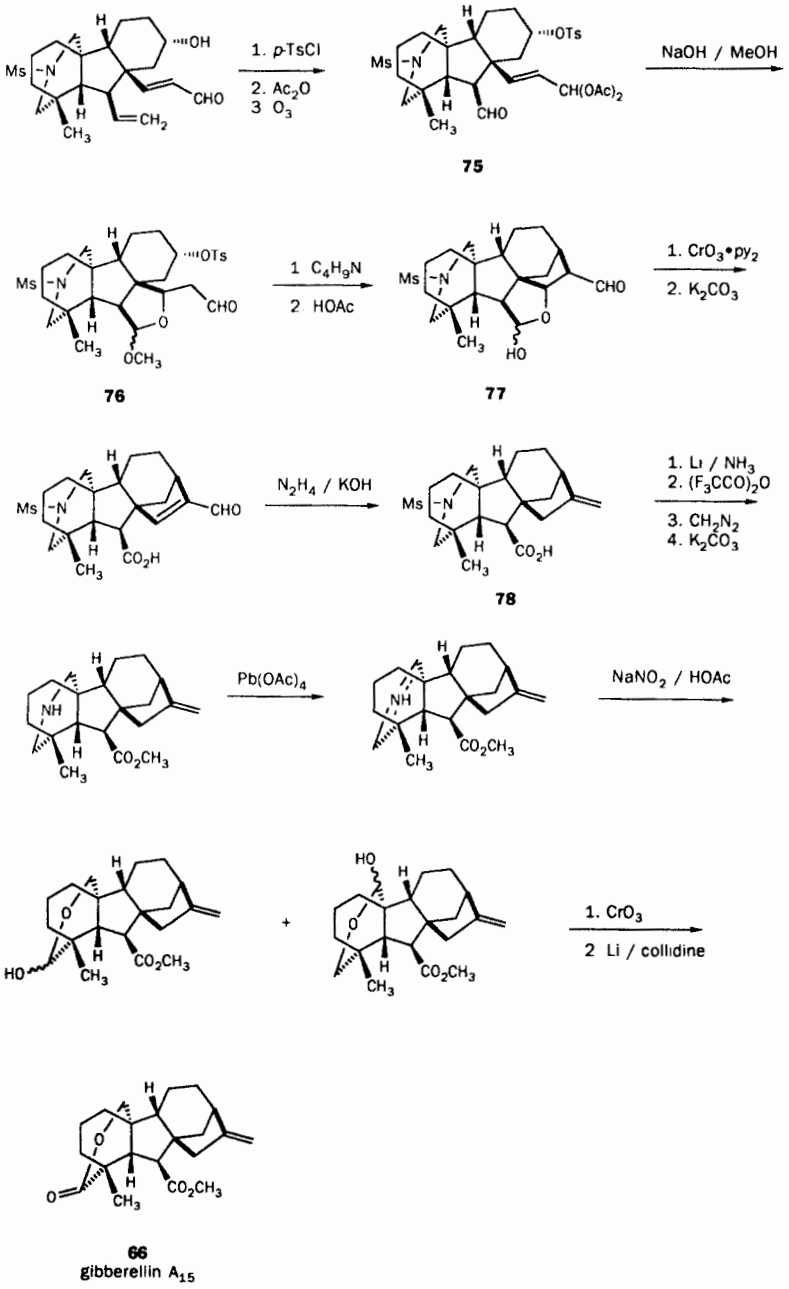
The pattern of the synthesis is (1) to build a standard tricyclic hydrophenanthrene ketone intermediate, **68**, by standard Reformatsky and acid-catalyzed cyclization chemistry; (2) to add the ring-A substituents in a stereocontrolled fashion; (3) to execute a contraction of ring B from five- to six-membered; and (4) to elaborate the C/D ring system. Thus, one of the



SCHEME 120. Epiallogibberric acid synthesis of House.



SCHEME 121. Nagata's synthesis of gibberellin A_{15}.



SCHEME 121. Nagata's synthesis of gibberellin A_{15} (*continued*).

"Nagata reagents" is added in a conjugate sense to the enone group of **68**, followed by the creation of a quaternary center at C-3 by Wittig addition, hydrolysis to an aldehyde, and subsequent methylation to afford cyano aldehyde **69**. The first step in the sequence, the hydrocyanation reaction yields a mixture of *cis*- and *trans*-fused tricyclic ketones, but the *cis* isomer after separation is equilibrated to a new 1:1 mixture by the action of hydrochloric acid. Repeated recycling in this fashion provides the *trans* isomer in high yield. This sequence creates three critical stereogenic centers. The hydrocyanation sets the stereochemistry of the C-10 substituent and the C-5 proton, while the alkylation of the aldehyde occurring as anticipated from the less-hindered "equatorial" face of the enolate renders the eventual carboxyl carbon at C-3 *trans* to the C-5 proton.

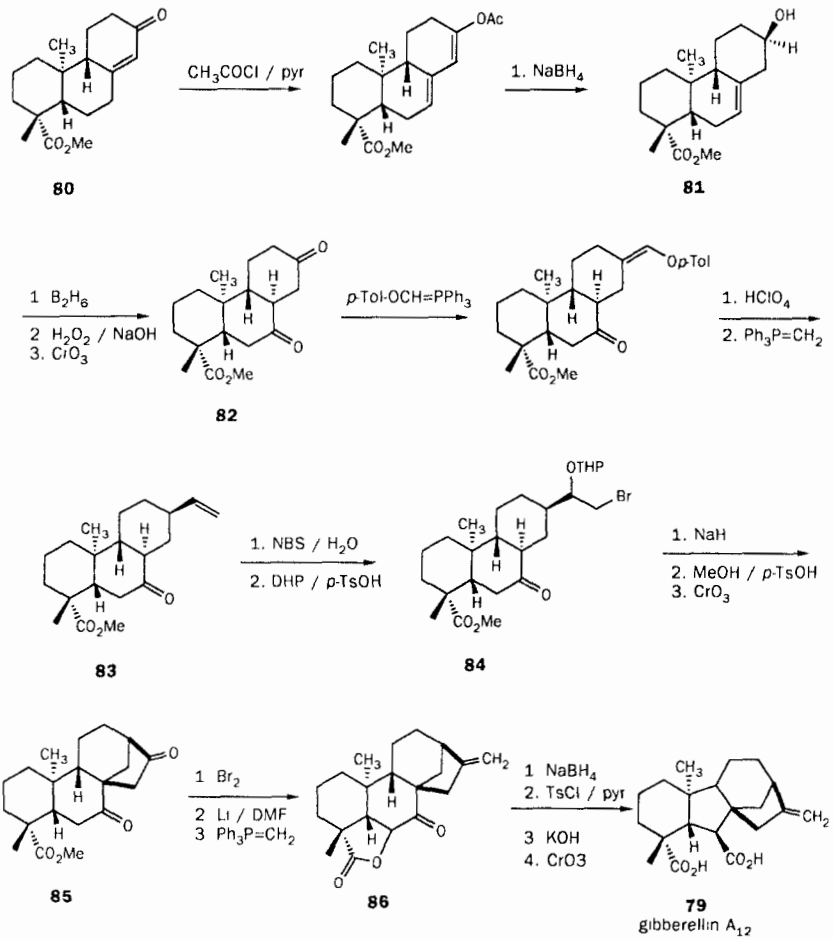
To complete the ring-A synthon the nitrile is partially hydrolyzed in base to give hemiaminal amide **70**. Lithium aluminium hydride reduction of the carbonyl functions is followed by mesylation of the nitrogen to produce **67**. The nitrogen function is thus rendered generally unreactive and preserved as the future means of creating the A-ring lactone unit.

The second major aspect of the synthetic plan is to now convert the tricyclic hydrophenanthrene system into a hydrofluorene unit. This is accomplished by a sequence which involves Birch reduction to **71**, conversion of the Birch product to an dienol acetate, and reduction of this substance to a homoallylic alcohol. Osmium tetroxide oxidation then provides triol **72**, which upon periodate cleavage and aldol cyclization yields aldehyde **73**. During this sequence two other stereocenters have been set. From the Birch reduction, the C-9 stereochemisty is determined and the final aldol step yields a β-oriented aldehyde group at C-6.

Addition of the carbons of the D ring by hydrocyanation with diethyl aluminium cyanide is successful only with enone–olefin **74**, derived from **73** by a multistep sequence. Derivatives of the aldehyde, for example, a dioxolane acetal, used to prepare **74** fail to undergo the conjugate addition reaction. The vinyl group therefore serves as a nonelectron-withdrawing surrogate for the aldehyde. The cyanation product is reduced, hydrolyzed, and eventually homologated to enal **75**. Completion of the last ring is accomplished by internal nucleophilic displacement of tosylate **76** to yield hemiacetal aldehyde **77**. Oxidation and elimination followed Wolff–Kishner reduction with accompanying double-bond migration is carried out to produce exocyclic olefin **78**, an intermediate with the carbon skeleton and stereochemistry of gibberellin A_{15} established. What remains is the removal of the *N*-mesyl group and conversion of the piperidine unit, using the method of ApSimon,[193] to a lactone. The accomplishment of this sequence provides gibberellin A_{15}, **66**.

Gibberellin A_{12}

A second synthesis of a C_{20} gibberellin is that of gibberellin A_{12}, **79**, by Mori, Takemoto, and Matsui.[194a] It is again a *relay* synthesis. The synthetic plan (Scheme 122), like that of the Nagata synthesis of gibberellin A_{15}, is based on the use of a hydrophenanthrene intermediate. Tricyclic enone ester **80** is converted through enol acetate formation and reduction to homoallylic alcohol **81**. After hydroboration of the double bond of **81** and oxidation to a



SCHEME 122. Mori's synthesis of gibberellin A_{12}.

diketone **82**, two sequential Wittig reactions yield a tricyclic intermediate **83** having the remaining carbons of the D ring present as a vinyl substituent at C-13. A kaurenoid ring system is then formed through displacement of a side-chain bromide, **84**, to yield tetracyclic diketone **85**. The steps to lactone **86** were carried out by Cross and co-workers[194b] on optically active **86**, and this product is then carried on to gibberellin A_{12}, **79**.

Gibberellin A_{38}

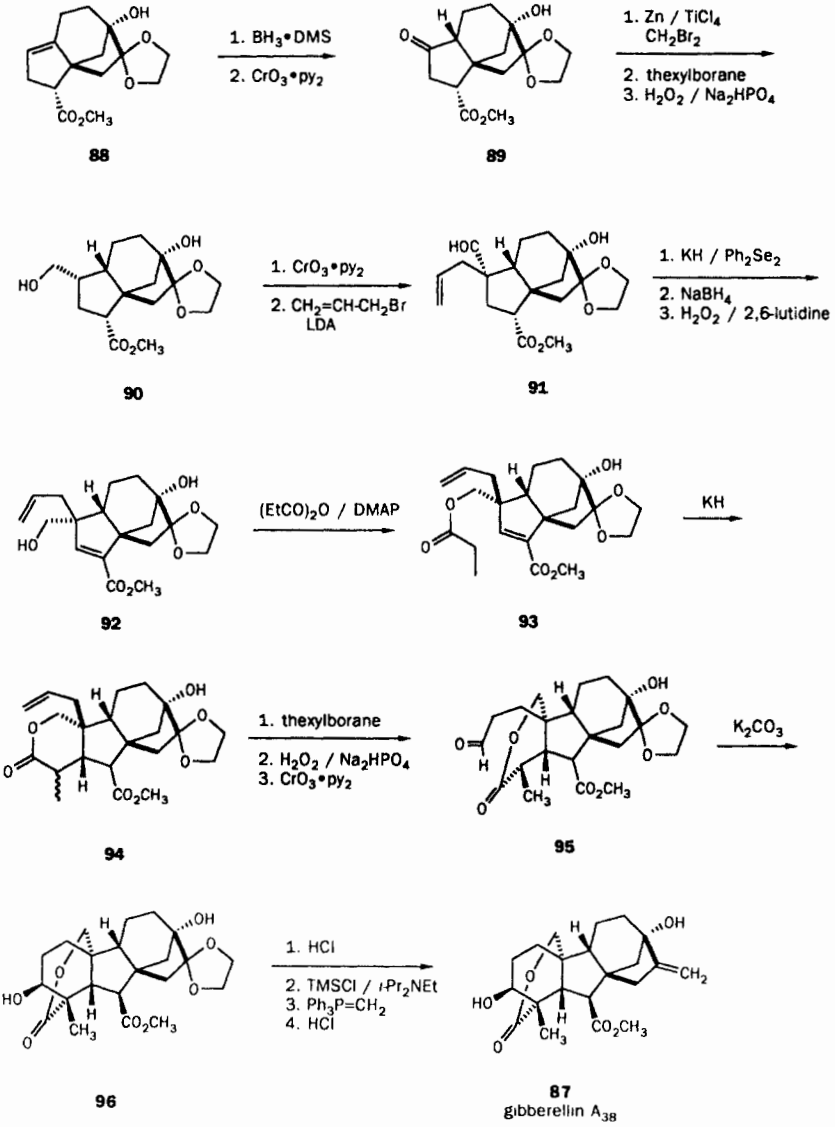
Lombardo and Mander[195] have carried out a total synthesis of a third C_{20} gibberellin, gibberellin A_{38}, **87** (Scheme 123). The starting material is dioxolane ester **88**, used also for the synthesis of gibberellic acid. Hydroboration occurs from the α face yielding, after oxidation, a ketone **89** with the correct geometry for the C/D ring junction. Homologation of the carbonyl group to the corresponding aldehyde is not accomplishable under a variety of conditions owing to enolization at C-9, but methylenation followed by a second hydroboration step affords alcohol **90**. Oxidation to the corresponding aldehyde is followed by allylation to afford **91**. Selenenylation alpha to the B-ring ester function, reduction of the aldehyde group, and oxidative elimination of the selenenyl group provides unsaturated hydroxy ester **92**.

A key concept in the Mander work[196] on gibberellin synthesis is the creation of ring A by the combination of a Michael addition to form the lactone unit and an aldol cyclization, patterned on the model studies of Dolby,[197,198] to complete the carboxylic A ring. Thus, esterification of **92** with propionic anhydride to form **93** is followed by base-catalyzed Michael addition under kinetic conditions to form lactone **94**. As expected, this reaction gives the *cis*-fused lactone which sets the stereochemistry at C-5. Conversion of the appended allyl group of **94** by hydroboration and oxidation provides aldehyde **95** and base treatment of this material now effects the closure of the A ring. The minor product (1:4) of the aldolization is the desired β-hydroxy ester **96**, but the major isomer may be oxidized and rereduced under thermodynamic conditions to afford additional quantities of the desired isomer. The final steps result in the introduction of the D-ring methylenation and provide gibberellin A_{38}, **87**.

(3) C_{19} Gibberellins

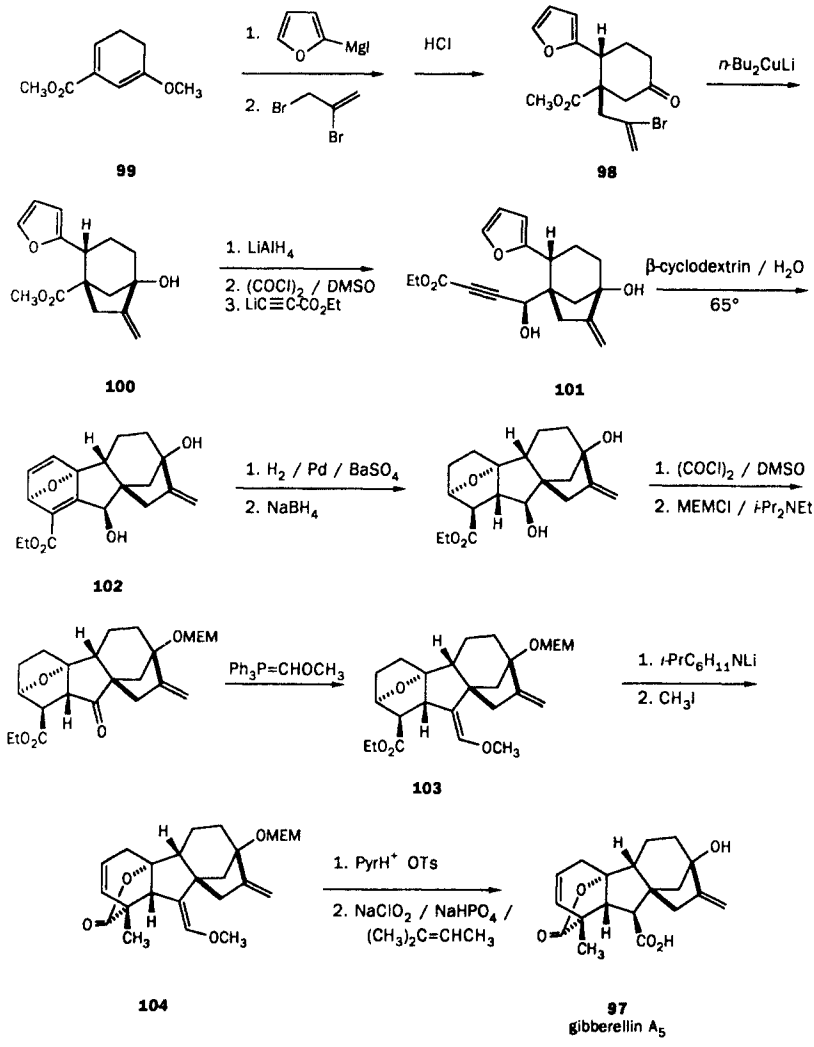
Gibberellin A_5

A novel synthesis of gibberellin A_5, **97**, involving an oxabicycloheptane intermediate (Scheme 124) has been reported by DeClerq and colleagues[199–202] at Ghent. A furanylcyclohexanone **98** is prepared by conjugate



SCHEME 123. Mander's synthesis of gibberellin A_{38}.

addition of 2-furylmagnesium bromide to diene ester **99** followed by alkylation of the intermediate enolate. The Corey method for formation of the bridged-ring system is then applied to **98** to form hydroxy ester **100**. The ester group of **100** is next converted into the corresponding aldehyde and to this



SCHEME 124. Gibberellin A_5 by DeClerq.

species is added an acetylenic anion with the formation of furanoalkyne **101**. The furano diene adds readily to the acetylenic system, but the maximum yield and the best selectivity for *endo* oxygen placement occurs in the presence β-cyclodextran. Presumably, the hydrophobic solvation of the reacting units by the cyclodextrin cavity is the key to producing **101** in high yield.

The synthetic goal at this stage is to introduce the necessary functionality in the A and B rings and to use the α-oriented oxygen of the bridged heterocyclic system for the corresponding lactone oxygen. After reduction of the $\Delta^{1,2}$ double bond, the stereochemistry at C-5 is set by 1,4 addition of hydride to the unsaturated ester function of **102**. Oxidation of the ring-B hydroxyl group is followed by a Wittig olefination to yield enol ether **103**. The bridged-oxygen atom of ring A is then caused to undergo elimination and the enolate ion of this elimination product is methylated selectively from the β face. Lactone **104** is formed spontaneously. Hydrolysis of the protecting groups and mild oxidation then affords gibberellin A_5, **97**.

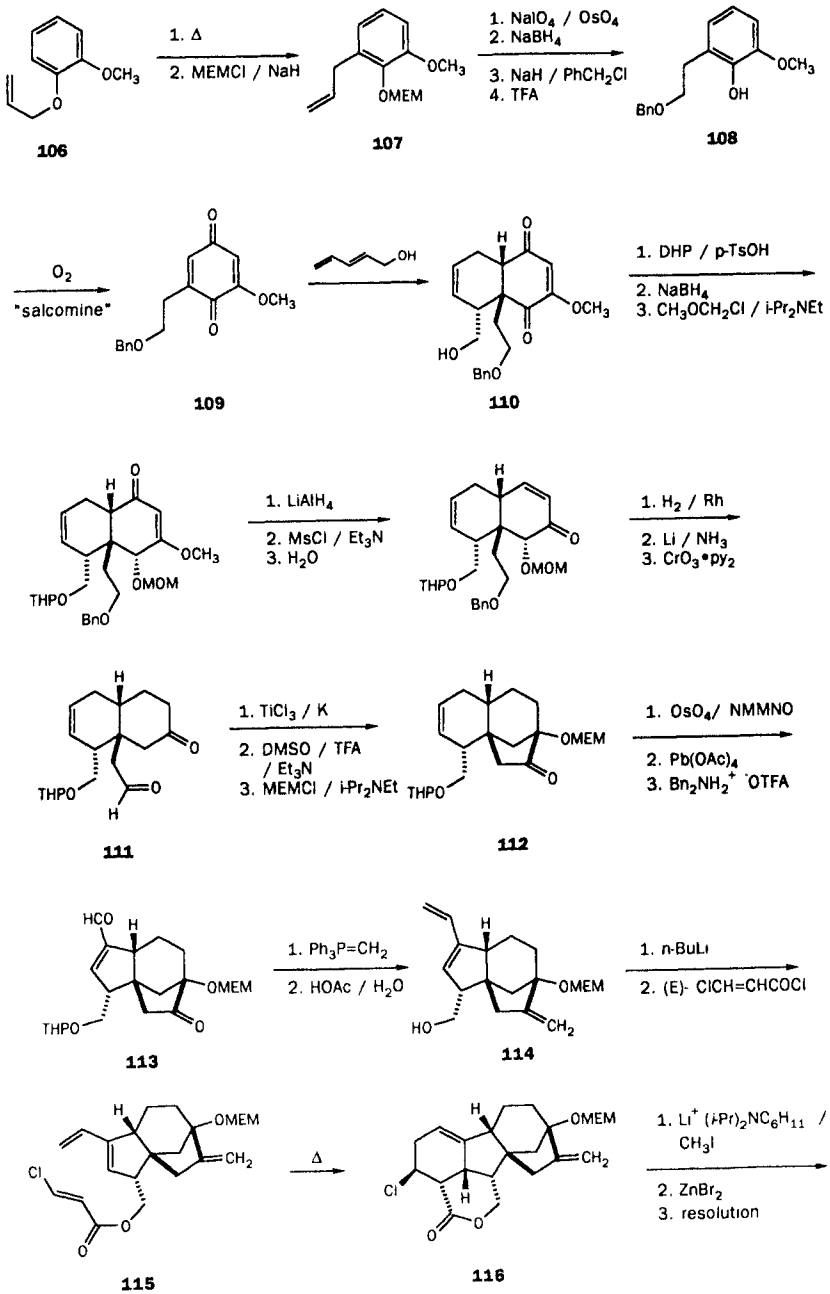
Gibberellic Acid, Gibberellin A_1, and Gibberellin A_4

The first total synthesis of gibberellic acid **105** was carried out by Corey and co-workers[203, 204] at Harvard. The synthetic design (Scheme 125) of the Corey work is to create first a tricyclic intermediate incorporating rings B, C, and D and to append to this, through intramolecular 4 + 2 cycloaddition chemistry, the components of ring A and the bridged-lactone function.[205] The critical stereochemistry at C-5 is then to be a function of the stereochemistry of the internally linked diene–dienophile pair.

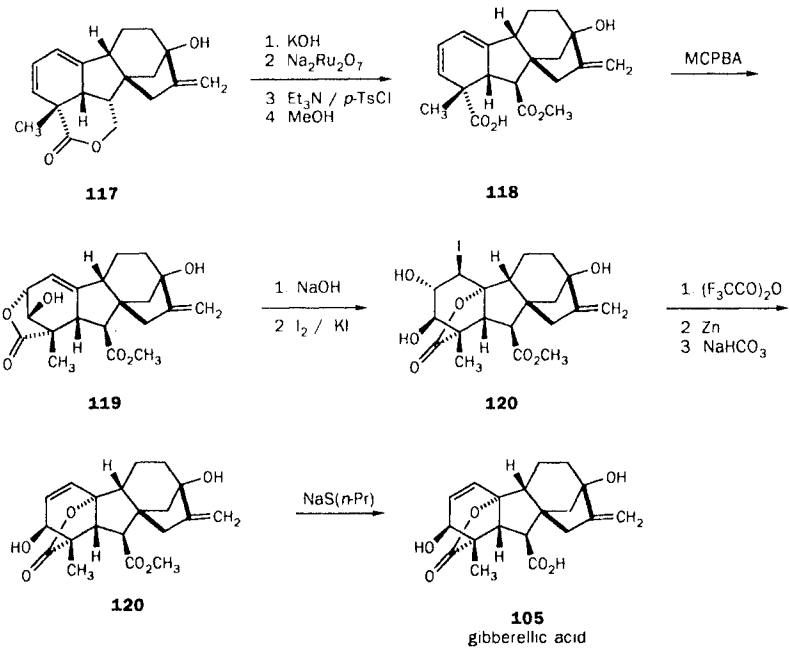
To this end the B/C/D unit is synthesized starting from *o*-allyloxyanisole, **106**. Rearrangement and protection of the new hydroxyl group as a methoxyethoxymethyl ether afford **107**, which in turn is converted into benzyl ether **108**. Oxidation then provides quinone **109** as a C-ring synthon. Diels–Alder addition of hydroxymethylbutadiene to **109** gives the *cis*-fused adduct **110**. The oxygen functions at the original quinone carbonyl positions are removed by a variant of the classical Woodward steroid synthesis protocol yielding keto aldehyde **111**. Reductive pinacol closure with a low-valent titanium species and protection of the resulting bridgehead hydroxyl function effects the formation of the tricyclic ketone **112**. The stereogenic centers of this intermediate, excepting the eventual C-6 position, are now set as a consequence of the stereoelectronics of the original cycloaddition reaction and the requirement for *cis* closure of the bridged system.

By oxidative cleavage of the double bond of **112**, a dialdehyde is produced which undergoes selective aldol closure to afford enal **113**. Interestingly, this aldol product is apparently not the result of an equilibrium process in which the enolates (or their equivalents) of both aldehyde groups are formed. If this were the case, a confusion of the stereochemistry at C-6 would most likely have resulted.

With the construction of the key intermediate **113** the diene component of the projected Diels–Alder ring-A construction sequence, **114**, can now be constructed by Wittig methylenation. The freed hydroxyl group of **114** is then



SCHEME 125. Corey's synthesis of gibberellic acid.



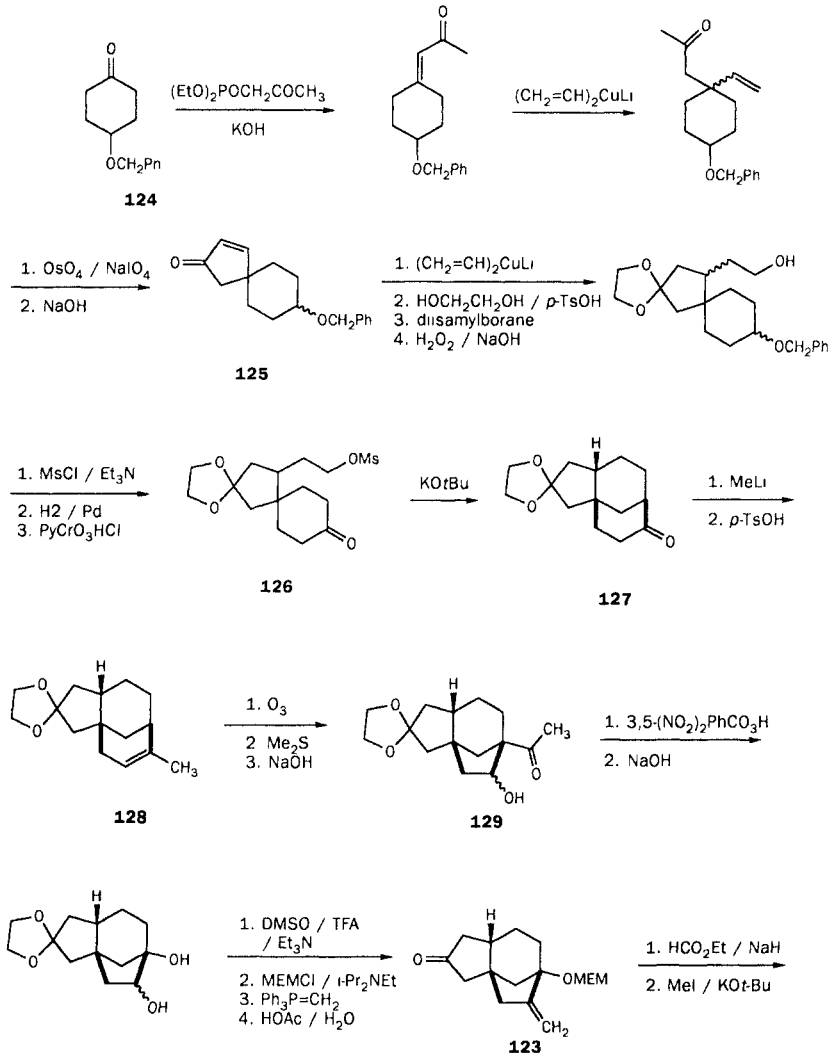
SCHEME 125. Corey's synthesis of gibberellic acid (*continued*).

esterified to yield chloro acrylate **115** and thermolysis produces internal adduct **116**, the product of endo addition. The linking of the dienophile to the C-7 hydroxyl group has also ensured that the proton at C-5 will have the natural β orientation.

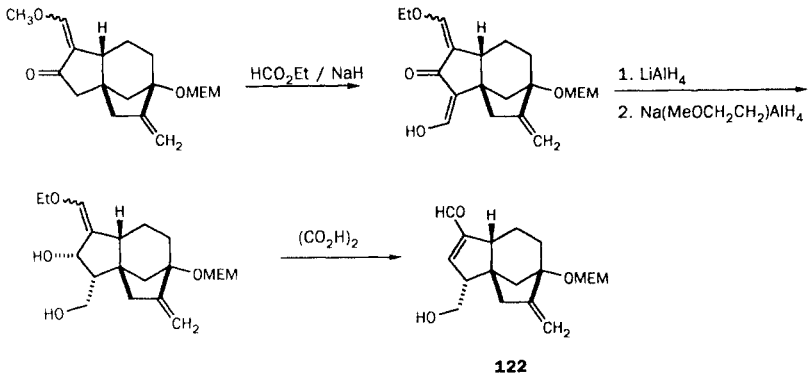
To complete the synthesis it is necessary to introduce one additional carbon, the C-4 methyl group, manipulate the A-ring functionality to produce the necessary unsaturated hydroxy lactone system, and oxidize the hydroxy methyl group at C-6 to a carboxyl function. To effect these changes the methyl group is first introduced through elimination of the β-chloro group of **116** and methylation to give a diene lactone. The ether-protecting group of this species is then hydrolyzed and the product, **117**, is resolved. Next, the two carboxyl functions of the natural product are established through hydrolysis of the lactone and oxidation. Differentiation between the two acid functions is made by formation of a mixed sulfonic–carboxylic anhydride intermediate, which undergoes base-catalyzed epimerization, followed by methanolysis to provide **118**.

An oxidative lactonization of **118** leads to **119**, which after base hydrolysis is subjected to iodolactonization to yield iodohydrin **120**. The free hydroxyl group at C-2 (along with the C-3 hydroxyl) is converted to a trifluoroacetate

leaving group to ensure that reductive elimination will effect only the iodohydrin unit and not the lactone function. Thus treatment of the di-trifluoroacetate of **120** with zinc yields gibberellic acid methyl ester **121**. To avoid epimerization at C-3, the ester group is cleaved with sulfide to afford gibberellic acid **105**.



SCHEME 126. Corey's second synthesis of gibberellic acid.



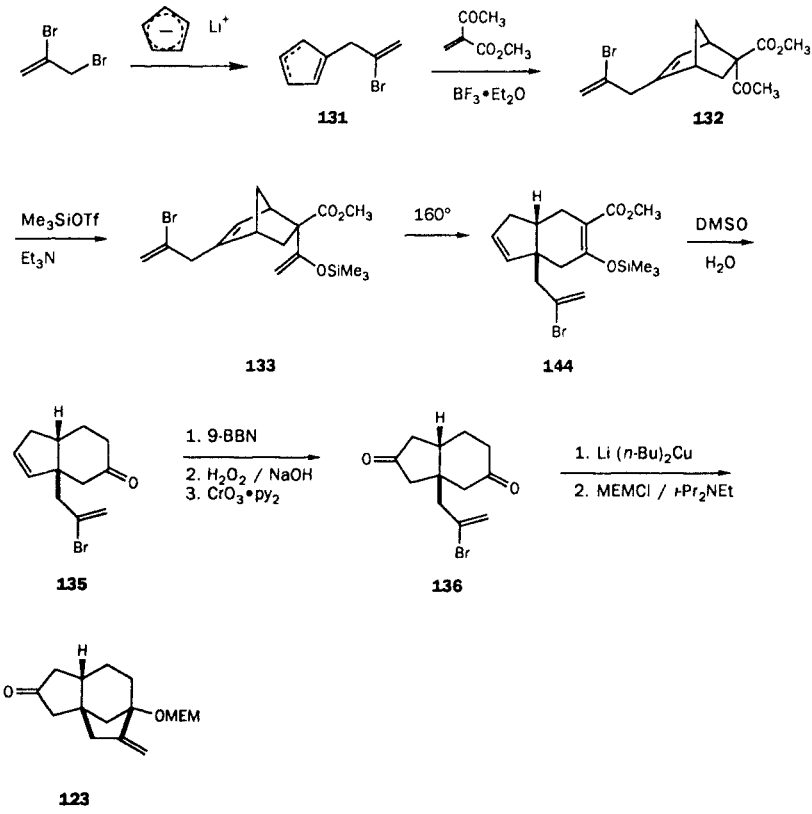
SCHEME 126. Corey's second synthesis of gibberellic acid (*continued*).

With the object of making the synthesis of gibberellic acid shorter and more efficient, Corey and Smith[206] carried out an alternative synthesis of the key aldehyde intermediate **122** (Scheme 126). The focus of this synthesis is ketone **123**.

For the synthesis of **123** an approach to the construction of the C/D ring system different from the original one is employed. Benzyloxycyclohexanone **124** is carried through a condensation, conjugative addition sequence to yield enone **125** after closure of an intermediate keto aldehyde. Conjugate addition to the enone function provides the remaining elements of ring C and manipulation of the oxygen functions leads to a keto mesylate **126**. Closure of the ring by displacement then yields a tricyclic intermediate **127** in which the D ring is subjected to a ring-contraction sequence by methyl lithium addition and elimination to **128**, followed by ozonization and reclosure by aldol condensation. The result is thus the 3.2.1-bicyclic ring system **129** which when subjected to Baeyer–Villiger oxidation affords **130**. Oxidation of the secondary hydroxyl group of **130** affords a ketone which is converted into the sought-after exomethylene ketone **123**. A sequence of formylation, reduction, and elimination yields the hydroxyenal **122** required for the completion of the gibberellic acid synthesis, although the synthesis is ultimately no less lengthy than the original effort.

A second and more efficient synthesis of ketone **123** was carried out by Corey and Munroe[207] (Scheme 127). Not only is the manner of constructing the carbon skeleton of the ketone different from that employed previously, but the manner of closing the bridged-ring system is again varied.

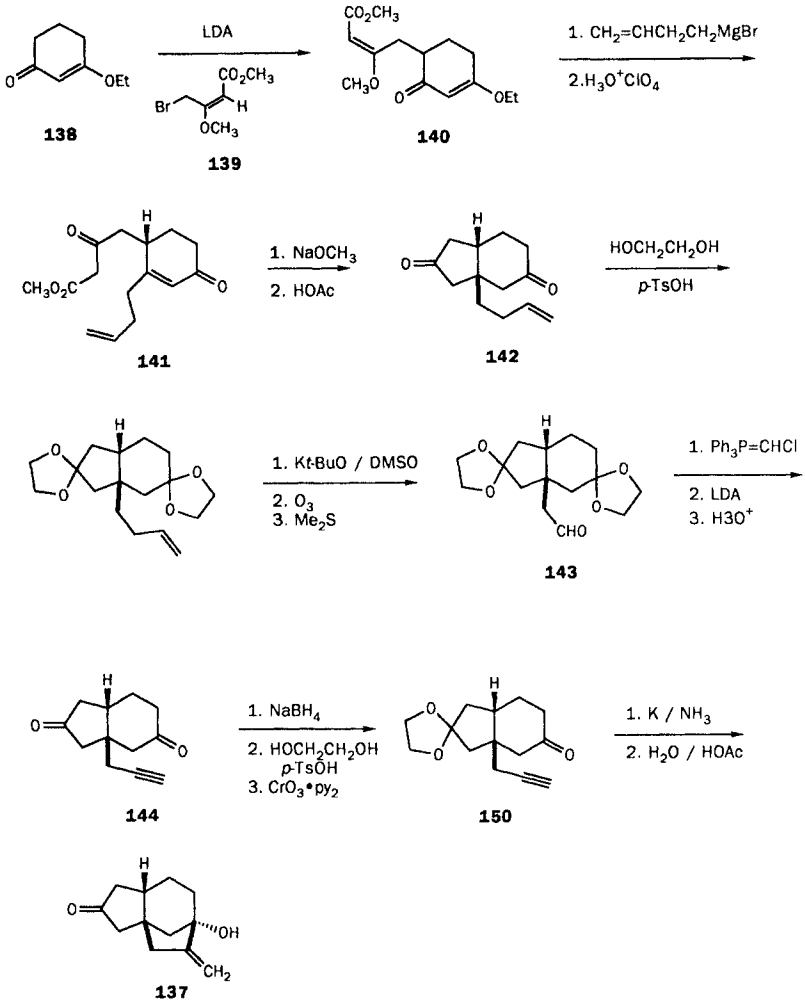
To this end the lithium salt of cyclopentadiene is alkylated with bromoallyl bromide to give a mixture of olefin isomers **131**. These react, in the presence of Lewis acid, to give a preferential Diels–Alder product, **132**, in



SCHEME 127. An alternative synthesis of a gibberellic acid intermediate by Corey.

modest yield. Silyl ether formation **133** is followed by thermolytic oxy-Cope rearrangement, affording the fused-ring B/C intermediate **134**. Hydrolysis and decarboxylation yields ketone **135**. Prior to formation of the third ring the double bond of **135** is subjected to hydroboration–oxidation and the resulting diketone **136** is cyclized in a copper-mediated closure reaction. Keto ether **123** results after protection of the bridgehead hydroxyl group.

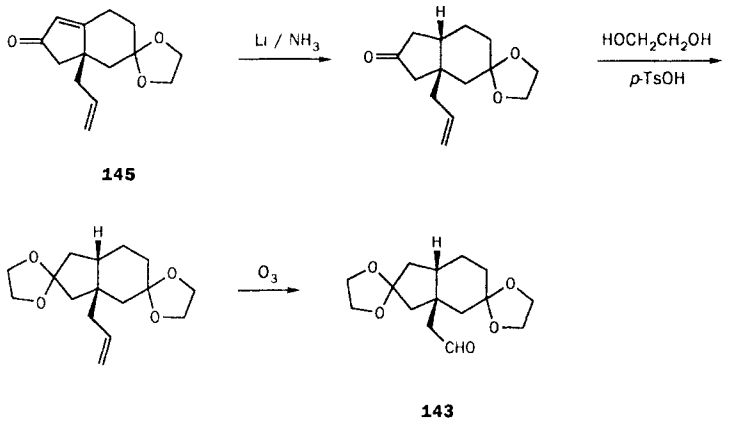
Ketol **137** (or its protected derivative **123**) is sufficiently attractive an intermediate for gibberellic acid synthesis that it was also prepared by several alternative routes by the Stork group[208] at Columbia. In the first of these (Scheme 128) the kinetic enolate of **138** is alkylated with the bromo ether **139**, derived from acetoacetic ester, and the resulting ketone product **140** is converted into enone **141** by Grignard addition and hydrolysis. Michael addition of the liberated β-keto ester of **141** to the enone affords bicyclic



SCHEME 128. Stork's synthesis of a gibberellic acid intermediate.

ketone **142**. A sequence of ketal formation, degradation of the angular substituent to give **143**, Wittig methynylation, and hydrolysis yields diketone **144**. In the second synthesis of **137** by the Stork group (Scheme 129), aldehyde **143** is produced through the intermediacy of enone **145**. The lithium–ammonia reduction, however, is not entirely stereoselective.

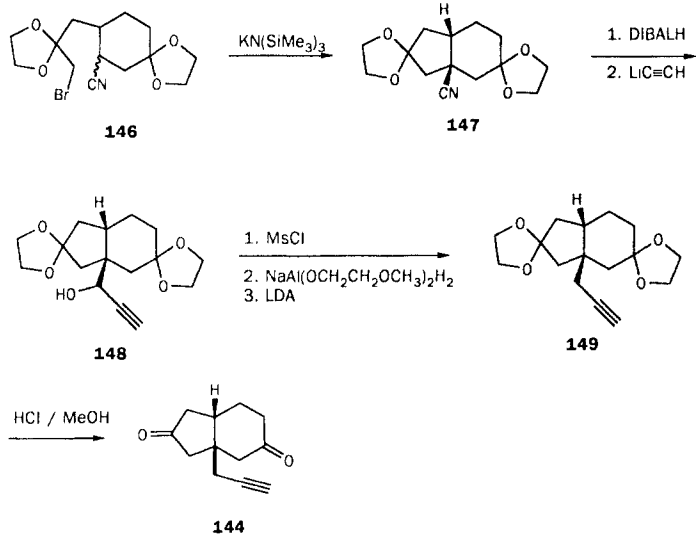
In the third synthesis of ketone **137** (Scheme 130) from the Columbia laboratory, cyano bromide **146** is first closed to bicyclic diketal **147**. The



145

143

SCHEME 129. Stork's second synthesis of a gibberellic acid intermediate.



146 147 148 149 144

SCHEME 130. Stork's third synthesis of a gibberellic acid intermediate.

cyano function is then converted through reduction and acetylide addition to form alcohol **148**. Further reduction yields acetylene **149**. Final hydrolysis affords diketone **144**.

The Stork method[209] for the formation of the C/D system is the reductive closure of the acetylenic group directly on the cyclohexanone carbonyl. This

reaction (Scheme 128), which served as the model for other closures of this type, is carried out on monoketal **150**, produced by selective reduction, ketalization, and reoxidation of **144**. Treatment of the acetylenic ketone **150** with lithium and ammonia effects closure and subsequent hydrolysis of the ketal function affords **137**.

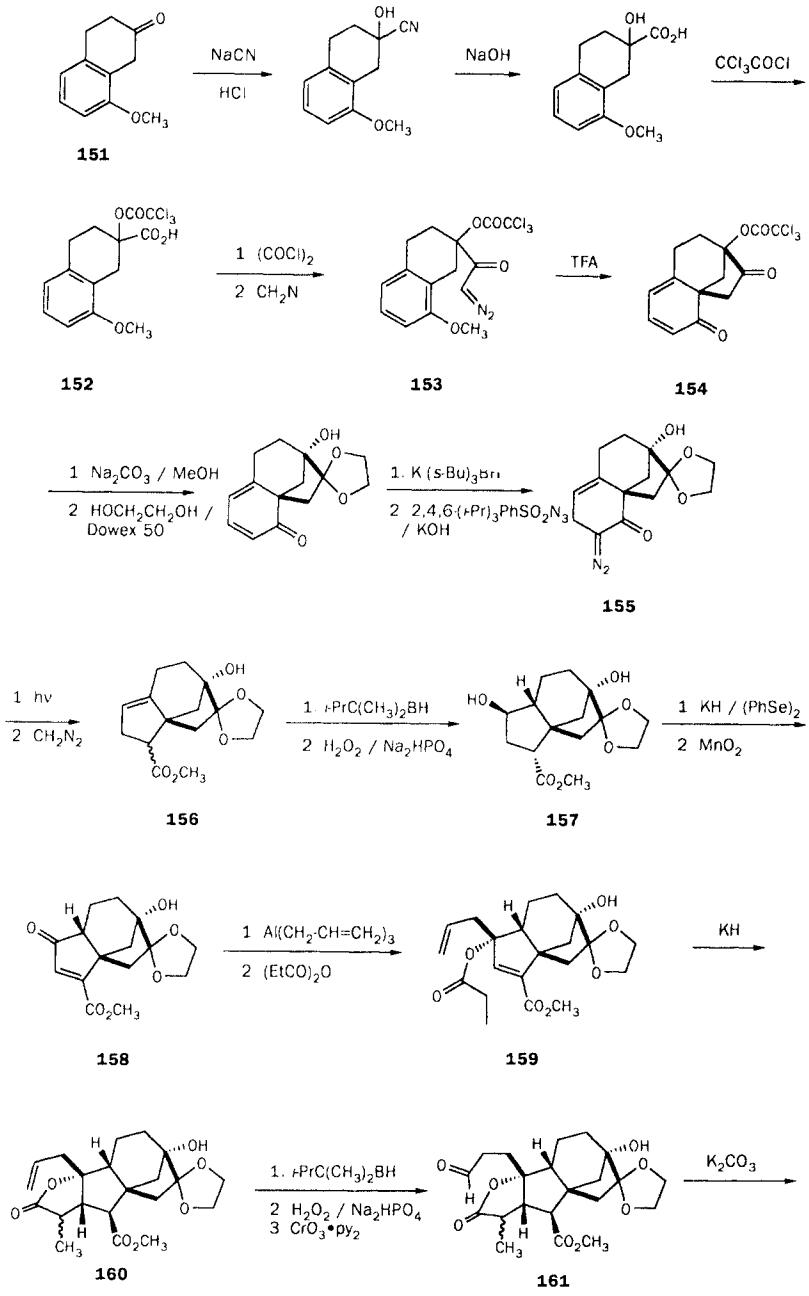
Extensive work[174,179,210,217] by the Mander group in Canberra has resulted in two syntheses of gibberellic acid as well as of related gibberellins. Two general routes to the gibberellins are followed. One of these features the creation of a "fluorene" intermediate to which the D ring is attached. In the other approach an octalone unit comprising rings B and C is elaborated to a B/C/D unit, the six-membered B ring is suffered to contract and the elements of ring A and the lactone function are then added. Critical to both of these approaches is the use of the Mander diazocarbonyl procedure for the closure of bridged-ring system.

The first synthesis of gibberellic acid **105** by Mander, Lombardo, and Turner[214] (Scheme 131) follows the hydronaphthalene approach beginning with tetralone **151**. Following reaction with hydrocyanic acid at the carbonyl group, a protected α-hydroxy acid **152** is prepared. Conversion to the corresponding diazoketone **153** is effected in the usual way.

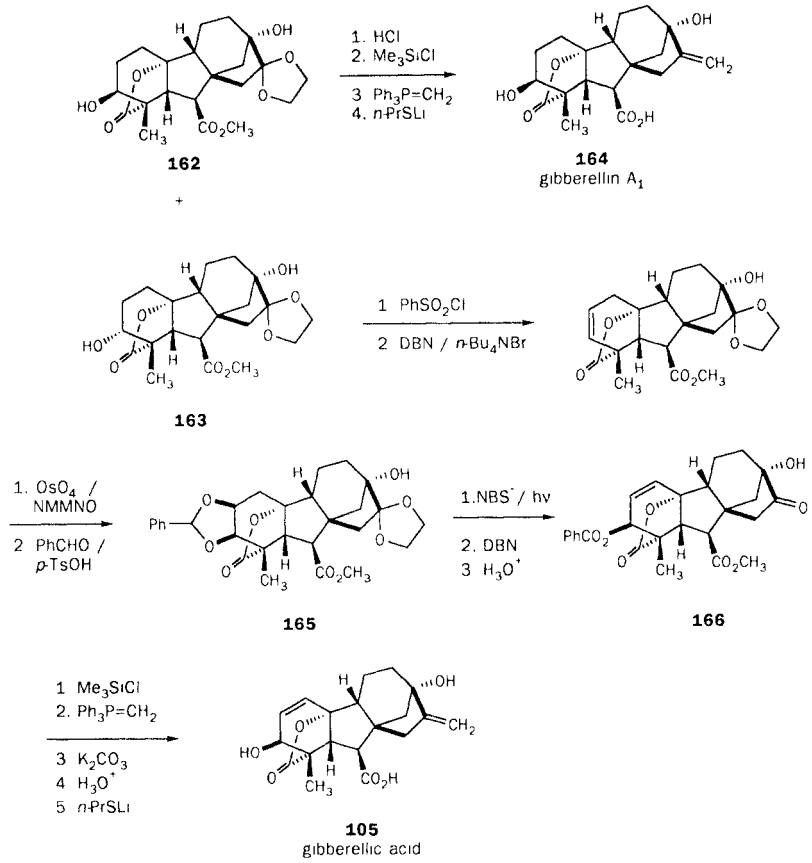
Treatment of the diazoketone with trifluoroacetic acid causes insertion into the aromatic ring with concomitant cleavage of the methoxy group. The ester function of the resulting dienone **154** is hydrolyzed, the less-hindered double bond of the diene system is reduced, and a diazo transfer reaction is carried out to provide diazoketone **155**. When this substance is subjected to photolysis followed by esterification, the gibberellin B/C/D synthon **156** is produced as a mixture of epimers at C-6. The first critical reaction for establishing the gibberellic acid stereochemistry is the reduction of 6-α-**156** with thexyl borane to yield the product of attack from the β face, diol **157**. Introducing a double bond through selenylation–elimination followed by allylic alcohol oxidation provides ketone **158**.

Although the stage is set here for the straightforward addition of the elements of ring A, considerable difficulty is encountered in nucleophilic addition to the ketone carbonyl group of **158**. Nevertheless, triallylalane is found to add from the convex face of the B/C ring system and the product alcohol is esterified with propionic anhydride to form **159**. With all of the atoms of the ring-A unit incorporated, a base-catalyzed internal Michael addition affords the mixture of epimeric lactones **160** and these are converted into aldehydes **161** by a hydroboration–oxidation sequence.

When base-catalyzed aldol cyclization is effected with **161**, a 1:1 mixture of the 3-hydroxy gibberellins **162** and **163** is formed. One of these, the β-isomer **162** is converted to gibberellin A_1, **164** by hydrolysis, Wittig methylenation, and ester cleavage.



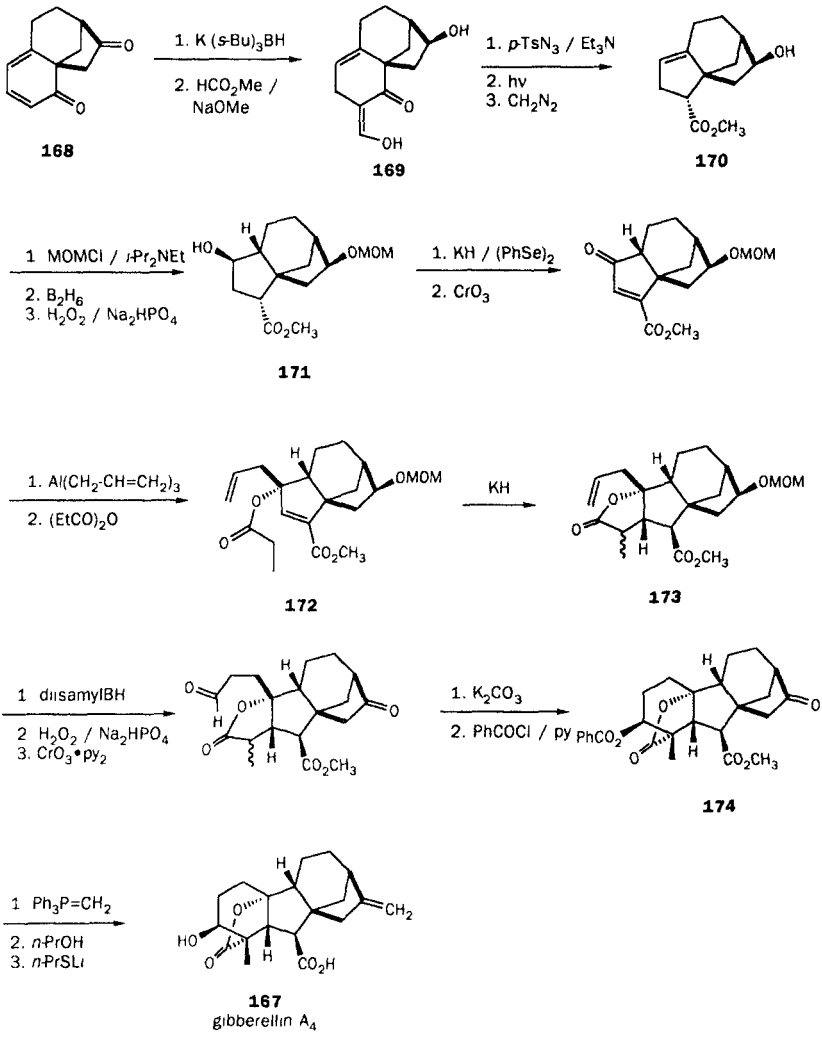
SCHEME 131. Mander's first synthesis of gibberellic acid.



SCHEME 131. Mander's first synthesis of gibberellic acid (*continued*).

To complete the synthesis of gibberellic acid, **105**, the 3α alcohol **163**, is derivatized and eliminated and the resulting olefin is hydroxylated to yield **165** after acetal formation with benzaldehyde. When the acetal is photolytically brominated, it suffers cleavage in the usual *trans*-diaxial fashion and the resulting bromide is eliminated in a subsequent step affording the $\Delta^{1,2}$-olefin **166**. Final Wittig methylenation and hydrolysis and cleavage of the ester functions yields the natural product gibberellic acid, **105**.

The Mander[213] approach (Scheme 132) is also applied to the synthesis of gibberellin A_4, **167**. Diene diketone **168**, fashioned in a manner equivalent to the preparation of **154** in the gibberellin synthesis, is partially and selectively reduced and the resulting product is formylated to yield **169**. Diazo transfer and Wolff rearrangement gives an unsaturated ester **170**. The hydroxyl group



SCHEME 132. Mander's synthesis of gibberellin A_4.

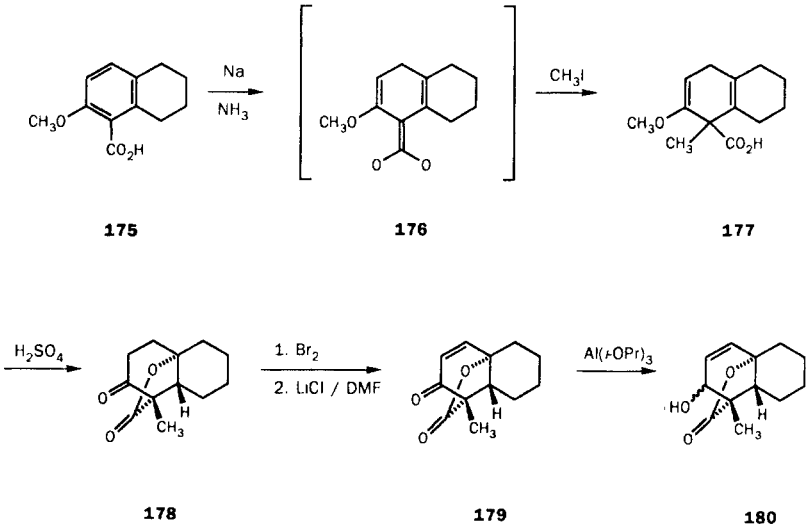
is then protected as a methoxymethyl ether and hydroboration is carried out to produce the product of borane addition from the less-hindered β face, alcohol **171**.

Following the same sequences employed for gibberellic acid leads to ester **172** which, again in concert with the results of the gibberellic acid synthesis, undergoes Michael addition under aprotic conditions to yield **173**. The lactone product is a mixture of epimers, but is isomeric only at the lactone α

position. Considering the anticipated problem in effecting this closure based on the difficulty of achieving appropriate orbital overlap of the enolate bond and the unsaturated ester π system, it is not clear why aprotic conditions should have been found to be the only successful mode of cyclization. Nevertheless, with the successful closure of the lactone the remaining critical step—the closure of ring A—can now be achieved once again by aldol cyclization. A 3:1 mixture of the desired C-3 β alcohol and its epimer are thus obtained in moderate yield and the major isomer is converted into benzoate **174**. Methylenation and ester cleavages lead to gibberellin A_4, **167**.

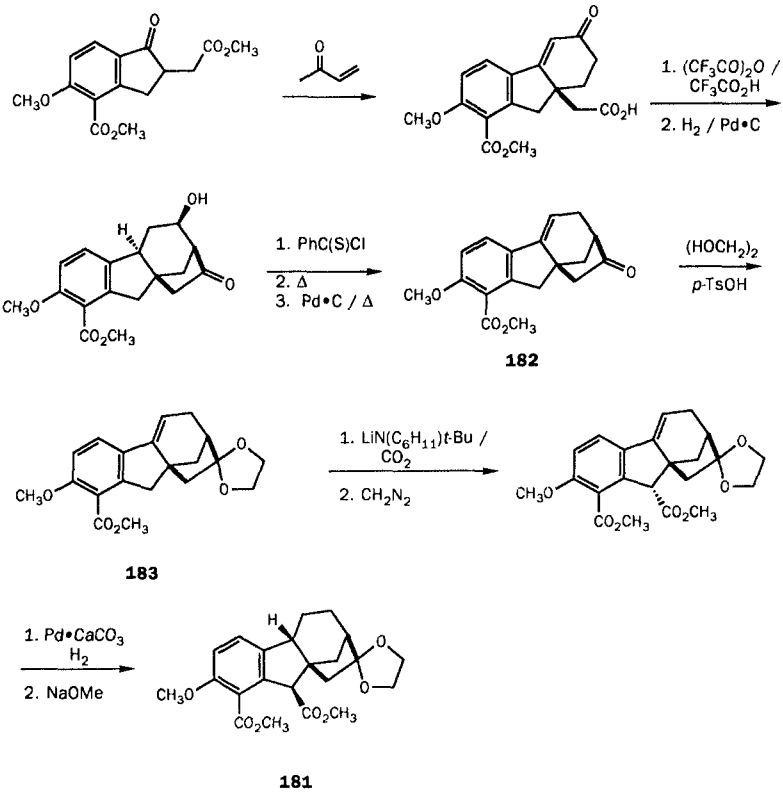
The second Mander synthesis[215,217] of gibberellic acid is based on the use of an aromatic ring-A synthon, incorporated as part of a hydrofluorene unit, and conversion of this ring by reductive methylation and functional group transposition into the fully functionalized gibberellin.

Pioneering work in the use of a benzenoid ring as the A-ring surrogate was carried out by Loewenthal and co-workers. Early in the history of gibberellin synthesis Loewenthal and colleagues[218] (Scheme 133) showed that reductive alkylation of *o*-methoxyhydronaphthoic acid **175**, via the derived dianion **176**, gives rise to enol ether **177** and that this, in turn, is converted to the characteristic gibberellin lactone structure **178** in the presence of acid. The unsaturated lactone **179** is then prepared by bromination–dehydrobromination. When the ketone carbonyl is subsequently reduced under thermodynamic control, a mixture of the 3β- and 3α-hydroxy lactones **180** is formed.



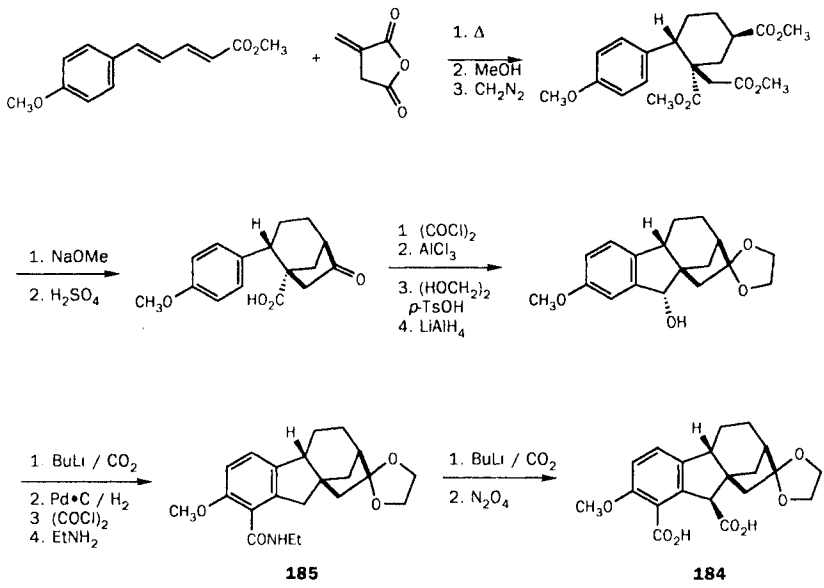
SCHEME 133. Lowenthal's gibberellin ring A methodology.

Loewenthal and Schatzmiller[219] also prepared (Scheme 134) the tetracyclic intermediate **181**, which is potentially useful for gibberellin A_4, **167**, if not for gibberellic acid itself. By application of the methodology developed for gibberone and epigibberic acid they prepared unsaturated ketone **182**. Deprotonation of the benzylic position of **183**, the derived ketal of **182**, and subsequent carbonation, reduction, and epimerization affords **181**. It is necessary to carry out the last reduction on the *epi* compound in order to achieve the correct stereochemistry at C-9.



SCHEME 134. Synthesis of a gibberelliin intermediate by Loewenthal.

Compound **181**, as the diacid **184**, was also synthesized (Scheme 135) by Baker and Goudie[220] at Glasgow, who prepared intermediate **185** using a Diels–Alder route to the construction of ring C. Two directed metalations and carbonations are used in this approach, but the product diacid **184**, when



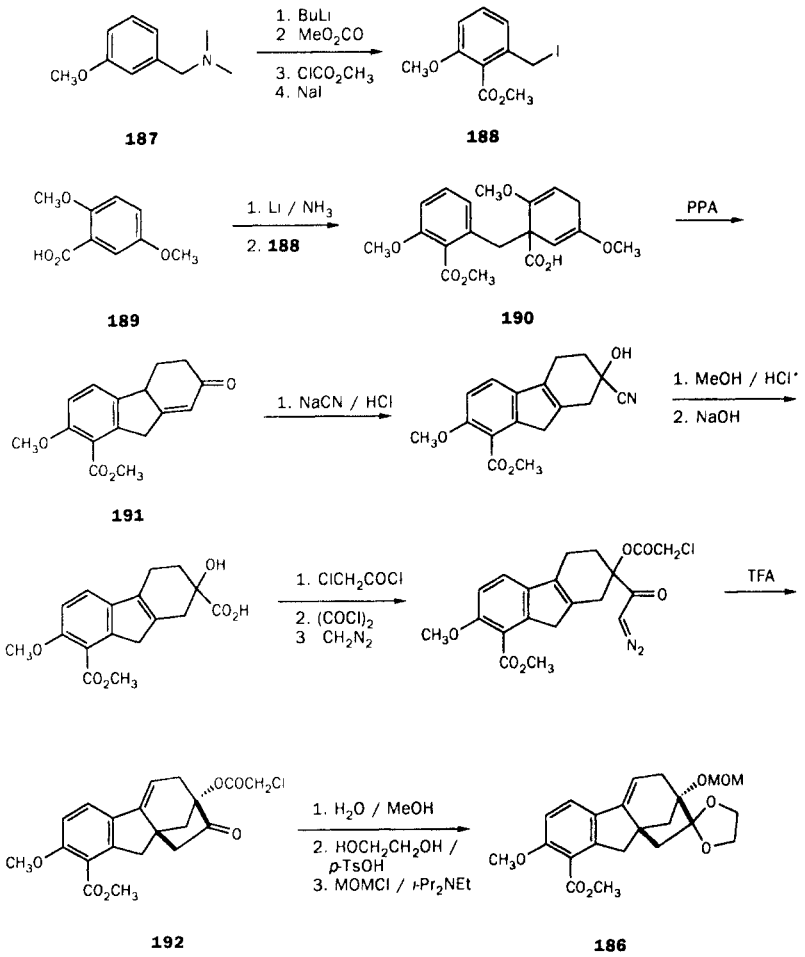
SCHEME 135. Synthesis of a gibberelliin intermediate by Baker.

subjected to reductive methylation, yields a dihydro product too unstable to be further useful.

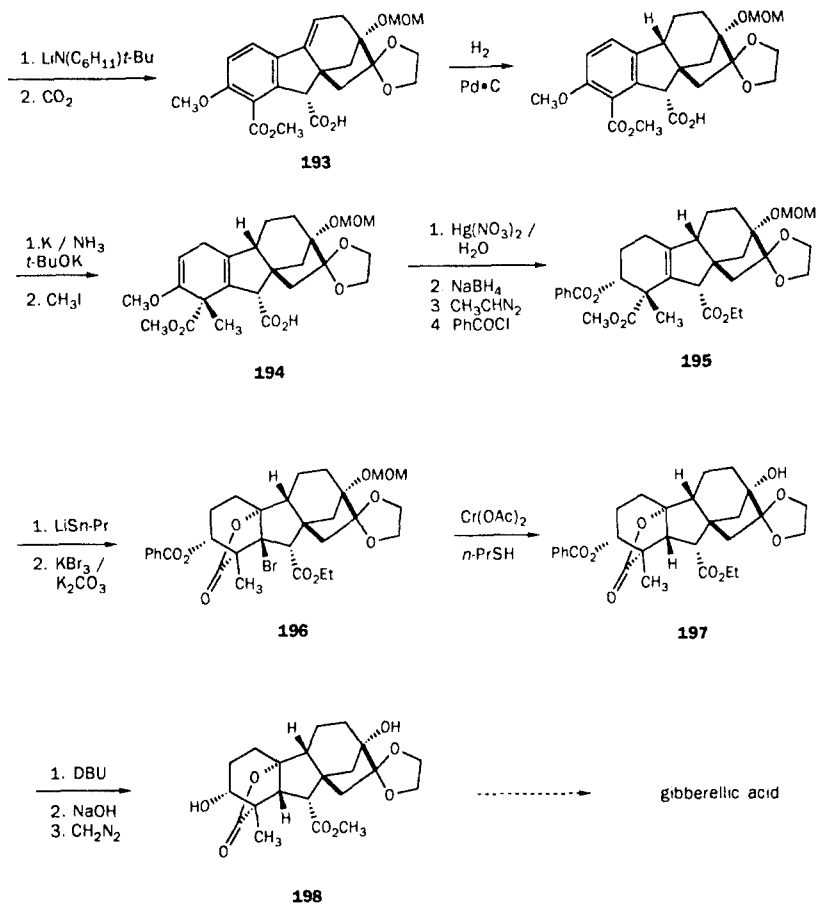
In the Mander hydrofluorenone synthesis of gibberellic acid **105**, the Loewenthal methodology is applied to ester **186**. The starting material for the synthesis of this key intermediate is *o*-dimethylaminoanisole, **187**. The amine is converted into the corresponding iodide **188** and this is used for alkylation of the dianion derived by dissolving metal reduction of substituted benzoic acid **189**. Treatment of **190** with polyphosphoric acid then effects the closure of the five-membered central ring of the hydrofluorenone unit with concomitant decarboxylation to afford ketone **191**. The Mander group protocol for the preparation of the kaurene–gibberellin bridged-ring system is applied to **191** in a seven-step sequence to yield tetracyclic ketone **192**. Since the reactions to follow for introduction of the ring-B carboxyl group and the ring-A functionality are to involve the use of basic reagents, the two oxygen functions of the C/D system are converted into base-stable protected functions. Thus the ketal ether **186** is carboxylated at the C-6 benzylic position to produce the α-oriented C-6 acid **193**. Reductive alkylation of **193** then leads to the dihydro aromatic product **194** in which methylation has occurred preferentially from the face opposite to the C-6 carboxyl group. Two critical factors determine the success of this reaction. First, the C-6 carboxyl stereochemistry determines the facial selectivity of the methylation. Second, the use

of an ester group at C-4 rather than a carboxylic acid group, as in the original Loewenthal work, prevents the decarboxylative oxidation of the A ring to a new aromatic unit.

A saturated oxygen function is now introduced at C-3 by hydrolysis of the enol ether in the presence of mercuric nitrate, and the resulting ketone is reduced to a C-3 α-alcohol. Esterification of the C-6 carboxyl group and formation of the benzoate ester of the C-3 hydroxyl group provides **195**. To complete the synthesis it is now necessary to form the A-ring lactone, to set the stereochemistry of a ring-junction proton at C-5, to introduce the 1,2-



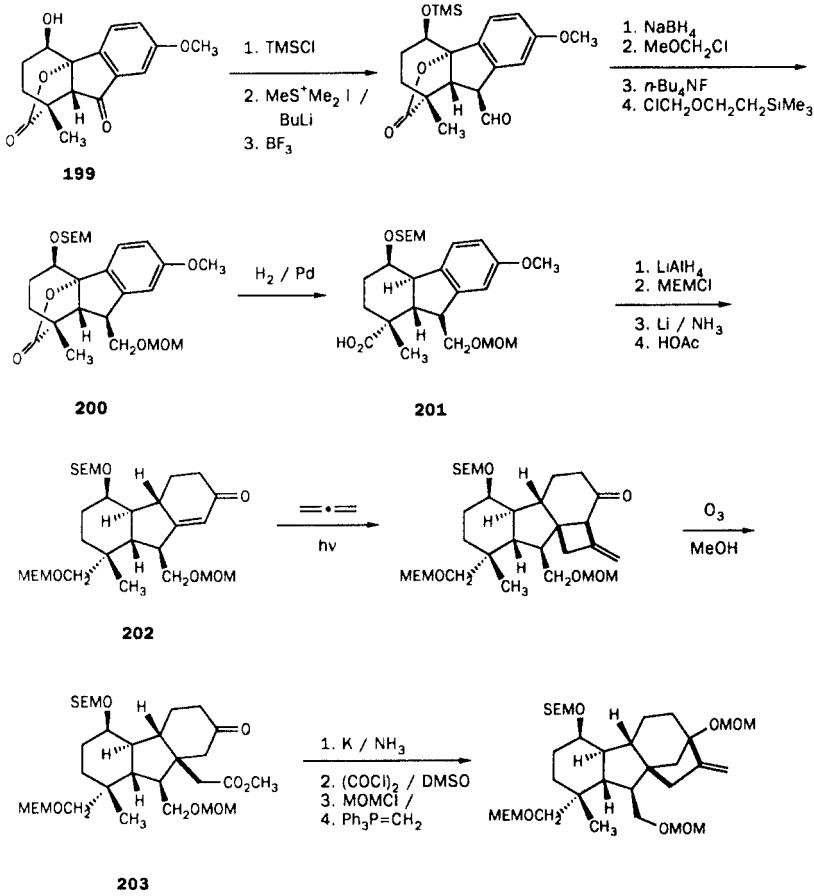
SCHEME 136. Mander's second synthesis of gibberellic acid.



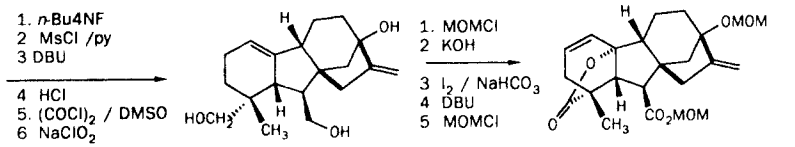
SCHEME 136. Mander's second synthesis of gibberellic acid (*continued*).

double bond, and to epimerize the centers at C-3 and C-10. The first two of these goals are achieved by selective cleavage of the carbomethoxyl group at C-4 of **195**, and bromolactonization followed immediately by reductive replacement of the C-5 bromine of **196** with a proton. The stereochemistry of this last process is shown to be entirely beta and the product is lactone **197**. A stepwise sequence is then followed for the epimerization of the C-6 carboxyl group and for the hydrolysis of the benzoate group at C-3. The result of these reactions, alcohol **198**, is an intermediate in the first synthesis of gibberellic acid by the Mander group[214] and has been successfully converted to the natural product.

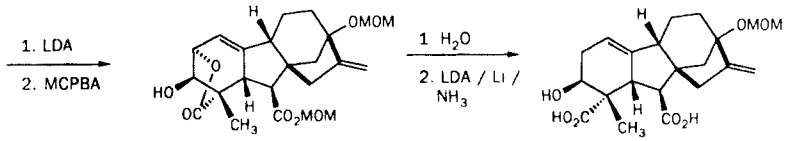
Yamada, Nagoaka, and Shimano[221, 222] carried out a total synthesis (Scheme 136) of gibberellic acid using hydroxy lactone **199**, originally prepared by Nakanishi and Hori[223] at Sendai (Scheme 137), as the starting material. Despite the presence of an A-ring lactone in the starting material, the oxygen function at C-10 must be removed. The Birch reduction to be carried out on the ring-C aromatic synthon not only reduces the benzenoid system, but both the benzylic C-10 oxygen function and the hydroxyl group at C-1 as well. As a consequence, hydrogenolysis at C-10 is carried out with **200** following a sequence which introduces the B-ring carboxyl function. The resulting product **201** is subjected to hydride reduction of the A-ring carboxyl

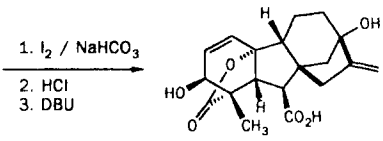


SCHEME 137. Yamada's synthesis of gibberellic acid.



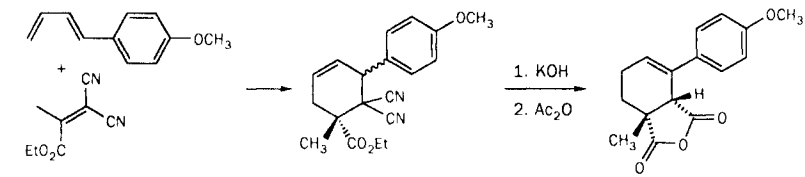
204

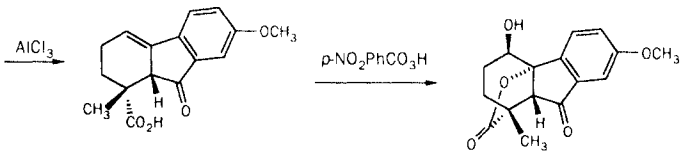




105
gibberellic acid

SCHEME 137. Yamada's synthesis of gibberellic acid (*continued*).





199

SCHEME 137a. Nakanishi's preparation of a gibberellin intermediate.

and then to the conditions of Birch reduction to afford protected triol-enone **202**.

To add the last ring, photocycloaddition of allene is carried out and the methylenecyclobutane product is ozonized and cleaved to keto ester **203**. Dissolving metal pinacol-like reduction affords the gibberellin ring system and following D-ring methylenation a multistep sequence is used to re-functionalize C-10. The product of this process is lactone **204**, and it is carried through a sequence similar to that used by Corey for the A-ring functionality to produce gibberellic acid, **105**.

L. Antheridiogens

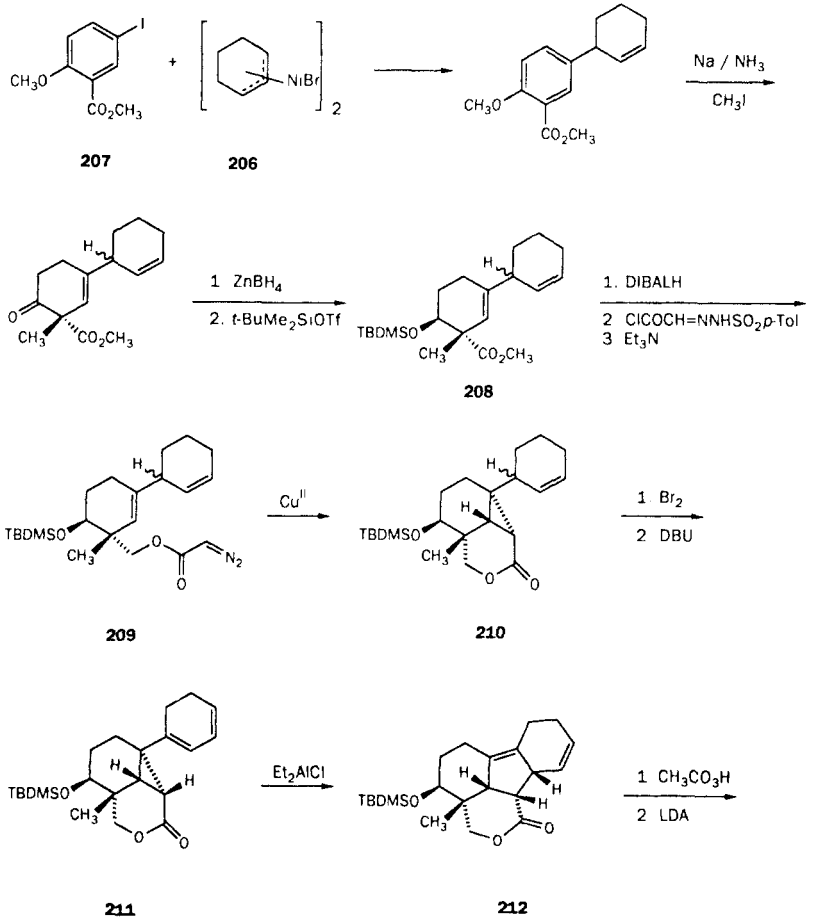
(1) Antheridiogen-An

Antheridiogen-An, **205**, is a gibberellin-like plant growth hormone. The C/D ring system of the antheridanes resembles that of atisirane, however, rather than the kaurane-derived gibberellin structure. The first synthesis of **205** was carried out by Corey and Meyers[224] and served, *inter alia*, to demonstrate the correct stereochemistry of the C-3 hydroxyl group.

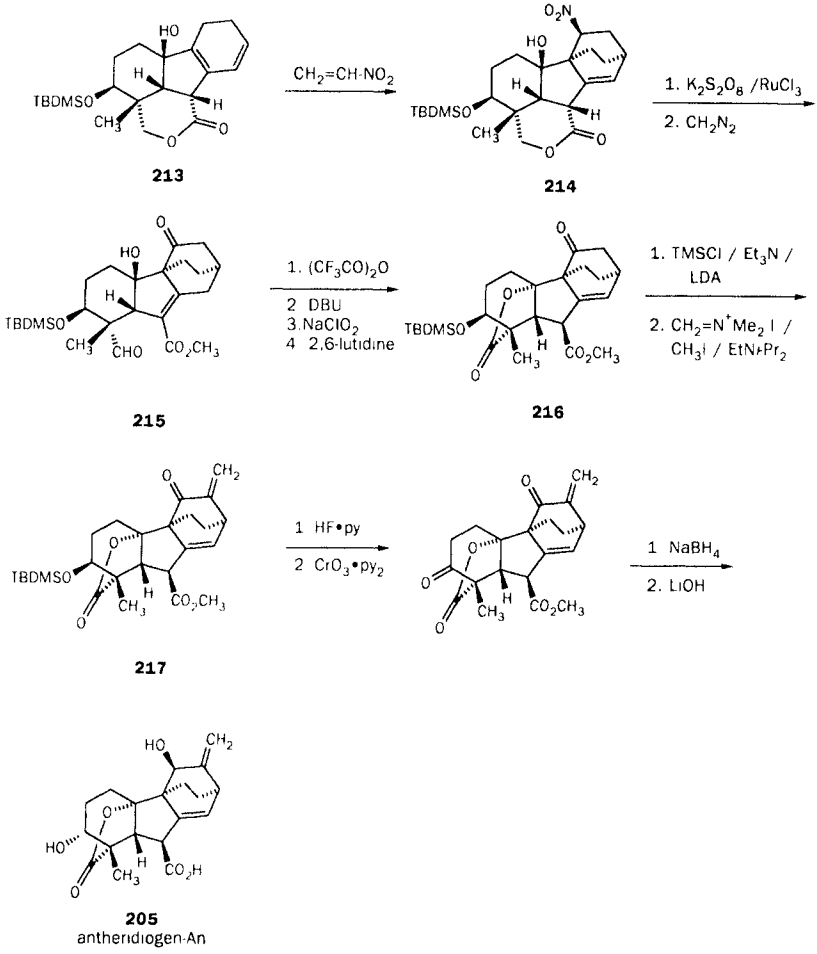
The synthetic plan (Scheme 138) is based on the initial construction of an A/C unit. The functionality and stereochemistry of the A ring is generated following the Loewenthal approach,[218] and the central B ring is to be added through a stereocontrolled, internal diazoketone cyclopropanation followed by vinyl-cyclopropane rearrangement. Completion of the plan is the elaboration of the final D ring on to the tricyclic intermediate.

To this end the A/C unit is constructed by the coupling of the π-allyl nickel reagent **206** to iodosalicyclate **207**. Reductive methylation of the A ring followed by further reduction of the C-3 carbonyl group and protection affords **208**. The incorporation of the B-ring elements in stereoselective fashion is carried out by reducing the carboxyl function of **208** and converting the resulting alcohol to a diazo ester, **209**. Copper-mediated carbenoid insertion affords lactone **210**. A second double bond is introduced into the C-ring unit by bromination and dehydrobromination. The bromination step affords a mixture of dibromides and those that do not yield **211** on base treatment are eventually recycled. A Lewis-acid-catalyzed, vinyl-cyclopropane rearrangement is effected to give the tricarbocyclic intermediate **212**. The stereochemistry at carbons 5, 6, and 8 follows necessarily from the initial stereochemistry of the cyclopropane unit and this in turn is governed by the relative configuration of the initial ring-A carboxyl group. For the eventual introduction of the C-10 oxygen function, diene **212** is epoxidized. Treatment of the product with base affords alcohol **213**.

The C/D ring system is constructed through Diels–Alder cycloaddition of nitroethylene to **213**, and both the nitro group and the lactone functions of **214** are hydrolyzed. Oxidation and esterification then yield ester aldehyde **215**. A four-step sequence then accomplishes the migration of the double bond to $\Delta^{8,9}$, establishment of the stable configuration of the C-6 carbomethoxyl, oxidation of the C-4 aldehyde to a carboxyl group, and finally formation of the A-ring lactone by displacement of the trifluoroacetate group formed in the first of these steps. The conversion of this product, **216**, into antheridiogen-An **205** is then carried out through Mannich condensation–elimination to **217** followed by a redox and hydrolysis sequence. Analysis of



SCHEME 138. Corey's synthesis of antheridiogen-An.



SCHEME 138. Corey's synthesis of antheridiogen-An (*continued*).

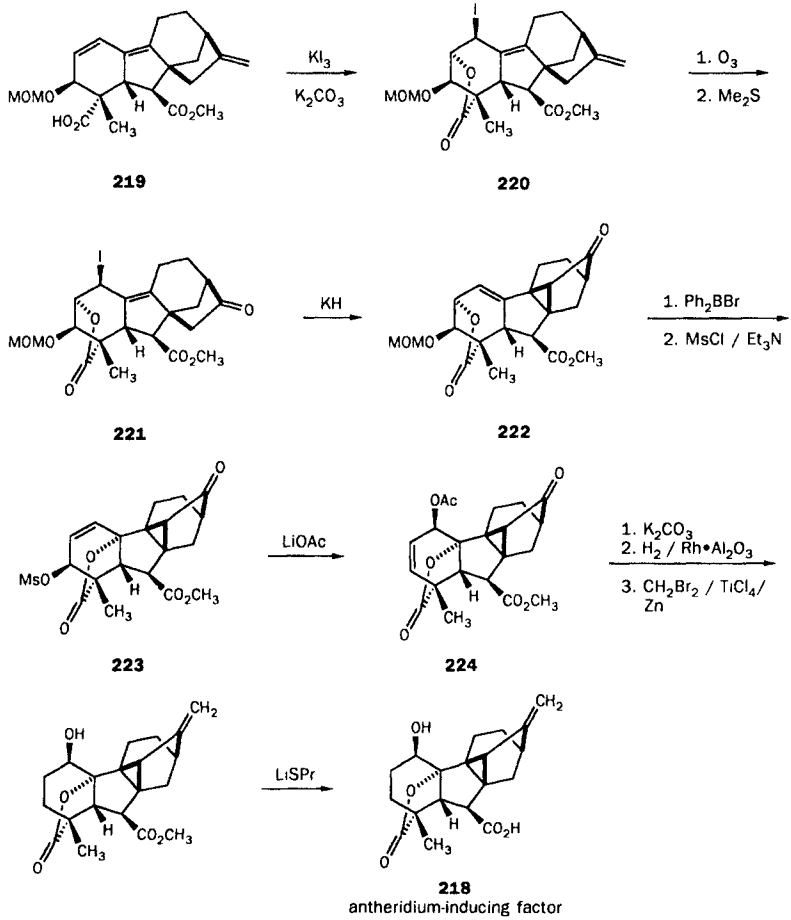
the spectroscopic and chromatographic characteristics of the synthetic material indicate that the C-3 hydroxyl group has an α orientation rather than the epimeric one originally suggested for the natural product structure.

(2) Antheridium-Inducing Factor

The antheridium-inducing factor, **218**, from the fern *anemia mexicana*, has a particularly unusual *pentacyclic* structure. Its synthesis (Scheme 139) starting

from **219**, a degradation product of gibberellin A_7, has been reported by Furber and Mander[225] and is illustrated in Scheme 139.

An iodolactone **220** is prepared from the starting acid and the exo-methylene unit of ring C is oxidatively cleaved to afford ketone **221**. The key step in the Mander approach to these pentacyclic members of the *antheridium* class of diterpenes is to create the cyclopropane ring by internal S_N2' alkylation. Thus treatment of **221** with potassium hydride provides cyclopropyl ketolactone **222**. Lewis-acid-catalyzed cleavage of the methoxymethyl protecting group also initiates a rearrangement of the ene-lactone system to the thermodynamically less stable isomer. Mesylation of the intermediate alcohol provides **223**.



SCHEME 139. Mander's synthesis of antheridium-inducing factor.

A second S_N2' substitution provides **224** in mixture (5:4) with its allylic isomer. The major isomer **224** is then carried through a reduction and hydrolysis sequence to produce the natural product **218**.

M. Aphidicolin

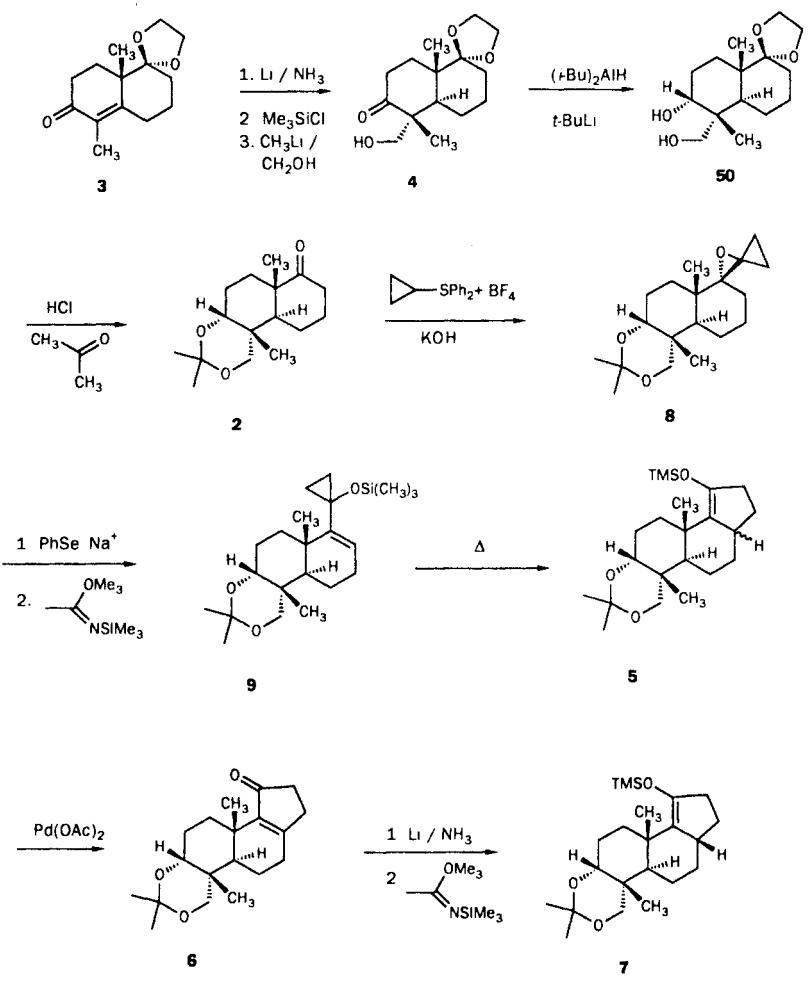
Aphidicolin **1** is a tetracyclic tetraol mold metabolite of the stemodia family which exhibits significant antiviral and antitumor activity.[226-227] Following the isolation of the compound and the demonstration of its potential pharmacological uses, a number of research groups pursued its total synthesis. The principal problems to be solved in the synthesis of aphidicolin are the construction of the tetracyclic ring system with the appropriate stereochemistry of the C/D ring system and the stereoselective introduction of four hydroxyl groups.

The first syntheses of aphidicolin were reported independently by McMurry[228, 229] and by Trost[230] and their colleagues in 1979. In the Trost synthesis[230] (Scheme 140) carried out at the University of Wisconsin, the key to the synthesis is the annulation of a five-membered ring onto an existing A/B bicyclic intermediate **2**. To prepare the bicyclic substrate the Kitahara[64] enone ketal **3** is subjected to a reductive formylation sequence to yield ketol **4**. Reduction and acetonide formation with concomitant cleavage of the dioxolane group then affords ketone **2**.

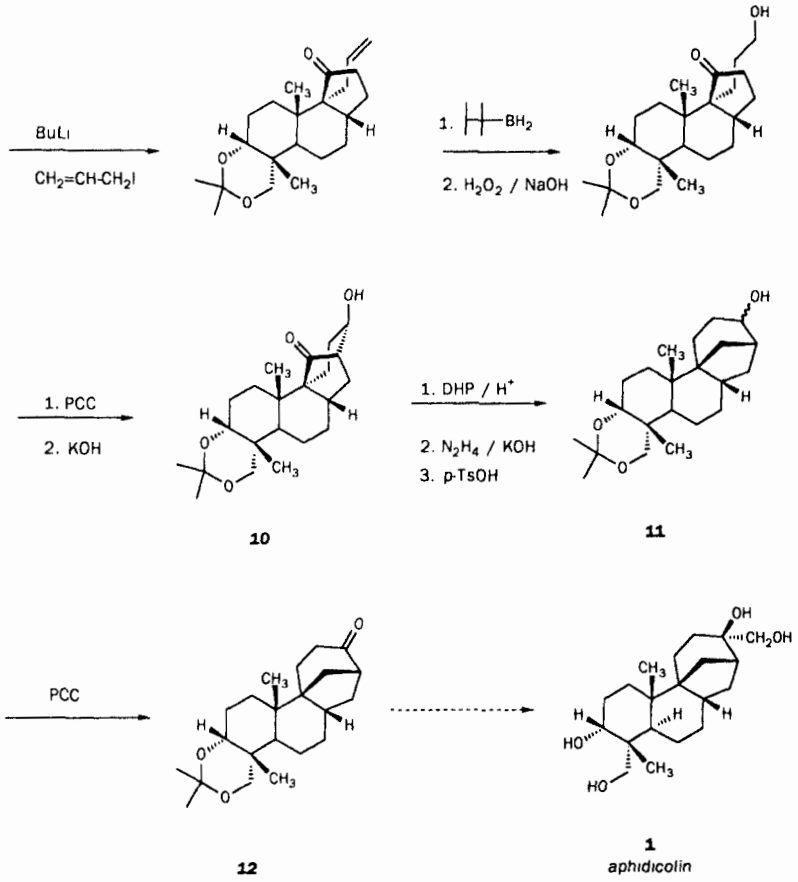
Using the spiro-annelation sulfur ylide chemistry[231, 232] developed in the Trost laboratory, **2** is converted into enol silyl ether **5**. Palladium acetate oxidation of the enol ether affords enone **6** and lithium–ammonia reduction and trapping of the enolate yields **7**. Two critical reactions in this route are the cleavage of spiro epoxide **8** by a "merged substitution–elimination" pathway to form cyclopropanol ether **9** and the generation of the correct stereochemistry at C-8 in **7**. Ketone **2**, used also by McMurry in an aphidicolin synthesis, is spiro-annulated under reversible conditions with a cyclopropyl diphenylsulfonium salt to yield **9**. This epoxide is impervious to normal *cis*-elimination conditions with alkyl lithium reagents, a result attributed to the equatorial nature of the C-8 α proton. Alternatively, exposure of **8** to phenylselenide anion effects elimination to form **9**. Thermal olefin–cyclopropane rearrangement of **9**, however, gives a mixture of epimers at C-8 of **5**. To overcome this lack of selectivity, the Trost group carried out an oxidation of **5** followed by a dissolving metal reduction and an enolate trapping reaction to produce **7** selectively. The stereochemistry of the bridged C/D system is then set by allylation of the enolate derived from **7** from the less-hindered α face. Completion of the tetracyclic system is then carried out by a standard sequence of hydroboration–oxidation and aldol closure to

provide ketol **10**. Wolff–Kishner reaction on the protected ketal followed by hydrolysis produces alcohol **11**, which on oxidation affords *nor* ketone **12**. Conversion of this *nor* ketone to aphidicolin is illustrated in Scheme 141.

The synthesis of aphidicolin by McMurry[228, 229] and co-workers, then at the University of California, Santa Cruz, like that of Trost, utilizes bicyclic ketone **2** as a key intermediate (Scheme 141). Its preparation is carried out in a similar fashion as well starting from the ketal **3**. From this point, however, the two routes are dissimilar. In the McMurry work **2** is methallylated to give



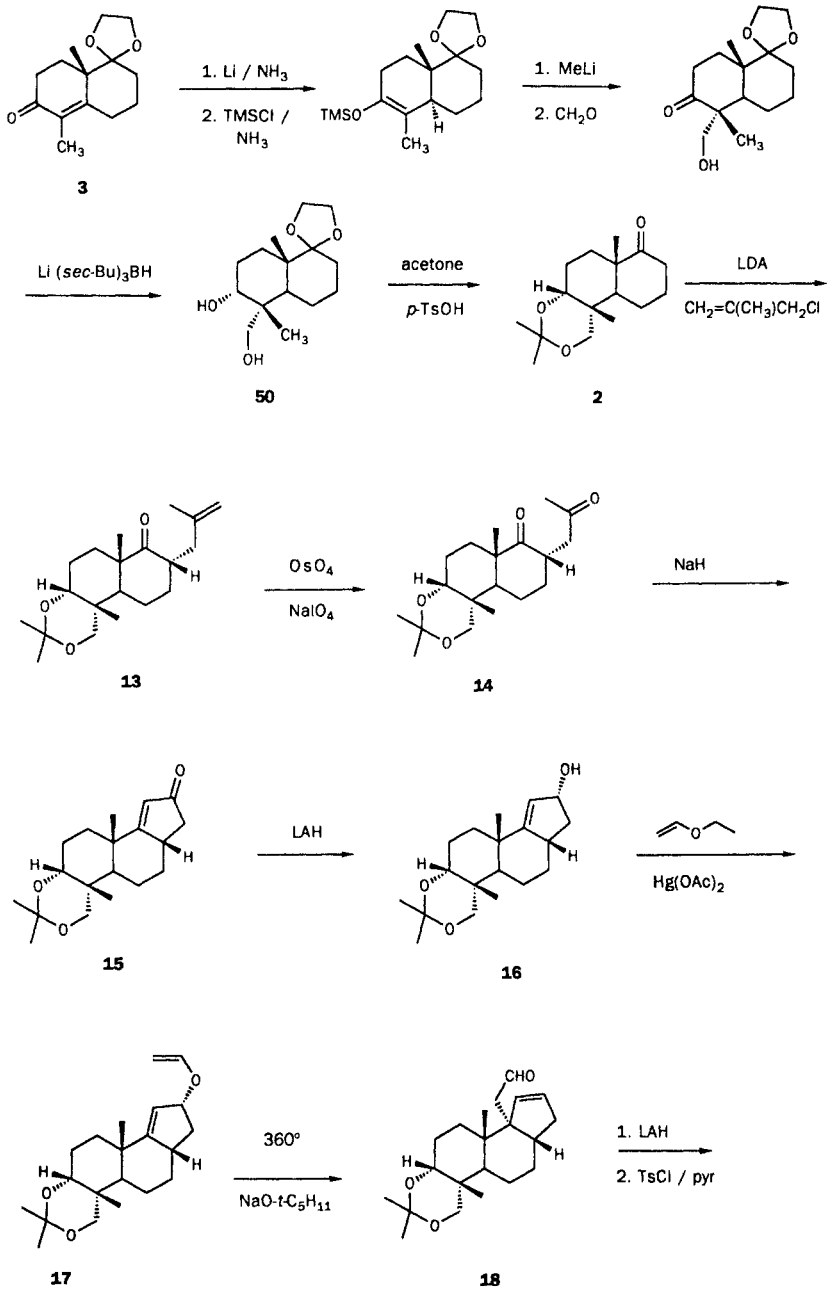
SCHEME 140. Trost's synthesis of aphidicolin.



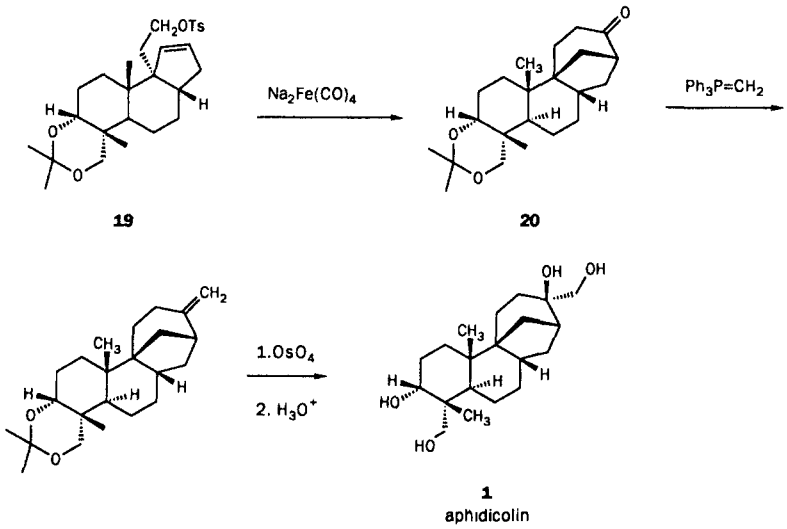
SCHEME 140. Trost's synthesis of aphidicolin (*continued*).

13 and the alkylation product is cleaved with osmium tetroxide–periodate to afford diketone **14**. The stereochemistry of the acetonyl side chain of the latter, as anticipated, is α and equatorial. Cyclization of **14** then affords tricycle **15**.

Stereoselective introduction of the carbon skeleton of the bridged-ring system is carried out utilizing a Claisen rearrangement. Thus conversion of **15** to the pseudo-equatorial alcohol **16** and formation of vinyl ether **17** insures that rearrangement will yield a product with an α-orientation of an acetaldehyde unit. Normal thermolysis conditions, however, result in significant elimination of the vinyl ether group of **17** and as a consequence the



SCHEME 141. The synthesis of aphidicolin by McMurry.

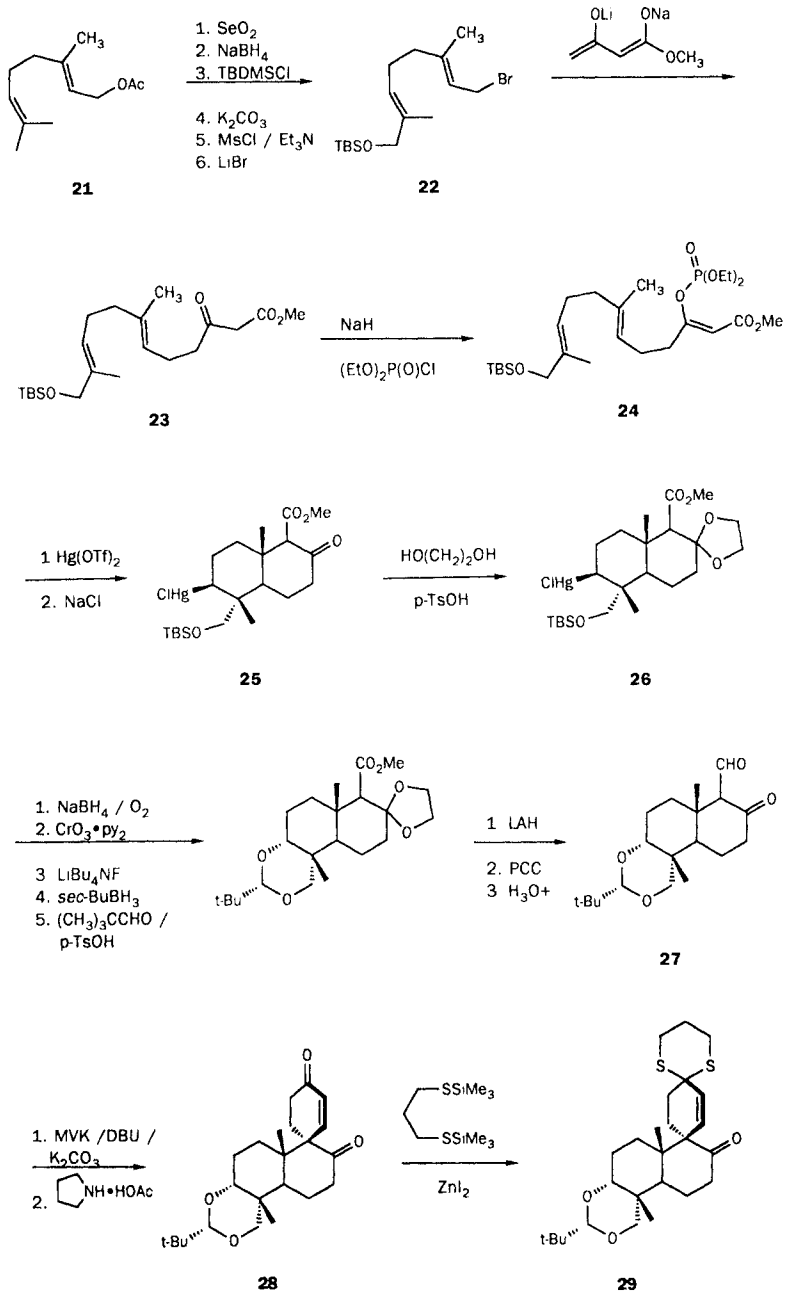


SCHEME 141. The synthesis of aphidicolin by McMurry (*continued*).

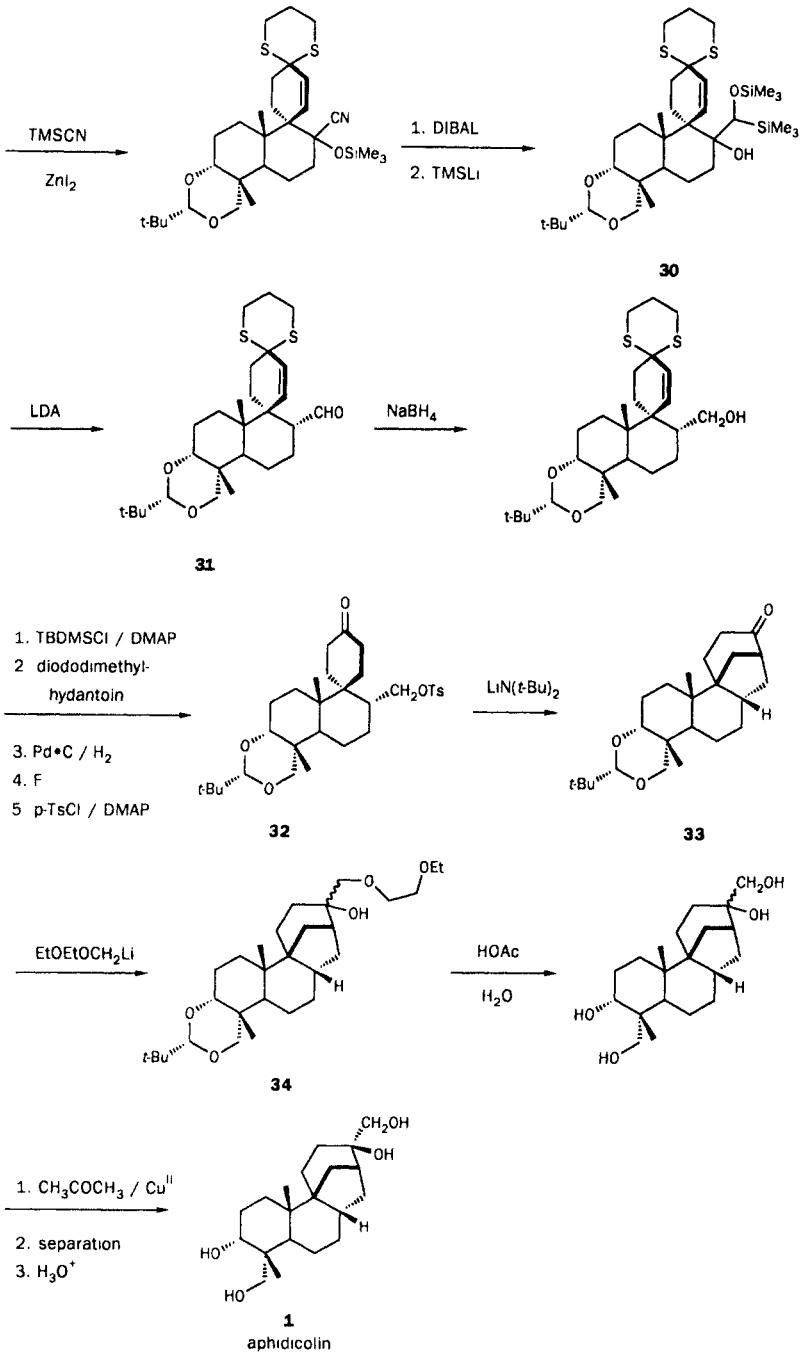
rearrangement is conducted in the presence of strong base. The thermal product **18** is then converted to tosylate **19**.

As this stage McMurry utilizes a carbonylation procedure that not only adds the one remaining carbon atom of the aphidicolin ring system, but also affects the closure of the final ring. Thus treatment of unsaturated tosylate **19** with "Collman's Reagent," disodium tetracarbonylferrate (a reaction that fails in a model system!), produces tetracyclic ketone **20** in 30% yield. The conversion of **20** to aphidicolin, **1**, is carried out by the method described by Hesp and co-workers[226, 227] by methylenation of the ring-D ketone function followed by hydroxylation and hydrolysis. Unfortunately, this step is only marginally selective (3:2) in favor of the aphidicolin stereochemistry.

An alternative approach to the formation of the bridged system of aphidicolin as well as the A/B decalin is illustrated in the work of Corey, Tius, and Das[233] at Harvard University. Here (Scheme 142) the decalin A/B unit is constructed by polyene cyclization. Starting from geranyl acetate **21**, a multistep sequence affords bromoether **22**, which upon treatment with the mixed dienolate of acetoacetic ester affords β-keto ester **23**. After conversion of the keto group to an enol phosphate, **24**, the polyenic system is cyclized with mercuric ion. Conversion of the initially formed triflate to the corresponding chloromercury compound affords keto ester **25**. Following ketalization of this material the chloromercury group of **26** is reductively hydroxylated to a mixture of C-3 epimers. These are then converted by an



SCHEME 142. Corey's synthesis of aphidicolin.



SCHEME 142. Corey's synthesis of aphidicolin (*continued*).

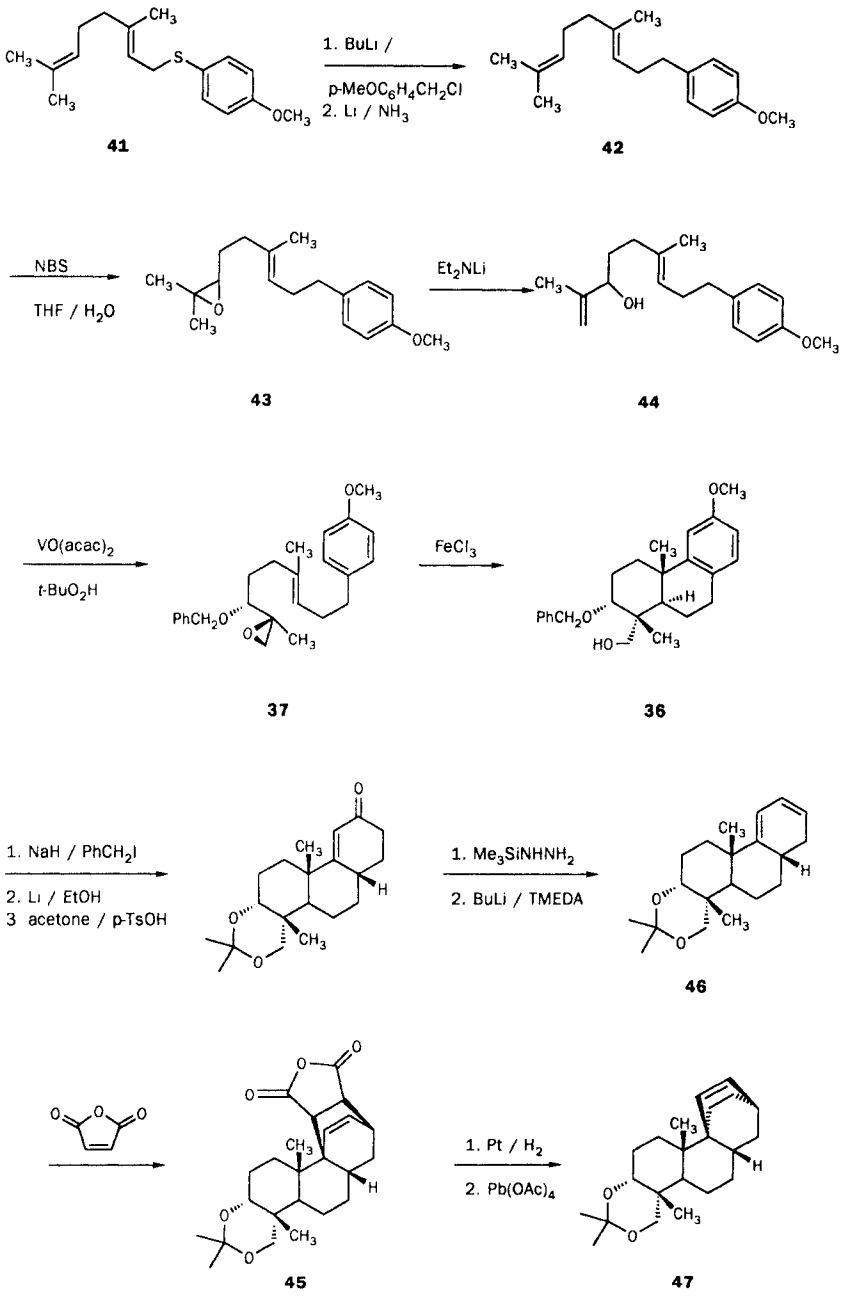
oxidation–reduction, and functional group manipulation sequence into ketoaldehyde acetal **27**. Addition of the 6-membered spiro-D ring is accomplished by Robinson annelation, yielding **28**.

With the finding that the C-8 carbonyl group of the derived thioketal **29** is more prone to enolization than to carbonyl addition, a five-step sequence is found necessary for the addition of the remaining carbon atom required for formation of the bridged system. The key step in this sequence is the base-catalyzed elimination reaction of silyl glycol **20** with eventual formation of alcohol **31**. A second five-step sequence is then employed for the hydrolysis of the thioketal and the formation of keto tosylate **32**. Kinetic enolate formation from **32** is favored from the β side of the spiro ketone and results in an internal alkylation to form **33**. At this stage, addition of ethoxyethoxymethyl lithium results in a 1:1 mixture of C-16 epimers, **34**, which are hydrolyzed to afford aphidicolin and its isomer, **35**. Interestingly, in the McMurry synthesis the addition of an alkyl lithium reagent to a similar intermediate, **20**, gives predominantly the wrong isomer. The epimers are separable, however, as their bisacetonides and hydrolysis after separation yields the natural product **1**.

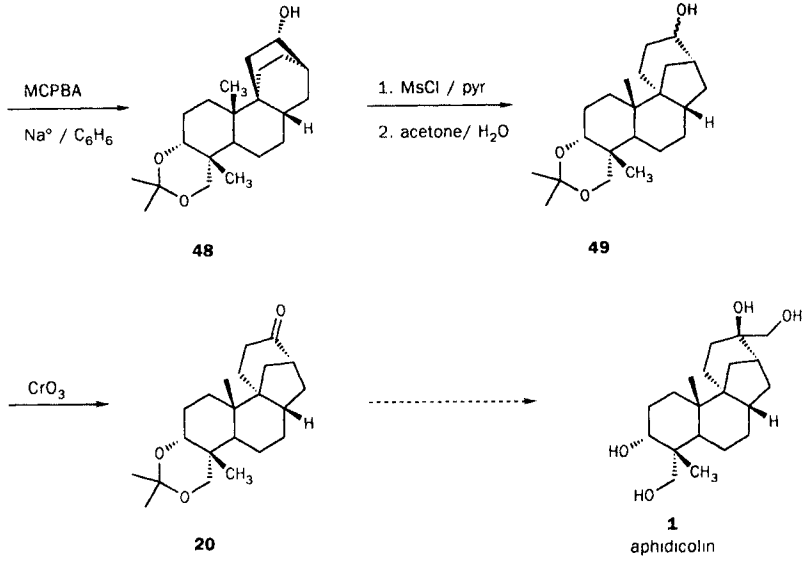
The van Tamelen approach[234] (Scheme 143) to the synthesis of aphidicolin is also based on a biomimetic polyene cyclization. In this scheme a tricyclic intermediate, **36**, results from the cyclization of **37**. The route is patterned on the cyclization of "exocyclic" epoxides of this type as an approach to diterpene synthesis first demonstrated by Goldsmith and Phillips[52] at Emory University, who converted **38** (Scheme 144) to a mixture of the abietane- and podocarpane-type tricyclic alcohols **39** and **40**. Unfortunately, in all of these cases the yield of cyclized material is low and in the van Tamelen synthesis only 12% of **36** is isolated.

To prepare **36**, sulfide **41** is alkylated to give **42** and this diene is subjected to selective epoxidation to yield **43**. Following conversion of **43** into allylic alcohol **44**, a Sharpless epoxidation affords **37** as the only diastereomer.

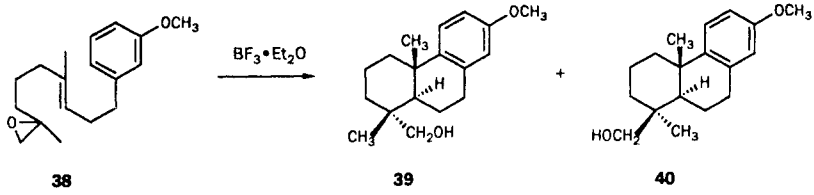
In contrast to the Trost–McMurry and Corey approaches, the bridged system in this approach is created first as a 2.2.2-bicyclooctane system and then rearranged to the 3.2.1-aphidicolin structure. The addition of the fourth ring is carried out via a Diels–Alder sequence that produces **45**. Interestingly, the least-hindered approach of maleic anhydride to the diene system of **46** is from the β face. As a consequence of the folding of the rings engendered by the two double bonds of ring C, cycloaddition from the α face of the diene is significantly encumbered. Following the Diels–Alder reaction, reduction and reintroduction of a double bond by bis-decarboxylation with lead tetraacetate gives **47**. Epoxidation followed by sodium metal reduction produces alcohol **48** in low yield. This 2.2.2-bicyclic system is then rearranged via the derived mesylate, in a second biomimetic sequence, to yield the 3.2.1-



SCHEME 143. Van Tamelen's synthesis of aphidicolin.



SCHEME 143. Van Tamelen's synthesis of aphidicolin (*continued*).

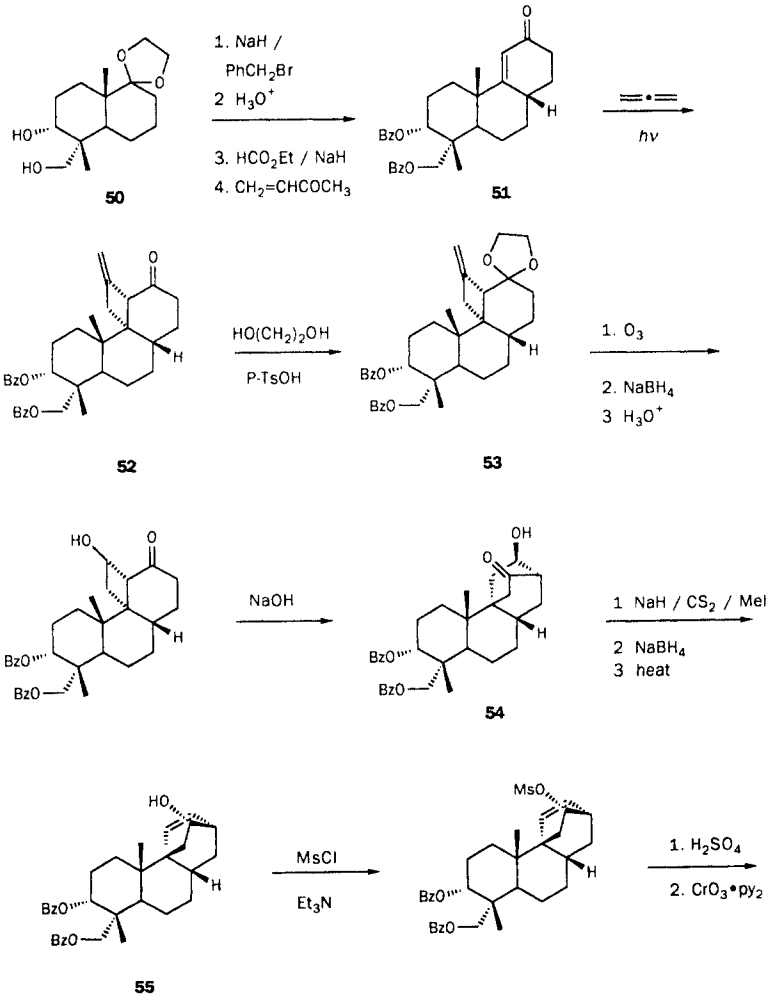


SCHEME 144. Goldsmith's diterpene intermediates from biomimetic epoxide cyclization.

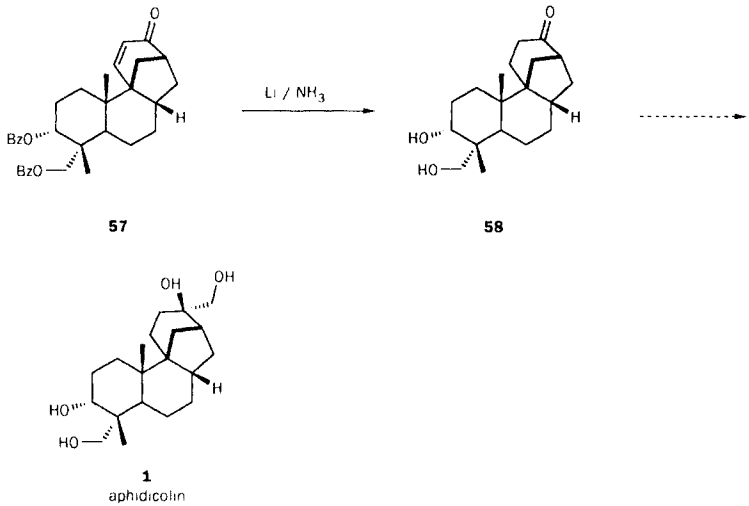
biclooctanol **49**, which upon oxidation affords **20**. The conversion of this ketone to aphidicolin had been carried out previously.

A synthesis of aphidicolin by Bettolo, Tagliatesta, Lupi, and Bravetti[235, 236] from Rome (Scheme 145) also makes use of the biomimetic rearrangement of a 2.2.2-bicyclooctane to a 3,2,1-system for formation of the C/D ring system. The 2.2.2 bridged-ring substrate is produced via aldol cyclization in this case rather than by cycloaddition, as in the van Tamelen synthesis. Starting from the McMurry–Trost diol **50**, a tricyclic enone **51** is produced via a Robinson annelation sequence. Wiesner allene photocycloaddition[165, 166] affords methylene cyclobutene **52**. In this case the facial selectivity of the cycloaddition is alpha. In contrast to diene **46** used in the

van Tamelen β-face addition to enone, **51** is blocked by the C-10 methyl group. Ozonolysis of the derived acetal, **53**, is followed by a sequence of reduction, hydrolysis, and aldol cyclization to yield bridged ketol **54**. After a Chugayev elimination of the hydroxyl group of **54**, the remaining ketone function is reduced with hydride to yield alcohol **55**. The success of this approach, as in that of van Tamelen, depends on generating the correct stereochemistry of the leaving group in the 2.2.2 to 3.2.1 rearrangement. The borohydride reduction in the case yields only the desired alcohol **55** and



SCHEME 145. Bettolo's synthesis of aphidicolin.

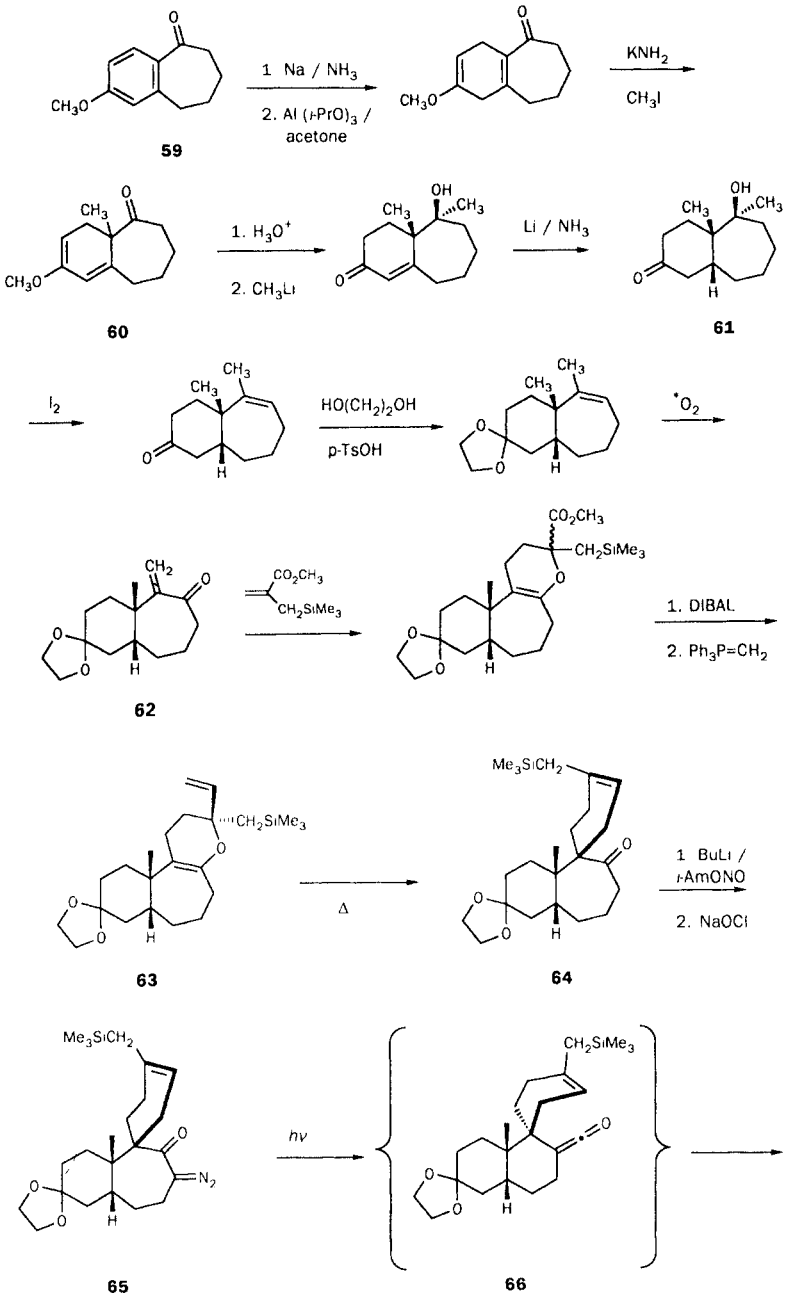


SCHEME 145. Bettolo's synthesis of aphidicolin (*continued*).

rearrangement of the derived mesylate **56** followed by oxidation of the allylic alcohol product affords ketone **57**. Finally, lithium in ammonia reduction yields dihydroxyketone **58**, which has been previously converted to aphidicolin.

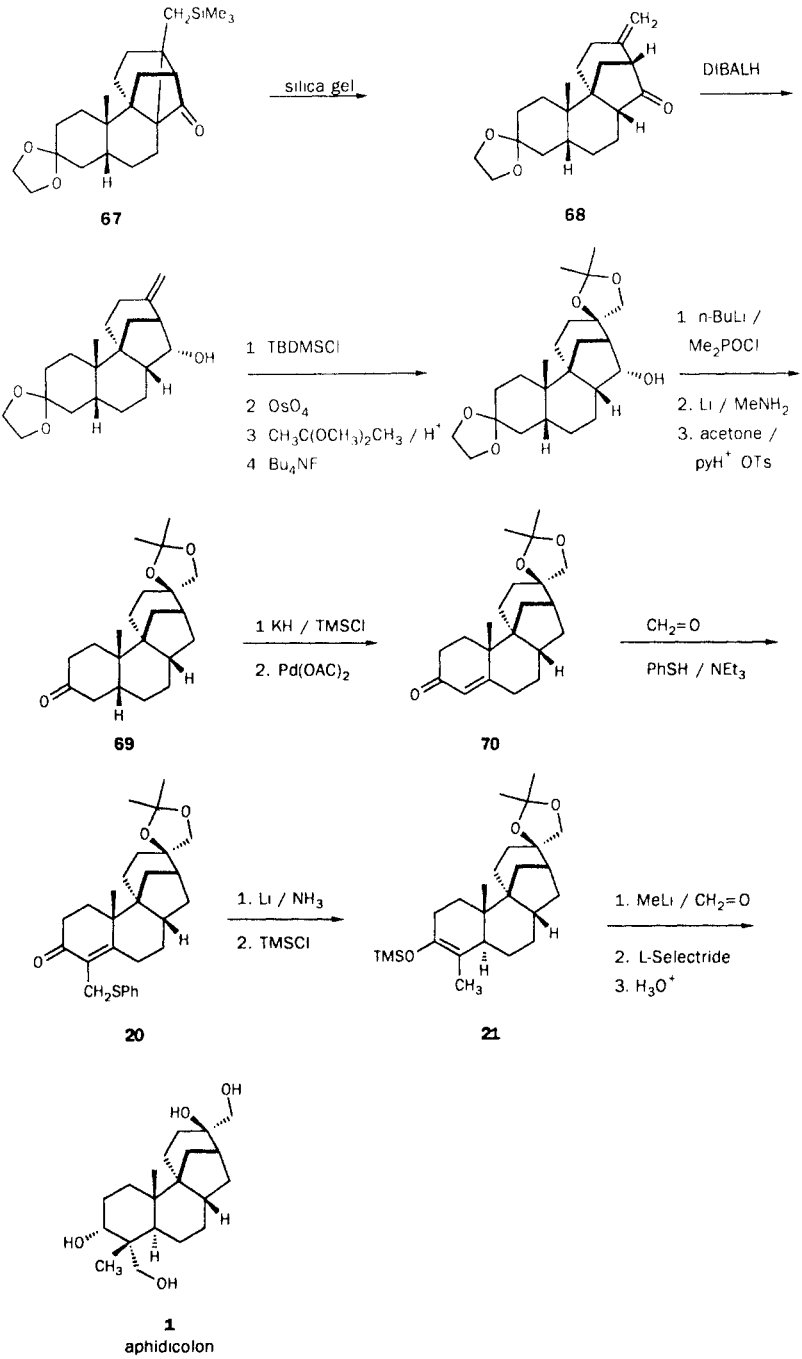
A marked difference in approach characterizes the synthetic approach (Scheme 146) to aphidicolin of Ireland and co-workers.[237–239] Their route, which incorporates a Claisen rearrangement, features a novel application of the Meinwald–Cava[240] (Wolff rearrangement) ring-contraction sequence to generate the B/C/D ring system in a single step. In addition the Ireland approach is selective for the natural stereochemistry of the C-ring diol unit. Overall, however, the scheme, like that of Corey, is lengthy.

The starting material for the Ireland synthesis is the benzosuberone **59**.[237, 241] Birch reduction, reformation of the ring-B keto group, and base-catalyzed methylation affords dienone **60**. Following hydrolysis of the enol ether group of **60**, methyl lithium is added to the more reactive saturated ketone function and the enone double bond is reduced to form the *cis*-fused ketol **61**. A four-step sequence featuring protection of the ring-A carbonyl group and introduction of an enone system through a singlet-oxygen photoene process leads to **62**. Hetero Diels–Alder reaction with a silyl-substituted methyl methacrylate followed by reduction and Wittig methylenation then affords the Claisen substrate **63**. The product of this thermolysis, allyl silane **64**, is subjected to diazotization to give **65**. Photolysis of **65** now causes contraction of ring B to give an intermediate ketene **66** which, in the absence



59 60 61 62 63 64 65 66

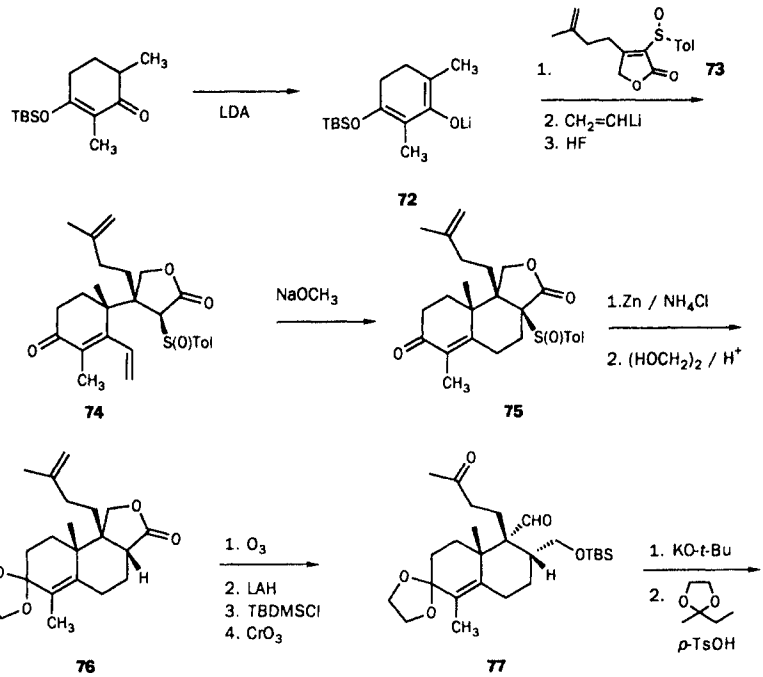
SCHEME 146. Ireland's synthesis of aphidicolin.



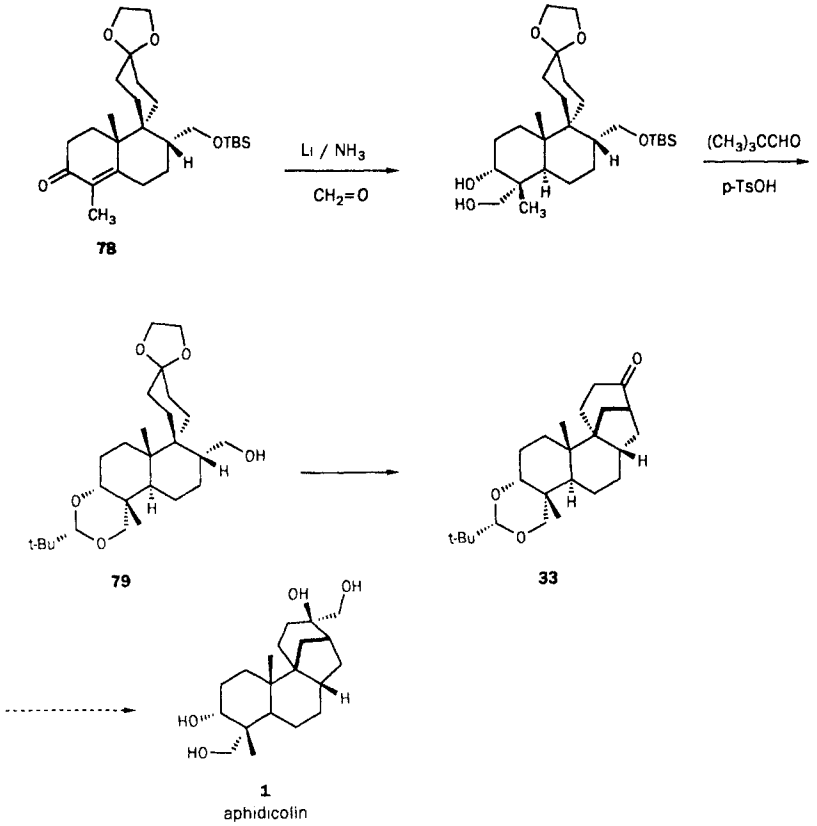
SCHEME 146. Ireland's synthesis of aphidicolin (*continued*).

of an external nucleophile, cycloadds to the C-ring double bond. The resulting cyclobutanone, **67**, when treated with silica gel, affords **68**, an intermediate having the aphidicolin skeleton. A multistep sequence is then employed for removal of the ring-D carbonyl group and the introduction of the C-ring diol group. The resulting intermediate, **69**, is converted into aphidicolin by introduction of a $\Delta^{3,4}$-double bond to give **70**, followed by a double formylation sequence to generate the C-4 methyl and hydroxymethyl units. Final reduction and hydrolysis yields the natural product **1**.

For their approach to aphidicolin (Scheme 147) Holton and collaborators[242] at Florida State University and Virginia Tech elected to follow the general route developed by Corey for the construction of the C/D ring system, but developed an efficient alternative route to optically active intermediate **71**. To this end the Holton group make use of the *diastereoselective* Michael addition of enolate **72** to a single enantiomer of chiral sulfoxide **73**. The resulting optically active product is eventually shown to have appropriate absolute and relative stereochemistry for aphidicolin. Addition of vinyl lithium to the Michael product then produces dienone **74**.



SCHEME 147. Holton's synthesis of aphidicolin.



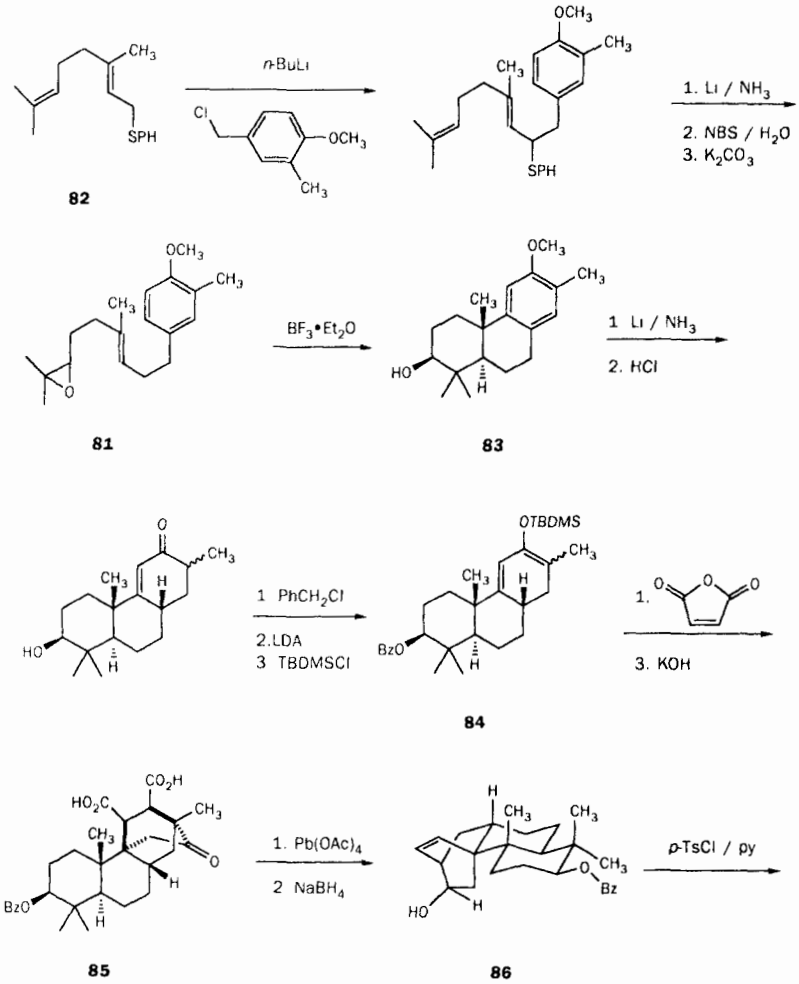
SCHEME 147. Holton's synthesis of aphidicolin (*continued*).

The chiral sulfoxide group, having provided activation for the initial Michael addition, is now used as an aid to closure of ring B in a vinylogous Michael addition to form **75** and is then reductively removed, leaving as its legacy an optically active intermediate **76**.

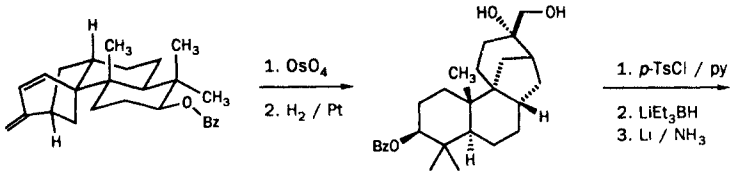
Lactone **76** is then subjected to ozonolysis and hydride reduction to give a triol which can be selectively silylated and oxidized to afford ketoaldehyde **77**. Following aldol cyclization and exchange of the dioxolane group in the standard saturated–unsaturated carbonyl competition to give **78**, reductive formylation of ring A and acetalization provides the Corey intermediate **79**.[233] To demonstrate that the absolute configuration of **79** is that of the natural product, it was carried through to the known pivaloyl *nor*-aphidicolin **33** previously obtained[226, 227] by degradation of aphidicolin itself.

N. Maritimol

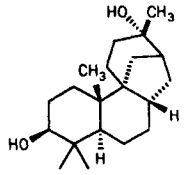
Maritimol, **80** (Scheme 148), a plant product of the stemodia family, has the same carbon skeleton as aphidicolin. The fusion of the five-membered D ring to ring B in maritimol is *cis*, however, in contrast to the *trans* fusion in aphidicolin. In addition, maritimol lacks two of the hydroxyl groups of its more oxidized cousin, as well as having the opposite configuration from



SCHEME 148. A synthesis of maritimol by Van Tamelen.



87



80
maritimol

SCHEME 148. A synthesis of maritimol by Van Tamelen (*continued*).

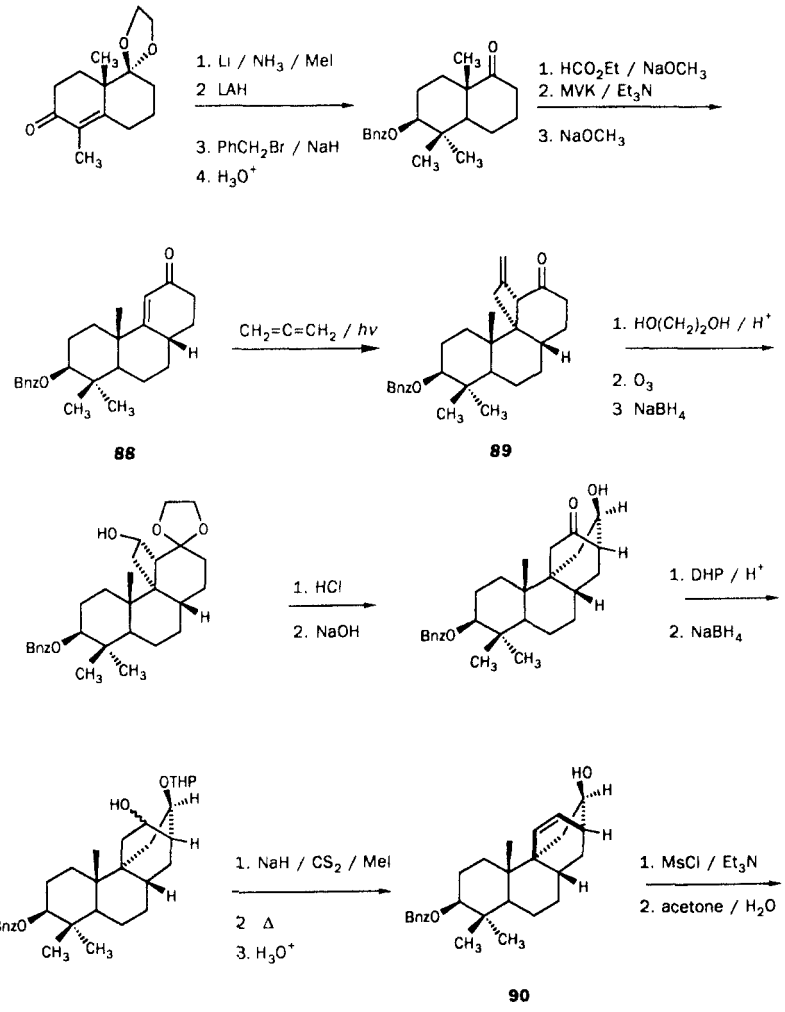
aphidicolin at the ring-C *tert*-hydroxyl position. Many of the basic routes used for aphidicolin have also been used for maritimol.

The first synthesis of maritimol, by the van Tamelen group,[243] again features a biomimetic epoxy polyene cyclization for formation of a tricyclic intermediate (Scheme 148). Thus epoxide **81** is constructed by alkylation of sulfide **82**, reductive removal of the sulfide group, and selective addition of NBS. Lewis-acid-catalyzed cyclization of **81** affords alcohol **83**, which is converted in a three-step sequence to dienol ether **84**. As in the aphidicolin synthesis, Diels–Alder addition of maleic anhydride occurs from the β face of **84** to yield a keto diacid **85** after hydrolysis. Decarboxylation and reduction leads to alcohol **86**. The positions of the hydroxyl group and the migrating carbon center of **86** are interchanged compared to the corresponding intermediate **48** in the van Tamelen aphidicolin synthesis. In this case rearrangement of **86** leads to the 3.2.1-diene **87** having the maritimol B/C *cis* stereochemistry. The remaining hydroxyl group is introduced by stereoselective hydroxylation and subsequent removal of the primary alcohol group to afford maritimol **80**.

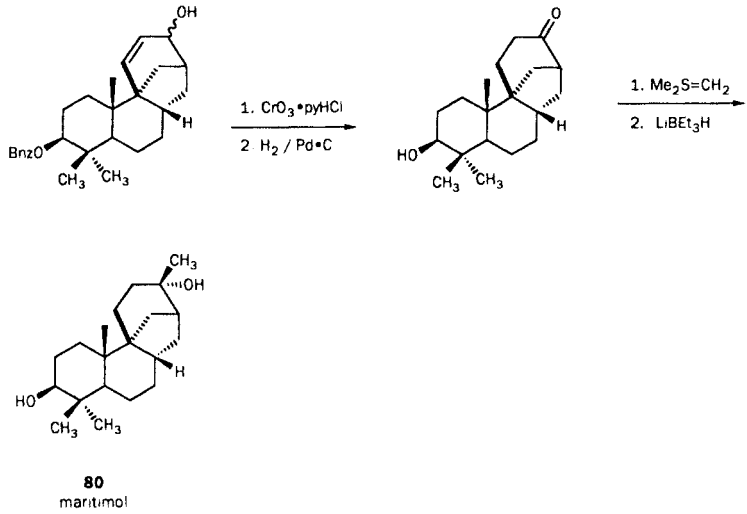
Photocycloaddition of allene[165] has been used extensively in the stemodia class of diterpenes and two approaches to maritimol are based on this reaction. In the synthesis of maritimol (Scheme 149) by Bettolo and colleagues[244] addition to tricyclic enone **88** produces **89**. By a sequence similar to that used in the Bettolo aphidicolin synthesis, **89** is converted into alcohol **90**. As in the van Tamelen synthesis, the positions of the hydroxyl group and the

double bond of this intermediate are reversed compared to the corresponding compound used for aphidicolin. Rearrangement of the derived mesylate of **90** followed by introduction of the C-13 methyl and hydroxyl groups affords maritimol, **80**.

Piers and co-workers[245, 246] at British Columbia have reported total syntheses of several stemodane diterpenes including maritimol, **80**, and stemodin, **91**, as well as formal syntheses of stemodinone, **92**, and 2-deoxystemodinone, **93**. These syntheses begin (Scheme 150) with the



SCHEME 149. Bettolo's synthesis of maritimol.



80
maritimol

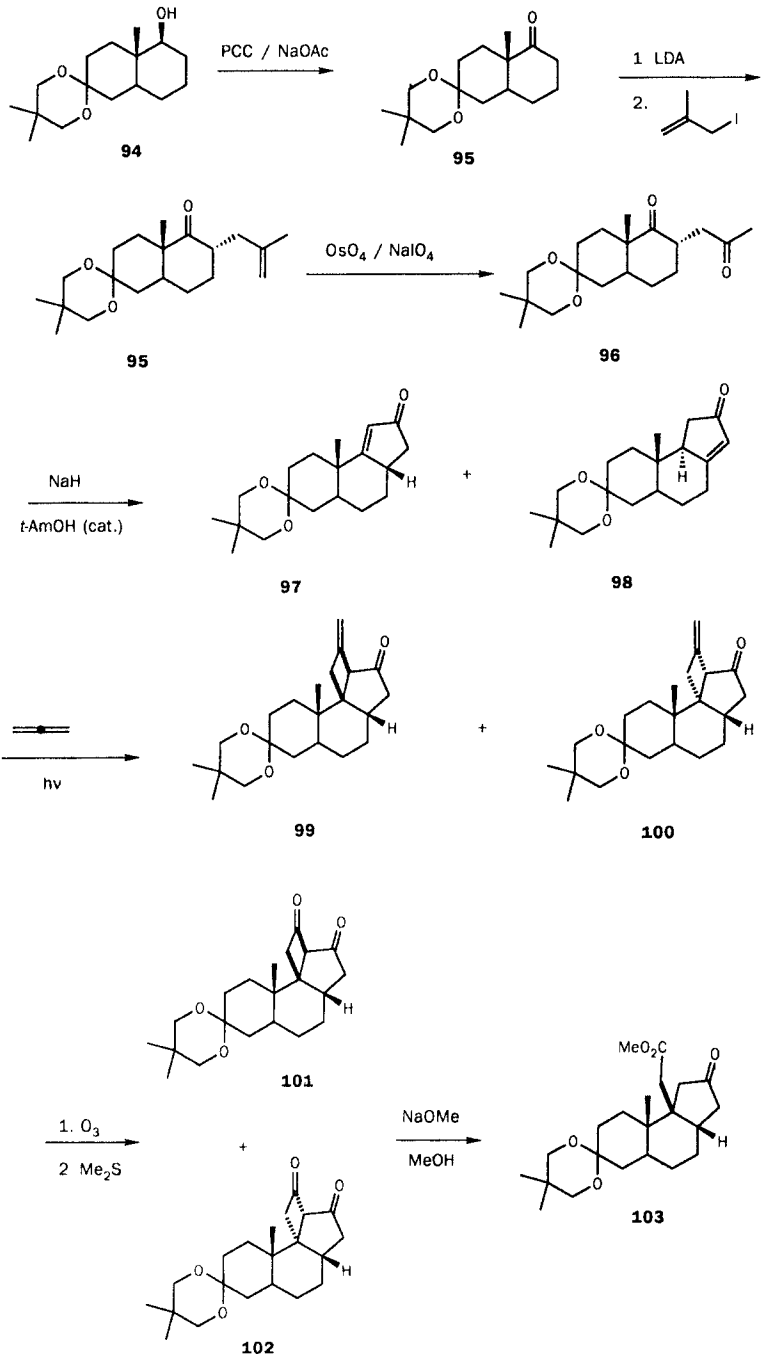
SCHEME 149. Bettolo's synthesis of maritimol (*continued*).

Wieland–Mischer ketone which is converted to the six-membered ketal **94**. PCC oxidation of **94** followed by methallylation affords the equatorially substituted ketone **95**. The methallyl group is cleaved with osmium tetroxide–periodate to afford diketone **96** and this in turn is cyclized to a mixture of diketones **97** and **98**. The latter undesireable isomer is the more stable one and the cyclization can only be carried out to the point at which **98** begins to appear in the mixture.

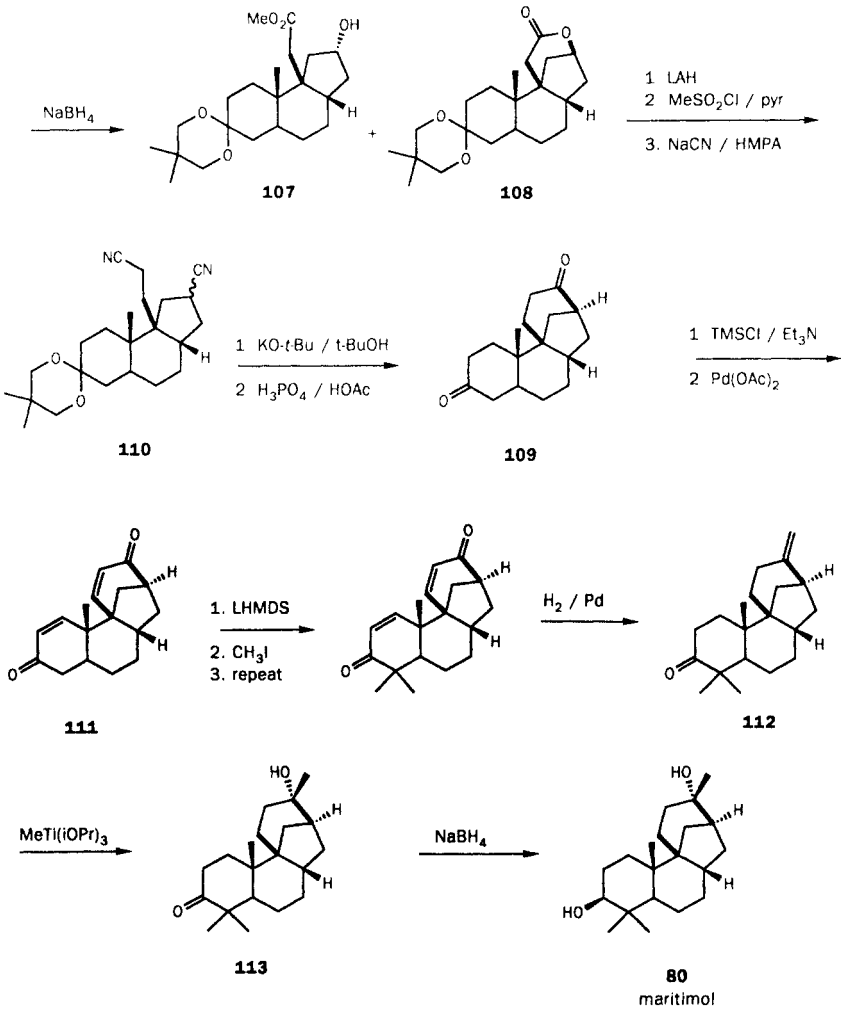
Photocycloaddition of allene to **97** also yields two isomers, **99** and **100**, both of which, in the event, may be carried forward to the target compounds. When the addition products are ozonized they yield diketones **101** and **102**, both of which in turn afford ketoester **103** when treated with sodium methoxide.

The explanation for this result (Scheme 151) lies in the fact that **102** is first converted into a mixture of **104** and **105**, both of which on further treatment with base eventually yield **103**. Ketoester **104** recyclizes to **106**, followed by cleavage to **103**, while the cyclobutanone ester **105** recondenses to **101**, thence to **103**. Thus the lack of stereoselectivity in the cycloaddition does not materially effect the preparation of intermediates with proper stereochemistry for the stemodia compounds.

The Piers synthesis (Scheme 150) is characterized by another step in which a lack of selectivity is irrelevant to the stereochemical outcome of the work. When **103** is reduced with sodium borohydride it yields an approximately 1:1 mixture of hydroxyester **107** and lactone **108**. Both of these compounds

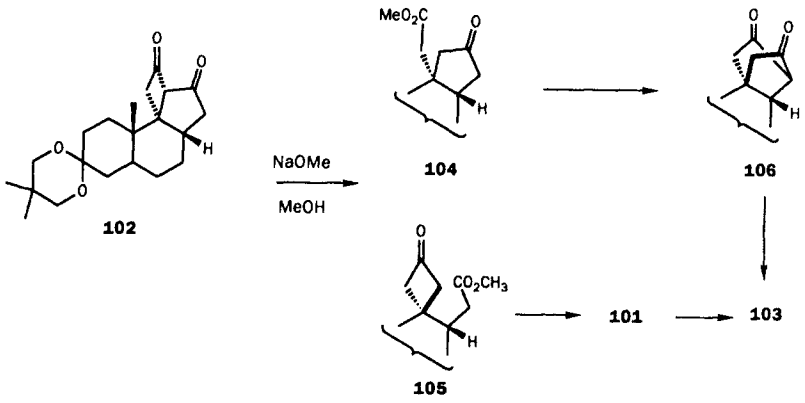


SCHEME 150. Pier's synthesis of maritimol.



SCHEME 150. Pier's synthesis of maritimol (*continued*).

are converted to diketone **109** via the epimeric dinitriles **110** and a Thorpe–Ziegler cyclization. In order to effect alkylation of only the A ring, both ketone groups of **110** are converted into their α,β-unsaturated cohorts, diketone **111**, by Pd^{II} oxidation of the derived TMS ethers. Two-stage methylation of **111** and saturation of the double bonds yields **112**. Addition of a methyl group to the less-hindered carbonyl of **112** affords **113**, which in turn gives maritimol, **80**.

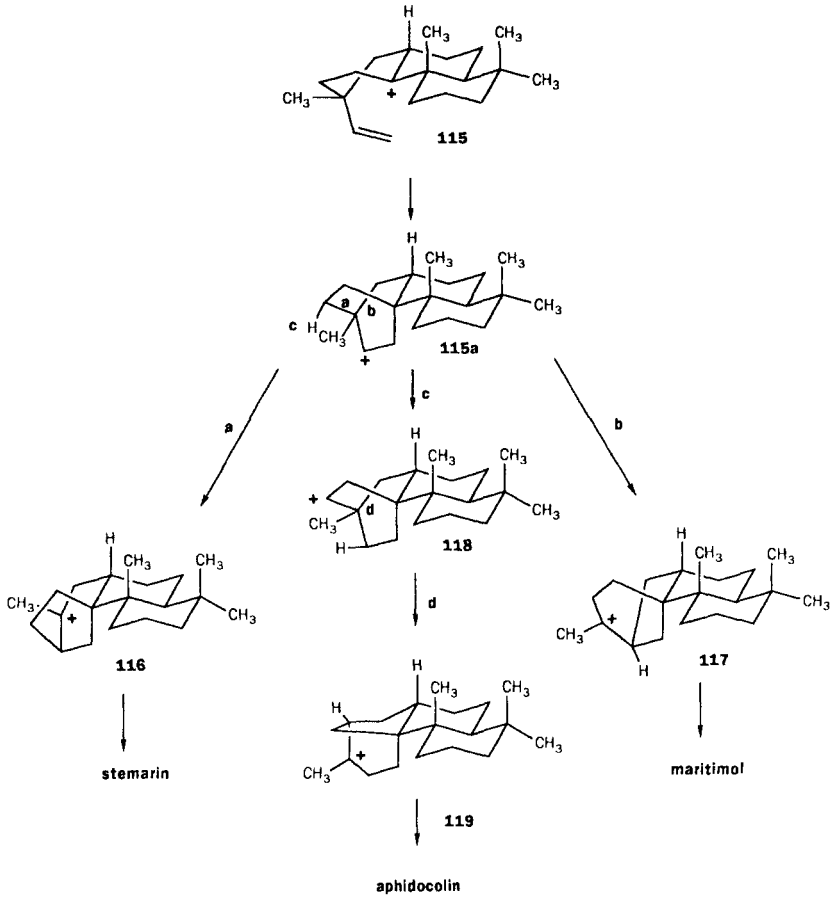


SCHEME 151. The interconversion of Pier's intermediates for maritimol.

O. Stemarin, 2-Desoxystemodinone, Stemodinone, and Stemodin

The first of the tetracyclic stemodia diterpenes to be synthesized was stemarin, **114**. Stemarin differs structurally from the other stemarane and aphidicolane compounds because it has a spiro-fused cyclopentane ring rather than a cyclohexane one. Nevertheless, all of the stemodia compounds presumably come from a common 2.2.2-bicyclooctane biogenetic precursor, the formation and rearrangements of which are represented in a stylized fashion in Scheme 152. Closure of tricyclic cation **115** leads to the first bridged intermediate **115a**. Rearrangement to a 3.2.1 system by migration of bond **a** affords the stemarin ring system **116**. Similar rearrangement via path **b** leads to intermediate **117** for maritimol and congeners. To achieve the aphidicolane system, path **c**, a hydride migration, occurs to give another 2.2.2 system, **118**. This in turn, upon rearrangement **d**, leads to a new 3.2.1-bicyclic cation, **119**. Appropriate trapping of this species and required oxidations leads on to aphidicolin.

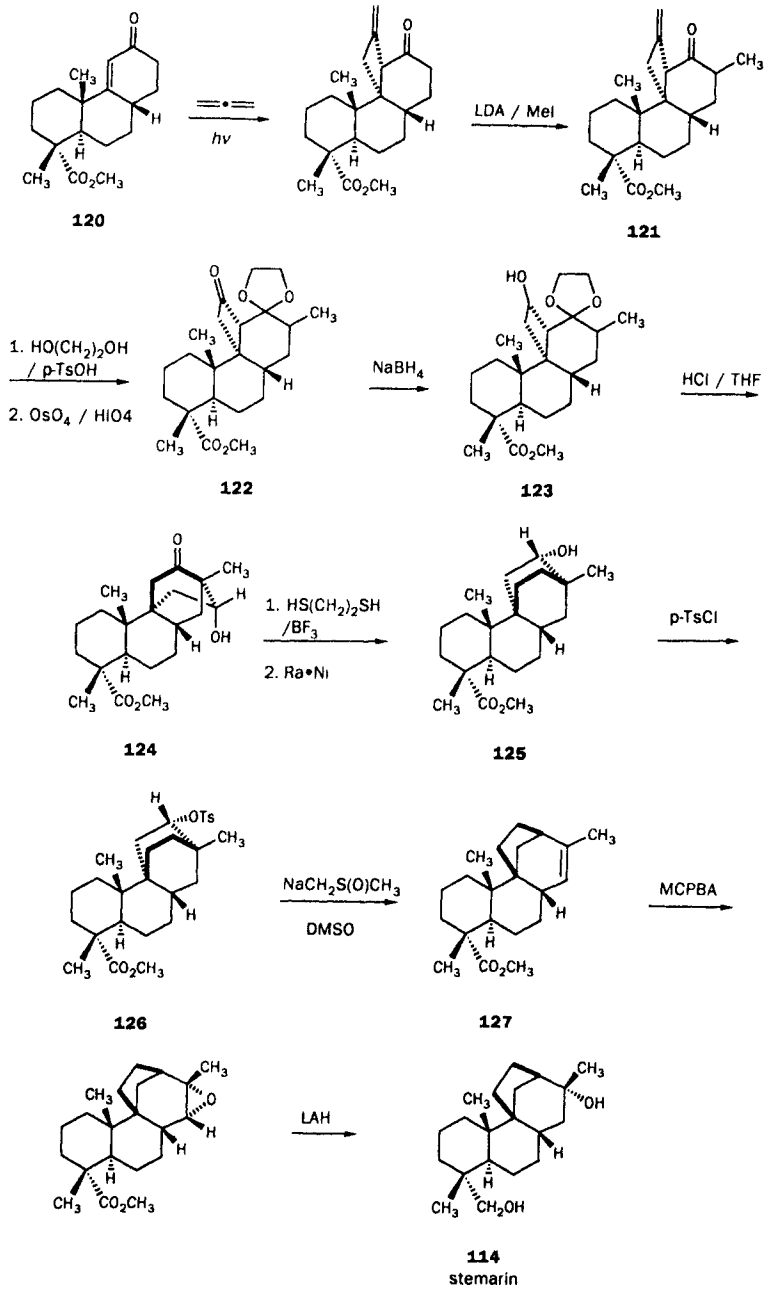
For the synthesis of stemarin (Scheme 153), Kelly and co-workers at New Brunswick with Manchand at Hoffman–La Roche[247] utilized the tricyclic intermediate **120** prepared by Spencer in the synthesis of deisopropyldehydroabietic acid. The Kelly approach to the C/D ring system, used also by Bettolo and Piers, is again the photocycloaddition of allene[165] to an enone. Thus enone **120** is converted via a two-step sequence into the methylenecyclobutane **121** and, after protection of the six-membered ring carbonyl group, the methylene group is oxidatively cleaved and the resulting ketone function of **122** is reduced to afford **123**. Acid hydrolysis of the ketal group of **123** is accompanied by dealdolization–realdolization to yield ketol **124** and



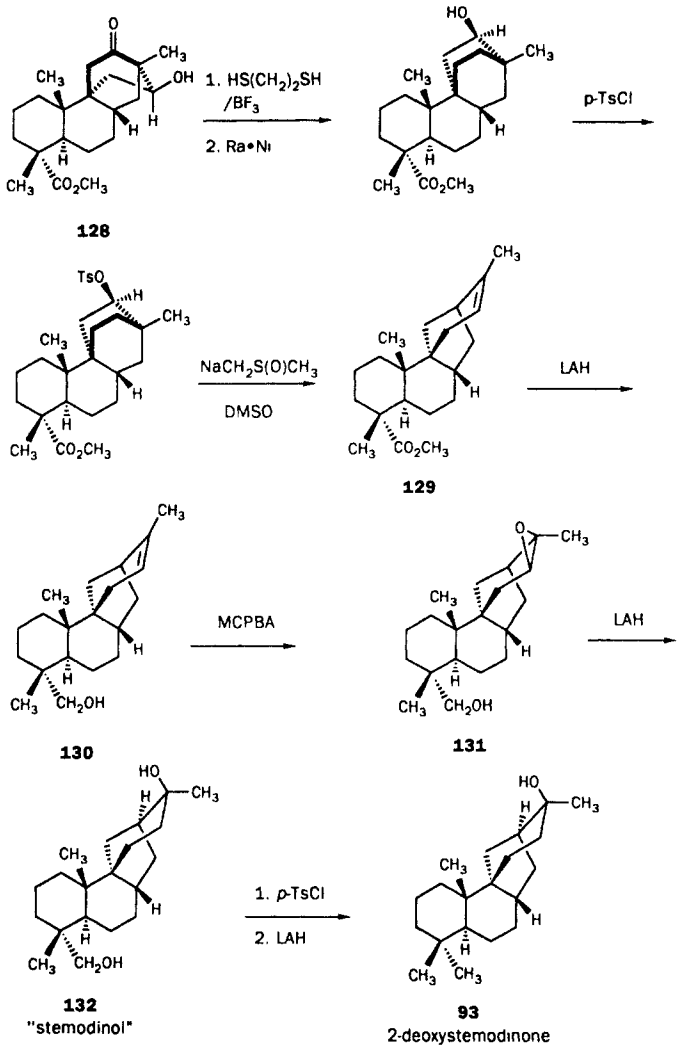
SCHEME 152. Stermodane diterpene structural relationships.

its carbinol carbon epimer. Alcohol **124**, obtained as the minor product (~ 3:1), has the appropriate configuration of the hydroxyl for rearrangement to the stemarin skeleton; that is bond **b** in Scheme 151. Removal of the carbonyl oxygen affords alcohol **125** which upon solvolysis of the derived mesylate **126** yields olefinic ester **127**. Conversion of this substance to stemarin **114** is accomplished by stereoselective epoxidation and hydride reduction.

To achieve the synthesis (Scheme 154) of 2-desoxystemodinone, **93**, Kelly and colleagues[248, 249] employed ketol **128**, formed as the major product in the dealdolization–realdolization sequence shown in Scheme 153. A series of transformations comparable to those used for the stemarin synthesis then



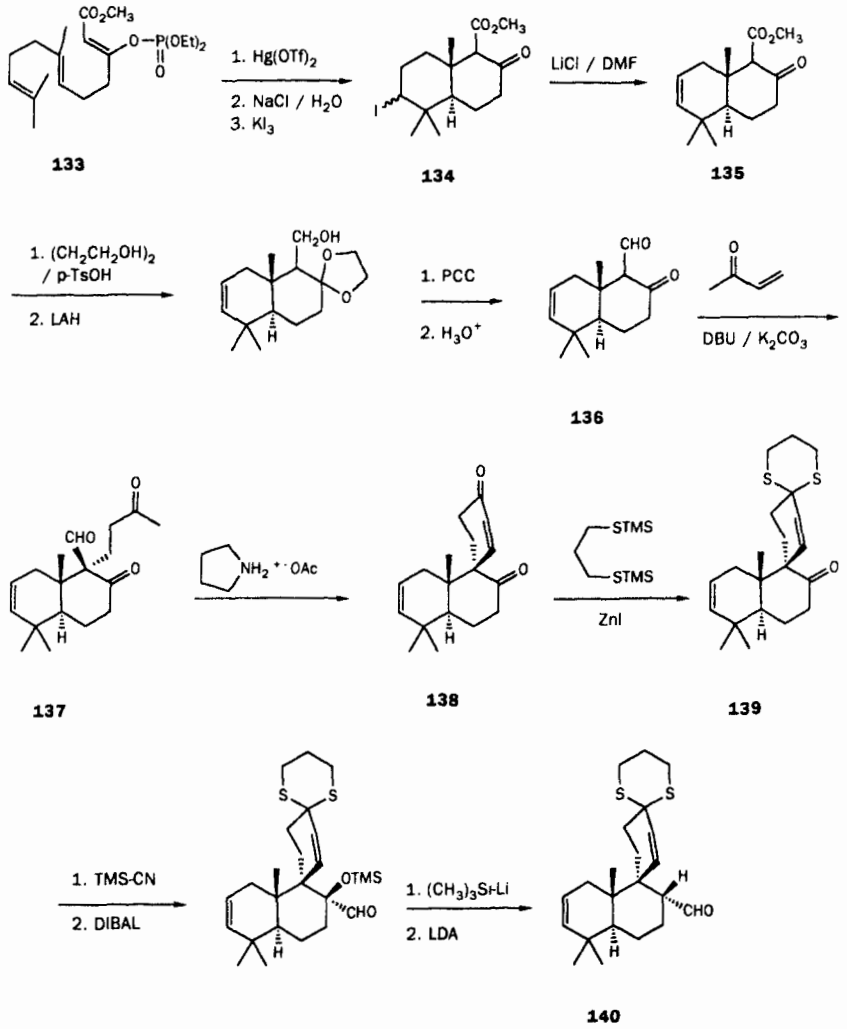
SCHEME 153. Kelly's synthesis of stemarin.



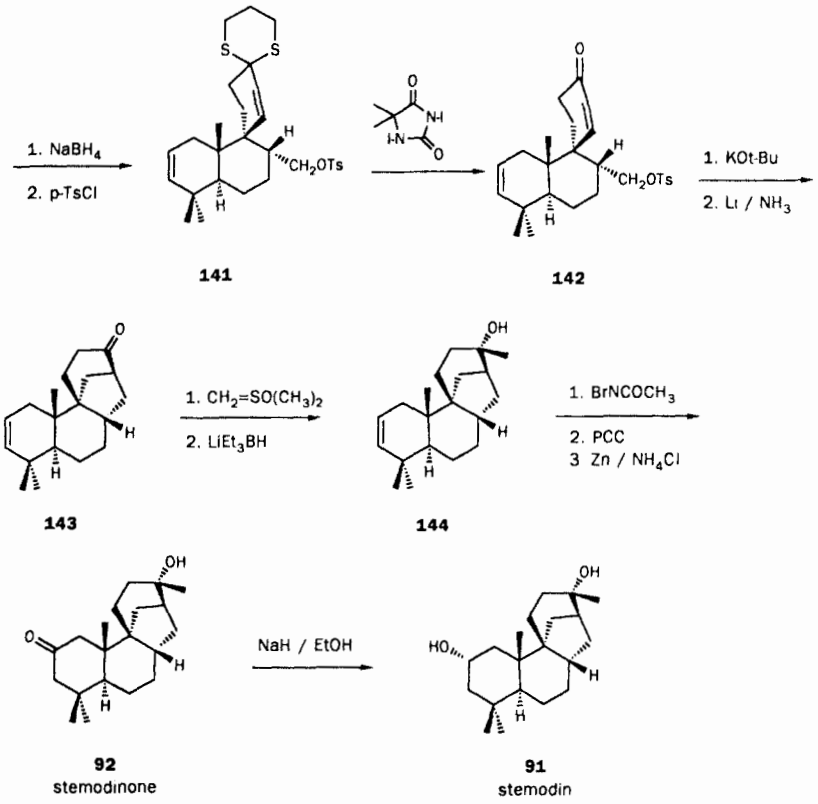
SCHEME 154. Kelly's synthesis of 2-desoxystemodinone.

affords olefinic ester **129**. This substance is reduced to primary alcohol **130** and epoxidation then affords **131**, the product of reaction from the least-hindered face of the double bond. Hydride reduction of the epoxide group yields a diol **132** (once erroneously thought to be a natural product), which upon conversion of the C-4 hydroxymethyl group into a methyl substituent yields 2-deoxystemodinone, **93**.

The syntheses of stemodin, **91**, and stemodinone, **92**, by Corey, Tius, and Das[250] follows the same approach (Scheme 155) used by this group for the synthesis of aphidicolin. In the aphidicolin work illustrated in Scheme 142, the bridged-ring system was produced by an internal alkylation reaction which led selectively to the *trans*-fused B/D ring system. To produce stemodin and stemodinone it is necessary to force alkylation to occur at the alternative α position of the spiro-ketone ring. The "trick" used to affect this



SCHEME 155. Corey's synthesis of stemodin and stemodinone.



SCHEME 155. Corey's synthesis of stemodin and stemodinone (*continued*).

result is to prevent enolization at the more favored α position by incorporating it in a double bond.

Thus, the A/B ring system of the stemarane diterpenes is constructed by Corey and co-workers through a mercuric-ion-catalyzed cyclization of the polyenic enol phosphate **133** in a fashion similar to that used for aphidicolin. Treatment of the bicyclic product with potassium triiodide yields a diastereomeric mixture of iodides **134**. These are then dehydrohalogenated to form the ring A olefin **135**. Through a sequence of protection, reduction, and reoxidation, β-keto ester **135** is converted into the corresponding keto aldehyde **136**.

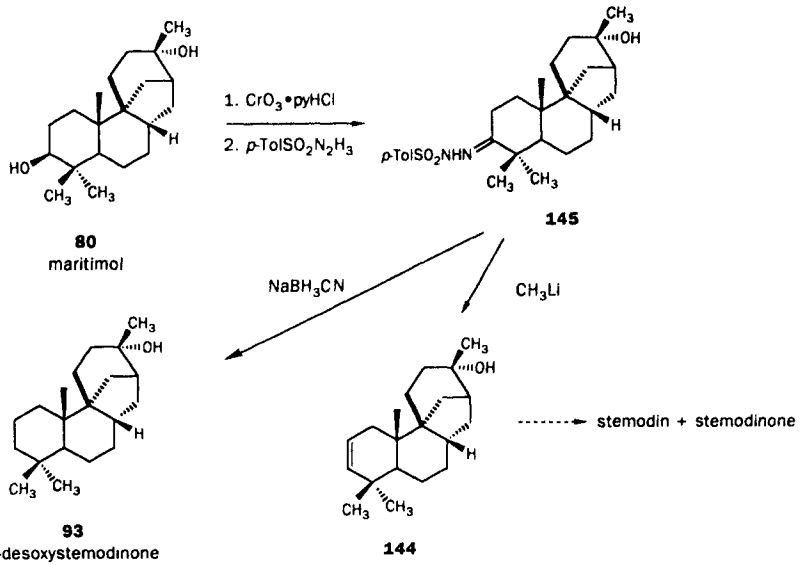
Michael addition of **136** to methyl vinyl ketone is accomplished stereoselectively with the production of diketo aldehyde **137**. This material in turn is cyclized to **138** under Knoevenagel–enamine conditions. Enone **138** is transformed into a mono thioketal **139**, in which only the less-hindered,

unsaturated, carbonyl group has reacted. Addition of a one-carbon unit through cyanohydrin formation and elimination of the original ketonic oxygen affords aldehyde **140**.

The aldehyde function is reduced and the resulting alcohol is converted into its tosylate derivative, **141**. Deprotection of the ring-C ketone group yields **142**. The last ring is then formed between the α-oriented tosyloxymethylene carbon atom and the only enolizable position of the carbonyl group. Thus treatment of **142** with base followed by metal–ammonia reduction affords **143**.

To achieve selectivity in the formation of the correct stereochemistry for the *tert*-hydroxyl group of stemodinone, the keto group of **143** is reacted with a sulfur ylide followed by hydride reduction of the resulting epoxide. This sequence yields **144** as the major product. Bromohydrin formation, oxidation, and reductive elimination then produces stemodinone, **92**. Reduction of **92** under equilibrating conditions affords stemodin, **91**.

The syntheses (Scheme 156) of desoxystemodinone, stemodinone, and stemodin by Bettolo and co-workers[244] are outgrowths of their synthesis of maritimol, **80**. Synthetic maritimol is oxidized to an A-ring ketone and the resulting carbonyl group is then disposed of in two ways. In one the derived tosylhydrazone, **145**, is reduced with cyanoborohydride to afford 2-deoxystemodinone, **93**, directly. In the second, a Shapiro reaction with **145**

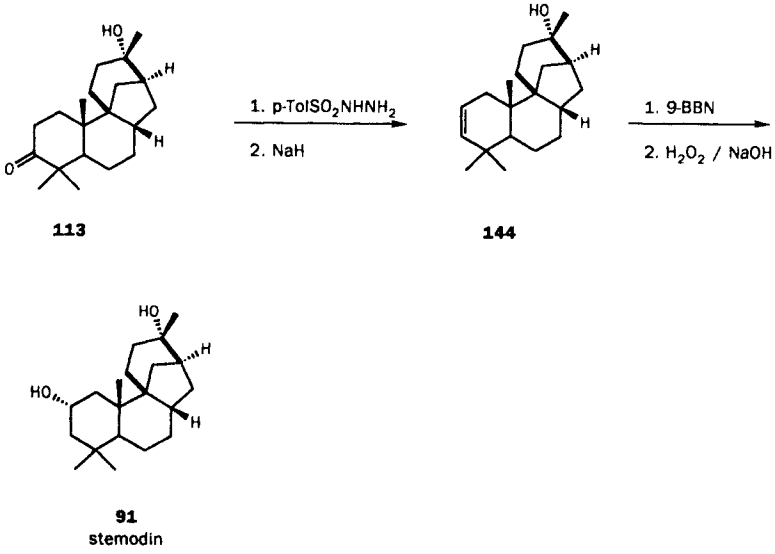


SCHEME 156. Bettolo's synthesis of 2-desoxystemodinone, stemodin, and stemodinone.

affords olefin **144**. This compound has been converted to stemodin and stemodinone in the Corey synthesis (Scheme 154).

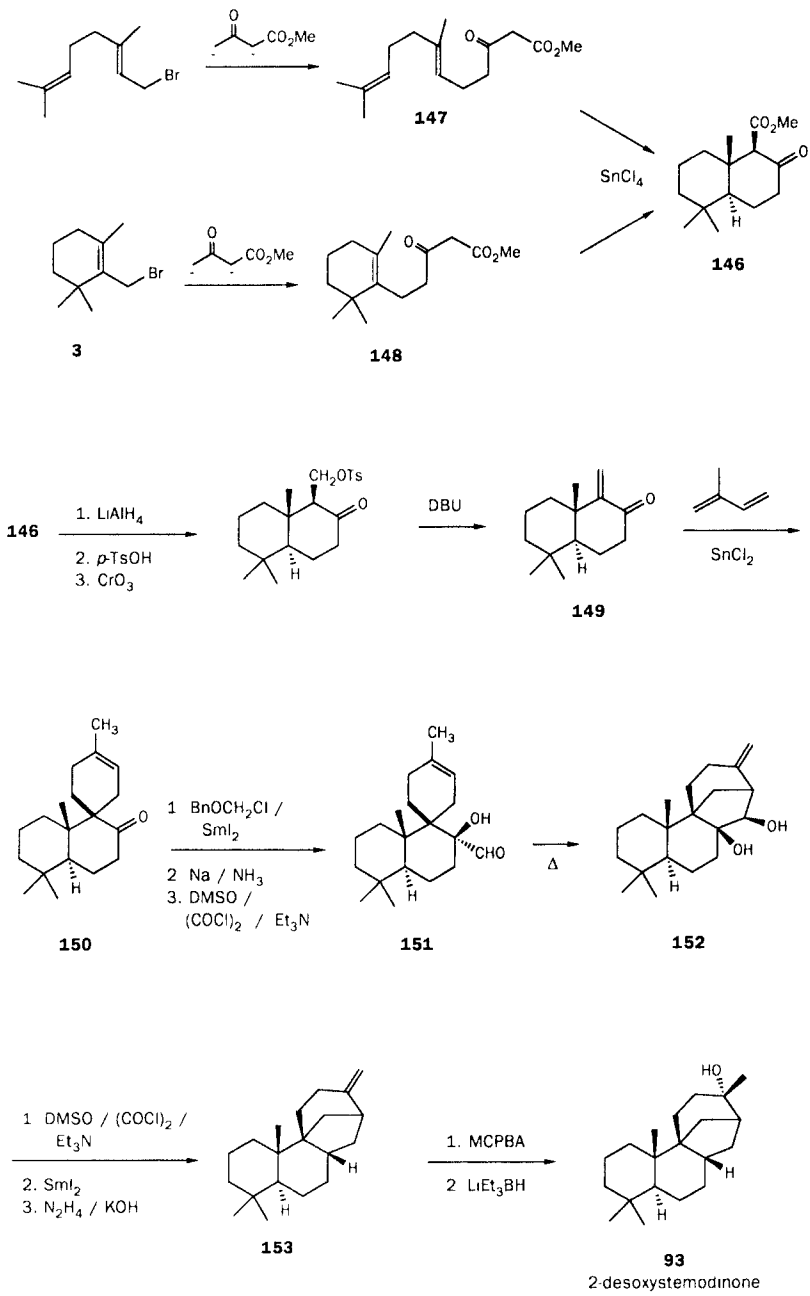
Stemodin, and by extension stemodinone and 2-desoxystemodinone, are also produced in the synthetic path toward maritimol described by Piers et al.[246] As shown in Scheme 157, a sequence similar to the Bettolo procedure produces alkene, **144**, from ketone **113**. Treatment of the olefin with 9-BBN affords stemodin, **91**, which upon oxidation yields stemodinone, **92**. Removal of the carbonyl oxygen produces the 2-deoxy compound, **93**.

In the synthesis of 2-desoxystemodinone (Scheme 158) by J. D. White and co-workers[251] at Oregon State University, the A/B ring system **146** is constructed by a polyene cyclization route starting from geranyl bromide. In contrast to the Corey approach, which employs an enol phosphate as one of nucleophilic centers, this sequence is accomplished directly with either of the β-keto esters, **147** or **148**. Diels–Alder addition to the methylene ketone **149** affords the spiro-fused C-ring intermediate **150**. The novel feature in this synthesis is the manner of attachment of the five-membered D ring. An ene reaction of hydroxy-aldehyde **151** thus affords diol **152**, which upon oxidation, samarium iodide deoxygenation, and Wolff–Kishner reduction yields tetracyclic olefin **153**. Standard epoxidation and reduction gives 2-desoxystemodinone, **93**.



113 **144** **91**
stemodin

SCHEME 157. Pier's synthesis of stemodin.

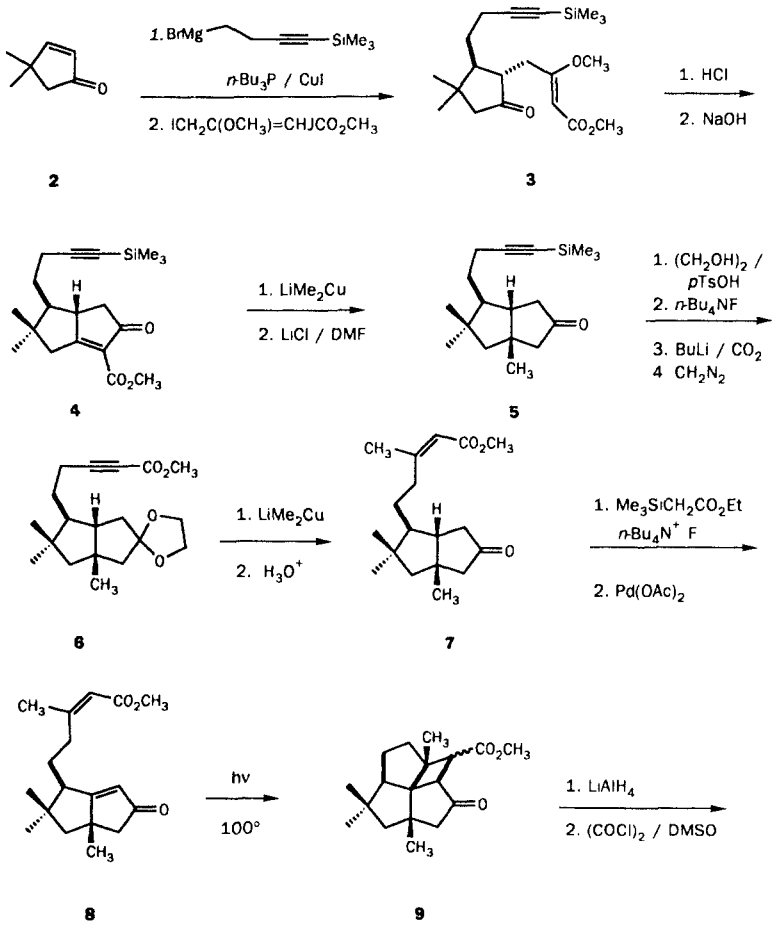


SCHEME 158. White's synthesis of 2-desoxystemodinone.

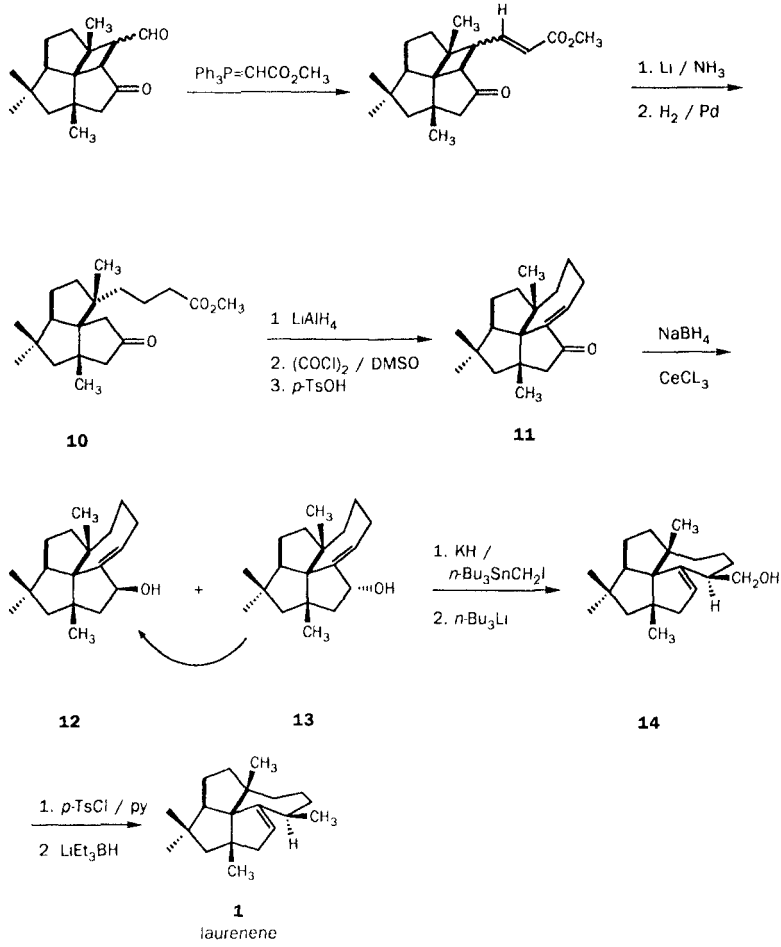
3. UNUSUAL SKELETAL TYPES

A. Laurenene

Laurenene, **1** (Scheme 159), is structurally related to the triquinane family of sesquiterpenes. At the time of its discovery it was the only known natural product with a fenestrane skeleton, a ring system constrained to have a virtually planar carbon at the spiro center of the four rings. Since its discovery three total syntheses have been accomplished.



SCHEME 159. The synthesis of laurenene by Crimmins and Gould.



SCHEME 159. The synthesis of laurenene by Crimmins and Gould (*continued*).

The first synthesis is due to Crimmins and Gould[252] at the University of North Carolina at Chapel Hill. Two key features characterize the synthesis illustrated in Scheme 159. First is the addition of the elements of the five-membered A and C rings to a preexisting cyclopentenone ring-B unit by analogy with much synthesis in the prostaglandin domain. Second is a 2 + 2 photocycloaddition designed to close ring C[253] and to set the stereochemistry at both the spiro center and the fusion of the C/D rings.

To achieve these results cyclopentenone **2** is caused to undergo copper-assisted conjugate addition of an acetylenic Grignard reagent, followed by

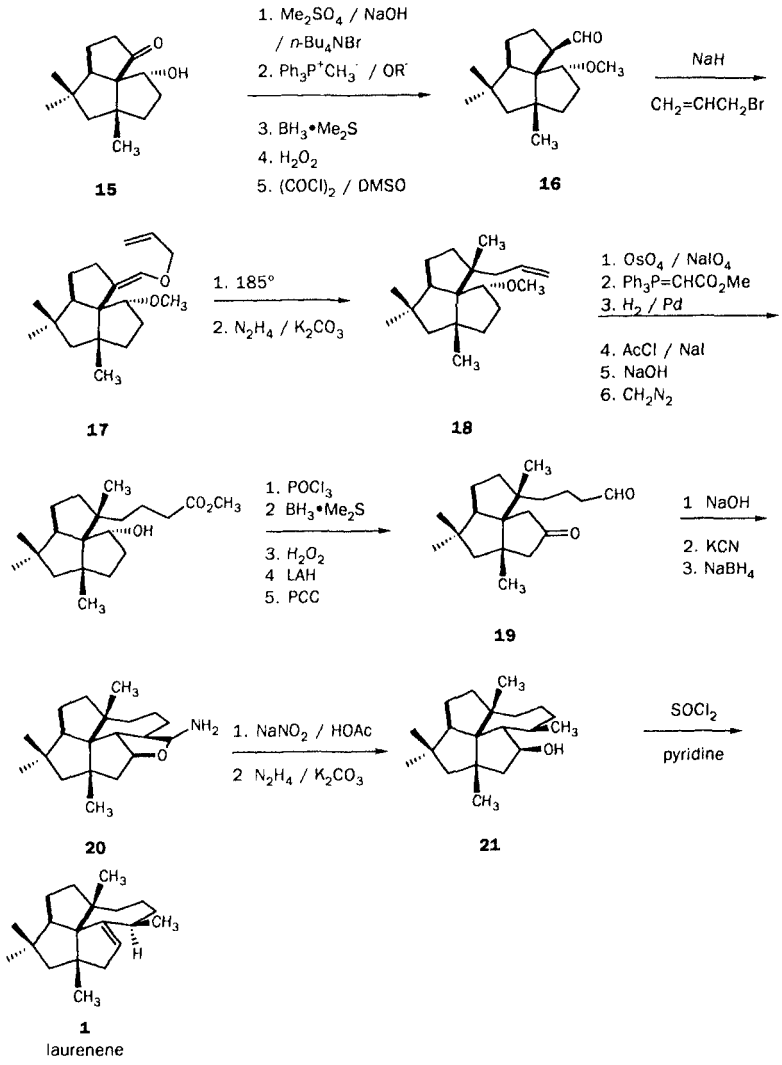
alkylation of the resulting enolate to produce disubstituted cyclopentanone **3**. Cleavage of masked β-keto ester system of **3** followed by aldol closure of ring A yields bicyclic enone **4**. The angular methyl group of the A/B system is then added by cuprate addition after the removal of the ester group by lithium-chloride-effected demethylation and decarboxylation producing saturated ketone **5**. Protection of the keto function is followed by a three-step sequence leading to ester **6**. The addition of another methyl group in conjugate fashion provides the α,β-unsaturated keto ester **7** after hydrolysis of the dioxolane function.

The cycloaddition reaction to be used for the completion of the C ring requires the introduction of a double bond in ring A. To effect this change a silyl ether is formed regioselectively and subjected to palladium acetate oxidation to produce enone **8**. Photocycloaddition at elevated temperature then yields a mixture of epimeric cyclobutane carboxylic esters **9** in which the stereochemistry of the angular methyl at the C/D ring junction and the geometry at the central carbon of the incipient fenestrane have been set.

To complete the synthesis, a five-step homologation sequence is carried out leading to tricyclic keto ester **10**. Conversion to a keto aldehyde followed by ring closure affords **11**, which in turn is reduced to a mixture of epimeric alcohols **12** and **13**. The principle product **13**, however, is cycled to the lesser one by reoxidation and rereduction. The "minor" alcohol **12** is then subjected to Still's alkylation and rearrangement method[254] to afford **14**. Final tosylation and reduction of the primary hydroxyl function affords laurenene, **1**.

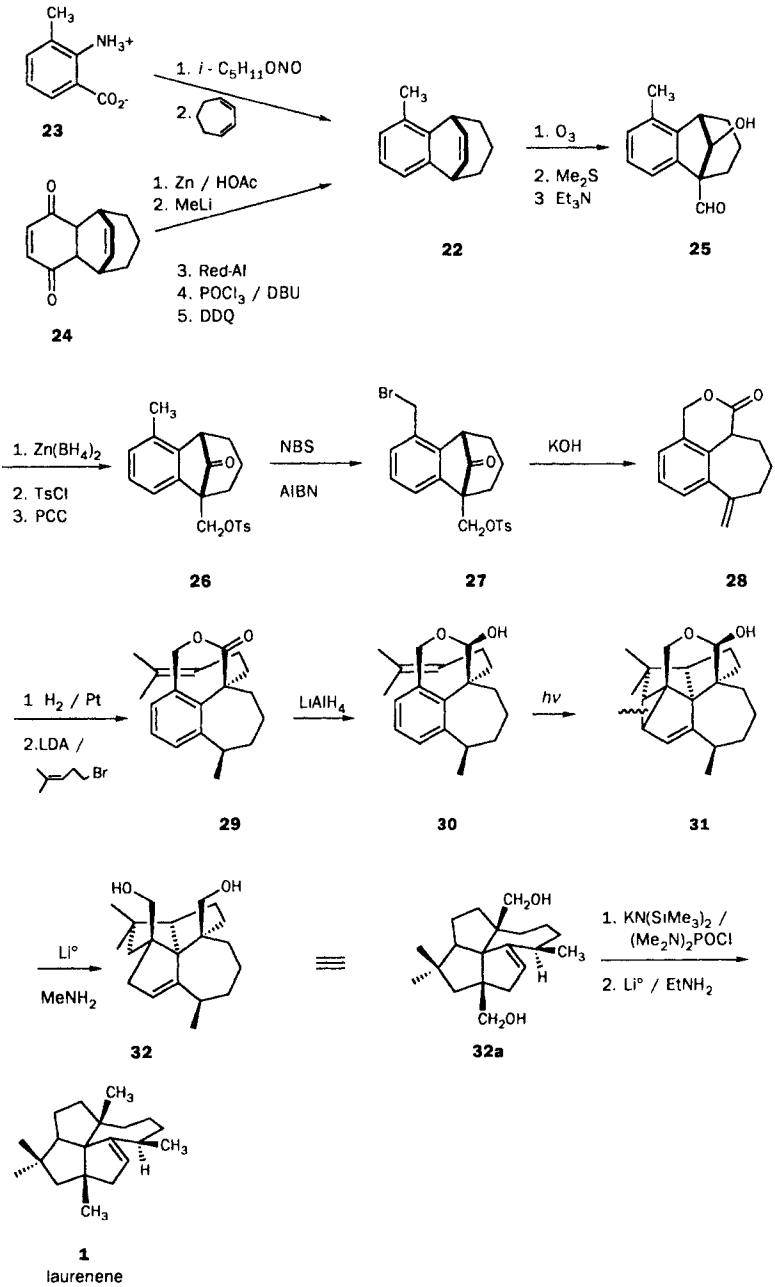
The starting material for the synthesis (Scheme 160) of laurenene by Tsunoda and colleagues[255] at Sendai and Tokushima is the triquinane intermediate **15**, prepared for a synthesis of the sesquiterpene silphenene. A multistep sequence converts ketol **15** into methoxy aldehyde **16**. *O*-alkylation of the aldehyde function is followed by Claisen rearrangement of **17** and Wolff–Kishner reduction to afford olefin **18**, the rearrangement having occurred preferentially from the less-hindered α face of the C ring. To effect closure of the last ring, it is necessary to extend the three-carbon appendage and to transpose the carbonyl group one position. A multistep sequence accomplishes this goal to provide keto aldehyde **19**. Aldol cyclization, cyanohydrin formation, and reduction produces hemiaminal **20**, which upon diazotization and reduction yields alcohol **21**. Final dehydration affords laurenene **1**.

The arene–olefin cyclization reaction of Wender at Stanford University used to such good advantage in the synthesis of sesquiterpenes is also employed in effective fashion by Wender, von Geldern, and Levine[256] for a short and efficient synthesis of laurenene, **1** (Scheme 161). To construct the substrate for the photochemical process the benzobicyclononene **22** is first prepared either by the 4 + 2 cycloaddition of the benzyne derived from **23**



SCHEME 160. Tsunoda's synthesis of laurenene.

with cycloheptadiene, or by a lengthier sequence starting from Diels–Alder adduct **24**. Cleavage of the double bond of **22** followed by aldol cyclization gives **25**. None of the product from the alternative mode of aldol closure was observed, resistance to the formation of an enolate at the benzyl position ortho to the methyl group being hindered by a *peri* interaction. Following manipulation of the oxygen functionalities of **25** to yield keto tosylate **26**, the



SCHEME 161. Wender's synthesis of laurenene.

methyl group is subjected to radical bromination to give **27**. Grob fragmentation with base then leads to lactone **28**. The exomethylene group of **28** is reduced catalytically and subsequent "prenylation" occurs selectively on the α face to yield **29**. Lactone **29** affords poor yields of photocyclization product and it converted, therefore, to a lactol, **30**. Irradiation of this intermediate yields the arene–olefin cyclization product **31**.

The vinyl cyclopropyl unit of **31** undergoes cleavage specifically at the bond indicated in Scheme 159 when subjected to dissolving metal reduction. Accompanying reduction of the lactol system leads to diol **32**. To complete the synthesis the two hydroxyl functions are converted into phosphorimidate groups which are then reductively deoxygenated to afford laurenene, **1**.

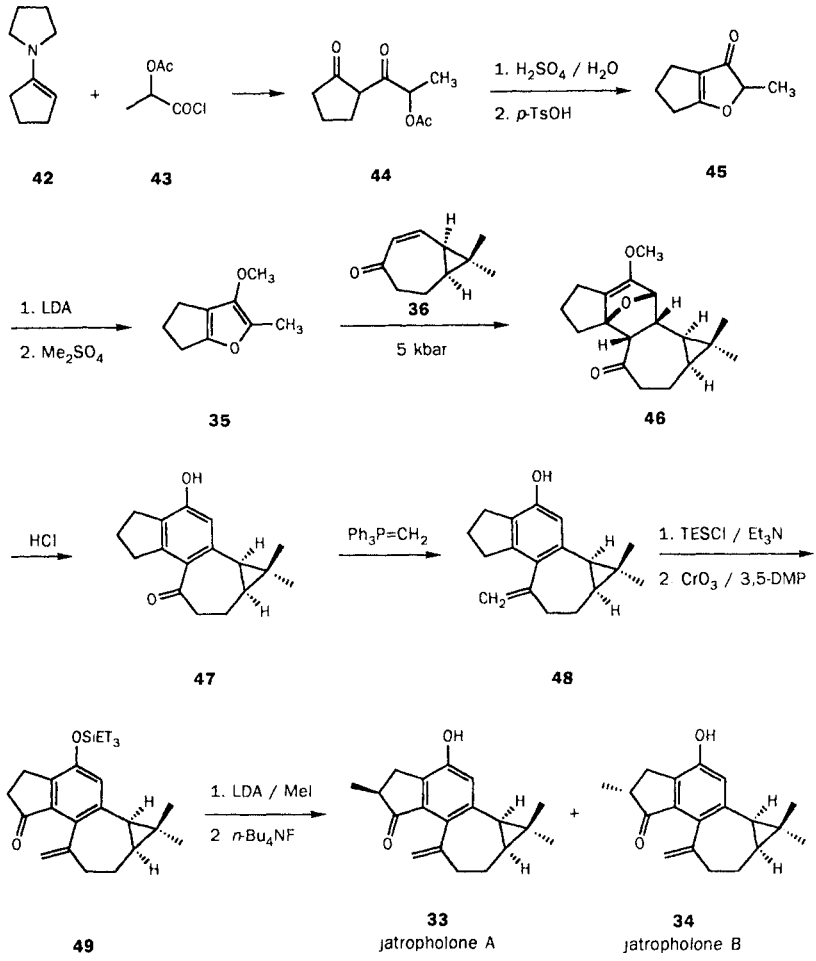
B. Jatropholone A and B

The jatropholones A and B, **33** and **34**, are aromatic diterpene ketones with an unusual ring system. For their construction (Scheme 162) Smith and coworkers[257] at Pennsylvania make use of the accelerating effect of high pressure on cycloaddition reactions, in this case the Diels–Alder reaction of a furanodiene **35** and an unsaturated ketone **36**.

The ketone is made from carvone **37** and its preparation,[258] shown in Scheme 163, is characterized by a sequence designed to avoid the five-membered ring that would be produced from **38** by ordinary and uncontrolled internal aldol condensation. Thus selective acetal formation, **39**, followed by formation of a silyl ether of the kinetic enolate **40**, followed by acid-catalyzed condensation, affords methoxyketone, **41**. The cycloheptenone **36** results when **41** is treated with base.

To prepare the furan component enamine, **42** (Scheme 160), is acylated with acetoxy acid chloride **43**. The resulting β-keto ester acetate **44** is hydrolyzed to the free alcohol and cyclized under acid conditions to give furanone, **45**. Base treatment and *O*-methylation affords bicyclic furan **35**.

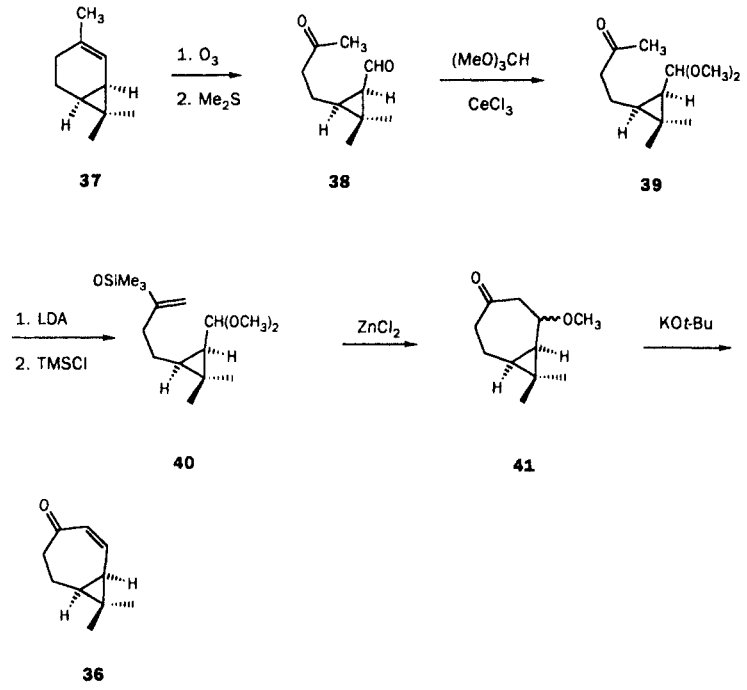
When **35** is combined with enone **36** at 5 kbar, adduct **46** results in good yield in contrast to the lack of product at ambient pressure. The adduct is hydrolyzed and aromatized in the presence of acid to provide phenol **47**, which in turn is subjected to Wittig methylenation to afford **48**. Conversion of **48** into the jatropholones requires that the introduction of a carbonyl group be specifically *ortho* to the seven-membered ring. To this end the phenolic hydroxyl is protected as a bulky silyl ether, and subsequent oxidation occurs with excellent selectivity to yield ketone **49**. Base-catalyzed methylation and removal of the protecting–blocking group produces both jatropholones A (**33**) and B (**34**).



SCHEME 162. A. B. Smith III's synthesis of jatropholones A and B.

C. Bertyadionol

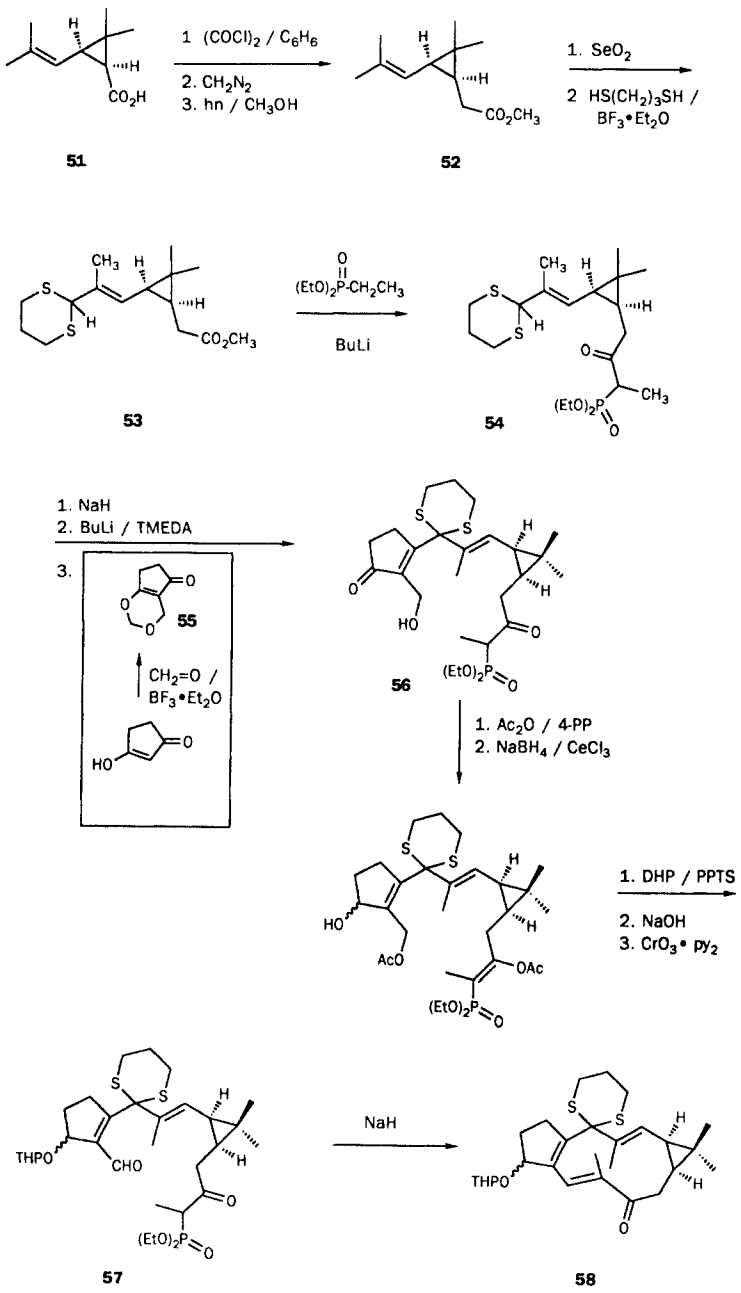
Smith and associates[259] carried out the first synthesis of a lathyrane diterpene, bertyadionol **50**. The 11-membered ring of this substance (Scheme 164) is constructed by an intramolecular Wadsworth–Emmons–Horner reaction. Two units, one bearing the cyclopentenoid portion of **50** and one carrying the dimethylcyclopropyl unit, are then joined and the whole is subjected to



SCHEME 163. Preparation of the starting material for the jatropholones A and B.

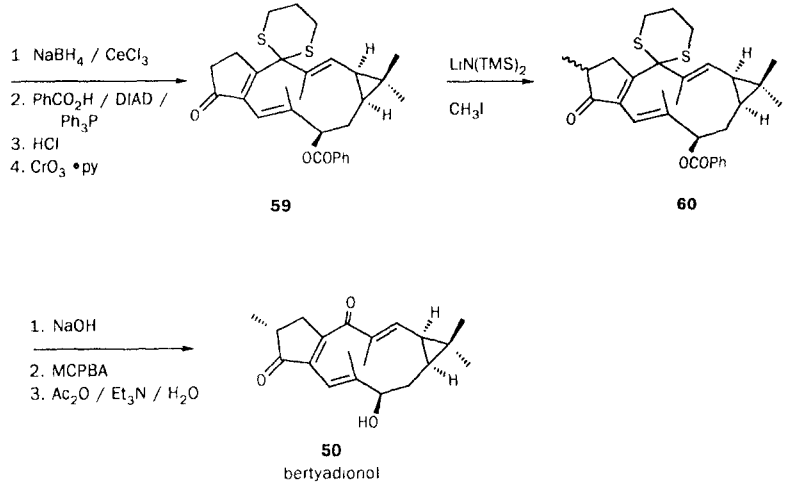
cyclization conditions. The starting material for one unit is the resolved (−)-*cis*-chrysanthemic acid **51**. An Arndt–Eistert sequence applied to **51** provides ester **52**. Following selenium oxidation of the less-hindered allylic methyl group of **52** a dithiane group is appended, **53**, representing the eventual macrocyclic enone carbonyl of **50** as well as providing the means of joining the cyclopropyl portion to the cyclopentanoid one. First, however, the ester group of **53** is converted to a β-keto phosphonate, **54**. This substance in turn as its dianion is added to the other unit, enone **55** (produced from cyclopentan-1,3-dione), to afford (after hydrolysis) ketone **56**. In order to achieve the central ring closure a sequence of functional group protection, reduction, additional protection–deprotection, and finally oxidation must be carried out to yield aldehyde **57**. Now treatment with sodium hydride effects cyclization to **58** in approximately 30% yield.

Reduction of the keto group of **58** affords only the α-alcohol. As a consequence, the reduction step is followed by Mitsunobo inversion to yield (after reconversion of the five-membered oxygen function into a ketone group) keto benzoate **59**. Methylation of **59** in apparently low yield provides



51 52 53 54 55 56 57 58

SCHEME 164. Smith's synthesis of bertyadionol.



59 60

50
bertyadionol

SCHEME 164. Smith's synthesis of bertyadionol (*continued*).

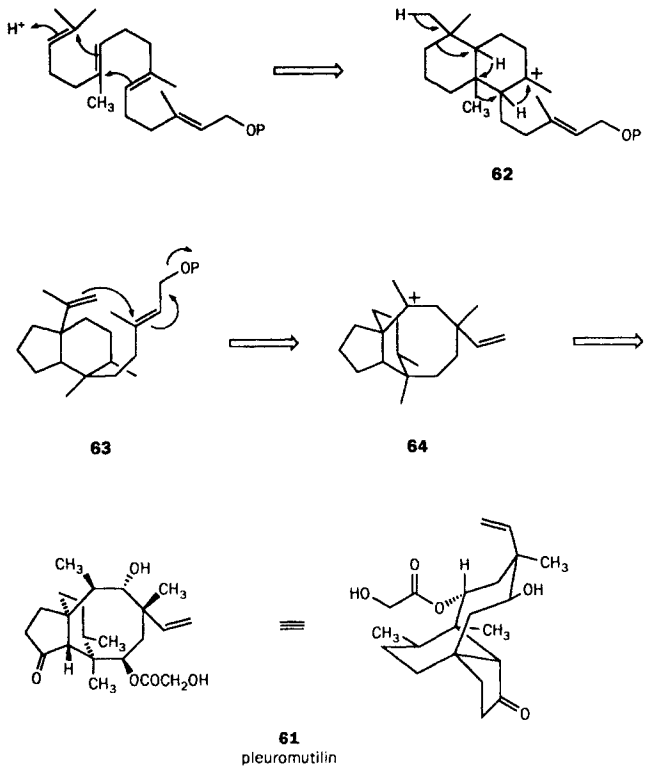
a mixture of epimeric substances **60**. These, carried through hydrolysis of the benzoate function and oxidative cleavage of the dithiane unit, provide a separable mixture of bertyadionol, **50**, and its C-2 epimer.

D. Pleuromutilin

Pleuromutilin, **61**, a fungal metabolite has a unique carbon skeleton derived from an unusual ring contraction–backbone rearrangement of a labdanyl cation intermediate, **62**, in the biosynthetic path (Scheme 165).[260] A second cyclization, **63** to **64**, produces the mutilin ring system, which after some number of oxidative processes evolves as pleuromutilin, **61**.

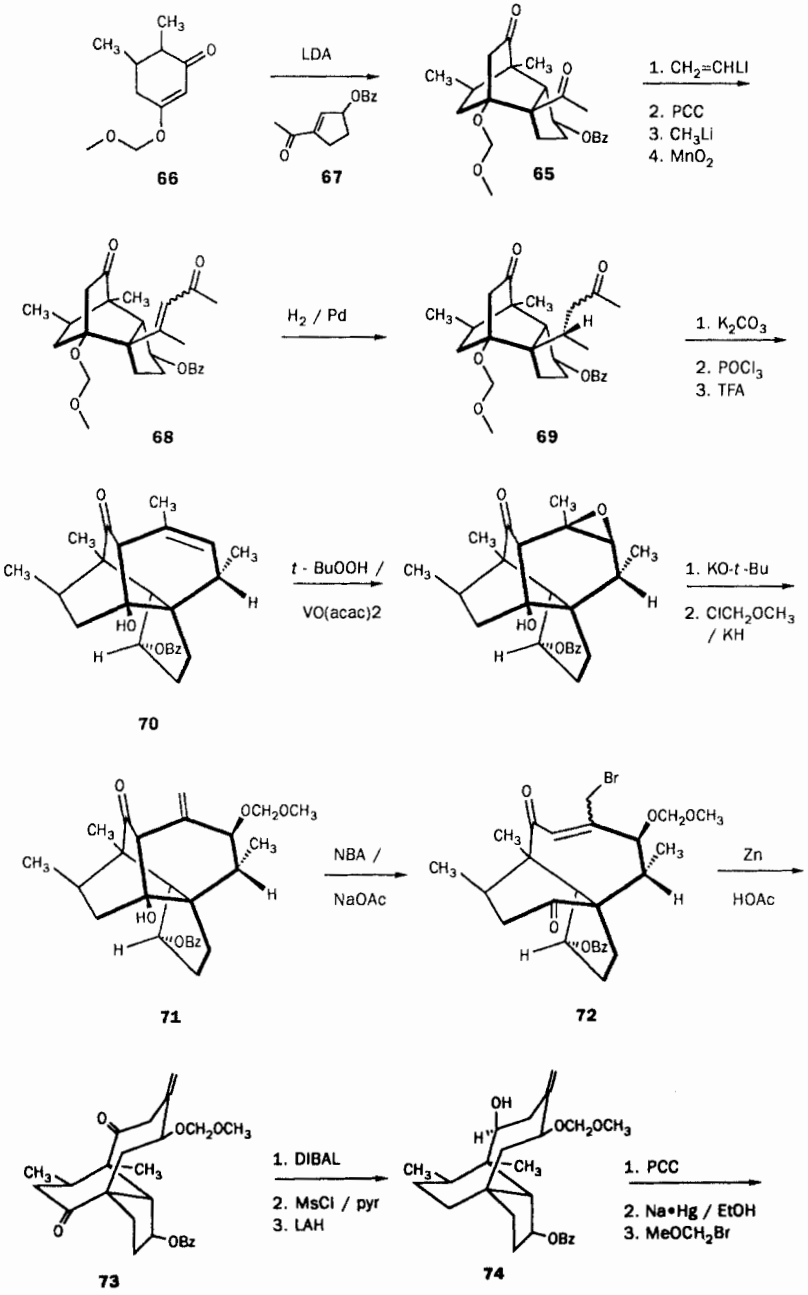
The synthesis of pleuromutilin (Scheme 166) accomplished by Gibbons[261, 262] in the Woodward laboratory at Harvard features a rapid and efficient construction of a bridged tricyclic intermediate, **65**, having the correct stereochemistry for the junctions of the three rings. The 2-carbon oxo-bridge of **65** serves as a surrogate for the eventual eight-membered ring of the natural product.

To produce **65** a double Michael (dienolate Diels–Alder) reaction of the kinetic enolate of **66** with enone **67** is carried out. The remaining elements of the eight-membered ring are then added through a four-step sequence yielding **68**. Hydrogenation of this intermediate occurs to give a mixture

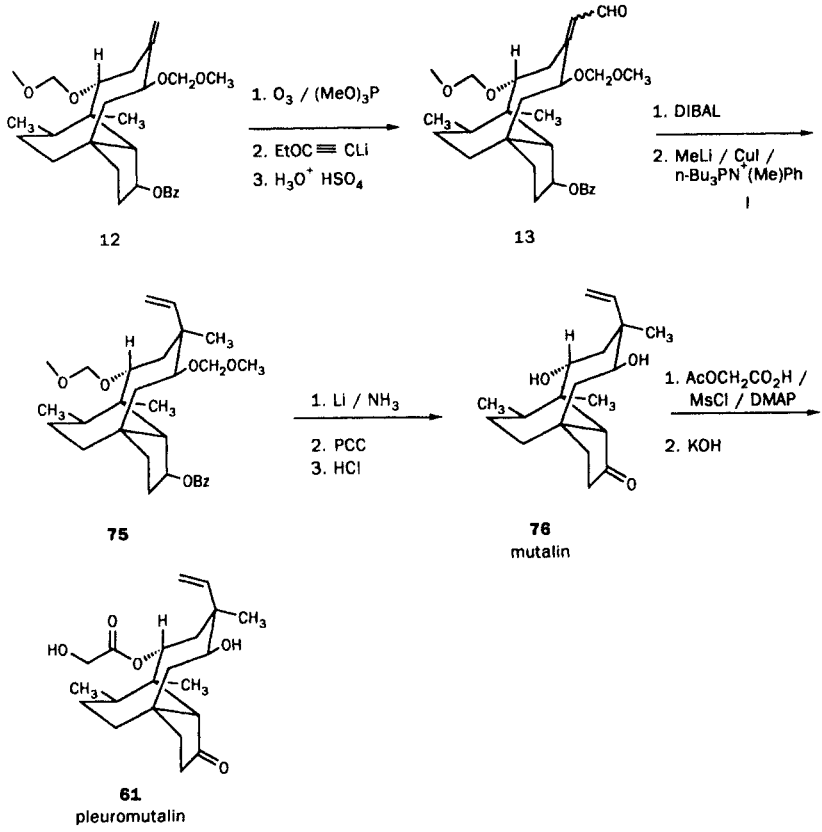


SCHEME 165. Biosynthesis of pleuromutilin.

(~ 3:1) with the desired isomer **69** predominating. Aldol cyclization, dehydration away from the bridgehead position, and protecting group cleavage then affords **70**. Epoxidation and base-catalyzed elimination followed by protection of the newly introduced hydroxyl group affords methoxymethyl ether **71**. The required eight-membered ring of the mutilins is then "unraveled" through a dealdolization–allylic bromination sequence to afford **72**. Bromoenone **72** is reductively debrominated to yield the exomethylene olefin **73** and this is selectively deoxygenated in the six-membered ring through a double reduction sequence yielding **74**. Through several steps the methylene group of **74** is removed and replaced by a quaternary center having the appropriate methyl–vinyl substitution of the natural product. Manipulation of the oxygen functions of **75** and addition of an hydroxyacetic acid unit to **76**, mutilin, affords pleuromutilin, **61**.



SCHEME 166. Gibbon's synthesis of pleuromutilin.



12 13

75 76 mutalin

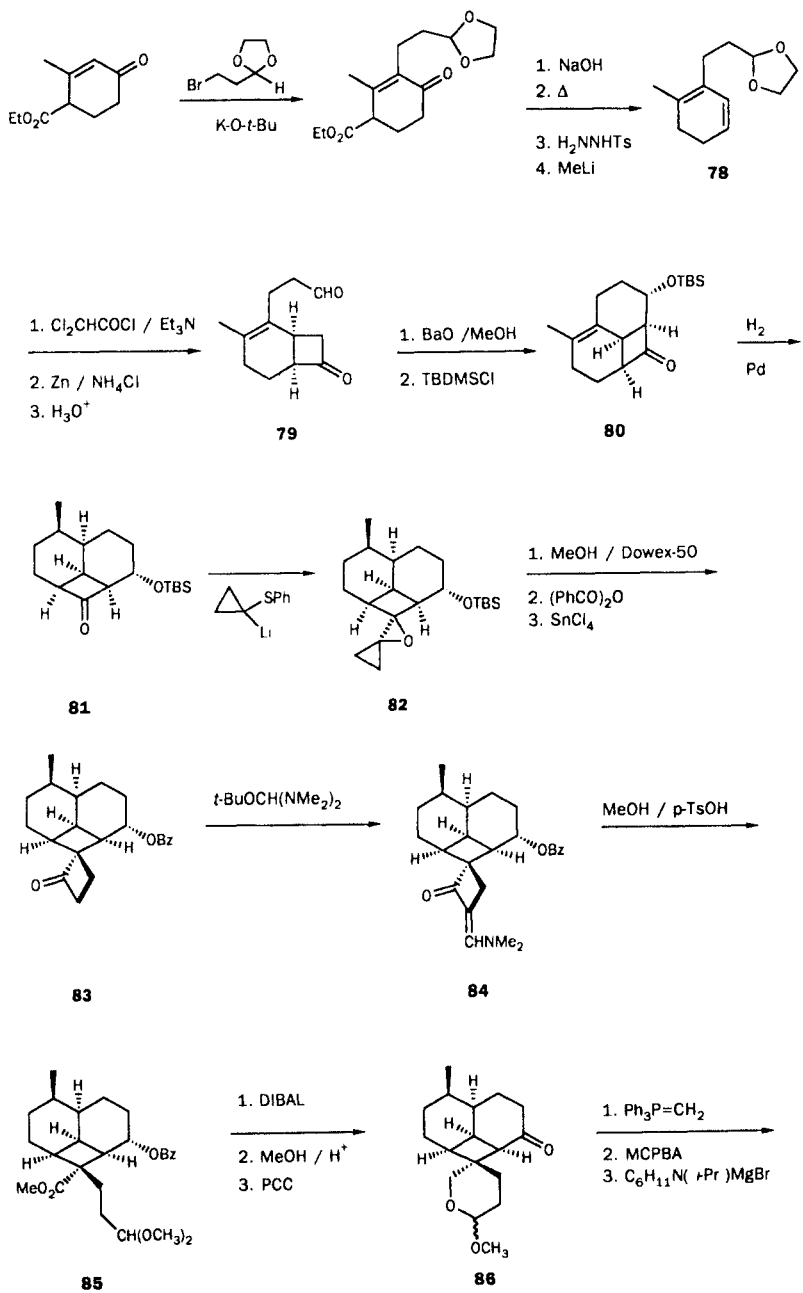
61 pleuromutalin

SCHEME 166. Gibbon's synthesis of pleuromutilin (*continued*).

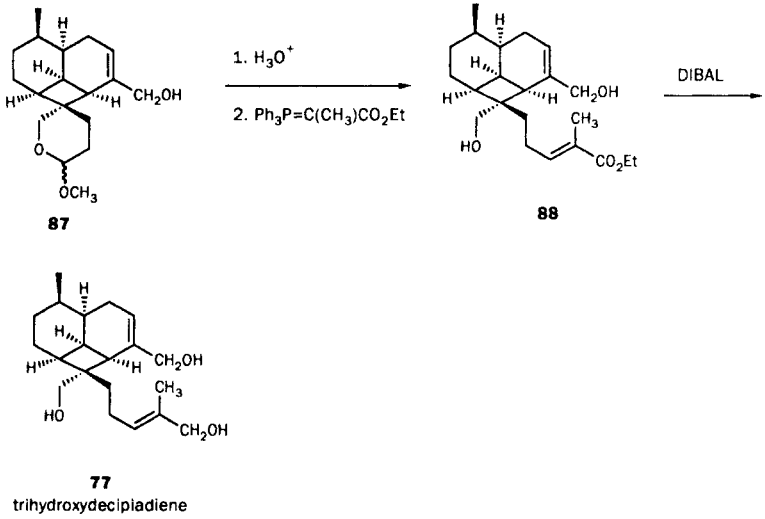
E. Trihydroxydecipiadiene

The decipiene diterpenes are characterized by a unique tricyclo-[5.3.1.$0^{3,11}$]undecane ring system. One of the natural products, trihydroxydecipiadiene, **77**, has been synthesized by Greenlee,[263] also in Woodward's laboratory, at Harvard.

The key to the synthesis, shown in Scheme 167, is the stereoselective construction of the core ring system followed by controlled introduction of the substituent units. To achieve the preparation of the ring system, diene dioxolane **78** is prepared in a five-step sequence from Hagemann's ester. Addition of dichloroketene followed by reductive removal of the chlorines affords *cis*-fused bicyclic ketone **79**. The third ring is then closed by internal



SCHEME 167. Greenlee's synthesis of trihydroxydecipiadiene.



SCHEME 167. Greenlee's synthesis of trihydroxydecipiadiene (*continued*).

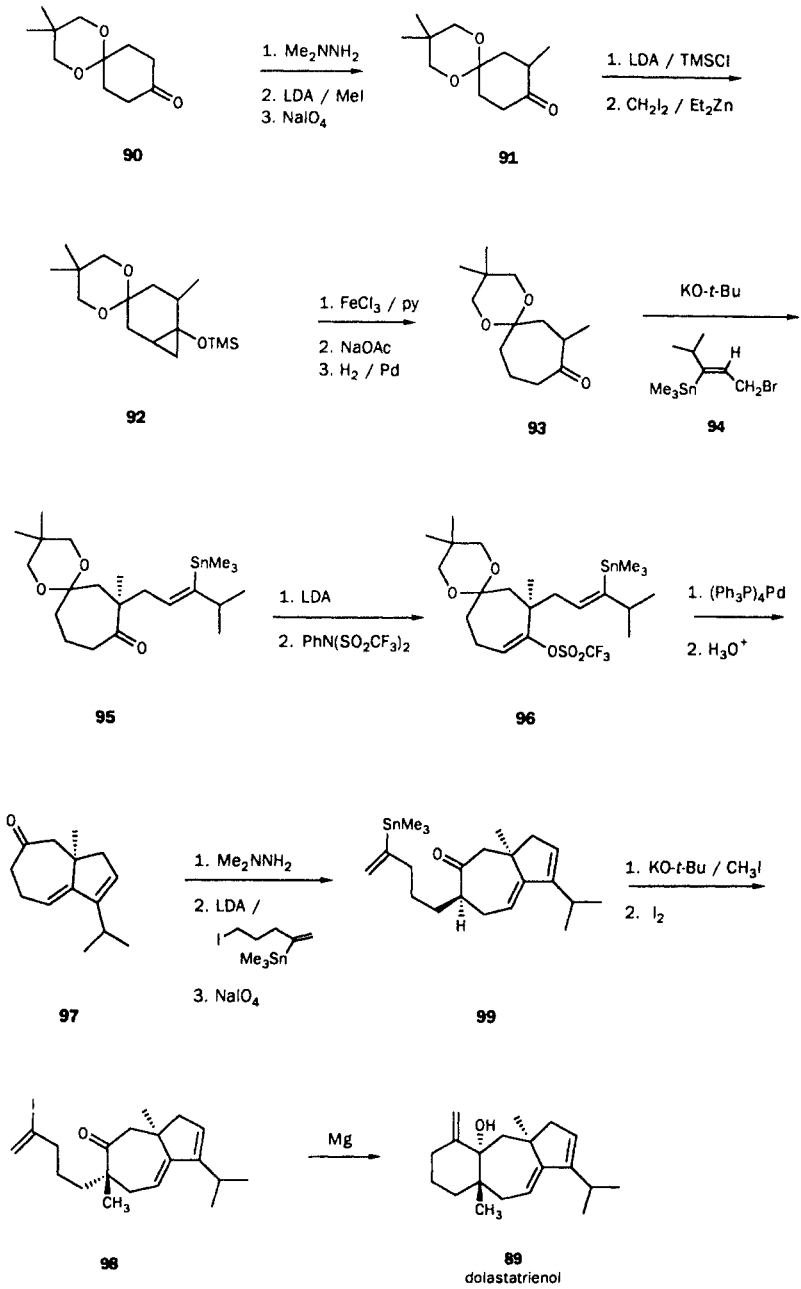
aldol cyclization using barium oxide and the resulting ketol is protected as a silyl ether, **80**. Hydrogenation, which can only occur from the relatively unhindered convex face of **80**, affords saturated ketone **81**.

To add the substituents appended to the cyclobutane ring in the natural product, a Trost spiroannulation sequence[231, 232] is carried out which, after rearrangement of the intermediate epoxide **82**, yields tetracyclic ketone, **83**. The vinylogous amide **84** is then prepared and cleaved with acidic methanol to give ketal ester **85**. The stereochemistry of the quaternary center formed in this sequence follows from the rearrangement reaction of the spiro epoxide **82**.

Completion of the synthesis is carried out by first converting **85** to the keto lactol ether **86**. Wittig methyleneation, epoxidation of the derived olefin, and base-catalyzed opening of the epoxide affords primary alcohol **87**. A second phosphorane reaction, in this case of a Wadsworth–Emmons–Horner type provides ester **88**. Finally, reduction with diisobutyl aluminium hydride yields the natural product.[77]

F. Dolastatrienol

The structurally unique dolastane tricyclic diterpenes have been the subject of several synthetic efforts. Piers and Friesen[264] from British Columbia have reported the synthesis of a naturally occurring dolastatrieneol, **89**.



SCHEME 168. Pier's synthesis of dolastatrienol.

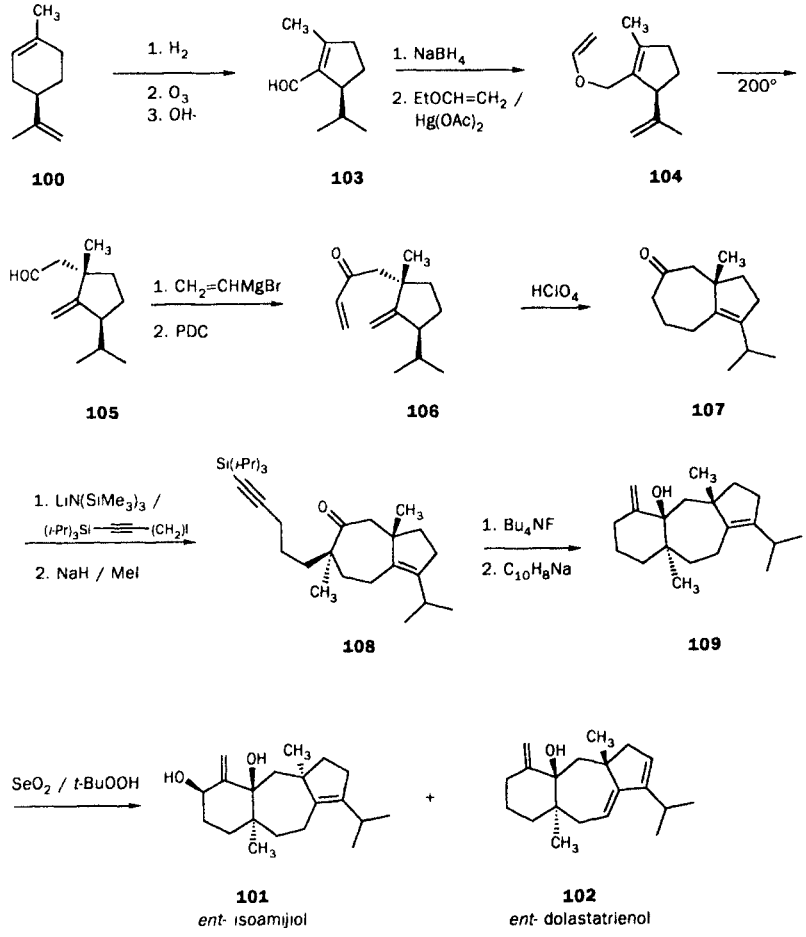
The key features of this "linear" synthesis (Scheme 168) are the preparation of the seven-membered B ring by ring expansion of a 4,1,0-bicycloheptanol, closure of the cyclopentenyl ring by palladium-mediated vinyl tin chemistry, and formation of the remaining methylenecyclohexanyl unit by internal Grignard addition.

The starting material is the cyclohexandione ketal **90** which is methylated to **91**. Conversion of the ketone to its silyl ether is followed by Simmons–Smith cyclopropanation to afford bicyclic silyl ether **92**. Cleavage of the cyclopropyl group in the presence of ferric chloride affords a ring-expanded chloro ketone which is subjected to hydrogenolysis to yield **93**. A second alkylation is then carried out using the complex alkyl halide **94**, the alkylating agent being prepared from methyl 4-methyl-2-pentynoate and a lithium trimethyltin cuprate complex. The keto group of **95** is converted into its corresponding enol triflate derivative **96** and the palladium-catalyzed cyclization is effected to provide, following hydrolysis of the ketal function, bicyclic ketone **97**.

A second vinyl tin unit is appended to **97** by alkylation of the derived dimethylhydrazone, followed by methylation and replacement of the stannyl unit by an iodine atom to form ketone **98**. The stereochemistry of this intermediate is determined by the order of introduction of the two alkyl groups, since the angular methyl group already present in **99** controls the approach of an alkylating agent. Finally, treatment of **98** with magnesium affords the dolastatrienol **89**.

Using (R)-(+)-limonene **100** (Scheme 169) as the starting material, Mehta and Krishnamurthy[265a] at Hyderabad synthesized the enantiomers of dolasta-1(15),7,9-trien-14-ol, **101**, and isoamijiol, **102**. The optically active monoterpenoid is converted to the C-ring enal synthon **103** by the method of Lange et al.[265b] Reduction, formation of the vinyl allyl ether **104**, and thermolysis provides aldehyde **105**. The remaining elements of the central ring are added through Grignard addition and oxidation, and the product dienone, **106**, is subjected to acid-catalyzed cyclization to yield the hydroazulene ketone **107**.

To construct the six-membered A-ring, ketone **107** is alkylated first with a silyl-protected alkynyl halide and second with methyl iodide. As in the Piers synthesis, the order of introduction of the ring-A carbons and the angular methyl group is dictated by the presence of a controlling stereochemical element, a methyl group, at the junction of rings B and C. Following removal of the silyl group of **108**, a radical cyclization, patterned essentially after the Stork method[209] for the generation of the gibberellic acid C/D ring system, is used to close the last ring and to produce intermediate diene **109**. Exposure of **109** to selenium dioxide affords a mixture of products from which *ent*-isoamijiol, **102**, and *ent*-dolasta-1(15),7,9-trien-14-ol, **101**, are separated.

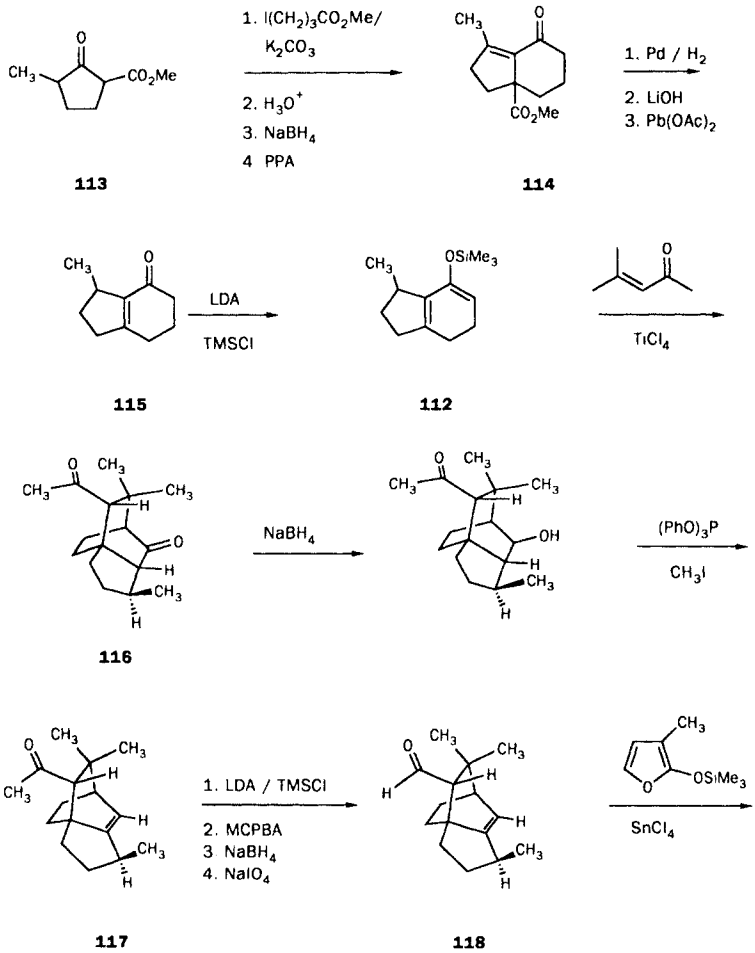


SCHEME 169. Mehta's synthesis of isoamijiol and dolastatrienol.

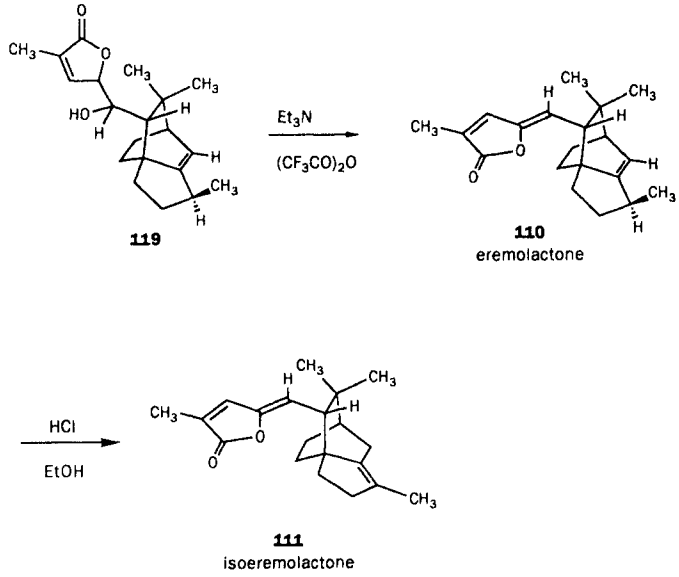
G. Eremolactone and Isoeremolactone

One of the more unusual diterpene carbon skeletons is that of eremolactone, **110**. The identification of the structure of the natural product was made on the basis of an X-ray crystallographic structure of the more stable double-bond isomer, isoeremolactone, **111**. As a consequence the stereochemistry of the methyl group in the cyclopentanyl unit of the natural product was not known prior to synthesis of the molecule.

Takei and co-workers[266] carried out synthesis of both eremolactone and isoeremolactone (Scheme 170). They prepared the 2.2.2-bicyclooctane system by Lewis-acid-catalyzed double Michael addition (or Diels–Alder 4 + 2 cycloaddition) of a dienol ether **112** to mesityl oxide. To prepare **112** ketoester, **113** is alkylated and the resulting keto diester is converted into a hydroxyacid and cyclized to form **114**. Double-bond reduction, hydrolysis, and lead-acetate-induced decarboxylation affords enone **115**. Kinetic enolization of **115** then yields dienol silyl ether **112**. Combination of **112** with mesityl oxide in the presence of Lewis acid affords all possible isomers at the



SCHEME 170. Takei's synthesis of eremolactone and isoeremolactone.

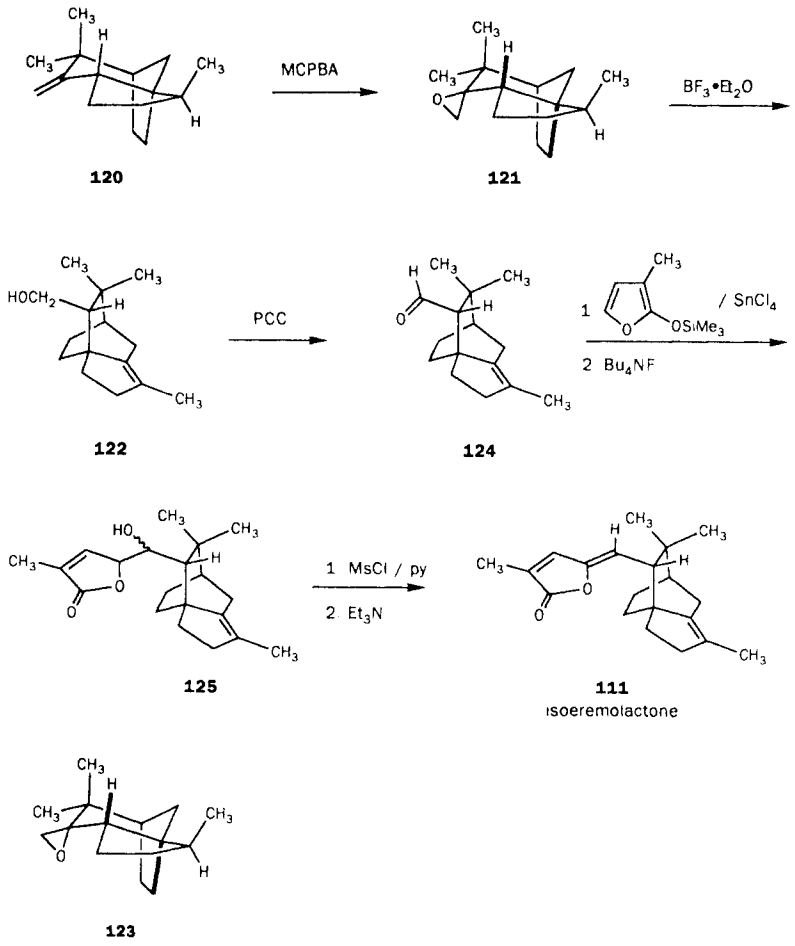


SCHEME 170. Takei's synthesis of eremolactone and isoeremolactone (*continued*).

site of the secondary methyl group and the methyl ketone unit. One of these, **116**, is carried forward to eremolactone **110**.

The double bond of eremolactone is introduced by reduction and elimination to form **117** and subsequent degradation of the methyl ketone group affords aldehyde **118**. The aldehyde is now condensed with a furanol ether to form hydroxylactone **119**. Dehydration affords eremolactone **110** and acid treatment of the natural product yields the more stable double bond isomer isoeremolactone **111**.

Isoeremolactone **111**, the isomerization product of eremolactone, was first prepared in a chiral synthesis by Ramage, Owen, and Southwell[267] in Manchester. The starting material (Scheme 171) is tricyclovetivene **120** prepared from zizanoic acid, a compound previously the subject of a total synthesis. Epoxidation of **120** affords **121** as the major isomer in which the epoxide oxygen is assumed to have been introduced equatorially. While this result is counter to the usual steric course of epoxidation of methylenecyclohexanes, it presumably results from severe hindrance to approach of the peracid by the two-carbon bridge of the bicyclooctane system. On the other hand, rearrangement of **121** yields 30% of the desired 2.2.2 system **122**, whereas the epimer affords a lower yield of the alcohol, a result more in



120 121 122 124 125 111 123

isoeremolactone

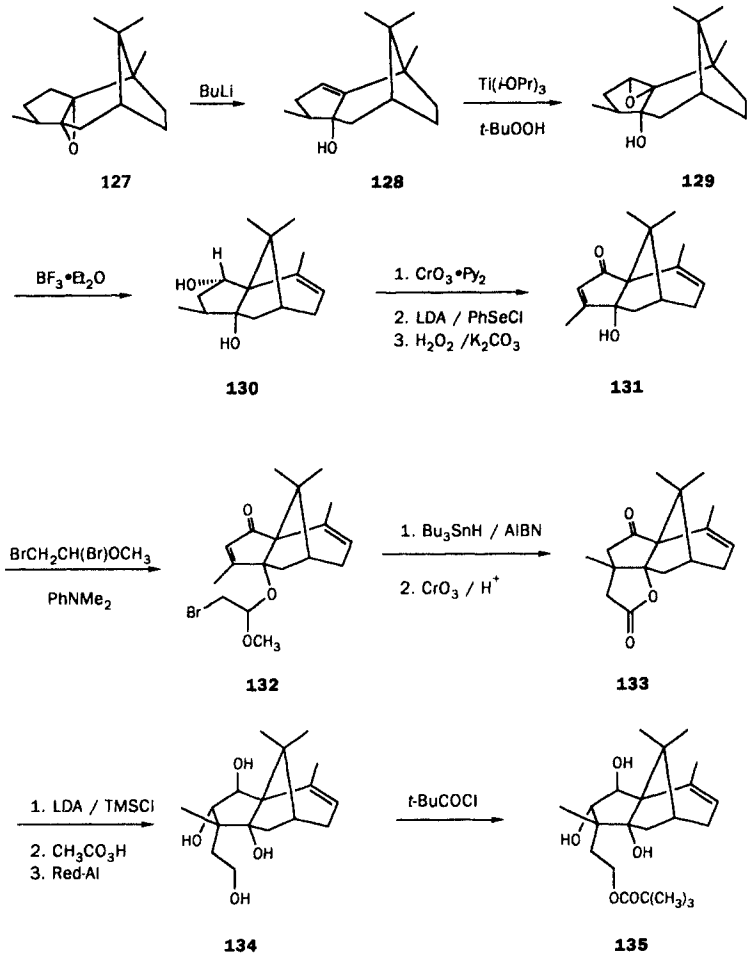
SCHEME 171. Ramage's synthesis of isoeremolactone.

keeping with an assignment of **123** to the epoxidation product. Nevertheless, the rearrangement product **122** has the correct stereochemistry of the hydroxymethyl group for elaboration to isoeremolactone. Accordingly, oxidation of **122** affords aldehyde **124** and the lactone ring is appended by condensation with a furanol silylether. The resulting hydroxybutenolide **125** on mesylation and elimination affords isoeremolactone **111**. On the basis of the known absolute stereochemistry of the starting material, **120**, the absolute configuration of isoeremolactone (and eremolactone itself) is also established.

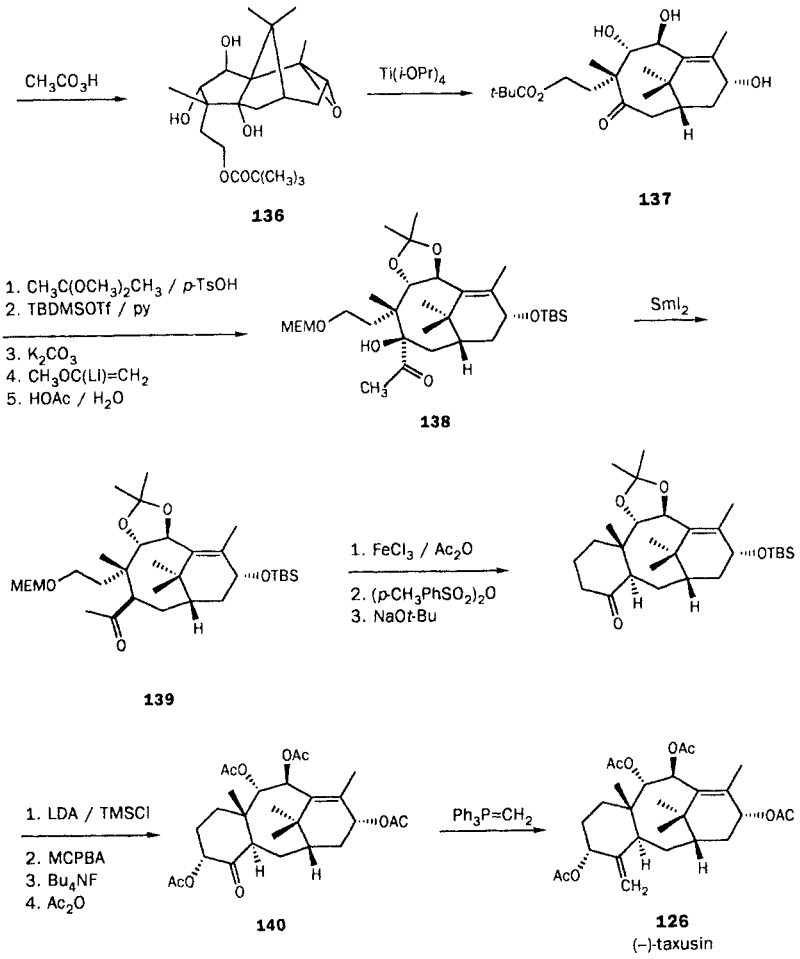
H. *ent*-Taxusin

The synthesis, by Holton and co-workers[268] at Florida State, of the first member of the taxane class of diterpenes is that of the enantiomer of naturally occurring taxusin, **126**. To generate the unique 5.3.1-bicycloundecene bridged-ring system of the taxanes, the Holton group employs a fragmentation reaction of a bicyclic epoxy alcohol as the pivotal step.

As the point of departure for the synthesis (Scheme 172), the naturally occurring sesquiterpene β-patchoulene oxide, **127**, is employed. When treated



SCHEME 172. Holton's synthesis of taxusin.



SCHEME 172. Holton's synthesis of taxusin (*continued*).

with *tert*-butyl lithium, the epoxide is opened by attack at the less-hindered α-methylene position to give an allylic alcohol, **128**, which is subjected to a Sharpless epoxidation to afford a second epoxy alcohol, **129**. Subjection of this substance to the influence of Lewis acid effects a skeletal rearrangement to produce diol **130**. A series of oxidative steps then generates enone alcohol **131**. To add the remaining members of the cyclooctene ring of taxusin the hydroxyl group of **131** is reacted to form the mixed bromoacetal **132**, which

upon application of the Stork radical cyclization methodology[269] and subsequent oxidation affords tetracyclic lactone **133**.

An additional hydroxyl group is added alpha to the ketone carbonyl of **133** by oxidation of the derived silyl ether. Hydride reduction of the carbonyl groups then provides a tetrol, **134**, of which the primary hydroxyl function is selectively protected as a pivalate. The double bond of **135** is now epoxidized to give **136**, and the key fragmentation, by which the 3.3.0 ring system is opened, is effected with titanium isopropoxide. The resulting triol **137** is differentially protected and the remaining elements of the fused cyclohexanyl portion of the molecule are added to afford **138**. Reductive deoxygenation to **139** is followed by a sequence which closes the last ring. Following introduction of the remaining oxygen function, the dioxolane ring and the silyl ether protecting group are cleaved and the tetraacetate **140** is produced. Wittig methylenation affords *ent*-taxusin, **126**.

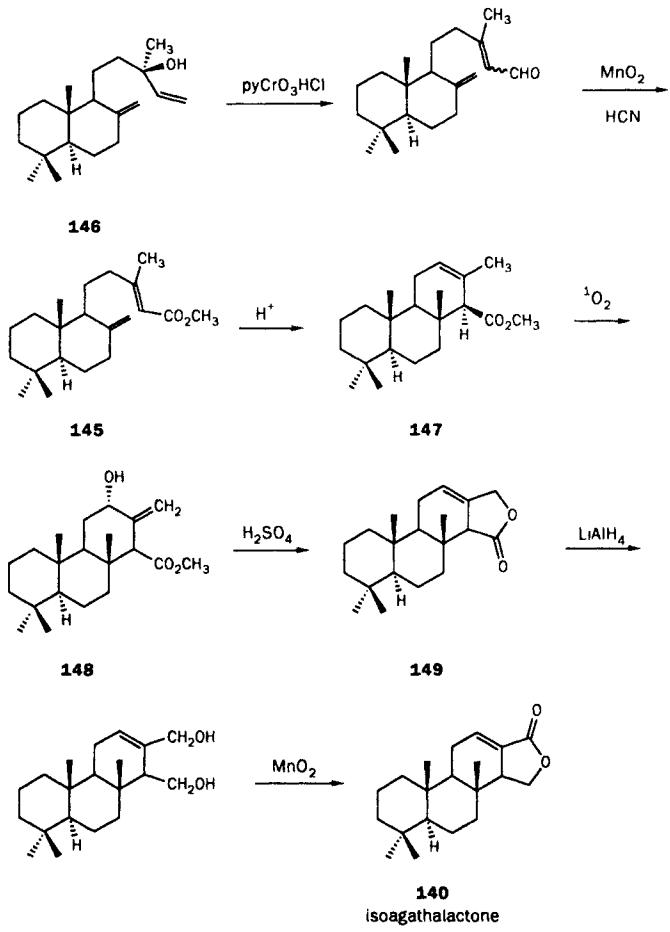
I. Isoagathalactone and Other Sponganes

The biogenetic cyclization of geranylgeraniol pyrophosphate to diterpenoids does not usually follow the path of triterpene biosynthesis; that is, there are few tri- or tetracyclic hydrophenanthrene diterpenes in which a methyl group appears at C-8 of the ring system. That carbon normally provides one of the members of a third ring. There are, however, a growing number of compounds, particularly from sponges, in which the pattern of cyclization of squalene is observed. Of these, isoagathalactone **140** and the related spongane compounds **141–144** have been prepared by partial synthesis from manool by Rúveda and associates[270–273] in Campinas.

Acid-catalyzed cyclization of methyl copalate, **145** (Scheme 173),[270, 271] derived from manool, **146**, by successive oxidations yields tricyclic ester **147**, which when subjected to a photoene process affords a mixture of alcohols from which **148** is separated. A second acid-catalyzed cyclization, this time of the carboxyl group onto an allylic cation, provides lactone **149**. Manipulation of the oxygen functions by taking advantage of the propensities of allylic alcohols to oxidize more rapidly than saturated ones yields isoagathalactone.

The remaining members of this class, **141–144** (Scheme 174), to be synthesized by the Rúveda group[272, 273] are prepared by similar functional group transformations of the ring-C substituents.

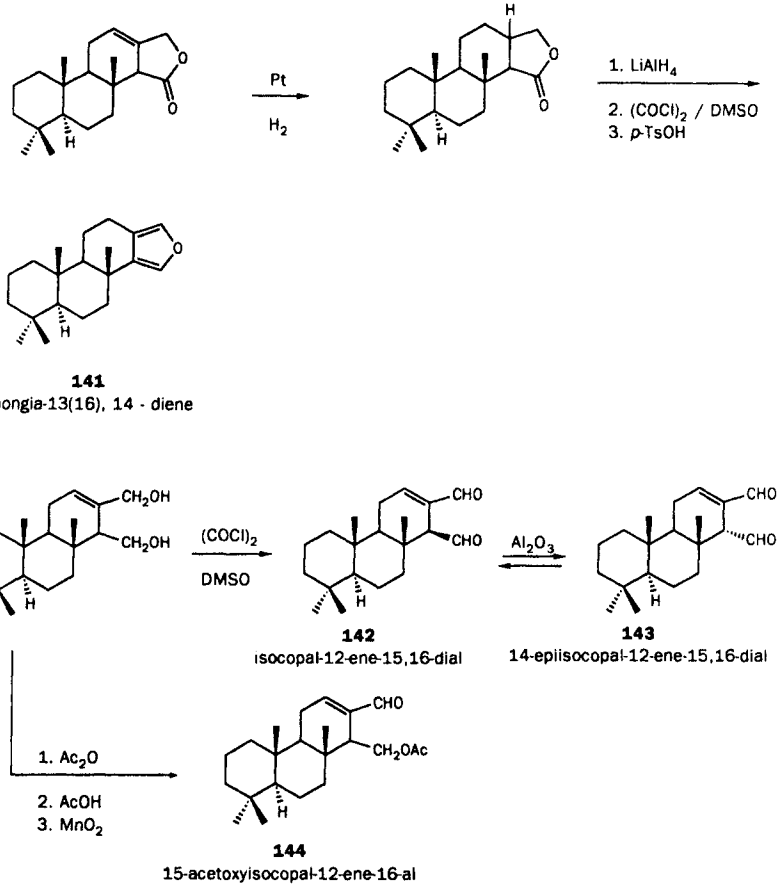
A synthesis of isoagathalactone has also been reported by Nakano and Hernández[274, 275] from Caracas. With minor exceptions in the choice of reagents, the route is identical to that of Rúveda.



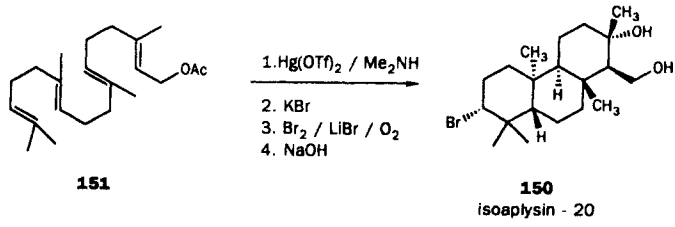
SCHEME 173. Ruveda's synthesis of isoagathalactone.

J. Isoaplysin-20

Isoaplysin-20, **150**, is another marine diterpene which has the "squalene" cyclization structural pattern. Nishizawa and colleagues[276] prepared isoaplysin-20 (Scheme 175) by just such a route, using geranylgeraniol acetate, **151**, as the substrate. Treatment of the polyene with mercuric ion followed by replacement of the mercury in an oxidative bromination step affords isoaplysin-20 acetate. Hydrolysis yields the natural product, but in extremely low yield.



SCHEME 174. Ruveda's synthesis of spongane natural products.



SCHEME 175. Nishizawa's synthesis of isoaplysin-20.

K. Ryanodol

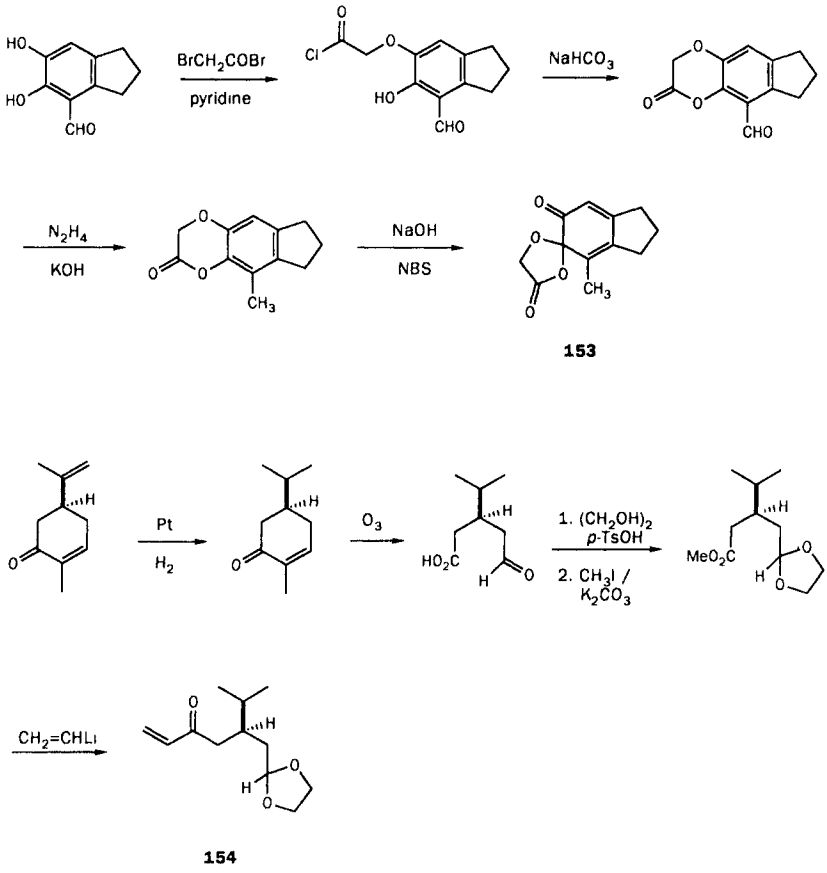
Ryanodol, **152** (Scheme 177), is a structurally unique diterpene alcohol found naturally as its pyrrole-2-carboxylate ester, ryanodine.[277] The chemistry of ryanodol is largely a function of its ball-like bridged structure and the presence of seven hydroxyl groups packed into a 14-carbon tetracyclic ring system. As a consequence, the reactions of ryanodol and of the intermediates prepared in its synthesis are characterized by a multiplicity of neighboring group participations, proximity effects, and fragmentations. Working with a large group of collaborators at the Université de Sherbrooke, Deslongchamps[278] carried out a total synthesis of the molecule.

The Deslongchamps synthesis, while lengthy, is characterized by an economy of reaction types. Once the ring system is constructed, a variety of relatively simple and largely oxidative transformations is employed for creating both the final carbon skeleton and the plethora of oxygen substituents. For starting materials the Deslongchamps group employ the Diels–Alder reactive partners diene **153** and dienophile **154**. The preparation of these substances is illustrated in Scheme 176.

The use of optically active carvone, **155**, as the starting material for enone **154** ensures that the synthesis is homochiral in outcome but has no effect on the stereoselectivity of the construction step for the ring system. Thus, the combination of **153** and **154** (Scheme 177) provides a 1:1 mixture of diastereoisomeric adducts of which only the useful one, **156**, is illustrated here. (In fact, **156** itself is a mixture of two adducts which differ in the *syn* or *anti* relationship of the lactone carbonyl to the newly appended acetal chain.)

Following separation of the two major diastereoisomeric adduct types, substance **155** is caused to undergo internal aldol condensation and lactone hydrolysis to afford diketo alcohol **157**. A second aldol cyclization, following acetal cleavage, is then accomplished in acid solution, and the product, aldehyde diol **158**, is protected by conversion to carbonate ketal **159**. The cyclopentanone ring present in **158** is not an integral part of the final ryanodol, and it is cleaved therefore in a Baeyer-Villiger reaction to afford lactone **160**. It is not clear however why this lactone rather than the one resulting from cleavage of the alternative C–C bond is the major product. Since the Baeyer-Villiger reaction also effects epoxidation of the double bond of **159**, the unwanted oxygen of **160** is removed to provide **161**.

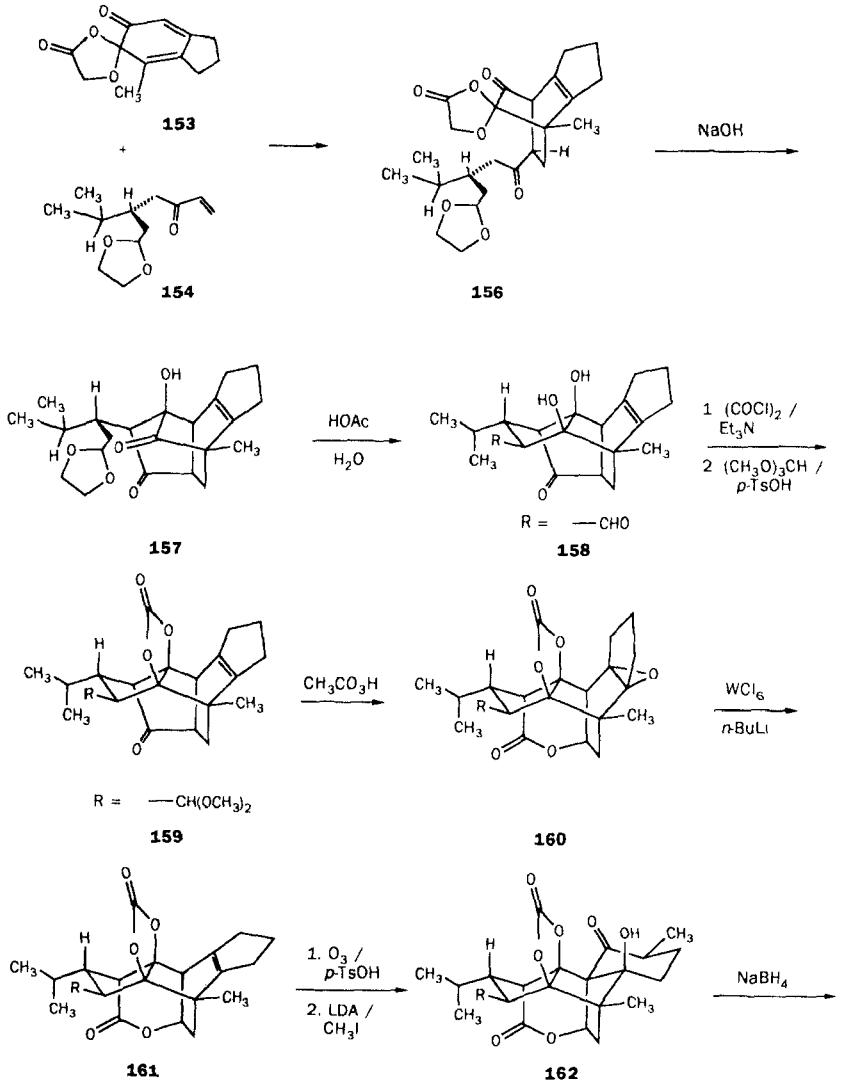
When the double bond of **161** is subjected to ozonization, the initial diketone cleavage product undergoes another aldol cyclization. The resulting ketol is then methylated and **162**, an intermediate with three of the rings of the ryanodol skeleton intact, is obtained and reduced to diol **163**. At this point the need to further functionalize the cyclohexyl ring requires that the axial hydroxyl group of **163** be selectively protected. Taking advantage again



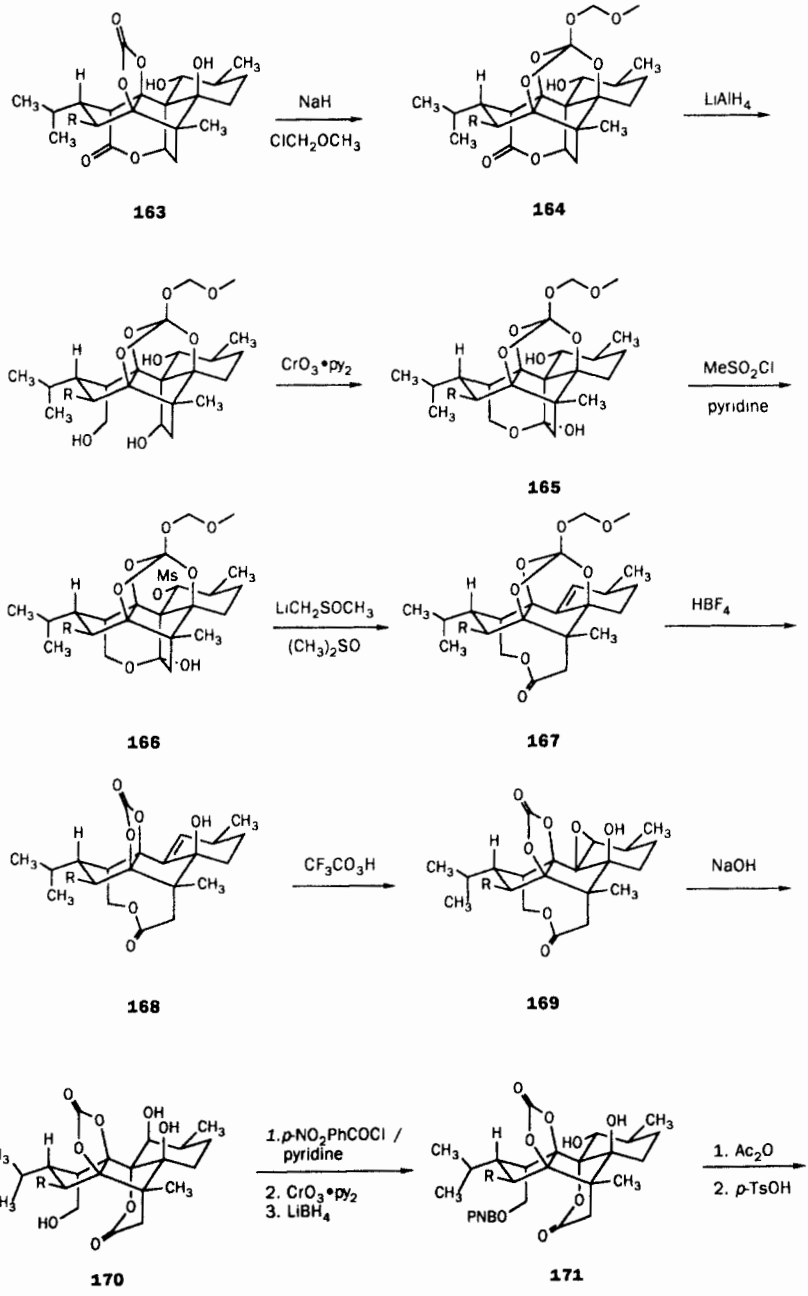
SCHEME 176. Deslongchamp's preparation of starting materials for ryanodol.

of the proximity of the functional groups, an orthocarbonate ester **164** is prepared by treatment of the simple carbonate, **163**, with base and chloromethyl methyl ether. As a consequence, the remaining equatorial hydroxyl group of the six-membered carbocyclic ring can be converted, after production of hemiketal **165**, to the mesylate **166**. Elimination of the mesylate function through fragmentation then provides both the carbon atoms of the bridged ring portion of the natural product as well as a means of introducing the remaining oxygen function in yielding olefin **167**. Epoxidation of **168**, resulting from cleavage of the orthocarbonate group provides **169**, and when the lactone ring is cleaved with base, the resulting carboxylate ion opens the β-oriented epoxide group to yield triol lactone **170**.

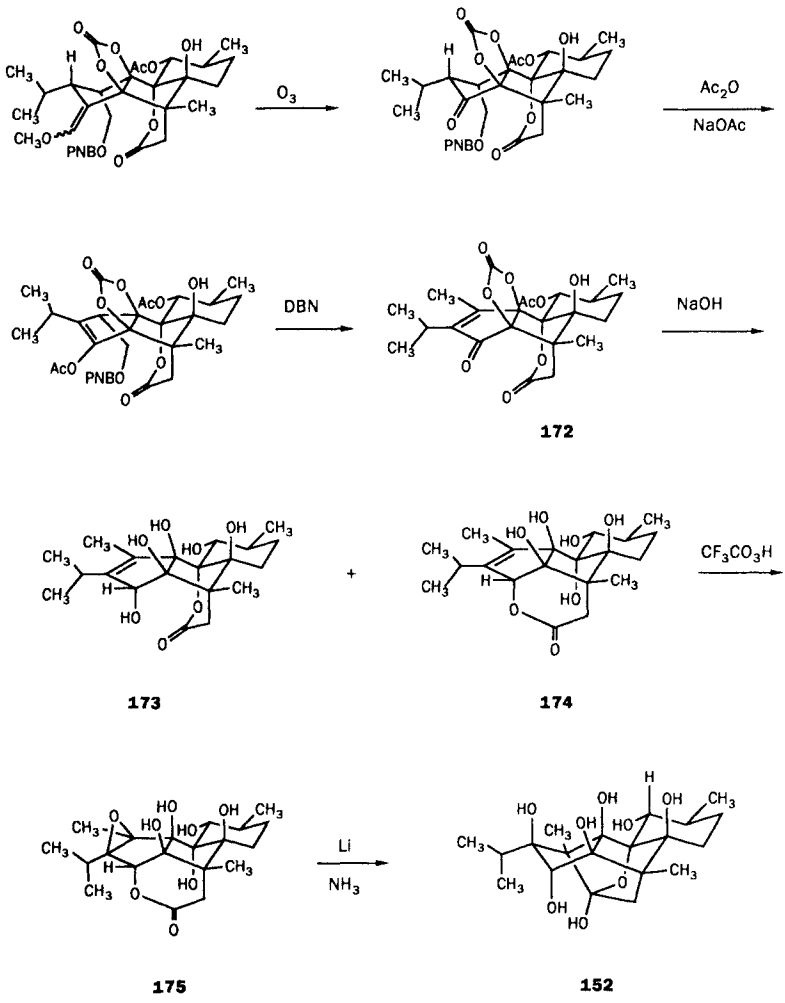
Lactone **170** bears all of the structural features of the carbon skeleton of ryanodol save two, a methyl group and the lower ketone (hemiketal) unit which bridges the upper cyclopentanohydroindane ring system. To establish the methyl group the primary hydroxyl group of **170** is first converted into its *p*-nitrobenzoate ester derivative, **171**. This intermediate is carried through a



SCHEME 177. Deslongchamps' synthesis of ryanodol.



SCHEME 177. Deslongchamps' synthesis of ryanodol (*continued*).



SCHEME 177. Deslongchamps' synthesis of ryanodol (*continued*).

five-step sequence resulting ultimately in the elimination of the *p*-nitrobenzoate group and the generation of a β-methyl-substituted cyclopentenone system, **172**. Base treatment of **172** then affords an equilibrium mixture of lactones **173** and **174**. Both of these isomers are useful for ryanodol as epoxide **175** is obtained from either one. In the last step, lithium in ammonia reduction of the lactone results in the formation of final carbon–carbon bond of the bridging ketone unit and the result is ryanodol, **152**.

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The Synthesis of Polysaccharides to 1986

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1. INTRODUCTION

Polysaccharides are widely distributed substances and make up the main part of organic material in the biosphere. Cellulose, for example, is the most abundant organic material on earth, and is of great importance for industry both by itself and as its numerous derivatives. A number of other polysaccharides are also very important for many branches of industry (starch and its derivatives, xanthan and other stabilizers, alginic acids, carrageenans and other algal polysaccharides, etc.).

Following proteins and nucleic acids, the polysaccharides also play a key role in the living process. Until recently, they were regarded largely as a structural material of the cell (cellulose, chitin) and its main energy source (starch, glycogen). However, in last 10–20 years a specific role of polysaccharides or polysaccharide structures, which are constituent parts of more complicated polymeric complexes of cells, has become ascertained. This role comes first of all to the formation of highly specific hydrophilic structures on the surface of cell and multicellular complexes, and perhaps of intracellular membranes. The specificity of these structures manifests itself in such important biological acts as, for example, cell interactions, serological reactions of microbial cells and primary stages of their interaction with bacteriophages, the specificity of some receptor interactions, and formation and differentiation of cell complexes of plants' wall.[1–4] Some carbohydrate derivatives act as highly specific phytohormons and seem to play a very significant role in plant development regulation.

Rapid progress in understanding the significance of carbohydrates for the life processes has evolved into the study of the structure and function of polysaccharides and other carbohydrate-containing polymers. This has inevitably stimulated the development in the synthetic field, and in the last 10–15 years an essential progress has been achieved in the synthesis of oligosaccharide structures, in particular the repeating units of microbial polysaccharides and carbohydrate chains of glycoproteins. These compounds represent fragments of natural carbohydrate-containing polymers, and served as important models in the study of structure, physicochemical properties, and function of natural biopolymers. A next step was naturally the search for the routes to the synthesis of polysaccharide structures themselves, as it was, for example, in the synthetic chemistry of polynucleotides. However,

the synthesis of polysaccharides has evolved quite new problems. The present review is devoted to these first steps in the synthesis of polysaccharides.

The polysaccharides are biopolymers consisting of monosaccharide units linked to each other by the glycosidic linkages,* which are present in a cell usually as a mixture of polymer homologues. Proteins and nucleic acids are linear unbranched polymers, and a large variety of their macromolecules results only from the unique irregular sequence of the constituent amino acids or mononucleotides. In contrast, general architectonics of natural polysaccharides is more diverse; they may have both linear and branched structure and various combinations of regular and irregular sequences of the constituent monosaccharides. Another fundamental distinction of polysaccharides, which is extremely important in the synthetic aspect, is that in addition to a stereochemical diversity of monosaccharides, the intermonomeric glycosidic linkage also involves a chiral center, and thus a variety of monomers and their sequences in the chain combines with structural and stereochemical distinctions in the intermonomeric linkage and its possible variations along the polysaccharide chain.

Basically, all polysaccharides can be divided into two main types. The polysaccharides of the first type have the structure in which the monomeric units (monosaccharides or oligosaccharides) are regularly repeated and, being linked by the same type of glycosidic linkage, form a polymeric chain with a strictly regular structure. This class includes homopolysaccharides with monosaccharides as the monomeric units, and heteropolysaccharides with oligosaccharide repeating units. The chain of the polysaccharides of the other type contains various monosaccharides, oligosaccharide blocks, and/or different types of intermonomeric glycosidic linkages arranged at random along the chain to give an irregular polymeric chain.

The synthesis of irregular polysaccharide structures is evidently possible only via a step-by-step elongation of a chain by adding respective monosaccharides or oligosaccharide blocks. Taking into account the complexity of the monomers's chemistry and the stereochemical problems involved, this appears to be a highly laborious task, especially when trying to obtain the polymer of sufficiently high molecular weight. One would assume that the solution to this problem is obviously a matter for future scientists. On the contrary, the synthesis of polysaccharides with a regular structure is being solved at present, and the progress achieved is discussed in this chapter.

In essence, the synthesis of the polysaccharides with a regular structure can be accomplished via three pathways:[5] (1) a step-by-step attachment of

* The synthetic polymers that consist of monosaccharide units linked by the other types of linkages (e.g., by the ether or carbon–carbon linkages) differ essentially by their physicochemical and biological properties and cannot be regarded as real polysaccharides.

either the monosaccharide (for homopolysaccharides) or the oligosaccharide (for heteropolysaccharides with repeating units) units; (2) the polycondensation or polymerization of the corresponding monosaccharide or oligosaccharide derivatives by chemical methods; (3) the enzymatic polymerization of the corresponding monosaccharide or oligosaccharide precursors, the structures of which are known from studies of the biosynthetic pathways of particular polysaccharides and which can be obtained by chemical synthesis.

Until recently, only the second route (i.e, the chemical polymerization or polycondensation) has been used rather extensively; the approach employing a step-by-step elongation of the chain proved to be highly laborious;[6, 7] the enzymatic polymerization of the biosynthetic precursors[8] is fairly promising but still insufficiently developed.

The most important requirement for the chemical polymerization or polycondensation of mono- and oligosaccharide fragments, aiming at the preparation of polysaccharides with a strictly regular structure, is its absolute regio- and stereospecificity. It is obvious that even a single variation in the structural and stereochemical regularity of the intermonomeric linkage within the polymeric chain immediately changes sharply the macromolecular conformation, altering essentially its physicochemical properties, and, therefore, its biological specificity. This is the main reason for the serious difficulties encountered in carrying out the specific polymerization or polycondensation.

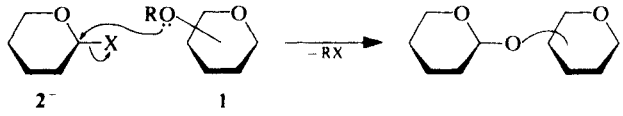
Regiospecificity of the polymerization or polycondensation, leading to a completely structurally regular polymer, can be ensured by the usual method, that is, by temporary protection of the hydroxyl groups which do not contribute to the glycosidic linkage formation, and this is achieved without particular trouble in the case of the simplest monosaccharide monomers. For more complex oligosaccharide blocks, the task becomes more complicated with complication in the structure of a monomer, and sometimes becomes very laborious; however, at the present state of sugar chemistry this task is rather of a technical character.

It is far more complex to ensure the total stereoregularity of the polysaccharide being synthesized, since this requires absolute stereospecificity of formation of the intermonomeric glycosidic linkage. In this connection the search for the reactions of glycosidic linkage formation ("glycosylation reaction"), which meet this fundamental requirement and, at the same time, may serve as the basis of the polymerization or polycondensation process, acquires a special significance. At this point one can recall that the development of adequate methods for the creation of peptidic and phosphodiester linkages also has been prominent in the progress of the synthetic chemistry of polypeptides and polynucleotides.

In this connection it is reasonable, prior to the discussion of particular syntheses of polysaccharides, to consider very briefly the general situation concerning stereospecificity of glycosylation reactions and the development on this basis of regio- and stereospecific polymerization or polycondensation procedures.

2. THE GLYCOSYLATION REACTIONS

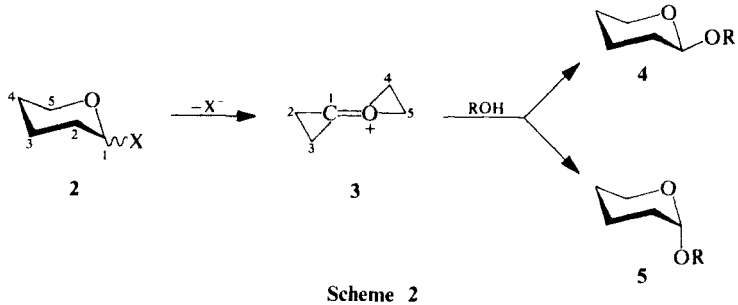
The choice of a reaction satisfying the above mentioned requirements is very restricted, since most of the presently known glycosylation reactions lack absolute stereospecificity. The classical reactions producing the glycosidic linkage are based on the nucleophilic attack of the anomeric carbon C-1 of the glycosylating reagent **2** by the oxygen atom of an alcoholic hydroxyl (or its derivative) of the component being glycosylated, **1** ("aglycone") (Scheme 1). The most important synthetic approaches make use of glycosyl haloides (**2**, X = Cl, Br); silver oxide or salts (Koenigs–Knorr reaction or its versions) or mercury salts (Helferich reaction) are used as promoters of the reaction, facilitating the removal of the leaving group in the form of its anion.[9, 10] Quite recently the thioglycosides (**2**, X = SR), which react in the presence of such promoters as mercury and copper salts and some sulphonic complexes,[11] have found ever-increasing use as glycosylating reagents. The versions of this reaction involving the formation of the glycosidic linkage directly on acid-catalyzed treatment of the sugar, carrying free hydroxyl (**2**, X = OH), or of the corresponding *O*-acetate (**2**, X = OAc) with an aglycone, are used far less frequently.



Scheme 1

The nucleophilic attack of the aglycone component is usually effected by a free hydroxyl group (**1**, R = OH), although the respective derivative with more nucleophilic oxygen, for example, triphenylmethyl (trityl) (**1**, R = Ph_3C),[12] or *tert*-butyl (**1**, R = Me_3C) sugar ethers[13] may also be used.

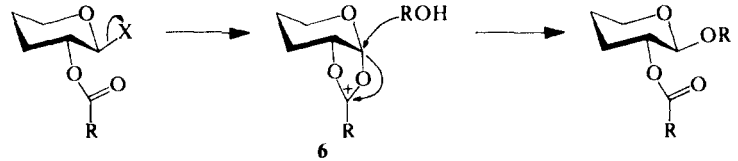
Because of the presence of the neighboring pyranosidic oxygen atom the nucleophilic attack of the glycosidic carbon C-1 does not proceed as a purely S_N2 reaction, but usually follows a more complex mechanism, which may involve, at least on one of its routes, an intermediate glycosyl cation **3** having



2 3 4 5

Scheme 2

a flattened conformation. The nucleophilic attack of the cation **3** proceeds in a nonstereospecific way to give both possible anomeric glycosides (**4** and **5**) (Scheme 2). Next, when the glycosylating component, particularly the glycosyl haloide (**2**, X = Hal), contains at C-2, neighboring with the glycosidic center, a substituent capable of participating in the reaction (e.g., the acetoxyl group), there appears as an intermediate a dioxolenium cation **6**. The attack of this intermediate, having a bicyclic *cis*-hydrindane system, can be effected only from its rear to give in a stereospecific way the 1,2-*trans* glycosidic linkage* (Scheme 3). However, usually there is an equilibrium between the intermediate **6** and the monocyclic glycosyl cation **3** with a flattened conformation, the attack of which is nonstereospecific; as a consequence, even in the presence in the glycosyl haloide of a participating substituent at C-2, directing the reaction to the formation of the 1,2-*trans* glycosidic linkage, full stereospecificity of the reaction most often is not attained. Because of all these complications the stereochemical result of the glycosylation reaction is ambiguous and frequently hardly predictable, as it depends not only on the structural peculiarities of both reaction components, but also on sometimes unobtrusive features of the experimental procedure. In fact, all these reactions



6

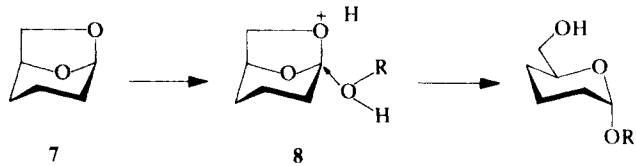
Scheme 3

* In this chapter along with the commonly adopted notation of the glycosidic linkage as α- and β-linkages, we use a definition, which is independent of the monosaccharide structure and chemically more unambiguous, as 1,2-*cis* and 1,2-*trans* glycosidic linkages, specifying its position with respect to the neighboring C_2–O bond.

are far from being strictly stereospecific, and attempts to use them for the development of a stereochemically unambiguous polycondensation process were so far unsuccessful. Similar in character, reactions of *trans*-glycosylation proceeding on acid-catalyzed treatment of the glycoside (**2**, X = OAlk) with alcohol, which are in essence the glycosylation reactions too, lack stereospecificity owing to the same complications.

Ambiguity of the processes which occur in the course of the glycosylation reaction involving monocyclic, conformationally labile derivatives of type **2** naturally has evoked an idea of a more strict steric control of the glycosylation reaction, which would direct the reaction to a less ambiguous route. In fact, first approaches to the synthesis of stereoregular polysaccharides were developed with just two reactions based on this principle.

One of these reactions is based on acid-catalyzed opening of the oxygen ring of anhydro sugars, for example, 1,6-anhydro pyranoses of type **7**. Actually, a nucleophilic attack on the glycosidic center C-1 of the arising conjugate acid **8** can proceed by steric reasons only from the side opposite to the anhydride ring, and as a result only the α-glycosidic linkage should be formed (Scheme 4). However, in this case as well to some extent, a side isomerization reaction converting an oxonium intermediate into a flattened carbenium ion of type **3** may occur, and this sometimes violates the stereospecificity of the reaction. Nevertheless, just this reaction of ring opening in 1,6-anhydro aldopyranoses and some other anhydrides served as a basis for the development of the polymerization reaction characterized usually by absolute stereospecificity, which allowed the synthesis of some stereoregular homopolysaccharides with a high molecular weight.



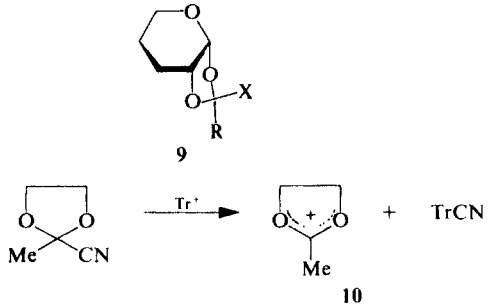
7 8

Scheme 4

The concept of a more strict stereochemical control of the nucleophilic attack on C-1 to ensure the unambiguous formation of a glycosidic linkage gives rise to the other, new class of glycosylation reactions, which employ glycosylating agents of some different structure. As it was pointed out, when the C-2 atom in glycopyranosyl haloides carries a participating substituent, an intermediate that controls the glycosylation reaction turns out to be a bicyclic dioxolenium cation **6**, which is subject to an unambiguous attack to give the 1,2-*trans* glycosidic linkage. However, **6** may also undergo a partial

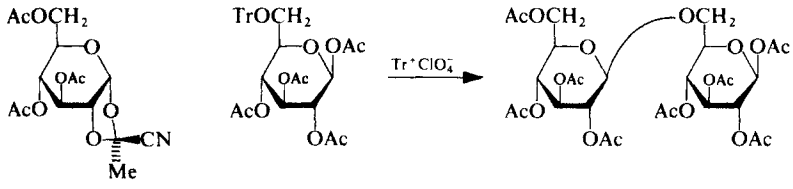
reversible isomerization into the monocyclic glycosyl cation **3**, which deprives the glycosylation reaction of absolute stereospecificity. In this connection, attempts were undertaken to find more effective methods of generation of the dioxolenium intermediate, which would hamper this isomerization. The compounds of type **9** with an already preexisting *cis*-hydrindane system proved most fruitful. One of the methods, based on this principle, is the "orthoester glycosylation," which involves an interaction of sugar's 1,2-orthoesters (**9**, X = OAlk) with an alcoholic (aglycone) component in the presence of pyridinium perchlorate or mercuric bromide.[14] The unambiguous attack of the dioxolenium ion, arising on alkoxyl abstraction, from a sterically accessible side should produce the 1,2-*trans* glycosidic linkage. However, this method of glycosidic linkage formation was found to miss absolute stereospecificity too because of some side reactions, and for that reason has not found application for the synthesis of polysaccharides with a regular structure.

In 1960 Meerwein[15] proposed an interesting approach for generation of the simplest cyclic ion of the dioxolenium (acyloxonium) type **10** starting from 2-methyl-2-cyano-1,2-dioxolane (Scheme 5). Triphenylmethyl (trityl) cyanide formed in this reaction leaves the reaction sphere, and the reaction shifts in the direction of formation of the dioxolenium cation. This principle for the generation of the dioxolenium intermediate was used as the basis for a new glycosylation reaction proposed by Kochetkov and co-workers. The essence of this reaction can be demonstrated by the synthesis of gentiobiose acetate **11** via the interaction of 3,4,6-tri-*O*-acetyl-1,2-*O*-cyanoethylidene-α-D-glucopyranose **12** with 1,2,3,4-tetra-*O*-acetyl-6-*O*-trityl-β-D-glucose **13** in the presence of tritylium perchlorate[16] (Scheme 6). An electrophilic attack of the tritylium cation on the nitrogen atom of the cyano group leads to its abstraction; a bicyclic dioxolenium cation **14**, formed as in the Meerwein reaction, is subject to a nucleophilic attack by the oxygen atom of the *O*-trityl group of the aglycone component **13**, giving rise to a glycosidic linkage and



9 10

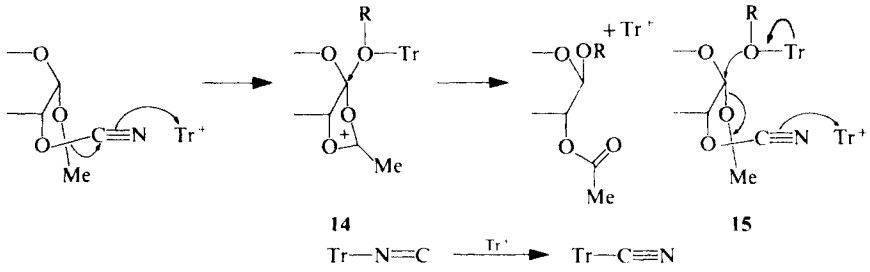
Scheme 5



12 13 11

Tr = Ph_3C

Scheme 6



14 15

Tr—N≡C $\xrightarrow{Tr^+}$ Tr—C≡N

Scheme 7

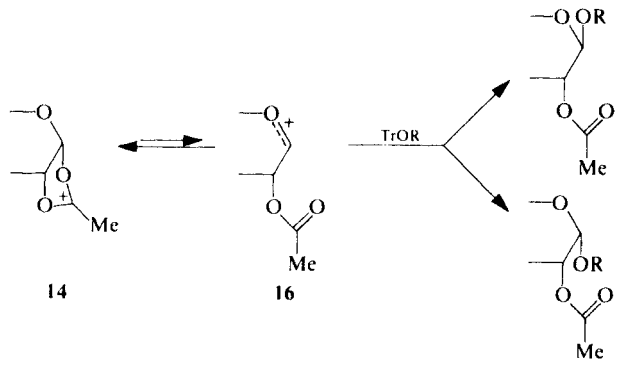
regenerating the trityl cation, which continues the process. Trityl isocyanide in the presence of the tritylium ion undergoes a rearrangement into trityl cyanide, which leaves the reaction sphere (Scheme 7). Thus, tritylium perchlorate, serving as a source of the tritylium cation, is merely an initiator of the reaction.

The bicyclic system of the dioxolenium cation **14** is open to an attack only from the rear side, and, hence, only the 1,2-*trans* glycosidic linkage is formed. The whole reaction seems to be close to a concerted process of type **15** with a push–pull attack of the tritylium cation and oxygen of the *O*-trityl group; this eventually explains the absolute stereospecificity of the reaction.

This new reaction of formation of the 1,2-*trans* glycosidic linkage ("trityl-cyanoethylidene condensation") proved to be of sufficiently general character, both for pyranoses and furanoses. It finds extensive application for the stereospecific synthesis of oligosaccharides, and served as a basis for the development of a general method for the synthesis of polysaccharides of various types, in which constituent monosaccharides are connected by the 1,2-*trans* glycosidic linkage.

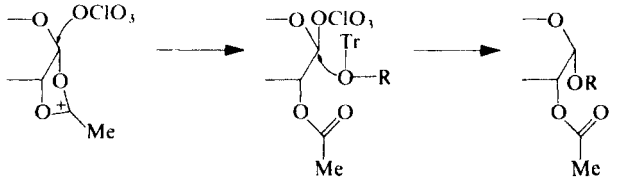
It should be noted, however, that absolute stereospecificity of this reaction may sometimes be violated. So far this has been observed on formation of the 1,4- and 1,3-glycosidic linkages in the glucopyranose, galactopyranose, xylopyranose, and arabinopyranose series; in these cases the reaction along with

1,2-*trans* glycosides afforded, sometimes in large amounts, the derivatives with 1,2-*cis* glycosidic linkage. This violation of stereospecificity seems to relate either to a partial isomerization of the dioxolenium cation into the flattened glycosyl cation **16**, followed by a nonstereospecific attack (Scheme 8), or to the competing attack of the dioxolenium cation **14** by rather nucleophilic perchlorate anion to give a covalent ester of perchloric acid **17** with the 1,2-*trans* configuration, followed by the attack of the aglycone on perchlorate; in this case double inversion of the configuration at C-1 affords the 1,2-*cis* glycosidic linkage[17] (Scheme 9).



14 16

Scheme 8



14 17

Scheme 9

Some attempts were undertaken to eliminate the violation of absolute stereospecificity of glycosylation. It was found that the nature of the initiator, or more exactly of its anion, may affect to some extent the reaction stereospecificity. Thus, the reactions initiated by tritylium tetrafluoroborate proceed with almost absolute stereospecificity even when tritylium perchlorate leads to its violation.[17] However, the reaction in the presence of tritylium tetrafluoroborate proceeds slowly and the yields sharply decrease, so from the practical viewpoint the use of this initiator is hardly reasonable.

Effective results can be obtained by carrying out the reaction under high pressure. As it turned out, the tritylcyanoethylidene condensation carried out under a pressure of 14 kbar proceeds with absolute stereospecificity to give in all cases so far investigated exclusively the 1,2-*trans* glycosidic linkage.[18]

3. THE REACTIONS OF POLYMERIZATION AND POLYCONDENSATION

A regular polysaccharide chain, just as a chain of any synthetic polymer, may be obtained by the polymerization or polycondensation of a monomer whose structure is consistent with that of the elementary repeating unit of the polymeric chain.*

Early attempts in the synthesis of polysaccharides with regular structures by polycondensation were based on the Koenigs–Knorr or Helferich reactions, on the interaction of sugars with the free glycosidic hydroxyl, as well as on the method of orthoester glycosylation. The polysaccharides obtained lacked either regio- or stereospecificity as a direct consequence of the violation of the regio- and stereospecificity in the elementary act of glycosylation. For a review of these works see reference 19.

The successful synthesis of regio- and stereoregular polysaccharides was performed on the basis of two abovementioned glycosylation reactions with the additional steric control, that is, the reaction of ring opening of anhydro aldoses and the trityl-cyanoethylidene condensation.

The first method, the polymerization of anyhydro sugars, allowed the synthesis of some linear homopolysaccharides and two comb-like polysaccharides with branchings. The tritylcyanoethylidene polycondensation, which offers much wider opportunities, has been employed for the synthesis of homopolysaccharides and regular heteropolysaccharides, including natural polysaccharides of microbial origin.

A. The polymerization of Anhydro Sugars†

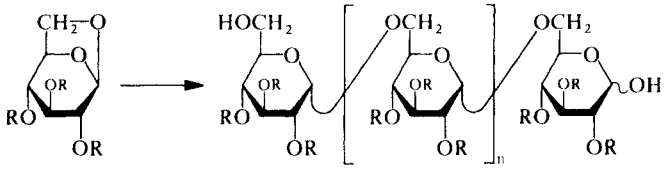
The polymerization of 1,6-anhydro hexopyranoses, which was discovered by Korshak[21] and worked out in detail by Schuerch,[22] has been studied most thoroughly and found extensive application. The scheme of the reaction

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* For a review, see reference 20.

† The early experiments on polymerization of unprotected sugars (e.g., by treatment of monosaccharides with acids) giving rise to very complex mixtures of polysaccharides with quite irregular branched structure are out of the scope of this review.

exemplified by the condensation of the derivatives of 1,6-anhydro glucose can be represented as follows (Scheme 10). As a rule, the reaction proceeds at low temperatures (− 60 to − 70°C) in methylene chloride solution in the presence of Lewis-acid-type catalysts, of which phosphorus pentafluoride proved to be most effective and widely used.[23] It was found that the amount of catalyst, or more exactly the catalyst–monomer ratio, influences noticeably the course of the reaction. A decrease in the amount of catalyst usually slows down the process and decreases the conversion of a monomer, but increases the molecular weight of the polymer formed. The polymerization under the action of phosphorus pentafluoride is usually performed with about 10 mol. % of the catalyst.



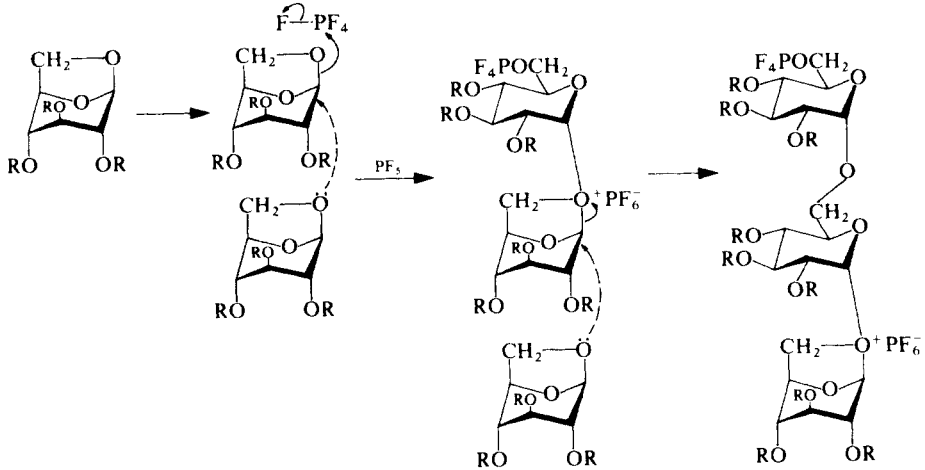
Scheme 10

Sometimes use is made of other catalysts such as antimony pentafluoride or pentachloride, boron trifluoride etherate, and so on.[23] These catalysts usually afford polysaccharides with a lower molecular weight and a lower degree of stereoregularity. The polymerization of 1,3-anhydro hexoses was performed in the presence of complex catalysts, such as triphenylmethylium (tritylium) perchlorate.[24]

The complete exclusion of traces of water and other nucleophiles is very important for the success of polycondensation, and the reaction is usually carried out with the use of high-vacuum techniques.[25] The reaction time varies within very broad limits (from an hour to several days) depending on the structure of the starting monomer, and the optimal time of polymerization is usually chosen in a series of experiments.

The polymerization of anhydro sugars is a typical example of the cationic polymerization of oxygen-containing heterocycles,[26] which proceeds with ring opening about the "chain-growth" mechanism,[20, 21] as is represented in Scheme 11.

An oxygen atom of the anhydro ring of 1,6-anhydro glucose increases the electrophilicity of the C-1 atom because the protonation or complexation with a catalyst (e.g., PF_5) thus initiates the polymerization process. The electrophilic center C-1 of the complex formed is subjected to attack by an oxygen atom of the 1,6-anhydro ring of the next molecule of the monomer; as a result, the anhydro ring of the initiating molecule of the monomer



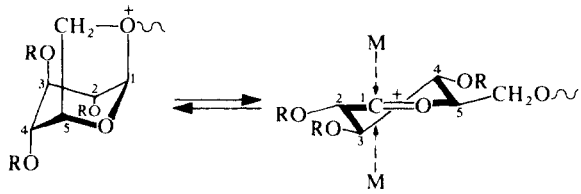
Scheme 11

undergoes cleavage to give a glycosidic linkage and the oxonium ion occurs at the reducing end of the molecule, whereas at the C_6 atom of the nonreducing monomer unit an OPF_4 group appears. The oxonium ion is then attacked at C_1 by the next monomer molecule to give, with formation of a glycosidic linkage, a new oxonium ion in the chain, and the polysaccharide chain grows further at the reducing end. This reaction mechanism has been confirmed by experiments.[27] Using ^{19}F- and ^{31}P-NMR spectroscopy it has been possible to observe the formation of a complex of a derivative of 1,6-anhydro glucose with PF_5 at low temperature. As the temperature increases the complex disappears to give an anion PF_6^-; there was also observed the formation of a CH_2OPF_4 group, which was assumed to occupy the non-reducing end of the growing polysaccharide chain.

Since the electrophilic anomeric center C-1 in the bicyclic system of the oxonium ion can be attacked, for steric reasons, only from the rear with respect to the 1,6-anhydro ring, the polymerization process leads to the stereochemically unambiguous result; are formed only α-glycosidic linkages. This determines strict stereospecificity of the reaction and high degree of stereoregularity of the polysaccharide chain formed.

However, the reaction stereospecificity in some cases may be violated on changing the polymerization conditions, in particular with growing temperature. Thus, for example, the polymerization of 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-glucose in CH_2Cl_2 in the presence of PF_5 at − 78°C proceeds fully stereospecifically, while with increasing temperature the β-linkages appear and at room temperature the reaction is completely nonstereospecific.[23]

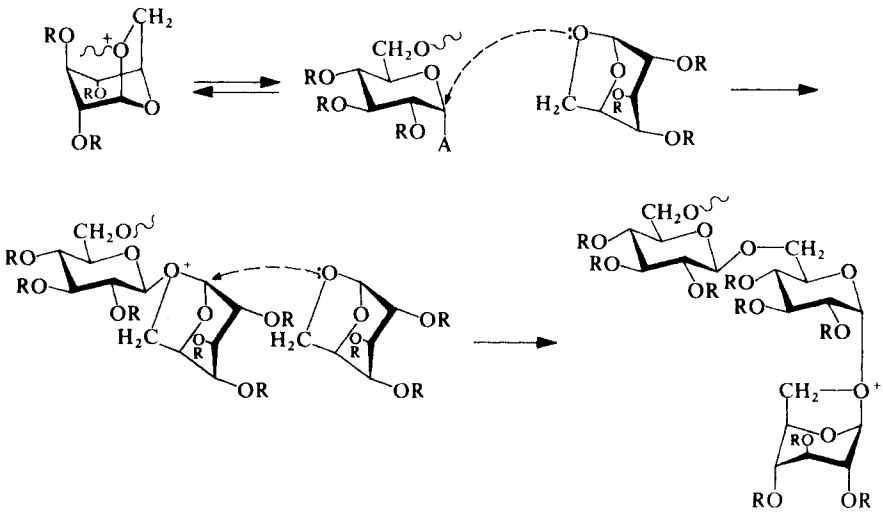
The formation of the β-glycosidic linkage in the polymerization of 1,6-anhydro hexoses is attributed to a side reaction of the oxonium ion, which controls the polymerization process. This side reaction is thought to consist in the cleavage of the oxonium ring to give on the end of the growing chain a monocyclic flattened glycosyl cation, which can be subjected to a non-stereospecific attack by the next molecule of the monomer resulting in the formation of both types of glycosidic linkages, and the stereospecificity of the polymerization is thus violated[20, 23] (Scheme 12).



Scheme 12

Another viewpoint concerning the loss of stereospecificity has been suggested[28] on the basis of the study of the kinetic isotopic effect in the reaction with the derivatives of ^{13}C-1,6-anhydro glucose; the authors attribute the formation of β-glycosidic linkage to a competing attack of a sufficiently nucleophilic anion (e.g., ClO_4^-) on the active site of the growing polymer, which affords a covalent ester. The subsequent attack of the ester by the monomer leads, owing to the double inversion at the glycosidic center, to the β-linkage (Scheme 13). This viewpoint is supported to a certain extent by the fact that the stereospecificity of the polymerization depends on the nucleophilicity of the catalyst's counter-ion and decreases in the series PF_6^-, SbF_6^-, BF_4^- > $SbCl_6^-$ > $CF_3SO_3^-$ > ClO_4^-.

In order to ensure the regiospecificity of polymerization all free hydroxyls of the anhydro sugars must be protected, since in the presence of an acid catalyst they may participate in an opening of the anhydro ring to give glycosidic linkages of other types. The study of the polymerization of the *O*-alkyl ethers of 1,6-anhydro glucose (levoglucosan) showed that the nature of the alkyl substituent influences insignificantly the course of the polymerization.[20, 29] In this connection, for the preparation of a polysaccharide with free hydroxyls, the polymerization is carried out usually with *O*-benzyl ethers of the anhydro sugars, and the *O*-benzyl derivatives of the polysaccharide obtained are then debenzylated by treatment with sodium in liquid ammonia. The polymerization of the *O*-acyl derivatives of anhydro sugars is complicated,[20, 29] since the carbonyl group of the ester moiety forms a complex with a catalyst, which hinders the reaction, and esters of anhydro sugars have not found application in synthesis.



Scheme 13

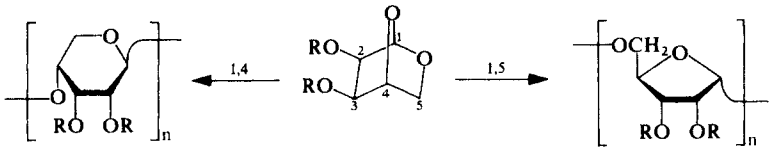
Derivatives of glucose, galactose, mannose, and allose can be polymerized to give the corresponding 1,6-α-glycans. The activity of different 1,6-anhydro hexopyranoses in the polymerization reaction varies essentially. Their relative reactivity, which was established on the basis of the results of copolymerization, decreases in the series: manno- > gluco- > galacto- > allo- > altro.[20] The reactivity of the first three anhydro pyranoses is close to each other—the allo-isomer polymerizes poorly; 1,6-anhydro-D-altropyranose under usual reaction conditions does not polymerize at all. Although some quantitative data on their reactivity are available,[20] the calculation on the basis of the copolymerization data on their reactivity is rather tentative. The main driving force of the polymerization process is regarded to be a decrease in the steric strain due to the elimination of the 1,3-interactions which is a result of an opening of the anhydro ring. There is no doubt, however, that the conformational changes ($^1C_4 \rightarrow B_{3,0}$) taking place in the monomer upon interaction with the oxonium ion, which controls the growing chain, are additional factors determining the reactivity of the anhydro hexose.

The polymerization of 1,6-anhydro hexoses in most cases allows us to obtain polysaccharides of high molecular weight. The latter increases with a decrease in the catalyst–monomer ratio, with an increase in the monomer concentration, and with an increase in the reaction time.[23] Still, it should be kept in mind that the Lewis acids serving as catalysts also cause the destruction of the polysaccharide by cleaving the glycosidic linkages,[30] and, hence, the optimal reaction time should be chosen in each case. The polymerization of 1,6-anhydro hexoses carried out under optimal conditions

affords usually 1,6-α-glycopyranans with a degree of polymerization of some hundred and sometimes up to a thousand hexose units, depending on the structure of the starting monomer. During the debenzylation of the polymerization product by treatment with sodium in liquid ammonia the polymeric chain is partially degraded to give a polysaccharide of a lower molecular weight. Uryu has estimated[30] that the molecular weight is reduced by a factor of 2.5–3.

The polymerization of the anhydro sugars of the other structure has come across much more serious difficulties, and the results obtained are rather modest. Since the most important natural polysaccharides (e.g. cellulose, amylose, xylane) have the structure of 1,4-glycopyranans, much attention has been paid to the synthesis of polysaccharide chains of this type by the polymerization of 1,4-anhydro aldoses. However, the attempts to polymerize *O*-methyl and *O*-benzyl derivatives of 1,4-anhydro arabinopyranose, 1,4-anhydro galactopyranose, and 1,4-anhydro glucopyranose in the presence of some simple Lewis acids (PF_5, BF_3, Et_2O, etc.) afforded irregular polymers[31–33] which contained both pyranose and furanose units distributed irregularly along the polysaccharide chain, the ratio of which varied depending on the polymerization conditions. In addition, the polysaccharide chain contained both α- and β-glycosidic linkages and, thus, the stereoregularity of the chain was also violated. These results are explained by the fact that the derivatives of 1,4-anhydro aldose may be considered both as the derivatives of 1,4-anhydro pyranose and as the derivatives of 1,5-anhydro furanose (actually they are the hydroxyl derivatives of 2,7-dioxabicyclo[2.2.1]heptane). The formation of the furanose or pyranose units is determined by the relative rate of scission of the 1,4 or 1,5 carbon–oxygen bonds (Scheme 14). This, in turn, is determined by the complexation with the catalyst's cation of the respective oxygen atoms, that is, by their relative basicity. Stereochemical ambiguity of the opening of the anhydro ring, and, hence, of the formation of a glycosidic linkage in the polymerization process was rationalized by the authors by assuming that the growth of the polymeric chain involves not only the oxonium ion but also the carbenium ion arising upon isomerization of the former.

A thorough study of the influence of the catalyst's nature and the type of substitution in the starting monomer on the polymerization of 1,4-anhydro



Scheme 14

sugar appears to have succeeded in finding the way to a more specific polymerization. Thus, according to the data of Japanese authors,[34, 35] the polymerization of *O*-substituted derivatives of 1,4-anhydro ribose in the presence of such catalysts as $SbCl_5$ and PF_5 afforded the polymers containing only ribopyranosidic units; in contrast, polymerization in the presence of NbF_5, $SnCl_4$, or $BF_3 \cdot Et_2O$ afforded ribofuranosidic structures. It was, however, pointed out that the structural and stereochemical regularity of the polymer is violated on changing the catalyst's nature, reaction time, and other features of the experimental procedure. Although the polymerization of some 1,4-anhydro aldoses allowed 1,4-glycans to be obtained, this method so far cannot be regarded as sufficiently general and reliable, and the structure of the polysaccharides obtained in this way should be carefully confirmed by spectroscopic and classical methods.

There are available only limited data on the polymerization of 1,3-anhydro aldoses, since the starting 1,3-anhydrides became available quite recently. After some unsuccessful attempts[36] to polymerize the *O*-benzyl ether of 1,3-anhydro glucose in the presence of PF_5 and some other catalysts, which led to a sterically irregular polymer, it was shown that a proper choice of the catalyst may direct the polymerization to a stereospecific route. Much higher stereospecificity was obtained by using such catalysts as tris-(4-bromophenyl)amminium hexafluoroantimonate, triphenylmethylium perchlorate (tritylium perchlorate), and trifluoromethanesulfonic anhydride (triflic anhydride);[37] this is explained by a more strong interaction between the counter-ions of these catalysts and the oxonium ion of the growing chain, which leads to the stabilization of the oxonium ion and directs the polymerization to the oxonium–ionic route. Higher stereospecificity of the reaction was also achieved with the *p*-bromobenzyl protection of the hydroxyl groups of the monomer, and it was observed that the stereoselectivity of the process drops in the series *p*-bromobenzyl > benzyl > *p*-methylbenzyl. The authors suggest that this distinction is caused by the fact that the electron-donating groups (*p*-methylbenzyl) increase the basicity of the ether oxygen atom, whereas the electron-withdrawing ones (*p*-bromobenzyl) reduce it. These data enabled two stereoregular 1,3-glycans with a sufficiently high molecular weight to be synthesized.

The cationic polymerization of 1,2-anhydro aldoses has not been studied thoroughly. Attempts to polymerize *O*-benzyl ether of 1,2-anhydro-α-D-glucose (Brigl' anhydride) and its manno-analogue in the presence of PF_5 and some other catalysts yielded a polymer with a low molecular weight, lacking stereoregularity.[38, 39] This route to the synthesis of polysaccharides has been abandoned.

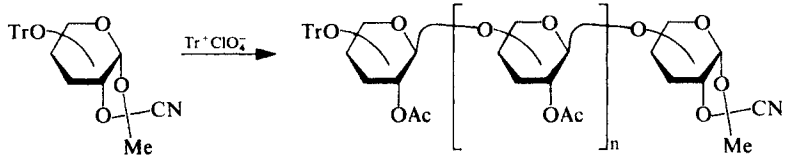
Thus, the polymerization of 1,6-anhydro aldoses is a convenient and effective method for the synthesis of stereoregular 1,6-glycopyranans. An

advantage of this method is that it yields the polymers with high molecular weights. However, it is naturally restricted to the synthesis of homopolysaccharide chains only. There are only a few examples of the syntheses of polysaccharides containing 1,4- and 1,3-glycosidic linkages by polymerization of the corresponding anhydrides, so the limits of this method cannot so far be estimated.

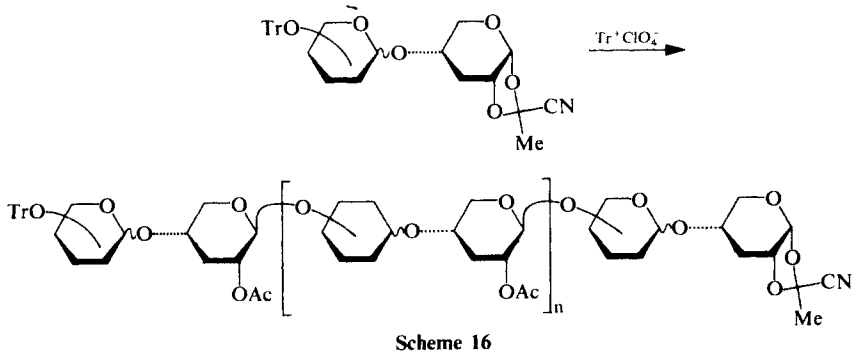
2. Trityl–Cyanoethylidene Polycondensation

Another approach to the synthesis of polysaccharides with a regular structure, which is of much more general nature, is based on the glycosylation of *O*-trityl ethers of sugars with 1,2-*O*-cyanoethylidene derivatives ("trityl–cyanoethylidene polycondensation") (for reviews see reference 40 and 41). This approach provides opportunities for the synthesis of a wide class of polysaccharides, in which monomeric units are linked by the 1,2-*trans* glycosidic linkage.

In fact, when the *O*-trityl moiety to be glycosylated and the glycosylating cyanoethylidene group are present in the same molecule, the glycosylation proceeds as the polycondensation reaction to give a polysaccharide chain. When both these groups belong to a single monosaccharide unit, the polycondensation yields a homopolysaccharide (Scheme 15); when these



Scheme 15



Scheme 16

groups are present in an oligosaccharide fragment, the polycondensation yields a chain consisting of repeating units, whose structure corresponds to the oligosaccharide monomer involved (Scheme 16).

In order to ensure full regiospecificity of the reaction and, hence, the structural regularity of the polysaccharide chain, all hydroxyl groups not participating in the reaction must be temporarily protected. This is accomplished most often by *O*-acetyl groups, since there are convenient methods for the introduction and removal of them under mild conditions. *O*-Benzoyl groups are employed for this purpose rather seldom, since their removal presents some difficulty, and, thus, they are used mainly in the synthesis of complex heteropolysaccharides. Occasionally, some other types of protecting groups have also been used, such as *O*-benzyl or *O*-isopropylidene groups.

Like the basal reaction of condensation of *O*-trityl ethers with cyanoethylidene derivatives of sugars, the trityl–cyanoethylidene polycondensation proceeds most often with absolute stereospecificity to give in most cases stereochemically regular polysaccharides with only 1,2-*trans* glycosidic linkages. However, the stereospecificity of the reaction is sometimes violated and the polysaccharide formed turns out to be stereochemically irregular. This has been observed solely in the synthesis of 1,4- and 1,3-glycans with the xylo and arabino configuration, and is, thus, consistent with the similar violation of the glycosylation reaction itself (see p. 253).

The polymer obtained by polycondensation is naturally a mixture of polymer homologues, and, hence, the degree of polymerization and the molecular weight of the polymer are average values for a given fraction of the polymer. It is also evident that often a fraction with higher molecular weight can be isolated at the cost of a drop in the yield of the product.

A most serious disadvantage of the trityl–cyanoethylidene polycondensation is a usually low degree of polymerization; the molecular weight of the polymer formed varies within wide limits, depending on the nature of the monomer. In some cases it is close to that of related natural polysaccharides. In other cases, as for example, in the polymerization of derivatives of simplest monosaccharides, the degree of polymerization is very low, and the polycondensation products should be regarded rather as higher oligosaccharides. However, it has been established quite recently that the polycondensation carried out under high pressure yields the polysaccharide with an essentially higher molecular weight.[42]

At the same time, the method of creation of the 1,2-*trans*-linked polysaccharide chains based on the trityl–cyanoethylidene polycondensation provides wide possibilities. It allowed the polysaccharide structures containing both neutral sugars and amino sugars or uronic acids to be obtained. The monosaccharide units may be both in the pyranose and furanose form, and can be linked by various types of intermonomeric linkages, excluding the 1,2-

glycosidic intermonomeric linkage. It should be emphasized in particular that the method for the first time opens the possibility for the synthesis of regular polysaccharides built of repeating units, to which type belong numerous natural polysaccharides possessing high biological specificity.

The trityl–cyanoethylidene polycondensation proceeds under the conditions close to those for the basal reaction of glycosylation of *O*-trityl ethers with 1,2-*O*-cyanoethylidene derivatives of sugars. It is usually carried out at room temperature in methylene chloride solution with tritylium perchlorate as practically the only initiator. The other tritylium salts, e.g., tritylium tetrafluoroborate), so far have not found preparative application, since they produce polymers with extremely low degrees of polymerization. Although the amount of the initiator has some influence on the course of the reaction, it has been found that the best results are obtained with the use of 5–10 mol.% of tritylium perchlorate. An increase in the amount of the initiator slightly accelerates the polycondensation process, while at low concentration of the initiator the reaction takes too long, which may lead to some undesirable side reactions. Thus, for example, the polycondensation of 3,4-di-*O*-acetyl-1,2-*O*-cyanoethylidene-6-*O*-trityl-α-D-glucopyranose in the presence of 1 mol.% of tritylium perchlorate was not completed even after 40 h, while in the presence of 20 mol.% of the initiator it was completed in 14 h.[43] On the other hand, a decrease in the initiator concentration does not produce the polymer with a higher molecular weight. So, the degree of polymerization of 1,6-galactan was not changed when either 1 or 10 mol.% of the initiator were used, although in the former case the reaction was not completed even in several days.[44]

The polycondensation is usually carried out at room temperature; an increase in temperature up to 50°C has only an insignificant effect. A decrease in temperature down to 0°C and below highly decelerates the process and it has not terminated even in several days.

The reaction time varies within a broad range. Although at room temperature the reaction is initiated practically at once upon addition of the tritylium salt, its rate depends on the structure of the monomer used. Attempts to increase the molecular weight of the polymer or its yield by increasing the reaction time (up to 250–300 h) were unsuccessful. This may find a tentative explanation in that the main portion of monomer enter the reaction rather rapidly and after that the reactive intermediate at the reducing end of the chain or *O*-trityl groups at the nonreducing end disappear almost totally, because of some still unknown side reactions, thus practically terminating the process.

Complete exclusion of traces of moisture and other nucleophilic impurities is very important for the success of polycondensation. The best results are obtained when the reaction is carried out with the use of conventional high-vacuum techniques, involving careful drying of reagents by repeated distillation of solvent.[16] The reaction may also be carried out in standard

equipment with the usual precautions, which leads to some decrease in the yield and sometimes in the molecular weight of the polymer. The polycondensation under high pressure is performed in conventional equipment used in high-pressure studies: the reagents are placed in a sealed Teflon vessel, which then is placed into a reactor with hydraulic generation of pressure.[18,42]

In order to decompose the remaining initiator and to stop the polycondensation process the reaction mixture is treated with methanol or trifluoroacetic acid; then pyridine is added for neutralization, and the protected polysaccharide is isolated by reprecipitation or column chromatography. The unprotected polysaccharide is obtained by deacetylation with dilute methanolic sodium methoxide; benzoyl protection may be also removed by treatment with hydrazine.

C. Analytical Control of the Structure of Synthetic Polysaccharides

The structural regularity of the resulting polysaccharides and, hence, the regiospecificity of the polycondensation or the polymerization process can readily be checked by the methylation analysis, followed by the GLC–MS analysis of acetates of partially methylated alditols. In the case of the polysaccharides of low molecular weight, this method allows determination of the degree of polymerization by the ratio of the corresponding alditols, obtained from the internal monosaccharide units and the terminal ones.

The ^{1}H- and especially ^{13}C-NMR spectroscopy is the most convenient and highly accurate method for the control of the glycosidic linkage stereochemistry. Frequently, even the number of signals in the anomeric region of the high-resolution ^{13}C-NMR spectrum quite decisively indicate the stereoregularity of the polysaccharide obtained, since the signals for 1,2-*trans* and 1,2-*cis* glycosidic linkages are usually resolved. The synthetic homopolysaccharides and simple heteropolysaccharides usually produce very clear spectra, which can be fully interpreted, including the assignment of signals for all carbon atoms. However, it is known[45] that the chemical shifts for the carbon atoms in the ^{13}C-NMR spectra depend on the structure of the neighboring monosaccharide units. Therefore, for the complete and reliable interpretation of the ^{13}C-NMR spectrum of the synthetic polymer the use of the data relating to the corresponding model disaccharides should be strongly recommended. It can be pointed out that a simple and distinct picture of the ^{13}C-NMR spectrum and the absence of unidentified signals are very strong evidence in favor of the high regularity of the polysaccharide chain. When the stereospecificity is violated and the polycondensation yields both 1,2-*trans* and 1,2-*cis* glycosidic linkages, the ^{13}C-NMR spectrum determines rather accurately the ratio of these two types of linkages from the integrated intensity of the corresponding signals.

4. THE SYNTHESIS OF HOMOPOLYSACCHARIDES

The synthesis of homopolysaccharides is a relatively simple problem of polysaccharide synthesis, and naturally the majority of the synthetic polysaccharides belong to this class. Until recently only the homopolysaccharides or higher oligosaccharides containing neutral sugars in the pyranose form, as well as several representatives containing amino sugars or uronic acids, have been synthesized. Some first representatives of polysaccharides containing the furanose units also have been synthesized.

A. The Synthesis of 1,6-Glycopyranans

There are numerous works devoted to the synthesis of glycans with the 1,6-linked hexopyranose units. 1,6-α-Glycans containing neutral sugars are obtained by the polymerization of 1,6-anhydro aldopyranoses in the presence of Lewis acids by the method developed by Schuerch and co-workers[20] (see page 255). In this way several high-molecular-weight polysaccharides, which are close analogues of some natural polysaccharides, have been synthesized.

The synthesis of the starting monomers, 1,6-anhydro aldopyranoses (see a review[46]), is well developed. The most simple of them, 1,6-anhydro-β-D-glucopyranose (levoglucosan), is a readily available material, which can be easily obtained by pyrolysis of various cellulose-containing materials, including waste material of the woodworking industry, as well as starch and its derivatives.[47] The other 1,6-anhydro hexopyranoses are obtained most frequently by the interaction of phenyl glycosides or acylglycosyl haloides with bases.[48, 49]

The preparative synthesis of unsubstituted polysaccharides is usually carried out with *O*-benzyl ethers of 1,6-anhydro hexoses[50] as monomers, and then the benzyl protection can easily be removed.

Almost all preparative syntheses of linear 1,6-α-glycans were carried out in the presence of PF_5 in CH_2Cl_2 at temperatures of $-40°$ to $-78°C$. The amount of the catalyst and the optimal conditions for the synthesis have been chosen specifically for each glycan. An indispensable condition of the successful synthesis is the high purity of the reagents, so the experiments were performed using a high-vacuum technique common in polymer chemistry. When the reaction came to the end, the process is ultimately terminated by the addition of methanol, and the protected polysaccharide is isolated and purified by the standard procedures. The unprotected polysaccharides were obtained by the removal of *O*-benzyl groups by treatment with sodium in liquid ammonia.

The polymerization of the corresponding *O*-benzyl ethers by this method afforded[23, 25, 29, 30, 51–57] 1,6-α-glucopyranan **18**, 1,6-α-galactopyranan **19**,[51, 52, 58] and 1,6-α-mannopyranan **20**.[52, 57] The glycans obtained were fully regio- and stereoregular. The molecular weight of the polymerization products amounted to 450,000–500,000 for **18** and **20**, and 200,000 for **19**; after deprotection the molecular weight reduced by a factor of 2–3.[30] Thus, the molecular weight of the synthetic 1,6-α-glycans is close to that of the corresponding natural polysaccharides, in particular of dextran. Quite recently it has been possible to polymerize much less reactive 2,3,4-tri-*O*-benzyl-1,6-anhydro-β-D-allose.[59] The best results have been obtained with the use of a high concentration of the monomer and short reaction time at − 60°C; the yield of 1,6-α-D-allopyranan[21] is rather high; depending on the reaction conditions, its molecular weight ranged from 37,000 to 62,000.

The structure of the obtained 1,6-α-glucopyranans has been studied by the ^{1}H- and ^{13}C-NMR spectroscopy techniques and optical rotation measurements; in some cases the regiospecificity has been confirmed by methylation analysis. The total regio- and stereospecificity of the synthetic glucopyranan **18** and mannopyranan **20** has also been supported by enzymatic hydrolysis by the specific enzymes dextranase[60] and α-D-mannanase;[61] the absence of branchings in the glucan has also been confirmed by the absence of precipitation with concanavalin A.[62] The synthetic mannan and glucan were used in the immunochemical studies; thus, for example, the glucan, which is close in structure to natural dextran was used to establish the sizes of the antigenic site of the latter.[63]

The polymerization of 1,6-anhydro sugars has been used recently for the synthesis of polysaccharides containing an amino group. Since the polymerization of a derivative of 1,6-anhydro-β-D-glucopyranose with the protected amino group was unsuccessful, attempts were undertaken to polymerize derivatives of 1,6-anhydroglucose containing a C-azide grouping, that is, di-*O*-benzyl ethers of 2-azido-2-deoxy-, 3-azido-3-deoxy-, and 4-azido-4-deoxy-1,6-anhydro-β-D-glucose.[64] All of them polymerize less readily than the derivatives of glucose. The polymerization of the 3-azido-3-deoxy-derivative **22** was carried out successfully in the presence of the complex of PF_5 and benzoyl fluoride at − 60°C for 20 h. The polymerization afforded a stereoregular polymer having a degree of polymerization of 130–150 (molecular weight 47,000–55,000). The polymerization of the 2-azido-2-deoxy-derivative yielded merely lower oligosaccharides containing three to six monosaccharide units. In the case of the 4-azido isomer, no polymeric product has been obtained as well. The polysaccharide obtained on polymerization of the 3-azido derivative was converted to the corresponding 3-aminoglucan by reduction of the azido group with $LiAlH_4$ and subsequent debenzylation; the

reduction was accompanied by some destruction and the resulting 3-amino-glycopyranan **23** had a rather low molecular weight.

The synthesis of the 1,6-hexopyranans containing the 1,2-*trans* glycosidic linkage was accomplished by the trityl–cyanoethylidene polycondensation. 1,6-β-Glucopyranan **24**,[43] 1,6-α-mannopyranan **20**,[65] and 1,6-β-galactopyranan **25**[44] obtained in this way were completely regio- and stereoregular, but had a low degree of polymerization (DP 10–16). The starting monomers for the polycondensation were the 1,2-*O*-cyanoethylidene derivatives of the respective hexoses containing an *O*-trityl group at C_6 of the hexopyranose ring. The remaining hydroxyls were protected by acyl groups, most often by acetyl groups. The use of the *O*-benzoyl protection seems to afford a polymer of a higher degree of polymerization (e.g., see reference[66]), but deprotection of the resulting product in this case is more difficult.

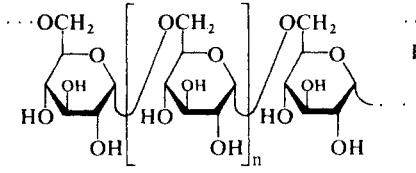
The synthesis of monomers at present is a routine procedure: the starting hexose is converted via the corresponding acetoglycosyl bromide into acetate of the cyanoethylidene derivative by treatment with KCN or NaCN,[67, 68] then the acetate is converted into an unsubstituted cyanoethylidene derivative by careful treatment with methanolic sodium methoxide;* the only primary hydroxyl in the latter derivative is selectively tritylated by treatment with trityl chloride in pyridine (for a review, see reference[70]), and the free secondary hydroxyls are acetylated with acetic anhydride in pyridine. The resulting monomers are stable, and can be easily purified by recrystallization or chromatography.

Since the introduction of the cyanoethylidene moiety gives rise to a new chiral centre, a mixture of exo and endo isomers at C_2 of the dioxolane ring is formed; its ratio varies depending on the structure of the hexose. Both isomers possess approximately equal reactivity, and the polycondensation may be performed directly with their mixture. If necessary, for example, in order to facilitate the spectroscopic control of the reaction, they can be separated by chromatography into the individual isomers, whose structure can easily be established by NMR spectroscopy.

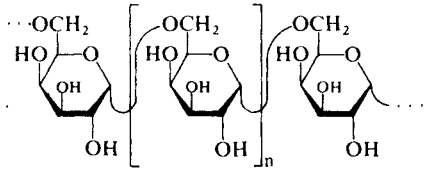
We exemplify the preparation of monomers with the synthesis of 3,4-di-*O*-acetyl-1,2-*O*-cyanoethylidene-6-*O*-trityl-β-D-mannopyranose **26**, a monomer for the synthesis of 1,6-α-mannopyranan (Scheme 17). 2,3,4,6-Tetra-*O*-acetyl-D-mannopyranosyl bromide by treatment with NaCN was converted into 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-exo-cyano)ethylidene-β-D-mannopyranose **27**,[67, 68] which was deacetylated with dilute methanolic sodium methoxide,

* When the acyl protection is removed by bases under more severe conditions the cyano groups are partially converted into the imidate groups and further into the ester groups, thus turning the cyanoethylidene moiety into the alkoxycarbonylethylidene grouping; in this case an additional purification of the monomer is necessary.[69]

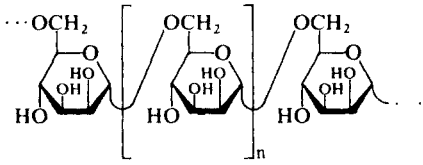
the unsubstituted cyanoethylidene derivative **28** was treated with trityl chloride in pyridine, and the trityl derivative **29** was acetylated to give **26**. In a similar way there have been synthesized 3,4-di-*O*-acetyl-1,2-*O*-(1-cyanoethylidene)-6-*O*-trityl-α-D-glucopyranose **30**[43] 3,4-di-*O*-acetyl-1,2-*O*-(1-exo-cyano)ethylidene-6-*O*-trityl-α-D-galactopyranose **31**.[44] For the preparation of the galactose analogue with the *O*-benzoyl groups, the trityl derivative was treated with benzoyl chloride in pyridine.



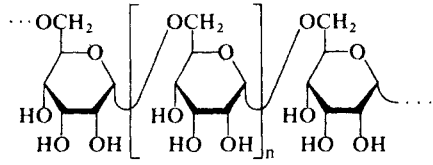
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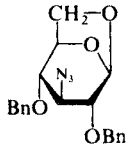
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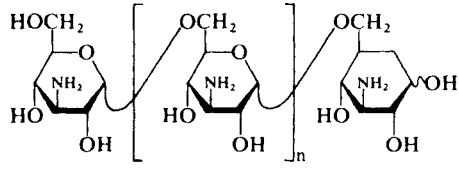
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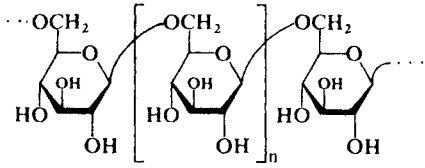
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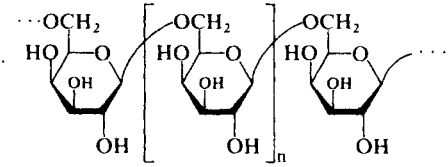
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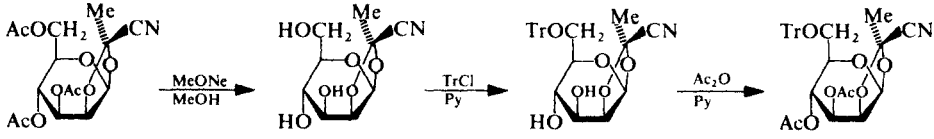
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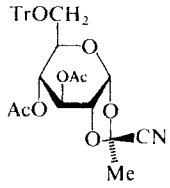


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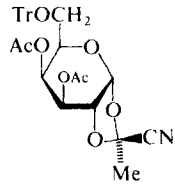


27 **28** **29** **26**

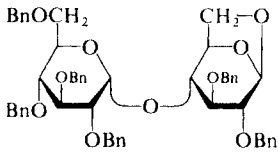
Scheme 17



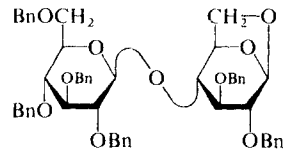
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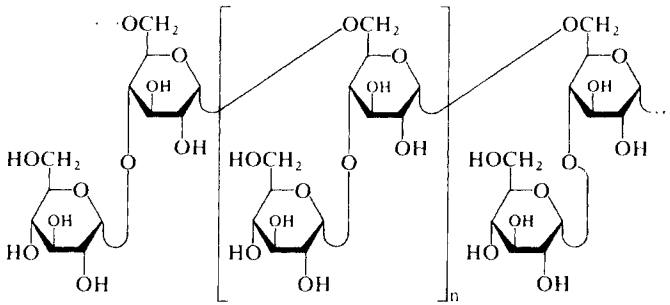
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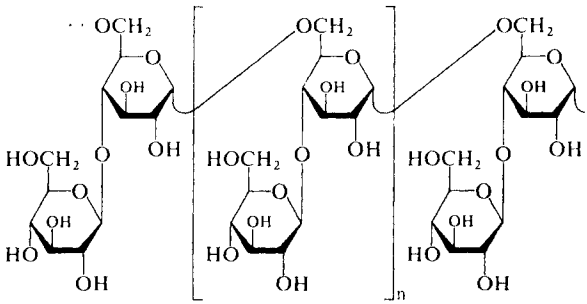
32



33



34



35

Scheme 17 (*continued*)

The monomers were polymerized under the conditions usually adopted for the trityl–cyanoethylidene polycondensation, that is, in the presence of 10 mol. % of tritylium perchlorate in CH_2Cl_2 at room temperature. The reaction was terminated by the addition of methanol and pyridine, and the acetylated polysaccharide was isolated by conventional methods, deace-

tylated without purification by treatment with dilute methanolic sodium methoxide, and purified by reprecipitation or chromatography. The ^{1}H- and ^{13}C-NMR spectroscopy confirmed the complete stereoregularity of the synthetic 1,6-hexopyranans; their regioregularity was usually supported by methylation analysis.

As was pointed out, the polysaccharides obtained had a low degree of polycondensation, particularly in the case of mannan and galactan, amounting to merely 8–16. The attempts to increase the degree of polymerization for galactan by increasing the reaction time (up to 200 h) or by decreasing the initiator quantity (to 1%) were unsuccessful. However, as it was shown, the polycondensation under high pressure offers a promising way for increasing both the degree of polymerization and the yield of polysaccharides. Thus, the polycondensation carried out under standard conditions at a pressure of 14 kbar gave a fully stereospecific 1,6-β-galactan with a higher degree of polymerization and 90% yield.[42]

The synthesis of two regular branched polysaccharides from 1,6-anhydrides of disaccharides has been reported. The polymerization of *O*-benzyl ethers of 1,6-anhydro-maltose **32** and -cellobiose **33** gave the comb-like polysaccharides **34**[71] and **35**,[72] which contained at C-4 of each α-linked glucose unit of the backbone α- and β-linked glucose residues, respectively. The disaccharide monomers polymerize less readily, and the molecular weight and the stereoregularity of the polymer depend more on the reaction conditions than in the case of monosaccharide monomers. The polymers of molecular weight 5,000–11,000 were obtained only when the polymerization was carried out in the presence of PF_5 with 20% of benzoyl fluoride for a longer period of time. Debenzylation of the polymers obtained with sodium in liquid ammonia yielded the unprotected comb-like polysaccharides. Although their stereoregularity was determined only by the optical rotation value, nevertheless they should possess a high stereoregularity, taking into account general data of the process of polymerization of anhydrohexopyranoses. The branched 1,6-α-glucopyranan of an irregular type, which is an analogue of natural dextran, was obtained by copolymerization* of 2,3,4-tri-*O*-benzyl-1,6-anhydro-β-D-glucose and 2,4-di-*O*-benzyl-3-*O*-crotyl-1,6-anhydro-β-D-glucose, followed by removal of the crotyl group and glycosylation of the deprotected hydroxyls at C_3 of the glucose units.[73] The other similar irregular polysaccharide was obtained by the copolymerization of the 1,6-anhydro derivatives of glucose and maltose.[74]

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* The copolymerization of two different 1,6-anhydro hexoses (derivatives of glucose, galactose, and mannose) has been studied by Schuerch and co-workers. The copolymerization has led to glycopyranans, containing the residues of these hexoses distributed irregularly along the chain. The discussion of these polysaccharides of irregular structure falls beyond the scope of this chapter. Details can be found in a review by Schuerch.[20]

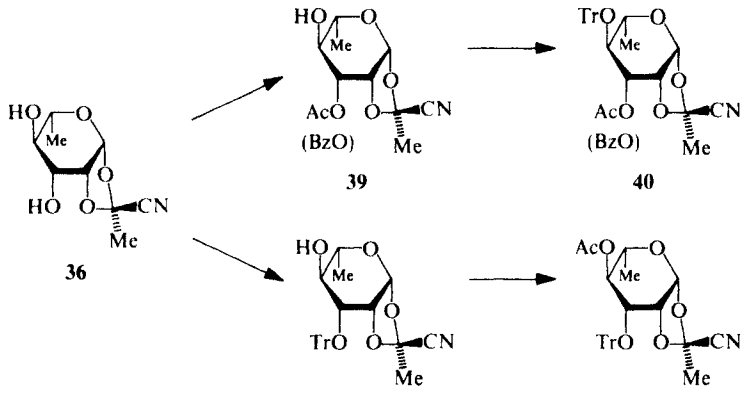
B. The Synthesis of 1,3- and 1,4-Glycopyranans

The synthesis of homopolysaccharides with the glycosidic linkage formed by a secondary hydroxyl is a more difficult problem. As yet no successful synthesis of 1,2-glycopyranans has been accomplished: the trityl–cyanoethylidene polycondensation cannot be employed in this case, while the polymerization of derivatives of 1,2-anhydro-pyranoses has led to unsatisfactory results.

A number of studies have been devoted to the synthesis of homopolysaccharides with 1,3- and 1,4-glycosidic linkages. Most syntheses have been performed using the trityl–cyanoethylidene polycondensation, and the polysaccharides containing pentopyranose and hexopyranose units have been obtained; along with the neutral sugars some derivatives of uronic acids were also synthesized. All the polymers obtained were fully regioregular, as was confirmed by methylation analysis; however, their degree of polymerization was, as a rule, very low, and their molecular weight amounted to merely some thousand daltons. The polysaccharides containing the residues of D-mannose and L-rhamnose proved to be stereoregular, whereas the polycondensation of derivatives containing the residues of L-arabinose, D-xylose, D-galactose, and D-glucose, carried out under the usual conditions, yielded nonstereoregular polysaccharides.

The synthesis of monomers comes to the introduction of the cyanoethylidene moiety into the monosaccharide by treatment of the corresponding acetohalogenose with NaCN or KCN,[67, 68] or, as in the case of uronic acid esters, by an interaction of the acetohalogenose with AgCN.[75] The peracetate of the cyanoethylidene derivative was then deacetylated with dilute methanolic sodium methoxide. The introduction of an *O*-trityl group at one of the secondary hydroxyls was performed by the reaction of tritylium perchlorate in the presence of a sterically hindered pyridine base.[76] As tritylation in these cases is not selective, there were two ways to achieve the desired result: (1) a direct tritylation of the cyanoethylidene derivative containing several hydroxyls, followed by the subsequent separation of the resulting mixture of mono-*O*-trityl derivatives, one of which is usually produced preferentially, or (2) a preliminary protection of hydroxyls of the polyhydroxyl derivative, followed by tritylation of an unprotected hydroxyl.

These two routes can be exemplified by the synthesis of the monomers for 1,3-[77] and 1,4-α-L-rhamnopyranans,[66] which takes advantage of a higher reactivity of the hydroxyl at C_3 of the rhamnopyranose ring (Scheme 18). To this effect 1,2-*O*-cyanoethylidene-β-L-rhamnopyranose **36**, obtained by the standard procedure on interaction of the corresponding bromide with NaCN,[67, 68] followed by deacetylation, was treated with tritylium perchlorate in the presence of 2,4,6-collidine to give preferentially a 3-*O*-trityl



Scheme 18

derivative **37**; acetylation of the latter yielded the monomer **38** for the synthesis of 1,3-α-L-rhamnopyranan.[77] On the contrary, for the synthesis of the monomer for 1,4-α-L-rhamnopyranan **36** was subjected to acetylation (Ac_2O–Py) or benzoylation (BzCl–Py) and the obtained 3-*O*-acyl derivatives **39** were tritylated with tritylium perchlorate to give **40**.[66]

The monomers thus obtained are crystalline substances and their structure was confirmed by NMR spectroscopy; the location of the *O*-trityl group can be supported by the methylation analysis data.

The polycondensation of monomers was carried out under standard conditions (10 mol. % of the initiator, room temperature); the reaction was practically completed in 50–70 h. Neither the degree of polymerization nor the yield of the polysaccharide have changed when the reaction time increased up to 120–150 h. The protected polysaccharide was deacetylated and free polysaccharide was isolated by column chromatography. Fully regio- and stereoregular 1,3- and 1,4-rhamnopyranans **41** and **42** were obtained in high yields and possessed a degree of polymerization of 30–40 and a molecular weight of 4000–6000. It is noteworthy that the monomer **40** with the benzoyl protection gave the polysaccharide of higher molecular weight.[66]

Likewise, a regio- and stereoregular polysaccharide was obtained from the mannose monomer **43**, which was synthesized by the selective *O*-benzoylation of the cyanoethylidene derivative of D-mannopyranose **44**, followed by tritylation of a free hydroxyl at C_4 of **45**. The polycondensation of **43** afforded 1,4-α-D-mannopyranan **46** with a degree of polymerization of about 15.[78]

The monomers for the synthesis of 1,3- and 1,4-D-xylopyranans **47** and **48** were obtained by *O*-benzoylation of the non-protected cyanoethylidene derivative **49**, followed by separation of a mixture of monobenzoates **50** and **51** and their tritylation. The polycondensation of these monomers gave fully

regioregular xylopyranans;[79] however, their stereoregularity was violated—the obtained 1,3- and 1,4-xylopyranans **52** and **53** contained about 10% of α-linkages (1,2-*cis* glycosidic bond); their degree of polymerization was 17 and 11, respectively.

Likewise, the polycondensation of the L-arabinose monomers **54** and **55** (which were prepared by tritylation of the unsubstituted cyanoethylidene derivative of L-arabinopyranose, followed by acetylation and separation of a mixture of **54** and **55**) gave low-molecular-weight regioregular 1,3- and 1,4-arabinopyranans **56** and **57**, whose stereoregularity again was violated; they contained about 25% of 1,2-*cis* glycosidic linkages.[80]

The synthesis of 1,3-glucopyranan[81] and 1,3-galactopyranan[82] has led to a still less satisfactory stereochemistry of products; the regioregular polysaccharides **58** and **59** had a low molecular weight and a fully nonstereoregular structure and contained 50 and 30% of α-glycosidic linkages, respectively. Just as unsatisfactory in this respect was the polysaccharide **60**, obtained by polycondensation of the 6-deoxy-D-gluco derivative, which contained 59% of α-linkages.[83]

Analysis of the data thus obtained shows that the polycondensation of monomers having the D-manno or L-rhamno configuration yields the stereoregular polymer, whereas the polycondensation of monomers having the arabino or xylo configuration occurs with violated stereospecificity of the trityl–cyanoethylidene polycondensation to give stereoregular polysaccharides. The only exception known so far is the polycondensation of monomers obtained from glucuronic acid **61** and **62**, which gave merely oligomeric products **63** and **64** with a degree of polycondensation of 5–7, but which were fully stereoregular.[84]

It should be pointed out that the above mentioned violations of absolute stereospecificity of formation of the 1,2-*trans* glycosidic linkage are so far unique for the synthesis of polysaccharides by the trityl–cyanoethylidene polycondensation. The reason for these violations of stereochemistry remains unclear. These violations are consistent with those found in the synthesis of the corresponding disaccharides, and seems to relate to the violation of stereochemistry of an elementary act of the process. It is evident that the important role is played by the position of the *O*-trityl group, which displays probably lower reactivity in positions 3 and 4 of pyranoses with the xylo and arabino configurations. At the same time, when the reactivity of the cyanoethylidene group, or, more exactly, of the bicyclic dioxolenium intermediate **14** derived from it, is high, the reaction proceeds with high stereospecificity in this case as well. Thus, for example, in the synthesis of natural heteropolysaccharide of *Shigella flexneri* (see page 294), the polycondensation of a complex oligosaccharide monomer, having a trityl group at O-3 of glucosamine and more reactive cyanoethylidene group at the rhamnose residue, was

completely stereospecific despite that the sugar carrying the *O*-trityl group had the xylo configuration.

Thus, the reason for stereochemical violations in polycondensation seems to be linked with the influence of the spatial structure of the monomer on the reactivity of both its functional groups. The investigations of the conformation of monomers and intermediates in solution as well as of their influence on reactivity would be very helpful for the elucidation of this question.

Some attempts have been undertaken to improve stereochemistry of polycondensation of monomers having the arabino and xylo configuration. Thus, the reaction in the presence of tritylium tetrafluoroborate as an initiator proceeded in a fully stereospecific way, although the degree of polymerization sharply dropped[79] and, hence, this initiator cannot be used in the preparative synthesis of polysaccharides. A more promising result has been obtained in the polycondensation under high pressure, which was observed to exert a striking influence on stereochemistry of trityl–cyanoethylidene condensation.[42] In this connection, one of the most unfavorable examples has been studied, that is, the synthesis of 1,3-β-6-deoxy-D-glucopyranan **60**; the polycondensation under the usual conditions gave 1,2-*trans* and 1,2-*cis* glycosidic linkages in the 1:1 ratio. The process carried out under high pressure (14 kbar) was completely stereospecific and gave regular (1-3)-β-6-deoxy-D-glucopyranan, containing only 1,2-*trans* glycosidic linkages, with the degree of polymerization (about 25) being twice that achieved without pressure.[42] The structural and stereochemical regularity of the polymer obtained has been demonstrated most clearly by its ^{13}C-NMR spectrum, very distinct and different from that of the polysaccharide obtained under normal pressure (see Fig. 1). A similar result has been obtained in the synthesis of 1,3-galactopyranan; the polycondensation under normal pressure gave the polysaccharide in 25% yield, which contained, according to the ^{13}C-NMR data, about 30% of 1,2-*cis* (α-galactosidic) linkages. The polycondensation under a pressure of 14 kbar afforded fully stereoregular 1,3-β-D-galactopyranan containing no α-galactosidic linkages and in 55% yield.[42]

There are good reasons to believe that the influence of high pressure, allowing the reaction to be directed to a fully stereospecific route and the molecular weight and the yield of the polymer to be increased, is of quite general character. If so, the synthesis of 1,3- and 1,4-glycopyranans by the trityl–cyanoethylidene polycondensation will become a sufficiently adequate route for the polysaccharides of this type, and relative simplicity of the synthesis of the corresponding monomers is one of its advantages.

The synthesis of several 1,3- and 1,4-glycopyranans has successfully been performed by the polymerization of 1,3- and 1,4-anhydro aldoses, respectively. The first attempt to synthesize 1,3-glycopyranans by the polymerization of 1,3-anhydro-2,4,6-tri-*O*-benzyl-β-D-glucopyranose and 1,3-

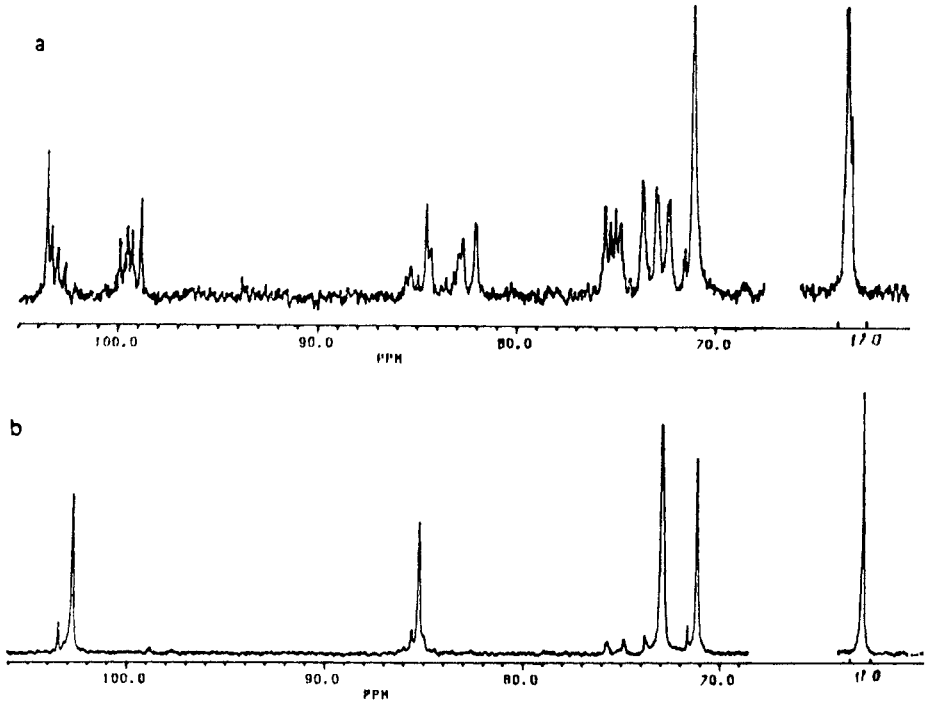
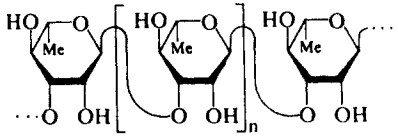


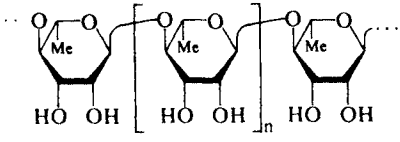
FIGURE 1. ^{13}C-NMR spectra of (1-3)-6-deoxy-D-glucan obtained at (*a*) normal pressure and (*b*) 14 kbar.

anhydro-2,4,6-tri-*O*-benzyl-β-D-mannopyranose in the presence of usual catalysts, for example, PF_5, has led to nonstereoregular polymers.[36] However, the use of other catalysts, such as tritylium perchlorate and trifluoromethanesulfonic anhydride obtained stereoregular 1,3-α-D-glucopyranan **65** and 1,3-α-D-mannopyranan **66**.

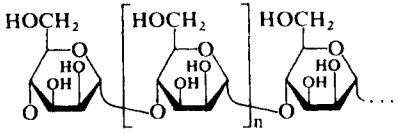
The synthesis of the monomer for 1,3-α-D-glucopyranan was performed by a rather complicated route[85] (Scheme 19). 3-*O*-Allylglucose **67**, obtained by *O*-allylation of 1,2,5,6-di-*O*-isopropylidene glucofuranose, followed by hydrolysis, was converted into a mixture of allyl 3-*O*-allyl-D-glucopyranosides and then benzylated to give allyl 3-*O*-allyl-2,4,6-tri-*O*-benzylglucopyranoside **68**, which was converted into the corresponding propenyl derivative **69**. The latter was treated with hydrogen chloride to give 2,4,6-tri-*O*-benzyl-D-glucopyranosyl chloride **70**, which under the action of potassium *tert*-butoxide in the presence of benzo-18-crown-6 was converted into the 1,3-anhydro-derivative **71**. The use of the *p*-bromobenzyl-protected monomer, which can be obtained according to the similar scheme, gives higher stereospecificity.



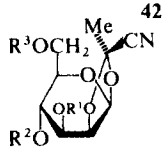
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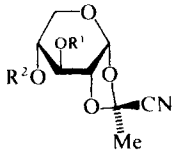
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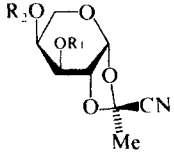
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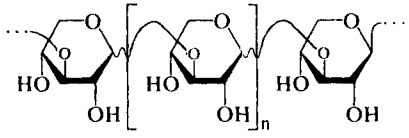
44 $R^1 = R^2 = R^3 = H$
45 $R^1 = R^3 = Bz$; $R^2 = Tr$
43 $R^1 = R^3 = Bz$; $R^2 = H$



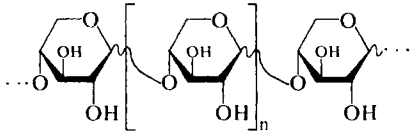
49 $R^1 = R^2 = H$
50 $R^1 = Bz$; $R^2 = H$
51 $R^1 = H$; $R^2 = Bz$
47 $R^1 = Tr$; $R^2 = Bz$
48 $R^1 = Bz$; $R^2 = Tr$



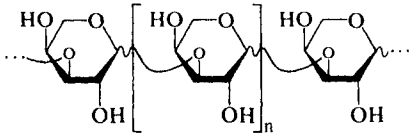
54 $R_1 = Tr$; $R_2 = Ac$
55 $R_1 = Ac$; $R_2 = Tr$



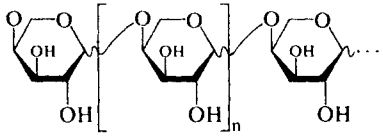
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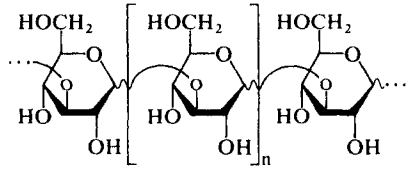
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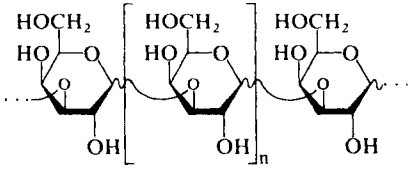
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57

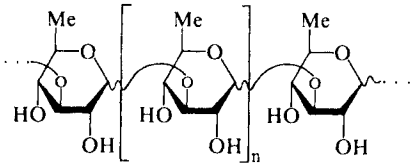


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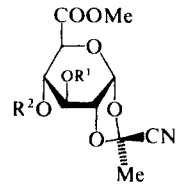


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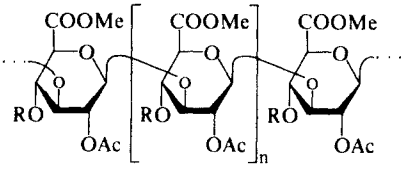
Scheme 19



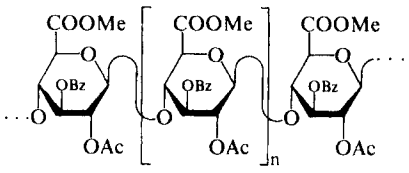
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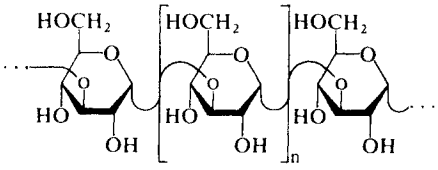
61 $R^1 = Tr$; $R^2 = Ac$
62 $R^1 = Bz$; $R^2 = Tr$



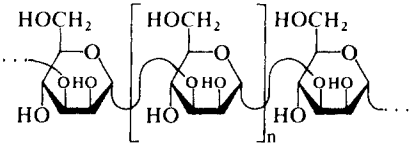
63



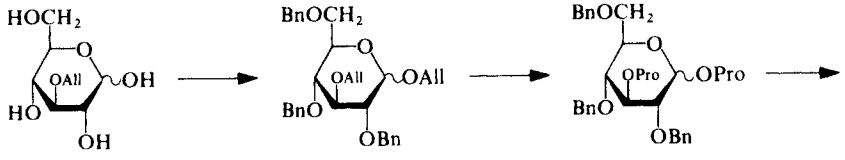
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65

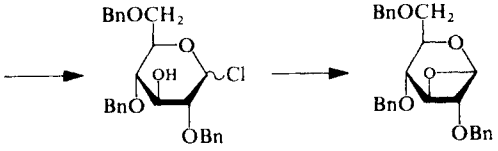


66



67 68 69

All = allyl
Pro = propenyl

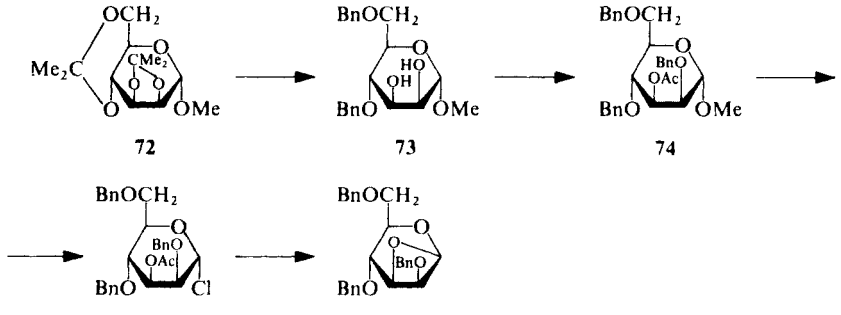


70 71

Scheme 19 (*continued*)

On the basis of these data, a linear 1,3-α-D-glucan **65** was obtained by polymerization of 1,3-anhydro-2,4,6-tri-*O*-(*p*-bromobenzyl)-β-D-glucose in the presence of trifluoromethane-sulfonic anhydride, followed by the standard deprotection.[37] According to the ^{13}C-NMR data the polymer is stereoregular and contains only α-linkages; its molecular weight amounts to 16,000–31,000.

The monomer for the synthesis of 1,3-α-mannopyranan was prepared by the similar procedure (Scheme 20).[86] Methyl-2,3,4,6-di-*O*-isopropylidene-α-D-mannopyranoside **72** was subjected to partial deisopropylidenation, *O*-benzylation, and after the removal of the second isopropylidene moiety, was converted into methyl 4,6-di-*O*-benzyl-α-D-mannopyranoside **73**, which by selective benzylation and subsequent acylation was converted into methyl 3-*O*-acetyl-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside **74**; the latter was treated with anhydrous hydrogen chloride to give 3-*O*-acetyl-2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride **75**. The final step of the synthesis consisted in closing the oxetane ring of the anhydro-sugar **76** under the action of potassium *tert*-butoxide. The *p*-bromobenzyl derivative was obtained analogously.



72 **73** **74** **75** **76**

Scheme 20

The polymerization of 1,3-anhydro-2,5,6-tri-*O*-(*p*-bromobenzyl)-mannose in the presence of tritylium perchlorate, or of its *O*-benzyl analogue in the presence of trifluoromethanesulfonic anhydride, yielded the corresponding polysaccharides with a degree of polymerization of 60–90, which after standard deprotection were converted into the unsubstituted 1,3-α-D-mannopyranan **66**;[87] the NMR spectrum of **66** confirmed its high stereoregularity. Again, the *p*-bromobenzyl derivative gives better results.

Many attempts have been undertaken to obtain 1,4-glycopyranans by the polymerization of 1,4-anhydro sugars (e.g., see references 31–33). As already

pointed out (see page 260), the cleavage of the 1,4-anhydro ring under the action of Lewis-acid type catalysts is a more complicated process than the opening of 1,6-anhydro sugars. As a result, the polymerization gives a chain containing both pyranose and furanose units, connected both by 1,2-*trans* and by 1,2-*cis* glycosidic linkages. However, there is so far a unique example of polymerization of the 2,3-di-*O*-substituted derivatives of 1,4-anhydro-ribose in the presence of more specific catalysts, which is claimed by the authors to give derivatives of regio- and stereoregular 1,4-β-D-ribopyranan.

The starting monomers with either 2,3-benzylidene protection **77**[88] or 2,3-isopropylidene protection **78**[89] were obtained by converting D-ribose into the 2,3-*O*-benzylidene or 2,3-*O*-isopropylidene derivative, respectively, and simultaneously generating the 1,4-anhydro ring by treatment with zinc chloride or sulfuric acid. 1,4-Anhydro-2,3-di-*O*-methyl-α-D-ribose **79** and its *O*-benzyl analogue **80** were prepared by alkylation of 1,4-anhydro-α-D-ribose, which is a product of pyrolysis of ribose. According to the available data,[34, 35] the polymerization of the 2,3-*O*-benzylidene **77** or 2,3-*O*-isopropylidene derivative **78** in the presence of $SbCl_5$, and of the 2,3-di-*O*-methyl derivative **79** in the presence of PF_5 or $SnCl_4$, carried out under quite definite conditions, yields regular 1,4-β-D-ribopyranan **81**. Any slight change in the reaction conditions, or replacement of the catalyst by related catalytic system leads to a polymer with a lower molecular weight, containing both pyranose and furanose residues. In order to prove these rather entangled results, NMR spectroscopy was employed. However, the assignment of signals was made on the basis of monosaccharide models only. At the same time it is known[45] that the "monosaccharide approximation" is inadequate for the correct analysis of the NMR spectrum of a polysaccharide, since the neighboring unit affects the chemical shift, and the accurate interpretation requires at least a disaccharide model.

C. The Synthesis of Glycofuranans

At present there are only a few studies dealing with the synthesis of polysaccharides consisting of furanose units. So far the trityl–cyanoethylidene polycondensation was used only in the synthesis of 1,5-α-L-arabinofuranan[90] and 1,3-α-L-arabinofuranan.[91] This route seems to be most promising as regards both the accessibility of starting monomers and unambiguity of results. In order to prepare the corresponding monomers 3,5-di-*O*-acetyl-1,2-*O*-(1-endo-cyano)ethylidene-β-L-arabinofuranose **82**, obtained by treatment of 1,2,3,5-tetra-*O*-acetyl-L-arabinofuranose with trimethylsilylcyanide in the presence of stannous chloride,[92, 93] was deacetylated and the resulting diol **83** was treated with tritylchloride in pyridine to give

regioselectively the 5-*O*-trityl ether **84**, which was benzoylated to yield the monomer for the synthesis of 1,5-arabinofuran **85**. Deacetylation of **82** with a more dilute methanolic MeONa allows only the 3-*O*-acetyl group to be removed selectively. Tritylation of the obtained monoacetate **86** with tritylium perchlorate in the presence of 2,4,6-collidine gives the monomer **87** for the synthesis of 1,3-arabinofuranan.

Polycondensation of the monomers **85** and **87** was carried out under the standard conditions of the trityl–cyanoethylidene polycondensation (room temperature, 10 mol. % of the initiator) and proceeded with high yields. The unprotected 1,5- and 1,3-α-L-arabinofuranans **88** and **89** were obtained by careful deacylation of the polymerization products, isolated by the standard procedure. The ^{13}C-NMR spectra of both the acylated and the unprotected synthetic arabinofuranans showed their full structural and stereochemical regularity and the presence of only 1,2-*trans* glycosidic linkages. The spectra are very clear and simple, and contain the only signal in the anomeric region and signals for the ring carbons, which were very easily interpreted using the spectral data for model disaccharides (Fig. 2). The degree of polymerization was 15–23 for 1,5-arabinofuranan (molecular weight of 2000–3000) and 42–45 for 1,3-arabinofuranan (molecular weight of 6000).

It is noteworthy that, in contrast to the monomers of the arabinopyranose series (see page 274), the polymerization of monomers containing the *O*-trityl moiety and cyanoethylidene group in the furanose residue proceeds with absolute stereospecificity.

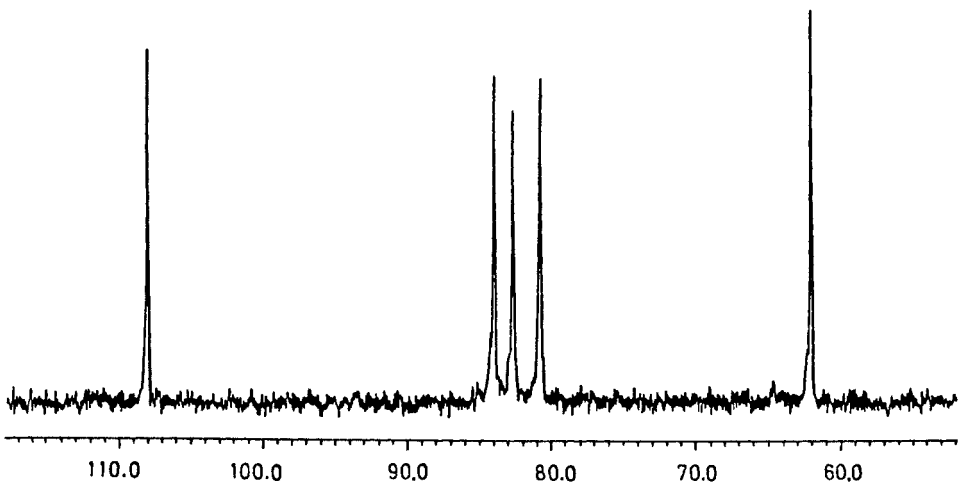


FIGURE 2. ^{13}C-NMR spectrum of (1-3)-α-L-arabinofuranan.

The polymerization of 1,4-anhydro sugars has found application also for the synthesis of some glycofuranans, although the process is complicated by the above mentioned unambiguity of opening of 1,4-anhydro-aldose systems under the conditions of cationic catalysis. According to the available data, the polymerization of the derivatives of 1,4-anhydro-ribose **79** and **80** in the presence of some catalysts, which are similar in character to those used for pyranans (see page 280), namely NbF_5 or $BF_3 \cdot Et_2O$, gave a quite different result: instead of ribopyranan there was formed a derivative of high-molecular-weight regular, 1,5-α-D-ribofuranan **90**.[34, 35] Similar results were obtained in the polymerization of 1,4-anhydro-2,3-di-*O*-benzyl-α-D-xylopyranose **91**. This monomer was prepared by *O*-benzylation of 1,4-anhydro-xylose acetate, which is a product of pyrolysis of xylose; the polymerization of **91** in the presence of BF_3 Et_2O or $SnCl_4$ at temperatures of -20 to $-60°C$ gave di-*O*-benzyl ether of 1,5-α-D-xylofuranan **92**, which was debenzylated to give an unprotected stereoregular polysaccharide.[94] The polymerization in the presence of PF_5, NbF_5, or SiF_4, which are very similar to those used above, did not give a regular polymer any more.

Although first attempts to polymerize derivatives of 1,4-anhydro-hexoses led to irregular polymers only, recently it has been reported[95] that the polymerization of 1,4-anhydro-2,3,6-tri-*O*-benzyl-α-D-glucopyranose in the presence of PF_5 at $-20°C$ gave regular 2,3,6-tri-*O*-benzyl-(1,5)-α-D-glucofuranan **93** with a comparatively low degree of polymerization.

Since an opening of the anhydro ring in 1,4-anhydro-aldose derivatives is ambiguous under the cationic catalysis conditions and the reaction course depends on very slight changes in the reaction conditions and the catalyst used, the regio- and stereoregularity of the obtained polysaccharide must be thoroughly checked. Unfortunately, the structure of the polymers prepared by this method was not always approved adequately: the structural regularity only occasionally has been supported by classical methylation analysis, while the stereochemical regularity was often confirmed by the ^1H- and ^{13}C-NMR data, obtained on the basis of hardly adequate monosaccharide models, and sometimes resulted only in comparative analysis of spectra of polysaccharides of different types.

5. THE SYNTHESIS OF HETEROPOLYSACCHARIDES

The synthesis of regular heteropolysaccharides with the oligosaccharide repeating units, to which class belong a lot of natural polysaccharides different in structure and function, is of particular interest. It is also very important that this class includes biopolymers with a high biological specificity, which is determined by fine details of their structure. In this connection

the synthesis of polysaccharides of this class or of their sufficiently long fragments, and of their close analogues, may be very helpful for the solution of many problems in the rapidly advancing field of life science.

For obvious reasons, of the two exisitng approaches to the creation of regular polysaccharide chains consisting of repeating oligosaccharide units, only the trityl–cyanoethylidene polycondensation is adequate. Until recently, some regular heteropolysaccharides consisting of disaccharide units, connected by the 1,2-*trans* glycosidic linkages, have been synthesized, and the first syntheses of natural polysaccharides of microbial origin, which possess high biological specificity, have been accomplished.

The synthesis of the starting monomers, whose structure corresponds to the repeating unit of the heteropolysaccharide and which contain a cyanoethylidene group at the reducing terminus of the oligosaccharide and a trityl moiety at the hydroxyl, producing the glycosidic linkage in the future polysaccharide (see Scheme 16), represented an independent and sometimes complex problem.

A most rational strategy is based on an initial formation of the cyanoethylidene group at the reducing end of the oligosaccharide, followed by the introduction of the trityl moiety at the proper hydroxyl, and the complete protection of the remaining hydroxyls, which do not participate in the glycosidic linkage formation. As in the synthesis of homopolysaccharides, the acyl groups, particularly *O*-acetyl and *O*-benzoyl, proved to be most efficient as the protection in this case as well. These groups may be introduced and removed under sufficiently mild conditions, which fact is of particular importance when handling the complex heteropolysaccharide molecule.

The main problem in the synthesis of complex oligosaccharide monomers consisted in a selective tritylation of one of the hydroxyls in the polyhydroxyl molecule, which already contained a cyanoethylidene group. In relatively simple cases, it was possible to perform direct tritylation followed by the separation of a mixture of trityl derivatives; however, this became unreasonable in more complex cases. Thus, for the synthesis of complex monomers another route has been used, that is, temporary selective protection of the hydroxyl to be tritylated, protection of the other hydroxyls with a "permanent" group, removal of the former protective group, and tritylation. The most important point in the realization of this strategy was the differentiation of the two simplest and most useful protective groups in carbohydrate chemistry, namely, *O*-acetyl and *O*-benzoyl groups, which was achieved by selective removal of the former in the presence of the latter by mild acid methanolysis.[96] Next, it has been established that the cyanoethylidene derivatives of mono- and oligosaccharides containing an unprotected hydroxyl can be glycosylated without affecting the cyanoethylidene group,[97] and this was the second important point for the development of a general

strategy for the synthesis of complex monomers. Thus, the oligosaccharide monomers can be assembled from the two fragments, one of which already has the cyanoethylidene group, while the other contains a potential site for the introduction of the trityl group; then, the "assembled" oligosaccharide derivative is subject to tritylation. This strategy will be exemplified later in this chapter.

A. The Synthesis of Heteropolysaccharides Consisting of Disaccharide Repeating Units

Until recently some polysaccharides of this type have been synthesized, containing both neutral and amino sugars or uronic acids. Although the synthetic polysaccharides are not exact copies of natural biopolymers, they represent important classes of polysaccharide systems with regularly repeating oligosaccharide units.

(1) Glucan with the Alternating (1-6)-β- and (1-4)-α-Glucosidic Linkages

The synthesis of this polysaccharide* built up of repeating units was the first example of the trityl–cyanoethylidene polycondensation of the oligosaccharide blocks with *O*-trityl and cyanoethylidene groups in different monosaccharide units.

The monomer was obtained[98] from the 4-*O*-(α-D-glucopyranosyl)-D-glucose (maltose) heptaacetate, which was converted via its bromide into the peracetate of the cyanoethylidene derivative **94**. The latter was deacetylated to give the unprotected cyanoethylidene derivative **95**, which was treated with 1 mole of trityl chloride to give a mixture of the trityl derivatives; after acetylation the required monomer 3,6,2′,3′,4′-penta-*O*-acetyl-1,2-*O*-cyanoethylidene-6′-*O*-trityl-4-*O*-α-D-glucopyranosyl-α-D-glucopyranose **96** was isolated by chromatography. Fortunately, of the two primary hydroxyls the tritylation affected predominantly that in the unsubstituted monosaccharide unit, which is obviously related to the conformational features of the maltose molecule.

The conditions for the polycondensation of this and other more complex oligosaccharide monomers were the same as in the standard trityl–cyanoethylidene polycondensation, although the reaction time and the post-

* According to the strict nomenclature this polysaccharide, containing only the glucose units, is not a heteropolysaccharide; however, as it can be regarded as a repeating unit system, it is more reasonable to discuss it in this section.

reaction treatment were slightly different and usually chosen in preliminary experiments.

The polycondensation[99] of the monomer **96** was carried out in the presence of 10 mol. % of the initiator at room temperature for 50 h; the reaction was terminated by the addition of methanol and then pyridine. The protected polymer was deacetylated without purification, and the free polysaccharide was isolated by gel chromatography. Its structural regularity was confirmed by methylation analysis, which also showed that the degree of polymerization of the polymer amounted to 10, referring to the disaccharide monomer, that is, its molecular weight was about 3200. The stereochemical regularity of the polymer was established by comparing the values of its specific rotation (+ 115°) with those for the higher oligomers of maltose and gentiobiose, which confirmed the 1,2-*trans* (*β*) configuration for the newly formed (1-6)-glycosidic linkages in the polymer.

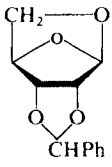
(2) Glucorhamnan

The synthesis of glucorhamnan,[100] containing the alternating units of D-glucose and L-rhamnose connected by the 1,4-glucosidic and 1,6-rhamnosidic linkages, was performed by the polycondensation of the corresponding monomer. In order to obtain the monomer peracetate of 1,2-*O*-(1-exo-cyano)ethylidene-4-*O*-*β*-D-glucopyranosyl-*β*-L-rhamnopyranose **98** was deacetylated, the only primary hydroxyl of the resulting compound was selectively tritylated with trityl chloride in pyridine, and the subsequent acetylation gave the monomer **99**. The polycondensation of **99** under the standard conditions (10 mol. % of the initiator, 50 h, room temperature), followed by the standard workup, deacetylation of the resulting polymer, and purification by chromatography, gave the polysaccharide **100** in high yield. Methylation analysis showed its full structural regularity. The stereoregularity of the polysaccharide was unambiguously confirmed by its ^{13}C-NMR spectrum, which contained in the anomeric region only two signals corresponding to the *β*-glucosidic (104.7 ppm) and *α*-rhamnosidic linkages (101.45 ppm). Moreover, in order to obtain more exact evidence on the structural homogeneity, the polymer was separated into two fractions by chromatography on Sephadex. Both of them were structurally identical and differed only in the degree of polymerization. Methylation analysis showed that the molecular weight of these fractions was about 9000 and 7000 Daltons, respectively.

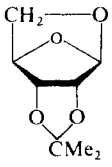
(3) Hexosaminoglycan

The synthesis of this heteropolysaccharide containing alternating glucosamine and rhamnose units was of particular interest, as it contained the amino

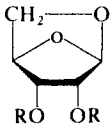
sugar residue; it is well known that many natural polysaccharides are hexosaminoglycans, and, hence, this synthesis is an essential extension of the trityl–cyanoethylidene polycondensation method. It served also as a model synthesis for two complex microbial polysaccharides (see pp. 291 and 294). The choice of a reasonable protection for the amino group was of considerable importance. Almost all natural hexosaminoglycans are the *N*-acetyl derivatives. However, preliminary model experiments have shown[101] that the glycosylation of *N*-acetylamino sugar derivatives with the cyanoethylidene derivatives proceeds very slowly, probably because of the complexation between the initiator (tritylium cation) and the *N*-acetyl group. For that reason the synthesis of glucosaminoglycan was carried out starting from the monomer with the phthaloyl-protected amino group, which after the polycondensation was replaced by the *N*-acetyl group.



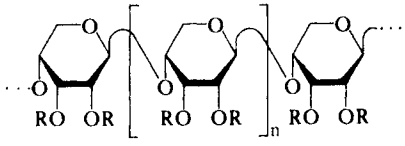
77



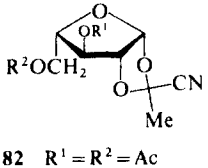
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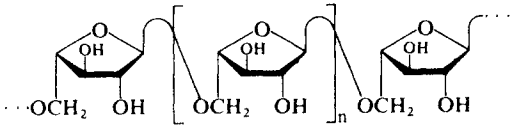
79 R = Me
80 R = Bn



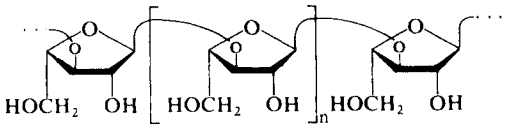
81



82 $R^1 = R^2 = Ac$
83 $R^1 = R^2 = H$
84 $R^1 = H$ $R^2 = Tr$
85 $R^1 = Bz$ $R^2 = Tr$
86 $R^1 = H$ $R^2 = Ac$
87 $R^1 = Tr$ $R^2 = Ac$

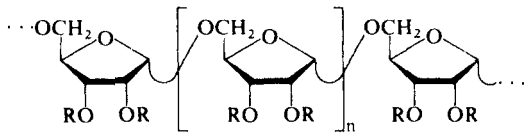


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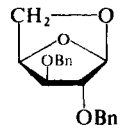


89

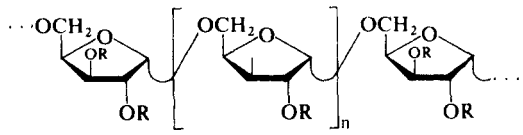
Scheme 21



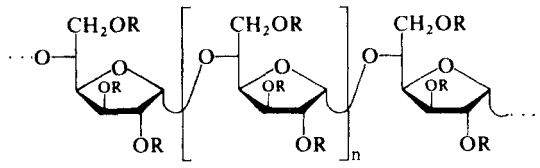
90



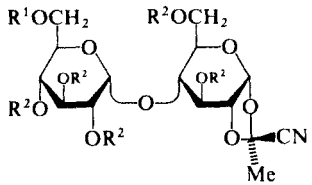
91



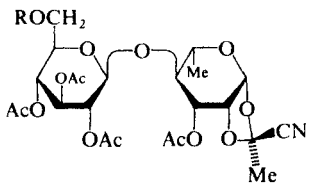
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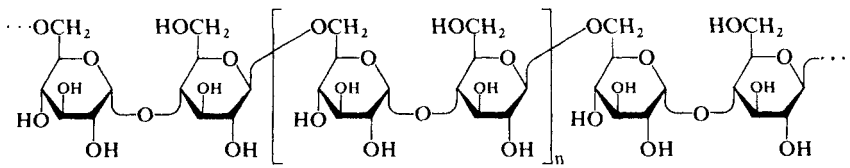
93



94 $R^1 = R^2 = Ac$
95 $R^1 = R^2 = H$
96 $R^1 = Tr$; $R^2 = Ac$

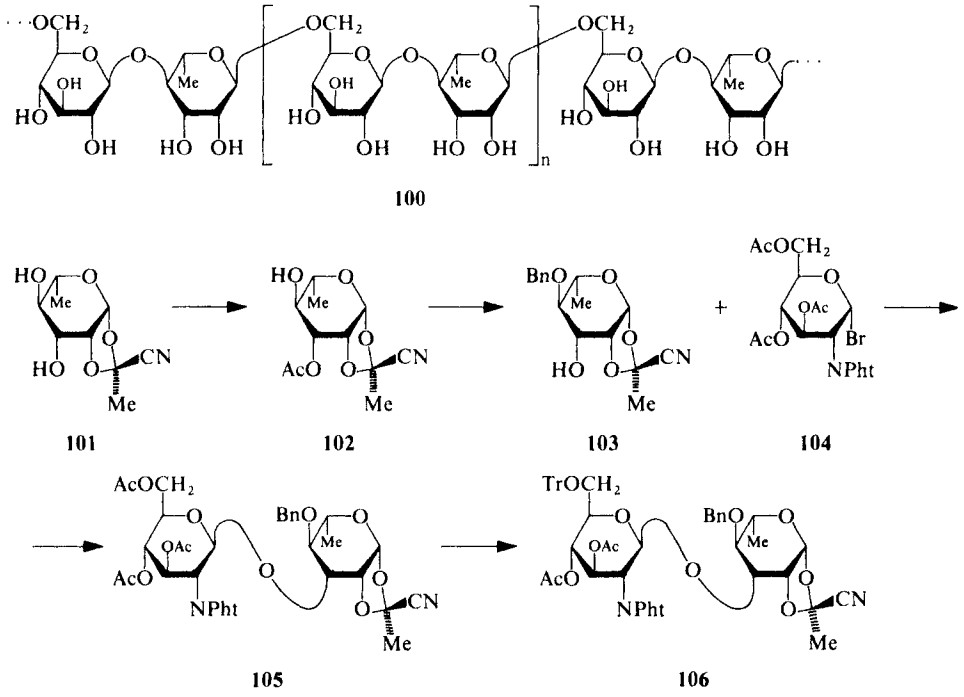


98 R = Ac
99 R = Tr



97

Scheme 21 (*continued*)



Scheme 21 (*continued*)

The key step in the synthesis of the monomer was the above mentioned glycosylation[97] of the cyanoethylidene derivative, which did not affect the cyanoethylidene group (Scheme 21).[101]

The unprotected cyanoethylidene derivative of L-rhamnose **101** was selectively acetylated, the 3-*O*-acetate **102** was benzylated with benzyl trichloroacetimidate, and then deacetylated. The 4-*O*-benzyl derivative **103** was glycosylated with 3,4,6-tri-*O*-acetyl-*N*-phthaloylglucosaminyl bromide **104** in the presence of $Hg(CN)_2$, the disaccharide derivative **105** was deacetylated, tritylated with trityl chloride, and then acetylated again to give the crystalline monomer **106**.

The polycondensation of **106**[102] proceeded smoothly under the standard conditions (10 mol. % of the initiator, room temperature) in 16 h; the presence of the phthaloyl group, unlike the acetyl group, did not complicate the polycondensation process. The reaction was terminated by the addition of trifluoroacetic acid and then pyridine, and the obtained polysaccharide was dephthaloylated by treatment with hydrazine, *N*-acetylated with acetic anhy-

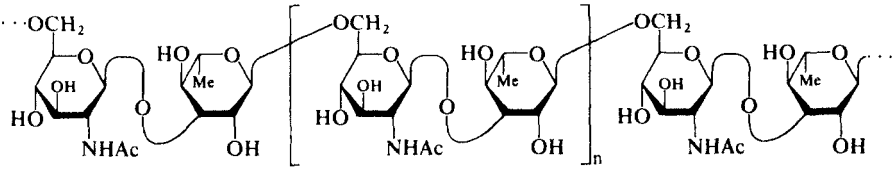
dride in methanol, and debenzylated by hydrogenolysis. The structure of the unprotected polysaccharide **107** was confirmed by the methylation data, which also showed its full regioregularity and rather high degree of polymerization (about 45, counting the disaccharide unit); this corresponds to a molecular weight of about 14,000 Daltons.

The ^{13}C-NMR spectrum clearly demonstrated stereochemical and structural regularity of the synthetic hexosaminoglycan. The presence of the signal for C-6 of *N*-acetylglucosamine (67.3 ppm) and the absence of signals in the region of 62–63 ppm, characteristic of the unsubstituted hydroxymethyl group, proved only 1-6 rhamnose–glucosamine linkage. The chemical shift for C-5 of the rhamnose unit (70.6 ppm) and the total absence of signals in the region 73–74 ppm and 83–84 ppm, which are typical of C-5 and C-3, respectively, of β-rhamnosidic linkage, evidenced in favor of the α-rhamnosidic linkage.

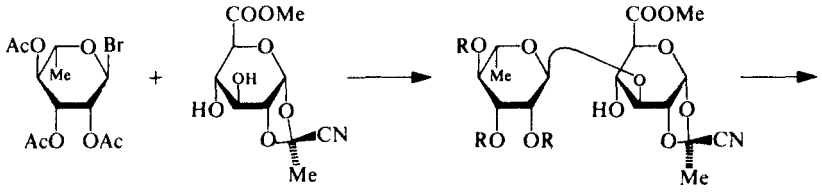
(4) Heteropolyuronide

The synthesis of polysaccharides containing the uronic acid residues was also of considerable interest, since such heteropolyuronides are very abundant in nature, and at the same time synthetic approaches to even the simplest oligosaccharides of this class are not well developed. The results achieved in this field are still very modest, and it has been possible to synthesize only oligosaccharides of low molecular weight. The synthesis of a heteropolyuronide with the alternating residues of L-rhamnose and D-glucuronic acid has been reported; this combination of monosaccharides is often encountered in natural polyuronides. The corresponding monomer was synthesized[103] (Scheme 22) by the glycosylation of the methyl glucuronate cyanoethylidene derivative **108** with 2,3,4-tri-*O*-acetylrhamnosyl bromide **109**. The 3-*O*-glycosyl derivative **110** was isolated from a mixture of disaccharides by chromatography, then carefully deacetylated by a brief treatment with sodium methoxide, and tetraol **111** was converted into the isopropylidene derivative **112**, which was tritylated with tritylium perchlorate in the presence of 2,4,6-collidine to give the monomer **113**.

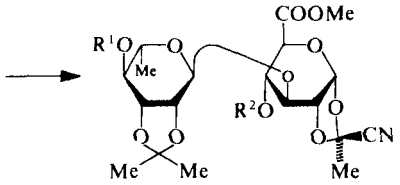
The polycondensation[84] of **113** in the presence of 10 mol. % of the initiator at room temperature was over in 17 h. The polymeric product **114**, isolated by the standard methods, proved to be regular, both structurally and stereochemically. The ^{13}C-NMR spectrum contained in the anomeric region, along with the signal for C-1 of the rhamnose unit (98.3 ppm), the only signal for C-1 of glucuronic acid (99.7 ppm), which was consistent with the β-glucosidic linkage. However, the degree of polymerization was very low, about 5, which corresponds to a molecular weight of 1800.



107



109 108 110 R = Ac
111 R = H



112 $R^1 = R^2 = H$
113 R^1 = Tr; R^2 = Ac

Scheme 22

B. The Synthesis of Microbial Heteropolysaccharides

The wide possibilities offered by the trityl–cyanoethylidene polycondensation have been clearly demonstrated by the synthesis of complex natural polysaccharides, *O*-antigenic polysaccharides of gram-negative bacteria, and a capsular polysaccharide. Somatic antigens of gram-negative bacteria are the lipopolysaccharides, in which a polysaccharide chain (the so-called *O*-polysaccharide) is linked to a lipid fragment; its structure determines a very high specificity of the antigen and of the surface of the bacterial cell as a whole. Capsular polysaccharides are the main polymer of the capsule of many bacteria, which, along with the protective function, also plays the role of a highly specific antigen.

The *O*-antigenic and capsular heteropolysaccharides have common structural features,[104] since they are the block polymers of regular structures built up of the repeating oligosaccharide units which may involve 2–10 mono-

saccharides. This explains an enormous diversity of these polysaccharides. It is the structural diversity of these biopolymers, occurring on the surface of the microbial cell or capsule, that ensures a fine differentiation and specificity of the cell surface of a countless number of microbial species.

As a synthetic target the bacterial heteropolysaccharides are both difficult and beneficial, and a natural strategy for their synthesis is the polymerization of a suitable oligosaccharide unit, which is consistent with the structure of a repeating unit of the natural biopolymer. At the same time, the identity of the natural and synthetic polysaccharides may be established by chemical, physicochemical, and immunochemical methods quite decisively.

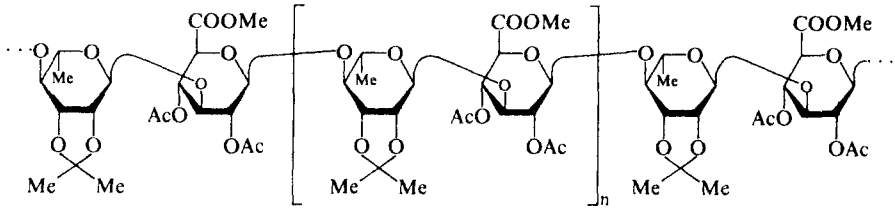
The most complex and laborious part of the synthesis was the synthesis of the oligosaccharide monomers, containing the cyanoethylidene group at the reducing terminus and the *O*-trityl group at the proper hydroxyl. This problem had to be solved in each case individually, using the known or specially developed methods of the oligosaccharide synthesis.

(1) O-Antigenic Polysaccharide of Salmonella newington

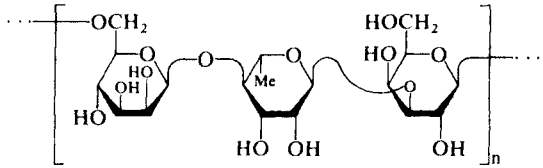
This polysaccharide is a constituent of the outer membrane of this bacteria and is its somatic antigen. The polysaccharide is built up of trisaccharide repeating units containing D-mannose, L-rhamnose, and D-galactose residues, and has the structure **115**,[105] with the oligosaccharide unit being repeated in the polysaccharide chains 2–27 times.[106] The most apparent route to its synthesis is the polycondensation of the block Man 1-4 Rha-1-3-Gal with the formation of the 1,6-galactosyl-mannose linkage with the 1,2-*trans* (β) configuration. Thus, the starting monomer must have the structure **116** with a trityl group at O-6 of the mannose residue and a cyanoethylidene group at the galactose residue.

The synthesis of this monomer was accomplished by a proper functionalization of the trisaccharide **117**, for which the most rational and convenient synthetic route has been developed[107] on the basis of the experience accumulated in last 10–15 years in the synthesis of oligosaccharide repeating units of gram-negative bacteria (e.g., see reference 108–111). Using the standard procedure the trisaccharide peracetate **118** was converted via the bromide into the acetate of the cyanoethylidene derivative **119** and then, by careful deacetylation, into the unsubstituted cyanoethylidene derivative **120**. The presence of two primary hydroxyl groups posed a problem for the subsequent selective tritylation. Nevertheless, treatment of **120** with 1.5 moles of trityl chloride in pyridine and acetylation, followed by chromatography, afforded the required monomer **116**, albeit in modest yield[112] (Scheme 23).

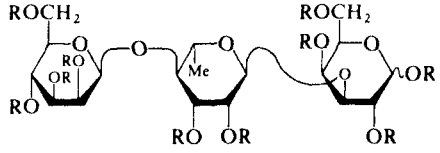
The monomer was subjected to polycondensation in the presence of 10 mol. % of the initiator at room temperature for 60 h.[112] The reaction



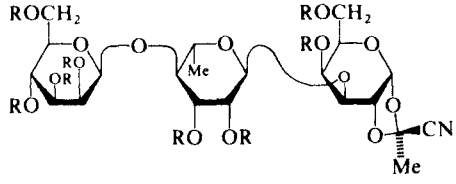
114



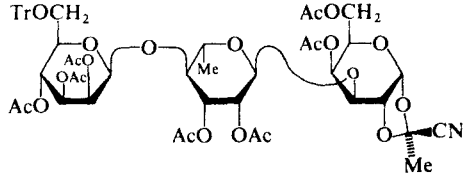
115



117 R = H
118 R = Ac



119 R = Ac
120 R = H



116

Scheme 23

Table 1 Comparative Data of ^{13}C-NMR Spectra of Natural and Synthetic *O*-Antigen Polysaccharide of *Salmonella newington*

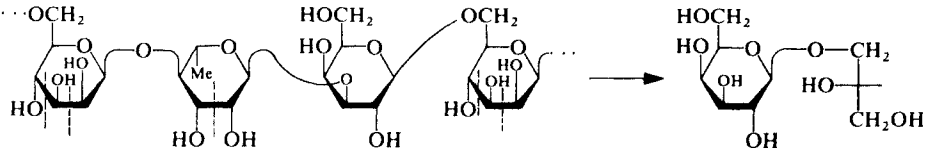
Unit	Polysaccharide	Chemical Shifts (ppm)					
		C^1	C^2	C^3	C^4	C^5	C^6
Man	Natural	101.75	71.7	74.3	68.1	76.25	70.55
	Synthetic	101.8	71.6	74.3	68.0	76.25	70.25
Rha	Natural	103.3	71.45	71.7	80.7	69.1	18.3
	Synthetic	103.4	71.4	71.6	80.8	69.1	18.5
Gal	Natural	104.4	71.45	81.8	69.75	76.4	62.1
	Synthetic	104.3	71.4	81.8	69.7	76.45	62.1

product was deacetylated without purification and the unprotected polysaccharide **115** was isolated by chromatography. Methylation of the polysaccharide, followed by GLC–MS analysis, showed its full regioregularity and a degree of polymerization of 8–12 (counting the trisaccharide unit), which corresponds to a molecular weight of 4000–6000. This is consistent with the average value for the natural *O*-antigenic polysaccharide of *S. newington*.[106]

The stereoregularity of the polysaccharide and stereochemistry of the newly formed β-galactosidic linkages have been checked very thoroughly. The ^{13}C-NMR spectrum contained in the anomeric region three signals of approximately equal intensity (104.3, 103.4, and 101.8 ppm), which correspond to the signals for C-1 of β-D-galactopyranose, α-L-rhamnopyranose, and β-D-mannopyranose; no signals for α-D-galactopyranose have been observed. It was possible to assign the signals of all the 18 carbons in the ^{13}C-NMR spectrum, and the spectrum itself resembled very closely that of the natural *O*-antigenic polysaccharide isolated from *S. newington* (Table 1).

The absolute stereospecificity of polycondensation and the absence of 1,2-*cis* glycosidic linkages was confirmed also by Smith degradation of the synthetic polymer **115** (Scheme 24). Treatment with $NaIO_4$ resulted in oxidation of the mannose and rhamnose residues, while galactose remained unaffected; subsequent borohydride reduction and hydrolysis gave 1-*O*-galactopyranosyl-glycerol **121**, which contained the galactosidic linkage formed on polycondensation. High-performance GLC analysis of galactosylglycerol with the authentic samples proved the degradation product to be pure β-isomer, and, hence, the synthetic polysaccharide contained only the β-galactosidic linkages, that is, the polysaccharide is fully stereoregular.

It is well known that the immunochemical methods are highly sensitive as regards the most important characteristic of any biopolymer, that is, its



121

Scheme 24

biological specificity. In order to examine the biological specificity of the synthetic polysaccharide of *S. newington*, the synthesis of its close analogue **122**, containing an α-mannosyl-rhamnose linkage instead of the β-mannosyl-rhamnose one was carried out in parallel.[112] This synthesis has been accomplished by the route identical to that proposed for the synthesis of the natural polysaccharide **115**, starting from the corresponding trisaccharide obtained by the specially developed procedure.[107] The structure of **122** was confirmed by the spectral data; its ^{13}C-NMR spectrum, which resembled generally that of the natural polysaccharide, contained the signal for C-1 of the α-mannose residue instead of that for C-1 of β-mannose in the former.

Comparison of the synthetic polysaccharide **115** and its α-mannosyl analogue **122** in passive haemagglutination test in the *O*-factor 3–anti 3 system of *S. newington* showed that the synthetic polysaccharide **115** was highly active as an inhibitor of passive agglutination, whereas its analogue **122** was practically inactive. These data prove convincingly that the structure of the synthetic polysaccharide **115** is completely identical to that of the natural polysaccharide. This, by the way, is the first direct synthetic proof of the structure of the natural heteropolysaccharide, and the comparative immunochemical study proved the extremely high structural specificity of polysaccharides of this class.

(2) O-Antigenic Polysaccharide of Shigella flexneri

This heteropolysaccharide is an *O*-antigenic polysaccharide of *Sh. flexneri* serotypes 3b, 3c, and variant Y, and also is the basic chain of the other serotypes of *Sh. flexneri*, which may contain some branchings in the form of single glucose units and/or *O*-acetyl groups. It is built up of the tetrasaccharide repeating units with one residue of *N*-acetyl-D-glucosamine and three L-rhamnose residues and has the structure **123**.[113] The synthesis of this polysaccharide was carried out[114] by polycondensation of the monomer **124**, containing a trityl group at O-3 of the nonreducing glucosamine terminus and a cyanoethylidene group at the reducing rhamnose residue. It was anticipated that the polycondensation of this monomer would be successful

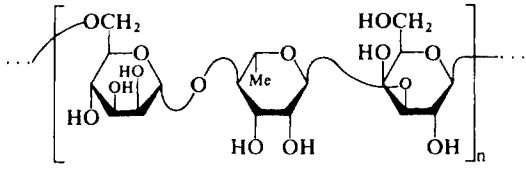
since it was already established that the rhamnose cyanoethylidene derivatives are highly reactive and stereospecific glycosylating agents, and the glycosylation of the *O*-tritylated *N*-phthaloyl-glucosamine proceeds very effectively.[101]

The synthesis of the monomer was based on the use of the monosaccharide synthons, relating to each of the monosaccharide units of the tetrasaccharide; the hydroxyls of each of these synthons, which did not participate in the subsequent transformations in the course of the monomer synthesis, were protected with the "permanent" protection (benzoyl groups), whereas the hydroxyls of the synthons participating in the formation of the glycosidic linkages of the tetrasaccharide were protected with a "temporary" protection (acetyl groups). Selective removal of the *O*-acetates, without affecting the *O*-benzoates, under the conditions of mild acid methanolysis[96] allowed at each step of the synthesis the selective recovery of required hydroxyl. The use of this new strategy, which proved helpful in the oligosaccharide synthesis in general, allowed a rational synthetic scheme to be elaborated. The preparation of the synthons **125–128**, each containing a specific protection, was carried out by using the traditional methods of synthetic carbohydrate chemistry.[115, 116] The tetrasaccharide monomer was assembled from these synthons in a blockwise route (synthesis of two disaccharides, followed by their connection in the tetrasaccharide, the 2 + 2 scheme) (Scheme 25). The synthon **125** was obtained from 3-*O*-acetyl-4-*O*-benzoyl-derivative of L-rhamnose via the corresponding glycosyl bromide, using the general method for the synthesis of the cyanoethylidene derivatives[67, 68] and selective deacetylation at O-3. Then **125** was glycosylated in the presence of mercuric cyanide with a glycosyl bromide derived from the synthon **126**, to give[117] a derivative of the disaccharide **129**, which contained along with the cyanoethylidene group the only "temporary" protected (by an *O*-acetyl group) hydroxyl, while the remaining hydroxyls were protected with the "permanent" benzoyl groups. For the synthesis of the second disaccharide block, the rhamnose dibenzoate **127** was glycosylated with the bromide obtained by the standard procedure from the synthon **128**, to give the dissaccharide **130** containing along with the other protective groups the only hydroxyl protected as *O*-acetate, which was replaced later by an *O*-trityl group.

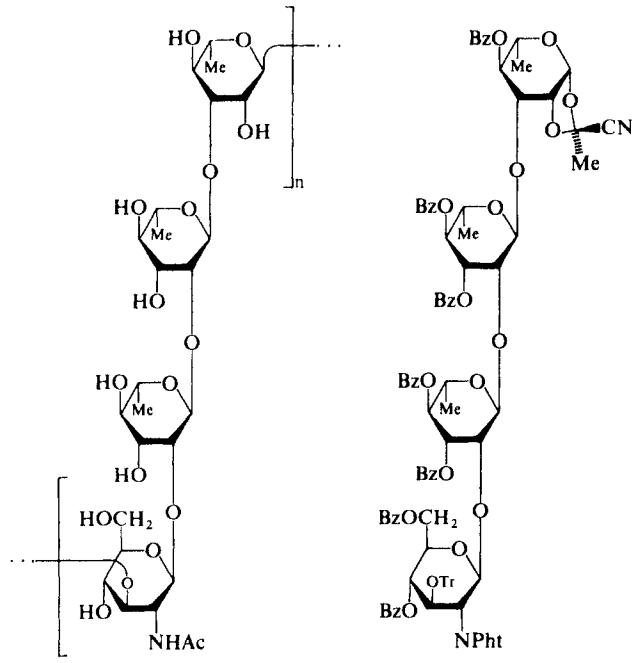
For the synthesis of the tetrasaccharide **131** the hydroxyl at C-2 of the rhamnose residue in the disaccharide **129** was selectively deprotected, and the disaccharide **130** was converted into the corresponding bromide by the sequential acetolysis of methyl glycoside and treatment with HBr. The condensation of the bromide with the monohydroxyl derivative of the disaccharide **129** in the presence of $Hg(CN)_2$ gave the tetrasaccharide **131**, which again contained the only *O*-acetyl-protected hydroxyl.[119] In order to transform **131** into the monomer **124**, the hydroxyl at C-3 of the glucosamine

moiety was deprotected by mild acid methanolysis, and then tritylated with tritylium perchlorate.

Another synthesis of the monomer **124** was accomplished[114] by the sequential chain elongation from the reducing end, using just the same synthons **125–128** (Scheme 26). For this purpose the disaccharide **132**, obtained from **125** and **126** and having the only hydroxyl group, was subjected to condensation with the bromide **133** obtained from **127**. In the resulting trisaccharide **134**, the only *O*-acetyl group was selectively removed and the product was glycosylated with the bromide **135**, obtained from the

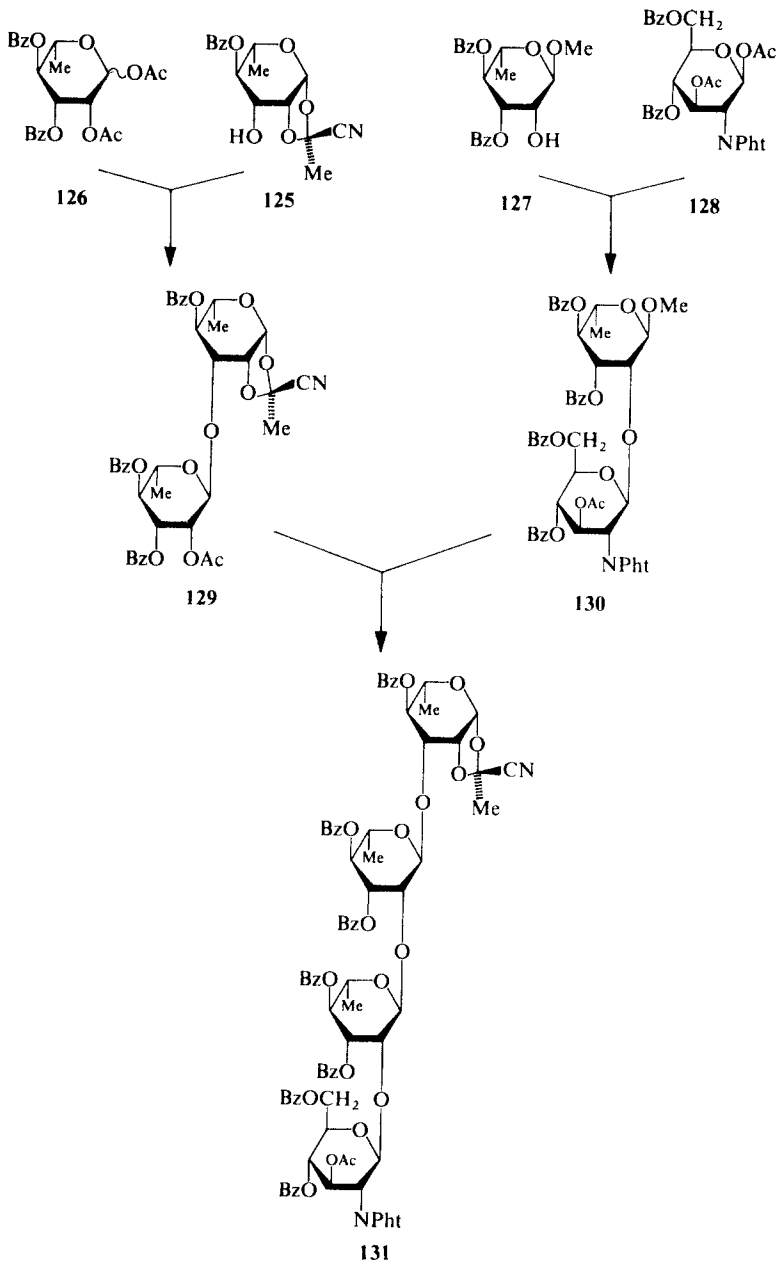


122

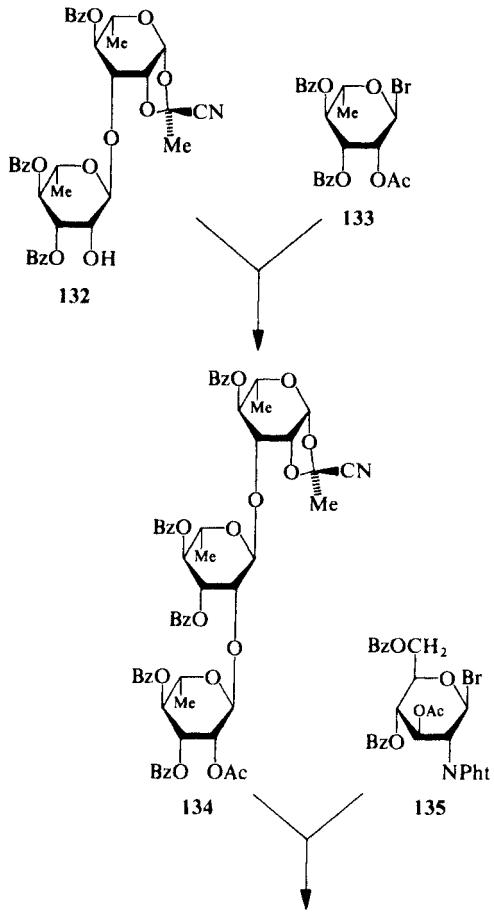


123 **124**

Scheme 25



Scheme 25 (*continued*)



Scheme 26

glucosamine synthon **128**, to give the tetrasaccharide derivative **131**, which proved to be identical to the compound prepared by the 2 + 2 scheme. The yield of **131** in this case is lower, and the blockwise synthesis of the tetrasaccharide is thus more effective, which is usual in the oligosaccharide synthesis.

The polycondensation of the monomer **124** was carried out under the standard conditions (10 mol. % of the initiator, room temperature), the reaction was terminated in 16 h, and the protected polysaccharide was isolated by chromatography. The ^{13}C-NMR spectrum of the polysaccharide supported full stereoregularity of the polysaccharide chain. All the protective

Table 2 Comparative Data of ^{13}C-NMR Spectra of Synthetic and Natural *O*-Antigen Polysaccharide of *Shigella flexneri*

Unit	Polysaccharide	Chemical Shifts (ppm)						$^1J_{C1,H1}$
		C-1	C-2	C-3	C-4	C-5	C-6	
Rha A	Synthetic	102.21	71.80	78.64	72.79	70.35	17.63	170.2
	Natural	102.3	71.41	78.10	72.45	69.81	17.22	169
Rha B	Synthetic	101.88	79.26	71.32	73.53	69.81	17.78	172.0
	Natural	101.62	78.91	70.82	72.96	69.14	17.47	171
Rha C	Synthetic	102.10	79.89	71.13	73.65	70.23	17.86	171.1
	Natural	101.85	79.52	70.58	73.10	69.94	17.47	172
GlcNAc	Synthetic	103.24	56.73	82.68	70.23	77.05	62.09	162.7
	Natural	102.95	56.46	82.29	69.94	76.68	61.56	162

groups were removed by treatment with hydrazine, and then the polycondensation product was *N*-acetylated with acetic anhydride in methanol.

The ^{13}C-NMR spectrum of the unprotected synthetic heteropolysaccharide **123** contained only four signals in the anomeric region (102.21, 101.88, 102.10, 103.24 ppm), and the values of the $^1J_{C1,H1}$ coupling constants for the rhamnose units (170.2–171.1 Hz) showed the presence of only the α-L-rhamnosidic linkages. These and some other spectral features confirmed the full stereoregularity of the polysaccharide and the absolute stereospecificity of the polycondensation process. Comparison of the ^{13}C-NMR spectra of the synthetic and natural polysaccharides of *Sh. flexneri* serotype 3b has demonstrated full agreement for all 24 carbons of the polymer (Table 2). The molecular weight of the synthetic polysaccharide was determined by gel chromatography and by comparison of intensities of the signals corresponding to the terminal monosaccharide unit with those of the signals of other monosaccharides in the ^{13}C-NMR spectrum. The average degree of polymerization was about 10 (counting the tetrasaccharide unit), which corresponds to a molecular weight of about 6000 and is very close to that of the natural polysaccharide.

(3) Capsular Polysaccharide of Streptococcus pneumoniae Type 14

This polysaccharide of a high molecular weight, isolated from the capsule of one of widespread types of *S. pneumoniae*, is built up of the tetrasaccharide repeating units containing glucose, galactose, and *N*-acetylglucosamine residues. It has a branched structure **136** with one galactose residue in the

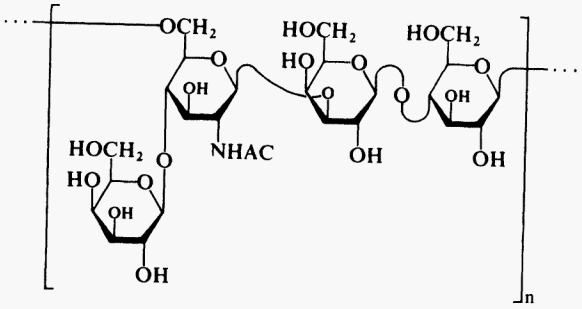
backbone chain, and the second in the branching.[121] Its synthesis[122] was the first example of the synthesis of the regular branched heteropolysaccharide.

The starting monomer was a tetrasaccharide with an *O*-trityl group at C_6 of the glucosamine moiety and the cyanoethylidene group at the terminal glucose residue to ensure the formation of the 1,2-*trans* glucosidic (β-glucosidic) linkage of the polysaccharide backbone upon polycondensation. The terminal galactose would form a regular branching in the polymer formed.

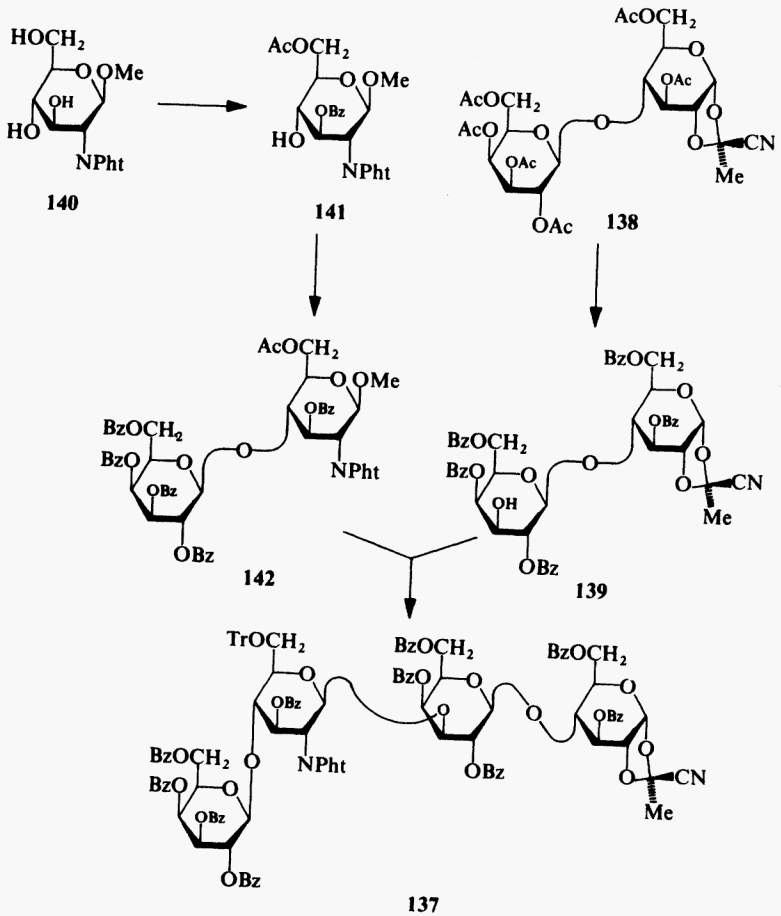
The synthesis of the monomer **137** was accomplished using the blockwise approach (the 2 + 2 scheme) based on the strategy described in the previous synthesis[122] (Scheme 27). The first disaccharide block was obtained from the cyanoethylidene derivative of lactose **138**, prepared from this disaccharide by the standard procedure.[67,68] It was deacetylated, converted into a 3′,4′-*O*-isopropylidene derivative by treatment with 2,2-dimethoxypropane and toluenesulfonic acid, free hydroxyls were benzoylated, the isopropylidene group was removed, and the diol was converted into the corresponding 3,4-orthobenzoate; the selective cleavage of the latter under the action of aqueous acetic acid afforded the corresponding 4-*O*-benzoyl derivative; as a result the disaccharide **139** was prepared, which contained the only free hydroxyl at C-3 of the galactose residue. The second disaccharide block was prepared from methyl 2-deoxy-2-phthalimido-β-D-glucopyranoside **140**, which by sequential 4,6-*O*-benzylidenation, 3-*O*-benzoylation, debenzylidenation, and selective 6-*O*-acetylation was converted into **141**, containing the only free hydroxyl. Condensation of **141** with 2,3,4,6-tetra-*O*-benzoyl-galactosyl bromide in the presence of silver triflate gave the disaccharide block **142**. Condensation of the glycosyl bromide obtained from **142** with the disaccharide **139** afforded the tetrasaccharide corresponding in structure to the repeating unit of the *S. pneumoniae* polysaccharide and having the cyanoethylidene group; the *O*-acetyl group in the resulting tetrasaccharide was removed by selective acid methanolysis,[96] and the only recovered hydroxyl was tritylated with tritylium perchlorate in the presence of 2,4,6-collidine[76] to give the monomer **137**.

The monomer was subjected to polycondensation (10 mol. % of the initiator, room temperature, 18 h). The reaction was stopped by the addition of aqueous pyridine, and the polycondensation product was isolated with high yield and purified by chromatography on silica gel. Hydrazinolysis removed the protective groups and the resulting compound was *N*-acetylated with acetic anhydride in methanol.

The full regularity of this branched polysaccharide was confirmed by methylation analysis. Its ^{13}C-NMR spectrum confirmed the configuration of all its glycosidic linkages, including the unambiguous proof of the β-configuration of the newly formed glucosidic linkage. The spectrum contained in the anomeric region four signals which correspond to C-1 of two galactoses



136



Scheme 27

(104.1 and 103.4 ppm), glucosamine (103.8 ppm), and glucose (103.6 ppm). The signals for the other 20 carbons also were easily assigned. Thus, the synthetic polysaccharide is fully stereoregular. Its optical rotation value (+ 8.4°) is close to that of the natural polymer (+ 5°); a good agreement of this sensitive constant is an excellent demonstration of the identity of the synthetic and natural samples. The molecular weight of the synthetic polysaccharide, as determined by gel filtration is about 6000, which value corresponds to a degree of polymerization of about 10.

6. CONCLUSION: SOME PERSPECTIVES

In this chapter we have summarized the progress achieved to 1986 in the synthesis of regular polysaccharides. Of course only first steps, although very important, have been made, but certain perspectives already become clearer. Additional investigations, such as (1) a detailed study of peculiarities in the polymerization of 1,4- and 1,3-anhydro aldoses, and (2) determination of ranges of high-pressure influence on the stereoregularity and molecular weight of polysaccharides obtained by the trityl–cyanoethylidene polycondensation, will allow the synthesis of many other homopolysaccharides.

On the other hand, the trityl–cyanoethylidene polycondensation offered a very general approach to the synthesis of regular polysaccharides built up of oligosaccharide repeating units.

However, this method is restricted as it does not allow us to obtain heteropolysaccharides with 1,2-*cis*-linked repeating units. Unfortunately, no sufficiently general methods for the synthesis 1,2-*cis* glycosidic linkage with high stereospecificity has been developed so far, and the solution of this problem still remains very urgent in the synthetic chemistry of sugars. Any method for 1,2-*cis* glycosylation, which might be used as a basis for the development of the corresponding polycondensation procedure, should compulsory possess absolute stereospecificity, and this makes the problem far more difficult. It seems that a fundamentally new version of the reaction of nucleophilic substitution at the anomeric center is required, which would direct the reaction to a pure S_N2 substitution or to the route of a sufficiently perfect concerted cyclic process.

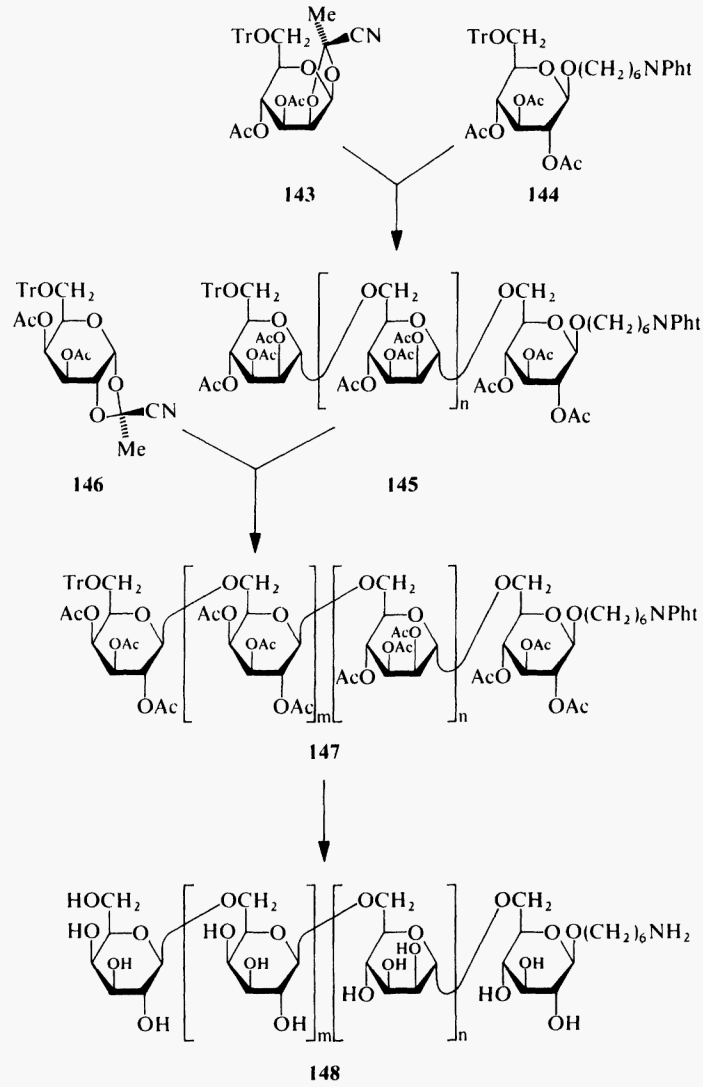
The perspectives for the solution of this problem are still unclear, and in this connection one should recall quite briefly another method for the synthesis of heteropolysaccharides with repeating units which is free of this restriction, although this method is not purely chemical. It is the so-called chemoenzymatic method for the synthesis of regular heteropolysaccharides (see a review in reference 8), which consists in the polymerization of the precursors of their biosynthesis, polyprenol-pyrophosphate-oligosaccharides,

prepared by chemical methods, under the action of polymerases isolated from bacterial cells. At present, a satisfactory source of poorly accessible polyprenol is found; the synthesis of polyprenol-pyrophosphate-oligosaccharides is now well developed in all its steps, as well as the obtaining of preparations of microbial polymerases. As it was established, the polymerases possess rather wide specificity, and this allows us to perform syntheses not only of natural microbial heteropolysaccharides, but also of their analogues consisting of other monosaccharide units. Although this method is quite new, and its limitations are still unclear, even now it may serve as an important supplement for the trityl–cyanoethylidene polycondensation, since it allows us to synthesize heteropolysaccharides consisting of oligosaccharide units linked by the 1,2-*cis* glycosidic linkages as well. Until recently several polysaccharides were synthesized by this method, including the polysaccharide of *Salmonella anatum*,[123] which is built up of the trisaccharide repeating units with the constituent mannose, rhamnose, and galactose residues being linked by the 1,2-*cis* glycosidic linkages. Further progress of this approach appears to offer wide perspectives in the polysaccharide synthesis.

Thus, at present the first pathways have been found for the synthesis of polysaccharides of two types, that is, homopolysaccharides and heteropolysaccharides with a regular structure, consisting of repeating oligosaccharide units. Although these types embrace the two most important and thoroughly studied classes of polysaccharides, still there are a wide diversity of polysaccharides of other types, and no real approaches are so far available to the synthesis of them. In this connection a new modification of the trityl–cyanoethylidene polycondensation should be mentioned, which is only beginning to develop and which may open a new route to the synthesis of another important and widespread type of natural polysaccharides, whose polymeric chain consists of homopolysaccharide blocks of different length, $(Sug_1)_m(Sug_2)_n(Sug_3)_p \ldots$, where Sug_1, Sug_2, ... are different monosaccharides.

If the trityl–cyanoethylidene polycondensation of monomer is carried out in the presence of a "primer" (i.e., the *O*-trityl ether of the monosaccharide) connected via anomeric center with an "anchor" group, then the oligomer is formed with a fixed reducing terminus, and its nonreducing end retains the *O*-trityl group. After the monomer has been spent, another monomer can be added to the reaction mixture, and the polysaccharide chain will grow to give an oligomeric block, consisting of residues of this new monosaccharide, thus forming the system $(Sug_1)_m(Sug_2)_n, \ldots$.

This can be exemplified by the following synthesis (Scheme 28). The polycondensation of the mannose monomer **143** in the presence of the glucose derivative **144**, containing a hexamethyle-nephthalimide aglycone, gives the oligosaccharide **145**, which contains about 5–7 mannose residues



Scheme 28

per a glucose unit. When the reaction is terminated and the monomer **143** is spent, the derivative of galactose **146** is added to the reaction mixture and the polycondensation proceeds further; this sequence gives as a result the polymer **147**, which consists of the oligomannose and oligogalactose blocks, each containing approximately 5–7 monosaccharide residues. In order to isolate

this polysaccharide from other polycondensation products, the phthalimide protection of the amino group is removed by treatment with hydrazine, and the combined polysaccharide **148** is easily isolated by ion-exchange chromatography, since it is the only polysaccharide carrying the amino group at the reducing terminus.

It is expected that this approach will allow us to prepare various polysaccharides consisting of homooligosaccharide blocks. The size of these blocks perhaps can be controlled by the concentration and ratio of monomers added sequentially to the reaction mixture. At the same time, the details of the experimental procedure and limitation of the approach are still to be determined.

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The Total Synthesis of Naturally Occurring Quinones

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1. INTRODUCTION

The synthesis of naturally occurring quinones began in 1868. In that year Graebe and Liebermann realized that alizarin, the principal pigment in the root of madder, *Rubia tinctorum*, was a dihydroxyanthraquinone and immediately sought a laboratory synthesis. Their success was announced in a preliminary communication to the Deutschen Chemischen Gesellschaft on January 14, 1869,[1] and details appeared later[2] after a patent application had been filed. As madder was a very important natural dyestuff at that time, the synthesis was of great commercial significance. It was also a major event in the history of organic chemistry as it was the first synthesis of an organic pigment, indeed the first synthesis of a natural product of more than two carbon atoms.

The "synthetic route" was itself remarkable as alizarin, subsequently recognized as 1,2-dihydroxyanthraquinone, was obtained by alkali fusion of a dibromoanthraquinone which was shown[3a] 50 years later to be the 2,3-dibromo isomer. Graebe and Liebermann obtained the latter by oxidation of 2,3,9,10-tetrabromoanthraquinone but, confusingly, they also prepared a dibromoanthraquinone by direct bromination, and assumed that they had made the same product (it is mainly the 2,7-isomer[3a, b]). The dibromoanthraquinone route was too expensive for commercial exploitation and was quickly followed by a cheaper alternative based on the alkali fusion of anthraquinone-2-sulphonic acid. The new process was promptly patented by Graebe and Liebermann in Germany and independently by W. H. Perkin in England, and synthetic alizarin was on the market within a year of the original synthesis.

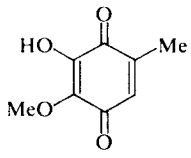
After the dramatic start in 1868 natural quinone synthesis advanced very slowly. By the turn of the century several hydroxyanthraquinones, including further madder pigments, and also the naphthoquinone, juglone, had been prepared, and by 1950 some 60 quinones from natural sources had been obtained synthetically, the great majority being simple benzoquinones, naphthoquinones, and anthraquinones bearing only hydroxy, methoxy, and

methyl substituents. At that time about 150 naturally occurring quinones were known, but that number has now increased to more than 1600, and they are present in virtually all forms of life. Most exhibit some sort of biological activity, notably the bioquinones (plastoquinones, ubiquinones, phylloquinones, menaquinones) which play an important role in electron transport in animals and plants, and a few show significant antibiotic and antitumor properties. All this has stimulated the interest of synthetic chemists, and many of the newer quinones are complex heterocyclic molecules which provide synthetic challenges of a high order. In consequence, naturally occurring quinone synthesis is now flourishing.

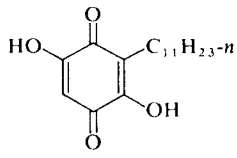
Numerous methods are available for the synthesis of quinones and several reviews are available.[4–13] In the earlier natural product work (pre-1950) most benzoquinones and naphthoquinones were derived from a precursor phenol by oxidation followed, as required, by further modification of substituents or perhaps introduction of a carbon side chain, while anthraquinones were usually obtained by condensation of substituted benzoic acids, cyclization of *o*-benzoylbenzoic acids and related procedures, or substitution reactions on simple and readily available anthraquinones. Brief details of all this earlier work can be found in reference 14 and will not be repeated here. While the simpler natural quinones continue to be synthesized using standard aromatic and quinone chemistry, this review concentrates on the more elaborate pigments and on recent methods, particularly those providing high regio- and stereo-selectivity. Short accounts of all natural quinone syntheses through 1984 can be found in references 14 and 15. This review covers the literature to the end of 1989.

2. BENZOQUINONES

The natural benzoquinones comprise very simple compounds such as fumigatin **1**, a few with long alkyl side chains of the embelin **2** type, 2,5-diaryl derivatives, furanobenzoquinones, and terpenoid and meroterpenoid quinones considered in Sections 8 and 9. Many have been synthesized by straightforward methods, usually leading to a phenol, and final oxidation.



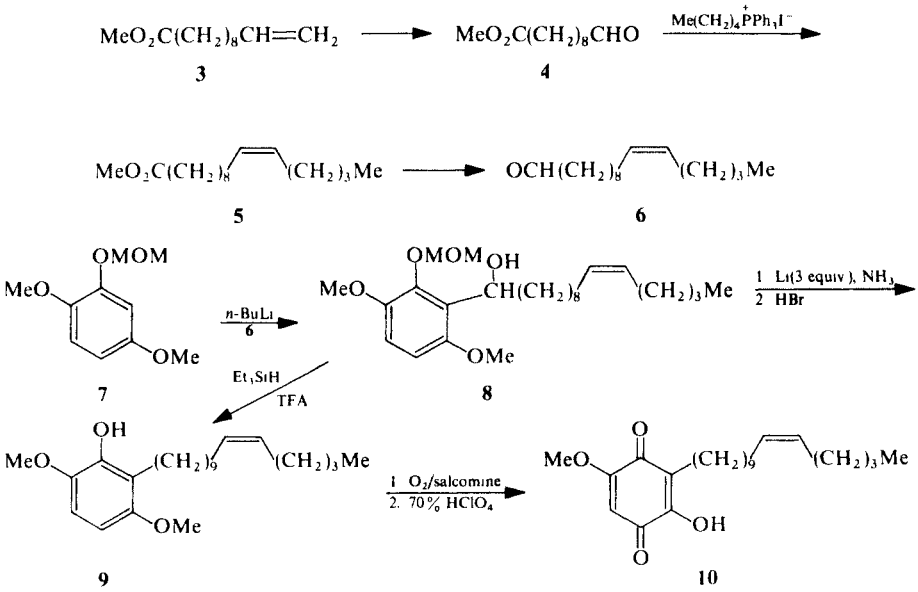
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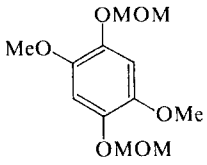
A. Alkyldihydroxybenzoquinones

Quinones such as embelin, to which diverse biological properties are attributed, can be obtained by free radical alkylation of a 2,5-dihydroxy-(acetoxy)benzoquinone using a diacyl peroxide[16] or a trialkylborane.[17] The route is attractively short but yields are low, and alkylation at the benzenoid level, as in Kubo's synthesis[18] of maesanin **10** is more efficient. Maesanin, from the fruit of *Maesa lanceolata*,[18] invokes a nonspecific host defense reaction in mice, a single small dose providing significant protection against an otherwise lethal attack by *E. coli*. The synthesis (Scheme 1) starts from the protected phenol **7**, which was alkylated *ortho* to the methoxymethoxy group using aldehyde **6** to give the alcohol **8**. Conversion of **8** to phenol **9** was best effected in one step (73%) by ionic hydrogenation[20] using trifluoroacetic acid and triethylsilane. The alternative reduction of **8** using lithium in liquid ammonia required 3 equivalents and if more was used Birch reduction of the ring occurred to some extent, leading to elimination of the methoxymethoxy group and formation of 1,4-dimethoxy-2-pentadecenylbenzene. Oxidation of **9** to the quinone proved to be difficult, but eventually an 81% yield was achieved using oxygen and the salcomine[12] catalyst; the final acidic hydrolysis displaced the more reactive methoxy group selectively.

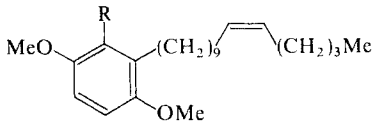


Scheme 1

An attempted synthesis of maesanin starting from the tetraalkoxybenzene **11** was unsuccessful.[21] Lithiation followed by reaction with aldehyde **6** gave the expected benzyl alcohol in only 27% yield, and the subsequent Birch reduction resulted in predominant demethoxymethoxylation to give **12** (R = H and OCH_2OMe).



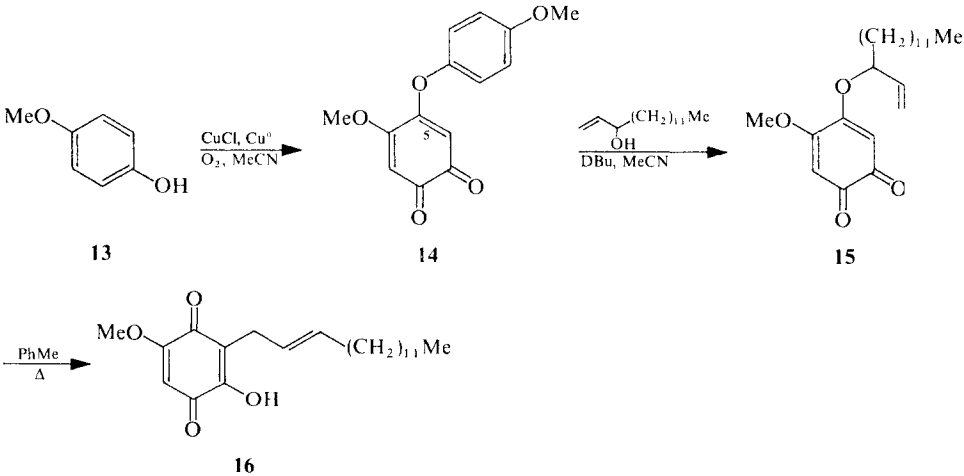
11



12

Irisquinone, a deoxy analogue of maesanin with a C_{17} side chain, found in the seeds of *Iris* spp,[15] has been synthesized[36] essentially by the successful maesanin route, the side chain being introduced by treating 3-lithioveratrole with *N*-methoxy-*N*-methyl-10-*cis*-heptadecenamide. However, the resulting ketone was then reduced by the old Clemmensen method and the yield was only 50%.

Maumy[51] has adopted an alternative approach to the synthesis of unsymmetrical alkylhydroxymethoxyquinone analogues of the maesanin type. The route, illustrated for a maesanin double-bond isomer (Scheme 2) is short, only four steps from *p*-methoxyphenol, and introduces the side chain regiospecifically *ortho* to the hydroxy group. Autoxidation of *p*-methoxyphenol



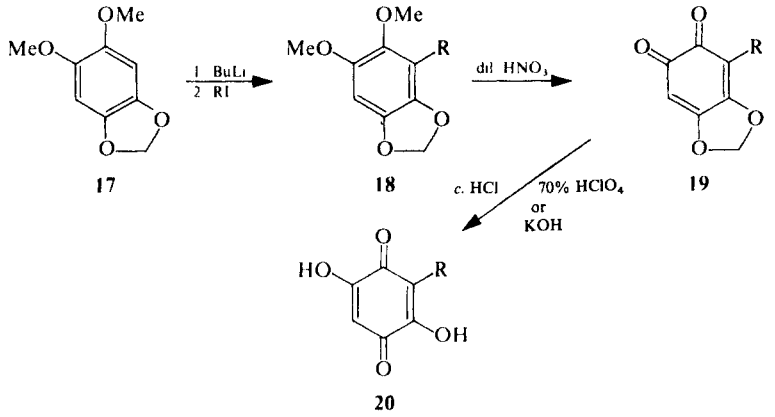
13 **14** **15**

16

Scheme 2

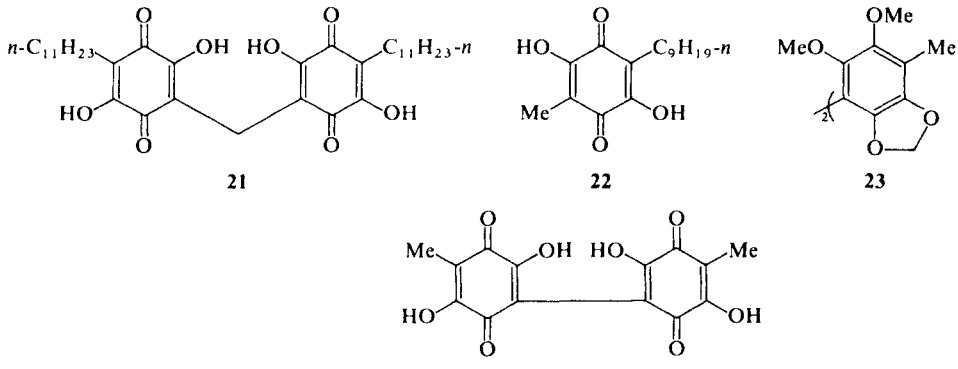
leads to intermediate formation of 4-methoxy-1,2-benzoquinone followed by nucleophilic addition of the phenol at C-5 and reoxidation to give **14** in high yield (after recovery of unreacted phenol). When **14** reacts with an alcohol, preferential nucleophilic attack occurs at C-5, displacing the better (phenolate) leaving group. Claisen rearrangement of **15** gives the desired product **16** in 60% overall yield.

Dallacker[22] has prepared a series of mono- and dialkyl-2,5-dihydroxybenzoquinones (Scheme 3) in good yields, starting from the methylenedioxybenzene **18**[23] which can be obtained from piperonal in four steps. Thus when $R = C_{11}H_{23}$, final hydrolysis of **19** under acid conditions yields embelin **20** ($R = C_{11}H_{13}$), but if aqueous potassium hydroxide is used, the liberated formaldehyde condenses with the embelin to form vilangin **21**, a biquinone which co-occurs with embelin in *Embelia ribes*.[14] If nonylation of **17** at C-2 is followed by methylation at C-5, the final quinone is the dialkyl



17 18 19 20

Scheme 3

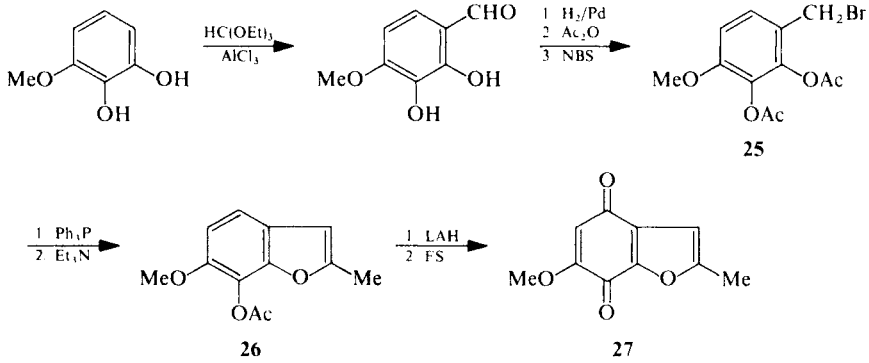


21 22 23 24

derivative bhogatin **22**, found in the leaves of *Maesa macrophylla*,[15] and in a further variation the methyl analogue **18** (R = Me) was lithiated and then oxidized to the dimer **23** with copper(II) chloride leading finally to the fungal metabolite oosporein[14] **24**.

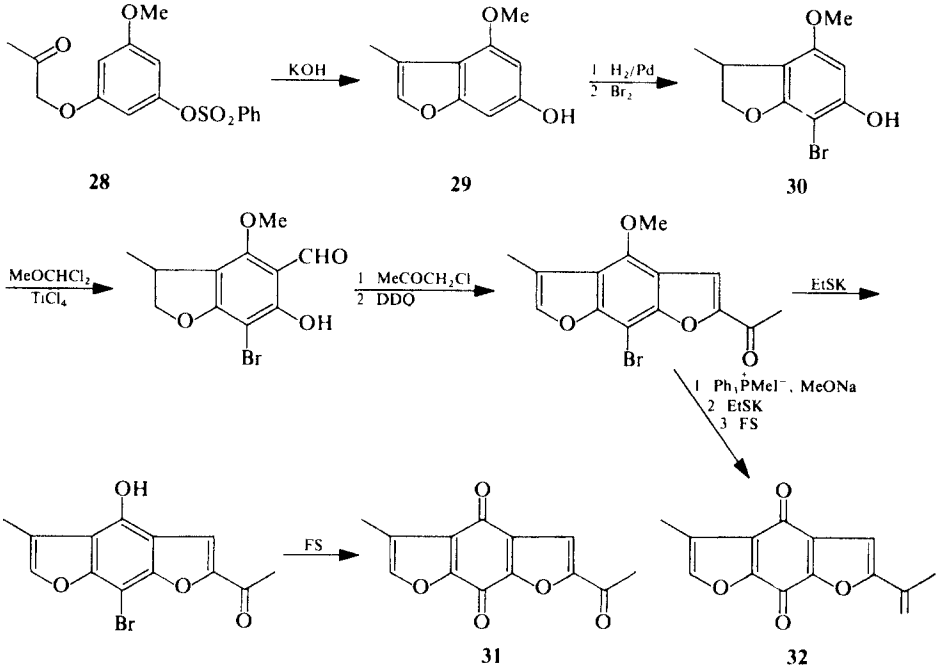
B. Furanobenzoquinones

A group of furano- and difuranobenzoquinones occurs in the Cyperaceae family of sedges, but acamelin[24] **27** is a notable heartwood constituent of Australian blackwood (*Acacia melanoxylon*). Workers using this commercial timber are prone to contract dermatitis and bronchial asthma for which acamelin and its cometabolite 2,6-dimethoxybenzoquinone are responsible.[25] Acamelin has been synthesized in two ways by Stevenson; the first[26] followed a standard benzofuran procedure starting from phloroglucinol, while the key step in the second[27] made use of an intramolecular Wittig reaction involving an ester carbonyl group (**25** → **26**) to effect the furan ring closure (Scheme 4).



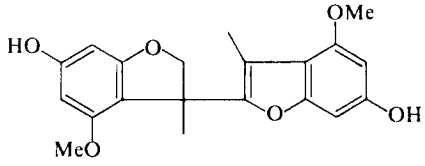
Scheme 4

Cyperus plants elaborate[14, 15] a group of quinones based on the benzo[1,2-b:5,4-b']difuran system (e.g., conicaquinone **31** and cyperaquinone **32**). As the structural evidence[28] for these did not exclude the possibility that the quinone ring might be 3,6- rather than 3,5- oxygenated, Wells[29] confirmed the latter by synthesis (Scheme 5). The β-methylfuran ring was derived from ketone **28** (obtained efficiently from phloroglucinol in five steps) by warming in alkaline solution when it cyclized smoothly to the benzofuran **29**, which has a hydroxyl group at C-6 available for elaboration of the second furan ring. The reaction is essentially an intramolecular nucleophilic attack on the ketonic group by the phenolate anion generated, and occurs exclusively in the *para* position. A minor byproduct of the reaction was the dimer



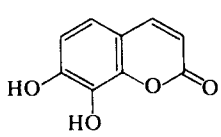
Scheme 5

33, resulting from acid-catalyzed dimerization of **29**; it was not formed when the final acidification of **29** was carried out below 5°C. To avoid acid sensitivity, **29** was then hydrogenated, and blocking C-7 by bromination (to **30**) was essential to ensure that the subsequent formylation occurred at C-5.

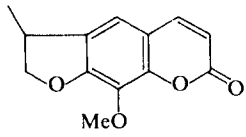


33

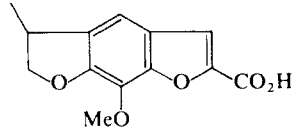
Another route[31] to conicaquinone and cyperaquinone is available starting from pyrogallol rather than phloroglucinol. Daphnetin **34**, obtained by von Pechmann condensation of pyrogallol and malic acid, was elaborated to **35** and then by a standard coumarin–benzofuran ring contraction procedure to the difurano compound **36**. Further manipulation by obvious steps yielded the required quinones. The weakness lies in the initial reaction, which gives daphnetin in only 25% yield.



34

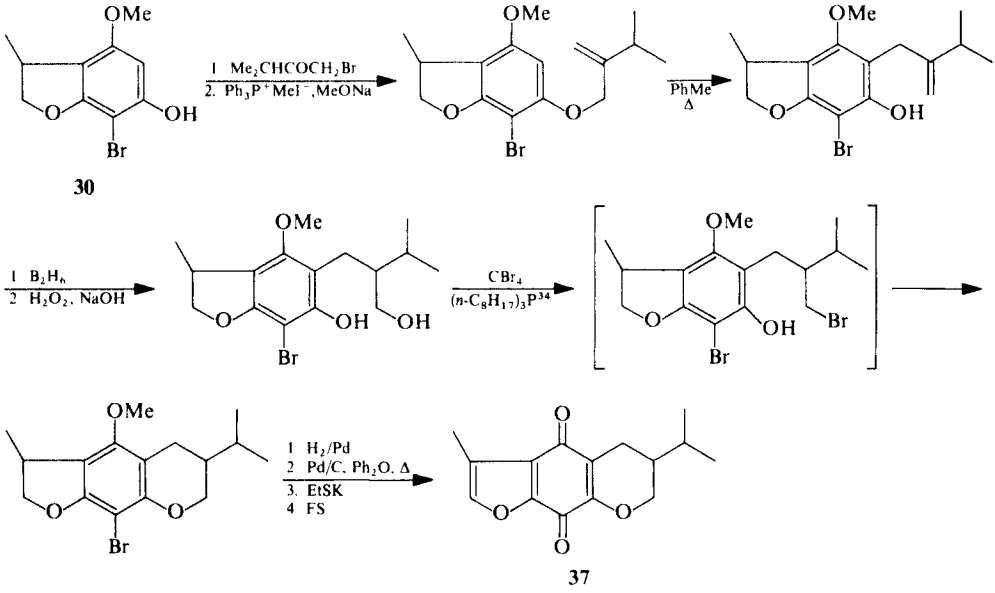


35



36

Scabequinone **37** represents a subgroup of furanobenzoquinones in the Cyperaceae in which the quinone ring is flanked by a dihydropyran system. The structure, based[32] mainly on spectroscopic data, suggested that the six carbon atoms of the isopropyldihydropyran ring might be biosynthesized from a C_5 isoprenyl unit and a C_1 unit, an unusual combination which prompted Wells[33] to confirm structure **37** by synthesis of the racemic form as indicated (Scheme 6).

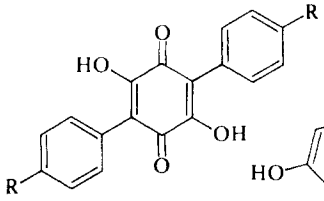


Scheme 6

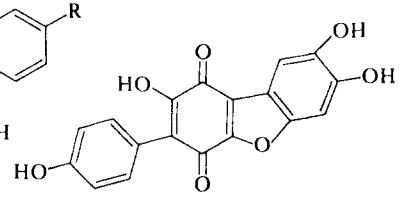
C. Diarylbenzoquinones

Numerous fungi and lichens elaborate 2,5-diarylbenzoquinones, generally known as terphenylquinones,[14, 15, 35] of which polyporic acid **38** (R = H) is typical. Structural variations include analogous *o*-quinones, related furano derivatives such as cycloleucomelone **39**, and a group of prenylated 2,5-

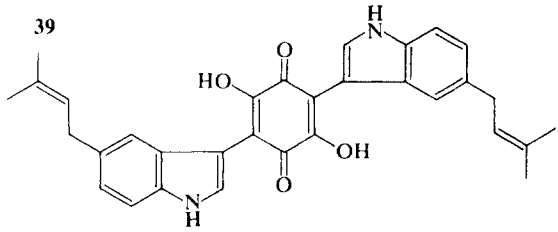
diindolyl analogues represented by cochliodinol **40**. Several members of the group have been synthesized and many analogues prepared, reflecting interest in the antioxidant and possible antileukemic activity of these compounds.



38



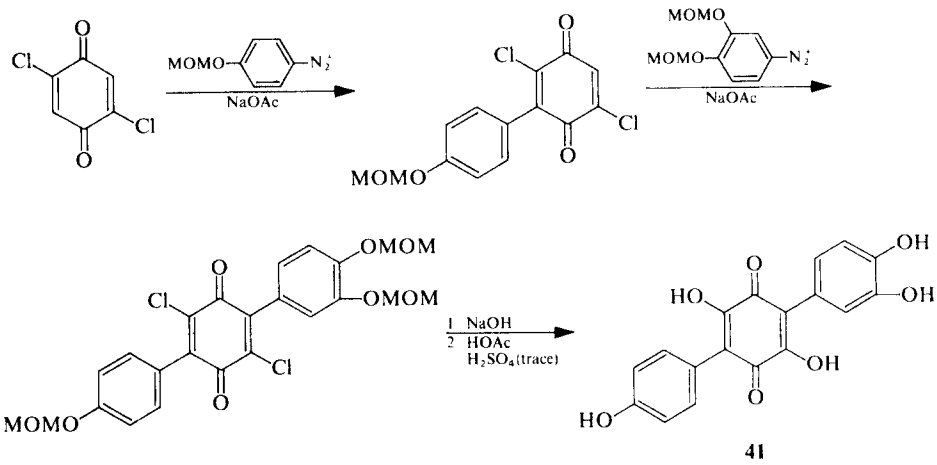
39



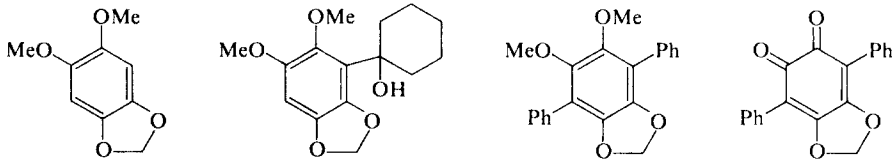
40

Hitherto the most widely used terphenylquinone synthesis[37–40] is the free radical arylation of 2,5-dichloro (or dihydroxy)-benzoquinones using a diazotized aniline or an *N*-nitrosoacetanilide as radical source. It has the advantage that the two aryl groups can be introduced sequentially, which permits the synthesis of unsymmetrical compounds, but the yields are only moderate. As the aryl groups are nearly always hydroxylated, this requires the use of hydroxyanilines which are best protected by *O*-methoxy-methoxylation.[41] In the synthesis[42] of leucomelone **41** (Scheme 7), arylation is followed by alkaline hydrolysis, and the final deprotection is effected under mild acid conditions. This allows the sensitive quinone **41** to be isolated without risk of oxidative cyclization to **39**. Natural leucomelone **41** has probably never been isolated, despite early claims,[37] but it is the obvious precursor of cycloleucomelone **39**, which occurs[43] in *Boletopsis leucomelaena* together with several leucoacetates. The synthetic leucomelone **41** can be easily oxidized to cycloleucomelone **39** using silver carbonate–celite.[43]

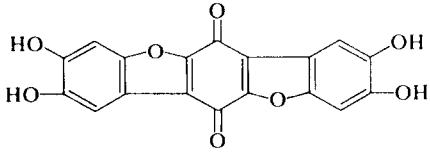
Synthetic polyporic acid **38** (R = H) has also been obtained by Dallacker's method.[44] Lithiation of **18** followed by quenching with cyclohexanone gave the alcohol **42**. After aromatization, by dehydration and dehydrogenation, these four steps were repeated to introduce the second phenyl group (**43**), followed by the usual oxidation and hydrolysis. The penultimate *o*-quinone **44** is phlebiaquinone, another natural terphenylquinone, also available from the potassium salt of polyporic acid by reaction with excess of methylene sulfate.[45]



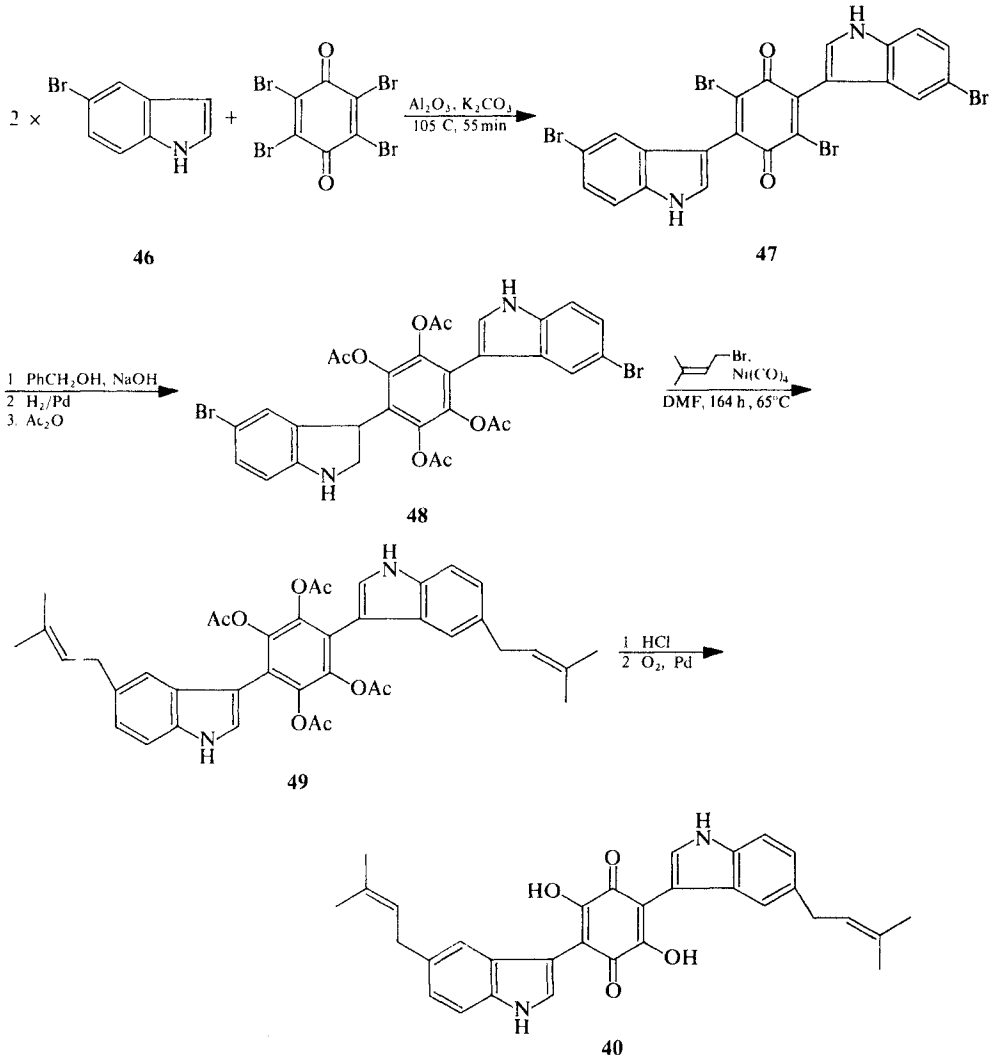
Scheme 7



The symmetrical difuranoquinone, thelephoric acid **45**, is most easily accessible,[46] although in poor yield, by condensation of chloranil with 3,4-dimethoxyphenol followed by demethylation, but the method is not of general application. Cochliodinol **40**, which has antibiotic properties, has been synthesized[52] from bromanil (Scheme 8). The carbon skeleton was very difficult to assemble. The di-indolylquinone **47** was obtained, as shown, by a solid-phase reaction which gave a mixture containing an equal amount of the 2,6-isomer (combined yield 34%). The bromoindole **46** was used as the reaction failed with 5-prenylindole. The prenyl side chains were then introduced by heating the tetraacetate **48** with the prenyl bromide–nickel carbonyl



45

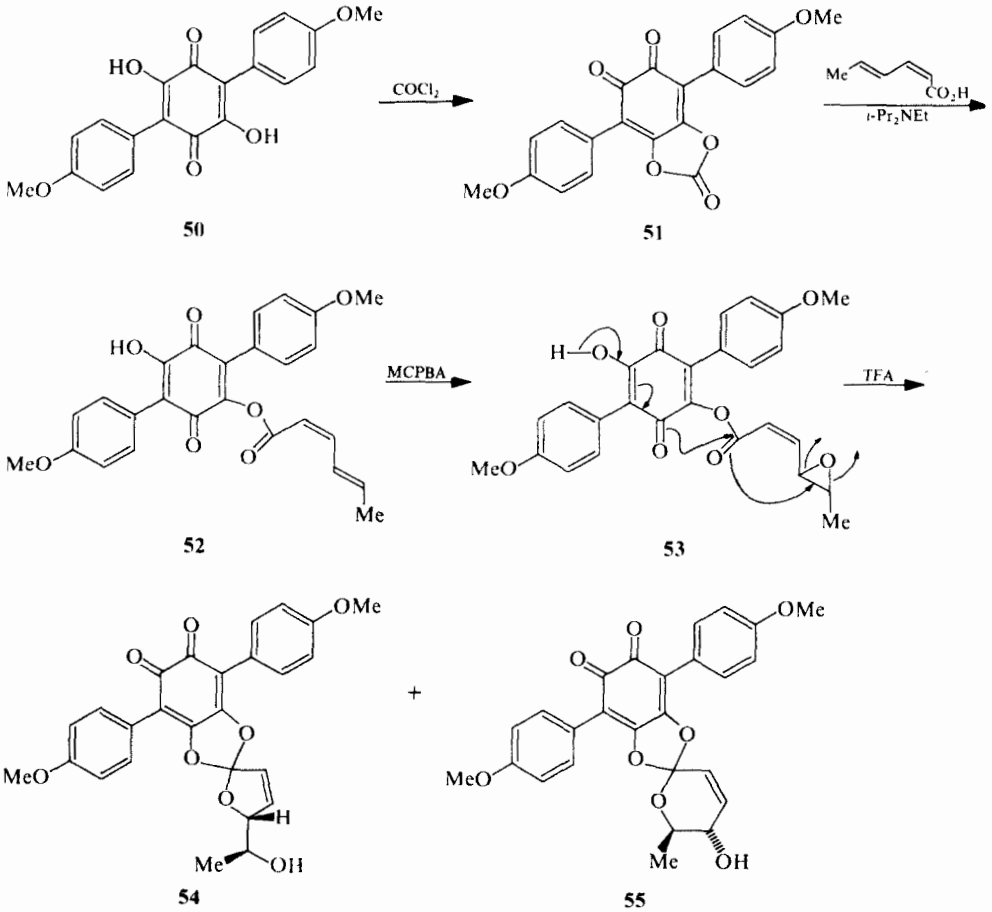


Scheme 8

complex to give **49** (20%), which yielded cochliodinol after hydrolysis and oxidation.

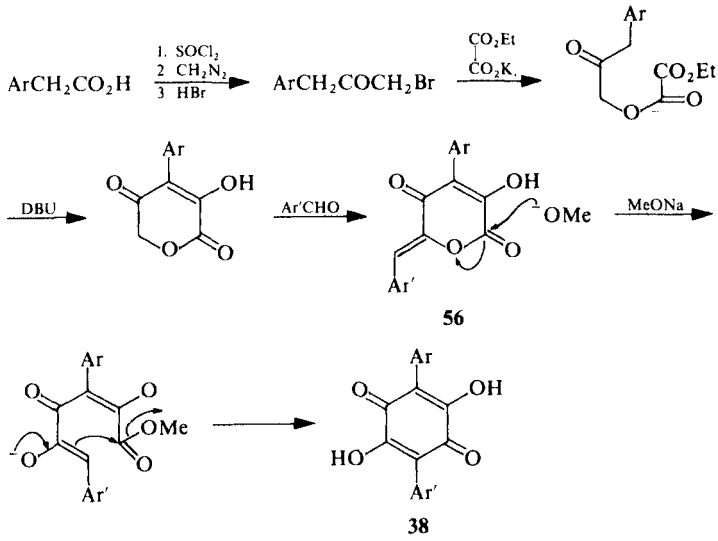
Steglich[47] has found recently that the toadstool *Paxillus atrotomentosus* contains several atromentins **38** (R = OH) esterified with 2,4-hexadienoic acid and 4,5-epoxy-2-hexanoic acid, and these orange pigments, the flavomentins (type **52**), are accompanied by small amounts of violet spiromentins

(types **54**, **55**) which are related to phlebiarubrone **44**. Support for these unusual structures was secured by synthesis of their racemic 4,4'-dimethyl ethers (Scheme 9). Atromentin dimethyl ether **50** was converted via the cyclic carbonate **51** into the monoester **52** (flavomentin C dimethyl ether). Selective epoxidation afforded **53** [(±)-flavomentin B dimethyl ether] (73%), which cyclized smoothly in cold trifluoroacetic acid forming predominantly (57%) (±)-spiromentin C dimethyl ether **55**, (±)-spiromentin B dimethyl ether **54** (16%), and a little (3%) spiromentin A dimethyl ether (anhydro **54**). It seems likely that the cyclization of epoxyester **53** to the spiromentins **54** and **55** parallels the biosynthetic route.



Scheme 9

All the terphenylquinone syntheses discussed so far start with a preformed central ring to which the aryl substituents are attached. Steglich[48] devised a new synthesis in which the central quinone ring is assembled last from a precursor containing the two aryl groups. The method is general and permits the formation of unsymmetrical terphenylquinones in excellent yield, illustrated by the synthesis of ascocorynin **38** (R = H and OH), leucomelone **41**, and several analogues. The procedure involves the methoxide-catalyzed rearrangement of grevillins **56** in cold methanol or on brief warming at 40–50°C. The grevillins[35] are fungal pigments closely related to the terphenylquinones and sometimes co-occurring, which are easily synthesized[49] (Scheme 10). One aryl group is derived from an arylacetic acid and the other from an aromatic aldehyde. It should be possible to obtain cochliodinol and other di-indolylbenzoquinones by this method.

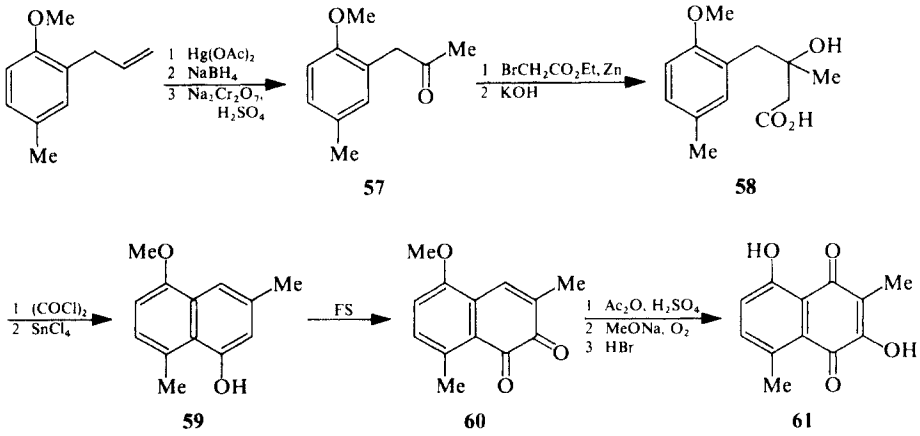


Scheme 10

3. NAPHTHOQUINONES

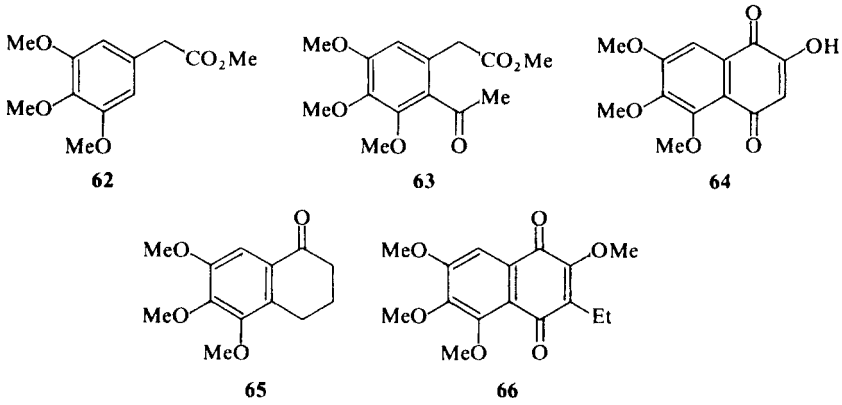
A substantial proportion of this large collection of quinones are 1,4-naphthoquinones having one to six simple constituents, particularly hydroxy, methoxy, and methyl, while short side chains of two to five carbons are infrequent except for prenyl substituents which are often incorporated into pyran or furan ring structures; there is a subgroup of polyprenylnaphthoquinones and a few sesquiterpenoid naphthoquinones (see Sections 8 and 9).

Many naphthoquinones have been synthesized by oxidation of naphthols elaborated from benzenoid precursors by standard methods.[53] Frequently, lengthy operations were required to obtain relatively simple compounds. This approach is illustrated by the synthesis[54] of aristolindiquinone **61** (Scheme 11). Starting from *o*-allyl-*p*-cresol, the side chain was transformed to the ketone **57**, extended by means of a Reformatsky reaction to **58**, and cyclized to the naphthol **59**. As direct oxidation of the latter to the desired *p*-quinone was unsuccessful, it was converted to the *o*-quinone **60** with Fremy's salt,[30] and then by acetic anhydride addition (Thiele acetylation) and oxidative hydrolysis to a hydroxy-*p*-quinone, and finally aristolindiquinone **61**.

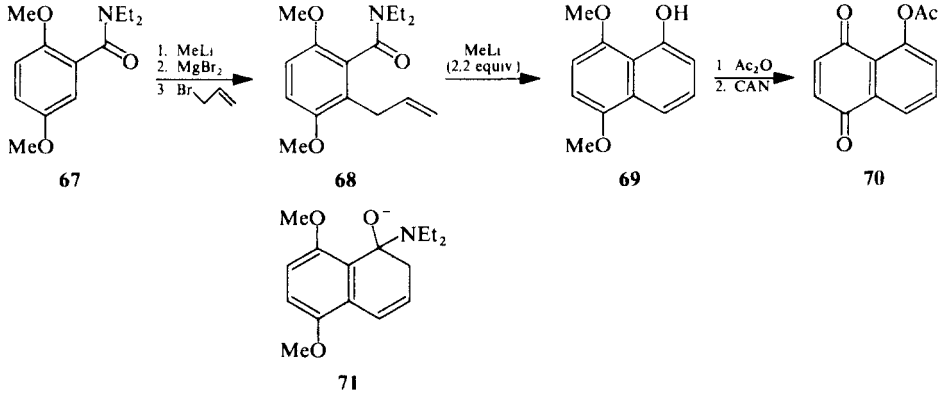


Scheme 11

In the synthesis[55] of lomandrone **66** the quinone system was elaborated from ester **62** (easily accessible from gallic acid) by *C*-acetylation with acetic anhydride in polyphosphoric acid and the resultant keto ester **63** then cyclized in base to give **64** directly. In this case, the intermediate 1,3-diol autoxidized immediately in alkaline solution. Alternatively, **64** can be obtained[56] by autoxidation of the tetralone **65** in *t*-butanol containing potassium *t*-butoxide, a reaction which can also be effected using potassium superoxide and a crown ether.[57] Transformation of **64** into lomandrone **66** was then achieved by *C*-ethylation using propionyl peroxide, *peri*-demethylation with hydrogen bromide, and methylation of the nonchelated hydroxyl with diazomethane.

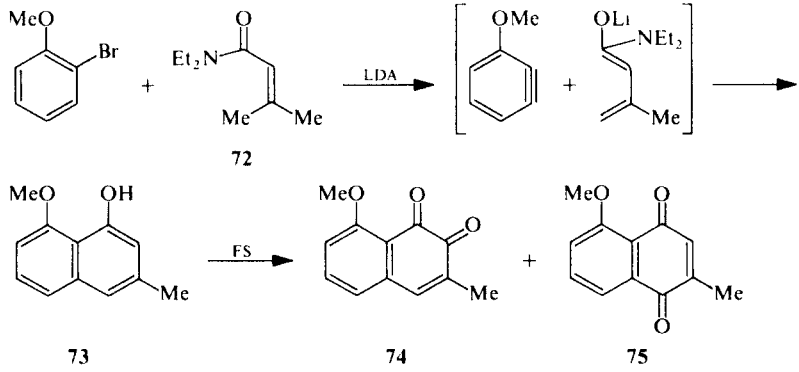


These earlier procedures are now being superceded by modern methods of naphthol synthesis. Snieckus[58] has devized a very useful regiospecific synthesis of 1-naphthols, and hence naphthoquinones, which is illustrated below for juglone acetate **70**. The key compound is the *o*-allyl-*N*,*N*-diethylbenzamide **68** derived from **67** by directed *ortho*-lithiation, followed by *trans*-metalation (ArLi → ArMgBr), and reaction with allyl bromide. *Trans*-metalation[59] is necessary as the lithiated product does not yield **68**. Treatment of **68** with methyllithium resulted in cyclization to naphthol **70**. The ring closure must proceed through anion **71**, but the intermediate stages are not clear. Final acetylation and oxidative demethylation with ceric ammonium nitrate gave juglone acetate **70**. Although this is a fairly trivial example of quinone synthesis, several mono- and dimethoxynaphthols were prepared by the *o*-allylbenzamide route in yields of 50–60%, and the method has potential for the synthesis of more complex quinones. Juglone has been made



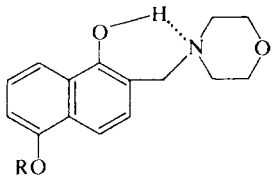
in many ways, most frequently by direct oxidation[12] of commercially available 1,5-dihydroxynaphthalene, although autoxidation with salcomine as catalyst is also a popular method.[50] Numerous natural quinones contain a juglone moiety and it is frequently the starting point of a complex synthesis.

Another useful approach to the synthesis of methoxy-methyl-1-naphthols and naphthoquinones makes use of cycloaddition of dienolate anions to benzynes (Scheme 12). Thus Watanabe[60] treated *N,N*-diethylsenecioamide **72** with excess LDA (or other hindered base) at − 78°C (the use of senecioate esters[61] gives lower yields), followed by addition of *o*- or *m*-bromoanisole to give naphthol **73**, regiospecificity being determined by the inductive and steric effects of the methoxy group.[62] About 15 naphthols were prepared using different starting materials in yields averaging 50%. In the example shown, final oxidation gave plumbagin methyl ether **75** (45%) and the isomeric *o*-quinone **74** (40%) (both natural compounds). Using salcomine-catalyzed oxidation **75** (69%) was the sole product. Plumbagin itself was obtained starting from *o*-bromomethoxymethoxybenzene and final deprotection.

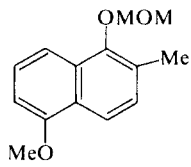


Scheme 12

Simple naphthoquinones like plumbagin are often accessible from readily available naphthalene compounds. Plumbagin itself is easily obtained from 1,5-dihydroxynaphthalene by conversion to the Mannich base **76** (R = H), hydrogenolysis, and oxidation with Fremy's salt.[63] However, that also produces the 6-methyl isomer, which can be avoided by selective monoacetylation[64] to **76** (R = Ac) before oxidation. Plumbagin methyl ether **75** is readily accessible[138] from 5-methoxy-1-naphthol via regiospecific lithiation of its methoxymethyl ether at C-2 to give **77**. Deprotection and oxidation then afford the quinone, and the method is general for 2-alkyl-1,4-naphthoquinones.



76

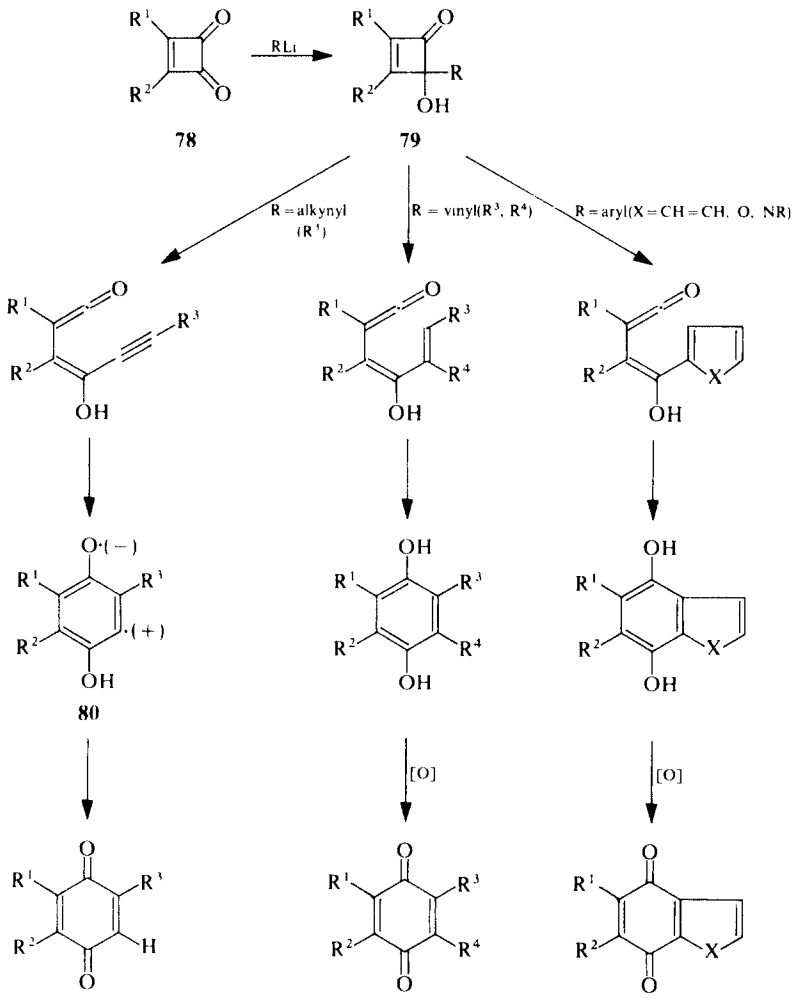


77

A. Synthesis by Rearrangement of Hydroxycyclobutenones

In 1986 Liebeskind[65] and Moore[66] simultaneously announced a new procedure for the synthesis of quinones in general. The key reaction is the electrocyclic ring opening of 4-substituted-4-hydroxycyclobutenones **79** to conjugated ketenes, which then undergo a remarkable ring closure and reorganization to form quinones or hydroquinones which are then oxidized. The rearrangement is effected by heating, usually in refluxing *p*-xylene, and the oxidative workup, where required, uses silver(II) oxide or CAN/SiO_2.[67] According to the substituent in **79** the products are benzoquinones or 1,4-naphthoquinones (Scheme 13), but variation of the aryl group leads to furanoquinones, isoquinolinequinones, and phenanthra-1,4-quinones, while replacing **79** by a benzocyclobutenone analogue also provides 1,4-naphthoquinones and 9,10-anthraquinones. The naphthoquinone syntheses are analogous to earlier ring expansions of cyclobutenones to naphthols.[68] With minor exceptions the reaction is regiospecific, yields are generally good and frequently high. The precise nature of the cyclized intermediate, **80**, biradical or zwitterionic, is still ambiguous, but it is apparent that the initial ring opening of the cyclobutenone **79** is conrotatory, the hydroxyl group moving away from the ketene function.

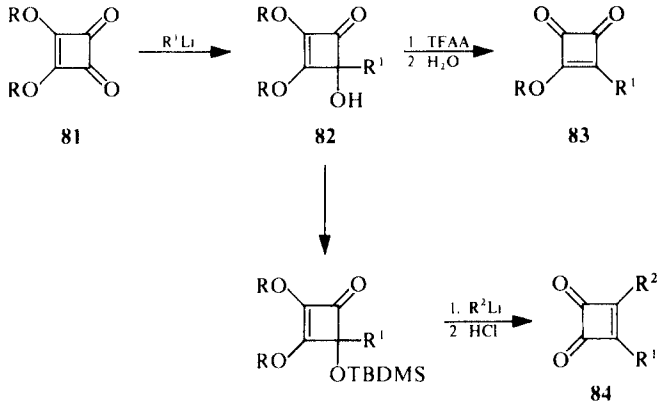
Clearly the success of Scheme 13 depends on the availability of cyclobutenones **79** which are derived from cyclobutenediones **78** by 1,2-addition of an organolithium reagent. Excellent syntheses of these compounds have been provided, again simultaneously by Liebeskind[69] and by Moore,[70] starting from dialkyl squarates **81**, the di-isopropyl analogue **81** ($R = Me_2CH$) being the ester of choice[69] (and now commercially available). In a very convenient one-pot process[70] the squarate is treated with an organolithium, as indicated (Scheme 14), and then quenched with trifluoroacetic anhydride followed by aqueous workup to give the alkoxyalkyl(aryl)cyclobutenedione **83**. Alternatively, **82** can be silylated and treated with a second organolithium reagent which affords, after deprotection, the cyclobutenedione **84**, in which the original alkoxy groups in **81** have been replaced by two different alkyl(aryl) functions. Such compounds enhance the flexibility of Scheme 13, and are of



Scheme 13

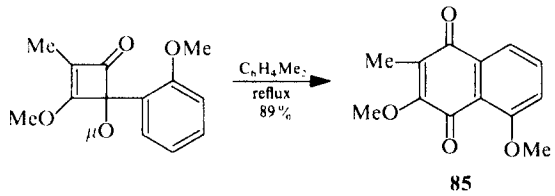
great value in another versatile benzoquinone synthesis[71] which proceeds by converting cyclobutenediones **84** into maleoylcobalt complexes followed by reaction with an alkyne. However, that method has not yet been used to synthesize natural benzoquinones (but see Section 7.C). A good practical synthesis of benzocyclobutenediones is also available.[72]

The general and convergent syntheses outlined in Scheme 13 are a major contribution to synthetic quinone chemistry, and numerous quinones, especially benzoquinones and naphthoquinones, have been produced in this way,



Scheme 14

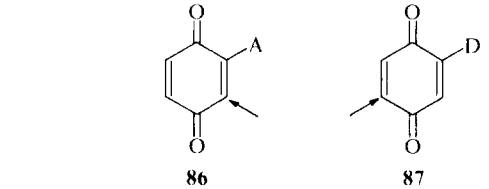
although very few are naturally occurring. A simple naphthoquinone example is that of didroserone methyl ether **85**,[65,73] and others are discussed later. More detailed discussion of the synthesis of nonnatural quinones by hydroxycyclobutenone rearrangement can be found in references 74–76.



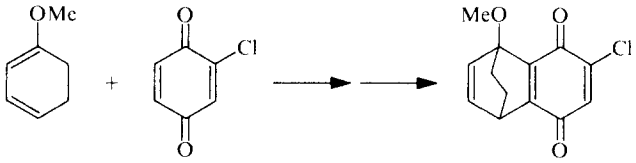
B. Diels–Alder Synthesis

The Diels–Alder reaction has been used extensively for the synthesis of anthraquinones and a handful of natural naphthoquinones have been obtained in this way. The process is direct and convergent, and generally more efficient than the multistage naphthol → naphthoquinone route provided regiocontrol is exercised where required. However, although yields can be very high, they can also be moderate to poor. For a simple compound like 6-methyl-1,4-naphthoquinone (a fungal metabolite[14]), synthesis by addition of isoprene to benzoquinone, and subsequent enolization and oxidation, presents no problems,[77] but when both diene and dienophile are unsymmetrical a mixture of isomers is likely to result. Fortunately this can be avoided in many cases by appropriate substitution of the starting quinone. An electron-acceptor group (A) strongly directs the nucleophilic end of the

attacking diene to the adjacent *ortho* position (arrowed in **86**, in practice A = Cl, Br, or occasionally ArS, ArSO, or $ArSO_2$[78]), whereas if the substituent is an electron-donor (D), the preferred reaction site is at the *para* position (arrowed in **87**, D is frequently Me or MeO). There are numerous examples of these directive effects which are explicable on the basis of charge distribution and are supported by FMO arguments,[79] although there are exceptions for which steric factors may be responsible. Addition of cyclohexadiene **88** to chlorobenzoquinone leads to quinone **89**[80] and Bohlmann[81] cites other examples. Lewis acids can be very effective in the regiocontrol of Diels–Alder reactions, particularly for weakly polarized dienes such as isoprene, but have been little used in the synthesis of natural naphthoquinones (for an example, see Scheme 23).

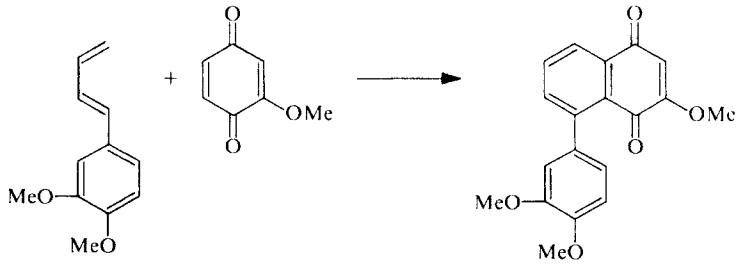


86 **87**



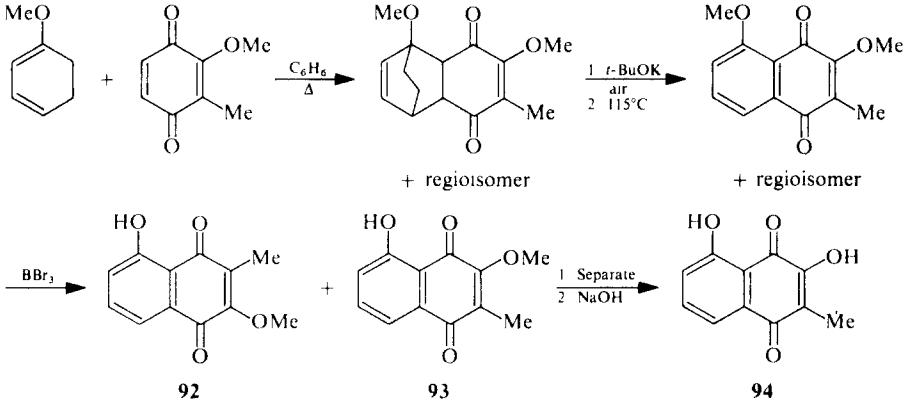
88 **89**

Of the natural naphthoquinones which have been synthesized via Diels–Alder addition, cassumunaquinone 1 **91**, an unusual arylated naphthoquinone found in the rhizomes of *Zingiber cassumunar*,[15] was obtained by addition of diene **90** (available from 3,4-dimethoxybenzaldehyde and an allyl Wittig reagent) to excess methoxybenzoquinone in refluxing xylene, the initial adduct being oxidized by the excess benzoquinone.[82]



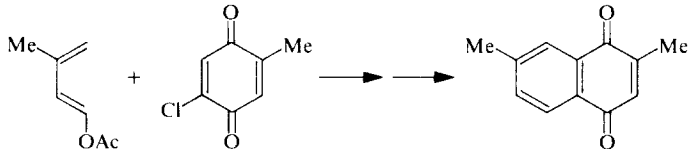
90 **91**

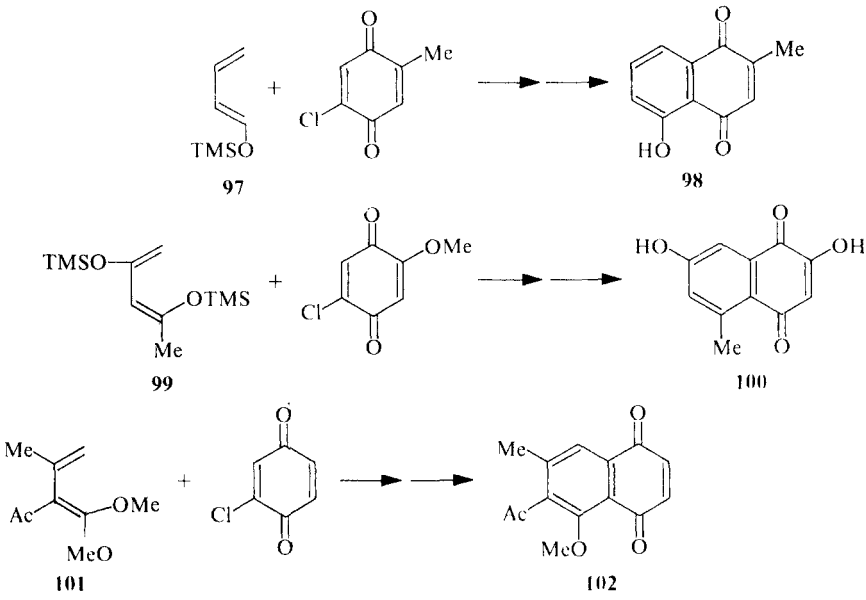
The dienophile used in the synthesis[80] of droserone **94** was 2-methoxy-3-methylbenzoquinone, which has two competing electron-donor substituents, and consequently the initial adduct was a mixture of two isomers. The mixture was carried through to the *peri*-demethylation stage (Scheme 15), when **92** and **93** were separated chromatographically in a 1:4 ratio indicating that the methoxyl group exerted the greater directive effect on the cycloaddition.



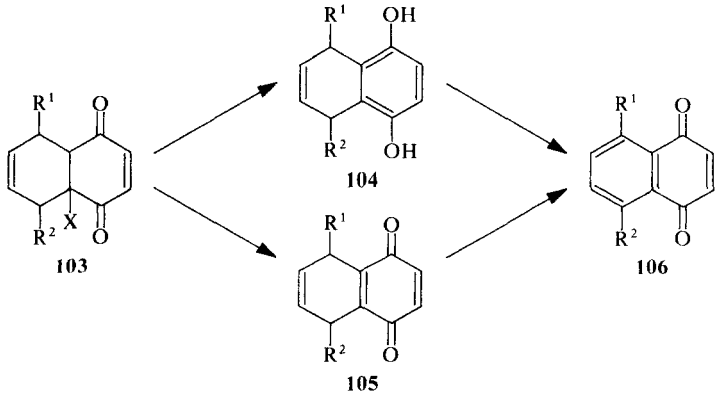
Scheme 15

In general, regiocontrol is more effective when electron-withdrawing groups are used. Examples are the synthesis of chimaphilin **96**[83] and plumbagin **98**[83] from 5-chloro-2-methylbenzoquinone and the appropriate dienes, and of the fungal metabolite 2,7-dihydroxy-5-methyl-1,4-naphthoquinone **100**[84] from 5-chloro-2-methoxybenzoquinone and diene **99**. (Quinone **100** also has been synthesized[85] via autoxidation of 7-methoxy-5-methyltetral-1-one in basic solution.) Stypandrone 5-*O*-methyl ether **102**, however, was only obtained[86] in 19% yield from chlorobenzoquinone as reaction occurred on both sides of the quinone ring.



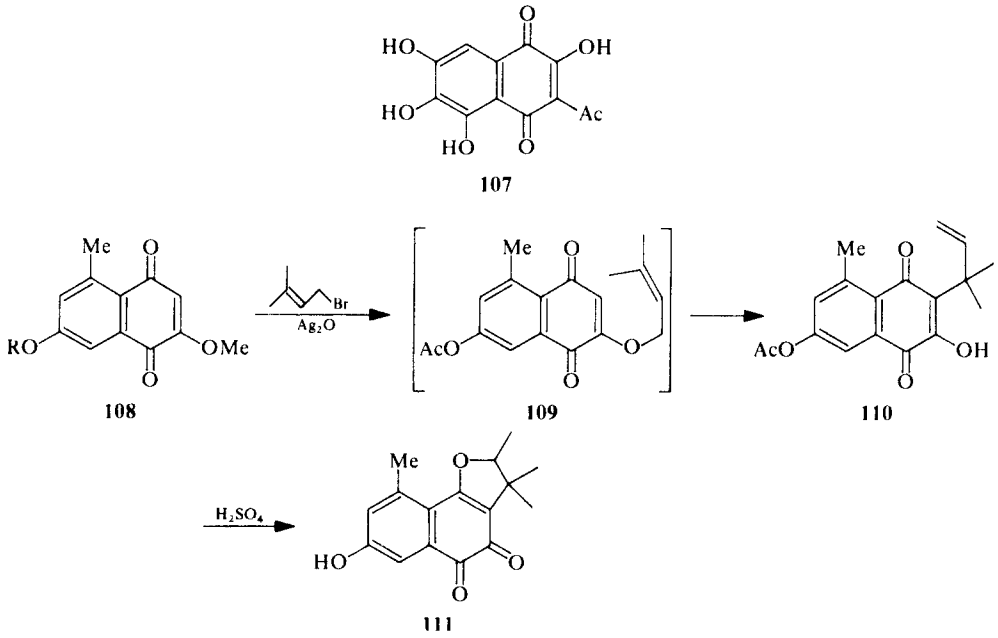


In early work, Diels–Alder adducts **103** (X = H) were converted into the desired quinones **106** by acid- or base-catalyzed enolization followed by oxidation of the dihydrohydroquinone **104**. A further advantage of the use of chloro (etc.) quinones as dienophiles is that the original quinone ring is very easily reformed by loss of HX from **103** (X = Cl, etc.) to give **105**, sometimes spontaneously, by treatment with a base, or merely by filtration through silica.[83] As many natural naphthoquinones have *peri*-hydroxyl/methoxyl groups, the dienes required for synthesis must carry terminal oxygen functions. These may be eliminated spontaneously, on pyrolysis, or on acid



treatment with resulting aromatization (see **99** → **100**). However, when the diene is also a ketal derivative, only one of the oxygen groups is eliminated (see **101** → **102**), and if the terminal oxygen function on the diene is silylated, the initial adduct can be oxidized with Jones' reagent[83] or PCC[87] with retention of the *peri*-substituent (see **98**). The efficiency of such Diels–Alder syntheses obviously depends on easy access to suitable oxygenated butadienes and a large number have been prepared.[196] Further uses of these dienes can be found in Section 4 on anthraquinones.

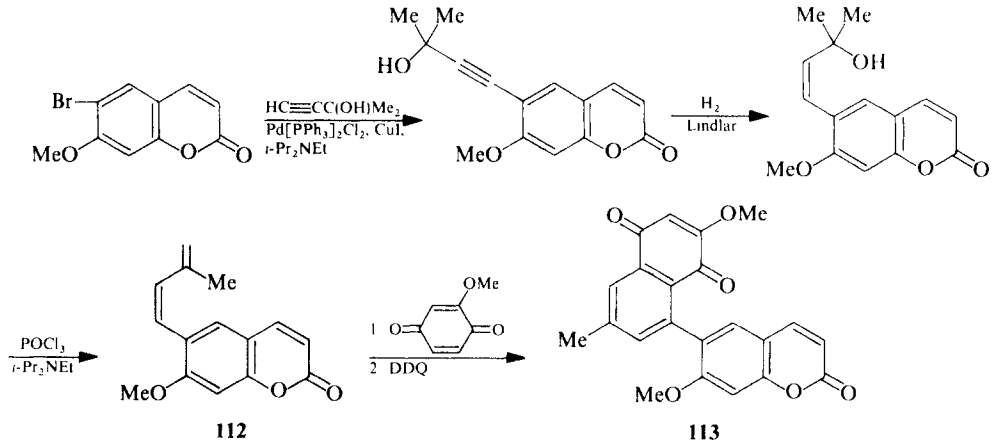
Other natural naphthoquinones synthesized in this way include ramentaceone (7-methyljuglone)[86, 87] directly, and the sea urchin pigment spinochrome S **107**,[91] 7- and 8-hydroxydunnione,[89] and the related lichen metabolite trypethelone **111**[84] by cycloaddition and further manipulation of the resulting quinone. For (±)-trypethelone (Scheme 16), the initial adduct was aromatized by pyrolysis to give quinone **108** (R = H). The acetate **108** (R = Ac) was then treated with prenyl bromide and silver(I) oxide in cold HMPT which gave the *C*-allylquinone **110** in one step. The initial allyl ether **109**, presumably formed by conversion of **108** into the silver salt of the corresponding 3-hydroxynaphthoquinone and reaction with the prenyl bromide, undergoes a spontaneous Claisen rearrangement. On final dissolution of **110** in cold concentrated sulphuric acid it cyclized to (±)-trypethelone **111** (plus a little of the regioisomer). 8-Methoxytrypethelone-7-*O*-methyl



Scheme 16

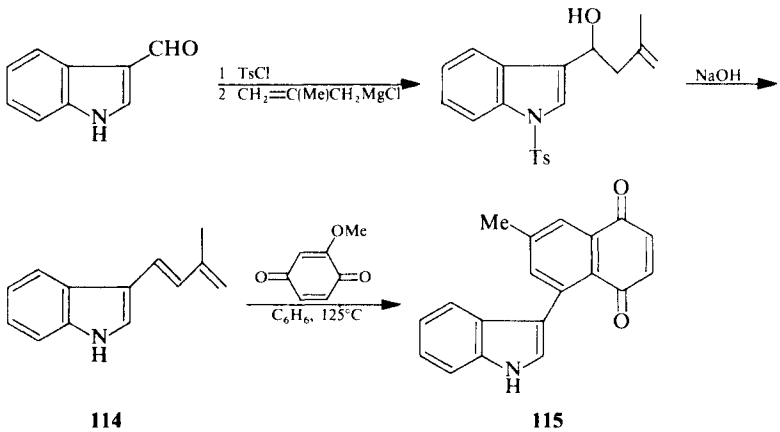
ether, also present in cultures of the mycosymbiont of the lichen *Trypethelium eluteriae*, was synthesized similarly.[84]

The unusual coumarinylnaphthoquinone naphthoherniarin **113**, from the roots of *Ruta graveolens*,[15] and the indolylnaphthoquinone murrapanine **115**, found with other alkaloids in the root bark of *Murraya paniculata*,[92] have both been synthesized by Diels–Alder addition of the appropriate prenyldiene to methoxybenzoquinone. The coumarinyldiene **112** was obtained[93] from 6-bromo-7-methoxycoumarin by a Heck reaction with 2-methylbut-3-yne-2-ol, followed by partial hydrogenation and dehydration (Scheme 17). The prenylindole **114**, derived from indole-3-aldehyde, was heated in a sealed tube with excess of methoxybenzoquinone which acted as both dienophile and oxidant (Scheme 18).[92]



112 **113**

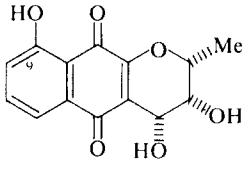
Scheme 17



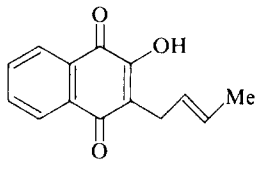
114 **115**

Scheme 18

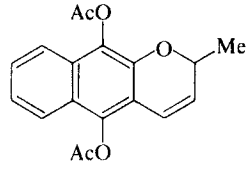
Cryptosporin. Most natural pyranonaphthoquinones carry a gem-dimethyl group at C-2 and are accessible from 2-hydroxy-3-prenylnaphthoquinone precursors. The fungal metabolite cryptosporin[15, 94] **116** with only one methyl group at C-2 is exceptional. Krohn[95] synthesized the (±)-9-deoxy analogue starting from the allylquinone **117**, which was rearranged[14] to the chromenol diacetate **118** with acetic anhydride–sodium acetate. *Cis*-hydroxylation of the olefinic double bond led to the required compound with the correct relative stereochemistry.



116

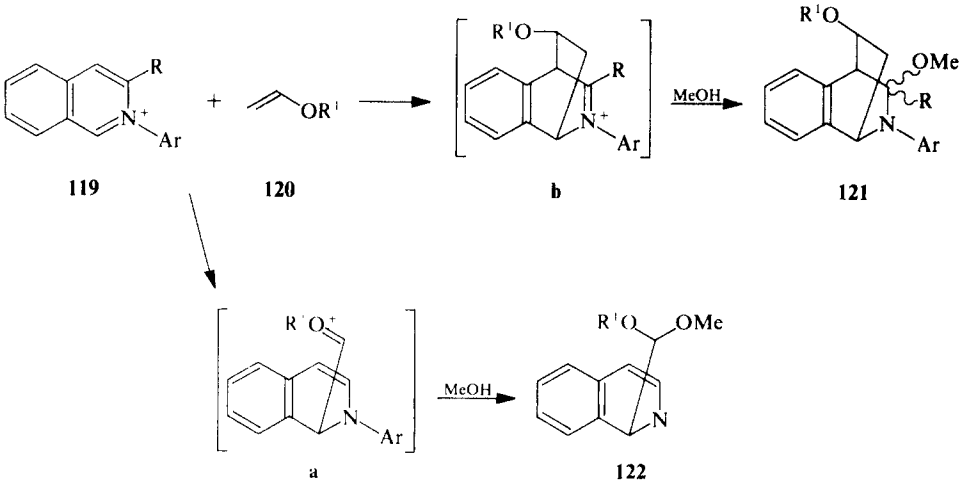


117



118

Gupta and Franck[96] adopted a completely different approach to cryptosporin by making use of the Bradsher reaction. This cycloaddition reaction, previously regarded as an inverse-electron-demand Diels–Alder reaction has been shown[97] to be a two-step process. Bradsher[90] previously observed that addition of a vinyl ether **120** to an *N*-arylisoquinolinium salt **119** (R = Me) gave adduct *b* (R = Me). Gupta and Franck[97] found, using **119** (R = H), that the initial adduct is ion *a*, which cyclizes to *b* (R = H). In methanol solution *b* is isolated as **121** and *a* can be trapped as the acetal **122** (Scheme 19). The



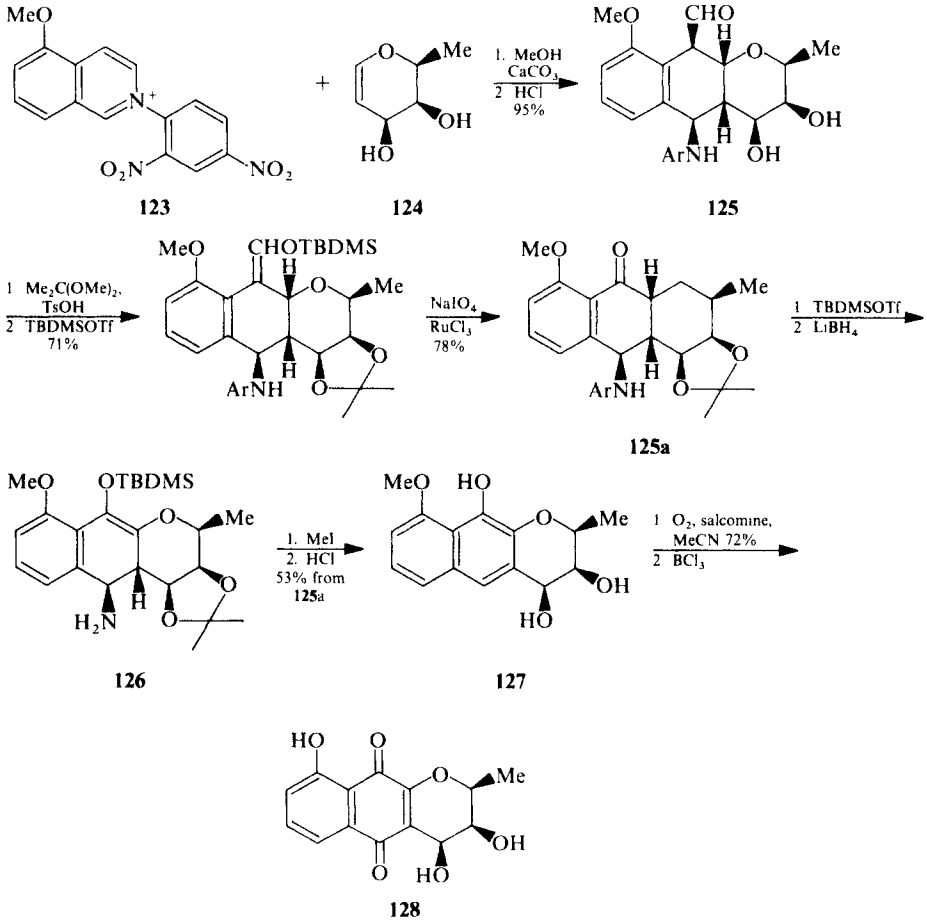
119 **120** **b** **121**

a **122**

Scheme 19

cycloaddition is regiospecific and remarkably stereospecific, and is an attractive synthetic route to highly substituted tetralins and products derived therefrom such as 1-naphthaldehydes.[99]

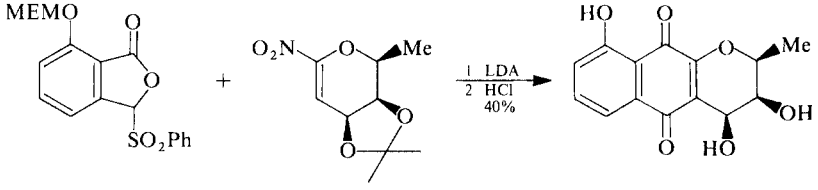
In the cryptosporin synthesis[96] (Scheme 20) the key step is the Bradsher cycloaddition of the enol L-fucal **124** to the isoquinolinium salt **123**, followed by acid treatment to open the *N*-heterocyclic ring. The resulting aldehyde **125** (95%) includes the whole of the cryptosporin skeleton. Remarkably, it was isolated as homogeneous material containing seven chiral centers. The "extra" aldehyde function was then eliminated after protecting the glycol, by 'conversion[100] to the silyl enol which was cleaved with sodium



Scheme 20

periodate–ruthenium trichloride.[101] After a second enol silylation the unwanted arylamine function was removed by reductive cleavage of the dinitrophenyl group, followed by a modified Hofmann elimination of the amino group in **126**. A final salcomine-catalyzed oxidation of the naphthol **127** and demethylation gave (−)-cryptosporin **128**, identical in all respects to the natural product except for opposite optical rotation and CD spectrum. The absolute configuration had been deduced[94] from the Cotton effect of the 3,4-dibenzoate according to the exciton-chirality rules,[102] but the interaction of the naphthoquinone chromophore with the 4-benzoate was overlooked and this is the dominating factor. Natural (+)-cryptosporin therefore has the revised structure **116**.

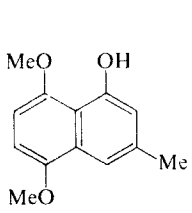
Following the Gupta–Franck synthesis, a much shorter and very attractive route to *ent*-cryptosporin was published by Brade and Vasella[98] in which the complete structure was neatly assembled using Hauser's phthalide annulation procedure, and the pyrone ring was again derived from an L-fucose derivative. Phthalide **129** and the nitroglycal **130** were obtained by standard procedures from *N*,*N*-diethyl-2-methoxybenzamide and L-fucose, respectively, and coupled by Michael addition to give *ent*-cryptosporin **128** directly, after deprotection.



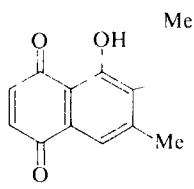
129 **130** **128**

C. Juglone Dimers

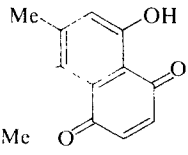
A number of naturally occurring naphthoquinones are dimers (strictly dehydro-dimers), and the majority, found mainly in the Ebenaceae and the Plumbaginaceae, are related to the monomers ramentaceone (7-methyljuglone) **134** and plumbagin (3-methyljuglone) **98**. *In vivo* dimerization probably occurs by phenolic coupling, which in principle can also be used for *in vitro* synthesis. In practice, this method has been little used for juglone-type dimers; one example is the preparation[103] of the unsymmetrical dimer isodiospyrin **132** via oxidation of naphthol **131** with silver(I) oxide. The product was a mixture of two binaphthols in low yield, attributable to steric hindrance. After acetylation CAN oxidation led to the biquinones **132** and **133**.

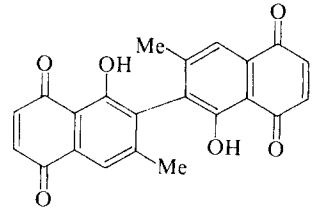


131



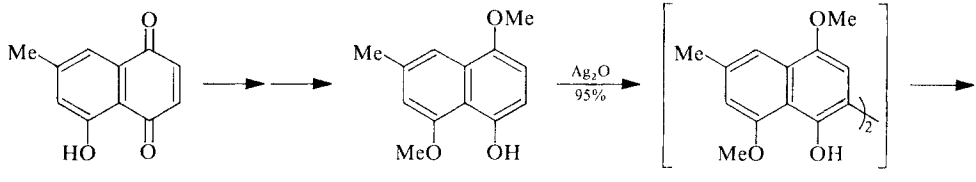
132





133

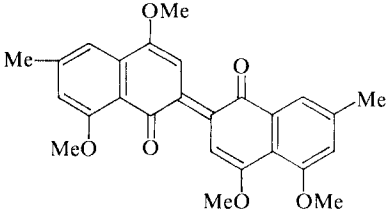
Two other methods are useful for symmetrical dimers. Laatsch[104] has published a two-step oxidative method applicable to 4-substituted-1-naphthols, particularly 4-methoxy-1-naphthols which are very easily oxidized, illustrated below for mamegakinone **138**. Naphthol **135**, derived from the monomeric quinone **134** by a methylation–reduction–methylation (CH_2N_2) sequence, was oxidized with silver(I) oxide, the initial dimer **136** rapidly undergoing further oxidation to the extended quinone **137**. Brief treatment with nitric acid then afforded the bi-1,4-quinone which was demethylated. Other natural binaphthoquinones obtained by this route in excellent yields include 3,3′-bijuglone,[104] biramentaceone,[104] and the diomelquinone A dimer **139**.[105]



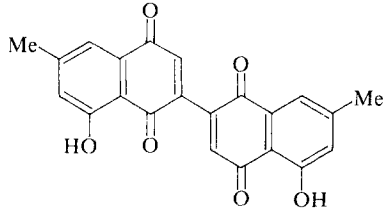
134

135

136



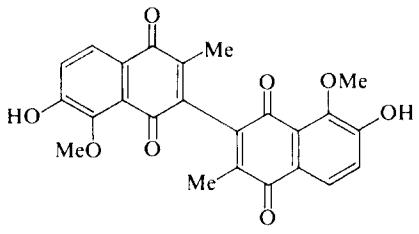
137



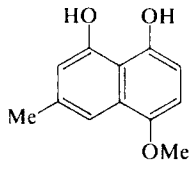
138

Two extended *o*-naphthoquinones of type **137** occur naturally in the Ebenaceae along with dimers of type **138**, and have been synthesized in the same way. Thus the blue pigment diosindigo A **141** was obtained by oxidation[104, 106] of naphthol **140**, derived[106] from **134** by reductive monomethylation using stannous chloride and phosphoryl chloride in methanol,[107] with silver(I) oxide,[104] lead(IV) oxide,[106] or air.[108] It is noteworthy

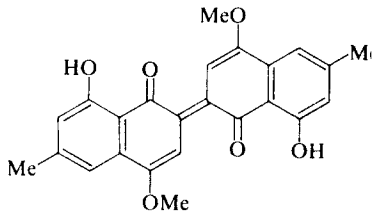
that the hydroxyl group *para* to methoxyl is much more readily oxidized than the other, indeed the parent 4-methoxy-1-naphthol is difficult to store in air and soon turns blue.



139

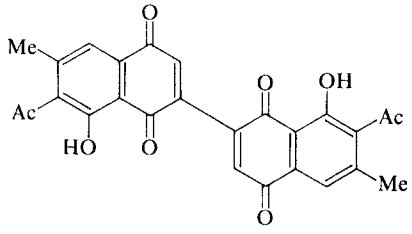


140

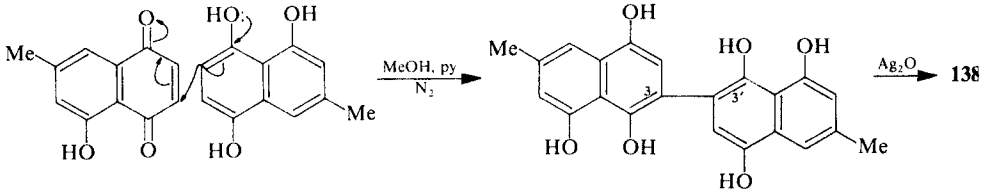


141

The symmetrical dimers 3,3′-bijuglone, mamegakinone **138**, and di-annellinone **142** have been synthesized by another oxidative route.[109] For mamegakinone the starting material is the monomeric quinone **134**, which was allowed to react with an equivalent amount of the hydroquinone **143** in methanol–pyridine in the absence of air, and the resulting dimer **144** was then oxidized with chloranil or silver(I) oxide. The procedure is very convenient if the parent quinone is available. Although oligomers are also formed, the yields are surprisingly high (66% for **138**, 94% for **142**), and the reaction is remarkably regiospecific with predominant 3,3′-coupling. If the coupling is conducted in acetic acid using a higher ratio of quinone **134** to hydroquinone **143**, the reaction continues further and the unsymmetrical trimer, isoxylo-

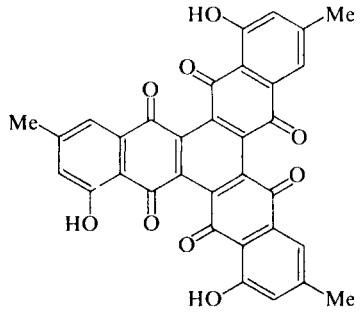


142

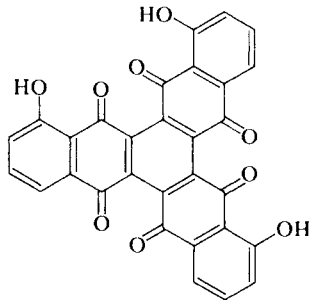


134 143 144

spyrin **145**, found in *Diospyros galpinii*,[15] can be isolated in 38% yield.[109] Introduction of the third monomer unit must entail coupling at two positions in the hydroquinone **144**. The unsymmetrical cyclo-trimers cyclo-trijuglone **146** and trianellinone (both natural compounds) can be obtained in the same way.[109]



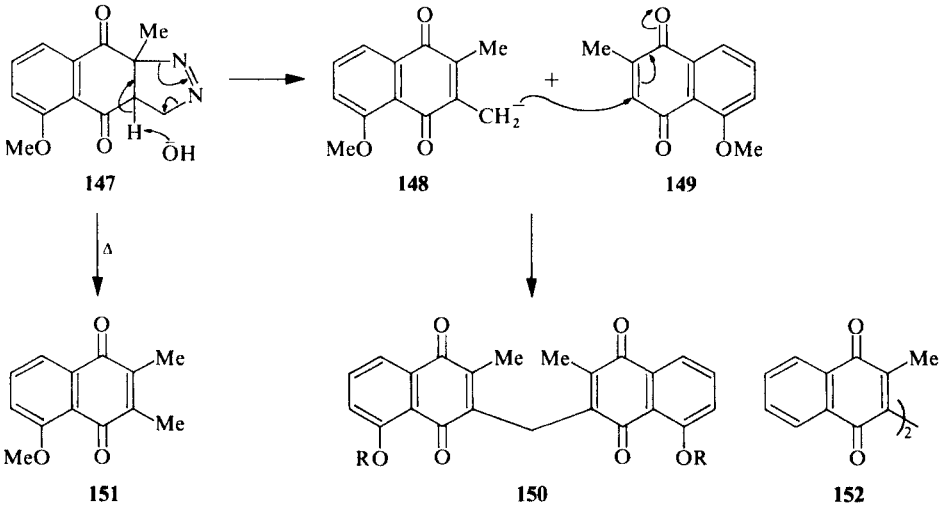
145



146

Numerous naphthoquinone dimers, including the natural compounds maritinone,[110] elliptinone,[103] and euclanone[111] have been synthesized from appropriate naphthols using a combination of oxidation methods and the initial dimers can be modified in various ways.[112, 113]

One of the quinones in *Plumbago zeylanica*[15] is the biquinone **150** (R = H) in which the quinone units are linked by a methylene group. The dimethyl ether of methylene-3,3′-biplumbagin **150** (R = H) was obtained[114] from plumbagin methyl ether **149** following Dean's[115] procedure. Cycloaddition of



147 **148** **149**

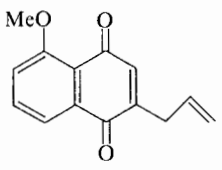
151 **150** **152**

diazomethane to **149** is regiospecific and yields the indazole **147**; on treatment with base in the presence of **149**, nitrogen is eliminated and the resulting anion **148** combines with **149** by nucleophilic addition. Thermolysis of indazoles of type **147** in boiling toluene also eliminates nitrogen to give, mainly, products of type **151** and small amounts of the cyclopropane isomers. This method of *C*-methylation has been used to convert 3,3′-bijuglone into 3,3′-biplumbagin,[112] and the parent 2,2′-1,4-binaphthoquinonyl into the fern metabolite **152**[116] found in *Asplenium laciniatum*.[117]

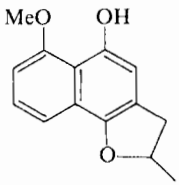
D. Benzoisochromanquinones

The first members of this group to be identified were eleutherin **156** and the *trans*-isomer isoeleutherin **157**. They were found in the tubers of *Eleutherine americana* by Schmid[118] who announced their synthesis[119] a few years later. Others have since been discovered in higher plants,[14, 15] particularly in the Rhamnaceae, and in microorganisms,[14, 15] especially Streptomyces. As several of them show significant antibiotic and antifungal activity, they have become of considerable synthetic interest, and the bacterial metabolites, deoxyfrenolicin, kalafungin, the nanaomycins, and the griseusins have been elaborated by several routes; the eleutherins have also been synthesized several times.

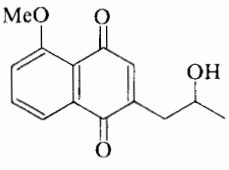
Eleutherins. The original synthesis[119] started from 5-methoxy-1-naphthol, which was converted into the allylquinone **153** and then into the hydroxypropylquinone **155** by reduction, cyclization to the dihydrofuran **154**, and reoxidation. Condensation of **155** with acetaldehyde in acidic conditions gave



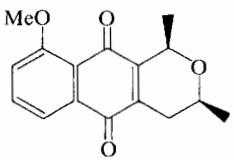
153



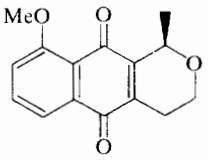
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155



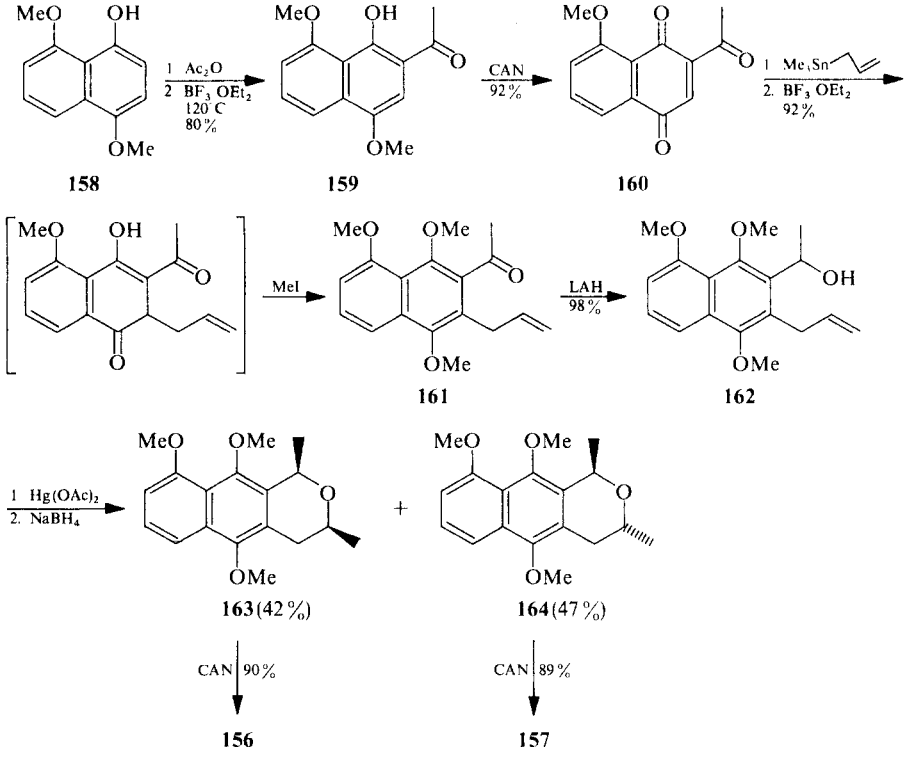
156



157

a separable mixture of (±)-eleutherin **156** and (±)-isoeleutherin **157**. This became the pattern for several of the later syntheses, namely formation of an 8-methoxy-1,4-napthoquinone or related naphthalene carrying a C_2 side chain at C-2 and a C_3 side chain at C-3, followed by cyclization, usually without stereocontrol. Cameron's[120] synthesis of the (±)-7-methoxy-eleutherins (the *cis* isomer occurs in the seeds of *Karwinskia humboldtiana*[15]), followed the Schmid route starting from 5,7-dimethoxy-1-naphthol. The *cis*:*trans* ratio was 3:1. However the *trans* isomer is thermodynamically more stable and when the pure *cis* compound was left in 90% phosphoric acid, it equilibrated to give a *cis*:*trans* mixture in the ratio ~ 1:4 (after separation). In pyranoquinones of this type both isomers can always be obtained by equilibration, so the lack of stereocontrol at the cyclization stage is of little consequence. The isomers are easily recognized from NMR data.

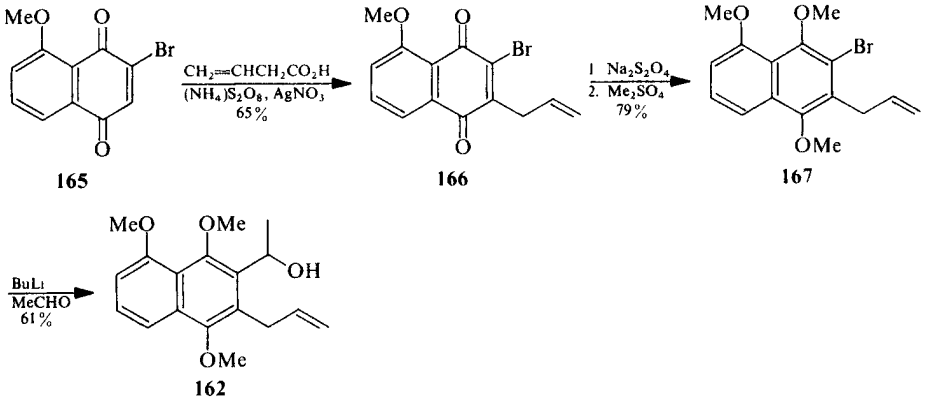
A high-yielding synthesis of the eleutherins has been devised by Naruta, Uno, and Maruyama,[121] the substituted naphthalene **162** being the key intermediate (Scheme 21). Starting from naphthol **158**, the C-2 side chain



Scheme 21

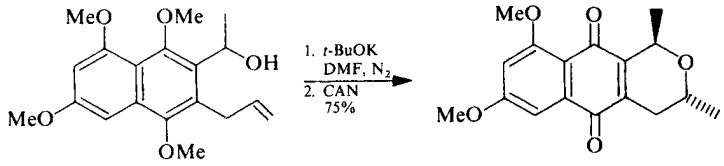
(**159**) was introduced by a Fries rearrangement, and the C-3 side chain by efficient allylation of quinone **160** by the allylstannane method.[122] Cyclization of the alcohol **162** by intramolecular oxymercuration, followed by borohydride reduction, gave the pyran isomers **163** and **164**, which were separated by chromatography. The acetyl group in **160** plays a useful role in enhancing the nucleophilicity of C-3 for the following Michael addition as well as providing the pyran ring oxygen.

Another Japanese synthesis[123] followed a similar route to **162**, but yields were lower. Starting from the bromojuglone methyl ether **165** (available from 1,5-dihydroxynaphthalene[124]), a free-radical alkylation was effected using vinylacetic acid and persulphate–silver ion,[125] and after converting **166** to the naphthalene **167**, the second side chain was introduced by lithiation and treatment with acetaldehyde.



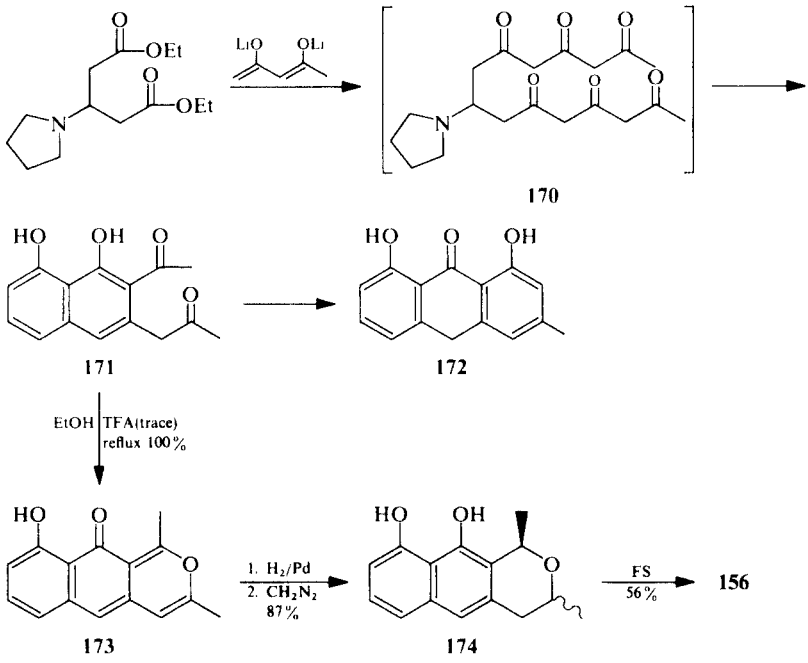
165 **166** **167** **162**

In contrast to earlier methods, Giles[126] discovered a new way to cyclize alcohol **162** which provided the *trans*-isomer **164** exclusively (88%), and thus isoeleutherin **157** after CAN oxidation. This stereospecific intramolecular nucleophilic attack on an unactivated double bond was achieved by brief treatment of alcohol **162**, in dimethylformamide, with potassium *t*-butoxide. In the same way the tetramethoxy analogue **168** was converted into *trans*-7-methoxyisoeleutherin **169** (the natural compound is the *cis*-isomer[127]).

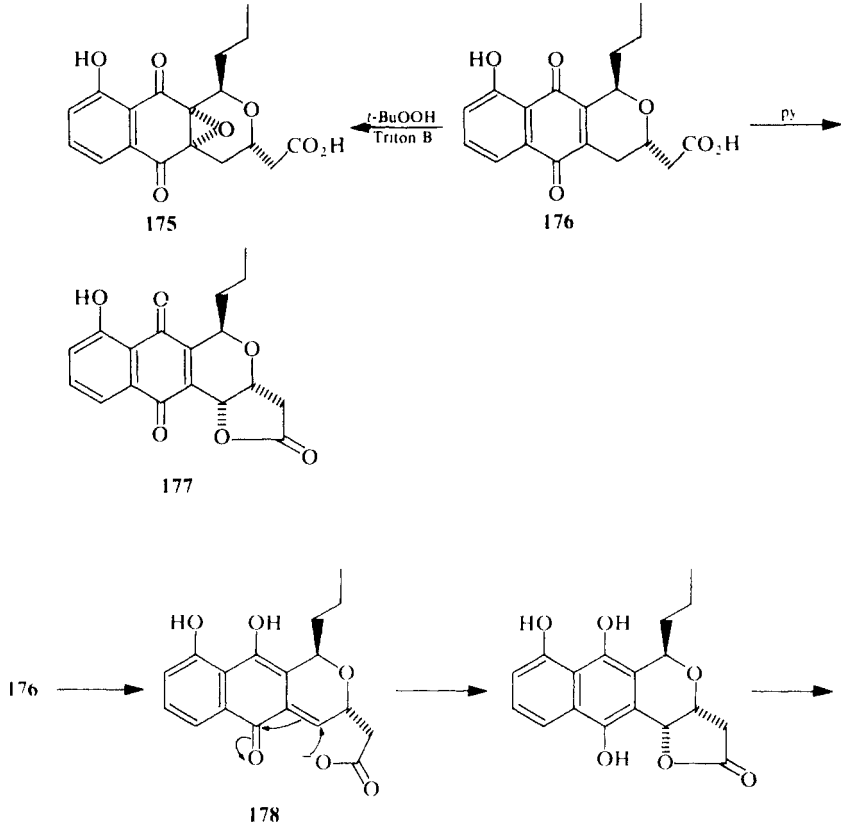


168 **169**

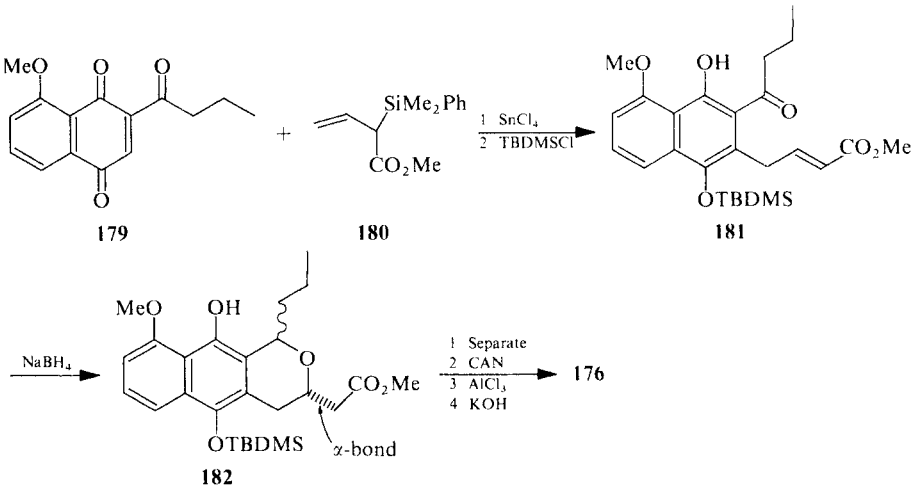
An interesting route to the eleutherins involves the use of β-polycarbonyl compounds. Harris[128] has prepared numerous polyketide aromatic compounds by this biomimetic method and for the eleutherins he made use of the β-polyketone precursor **170** originally devised for the synthesis of the anthraquinone chrysophanol. Previously, it was found that treatment of the diketone **171** with base gave the anthrone **172**, but on changing to acidic conditions cyclization occurred without involving a methyl group to form the pyran **173** with remarkable efficiency. Hydrogenation and monomethylation, in the dark, then gave **174** (*cis*:*trans* ratio ~ 9:1), and the final oxidation with Fremy's salt afforded (±)-eleutherin **156** with only slight contamination by its isomer **157**.[129]



Frenolicin, Deoxyfrenolicin, Frenolicin B. In this group synthetic work has been concentrated on deoxyfrenolicin **176**, which can be converted into frenolicin **175** and frenolicin B **177**. Epoxidation of (±)-deoxyfrenolicin, as indicated, gave a 1:1 mixture of (±)-frenolicin **175** and its epoxy epimer, which were separated as their methyl esters.[130] Conversion of deoxyfrenolicin into the lactone, frenolicin B **177**, occurs on keeping in pyridine overnight, presumably by intramolecular nucleophilic addition of the quinone methide isomer **178**.[131]



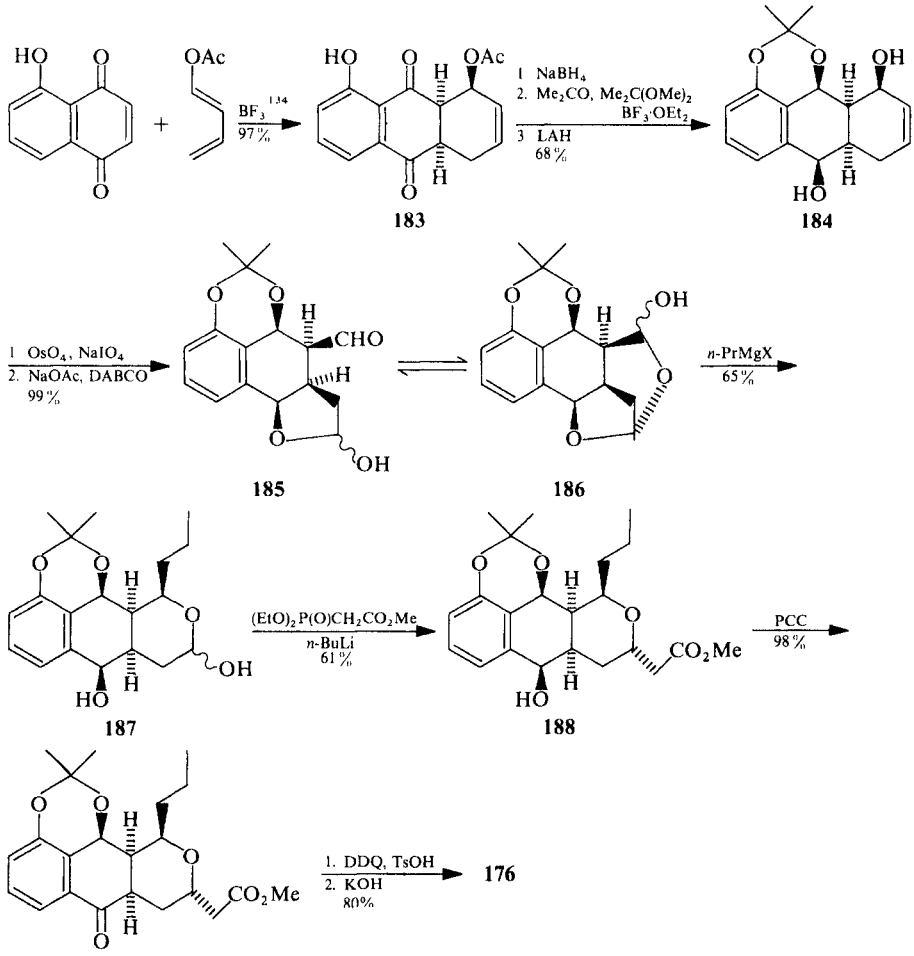
A short and very efficient synthesis of deoxyfrenolicin is that of Naruta, Uno, and Maruyama,[132] which follows essentially the same route as their synthesis of the eleutherins. (±)-Deoxyfrenolicin was obtained in 43% overall yield starting from the butanoylquinone **179**, itself derived from the naphthol **158** as for the acetylquinone **160** (Scheme 22). The second C_4 side chain was introduced by allylation with the silylated butenoate **180** and the hydroxyl group at C-4 was immediately protected (**181**) to prevent cyclization onto the allylic side chain. Reduction of the ketone with excess of sodium borohydride gave the alcohol, followed at once by Michael addition to the enoate side chain to form the pyran isomers **182** (*cis*:*trans* ratio 2:5). After chromatographic separation, oxidation and demethylation provided (±)-deoxyfrenolicin **176** and its *cis* isomer. The methyl ester of the *cis* isomer epimerized in cold concentrated sulphuric acid to give mainly the required *trans* ester.



Scheme 22

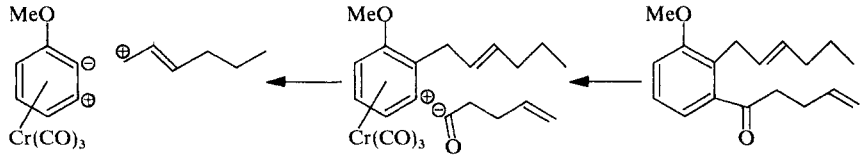
The first synthesis of deoxyfrenolicin (Ichihara[130]) followed a completely different strategy. The cyclohexene ring of the Diels–Alder adduct **183**[134] of 1-acetoxybutadiene and juglone was cleaved to provide a tetralin with two short *ortho* side chains, which were then extended in a highly stereospecific manner (Scheme 23). Sodium borohydride reduced the chelated carbonyl of **183** regio- and stereoselectively (100%), and after formation of the acetonide further reduction with lithium aluminum hydride afforded the diol **184**. Periodate cleavage, followed by treatment with base to effect a reverse aldol reaction, gave the aldehyde **185** in equilibrium with the hemi-acetal **186**. This epimeric mixture was used for the synthesis of both nanaomycin A **216** and deoxyfrenolicin **176**. For the latter, a Grignard reaction introduced the propyl side chain with concomitant formation of the pyran ring **187**, and the other side chain was put in place by a Wittig–Horner reaction which yielded **188**.

The syntheses of deoxyfrenolicin discussed so far start from a naphthoquinone and then elaborate the pyran system. Other routes have been developed which start from a benzenoid precursor. One of these, due to Semmelhack,[135] starts from *o*-bromoanisole and makes use of an arene–chromium complex for the introduction of side chains from which the other two rings are constructed (Scheme 24). η^6-Arene-Cr(CO)$_3$ complexes are useful[136] for a variety of carbon–carbon coupling reactions including substitution *ortho* to a methoxyl group via metalation, and direct *meta*-substitution with carbon nucleophiles.[137] The last steps of the retrosynthesis below outline the strategy for side-chain assembly, an obvious weakness

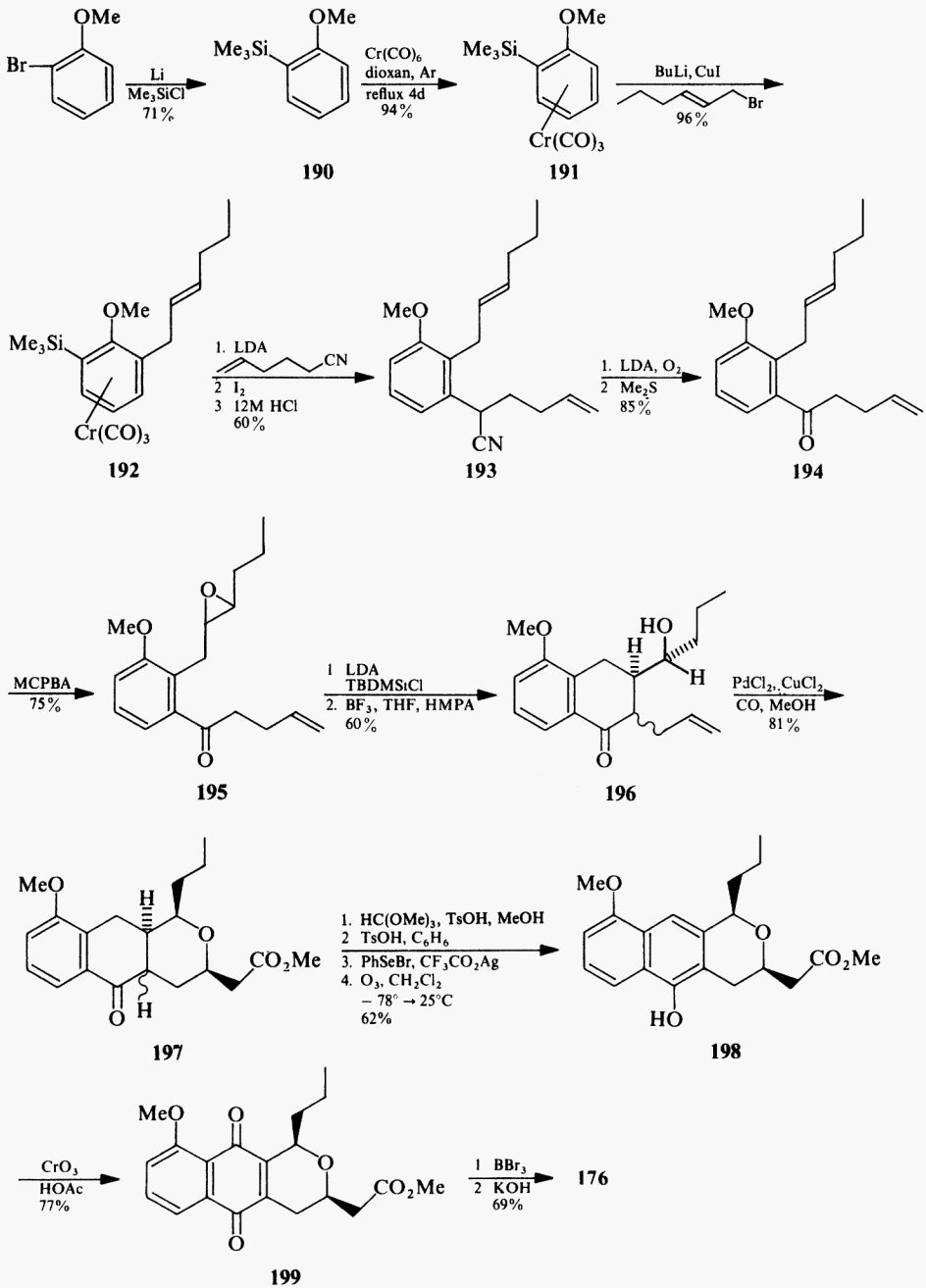


Scheme 23

being that in the actual synthesis the intermediate **189** would have two positions *meta* to the methoxyl group which are not equivalent. That problem was overcome by inserting an *o*-trimethylsilyl group (see **190**) which is strongly *para*-directing, and easily introduced and removed.[138]



189

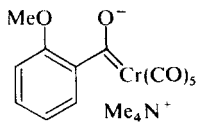

OMe
Br
Li
Me3SiCl
71%
Me3Si
Cr(CO)6
dioxan, Ar
reflux 4d
94%
Cr(CO)3
BuLi, CuI
96%
Br
190
191
1. LDA
2 I2
3 12M HCl
60%
CN
MeO
1. LDA, O2
2 Me2S
85%
O
192
193
194
MCPBA
75%
1 LDA
TBDMSiCl
2. BF3, THF, HMPA
60%
HO
H
PdCl2, CuCl2
CO, MeOH
81%
195
196
1. HC(OMe)3, TsOH, MeOH
2 TsOH, C6H6
3. PhSeBr, CF3CO2Ag
4. O3, CH2Cl2
– 78° → 25°C
62%
CO2Me
197
198
CrO3
HOAc
77%
1 BBr3
2 KOH
69%
176
199

Scheme 24

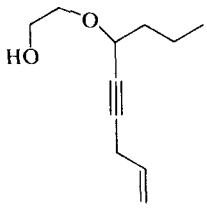
The C_6 electrophilic synthon was (*E*)-2-hexenyl bromide, which reacted very efficiently with **191**, after lithiation and copper replacement, forming **192** (Scheme 24). For the C_5 carbonyl nucleophilic synthon required for the second side chain, lithiated 5-cyanohex-1-ene was found convenient, and after oxidation with excess of iodine and proto-desilylation, **193** was obtained in 60% yield, giving the ketone **194** after oxidative decyanation.[139] With both side chains in place, two cyclizations are now required. The first was achieved by selective epoxidation of the disubstituted double bond, formation of the enol silyl ether, and treatment with boron trifluoride to give **196** as a mixture of *cis* and *trans* isomers. The second cyclization was combined with palladium-catalyzed carbonylation, model experiments showing that this intramolecular alkoxy-carbonylation proceeds with remarkable stereospecificity, the pure *cis* form of **196** giving **197** as a single diastereoisomer (81%), while the isomeric *cis–trans* mixture of **196** gave **197** as a epimeric mixture (87%). Aromatization of the central ring of **197** was difficult, and eventually a multistep procedure led to the α-phenylselenoxide which fragmented at 25°C to form **198**. Jones oxidation converted naphthol **198** into the *cis*-quinone **199**, which on demethylation simultaneously equilibrated to the *trans*-isomer (±)-deoxyfrenolicin methyl ester.

Another Semmelhack organometallic synthesis[140] of deoxyfrenolicin also starts from *o*-bromoanisole. It involves the cycloaddition of an alkyne to a carbene–chromium complex, but a rather elaborate procedure was required to maintain regioselectivity by an intramolecular process. Some interesting chemistry was revealed. Reaction of *o*-lithioanisole and chromium hexacarbonyl gave a product isolated as the salt **200**. Conversion to the acetate followed by reaction with the alcohol **201** afforded the complex **202** (88%), which on prolonged heating in ether cyclized to the naphthalene complex **203**. Oxidation of the crude product with DDQ afforded the quinone **204** (51%), and surprisingly it lost the unwanted side chain by simple treatment with aqueous acid to give the ketohydroquinone **205** (95%). This can be explained[140] by tautomerization of **204** to the quinone-methide **206**, ketal formation of **207**, and hydrolysis. Reduction of ketone **205** to the alcohol followed by alkoxycarbonylation gave the pyran isomers **208** (*cis*:*trans* ratio 1:3), and the major *trans* component was converted to (±)-deoxyfrenolicin.

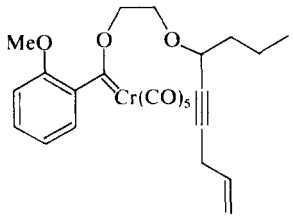
A more direct synthesis starting from a benzenoid precursor is due to Kraus[141] using Hauser's phthalide annulation methodology. (±)-Deoxyfrenolicin was obtained very efficiently in only seven steps from phthalide **209**.[142] The butanoylquinone **179** was secured in only two steps (Scheme 25). Diels–Alder addition of diene **210** (derived from ethyl crotonate) gave **211**, which on treatment with fluoride ion underwent a retro-Claisen reaction leading to **212**, which immediately cyclized to **213**. In the next step CAN oxidation produced the quinone with simultaneous formation of a pyran



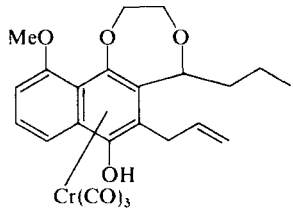
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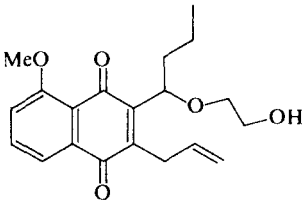
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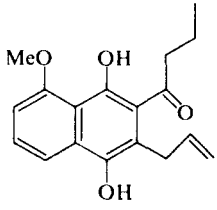
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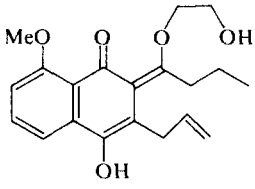
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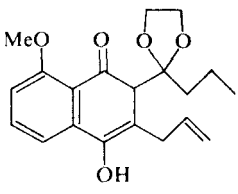
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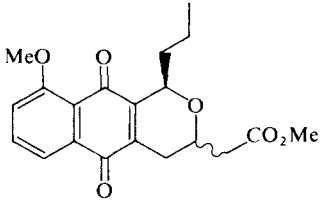
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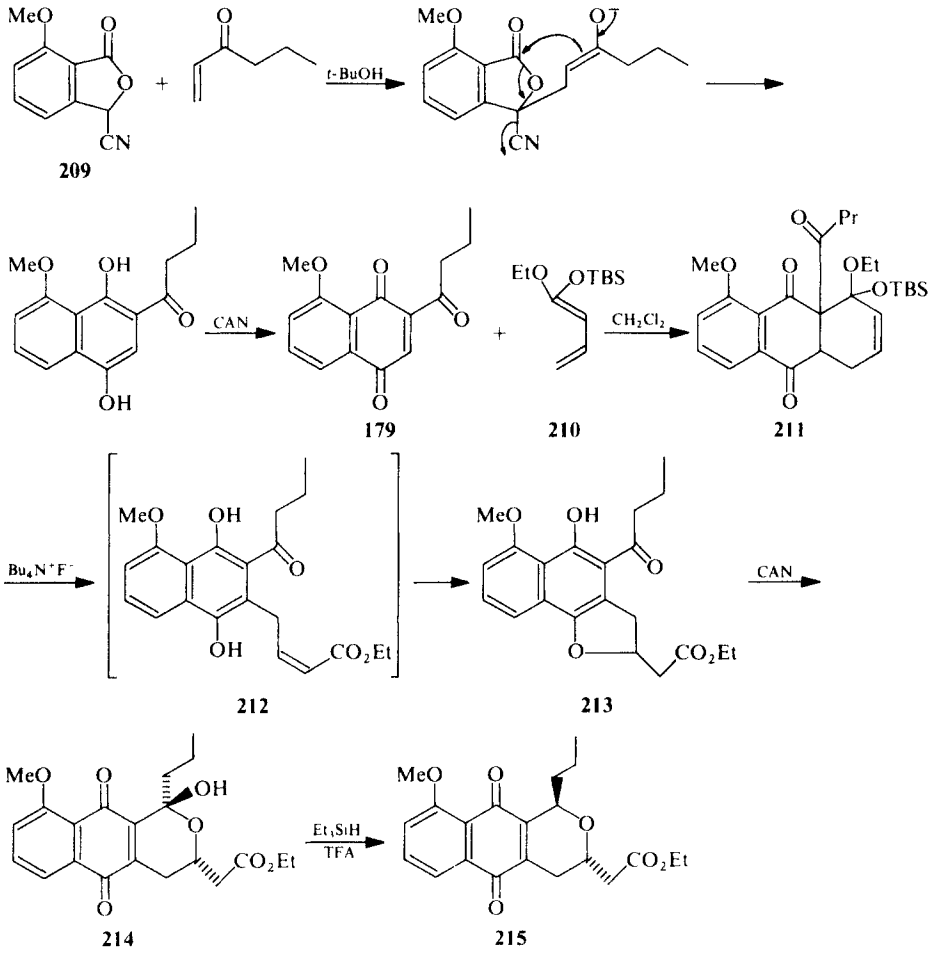


207



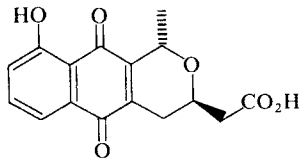
208

ring, and the hemiketal **214** was isolated as a single entity (structure confirmed by X-ray analysis), in overall yield of 32% from phthalide **209**. Model experiments showed that reduction of such hemiketals to pyrans can be achieved by ionic hydrogenation with a marked preference for the production of *cis* isomers indicating axial delivery of hydride ion from triethylsilane. In the event reduction of **214** proceeded in high yield to form quinone **215** only, which had previously been converted into (±)-deoxyfrenolicin **176**. Kraus has also synthesized nanaomycin A **216** by the same route.[141]



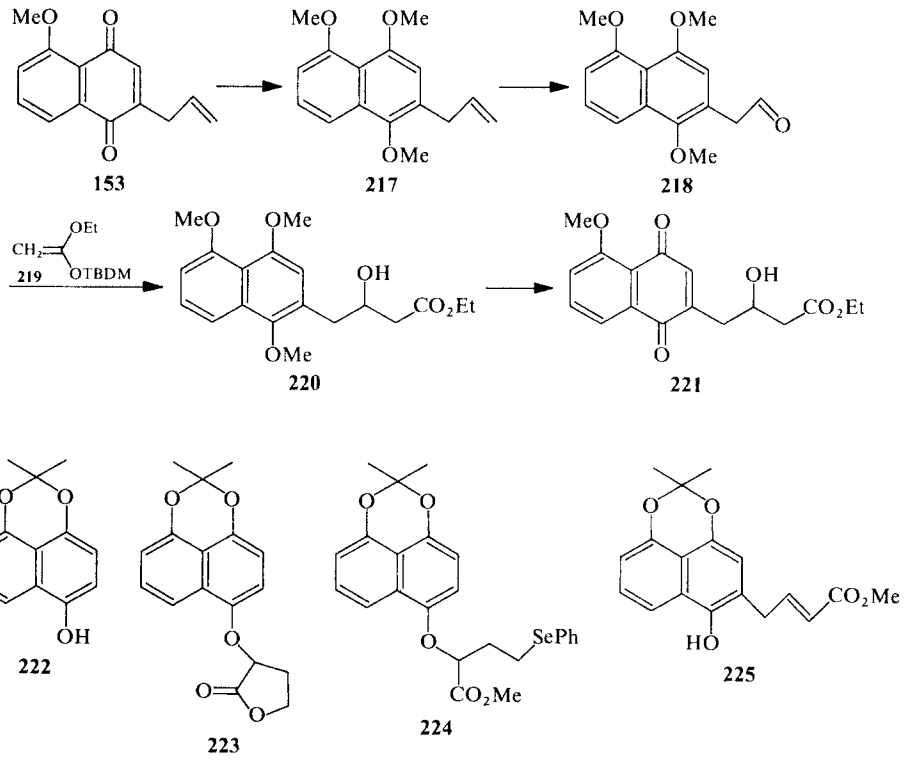
Scheme 25

Nanaomycin A. As already mentioned, some of the synthetic routes to deoxyfrenolicin have also been adopted for the synthesis of its close relative nanaomycin A **216**; other methods have been developed for nanaomycin A synthesis and likewise some of these are applicable to deoxyfrenolicin. The first synthesis of nanaomycin A (Li and Ellison[143]) was a variation of Schmid's original eleutherin route starting from the same quinone **153**. Reduction and methylation gave the allylnaphthalene **217** whence a two-stage oxidative cleavage afforded the aldehyde **218**. Chain extension to the hydroxy ester **220** was achieved by reaction with the ketene acetal **219**, and



216

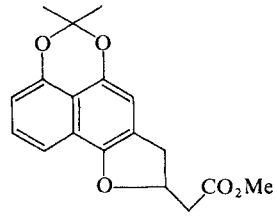
then a CAN oxidation provided the quinone **221** in 21% yield from quinone **153**. The remaining steps followed known procedures. The *O*-demethyl analogue of quinone **221** has been prepared by a different approach.[144] The protected hydrojuglone **222** was converted into **223** by reaction with α-bromo-γ-butyrolactone, and then treatment with phenyl selenolate opened the lactone ring to give the ester **224**, after methylation. Next, a terminal double bond was introduced via the selenoxide. The resulting allyl ether suffered a Claisen rearrangement on heating to form the unstable ester **225**, which cyclized to the dihydrofuran **226** under mild alkaline conditions. Oxidation with silver(II) oxide converted **226** into *O*-demethyl **221**.



153 217 218

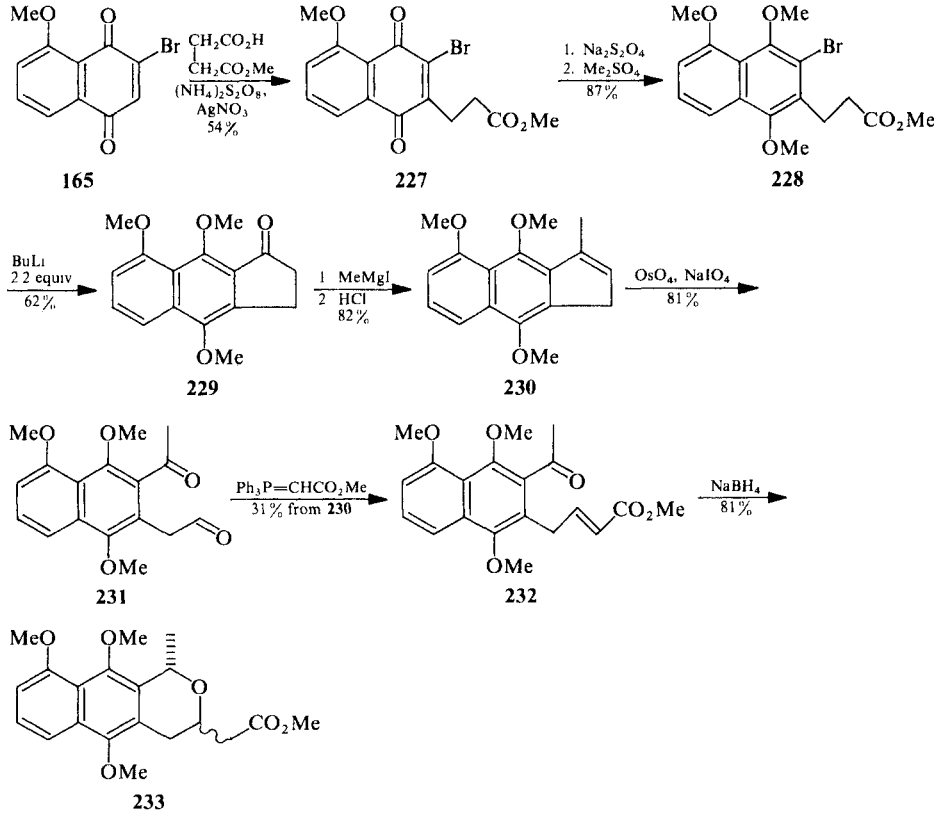
220 221

222 223 224 225



226

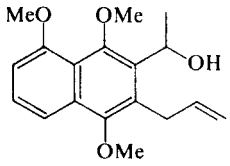
Yoshii[123] has also synthesized (±)-nanaomycin A by a different route, whereby a naphthoquinone was converted into a benzindanone and then back into a quinone with two side chains (Scheme 26). Starting again from quinone **165** it was subjected to free radical alkylation to form **227**, which cyclized via **228** to the indanone **229**. This was cleaved to the keto-aldehyde



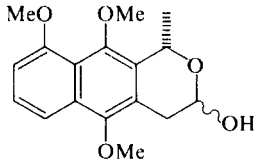
Scheme 26

231, and then a Wittig reaction was carried out selectively with the aldehyde function to form the ester **232** as the homogeneous *trans* isomer (31% from **230**). Reductive cyclization of **232** provided the *cis* and *trans* isomers (ratio 1:1.9) of **223**, which were separately converted to (±)-nanaomycin A **216** and its *cis* isomer.

In the same paper Yoshii[123] reported an alternative route to nanaomycin A utilizing the alcohol **162**. Periodate cleavage of the double bond gave the lactols **234**, whence a Wittig–Horner reaction with trimethylphosphonoacetate and sodium hydride again gave the pyran isomers **233** (*cis*:*trans* ratio 2.1:1).

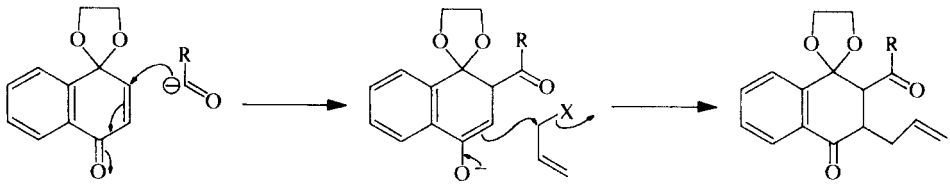


162

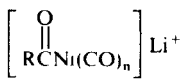


234

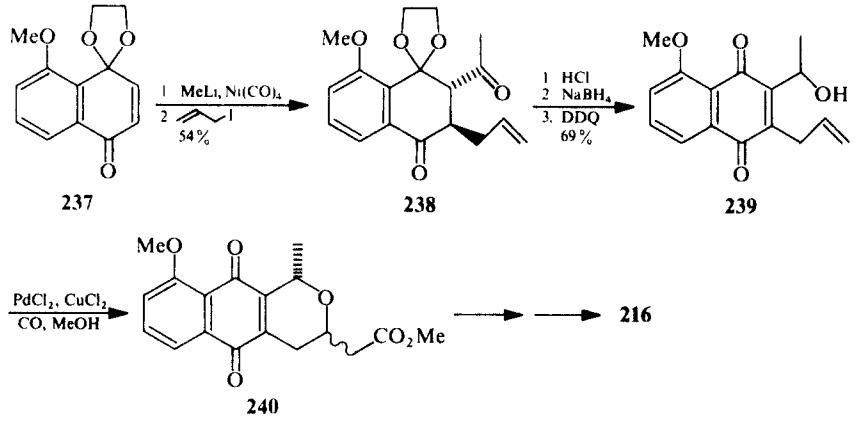
Semmelhack[145] used a quinone monoketal as the starting point for another approach to nanaomycin A (and also deoxyfrenolicin). The strategy is outlined below; Michael addition of an acyl anion equivalent leads to an enolate anion **235**, which can be trapped by adding an allyl iodide, thus neatly attaching two side chains to the quinone nucleus in a one-pot reaction. Model experiments showed that this was feasible, and acylnickel carbonylate anions[146] **236** were found to be promising acylating agents. This led to an attractive short synthesis of (±)-nanaomycin A using ketal **237**,[147] which is easily prepared from 5-methoxy-1-naphthol (Scheme 27). After acylation–allylation, the product **238** was converted into **239**, the quinone equivalent of **162**, and under alkoxycarbonylation conditions this gave predominantly the *trans* isomer of **240**, isolated by crystallization, and finally (±)-nanaomycin A. In practice **239** is obtained much more conveniently by allylstannane allylation of the acetylquinone **160** (Scheme 21).



235

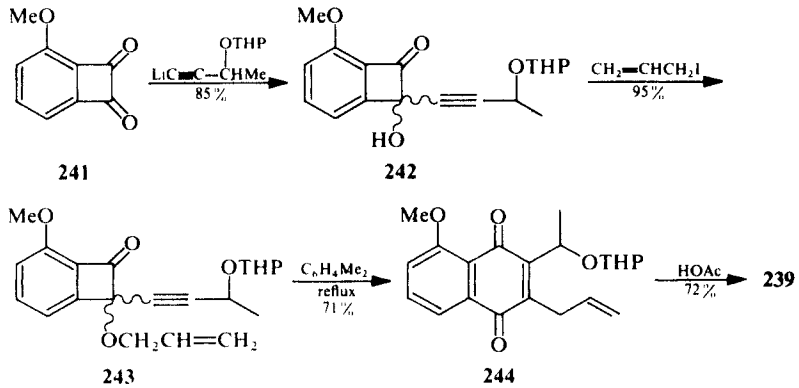


236



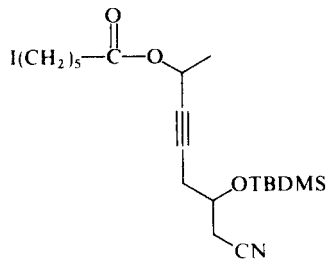
Scheme 27

Moore[148] has used his hydroxycyclobutenone thermal arrangement (see p. 328) to secure **239** in a short synthesis starting from dione **241**. On reaction with the lithium salt of protected 3-hydroxybut-1-yne, dominant attack occurs on the more electron-deficient carbonyl, giving an 85% yield of **242** and its regio-isomer (each a mixture of diastereomers). By adjusting the solvent and temperature the regiospecificity could be increased to 98:2, but the yield was reduced to 54%. On thermolysis the allyl ether **243** rearranged to quinone **244**, and thus **239** after deprotection, giving an overall yield of 28% from dione **241**. The deoxyfrenolicin precursor **239** (Pr in place of Me) was prepared in the same way.[148]

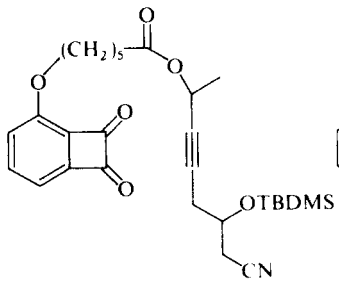


Liebeskind[149] has shown that naphthoquinones can be obtained by insertion of alkynes into phthaloylmetal complexes, and has applied the method to the synthesis[150] of nanaomycin A using an intramolecular varia-

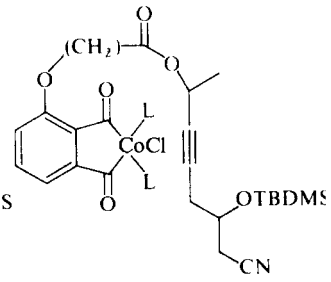
tion to control the regiochemistry, a strategy deployed in his deoxyfrenolicin synthesis. It is fascinating chemistry, but straightforward syntheses starting from a naphthoquinone are more expedient. A model synthesis showed that a phthaloylcobalt complex was satisfactory, no reaction occurring with the alkyne until catalyzed by silver tetrafluoroborate. The nanaomycin A precursor **246** was assembled from 3-hydroxycyclobutenedione[72] and the iodoalkyne **245**, prepared in several steps from but-l-yne-3-ol, and was converted to the cobalt complex **247** (L = PPh_3) (76%) in warm benzene, and then into the naphthoquinone **248** (a mixture of diastereomers) on heating in the presence of silver tetrafluoroborate (47%). Pyran formation was then neatly achieved by treatment of **248** with zinc and acid as a two-phase aqueous ether system, followed by oxidative workup with silver(II) oxide to give **249** (83%) as a *cis*:*trans* mixture. The C_6 side chain was detached using



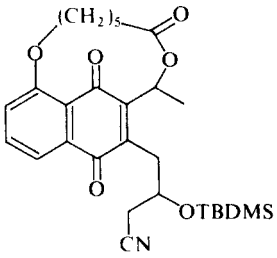
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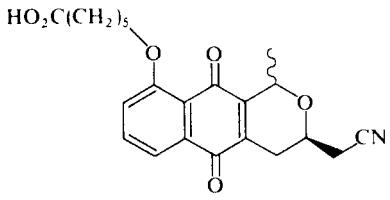
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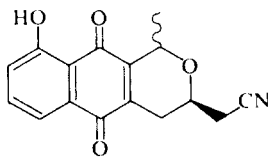
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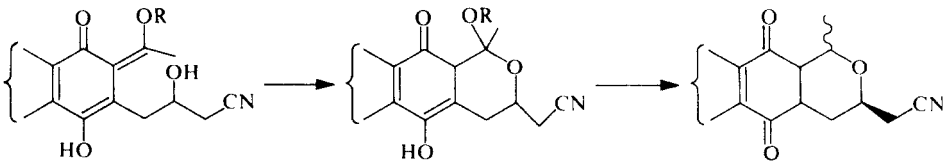
248



249



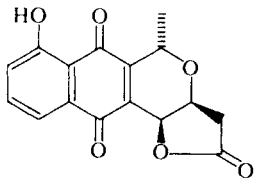
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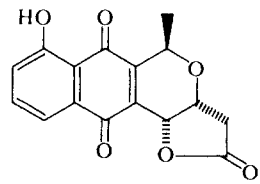
251 252

aluminum chloride leaving quinone **250** (83%), and final acid hydrolysis yielded nanaomycin A and its *cis* isomer (70%) in a 3:1 ratio. The critical pyran ring closure is considered[150] to proceed by Michael addition of the deprotected hydroxyl group to the quinone–methide tautomer (as **251**), followed by elimination of ROH from **252**. This may well be the mechanism of the frequently-employed pyranoquinone synthesis involving reaction of an aldehyde with a 3-(2-hydroxyalkyl-quinone), for example, **155** → **156**, under acid conditions, it being assumed that initially some hydroquinone is formed by a redox process, followed by aldol reaction with the aldehyde.

Nanaomycin D and Kalafungin. Nanaomycin D **253** is the lactone analogue of nanomycin A **216** and kalafungin **254** is its enantiomer. In the original report[151] of the isolation of nanaomycin D from *Streptomyces rosa* var. *notoensis* it was noted that A could be oxidized to D simply by exposure to air in methanol solution. Later Li and Ellison[143] subjected their synthetic nanaomycin A to the same treatment and obtained a racemic mixture of nanaomycin D and kalafungin (cf. p. 352). Consequently, all syntheses of (±)-nanaomycin A are formally syntheses of nanaomycin D and kalafungin.



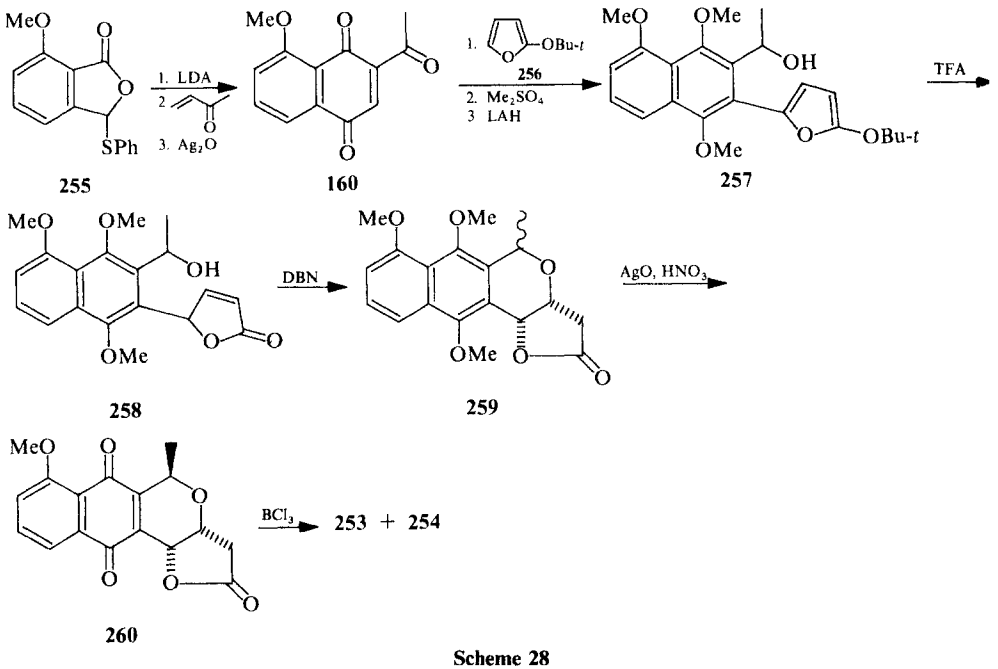
253



254

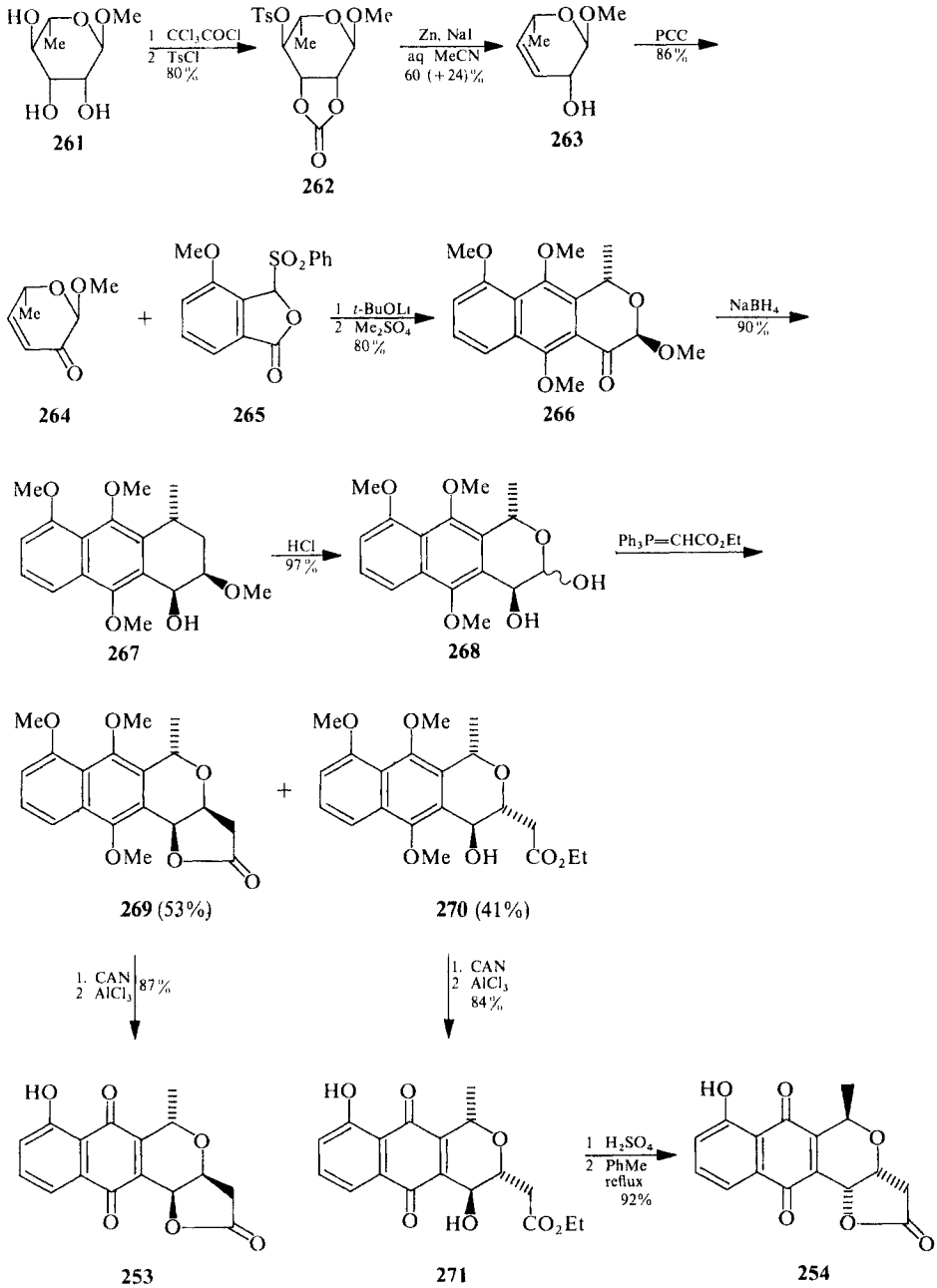
Kraus[152] has synthesized kalafungin, again making use of quinone **160**, which was prepared by a phthalide annulation sequence with methyl vinyl ketone. This is a very direct route to **160**, but the yield is described as modest. The lactone moiety was then introduced prior to pyran formation (Scheme 28). This was done by nucleophilic addition of 2-*t*-butoxyfuran **256** (from 2-metalated furan and *t*-butyl perbenzoate) to the acetylquinone **160**—no catalyst required—to give a hydroquinone which was converted to **257**, and the enol was then hydrolyzed in trifluoroacetic acid. Cyclization of lactone **258** was almost quantitative, yielding a *cis–trans* mixture of pyranolactones **259**, which gave a single *trans* isomer **260** after oxidation to the quinone. However, final demethylation gave an enantiomeric mixture of kalafungin and nanaomycin D.

An enantiospecific total synthesis of nanaomycins A and D and kalafungin has been accomplished by Tatsuta[153] and his colleagues. The key to success was the use of the enone **264**, derived from rhamnose, to establish the



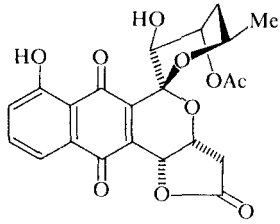
Scheme 28

stereochemistry at C-1, while at a later stage in their "enantiodivergent" strategy both *cis* and *trans* side chains were established at C-3 by a Wittig reaction (Scheme 29). Enone **264** was derived from methyl α-L-rhamnoside **261**, after protection (**262**), by conversion to the alcohol **263**, probably via the 3,4-epoxide. In the formation of **263** the isomeric allylic alcohol was also formed, but could be recycled to **263** in two steps. The pyrano-naphthalene was then assembled by phthalide annulation using the sulphonyl-phthalide[154] **265** to produce **266** with established stereochemistry. Sodium borohydride reduction furnished the alcohol **267** exclusively, whence acid hydrolysis of the hemiacetal gave the key acetal **268**. A Wittig–Horner reaction then afforded the two desired compounds **269** and **270**. In the former case, Wittig formation of the unsaturated ester was followed by an intramolecular Michael reaction and concomitant lactonization, but the 4,3-*trans*-hydroxyester **270** did not lactonize. Oxidation and demethylation of **269** yielded (−)-nanaomycin D **253** identical to the natural material. Similar treatment of **270** gave **271**, which epimerized at C-1 and C-4 in sulphuric acid to the preferred 1,3-*trans* configuration, and lactonization was completed in refluxing toluene to form (+)-kalafungin **254**. Hydrogenolysis of **253** provided (−)-nanaomycin A.

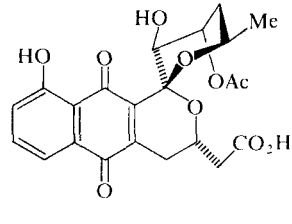

1 CCl3COCl
2 TsCl
80%
Zn, NaI
aq MeCN
60 (+24)%
PCC
86%
261
262
263
1 t-BuOLi
2 Me2SO4
80%
NaBH4
90%
264
265
266
HCl
97%
Ph3P=CHCO2Et
267
268
269 (53%)
270 (41%)
1. CAN
2 AlCl3
87%
1. CAN
2 AlCl3
84%
1 H2SO4
2 PhMe
reflux
92%
253
271
254

Scheme 29

Griseusins. These metabolites isolated from cultures of *Strep. griseus*[155] are unique members of the benzisochromanquinone group by virtue of their spiroketal system. The structures originally assigned[156] to A and B were, respectively, the enantiomers of **272** and **273**. They were revised following an X-ray determination[157] of the absolute structure of 6,8-dibromogriseusin A, and Yoshii's earlier chiral synthesis[158] of (+)-deoxygriseusin B, which gave a product whose CD spectrum was the mirror image of that of natural (−)-griseusin B. Yoshii[159] then followed that work by a similar total synthesis of (+)-griseusins A and B, the enantiomers of **272** and **273**.

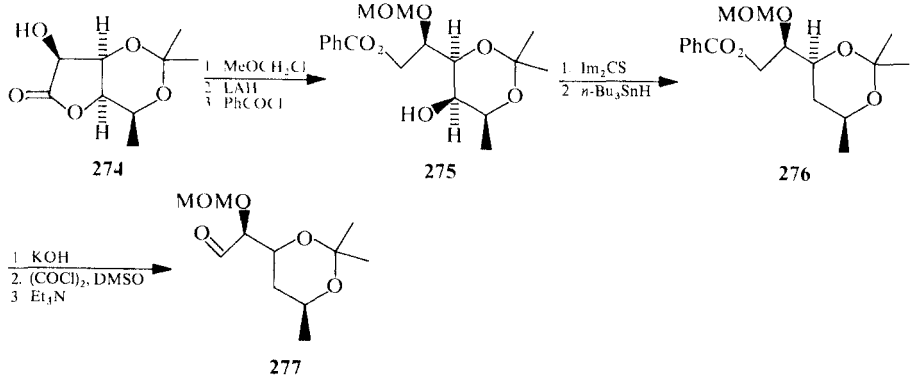


272



273

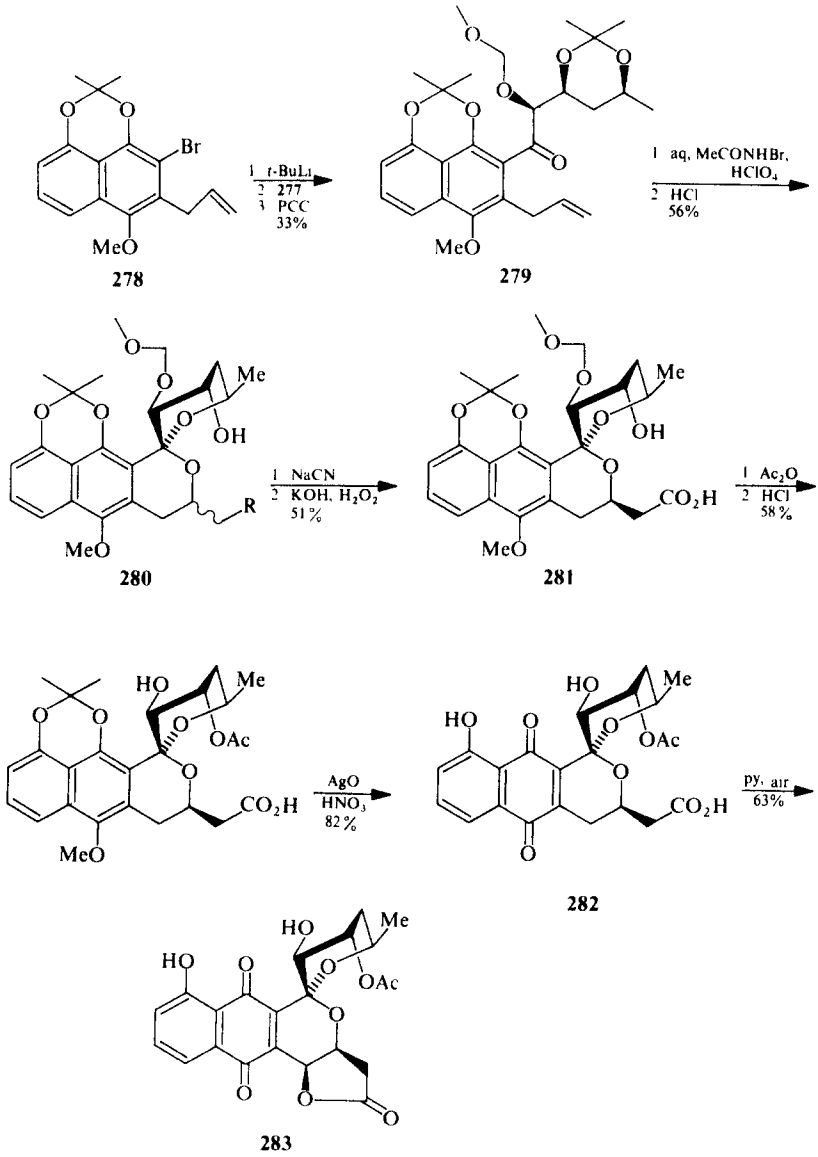
The precursor of the pyranoquinone moiety was the allylnaphthalene **278**, derived from 3-bromojuglone in four steps, while the chiral precursor for the sugar component was the L-gulose derivative **277** previously prepared,[158] as indicated, from the known 6-deoxy-3,5-*O*-isopropylidene-L-gulono-γ-lactone **274**.[160] Deoxygenation of **275** was effected by Barton's[161] procedure to give the benzoate **276**, which was hydrolyzed and then converted to the required aldehyde **277** by Swern oxidation.[19] The griseusin skeleton was then assembled in two steps (Scheme 30). Lithiation of **278**, coupling to the aldehyde **277**,



274 **275** **276**

277

Scheme 30

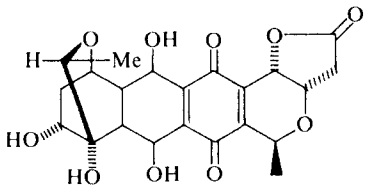


Scheme 30 (*continued*)

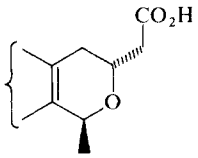
followed by oxidation of the resulting alcohol produced ketone **279**. Then, following a previous procedure,[163] addition of HOBr to the double bond and selective hydrolysis of the side chain acetonide led to formation of the spiroketal **280** (R = Br) as a mixture of two diastereomers. Conversion to the

nitrile **280** (R = CN) and alkaline hydrolysis gave the acid **281** as a single (3R) epimer. Epimerization at C-3 under alkaline conditions was also observed in the preceding (+)-9-deoxygriseusin B synthesis. After acetylation and selective removal of the methoxymethyl group, a final oxidation gave (+)-griseusin B **282**, which was converted into (+)-griseusin A **283** by exposure to air in pyridine solution.

*Granaticin A**. This pigment **284** has been isolated from several Streptomyces spp.,[164] and in some cultures it coexists with dihydrogranaticin **285**.[164] Granaticin A is active against Gram-positive bacteria and protozoa, and exhibits cytotoxicity and other biological activities.[164, 165] These compounds are unique in that a 2-oxabicyclo[2.2.2]oct-5-ene moiety, derived biosynthetically from a C-glycoside,[165] is fused to the benzoisochromanquinone system, thereby providing a challenging synthetic target. The challenge has been met, systematically and successfully, by Yoshii and his colleagues, who first found methods to construct the oxabicyclo[2.2.2]octene system fused to a benzene ring. They promptly applied this knowledge to the synthesis of the natural quinone sarubicin A **289**, followed in succession by synthesis of a close relative of (±)-granaticin, (±)-granaticin itself, and finally the natural compound.



284

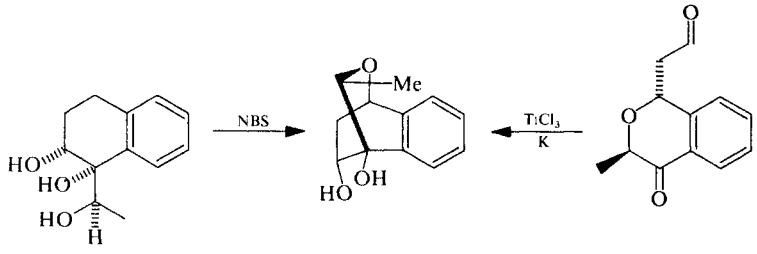


285

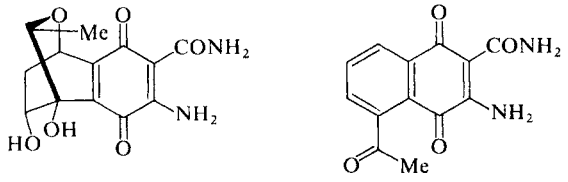
Initially, two stereoselective routes were developed for the synthesis[166, 167] of the model compound **287**; in one the bridged structure was formed by cyclization of the triol **286**, prepared from α-tetralone, while in the other the final step was the pinacol cyclization of the ketoaldehyde **288** derived from *o*-bromobenzaldehyde. The former was more efficient and was used in subsequent synthetic work, and first for the synthesis of sarubicin A (= U-58, 431) **289**, another *Streptomyces* metabolite[15] which has the same oxabicyclo–octene system as granaticin A. On melting[168] it dehydrates to form sarubicin B **290**, which has been isolated from cultures of *Strep. violaceoruber*.[169]

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* Granaticin = litmocyanin. To be consistent with most of the literature, the pyranolactone ring is inverted with respect to the structures of nanaomycin D, and so on.



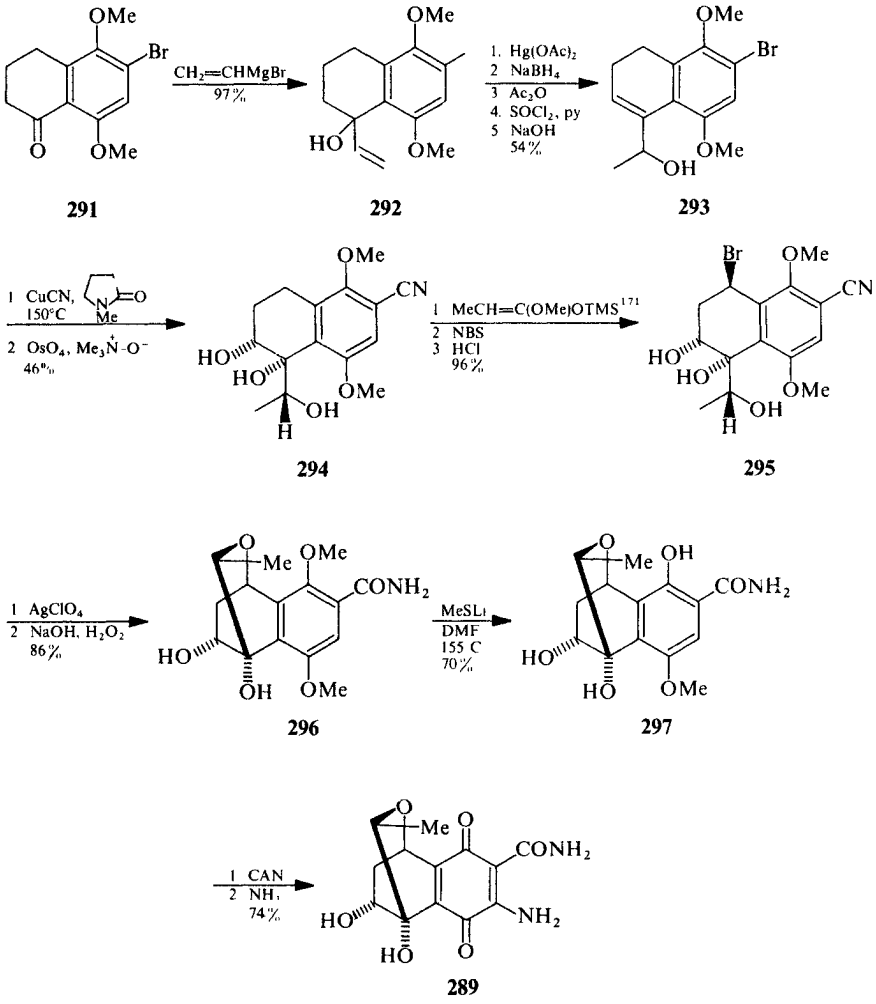
286 287 288



289 290

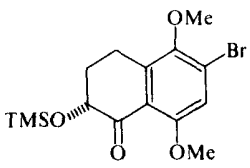
The tetralone **291**, obtained from 3-(2,5-dimethoxybenzoyl)propionic acid, was converted to the vinyl alcohol **292** and then rearranged to the isomer **293** by the sequence oxymercuration–demercuration, selective acetylation of the secondary hydroxyl group, dehydration, and final hydrolysis of the acetate (Scheme 31). After replacement of the bromine in **293** by a cyano group, stereoselective osmylation gave the triol **294** as a single stereoisomer. Trimethylsilylation followed by benzylic bromination led to **295**, and the ether bridge was then introduced efficiently with the aid of silver perchlorate, giving **296** after hydrolysis of the nitrile. Oxidative demethylation of **296** to form a quinone proved to be difficult, and the problem was overcome by partial demethylation. CAN oxidation of the phenol **297** was successful and was followed by immediate treatment with ammonia in acetonitrile to give (±)-sarubicin A **289**.[170]

Later Semmelhack[172] published a very efficient formal synthesis of (±)-sarubicin A, again starting from the tetralone **291** and leading to amide **297**. A two-step conversion to the protected hydroxyketone **298** was followed by cyanhydrin formation using trimethylsilyl cyanide which gave the desired *trans* isomer **299** in 86% yield, after chromatography, and thereafter the important aldehyde **300**. The next step required the diastereoselective addition of a methyl nucleophile to the aldehyde function, and that was achieved using methyltriisopropoxytitanium, which gave the desired triol **301** as a single isomer (80%). Presumably, Ti(IV) coordinates to the carbonyl oxygen and the adjacent hydroxyls in **300**, which ensures that methylation occurs at the less-hindered face. Methylmagnesium bromide was much less selective.[173]

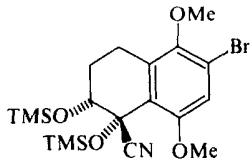


Scheme 31

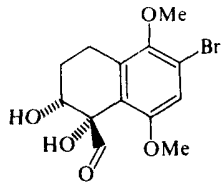
The triol **301** is an analogue of Yoshii's **294** and was cyclized in the same way by benzylic bromination and treatment with silver perchlorate, so forming **302** (53%). To introduce the amide function to **302**, Heck's Pd(0)-catalyzed carbonylation reaction[174] was employed, trapping the intermediate with 2,4-dimethoxybenzylamine to give **303** (71%) as ammonia was not successful. The unwanted aryl group in **303** was then removed, after protecting the diol, by Ce(IV) oxidation which yielded, after deprotection, amide **297** (77%).



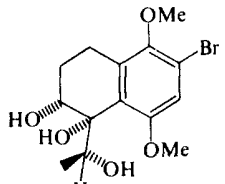
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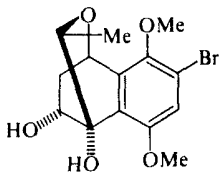
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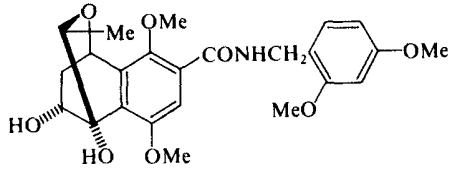
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301

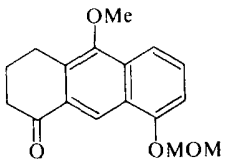


302

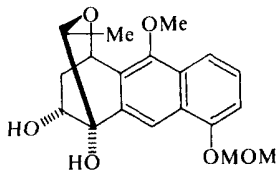


303

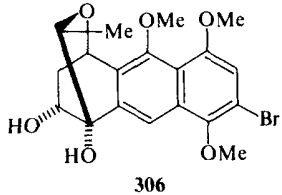
Following the synthesis of sarubicin A, Yoshii then grappled with the granaticin A problem and initially elaborated the close analogue **309**.[175] Unfortunately, they were unable to convert **309** into granaticin A, as the oxabicyclic system could not withstand *O*-demethylation conditions. In



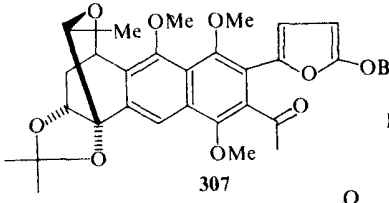
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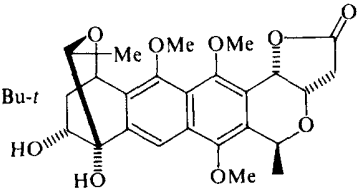
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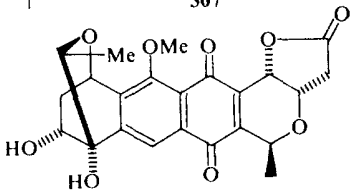
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307



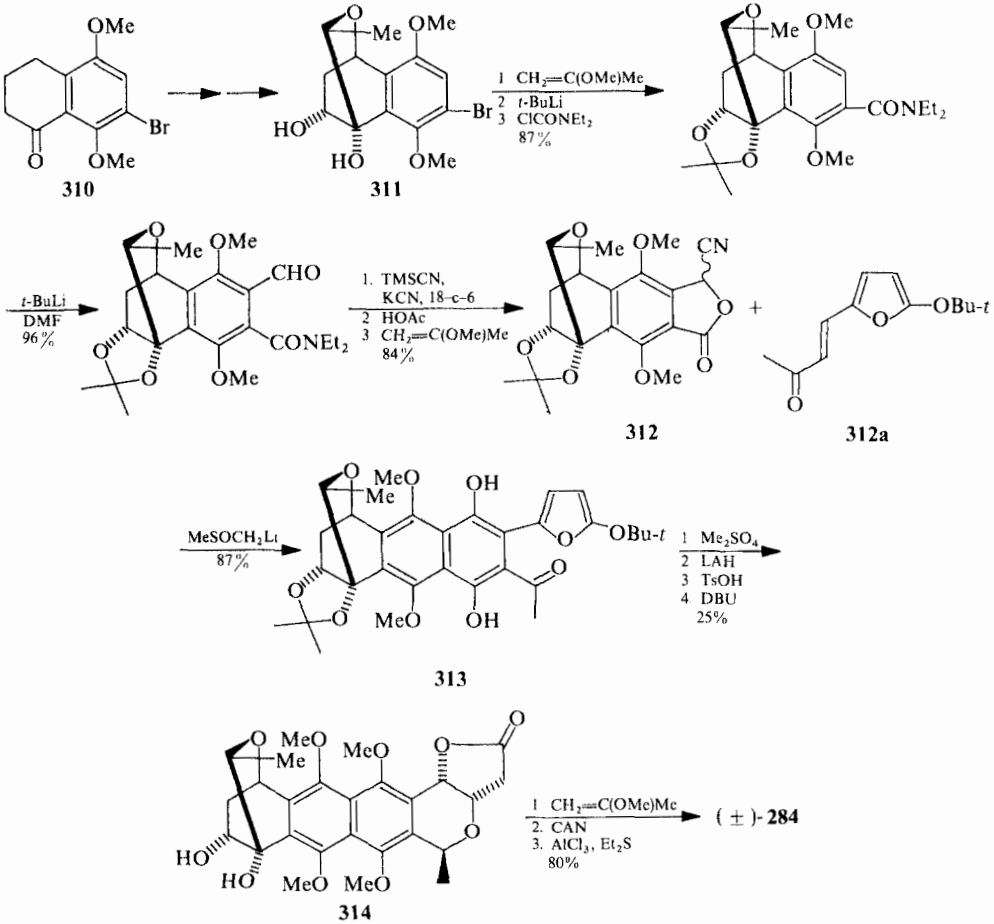
308



309

outline, the route to **309** was as follows, starting from 1,8-dihydroxyanthraquinone. This was first converted, in four steps, to the benzotetralone **304**, which was transformed into **305** along the lines of Scheme 31. By methods described above **305** was converted to **306**, and after replacing the bromine by an acetyl group and oxidation to a quinone, a *t*-butoxyfuran unit was introduced by Michael addition. Immediate methylation then gave **307**, from which the pyranolactone system **308** was derived, and finally **309**.

This approach to granaticin A was therefore abandoned and the well-tried strategy of phthalide annulation was adopted, the requisite phthalide **312** possessing the oxabicyclic system, while the complementary enone **312a** carries the *t*-butoxyfuran precursor of the lactone ring[176] (Scheme 32). The

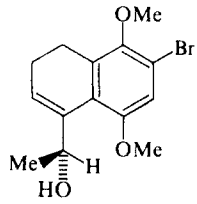


310 311 312 312a 313 314

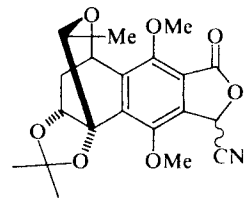
Scheme 32

bromo compound **311**, derived from tetralone **310** (isomeric with **291**) according to Scheme 31, was elaborated to phthalide **312**, as shown, the anion of which was linked to enone **312a** by Michael addition followed by cyclization to **313** in the usual way. Conversion to the pyranolactone then followed (cf. Scheme 28) to give **314** as the major component of four isomers which were separated by HPLC. In the final stages, CAN oxidation of protected **314** yielded an inseparable mixture of two quinones, both of which gave (±)-granaticin A on demethylation. The last step was difficult, but was finally achieved at ambient temperature using the $AlCl_3$–Et_2S complex[177] in dichloromethane.

Since this synthesis of racemic granaticin A was accomplished, a total synthesis of the natural pigment has been reported briefly.[178] The phthalide annulation procedure was used again with optically active components. The alcohol (+)-**293** was obtained by resolution of the racemic form (see Scheme 31) through the (−)-*N*-(1-phenylethyl)carbamates, and the absolute configuration was determined by the exciton chirality method. It was elaborated to the phthalide **315** as for the regioisomer **312**. Synthesis of the optically active enone **320** started from the di-*O*-acetylrhamnal **316** and proceeded to the ester **318** by reaction with the ketene acetal **317**. It was separated from the C-1 epimer after hydrolysis, and the mesylate **318** was smoothly transformed to the lactone (+)-**319** by an intramolecular S_N2' reaction which occurred on silica gel chromatography. Aminolysis,[179] followed by oxidation, gave the desired enone **320** (Scheme 33).

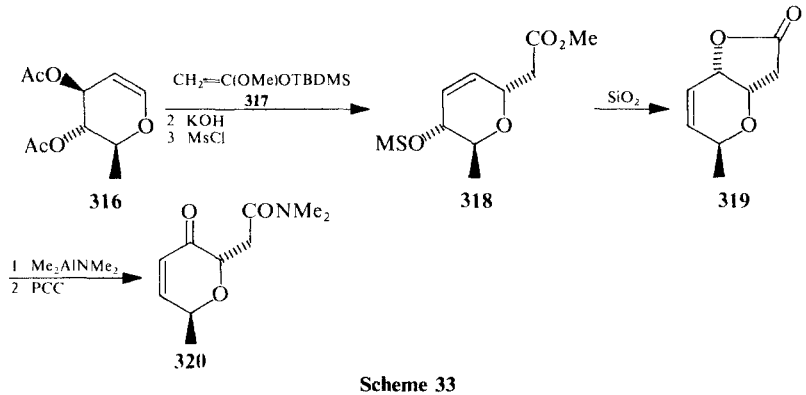


(R)-293

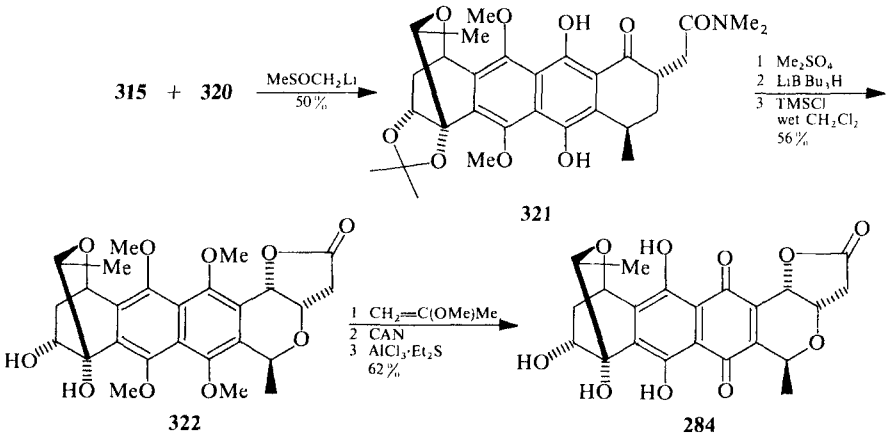


315

Coupling of **315** and **320** provided the pyranone **321** (Scheme 34) and, after methylation, reduction of the ketonic group gave predominantly the *cis*-hydroxyamide, which lactonized on treatment with chlorotrimethylsilane in methylene dichloride.[180] Finally, oxidation and *O*-demethylation as in Scheme 32 afforded optically active granaticin A identical with natural material.



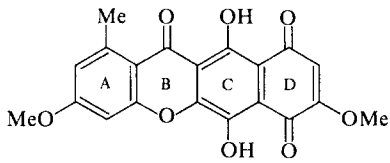
Scheme 33



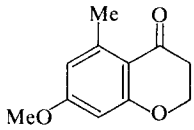
Scheme 34

E. Bikaverin

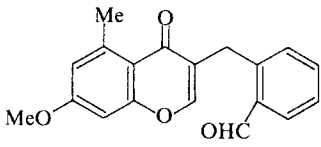
This pigment has been isolated from several fungi.[15] It has a unique benzoxanthone structure **323**, interesting chemical properties, and is credited with a variety of biological activities.[181] It was first synthesized by Barton.[182] His initial approach was to condense the chromone **324** with *o*-phthalaldehyde to give aldehyde **325**, which was converted into the acetal **326**. Irradiation of **326** in benzene containing *o*-dichlorobenzoic acid (2 equiv) effected cyclization to **327** (initially *cis* but converted to the more stable *trans* on workup). This model scheme worked well, but it was not possible to extend it



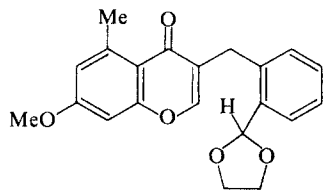
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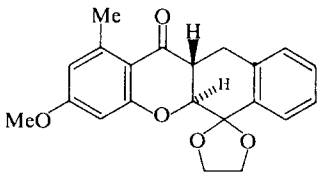
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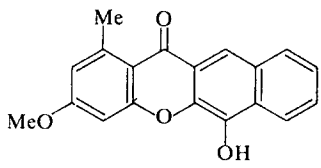
325



326



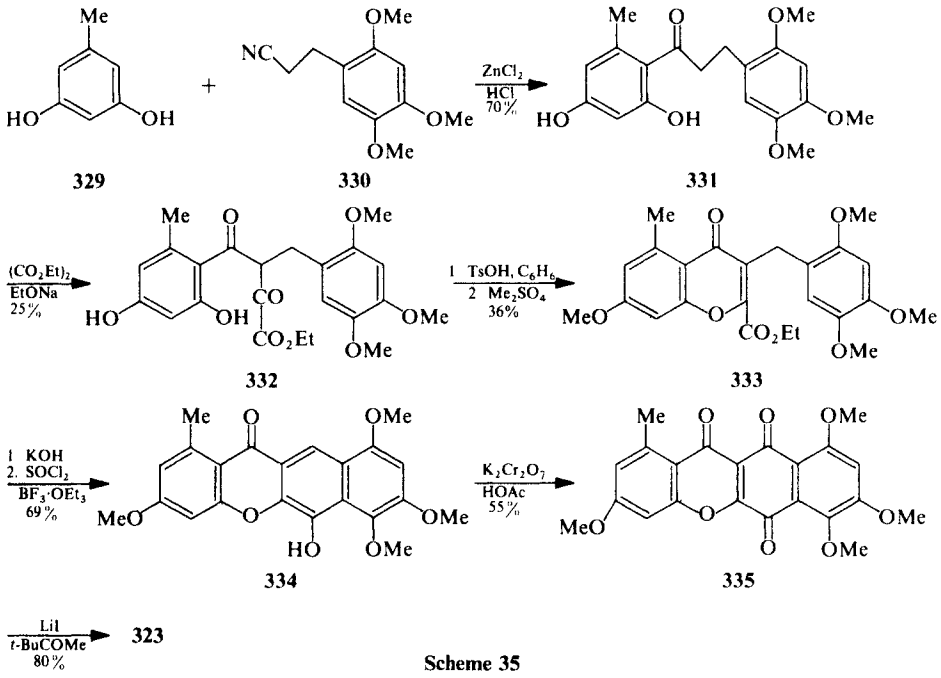
327



328

to obtain **328** with the requisite substitution for bikaverin synthesis. The route was therefore abandoned in favor of another strategy which started by linking rings A and D by a three-carbon chain and introducing a branch at the center carbon which was then cyclized to form first ring B and then ring C. Model experiments demonstrated that it was possible to prepare the tetracycle **328** in that way, and the method was then applied to the synthesis of bikaverin (Scheme 35). The ring D precursor **330**, derived from 2,4,5-trimethoxybenzaldehyde, was condensed with orcinol **329** to give ketone **331**. Ring B was then formed by condensation with ethyl oxalate and azeotropic cyclodehydration of **332** yielded, after methylation, the chromene ester **333**. After adjustment to the acid chloride another ring closure yielded the tetracyclic phenol **334**, which could not be oxidized with Fremy's salt, but chromic acid furnished the quinone **335**. Final *peri*-demethylation using lithium iodide completed the synthesis. The tautomeric form shown **336** is the solid-state structure determined by X-ray analysis.[183]

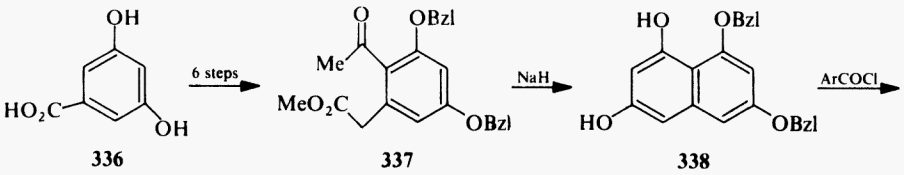
Kato[184] has reported another synthesis of bikaverin starting from 3,5-dihydroxybenzoic acid **336** and acid **337**, based in part on the ready availability of the latter to the Japanese group.[185] The strategy adopted was D → CD → ACD → ABCD, a crucial step being a photo-Fries reaction on the esterified CD intermediate **339**. Unfortunately that was not a very



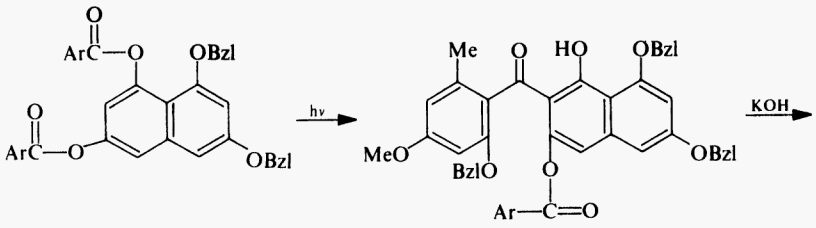
Scheme 35

successful operation and generally yields were less than 50% (Scheme 36). The CD moiety, obtained by a Dieckmann reaction on **337**, was immediately acylated with the acid chloride of everninic acid (2-hydroxy-4-methoxy-6-methylbenzoic acid) benzyl ether to form the key diester **339**. Photo-Fries rearrangement of **339** afforded the phenolic ketone **340** (27%) and the *para* isomer (19%).

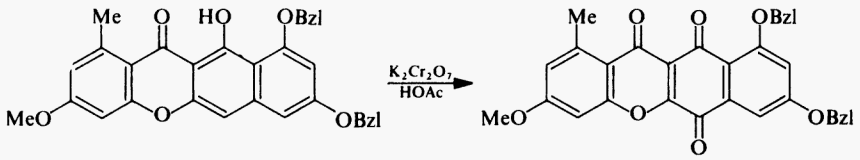
On treating **340** with ethanolic potassium hydroxide it cyclized to the benzoxanthone **341** (9%), but the main product was the angular isomer (32%). That was not as discouraging as it appears. Chromic acid oxidation of **341** afforded **342** (65%), and to introduce the last oxygen function quinone **342** was oxidized with manganese dioxide in concentrated sulphuric acid, a reaction known[186] in anthraquinone chemistry to give norbikaverin **343** (also a natural product[187]) in 28% yield, and hence bikaverin **323**. A similar oxidation of the angular isomer of **341** afforded **344**, the *o*-quinone isomer of **342**, and unexpectedly, it isomerized quantitatively to the *para* isomer **342** when left in chloroform–methanol in contact with silica gel for 3 days. The conversion of **344** into **342** is another example of an intramolecular rearrangement of a 4-alkoxy(aryloxy)-1,2-naphthoquinone to a 2-alkoxy-(aryloxy)-1,4-naphthoquinone usually effected under acid or alkaline conditions.



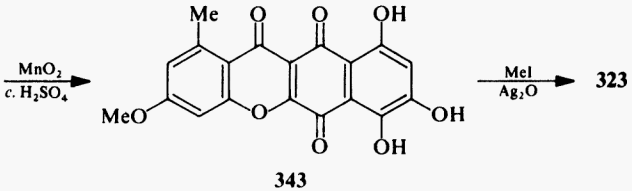
336 337 338



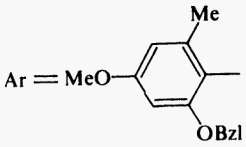
339 340



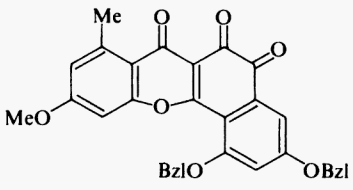
341 342



343

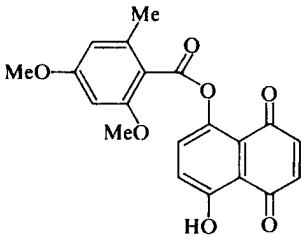


Scheme 36

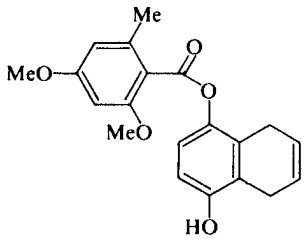


344

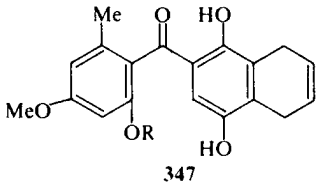
Lewis[188] also approached the synthesis of bikaverin using a photo-Fries rearrangement to construct an ACD assemblage. The reaction proved to be impossible with the naphthazarin ester **345**, but ester **346** rearranged to the hydroquinone **347** (R = Me) on irradiation, and after *ortho*-demethylation the phenol **347** (R = H) was oxidized with DDQ. The product was not the expected xanthonequinone but the spirotriketone **348**, that is, 5-*exo*-trig cyclization occurred rather than 6-*endo*-trig. However, on heating above its melting point (202°C), **348** rearranged and was oxidized to the desired quinone **349**, but that could not be converted into bikaverin.



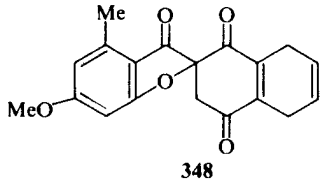
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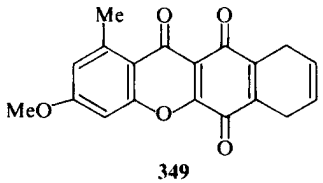
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347

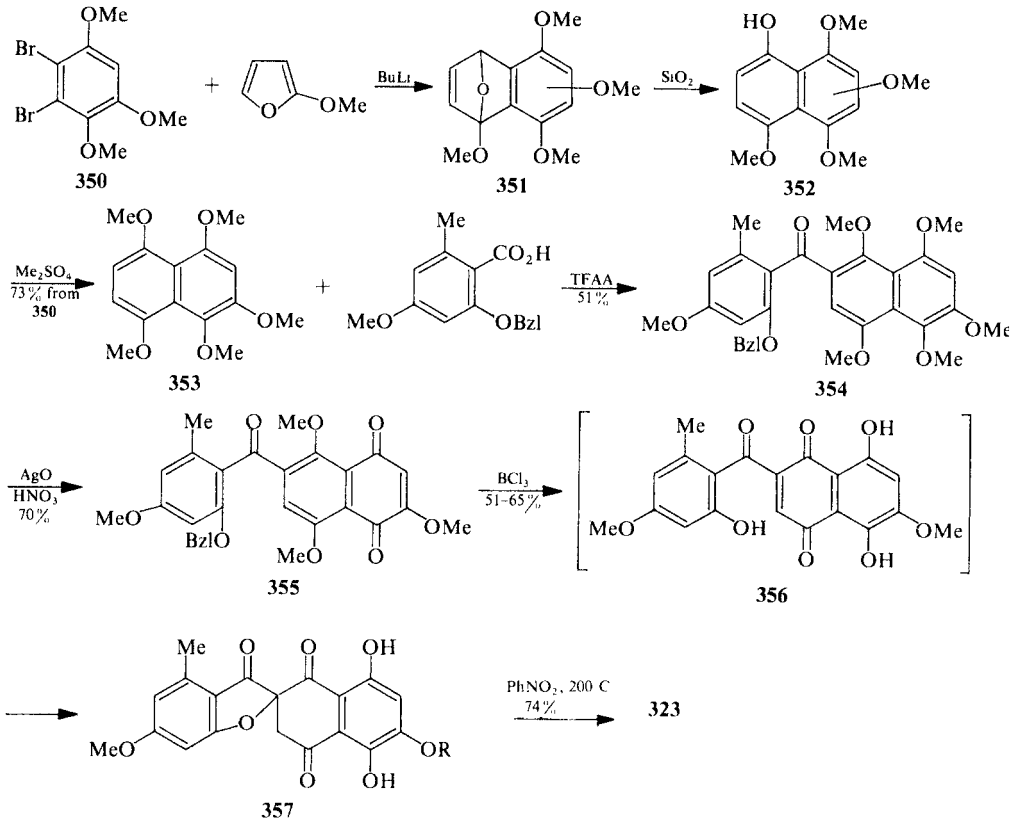


348



349

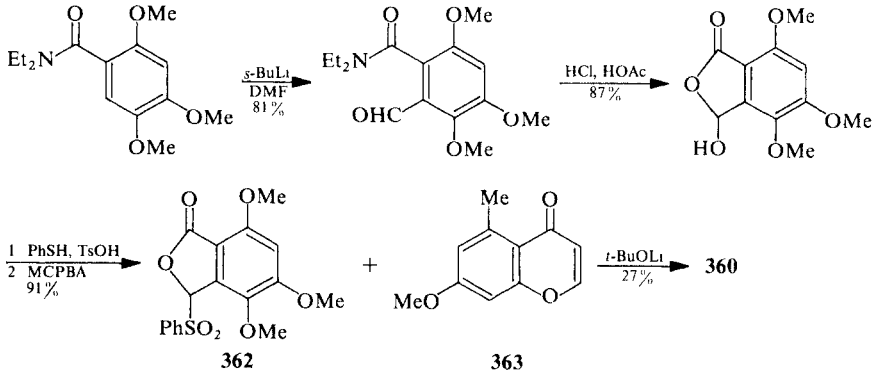
The recent bikaverin synthesis of Giles[189] (Scheme 37) also follows the D → CD → ACD → ABCD route, but all the oxygen functions in the CD moiety were assembled initially and the link to ring A was achieved by a regiospecific Friedel–Crafts acylation. This was much more efficient than Kato's photo-Fries reaction and yields throughout were superior. The pentamethoxynaphthalene **353** was obtained in 73% yield from the dibromotrimethoxybenzene **350**[190] by adding 2-methoxyfuran to the derived benzyne; the adduct **351** was rearranged to the naphthols **352** during flash chromatography, yielding a single product **353** on methylation. The naphthalene **353** was then linked to the ring A unit by regiospecific acylation with protected everninic acid to give **354**. Two routes were then followed to complete the synthesis. First, **354** was subjected to oxidative demethylation yielding **355**, reaction occurring at the more electron-rich ring. The hope then was that deprotection would give a naphthazarin derivative carrying a phenolic group in ring A (**356**), which would cyclize to form the desired pyrone ring. In practice, on treating **355** with excess of boron trichloride, it cyclized to the



Scheme 37

spiro compound **357** (R = Me) (cf. **347** → **348** above). Like **348**, the spiro compound **357** rearranged on thermolysis in nitrobenzene at 200 °C, yielding bikaverin **323**. It was thought that the yield in the final steps might be improved by methylating the phenolic groups in **357** to protect the intermediate hydroquinone. As direct methylation was unsuccessful, an alternative route was followed starting from **354**. Hydrogenolysis, followed by DDQ oxidation of the phenol, gave the enolic spiro compound **358** by either radical or electrophilic cyclization. The enol ether was easily hydrolyzed to **359**, the desired dimethyl ether of **357**, and on heating at 200 °C it rearranged to the red hydroquinone **360**. Oxidation gave the quinone **361** which had previously been converted by Barton into bikaverin (80%). The overall yield of bikaverin from the dibromobenzene **350** by both route was 12%.

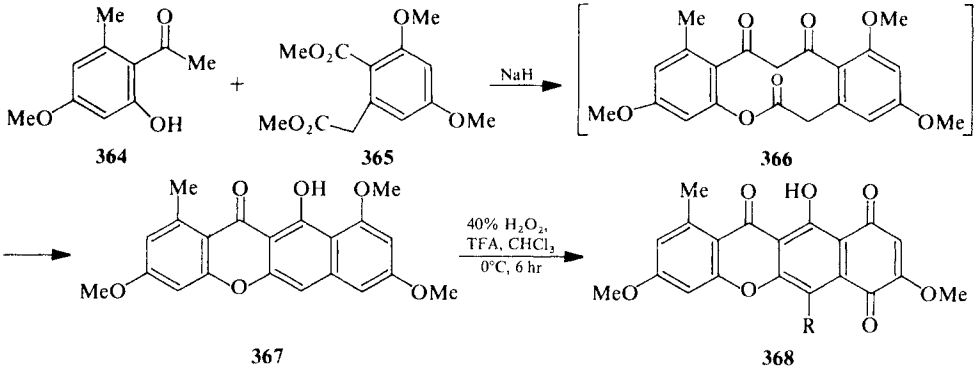
A very short route to bikaverin has been reported by Hauser[191] using his phthalide annulation procedure with a chromone as both Michael acceptor and AB synthon (Scheme 38). The requisite phthalide **362** was prepared, as shown, and the chromone **363** by a standard procedure from 2-hydroxy-4-methoxy-6-methylacetophenone and ethyl formate. Coupling **362** and **363** led directly to hydroquinone **360**, which had been converted to bikaverin previously. The relatively low yield in the key condensation step is compensated by the high yield at all other stages and the brevity of the synthesis.



Scheme 38

The Kjaers[181] have published another short and convergent synthesis of bikaverin of the type A + D → ABCD. A substituted benzoxanthone is formed in one step and converted into bikaverin by one further reaction (Scheme 39). The starting materials are the hydroxyacetophenone **364**, readily accessible from orcinol, and the homophthalate **365**, easily obtained from orsellinic acid by standard reactions. The condensation of **364** and **365**

gives the benzoxanthone **367** in only modest yield (20–25%), which is not surprising if the 10-membered ring **366** is an intermediate compound. With other *o*-hydroxyacetophenones in place of **364** and careful control of reaction conditions, **367** analogues were obtained in yields up to 70%.[181] The conversion of **367** into bikaverin requires the introduction of two oxygen functions, *peri*-demethylation and oxidation to the quinone level. After considerable experimentation it was found possible to accomplish all three reactions in one step using peroxytrifluoroacetic, which afforded **368** (R = OH) (= bikaverin) and **368** (R = H), each in 37–38% yield.



364 365 366 367 368

Scheme 39

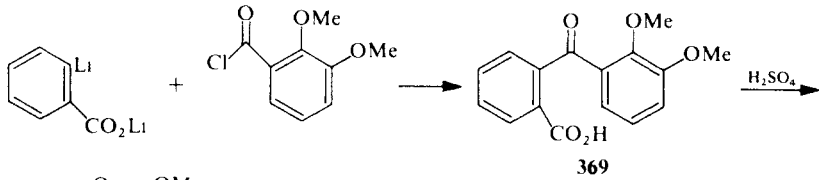
4. ANTHRAQUINONES*

There are several hundred natural 9:10-anthraquinones widely distributed[14, 15] in flowering plants and microorganisms, insects, and marine animals, the great majority having up to seven simple substituents (hydroxyl, methoxyl, methyl, and oxidized methyl). Some possess longer side chains, up to six carbons, which may be cyclized, and occasionally one ring is alicyclic, but otherwise there is relatively little structural variation and there are very few complex structures. It should be noted that Brassard[192] has drawn attention to the unreliability of many published anthraquinone structures which are based on flimsy evidence, and has frequently synthesized such structures only to find that the synthetic products were quite different from the natural pigments.

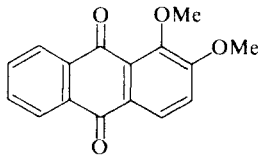
The main synthetic problem therefore is to find regiospecific methods to elaborate polysubstituted anthraquinones. Formerly anthraquinones were

* Excluding anthracyclinones.

prepared using anthraquinone substitution chemistry where appropriate, and by Friedel–Crafts and related methods. While the latter procedures, particularly *o*-benzoylbenzoic acid cyclization, can give very good yields, regiocontrol is poor, and since most of the natural quinones are unsymmetrical, the reactions often result in mixtures and low yields. Moreover, depending on the substitution pattern, cyclization can be very difficult to achieve or may result in a Hayashi rearrangement. A regiospecific route to *o*-benzoylbenzoics is exemplified in the syntheses of **369**[193a] and **370**,[193b] but the method is seldom used as the inherent difficulties of cyclization remain. Fortunately, several new routes have been developed in recent years, spurred on in part by the great interest in anthracyclinone synthesis, which are highly regiospecific.



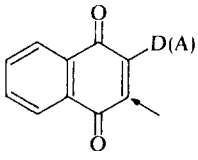
369



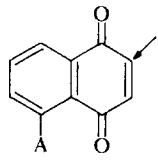
370

A. Diels–Alder Synthesis

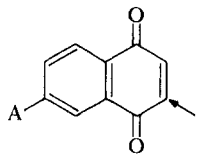
Probably more natural anthraquinones have been synthesized using this reaction than by any other method, usually by addition of a diene to a naphthoquinone, but on occasion a benzoquinone is used to provide the central ring and the flanking rings are elaborated by two successive cycloadditions. This is not surprising as the method is direct, dienes and dienophiles are readily available, and powerful regiocontrol can be exercised. As mentioned earlier (p. 331), benzoquinone substituents exert strong regiocontrol over the reaction. In naphthoquinones substitution at C-2 generally promotes attack of the nucleophilic end of the diene at C-3 and electron-donating or -withdrawing substituents in the benzene ring also exert regioselective control (preferred reaction sites are arrowed in **372–375**).[79] Juglone **376** is a special case; the chelated hydroxyl group behaves as an electron acceptor promoting attack at C-2, but this can be enhanced, or reversed, to a remarkable extent by use of an appropriate Lewis acid. Thus the addition of 1-acetoxybutadiene to juglone, without catalyst, gives a mixture of adducts



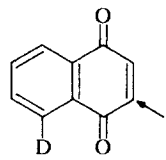
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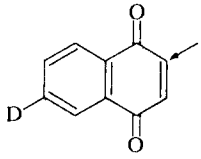
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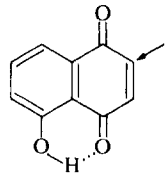
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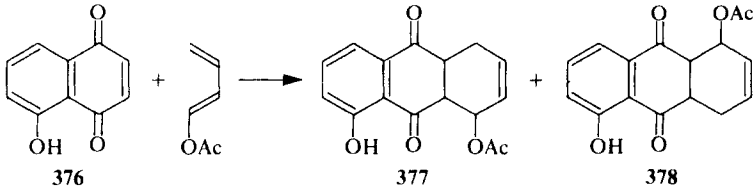


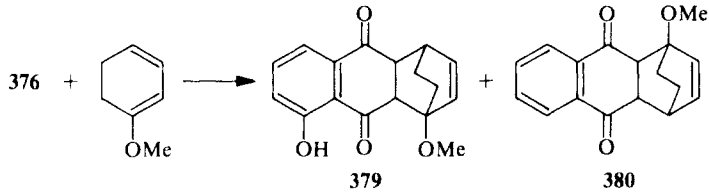
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376

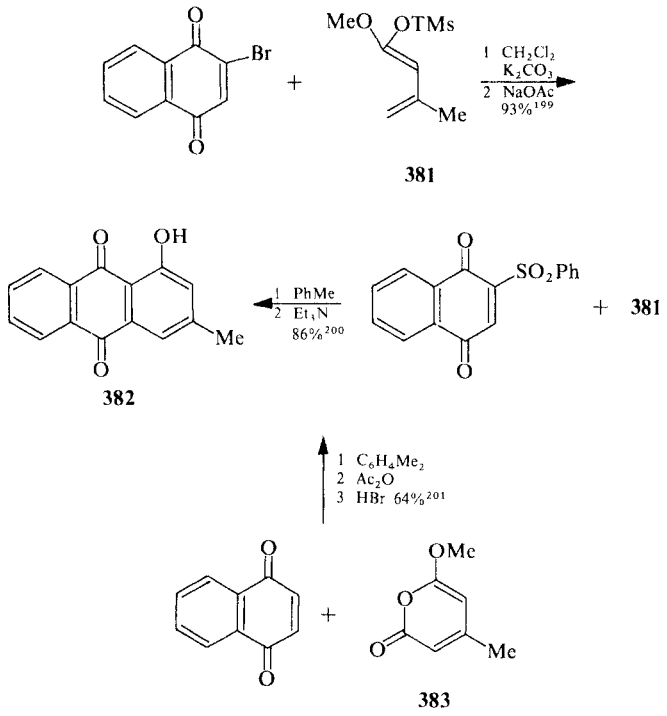
377 and **378** in the ratio 3:1, but addition of boron trifluoride etherate to the reaction dramatically increases the ratio to > 99:1.[134, 194] On the other hand, addition of 1-methoxycyclohexa-1,3-diene to juglone, without catalyst, affords **379** and **380** in the ratio 95:5, which is reversed to 15:85 in the presence of magnesium iodide.[195]





The list of natural anthraquinones synthesized using a Diels–Alder reaction is extensive, and as the procedure is identical in many cases it will suffice to consider some representative syntheses. As virtually all of them carry oxygen substituents, Danishefsky's introduction of siloxydiene[197] synthons was an important advance, and Brassard's[198] vinyl ketene acetals, especially siloxy derivatives, have been widely used.

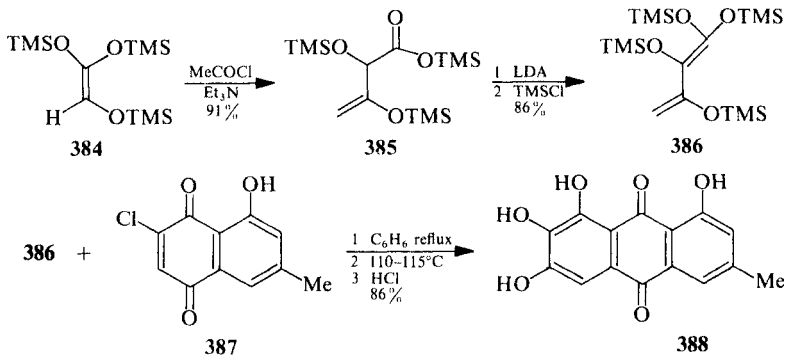
A simple example is the preparation of pachybasin **382** found[14, 15] in fungi and higher plants, which has been accomplished[199–201] by three cycloaddition routes (Scheme 40). The Japanese route[200] illustrates the use of a



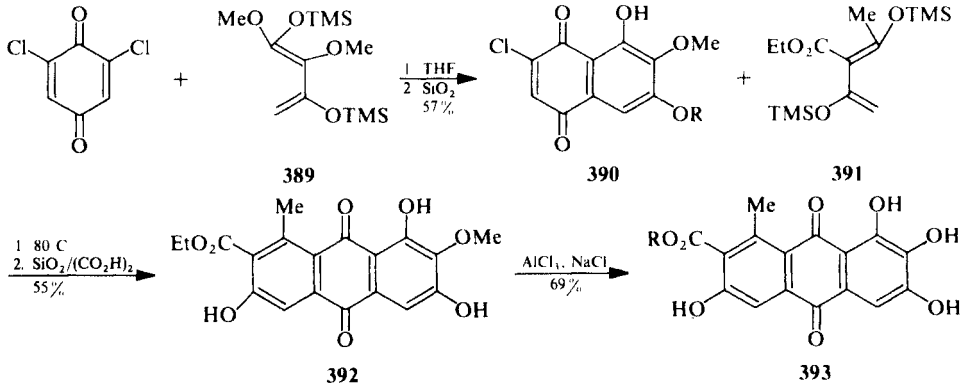
Scheme 40

sulphonyl group in place of halogen as leaving group, and the advantage of using diene **381** is apparent. The diene was prepared from methyl 2-methylcrotonate by silylation of the lithium enolate.

Highly oxygenated anthraquinones can also be obtained, the key being an efficient synthesis of suitable dienes. For example, the ketene acetal **384**, derived from glycollic acid in three steps (80%),[202] reacts with ketene, prepared *in situ*, to form the butenoate **385** via TMS transfer leading to the diene **386**.[203] This was utilized by Brassard[203] to synthesize anthragallol and the insect pigment[15] 7-hydroxyemodin **388** (Scheme 41). In fact, the naphthoquinone **387** was also prepared by diene addition[204] and numerous anthraquinones have been synthesized by way of two consecutive Diels–Alder reactions. Cameron,[205] for example, has prepared another insect pigment, ceroalbolinic acid[15] **393** (R = H), starting from 2,6-dichlorobenzoquinone (Scheme 42). Addition of diene **389** followed by aromatization on silica gel gave the naphthoquinone **390** (R = H). After conversion to the monoacetate **390** (R = Ac), cycloaddition of diene **391** led to anthraquinone **392**, and final dealkylation gave ceroalbolinic acid **393** (R = H) and its ester **393** (R = Et).

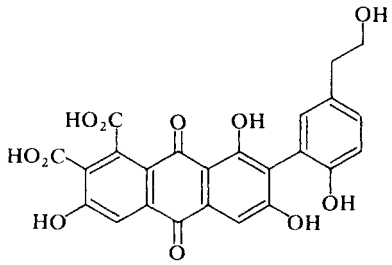


Scheme 41

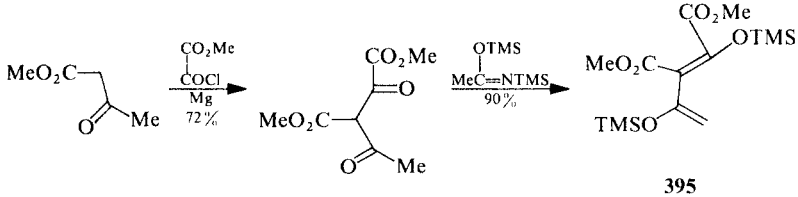


Scheme 42

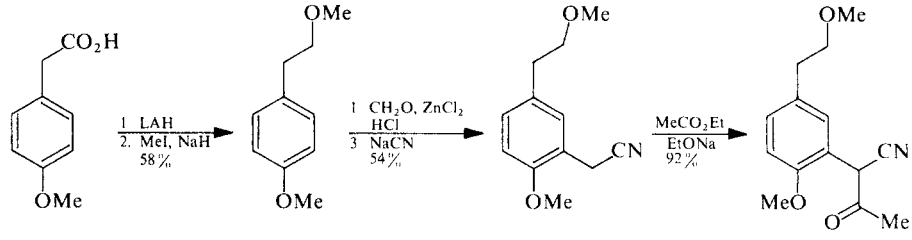
The synthesis was also accomplished in the reverse order by adding diene **391** to 2,6-dichlorobenzoquinone followed by reaction of the resulting naphthoquinone with diene **389**. Cameron[206] then proceeded to synthesize the permethyl derivative of xantholaccaic acid B **394**, one of the more complex

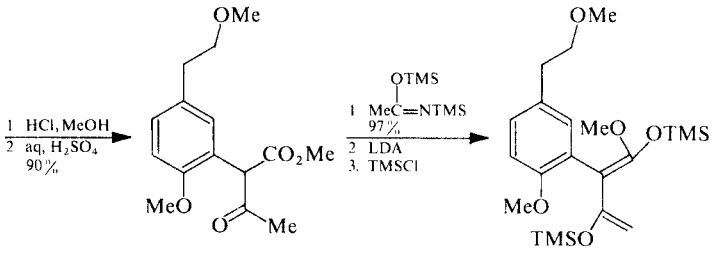


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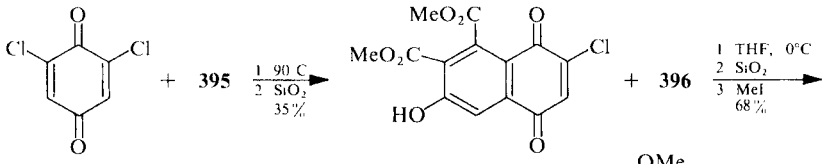


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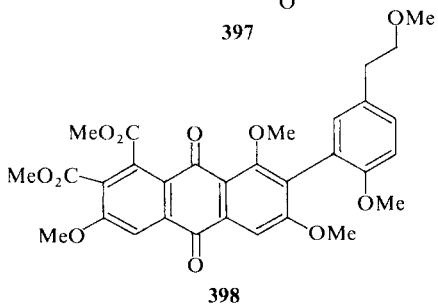




396



397

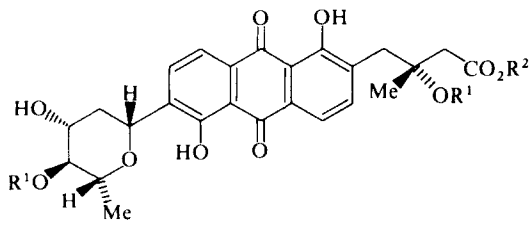


398

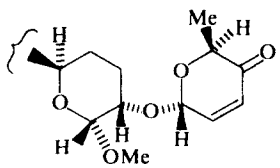
Scheme 43

laccaic acid group of coccid insect pigments[14, 15] which are characterized by an aromatic side chain derived from tyrosine. This in turn required access to the dienes **395** and **396**. The diester diene **395** was obtained in two steps from methyl acetoacetate, as indicated, but diene **396** required a sequence of reactions starting from 4-methoxyphenylacetic acid (Scheme 43). In the final convergent synthesis the desired quinone was assembled first by reaction of 2,6-dichlorobenzoquinone with diene **395** to give the naphthoquinone **397**, after aromatization during chromatography, and then cycloaddition of the unstable diene **396** led to the anthraquinone **398**.

Vineomycinone B_2 aglycone. The synthesis of **398** demonstrates the power of the Diels–Alder approach, which was reinforced by Danishefsky's total synthesis[207] of vineomycinone B_2 aglycone methyl ester, which involves three diene cycloadditions. The vineomycins, isolated[208] from *Strep. matensis vineus*, are active against Gram-positive bacteria and show antitumor activity. Vineomycin B_2 is the glycoside **399** (R^1 = **400**; R^2 = H), which on hydrolysis in acidic methanol yields the vineomycinone B_2 aglycone methyl ester **399** (R^1 = H; R^2 = Me). The main synthetic challenge lies in the *C*-glycoside structure and there is the further problem that chiral centers are located on both sides of the anthraquinone nucleus and must be generated independently. The strategy adopted was to elaborate a 1,5-dialkoxyanthraquinone with side chains at C-2 and C-6 which could be subsequently manipulated, and in particular the location of an aldehyde function at C-6 would serve as a heterodienophile for the construction of the *C*-glycoside moiety by cycloaddition. Ketoaldehyde **406** was a key compound derived from **405**, the synthesis of which required dienes **402** (R = H and Me) (Scheme 44).



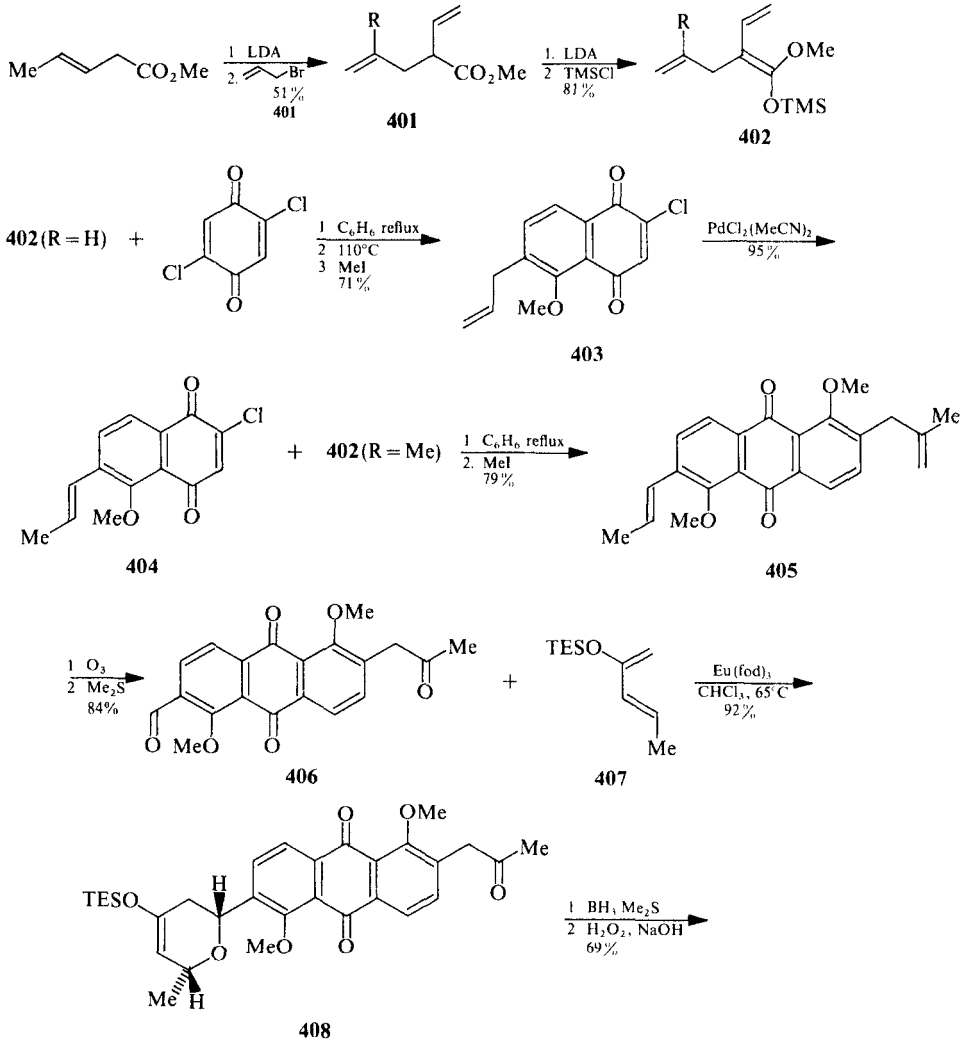
399



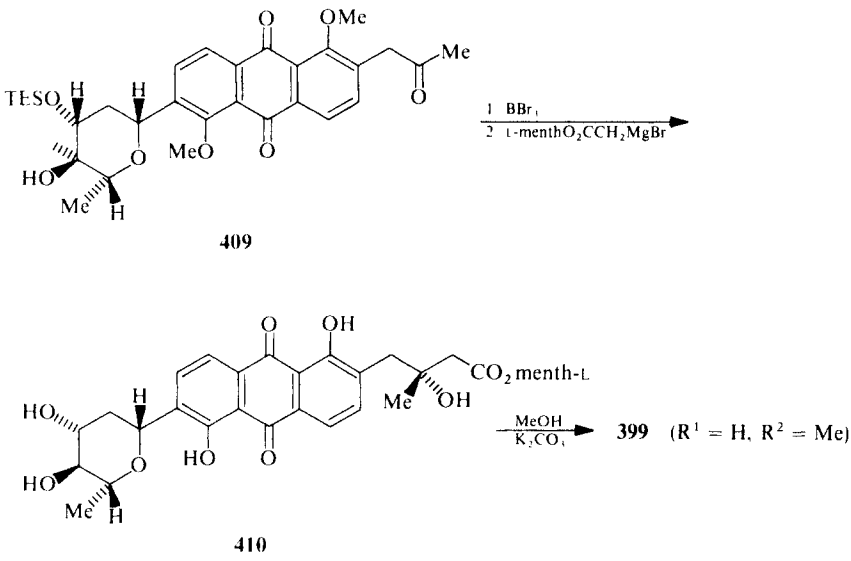
400

Diene **402** (R = H) was secured from methyl crotonate by deconjugative allylation using the "LDA–HMPA complex"[209] followed by enolate silylation, and the homologue **402** (R = Me) was obtained via methallylation. Cycloaddition of diene **402** (R = H) to 2,5-dichlorobenzoquinone afforded the allylnaphthoquinone **403**, after methylation, which was isomerized to the

more stable propenyl isomer **404**. A second cycloaddition using **402** (R = Me), followed by ozonolysis, provided the ketoaldehydoanthraquinone **406**. Following model studies, the *C*-glycoside unit was then elaborated, the first step being the cycloaddition of diene **407** (from methyl propenyl ketone), catalyzed by $Eu(fod)_3$,[210] which occurred selectively at the aldehyde function with strict *endo* topology to give **408** as sole product. The next step,



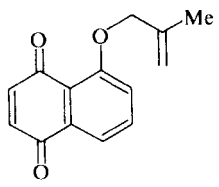
Scheme 44



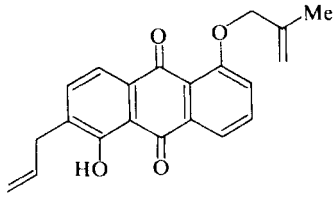
Scheme 44 (*continued*)

hydroboration of the double bond, required very mild conditions to avoid reduction of the ketonic group, and that was achieved using borane–dimethyl sulphide, although the reaction did not go to completion. Hydroboration occurred anti to the methyl group, giving **409** with all four methine protons axial. The last stage, namely extension of the C-2 side chain, proved to be unexpectedly difficult but the problem was resolved, after *O*-demethylation, by use of a chiral Grignard reagent derived from L-menthyl acetate. The reaction not only lengthened the C-2 side chain, it also "resolved" both ends of the molecule. The product was a mixture of stereoisomers from which the desired ester **410** and its epimer could each be isolated as a pure component by repeated HPLC. The other two components were not separable. A similar result was obtained using the D-menthyl Grignard reagent. The yield of **410**, the L-menthyl ester of vineomycinone B_2, was inevitably low owing to separation difficulties and the impossibility of simultaneous steric control on both sides of the molecule. Final conversion of **410** to the methyl ester gave a product identical with (+)-vineomycinone B_2 methyl ester.

Danishefsky[207] devised another but less practical route to ketoaldehyde **406**. Cycloaddition of diene **402** (R = H) to the juglone allyl ester **411** afforded the anthraquinone **412**, which was rearranged and methylated to provide **405**, and hence **406**.

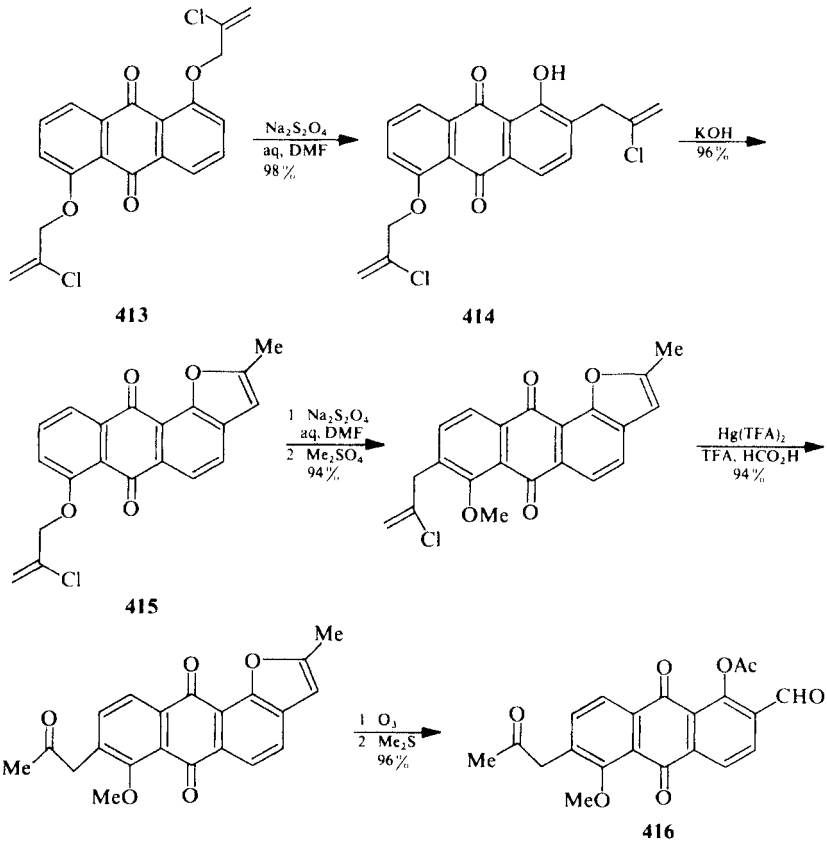


411



412

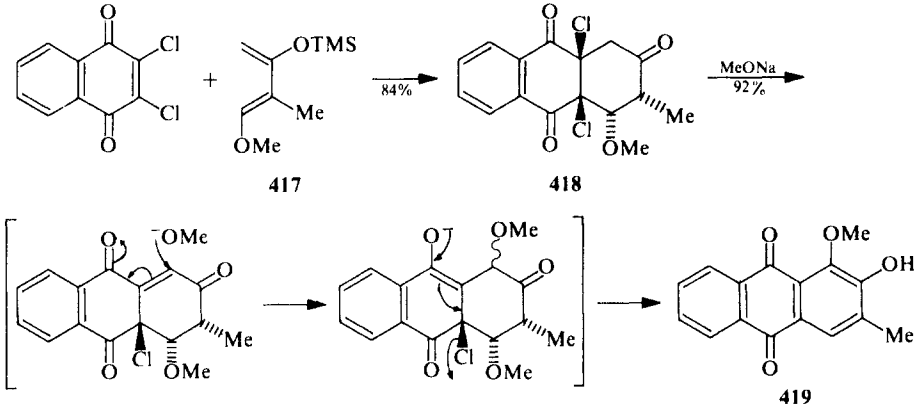
With a view to the synthesis of vineomycinone analogues, Cambie[211] has developed a very efficient route to a close analogue of the ketoaldehyde **406** starting from 1,5-dihydroxyanthraquinone (Scheme 45). A single reductive Claisen rearrangement[212] of the bis-chloroallyl ether **413** gave an almost



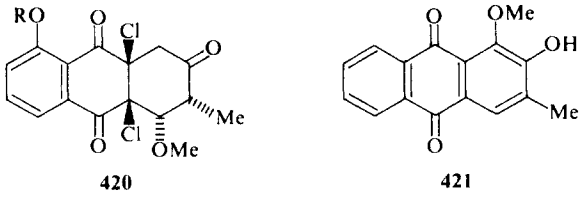
Scheme 45

quantitative yield of **414**, which was cyclized and the rearrangement repeated on **415**. The keto function was then introduced by mercuration[212] and the aldehyde by ozonolysis, giving the ketoaldehyde **416** in 80% overall yield from **413**.

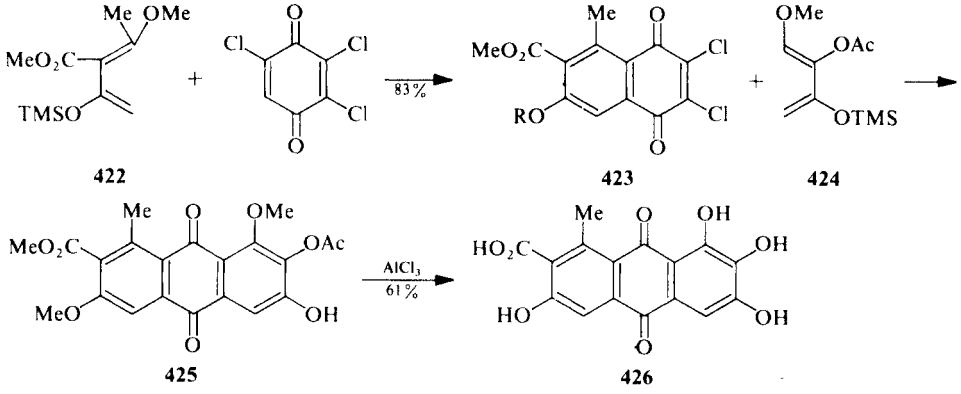
Cameron[213] has discovered recently that diene cycloaddition to 2,3-dichloroquinones provides scope for new chemistry. In a brief report it is demonstrated, for example, that digitolutein **419**, found in many *Digitalis* spp.,[14, 15] can be obtained from 2,3-dichloronaphthoquinone and diene **417** in two steps by treating the deprotected adduct **418** with sodium methoxide. The reaction proceeds by a series of eliminations, probably as indicated in Scheme 46. Adducts of type **418** are relatively stable and withstand chemical manipulations on the benzenoid ring. Thus the analogue **420** (R = Me) from diene **417** and 2,3-dichlorojuglone methyl ether can be demethylated with aluminum chloride to give **420** (R = H) (84%), which on methoxide aromatization affords obtusifolin **421** (97%), found in the seeds of *Cassia obtusifolia.*[14] This procedure of cycloaddition followed by methoxide aromatization can be extended to more complex structures by double annulation. This was demonstrated by a short synthesis of ceroalbolinic acid[14, 15] (Scheme 47) (cf. Scheme 42). Addition of diene **422** to trichlorobenzoquinone occurred exclusively



Scheme 46

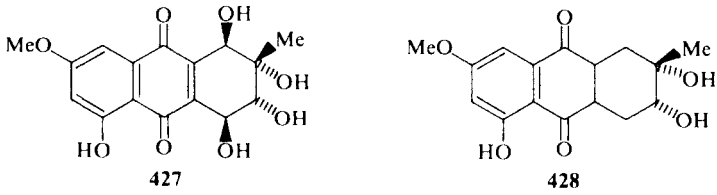


on the monochloro side of the molecule to give, after aromatization and methylation, the dichloronaphthoquinone **423** (R = Me). Subsequent addition of diene **424** and aromatization afforded the anthraquinone **425**, isolated as the acetate (43%), and final deprotection yielded ceroalbolinic acid **426**.



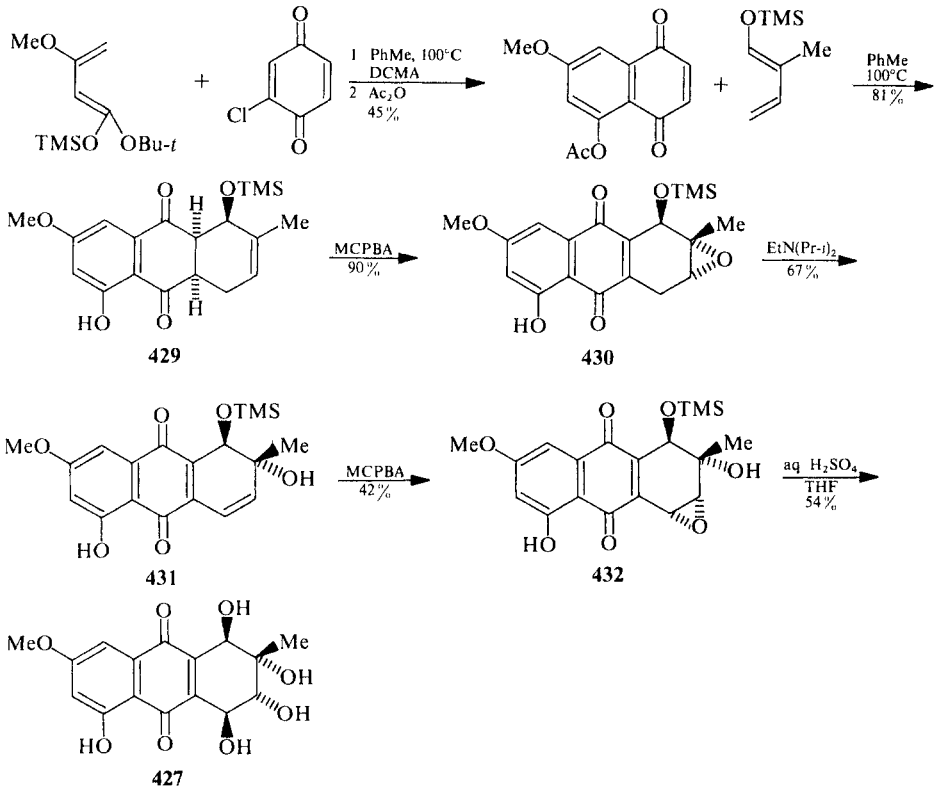
Scheme 47

1,2,3,4-Tetrahydroanthraquinones. Diels–Alder adducts not derived from halogenated dienophiles can also be modified to form derivatives of 1,2,3,4-tetrahydroanthraquinone, a few of which occur naturally. Two of these are altersolanol A (= stemphylin[214]) **427** and B **428** found in cultures of *Alternaria solani* and other fungi;[14, 15] they show modest phytotoxic and cytotoxic activity.



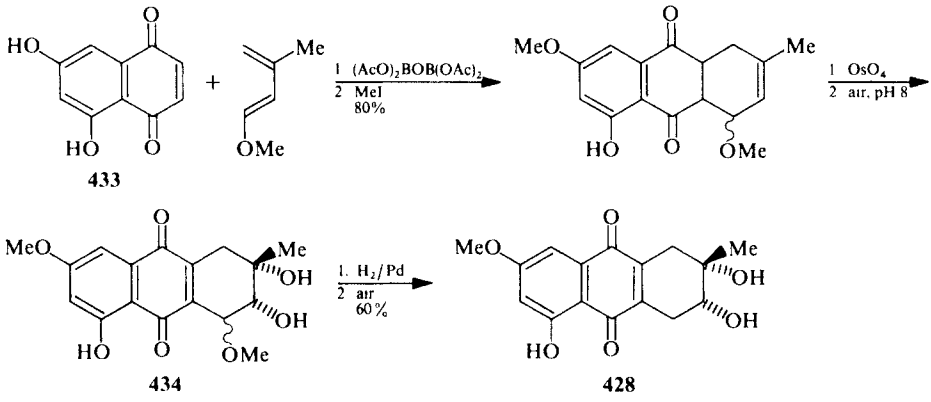
Krohn[215] has synthesized (±) altersolanol A, constructing the carbon skeleton first by two consecutive Diels–Alder additions onto chlorobenzoquinone, followed by modification of the adduct **429** (Scheme 48). The first cycloaddition was catalyzed by dichloromaleic anhydride (DCMA),[216] and aromatization proceeded spontaneously, giving 7-methoxyjuglone directly. After acetylation, the second addition afforded the expected adduct **429**, whose structure was confirmed by X-ray analysis. Stereospecific introduction

of two hydroxyl groups then proceeded in four steps. Epoxidation of the double bond was accompanied by oxidation to the quinone, giving the *trans* isomer **430** which was rearranged to the allyl alcohol **421** by treatment with Hunig's base. Epoxidation of **431** was very slow and, as it was not stereoselective, the required *cis* isomer **432** had to be separated by chromatography. Fortunately the final acidic hydrolysis proved to be selective and gave the desired product (±) **427**; presumably nucleophilic attack at C-4 was assisted by the adjacent carbonyl group.



Scheme 48

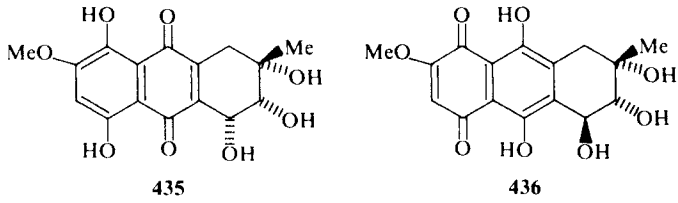
Prior to Krohn's work on altersolanol A, Kelly[218] had briefly reported a short synthesis of (±)-altersolanol B **428** (Scheme 49). The regiospecific Diels–Alder reaction was catalyzed by tetra-acetyl diborate (= "boron triacetate"). Partial methylation of the adduct was followed by osmylation and aerial oxidation giving **434**, which was obtained from **433** in 60% overall



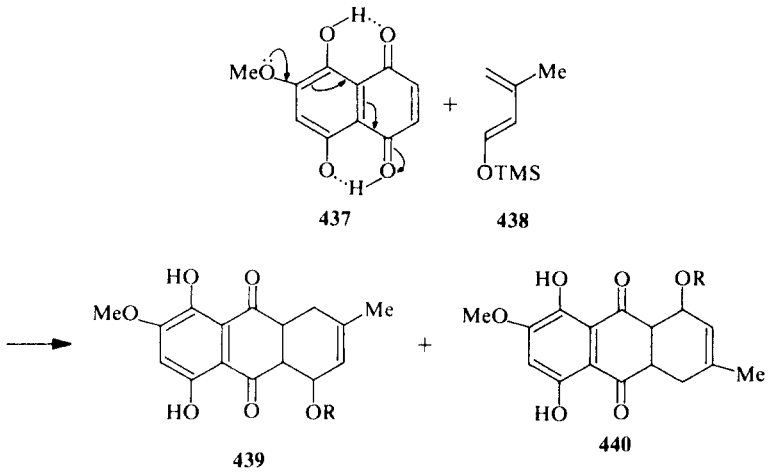
Scheme 49

yield without purification of intermediates. Removal of the methoxyl group by hydrogenolysis led to (±)-altersolanol B, **428**.

Bostrycin. This mould metabolite[14, 15] is closely related to the altersolanols, but has three chiral centers which have been the subject of much debate. Noda et al.[219] originally proposed structure **435** on the basis of spectra, chemical transformations, and an X-ray analysis of a derivative with no substituent at C-4. The stereochemistry at C-4 was later revised and structure **436** was adopted following Kelly's[220] synthesis of (±)-bostrycin and an X-ray analysis of the acetonide derivative.



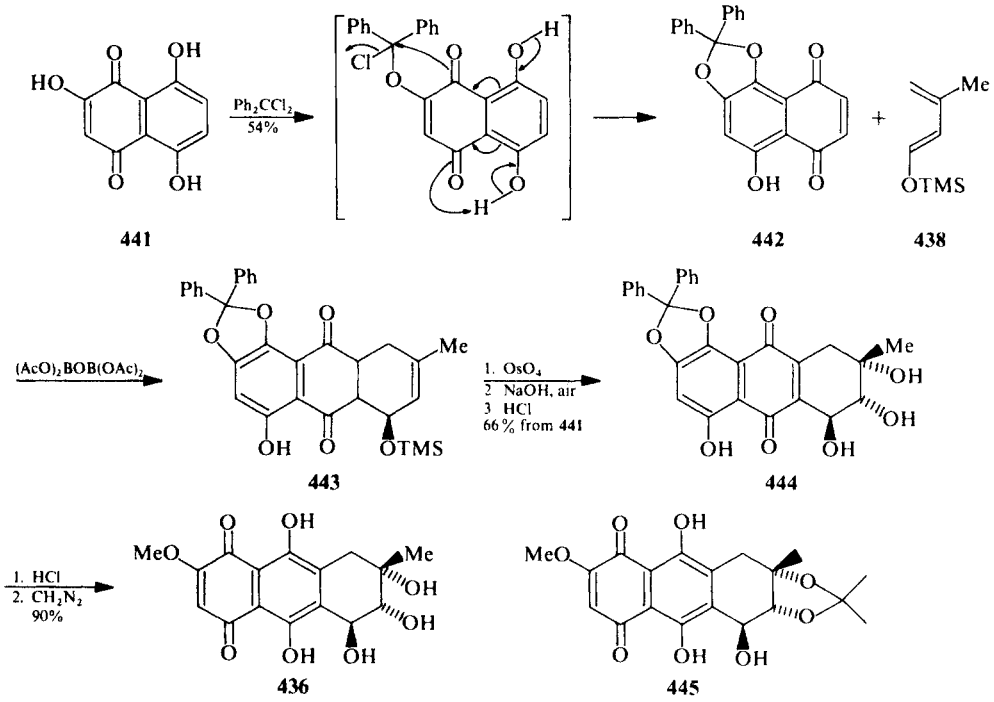
Krohn's[221] synthesis of demethoxybostrycin began with the cycloaddition of diene **438** to naphthazarin, and the corresponding addition to methoxynaphthazarin **437** seems an obvious route to the carbon skeleton of bostrycin. However, model reactions revealed that regioselectivity is poor and the "wrong" isomer (**440**) predominates, as predicted[220] on the grounds that the influence of the two chelated hydroxyls should cancel out so that electron release from the methoxyl group would control the regiochemistry (see **437**). Following previous work,[222] this problem of regiocontrol was



437 438 439 440

overcome[220] by adopting the diphenylmethylene ether **442** as the starting dienophile, arguing that the electronic of the ether functions would cancel, leaving the chelated hydroxyl in control of the cycloaddition. In practice, reaction of **442**, prepared from naphthopurpurin **441**, as shown, and diene **438**, using tetra-acetyl diborate as catalyst, gave **443** as the sole adduct. The rest of the synthesis (Scheme 50) followed that of Krohn,[221] leading to **444** (66% from **441**) and finally (±)-bostrycin **436**. The stereochemistry of **436** was established by X-ray analysis of its acetonide **445**, which also showed that ring A was quinonoid in the crystalline state. The chemical shift of H-6 in **445** at δ 6.15 ($CDCl_3$) (δ 6.44 in DMSO-d_6 solution) indicates that the same tautomer predominates in solution,[223] and by the same reasoning **444** also exists in the form shown ($\delta_{H\text{-}6}$ 6.45 in DMSO-d_6 solution). Accordingly, the structure of bostrycin was revised from **435** to **436**.[220]

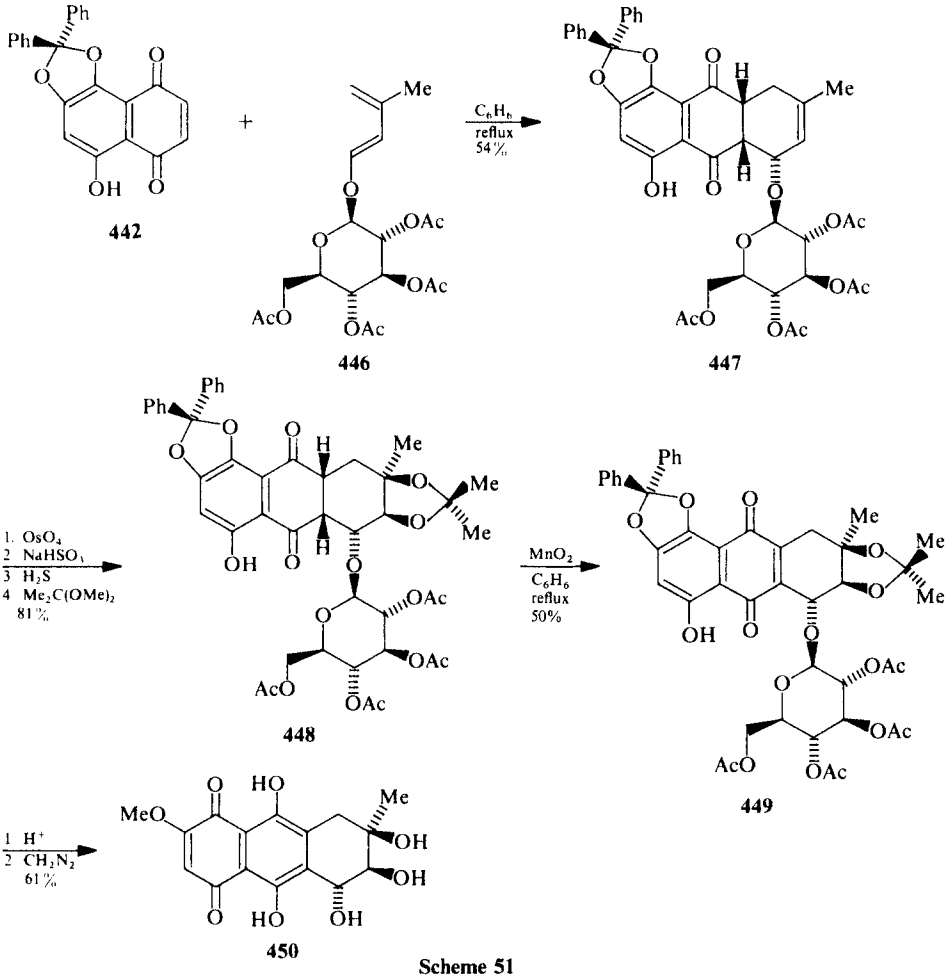
This was further confirmed by an asymmetric synthesis of the enantiomer reported briefly by Stoodley.[224] The Kelly synthetic route was followed using his dienophile **442**, but replacing diene **438** by the chiral diene **446** derived from glucose.[225] Previous experience[226] based on the diastereofacial reactivity of the analogue **446** (TMSO in place of Me) indicated that addition of **446** to **442** should give mainly the adduct **447**, which could be transformed into optically active bostrycin. In practice, the cycloaddition (Scheme 51) gave a 63:21:13:3 mixture of adducts from which the major component **447** crystallized (54%) on adding ether. Osmylation of **447** gave an osmium dimer which was cleaved to the diol with hydrogen sulphide and isolated as the acetonide **448**. Oxidation to the quinone **449** was achieved with activated manganese dioxide in boiling benzene, and the absolute structure was established by an X-ray crystallographic analysis. Finally, removal of the



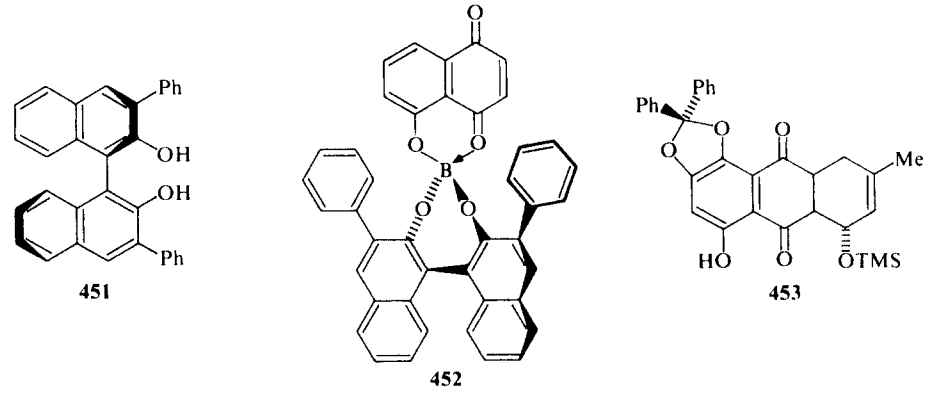
Scheme 50

protecting groups and treatment with diazomethane yielded (+)-bostrycin **450** spectroscopically identical to natural bostrycin but of opposite rotation. Clearly **450** is *ent*-bostrycin and the absolute configuration of the natural pigment, (−)-bostrycin, is represented by **436**.

Prior to Stoodley's work, Kelly[227, 228] briefly reported another approach to the asymmetric synthesis of bostrycin, in which one face of a juglone dienophile was blocked using Cram's[229] chiral binaphthol **451**. Thus, treating juglone with $BH_3 \cdot THF$ in tetrahydrofuran containing acetic acid, followed by addition of (S)-**451**, gave a complex, regarded as **452**, which should enforce diene cycloaddition at the "underside" of the juglone moiety. Model experiments showed that to be the case, cycloaddition proceeding regiospecifically to give adducts in high yields and very high enantiomeric excess with full recovery of the chiral ligand. Repeating the procedure starting with dienophile **442** and diene **438** afforded adduct **453** in optically active form, which was converted, following Scheme 50, into (+)-bostrycin **450**. In a later amendment[228] it was reported that (−)-bostrycin has also been obtained by repeating the synthesis using (R)-**451**.

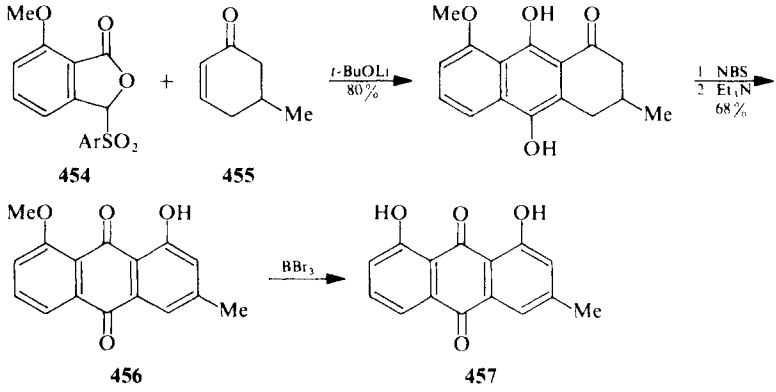

442
446
C_6H_6
reflux
54%
447
1. OsO_4
2. $NaHSO_3$
3. H_2S
4. $Me_2C(OMe)_2$
81%
448
MnO_2
C_6H_6
reflux
50%
449
1. H^+
2. CH_2N_2
61%
450

Scheme 51

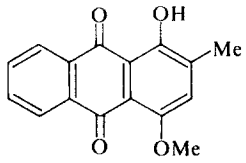

451
452
453

B. Phthalide Annulation and Related Methods

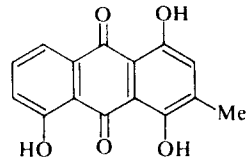
As already indicated, anthraquinone synthesis by cyclization of *o*-benzoylbenzoic acids is obsolescent and the methods to be considered now are the modern regiospecific equivalents. Hauser's phthalide annulation is an excellent method for the synthesis of a wide range of polycyclic aromatic compounds; it is convergent, under strict regiocontrol, and allows the use of a variety of Michael acceptors. The syntheses of the naphthoquinones cryptosporin, deoxyfrenolicin, and bikaverin have already been described. A handful of natural anthraquinones have been made in this way, the first being Hauser's[230] preparation of the very common chrysophanol[14, 15] **457** from phthalide **454**[231] and cyclohexenone **455**, as shown. The intermediate 8-methyl ether **456** is also a natural quinone.[15] 1-Hydroxy- and 1-hydroxy-2-methylanthraquinone, pachybasin **382**, and rhein were secured by the same sequence, and similar results were reported by Kraus[152] the following year. Several routes[152, 243] are available to phthalides with suitable substituents at C-3 which both assist anion formation and serve as final leaving groups.



Russell and Warrener[232] used a quinone monoketal[235] as Michael acceptor in their syntheses of madeirin **458** and digitopurpone **459** found in *Digitalis* spp.[15] and islandicin **463** originally isolated from cultures of *Penicillium islandicum*.[14] The route to islandicin is outlined in Scheme 52. Adding the anion of phthalide **460** to ketal **461** leads directly to anthraquinone **462**, and hence islandicin **463**. Alternatively, islandicin can also be secured by treating ketal **464** with the anion of **454**. Conversely, the isomeric digitopurpone **459** is accessible starting from **464** and **460**. Yields were around 50–60%; the extent, if any, to which Michael addition occurs to the methyl enone in **461** and **464** was not mentioned in a brief report.[232] The use of quinone monoacetals

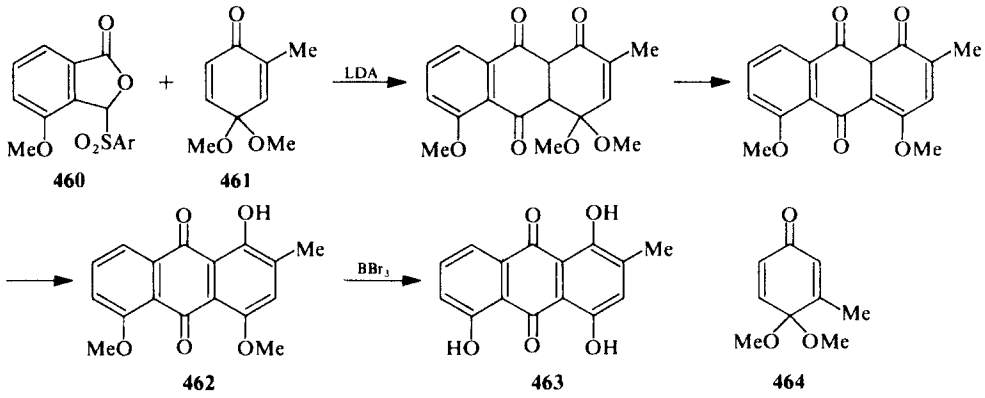


458



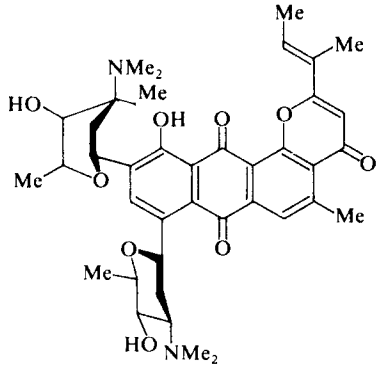
459

restricts the method to the preparation of quinizarin (1,4-dihydroxyanthraquinone) derivatives which can be obtained by Diels–Alder reactions, for example, islandicin,[233] digitopurpone,[233] erythroglaucin,[233] and others[234] have been synthesized using appropriate dienes.



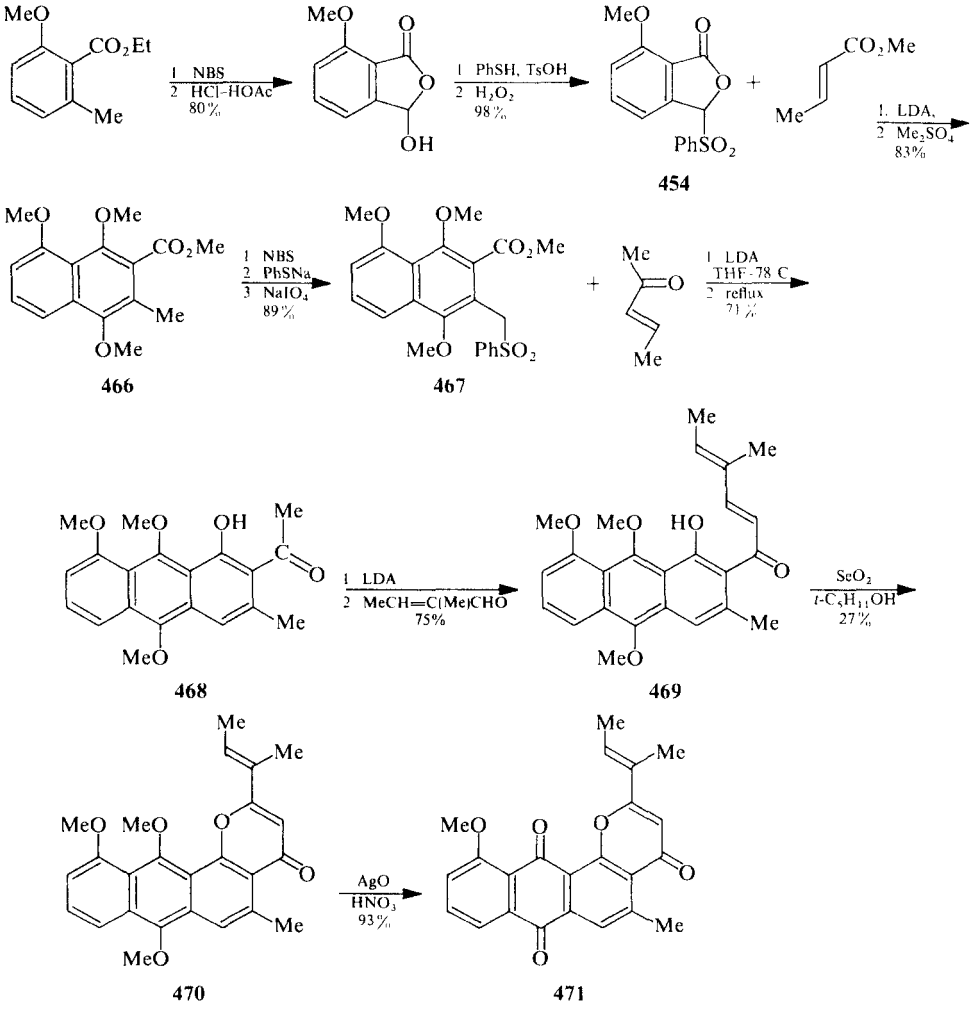
460 461 462 463 464

Scheme 52



465

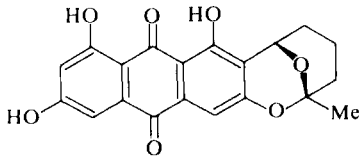
Kidamycinone. Kidamycin **465** is one of a small group of anticancer antibiotics produced by *Streptomyces* spp. which are anthraquinones of an usual type found as *C*-glycosides.[15] Synthetic work in this area is confined to that of Hauser and Rhee,[236] who secured the aglycone of kidamycin as its methyl ether **471** via phthalide annulation. The tetracyclic system of **471** is common to the whole group. The synthesis (Scheme 53) progresses through a series of annulations leading to naphthalene and then anthracene intermediates, the pyrone ring and side chain being added last. The naphthalene **466** was made



Scheme 53

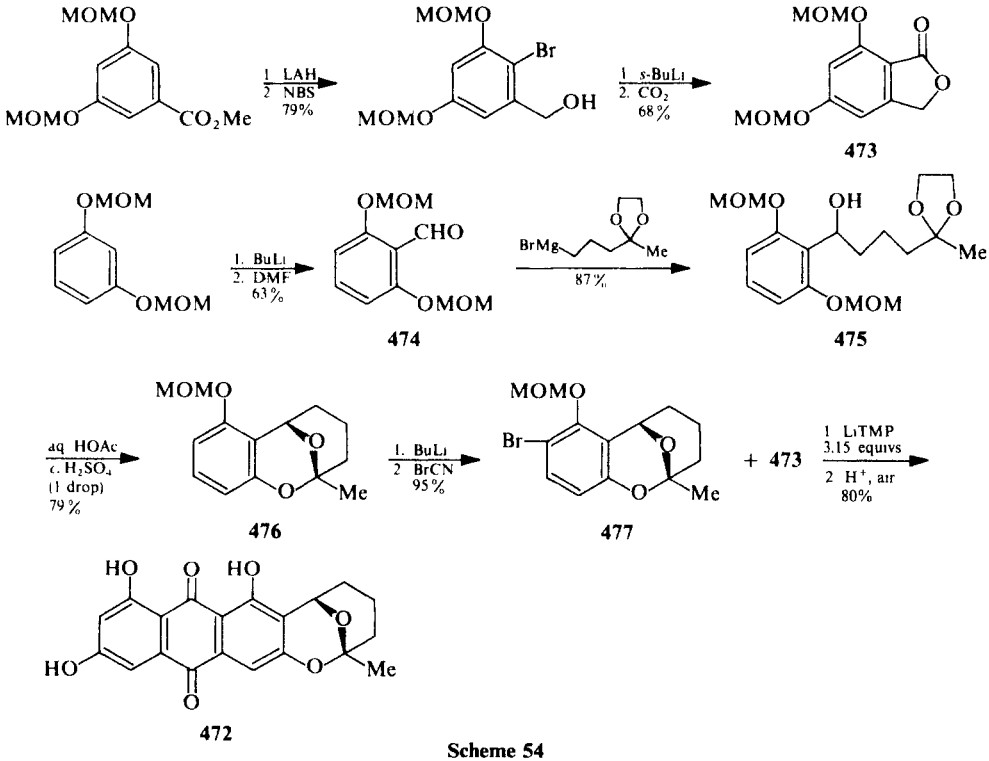
by Michael addition of phthalide **454** to methyl crotonate, and then enlarged to the anthracene **468** by activation of the aromatic methyl group and addition of the anion of **467** to 3-penten-2-one, followed by heating to eliminate benzenesulphinic acid. With the *o*-hydroxy acetyl groups in place the stage was set to construct the pyrone ring and side chain. After pursuing a false trail based on prior model reactions starting from *o*-hydroxyacetophenone, ketone **469** was secured by treating the dianion of **468** with tiglaldehyde, but cyclization to the pyrone was surprisingly difficult. It was eventually achieved by refluxing **469** with selenium dioxide in *t*-pentyl alcohol to give **470** in low yields (50% **469** recovered). Final oxidative demethylation yielded kidamycinone methyl ether **471**.

Averufin. A variation of the phthalide + enone annulation method is the regiospecific addition of a phthalide anion to a benzyne.[237] It was used by Townsend[239] in one of his syntheses of averufin **472**, a mould metabolite[14, 15] of great interest as an intermediate in aflatoxin biosynthesis. The key compounds, phthalide **473** and benzyne precursor **477**, were protected by methoxymethylation to ensure that the conditions of the final deprotection step would not disturb the bicyclic acetal, and in addition they ensured regiospecific metalation at an earlier stage (Scheme 54). The acetal **476** was obtained from the unstable alcohol **475** by careful cyclization with retention of the second methoxymethyl group. The latter then directed the ensuing metalation to the *ortho* position leading to the benzyne precursor **477**. The next step was critical and again the regiochemistry was controlled by the methoxymethyl group in **477**. Treatment of phthalide **473** with excess of lithium 2,2,6,6-tetramethylpiperidide and then bromide **477** gave, after exposure to air, a mixture of fully and partially protected anthraquinones easily deprotected under mild acid conditions to give (±)-averufin[238] **472**. A good yield was obtained despite the absence of a leaving group in phthalide **473**.



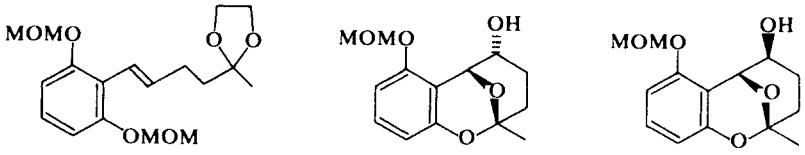
472

A synthesis of (+)-averufin was briefly reported later by Townsend.[240] The same benzyne cycloaddition route was followed, while the approach to the optically active acetal **476** was different. The protected aldehyde **474** was converted to the *trans* alkene **478** by a Wittig reaction, and then by osmylation and mild acid treatment, which selectively removed one of the

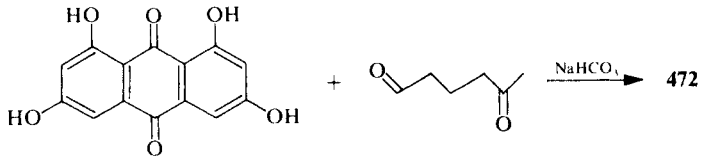


Scheme 54

MOM groups, into the (±)-*endo* or *exo* alcohol, **479** or **480**. Resolution of the *endo* alcohol afforded the (+) and (−) enantiomers, and the former was shown to have the absolute configuration depicted in **479** by the exciton chirality method[102] using the bis-*p*-chlorobenzoate of the diol derived from **479** by deprotection. Dehydroxylation of (+)-**479** by conversion to its phenyl thionocarbonate and reduction with tri-*n*-butyltin hydride[241] then provided (*S*)-(−) **476** which was transformed into (*S*)-(+)-averufin **472** following Scheme 54. Another synthesis by Townsend is discussed below.

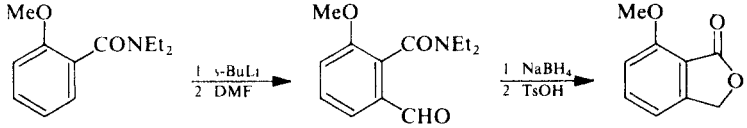


An attractively simple approach[242] to (±)-averufin consists in the reaction of anthraquinone **481** with 5-oxohexanal. The initial hydroxyalkylation is followed by acetal formation, but unfortunately the yield was only 6.5% despite much effort.



481

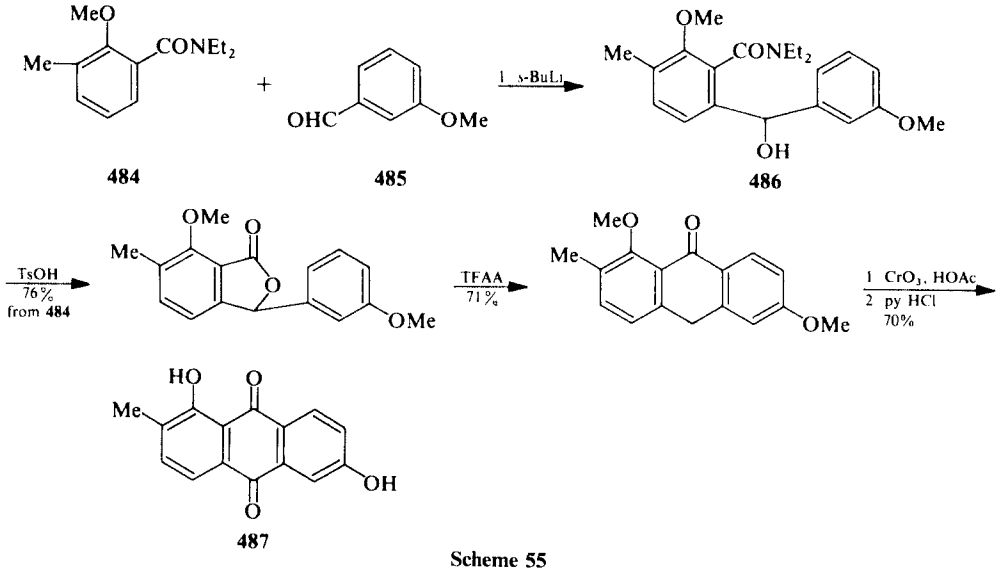
Another useful synthetic route to anthraquinones also involves phthalide intermediates. It proceeds by the reaction of an *o*-lithiated tertiary benzamide (in particular) with an aromatic aldehyde and subsequent cyclization,[243] and is both convergent and regiospecific. The method can be used to make a variety of polycyclic and heterocyclic compounds, not least providing a useful short route to simple phthalides from convenient starting materials (e.g., **482** → **483**).[244] This approach to anthraquinones was demonstrated by Snieckus[245] in syntheses of islandicin, digitopurpone, erythroglaucin, cynodontin, and soranjidiol **487**, which is outlined in Scheme 55. The intermediate alcohol **486**, obtained by coupling **484** and **485**, was not purified. Deprotonation of the methyl group in **484** did not present a problem apparently, but if necessary, prior protection is available.[247, 250]



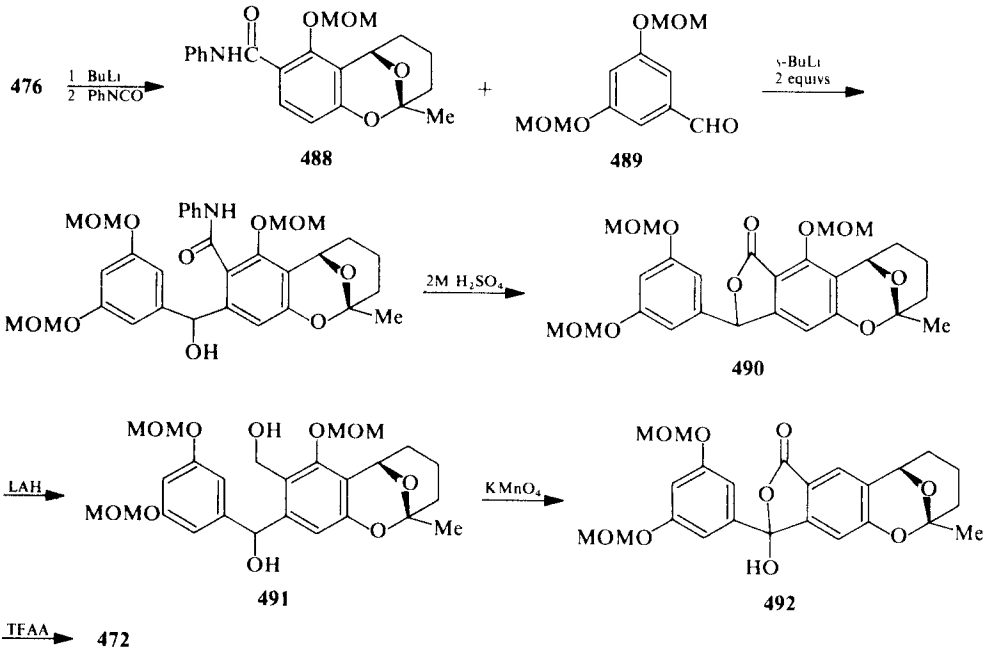
482 **483**

Secondary amides can also be used for initial *ortho* metalation without significant disadvantage,[243, 246] an example being Townsend's alternative synthesis[239] of (±)-averufin (Scheme 56). The cyclic ketal **476** was converted to anilide **488**, as shown, and after lithiation allowed to react with protected aldehyde **489**. The resulting phthalide **490** was resistant to hydrogenolysis, and was therefore reduced to the diol **491** and reoxidized to pseudoacid **492**. Final cyclization and deprotection afforded (±)-averufin in 40–45% overall yield from ketal **476**, compared to 25–30% by the shorter benzyne route shown in Scheme 54.

Despite the high regioselectivity observed in benzamide metalation, situations arise where reaction can occur at more than one site, the dimethoxy-

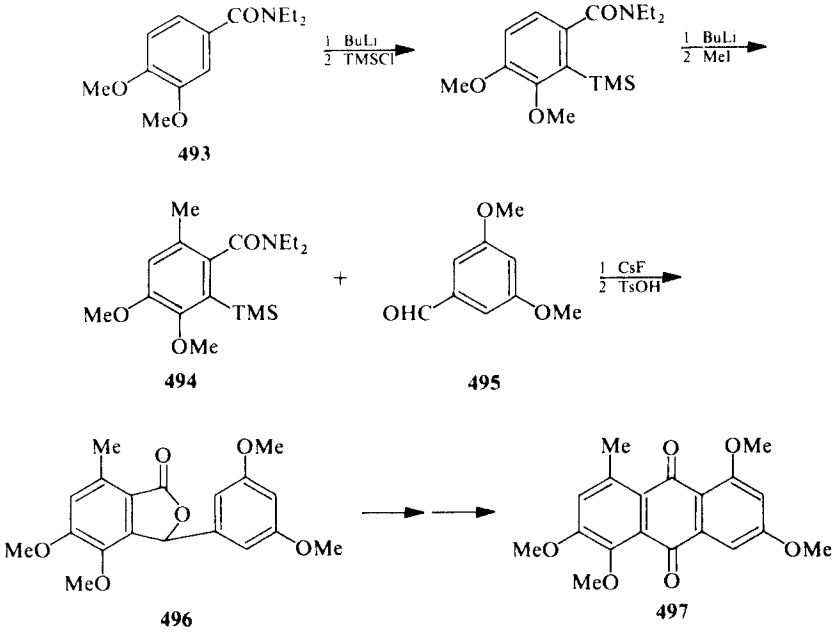


Scheme 55



Scheme 56

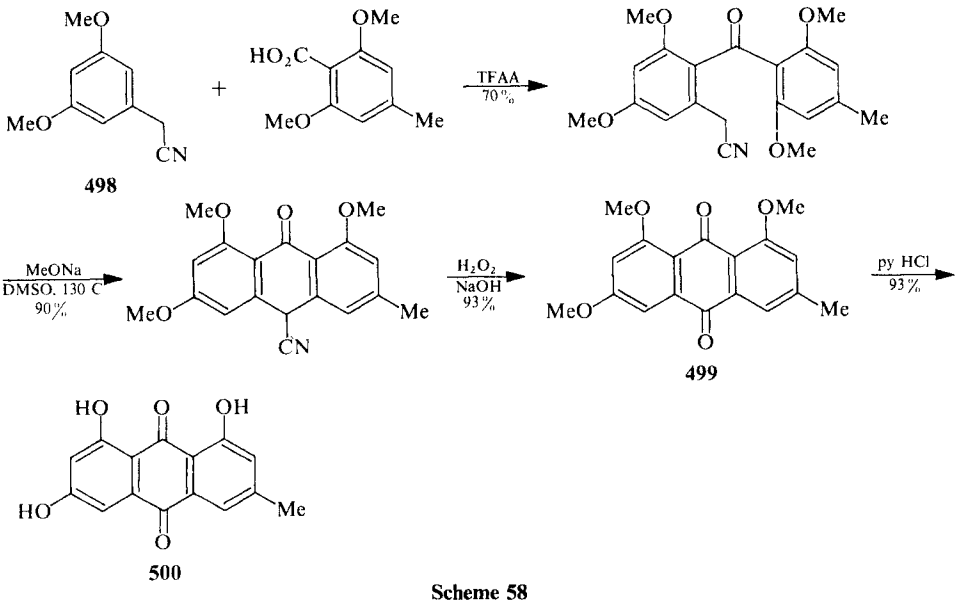
benzamide **493** is an example. However Snieckus[247] showed that metalation at C-6 can be ensured by first blocking the more reactive C-2 position by silylation, and used that to advantage in a synthesis[248] of erythrolaccin tetramethyl ether **497**. Successive substitution via metalation converted **493** into **494** in a one-pot sequence (95%), and **494** was then desilylated with caesium fluoride in the presence of aldehyde **495** to give the phthalide **496** (40%) and finally quinone **497** by the standard procedure (Scheme 57). Alternatively, the silyl group in **494** could be replaced by bromine and then exchanged with lithium before reaction with aldehyde **495**. α-Methyl-substituted anthraquinones were formerly known only in insects, but several have now been found in higher plants.[249]



Scheme 57

C. Other Methods

Another approach to anthraquinone synthesis, akin to the *o*-benzoylbenzoic acid method, is the cyclization of *o*-benzoylbenzyl cyanides introduced by Hassall[251] before the regiospecific methods described above were available. The required precursors are an *o*-methoxybenzoic acid and a suitably substituted benzyl cyanide, and the preparation of emodin **500**,[252] one of the

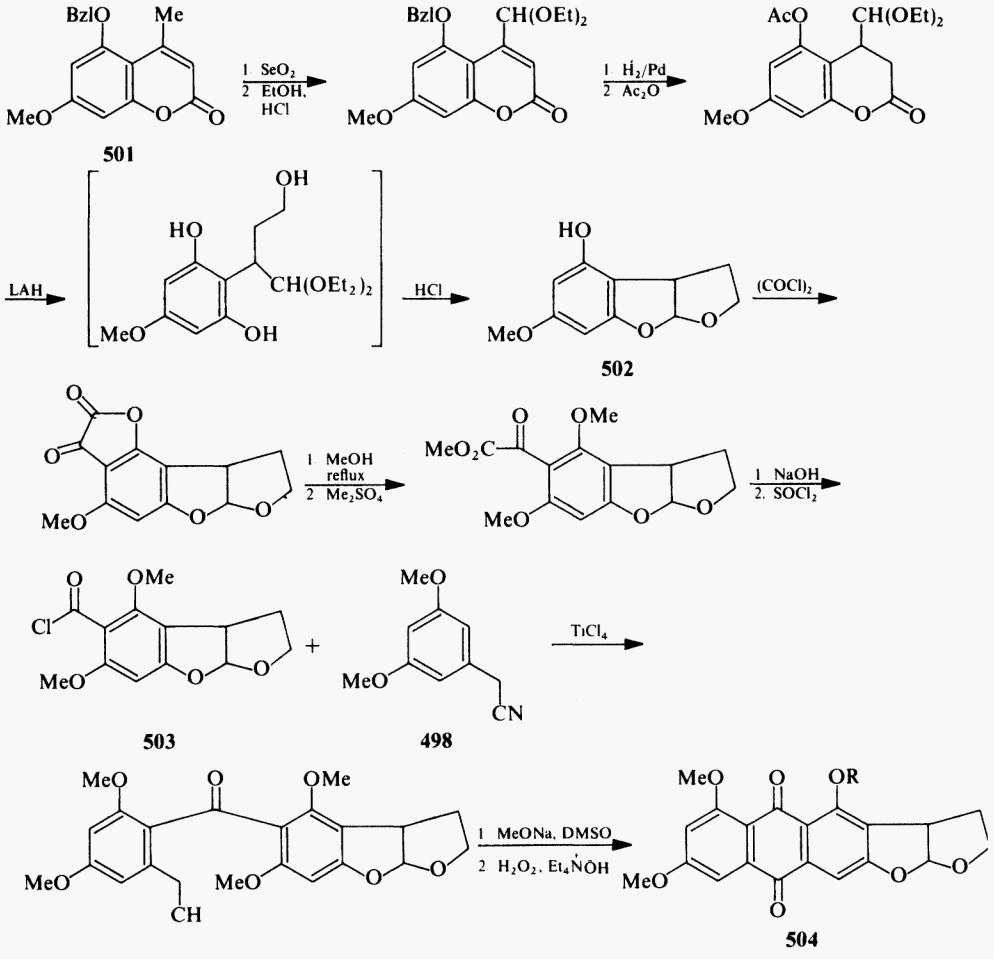


Scheme 58

most widely distributed natural anthraquinones,[14,15] is illustrative (Scheme 58). Partial demethylation of **499**[254] with boron tribromide gave physcion, the 6-*O*-methyl ether of emodin, another quinone frequently encountered in higher plants and fungi.[14,15] The method has been used to prepare the crinoid pigment ptilometric acid[253] and the methyl ether of the mould metabolite aversin **504** (R = H), using the same nitrile **498** in each case. As the initial condensation is not regiospecific, the method is inferior to those described above, but the elaboration of the tetrahydrofuranofurano-quinone **504** is of interest (Scheme 59).

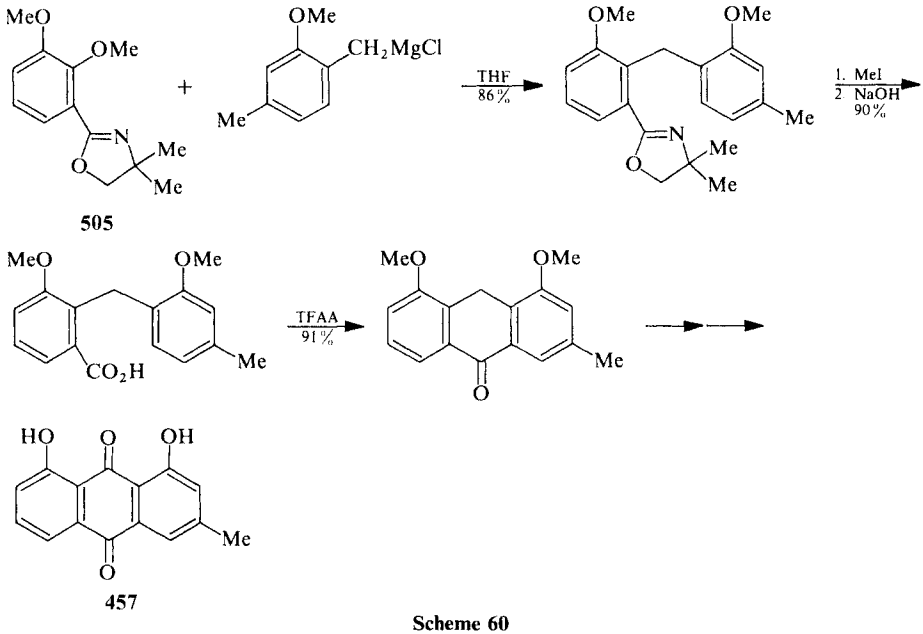
Phenol **502**,[255] derived from the protected coumarin **501**, as shown, was converted into the acid chloride **503** and condensed with nitrile **498**. Hassall cyclization of the product and oxidation then provided (±)-aversin methyl ether **504** (R = Me).[254]

o-Benzylbenzoic acids are now available by a new route. Meyers[256] found that nucleophilic displacement of *o*-methoxy groups in aryloxazolines such as **505** could be effected with Grignard reagents, but the yield was very poor with benzylmagnesium chloride. Sargent[257] has found that if the Grignard reagent is prepared using the anthracene–$Mg(THF)_3$ complex[258] as magnesium source, the displacement reaction then proceeds in good yield. The sequence in Scheme 60 leads to chrysophanol, and the permethyl ethers of emodin, digitopurpone, islandicin, and soranjidiol were prepared in the same way.

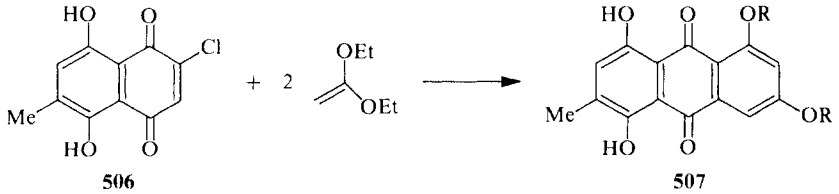


Scheme 59

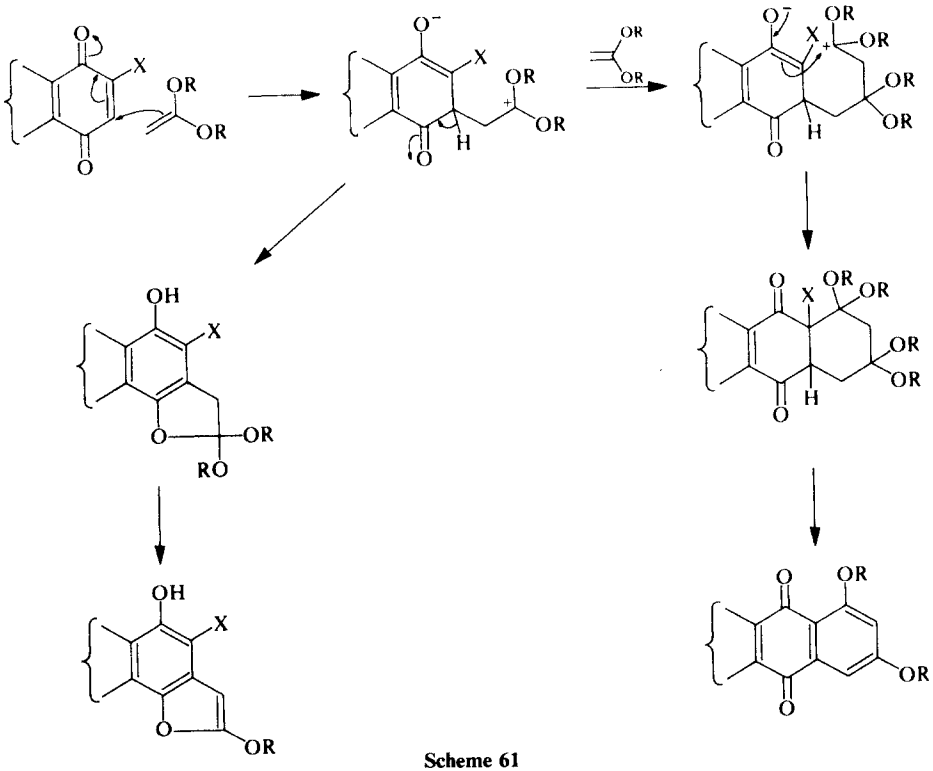
In early studies McElvain[259] observed that 2-bromo-1,4-naphthoquinone and ketene diethyl acetal gave a modest yield of 1,3-diethoxyanthraquinone by a 1:2-addition process, whereas naphthoquinone itself and simple benzoquinones formed ethoxyfurans and related compounds resulting from 1:1-addition. Pursuing this, Brassard[260] made the important observation that the 1:2 process was regiospecific and therefore of potential synthetic value. For example, the naphthazarin **506** gave **507** (R = Et) (34%) and no isomer was detected; dealkylation provided the mould metabolite catenarin **507** (R = H). The mechanism of the reaction is not established, but Cameron's[261] proposal



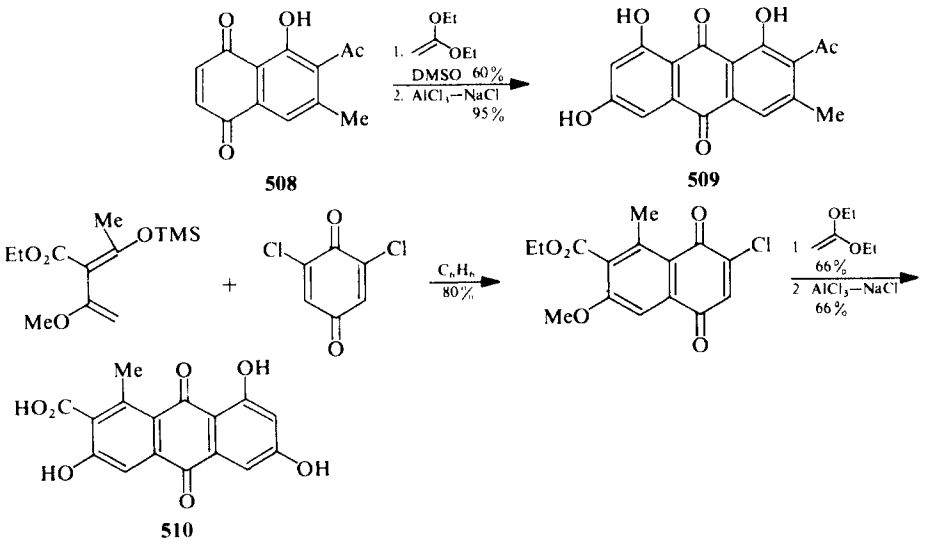
Scheme 60



(Scheme 61) is very plausible, and the zwitterionic intermediates explain the need for highly polar solvents to ensure quinone formation. Regiocontrol of the initial nucleophilic addition is exerted by the electronic effects of substituents as in Diels–Alder addition, and the presence of halogen is desirable but not essential. The 1:2-addition sequence is inferior to diene cycloaddition, but under appropriate reaction conditions acceptable yields can be obtained, and a few 1,3-dioxygenated natural anthraquinones have been synthesized in this way. Cameron,[262] for example, prepared the insect pigments 2-acetylemodin **509** from stypandrone **508** (which has been synthesized), and laccaic acid D **510** by diene addition to 2,6-dichlorobenzoquinone followed by ketene acetal addition.[263] By further manipulation a hydroxyl group was introduced at C-4 to give kermesic acid, which Brassard[264] has obtained by Diels–Alder reactions.

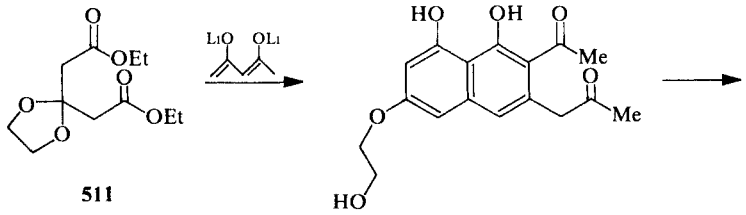


Scheme 61

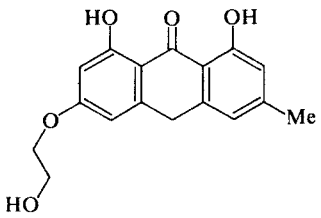


Despite McElvain's experience,[259] naphthoquinones can be obtained[265] from benzoquinones by ketene acetal addition, but is not a significant route to natural products.[266]

A number of biomimetic syntheses of anthraquinones have been successfully accomplished, some in excellent yield. In this way Harris[267] obtained emodin and chrysophanol, which are typical polyketide-derived pigments. The steps to chrysophanolanthrone **172** were indicated on page 141, and a final oxidation gave the quinone. Emodin was obtained similarly, starting from the protected 3-oxoglutarate, **511**. After treatment with dilithioacetylacetone, the resulting poly-β-ketone cyclized to a naphthol (39%), whence further aldol cyclization and dehydration gave the anthrone **512** and thus emodin in good yield. These elegant syntheses of anthraquinones from poly-β-ketones served their purpose in providing experimental support for the polyketide theory of biogenesis, but are unlikely to be further extended.*



511

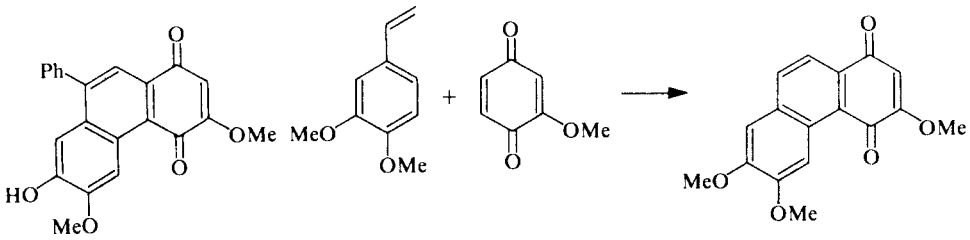


512

5. PHENANTHRAQUINONES

Apart from those of diterpenoid origin, about 10 other natural phenanthraquinones are known, the majority being simple 1,4-quinones found in higher plants, particularly in the Orchidaceae, a good source of phenanthrenes and 9,10-dihydrophenanthrenes. In the biosynthesis[268] of the latter, two rings are derived from phenylalanine and the third from acetate–malonate. This could be true for all the plant quinones, excepting latinone **513**,[269] which has a

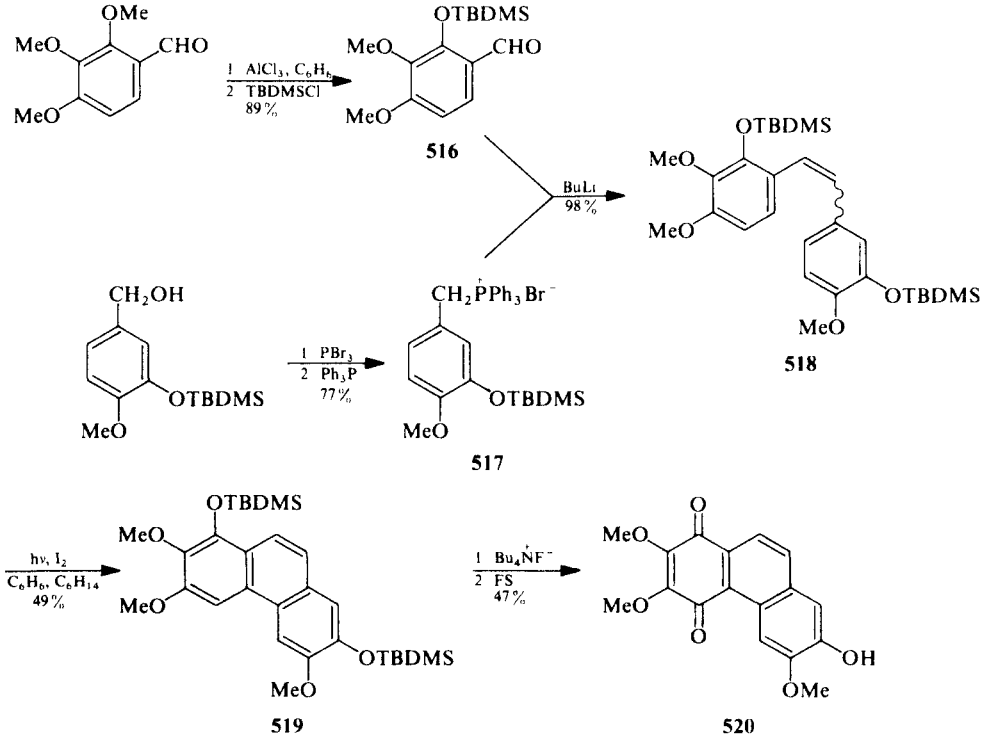
* However, see reference 88.



513 514 515

phenyl side chain. A smaller group of phenanthraquinones, elaborated mainly by *Streptomyces* spp., are more highly substituted 9,10-quinones of polyketide origin.[270]

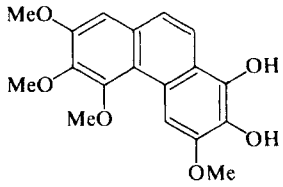
Latinone,[269] sphenone-A,[271] and annoquinone-A[272] have all been synthesized by addition of the appropriate styrene to methoxybenzoquinone. The formation[271] of the cytotoxic sphenone A **515** from styrene **514** is illustrative.



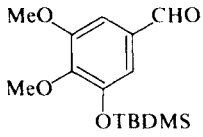
516 517 518 519 520

Scheme 62

Photochemical cyclization of *cis*-stilbenes is a general method of phenanthrene synthesis and it was used by Pettit[273] for the synthesis of the PS cell-growth inhibitor combretastatin C-1 **520**, which accompanies combretastatin A-1 **521** in *Combretum caffrum*. A Wittig reaction between **516** and **517** afforded a *Z*/*E* mixture of stilbenes **518** which, when irradiated in the presence of iodine, gave phenanthrene **519** and the regioisomer which were separated (Scheme 62). An alternative route involving aldehyde **522** in place of **516** gave a lower overall yield.



521



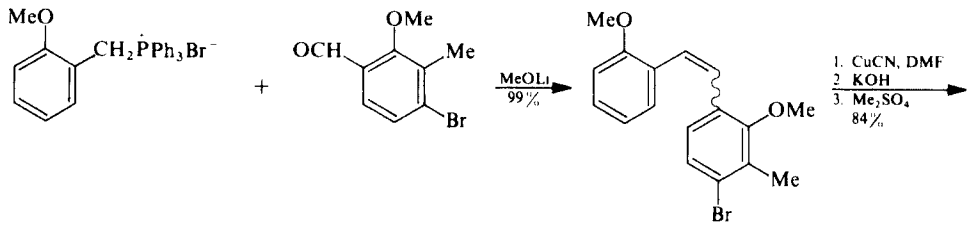
522

The synthesis of piloquinone **527** (R = H) was approached in the same way (Scheme 63). As acylated stilbenes do not undergo photocyclization, stilbene **523** was prepared (mainly *cis* when formed in dimethylformamide solution, and mainly *trans* in methanol) and the bromine was then replaced by an ester group by standard reactions. Cyclization of **524** provided the phenanthrene **525** (35%), accompanied by 16% of the 1-demethoxy compound by elimination of methanol.[275] To introduce the side chain it was found necessary to replace the ester group in **525** by an aldehyde function. The final oxidation, on the diacetate corresponding to **526**, was difficult. The trimethyl ether of 4-hydroxypiloquinone **527** (R = OH) was synthesized by the same route.[276]

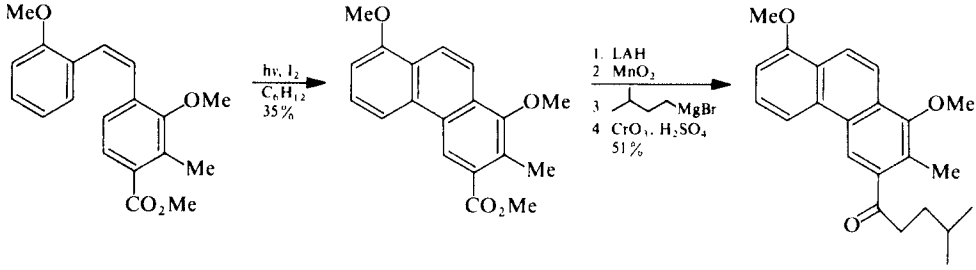
6. POLYCYCLIC QUINONES

Benz[a]anthraquinones. This is a small group of bacterial quinones[14,15] which show antibiotic and antitumor activities. They differ in structure mainly in the oxidation level of ring D and the presence or absence of sugars. Synthetic interest has been limited so far to the most simple examples, tetrangulol **528** and ochromycinone **539**, and the challenge of more difficult targets, for example, aquayamycin **529**, remains.

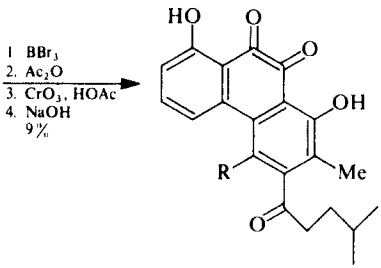
Tetrangulol has been obtained,[277] in very poor yield, by oxidative alkylation of quinone **530** with **531** to give **532** (82%), but on treatment with sodium carbonate cyclization occurred mainly *para* to the phenolic group to form **533** (70%). The yield of tetrangulol **528** was only 6%, dehydrogenation occurring during workup.



523

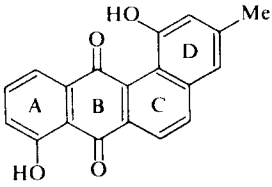


524 525 526

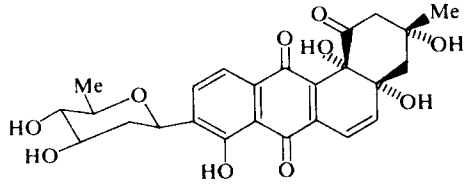


527

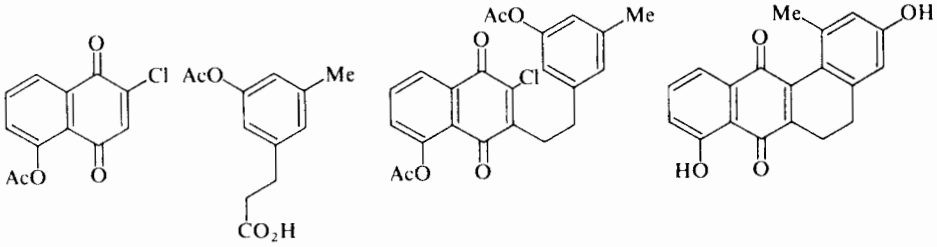
Scheme 63



528

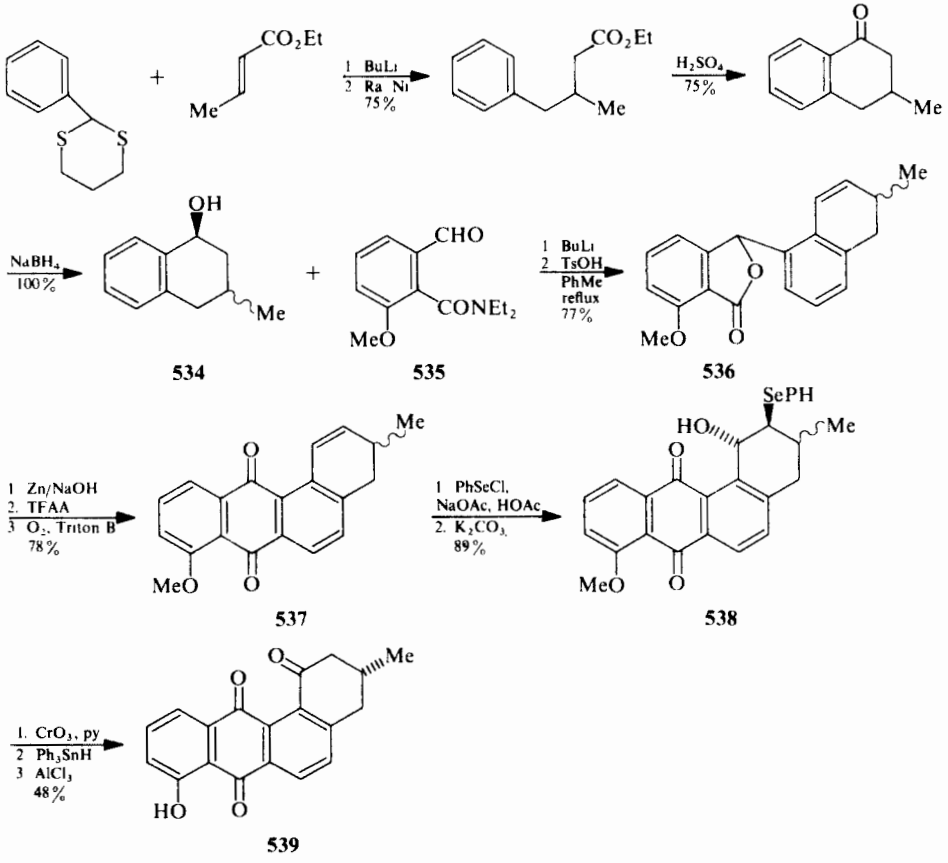


529



530 531 532 533

Snieckus[278] has extended his earlier work on anthraquinones to a synthesis of (±)-ochromycinone **539** and its methyl ether (=X-14881C,[279] also a natural compound). Starting from a commercially available phenyldithiane, a precursor to rings C and D was constructed in the form of the tetralol **534**

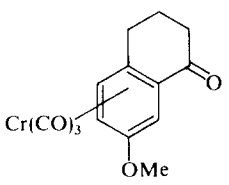


534 535 536 537 538 539

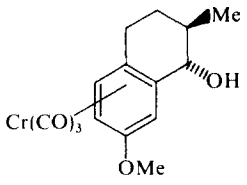
Scheme 64

which, in the key step, was coupled to aldehyde **535** (readily available by lithiation of the methoxyamide and quenching with dimethylformamide), thus leading to phthalide **536** and the tetracylic quinone. The alcohol **534** was obtained as a *cis–trans* mixture which had been separated previously.[280] Metalation *ortho* to the benzyl alcohol function was examined by dilithiation of the separate isomers, followed by quenching with deuterium oxide. It was found that deuterium incorporation was 86% for *cis*, but only 25% for *trans* **534**. Consequently, the *cis* isomer was used in the next step. Coupling with aldehyde **535** and immediate dehydration of the crude product gave phthalide **536** in good yield. In the final modification of ring D in **537**, selenohydroxylation was followed by oxidation of **538** to the ketone and then reductive elimination of the selenium (Scheme 64).

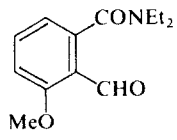
The Snieckus route to ochromycinone broadly followed the earlier strategy of Uemura[281] in his synthesis of the 3-deoxy analogue **546** (R = H) of the *Streptomyces* pigment rabelomycin. The Japanese group had shown[282] earlier that deprotonation of 7-methoxytetral-1-ol occurred selectively at C-6 if the (η^6-arene)chromium tricarbonyl complex was used. Accordingly, the complex **540** was converted by standard reactions into **541**, which was treated with butyllithium followed by aldehyde **542**. Exposure to sunlight decomposed the complex, leaving a diastereoisomeric (but not regioisomeric) mixture of hydroxyphthalides (40–50%) which on dehydration yielded phthalide **543**. The latter was also obtained by lithiation of **541** at C-6, treatment with dimethylformamide, decomplexation, and dehydration to give the aldehyde **544**, which in turn was condensed with dilithiated 3-methoxy-benzanilide. Phthalide **543** was then converted to the benz[a]-anthrone **545**, which was oxidized with chromic acid to the ketoquinone **546** (R = Me). Final demethylation provided the targetted benz[a]anthraquinone **546** (R = H).



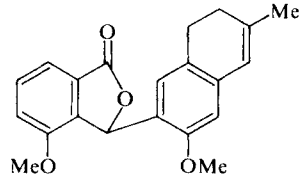
540



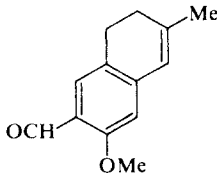
541



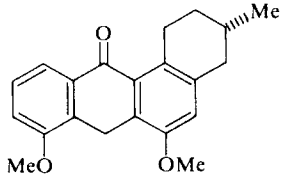
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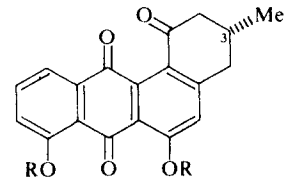
543



544

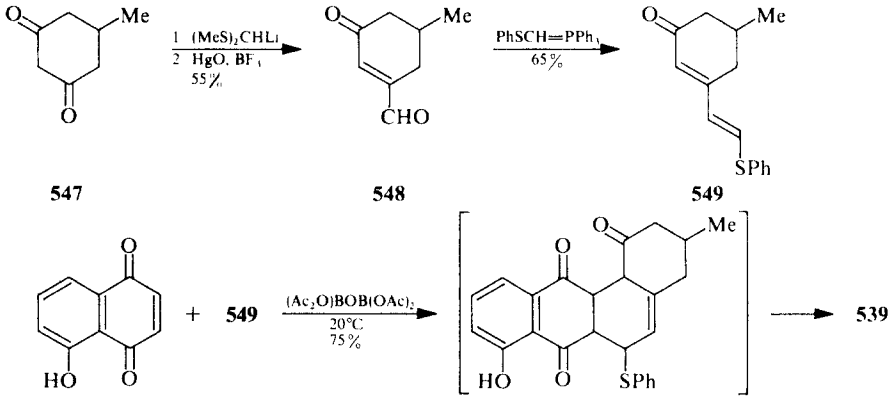


545



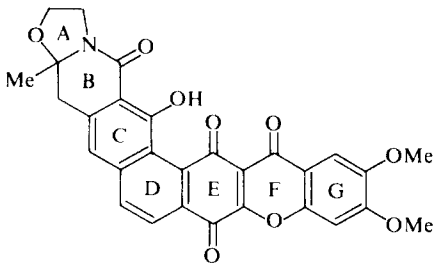
546

The Snieckus synthesis of ochromycinone achieved an overall yield of 21%, and it was reasonably suggested that further development of that strategy would be rewarding.[278] However, shortly afterwards Guingant[283] published briefly a short Diels–Alder synthesis in 25–40% overall yield, demonstrating once again the enormous value of the reaction. Starting from the commercially available diketone **547**, it was converted to the keto aldehyde **548** by Schlessinger's[284] method, followed by a selective Wittig reaction to give the dienone **549** obtained as the sole stereoisomer. Cycloaddition of **549** to juglone then yielded ochromycinone **539**, the intermediate adduct aromatizing spontaneously (Scheme 65). In previous work[285] with such push–pull dienes, the cycloadditions were effected under high pressure, but in this case catalysis by tetraacetyl diborate enabled the reaction to proceed at 20°C.



Scheme 65

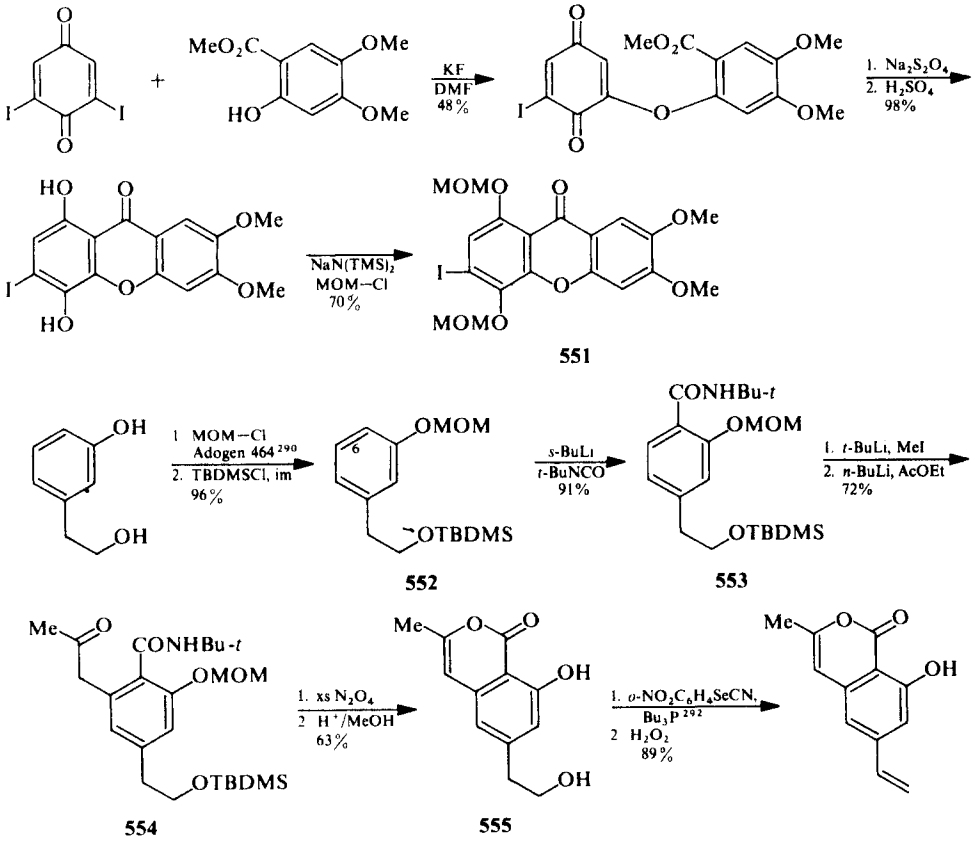
Cervinomycin A_2. Among quinone structures cervinomycin A_2 **550** is unique, although a few other natural products have related polycyclic structures which include xanthone and isoquinolone moieties. Both A_2 and the hydroquinone A_1 were isolated[286] from *Streptomyces cervinus* and were found to be



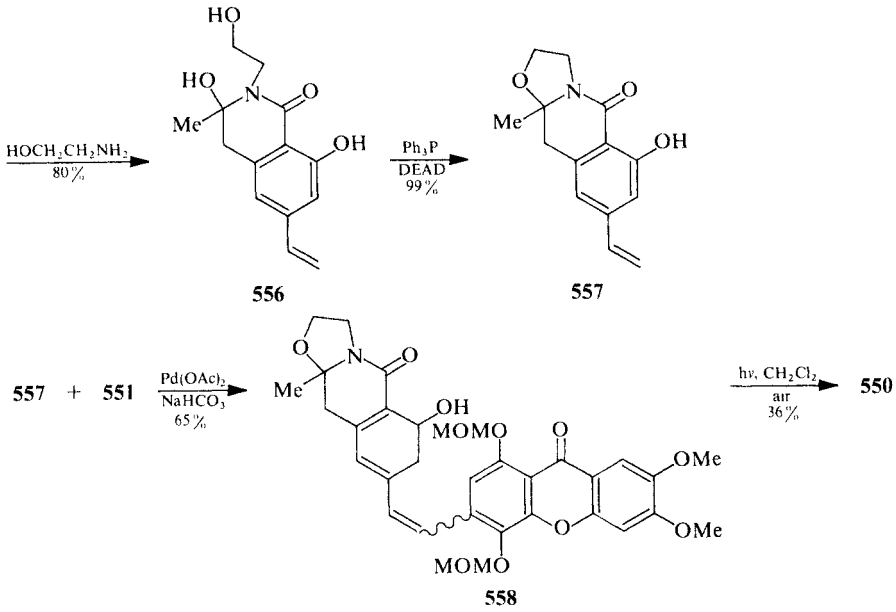
550

active against anaerobic bacteria and mycoplasmas, and the more soluble triacetate of A_1 "is being developed as a drug."[287]

Kelly[288] has designed a convergent synthesis of this heptacycle by constructing rings ABC and EFG separately, linking them in the form of a stilbene followed by a photochemical cyclization to create the phenanthrene portion of the molecule (Scheme 66). The protected xanthone **551** was readily prepared following Brassard's[289] procedure. In the construction of the ABC tricycle the protected diol **552** was selectively lithiated at C-6 under carefully chosen conditions (not disclosed in a brief communication) leading to amide **553**, the function of which was twofold, to provide eventually the quinolone carbonyl group in **550** and to serve as the activating group for the two successive metalations which led to **554**. The amide function was then removed by decomposition of the *N*-nitroso derivative[291] with simultaneous



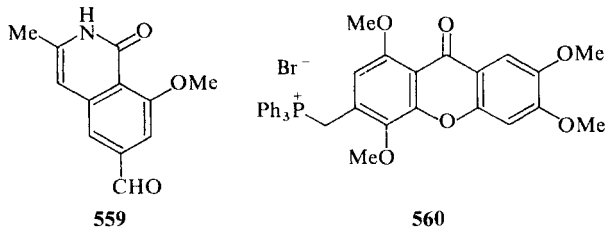
Scheme 66



Scheme 66 (*continued*)

cyclization to the coumarin and deprotection to form **555**. After dehydration of the alcohol, treatment with ethanolamine afforded **556** which, after some difficulty, was cyclized[293] to the oxazolidine **557**. The final steps proceeded very smoothly; the styrene **557** was linked to **551** by palladium-catalyzed arylation (the MOM protecting groups were essential) to form the stilbene **558**, which on irradiation while exposed to air cyclized regioselectively and very conveniently underwent deprotection and oxidation to give (±)-cervinomycin A_2 directly.

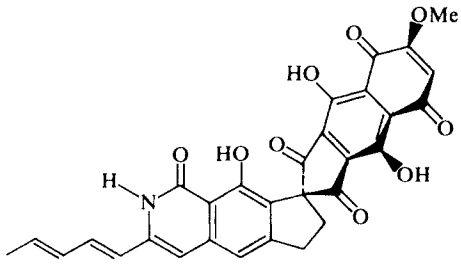
Prior to Kelly's synthesis Rama Rao[294] developed a route to the ABC ring moiety of cervinomycin, while Mehta[295] planned a synthesis which would lead to the stilbene **558** (unprotected) and finally cervinomycin A_2 by



559 **560**

photochemical cyclization. The BC and EFG synthons **559** and **560**, respectively, were successfully synthesized, but had not been combined at the time of publication.

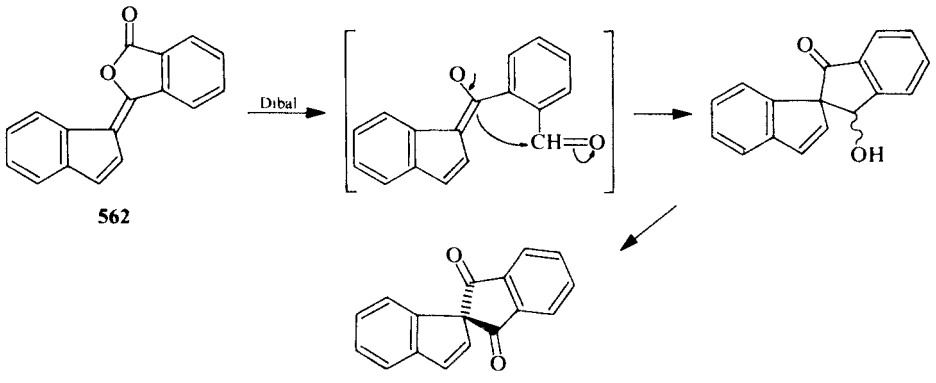
Fredericamycin **561**. The fredericamycins were isolated[296] from *Streptomyces griseus* collected at Frederick, Maryland. The main component fredericamycin A **561** exhibits[297] significant anticancer activity *in vivo*, and that coupled with the unique spiro[4,4]nonane structure flanked by naphthazarin and isoquinolone systems has inspired many synthetic endeavors. Most studies have focused on the spirononane system with some attention paid to the synthesis of the left (lower) and right (upper) "halves" of the molecule, but only Kelly[298] has succeeded in elaborating the whole molecule in another masterly synthesis of a complex quinone.



561

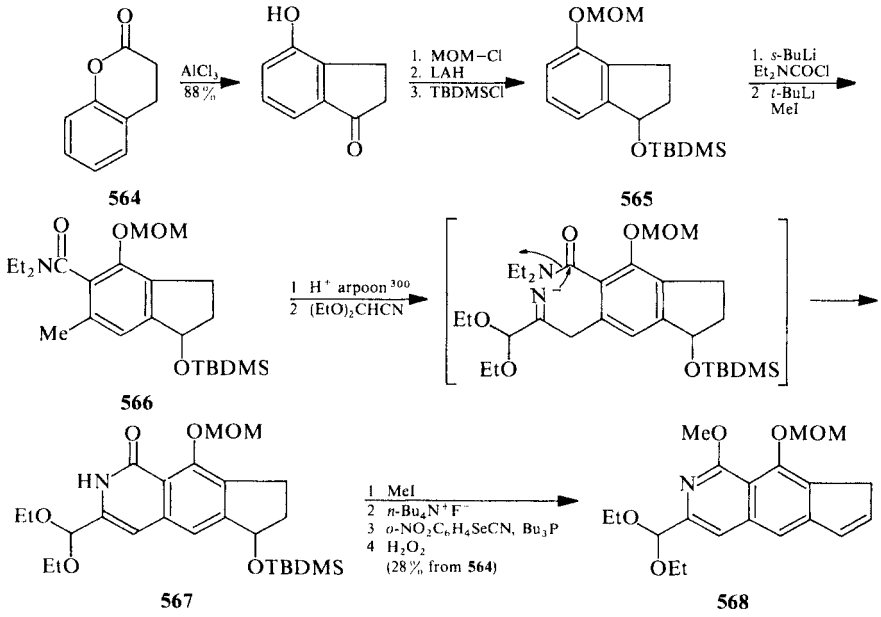
The synthetic approach envisaged was to construct the ABC and EF sections and then combine them in such a way as to elaborate the spiro system in the process. Model experiments demonstrated that if the two synthons could be linked to form a lactone of type **562**, then reduction with Dibal, followed by an *in situ* aldol reaction, would lead directly to the required spiro structure **563**. Lactone **562** is derived from indene and phthalic anhydride and the corresponding intermediates in the eventual fredericamycin synthesis were the "indene" **568** and the anhydride **570**. Much experimentation was required before these particular compounds were selected, and the overall synthesis was not without difficulties, occasionally of "Sisyphean" proportions.

The ABC "indene" synthon was elaborated as shown in Scheme 67. The known[299] rearrangement of dihydroisocoumarin **564** to 4-hydroxyindanone was improved (88%), and after protection of the indandiol (**565**) two side chains were introduced under careful control by successive *ortho*-directed metalations to give **566**, which was then neatly converted into the quinolone **567** by deprotonation and treatment with cyanoacetal. The yield of quinolone **567** from **564** was 33%. Conversion of **567** to the required indene **568** was



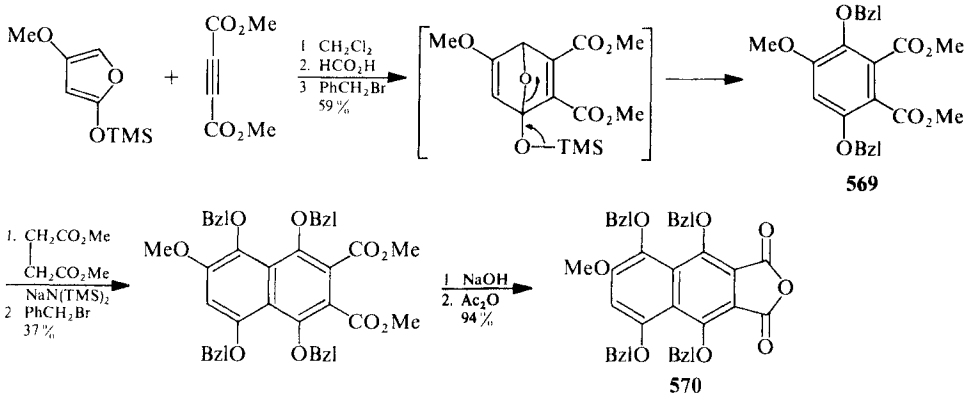
562 563

accomplished in four more steps in high yield. The acetal function was used later to attach the diene side chain. Synthesis of the highly substituted DEF anhydride **570** was achieved by condensing dimethyl succinate with phthalate **569**, which was prepared in two ways but preferably using a Diels–Alder cycloaddition as indicated (Scheme 68).



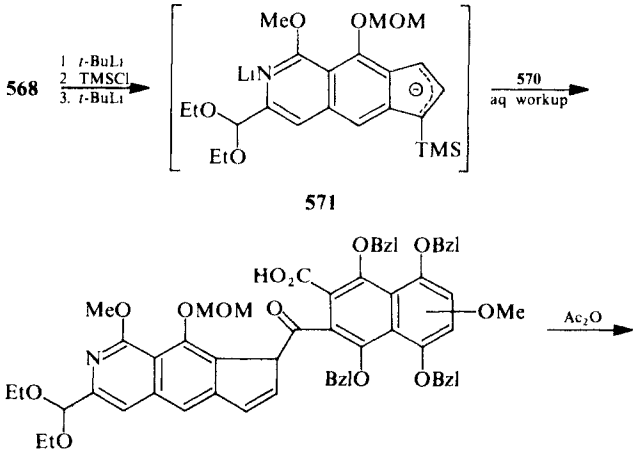
564 565 566 567 568

Scheme 67

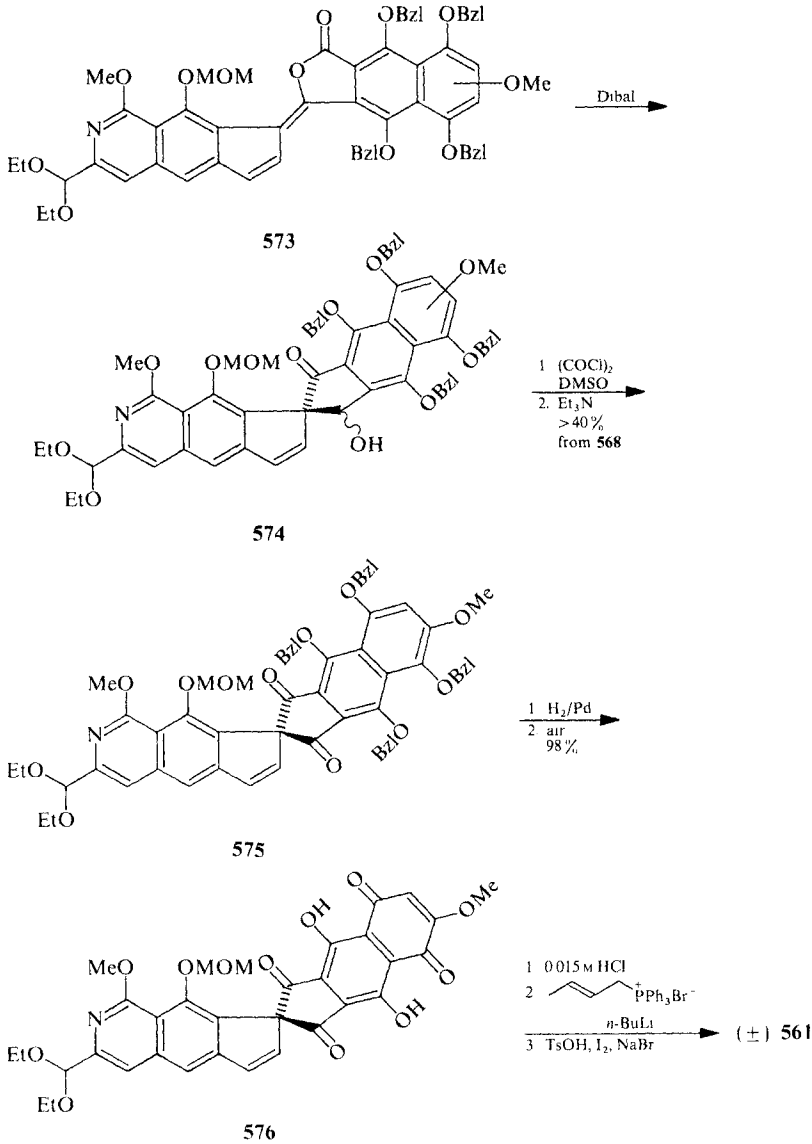


Scheme 68

The convergence of **568** and **570** was then achieved as follows (Scheme 69). Silylation of the cyclopentadiene ring in **568** occurs at the benzylic position remote from the MOM group, thus blocking that position; consequently, after the second deprotonation, acylation with **570** occurs at the desired position to give **572** as a mixture of tautomers/double bond isomers. If there is no TMS group present in **571**, acylation occurs at the "wrong" position in high yield. After conversion of **572** to lactone **573**, reduction with Dibal and *in situ* aldol reaction (see **562**) gave **574** as a mixture of diastereomers, which afforded a single compound **575** (40% from **568**) after Swern[301] oxidation.



Scheme 69

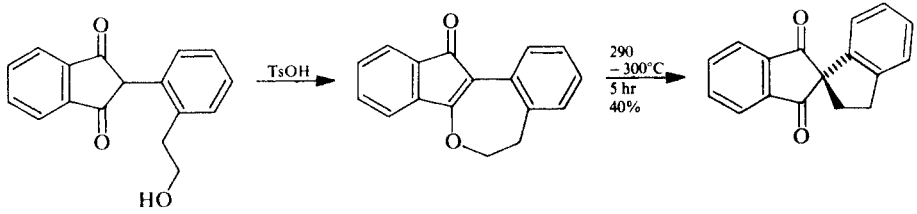


Scheme 69 (*continued*)

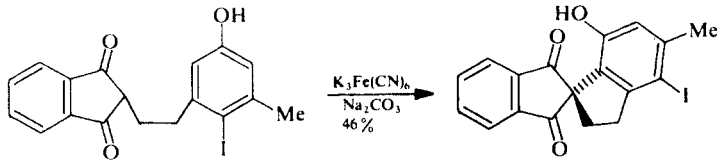
Hydrogenation of **575** reduced the olefinic bond and cleaved the benzyl ethers, and the resulting tetrahydroxynaphthalene was oxidized to the quinone **576** on exposure to air. Controlled hydrolysis of the acetal function in **576** without disturbing the MOM group gave an aldehyde to which the side chain

was attached by a Wittig reaction. The product was a mixture of stereoisomers which could be converted into the natural *trans*, *trans* isomer by treatment with iodine, which was conveniently done in one pot together with removal of the remaining protecting groups. (±)-Fredericamycin A thus obtained was identical with the natural material apart from chiroptical properties.

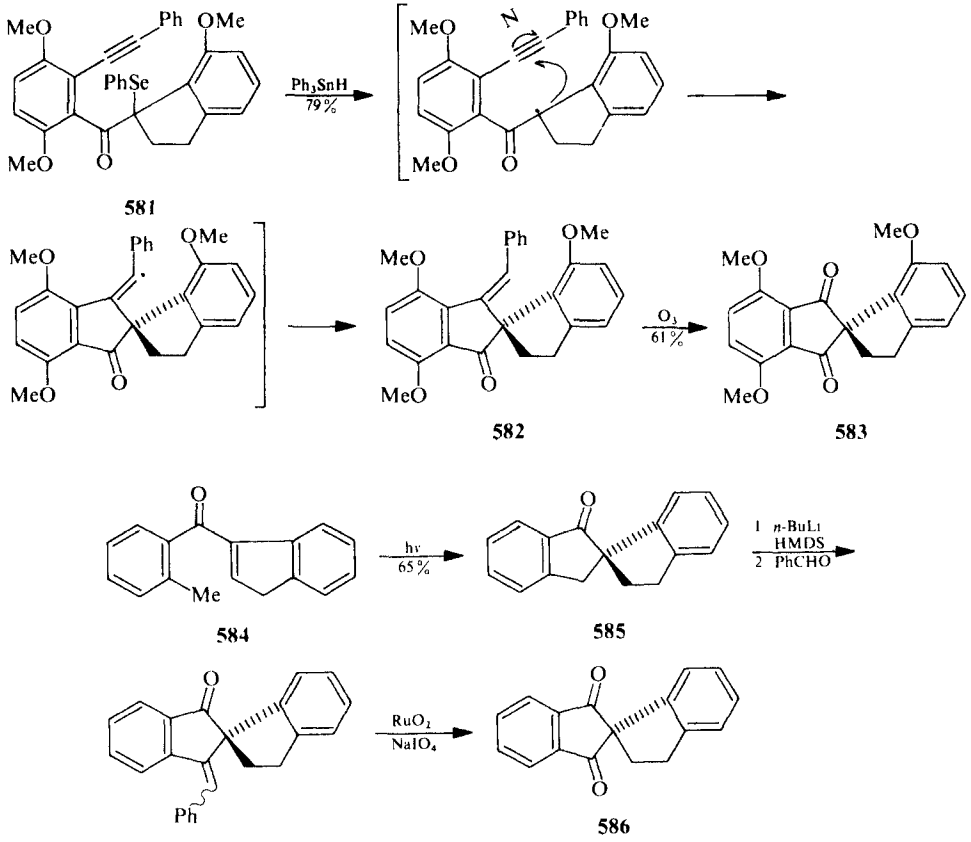
Other work directed toward a synthesis of fredericamycin A produced some interesting chemistry, particularly with respect to formation of the spiro system. Thus Rama Rao[302] was unable to convert diketone **577** directly into **578** as cyclization invariably led to an oxepinone, but conversion of the latter into the spirodiketone **578** could be achieved by thermolysis. In contrast to those extreme conditions, Kende[303] found that the spirodiketone **580** could be obtained by ferricyanide oxidation of phenol **579**, in the cold, by enol–phenol radical coupling. In another radical process, Clive[304] treated the phenylselenoketone **581** with triphenyltin hydride to form **582** and hence the spirodiketone **583**. Radical addition to the triple bond takes precedence over hydrogen abstraction from triphenyltin hydride. In another approach, Mehta[305] showed that ketone **584** underwent photochemical spirocyclization on irradiation to give **585**, which was converted into the diketone **586** in two steps (50%). Several other routes to the spiro system were explored[306] and although neither these nor other syntheses[307] of rings ABC and DEF have been extended to fredericamycin A, new chemistry was discovered which is the most important outcome of research on natural products.



577 578



579 580



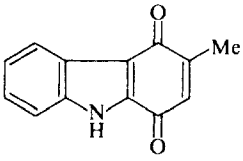
7. *N*-HETEROCYCLIC QUINONES

The *N*-heterocyclic quinones are found in microorganisms, sponges, and higher plants. Most of the simple ones have been synthesized and also several of the more complex polycyclic compounds, which show significant antibiotic and antitumor properties. Cochliodinol and murrapanine have alreay been considered (pp. 320 and 335).

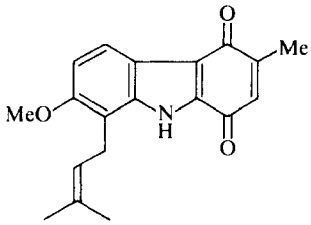
A. Carbazolequinones

Murrayaquinones and Pyrayaquinones. The nomenclature in this small group is confusing. Murrayaquinones (e.g., A **587** and B **588**) occur[308] in the

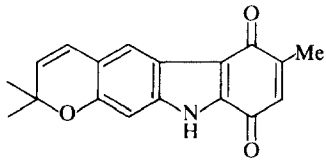
root bark of *Murraya euchrestifolia* with related alkaloids, but murayaquinone (one r) found [309] in cultures of *Streptomyces murayamaensis* is a homologue of the phenanthraquinone piloquinone (p. 407). Carbazolequinones that possess a fused terpenoid pyran ring also occur in *M. euchrestifolia* and are called pyrayaquinones,[310] (e.g., A **589** and B **590**).



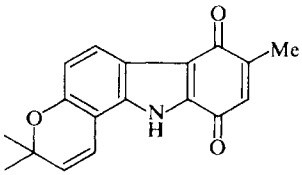
587



588



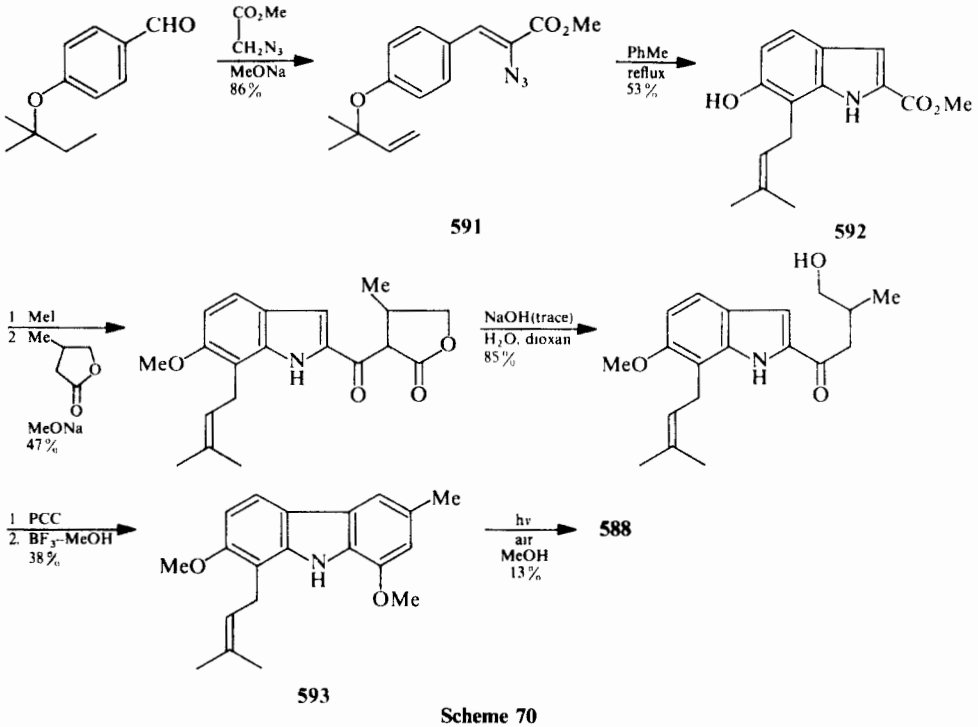
589



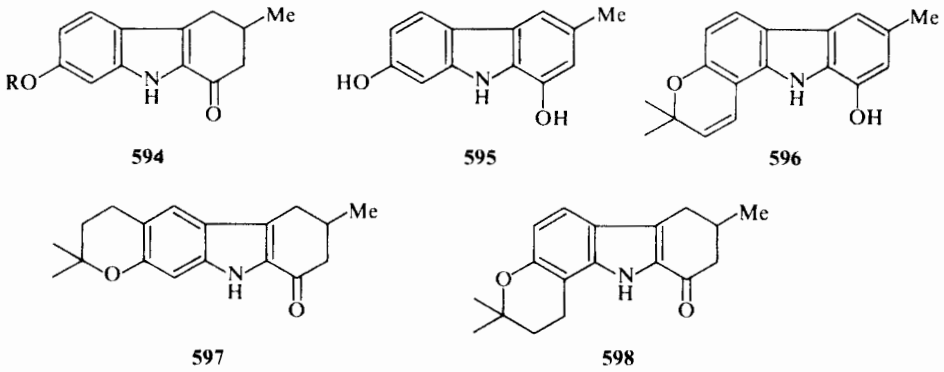
590

Moody[311] has synthesized murrayaquinone B, as indicated in Scheme 70. An interesting feature is the conversion of azide **591** into indole **592** by thermolysis which was accompanied by a regioselective Claisen rearrangement.[313] As selective demethylation of dimethoxycarbazole **593** seemed unlikely, it was transformed into murrayaquinone B **588** by photochemical oxidation, but the yield was poor. Murrayaquinone A **587** was obtained[312] by the same route, but as the penultimate compound 1-methoxy-3-methylcarbazole (murrayafoline-A) contains only one methoxyl group, it was demethylated followed by oxidation of the phenol with Fremy's salt. 1-Hydroxy-3-methylcarbazole had previously been synthesized[314] by the Fischer indole route and oxidized[315] to **587** with PCC. Murrayaquinone B **588** was also prepared[316] in poor yield from the known tetrahydrocarbazole **594** (R = Me) by a sequence of manipulations.

Pyrayaquinone B **590** was first obtained[315] by converting **594** into **595** followed by condensation with 3-hydroxyisovaleraldehyde dimethyl acetal in boiling pyridine (48 hrs) to give the pyran **596** (and the regio isomer by reaction with the C-1 hydroxyl), which was oxidized with PCC to quinone **590**. Later, Kapil[317] condensed **594** (R = H) with 2-methylbut-3-en-2-ol and obtained the dihydropyrans **597** (15%) and **598** (16%). After separation they were oxidized with DDQ in refluxing dioxan to give, respectively, pyrayaquinone A **589** (18%) and B **590** (19%) directly.



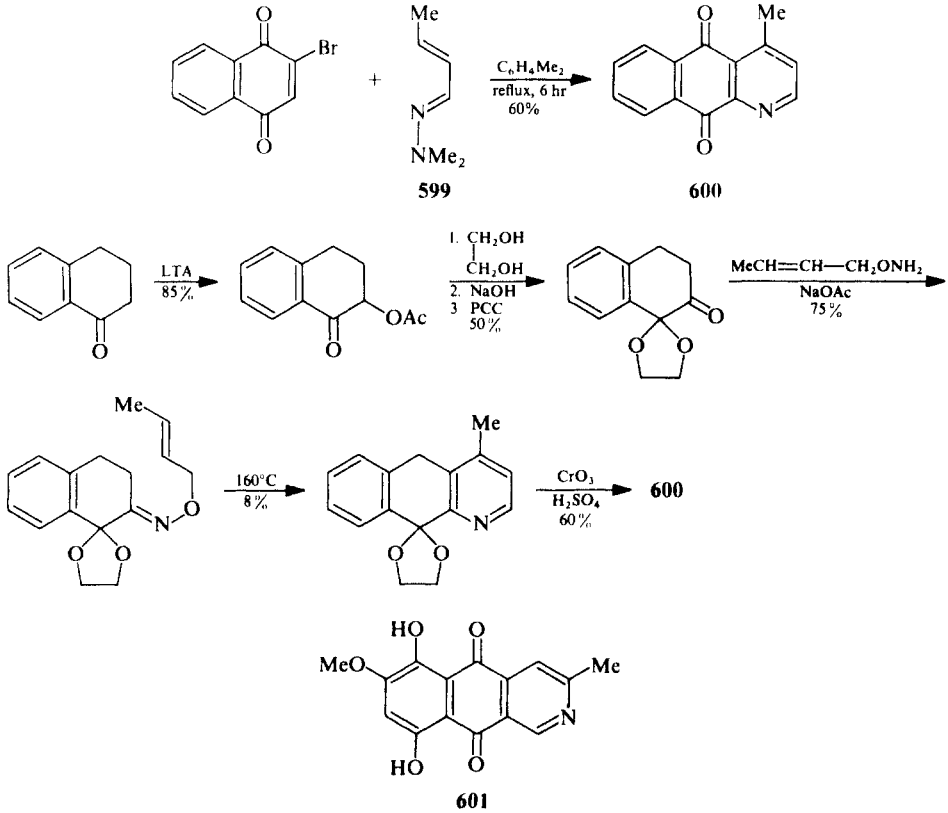
Scheme 70



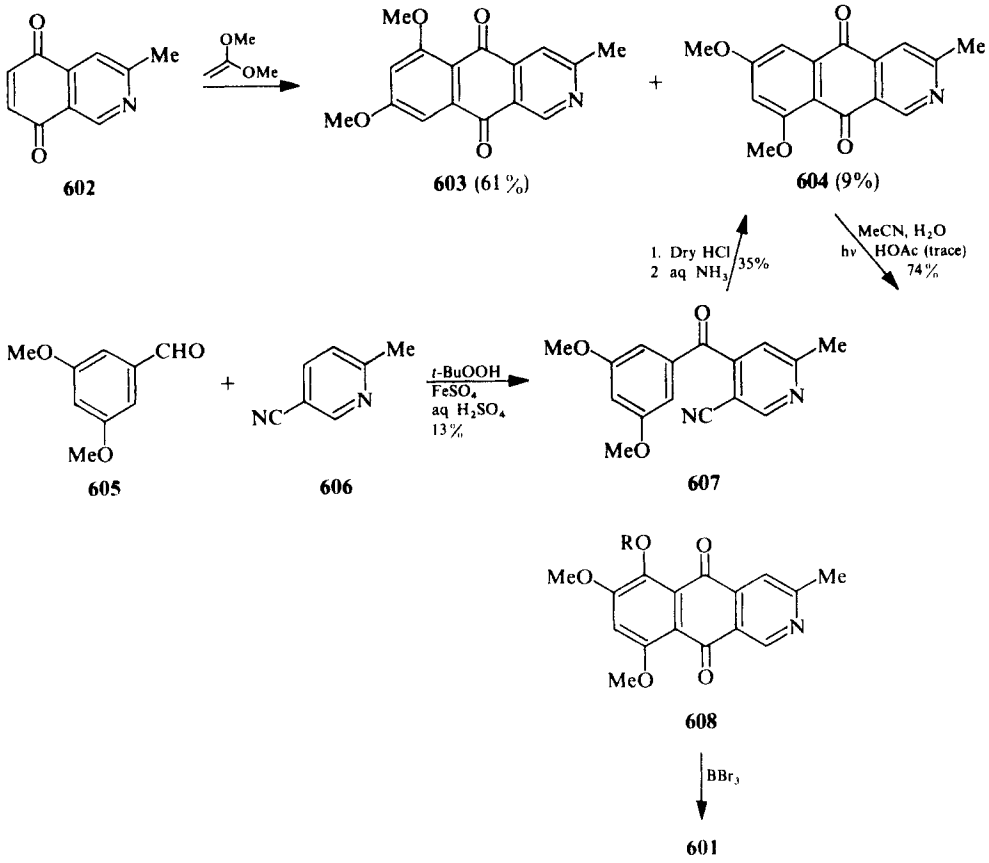
B. Aza-anthraquinones

Cleistopholine. This very simple aza-anthraquinone **600** occurs in the root bark of *Cleistopholis patens*[318] and in seeds of *Annona cherimolia*[319] (both Annonaceae). Bracher[320] obtained the synthetic product in a one-pot reaction by cycloaddition of crotonaldehyde dimethylhydrazone **599** to 2-bromo-

1,4-naphthoquinone. Shortly afterward, a Japanese group[321] reported a much longer synthesis outlined below. The yield at the thermolysis stage was very poor; the 2-methyl isomer was also formed (5%) and 60% of the oxime was recovered.



Bostrycoidin. This is the only natural 2-aza-anthraquinone so far recorded. It is produced in cultures of several *Fusarium* spp.[14,15] and has been synthesized three times. Cameron's first synthesis[322] is attractively short (Scheme 71). However, 1:2-ketal addition (see p. 403) to the known[323] isoquinolinequinone **602** was controlled mainly by the more electron-deficient carbonyl at C-5 and the product mixture was predominantly the "wrong" isomer **603**. Introduction of a hydroxyl group to C-5 of isomer **604** appeared to be a trivial task using known anthraquinone chemistry, but attempts to effect this via bromo and nitro intermediates were unavailing. Fortunately, it was noticed that when a methanolic solution of **604** was left exposed to light it gradually formed the trimethoxyquinone **608** (R = Me).

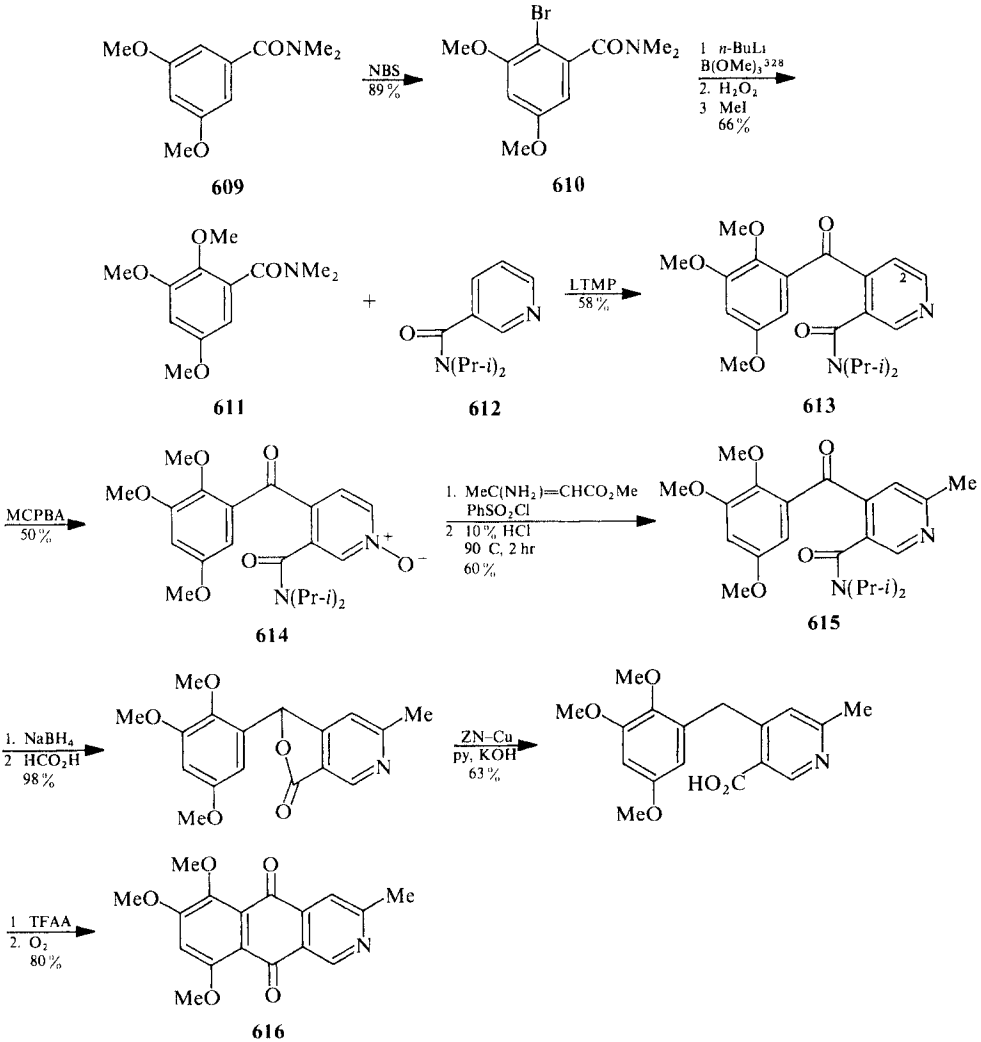


Scheme 71

Repeating this deliberately with other nucleophiles (ammonia, water) showed that photochemical nucleophilic substitution[324] gave the corresponding 8-amino and 8-hydroxy derivatives of **604** in moderate yields. Accordingly, quinone **604** was then irradiated in an aqueous medium to give bostrycoidin 8-*O*-methyl ether **608** (R = H), another *Fusarium* metabolite,[15] in 74% yield (allowing for some recovered **604**), and hence bostrycoidin **601** after *peri*-demethylation.

Minisci[325] has established that acyl radicals having nucleophilic character will substitute pyridine in the α- and γ- positions in acid solution. Cameron[326] employed this reaction in another synthesis of bostrycoidin, but again the low yields and lack of regiospecificity were disappointing (Scheme 71). Acylation of pyridine **606** (from commercially available 5-ethyl-2-methylpyridine) with the radical generated from aldehyde **605**, using the

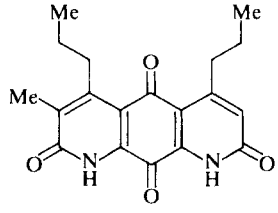
t-butyl hydroperoxide-Fe(II) system, gave only 13% of the desired compound **607** together with 38% of the regioisomer formed by acylation at C-1. An intramolecular Houben–Hoesch reaction on nitrile **607** then yielded aza-anthraquinone **604**, which was converted into bostrycoidin as before. A more direct route using 2,3,5-trimethoxybenzaldehyde in place of **605** led to difficulty at the cyclization stage.



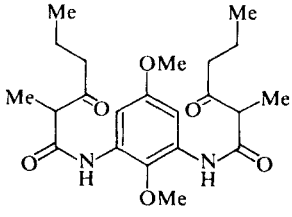
Scheme 72

Watanabe's[327] regiospecific synthesis of bostrycoidin was much more efficient and was modelled on earlier anthraquinone syntheses. A nicotinamide derivative **612** served as the pyridine component and benzamide **611** provided the benzenoid ring. They were coupled by lithiation of **612** (known[329] to react at C-4) to give ketone **613** (Scheme 72). To complete the carbon skeleton a methyl group is required at C-2. This was not included in **612** as an α-methyl group in a pyridine ring would be deprotonated on lithiation. The C-2 methyl group was therefore introduced next by converting **613** to the *N*-oxide **614** and methylation by the method developed by Iwao and Kuraishi[330] to give **615** exclusively, presumably for steric reasons. The synthesis was completed by standard reactions to give bostrycoidin dimethyl ether, which had previously been converted to bostrycoidin.

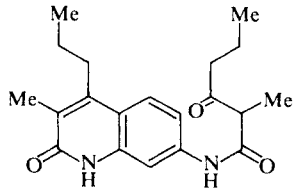
Diazaquinomycin A. This bacterial metabolite[331] **617** is the only natural diazaanthraquinone known. Kelly[332] has reported a very short synthesis in a very brief communication. The quinone **617** can be regarded as a bis-2-quinolone, which suggested that it might be accessible by a double Knorr cyclization. However, repeated attempts to convert **618** to a tricyclic system were a total failure, although frequently the first Knorr cyclization proceeded smoothly to give the quinolone **619**. Efforts to repeat the reaction on **619** usually produced **620**, even under anhydrous conditions. Surprisingly, a very large change in reactivity was observed when the dimethyl ether **618** was replaced by the hydroquinone **621**, prepared as shown, which could be converted in one pot directly to diazaquinomycin A in 95% yield. It is possible to isolate the hydroquinone **622** (diazaquinomycin B) if required.



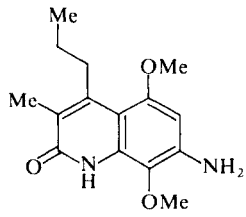
617



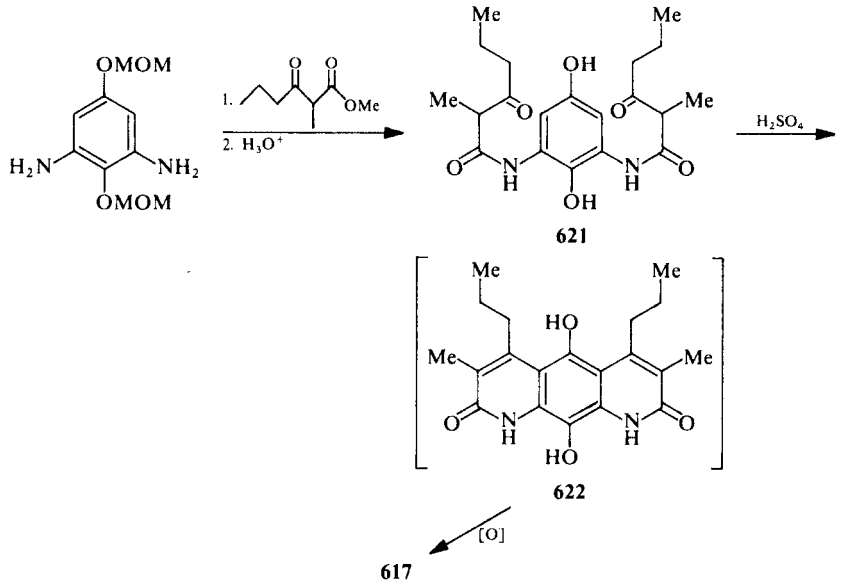
618



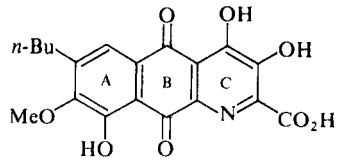
619



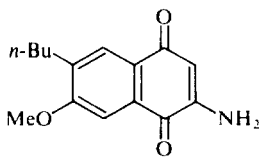
620



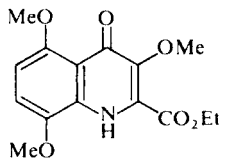
Phomazarin. Isolated from cultures of *Phoma terrestris*[333] in 1940, phomazarin is the best known, and most studied, aza-anthraquinone, but it has not yet been synthesized. The original structural proposal[334] has been twice revised [335] so that confirmation of structure **623** is highly desirable. Brassard[336] has made considerable progress and to date has elaborated **624** and **625**, which incorporate the AB and BC rings, respectively, and has come closer to the natural quinone in his synthesis of the aza-anthraquinone **626**.



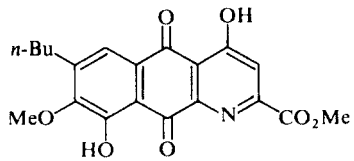
623



624



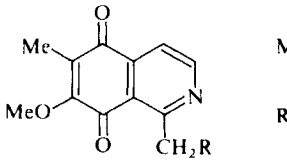
625



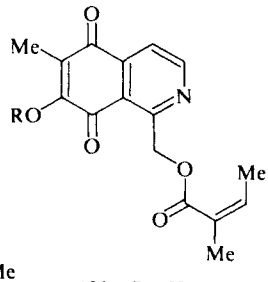
626

C. Isoquinolinequinones

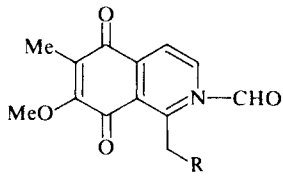
The natural isoquinolinequinones comprise a collection of relatively simple compounds which co-occur with related complex dimeric diquinones in marine sponges and actinomycetes. Of the first group 7-methoxy-1,6-dimethylisoquinoline-5,8-quinone **627**, which may be regarded as the parent compound, was found[337] together with renierone **633**, *O*-demethylrenierone **632**, *N*-formyl-1,2-dihydrorenierone **636** (a mixture of two rotamers), and mimosamycin **637** in an unidentified *Reniera* sponge. Mimosamycin **637** and also renierol **628** have been isolated[338] from the sponge *Xestospongia caycedoi*, while renierol acetate **629** and propionate **630**, *N*-formyl-1,2-dihydrorenierol acetate **634**, and propionate **635** occur[343] in an unidentified *Xestospongia* sp. and its associated nudibranch *Jorunna funebris*. Mimosamycin **637**[340] and mimocin **631**[341] have been extracted from cultures of *Streptomyces lavendulae*. All of these antimicrobial metabolites have been synthesized, mainly by Kubo's group. Scheme 73 outlines routes[342] to **627**, **633**, and **636** from **638**, and the others (except mimosamycin) were obtained[343] by similar methods starting from **639**. The CAN oxidations in Scheme 73 were catalyzed by pyridine-2,6-dicarboxylic acid *N*-oxide,[344] and in each case a mixture of *ortho* and *para* isomers was formed, the *o*-quinone in greater amount.



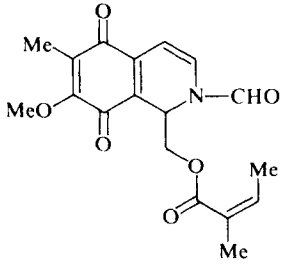
627 R = H
628 R = OH
629 R = OAc
630 R = OCOEt
631 R = NHCOCOMe



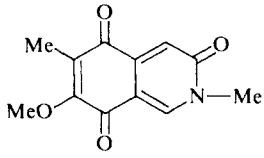
632 R = H
633 R = Me



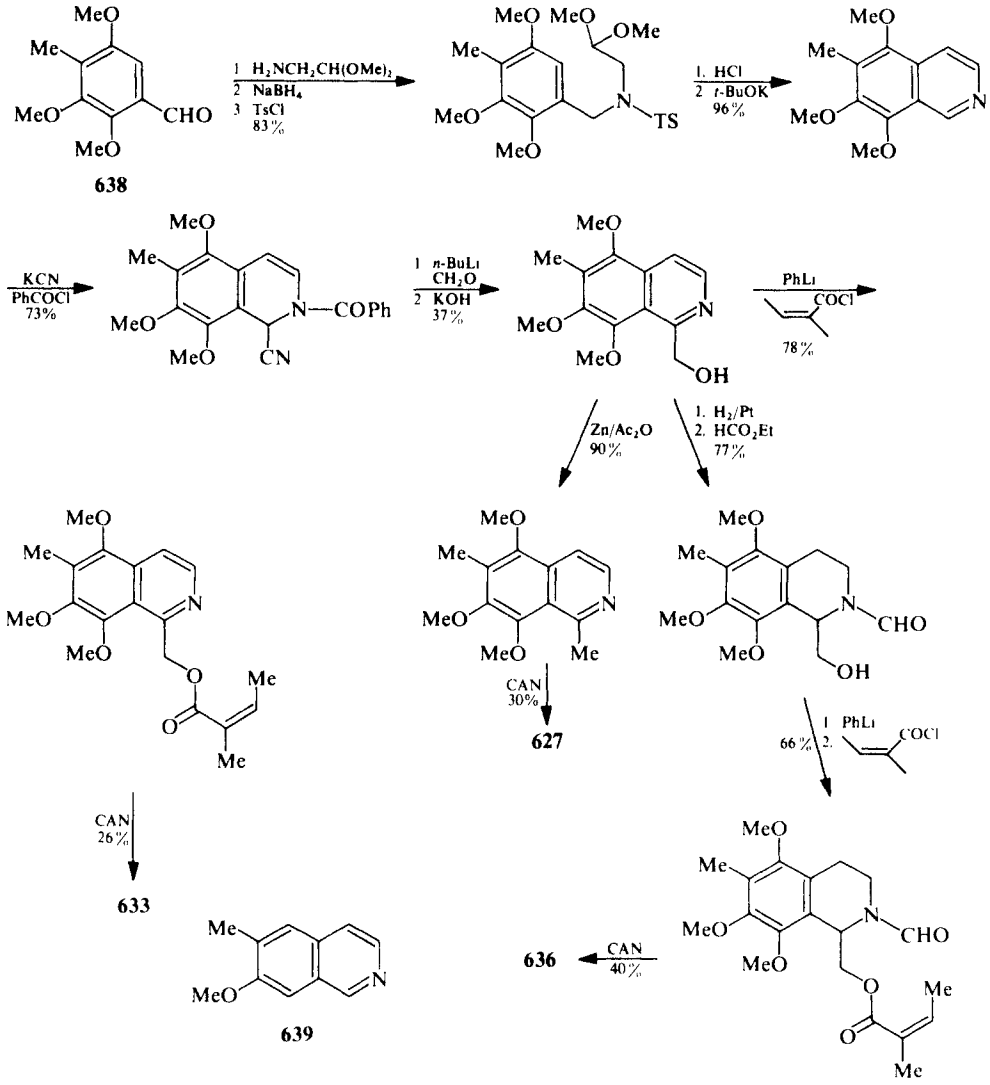
634 R = OAc
635 R = OCOEt



636

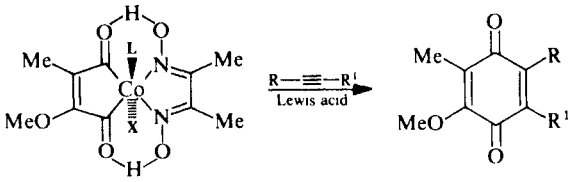


637



Scheme 73

Liebeskind has found a general route to benzoquinones whereby a maleoylcobalt complex reacts with an unsymmetrical alkyne as shown below. Initially,[339a] this was a thermal process, but later[339b] it was demonstrated that under the influence of Lewis acids the reaction would proceed in the cold and with improved regioselectivity. If the R and R′ quinone substituents can be subsequently linked to form a ring, the scope of the synthesis can



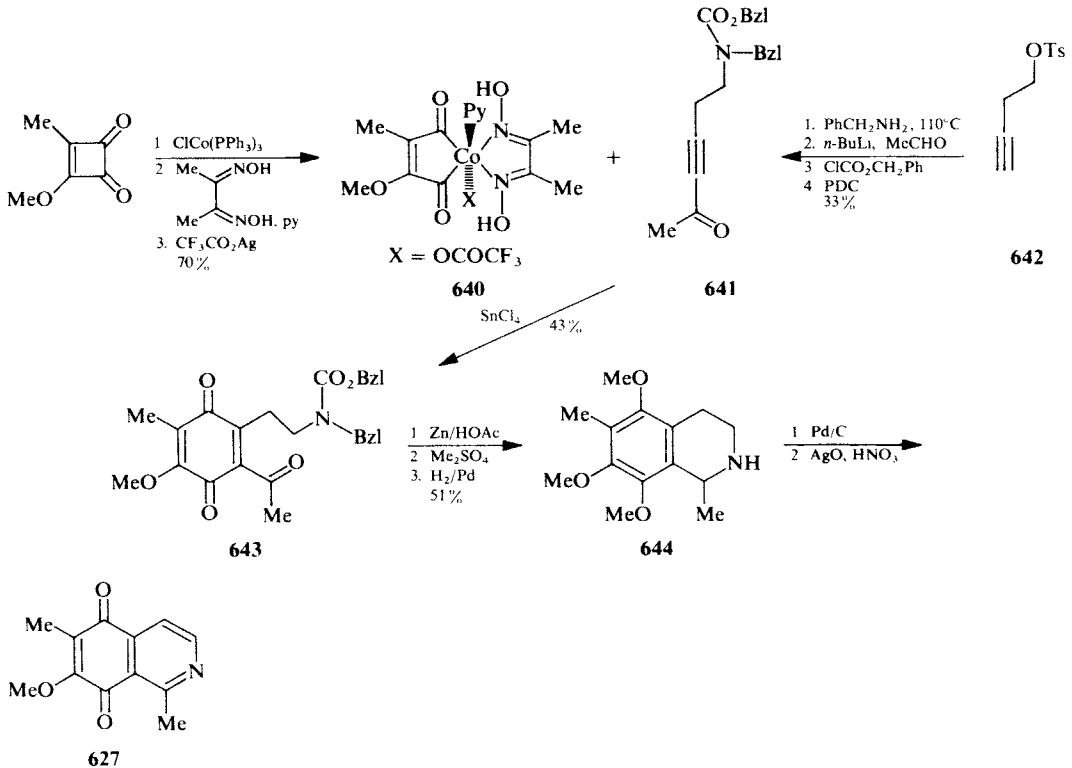
obviously be extended, and this was demonstrated in a synthesis of the parent member of the isoquinoline group **627** (Scheme 74).

Starting from tosylated 3-butyn-1-ol **642**, it was converted in five steps into the protected ketoalkyne **641**, and complex **640** was prepared in the usual way from 3-methoxy-4-methylcyclobutene-1,2-dione. Reaction of **641** with **640** at room temperature in the presence of stannic chloride afforded the benzoquinone **643** in 43% yield. After reduction and methylation, deprotection led to cyclization and hence the tetrahydroisoquinoline **644**, which was converted to the quinone **627**. The thermal reaction of **641** and **642**, without catalyst, gave an 80% yield of **643** (+ isomer) but the regiospecificity fell from 20:1 to 3:1.

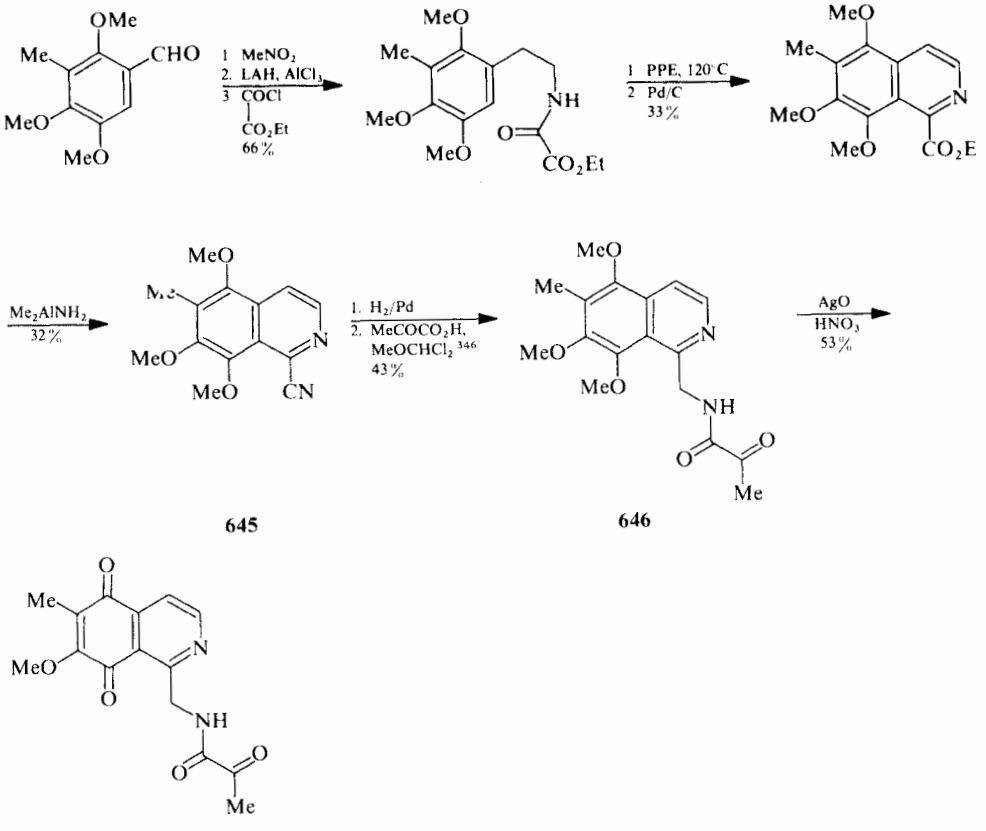
Matsuo[345] has synthesized the bacterial metabolite mimocin **631** using standard isoquinoline chemistry. The isoquinoline **645**, elaborated as shown, was reduced to the primary amine and then treated with pyruvoyl chloride generated *in situ*.[346] Final oxidation of **646** afforded mimocin **631** (Scheme 75).

A novel approach to isoquinoline synthesis was Danishefsky's[347] use of an intramolecular Ben-Ishai reaction[348] in the first synthesis of renierone **633** (Scheme 76). The chloromethyl side chain in **647** was extended to the urethane **648**. Treatment with glyoxylic acid then gave an adduct which was cyclized with dichloroacetic acid and methylated to give the tetrahydroisoquinoline **649** in good yield. The final oxidation of **650** gave renierone **633** and the *ortho* isomer **651**. Acid hydrolysis of the latter afforded *O*-demethylrenierone **632**, which could be methylated to give renierone in a total yield of 83% from **650** (Scheme 76).

The other metabolite which belongs to this group is the unique natural product mimosamycin **637**, which is not actually a quinone. It has been synthesized in three ways. Fukumi[349] discovered that when the phenol **652**, prepared by standard methods, was autoxidized in the presence of piperidine (or morpholine), *o*-quinone formation was followed by a nucleophilic addition–oxidation–nucleophilic addition–oxidation sequence to give **653** (or the morpholine analogue). On acid hydrolysis the product isomerized, giving the *p*-quinone **654**. After reduction to **655** it was quaternized on the ring nitrogen, giving **656**, from which mimosamycin was obtained by oxygenation under basic conditions (Scheme 77).


1 ClCo(PPh3)3
2 Me, NOH
Me NOH. py
3. CF3CO2Ag
70%
X = OCOCF3
640
641
642
1. PhCH2NH2, 110°C
2. n-BuLi, MeCHO
3 ClCO2CH2Ph
4 PDC
33%
SnCl4
43%
643
1 Zn/HOAc
2 Me2SO4
3. H2/Pd
51%
644
1 Pd/C
2 AgO, HNO3
627

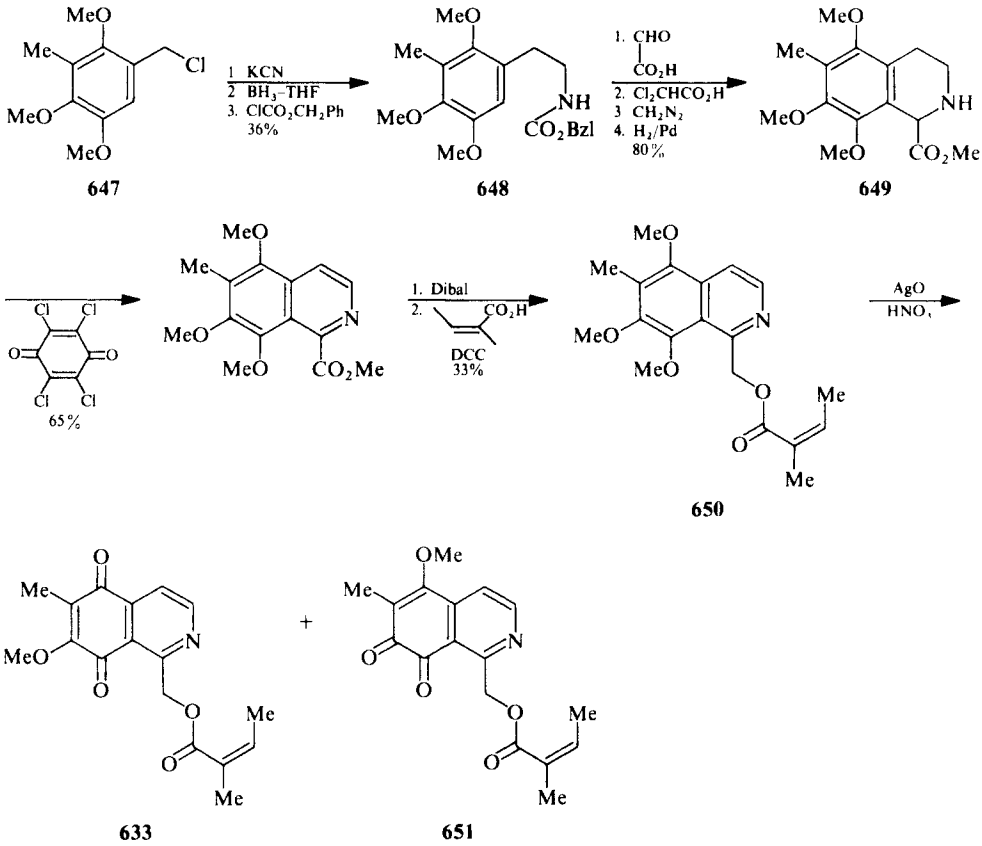
Scheme 74



Scheme 75

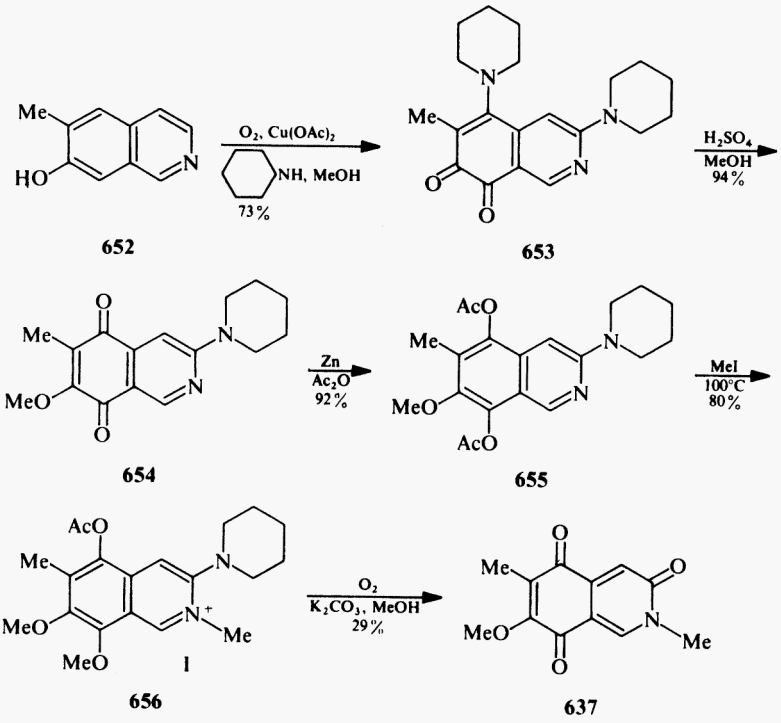
The Parker[350] approach to mimosamycin was quite different. Starting from the nitrile **657**, prepared by standard methods, careful hydrogenation in the presence of acetic–formic anhydride and a large amount of Raney nickel gave the formamide **658**. Reduction with borane was followed by ring closure to **659**, which was oxidized directly to mimosamycin **637** (Scheme 78).

McKillop[351] has devised a very attractive short synthesis of mimosamycin based on heterodiene cycloaddition (Scheme 79). The azadiene **660**, readily accessible by silylation of *N*-formylacetamide, added to 2-methoxy-3-methylbenzoquinone regiospecifically to form an unstable adduct **661** which was converted to the amide **662** on deprotection. Final methylation with the help of a phase-transfer catalyst[352] afforded mimosamycin **637** (80% from **660**). This is clearly the method of choice.

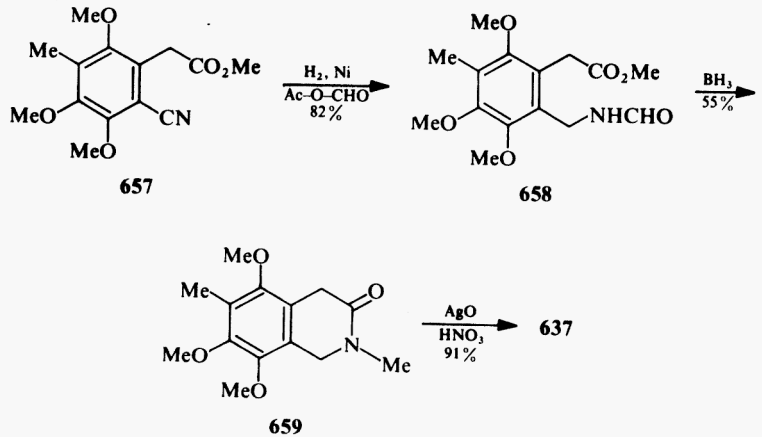


Scheme 76

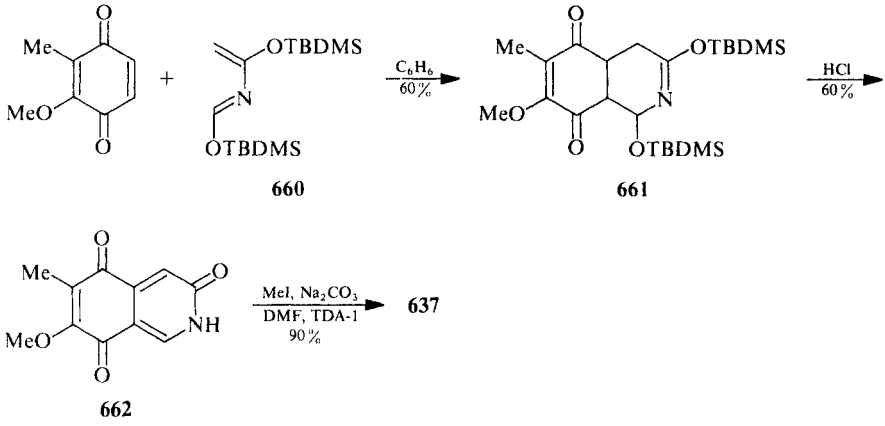
It is pertinent to mention here another metabolite occurring[337] with the isoquinolinequinones in a *Reniera* sponge. This is the isoindoledione **667**, first synthesized by Faulkner[337] with considerable experimental difficulty. Starting from the pyrrole diester **663**, the 6-membered ring was constructed in four steps. In the first the yield of ketoester **664** was limited by the tendency of the dithiane reagent to react with both ester functions in **663**. Removal of the dithiane group from **664** by standard methods was also difficult, but eventually it was converted directly to the diketone **665**, which was then cyclized to **666**. Final methylation with methyl iodide (sulfate)–potassium carbonate was frustrated by hydrolysis back to **660** during workup. Diazomethane was therefore used, but the amount had to be limited to avoid addition to the pyrrole ring (Scheme 80). Subsequently, Parker[353] obtained the dione **667**



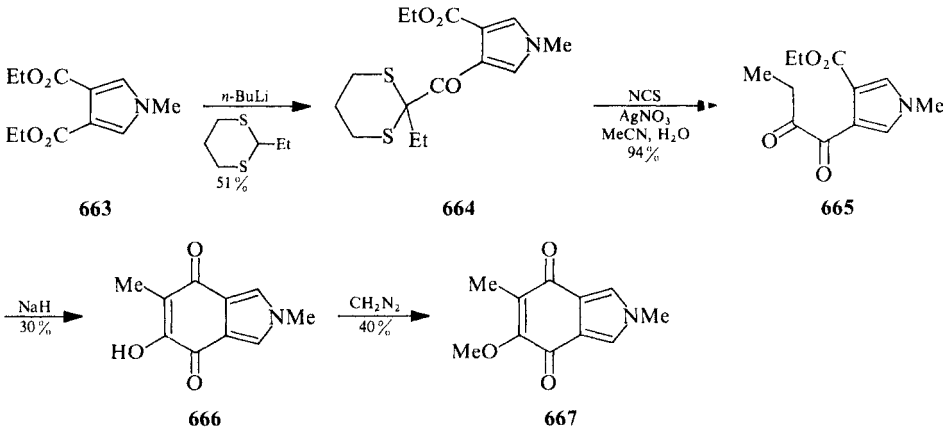
Scheme 77



Scheme 78



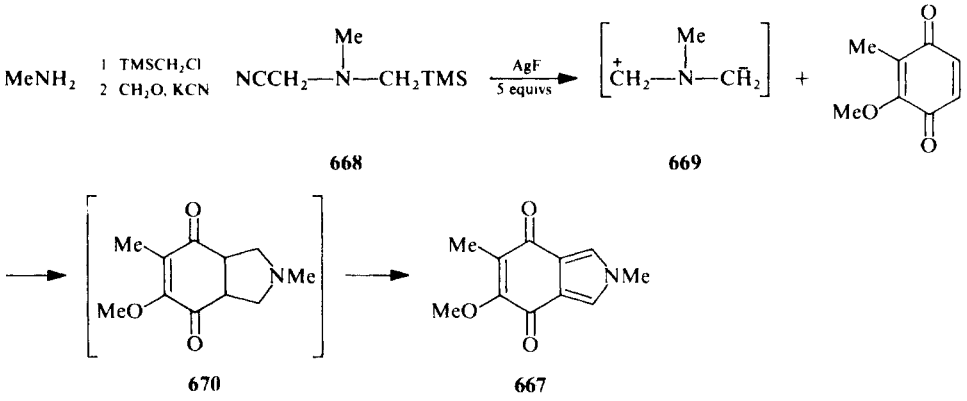
Scheme 79



Scheme 80

very conveniently by cycloaddition of the azomethine ylide **669** to 2-methoxy-3-methylbenzoquinone (Scheme 81). The ylide was derived from the α-cyanaminosilane **668** by treatment with silver fluoride,[354] which also served to oxidize the adduct **670**. The yield of dione **667** was 68%. Several analogues were prepared.

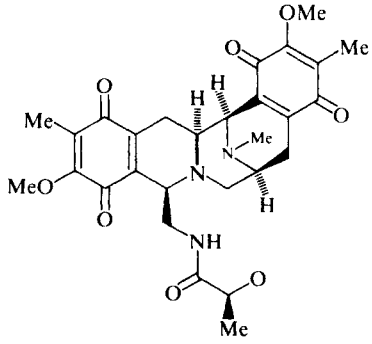
The complex dimeric isoquinolinequinones comprise more than a dozen saframycins found in cultures of *Streptomyces lavendulae*[15, 355] and *Myxoco-*



668 669 670 667

Scheme 81

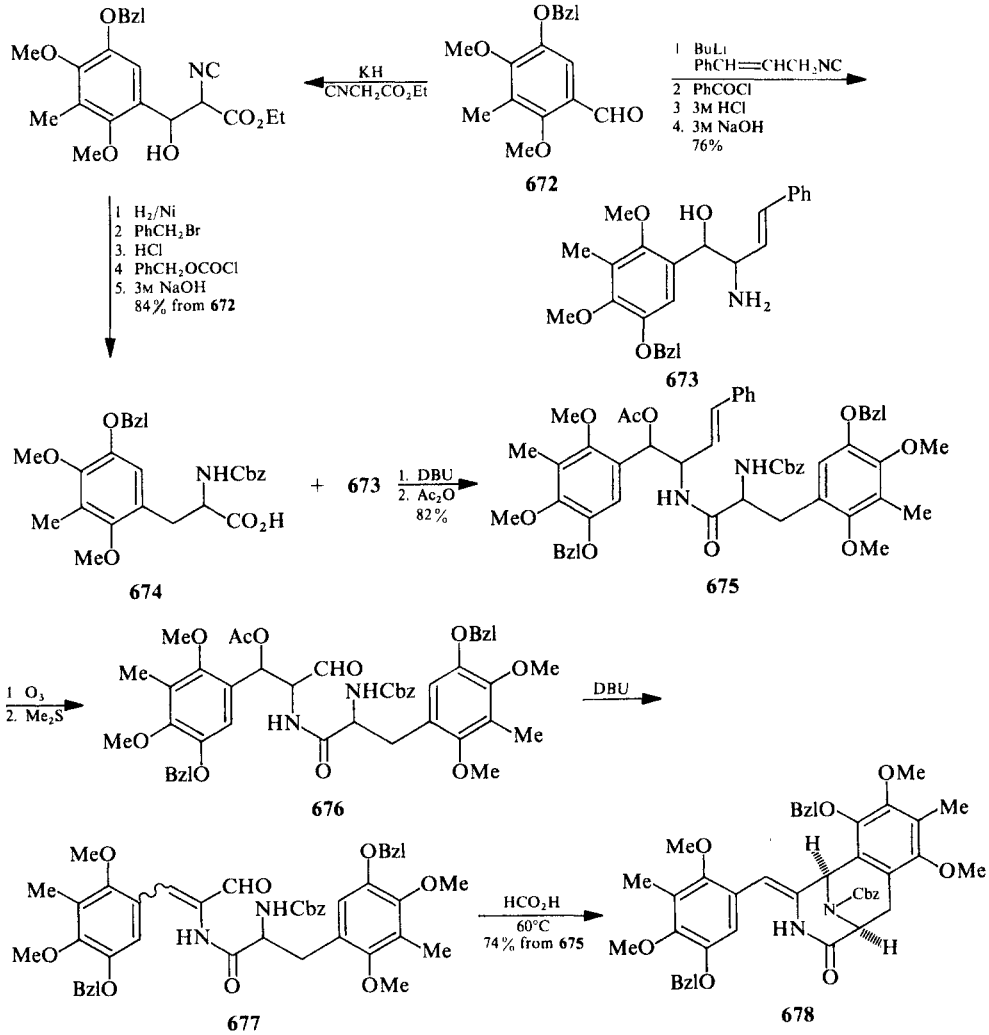
ccus xanthus,[356] safracins A and B from *Pseudomonas fluorescens*,[15] and the renieramycins found in a *Reniera* sponge.[357] The antibiotic and antitumor activities[358] of these compounds have attracted attention,[359] but to date only (±)-saframycin B **671** has been synthesized.



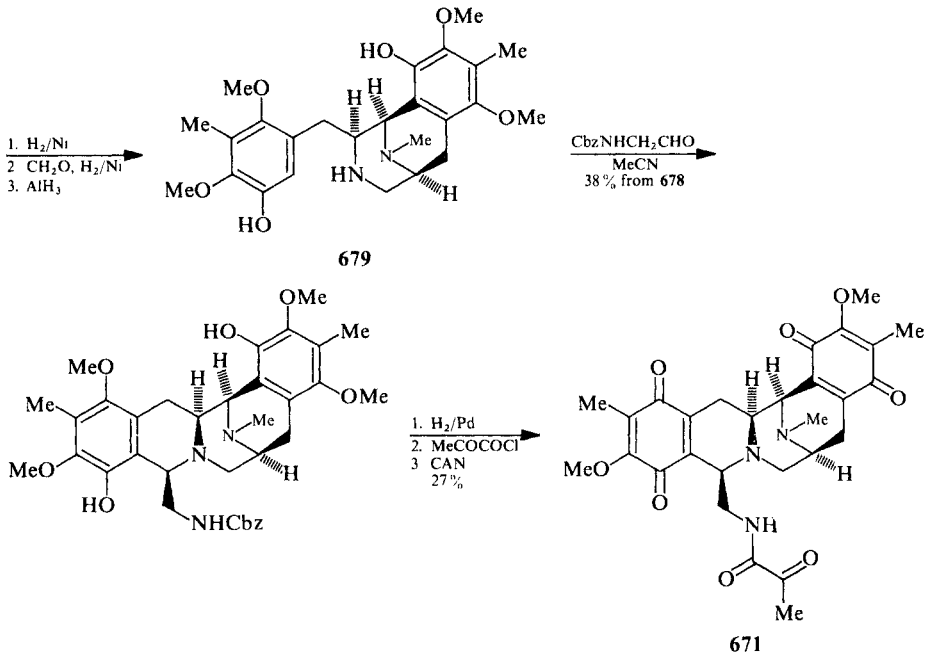
671

Saframycin B. In Fukayama's[360] synthesis, outlined in a brief communication, the plan was to construct a suitably substituted peptide chain linking two benzenoid units **676**, from which to elaborate the pentacyclic system by carefully controlled cyclization. Particularly striking is the one-step double cyclization **677** → **678**. Both terminal units were derived from the highly substituted aldehyde **672**, itself obtained in seven steps (37%) from 2,4-dimethoxy-3-methylbenzaldehyde, using a metalated isonitrile[361] for chain extension in each case (Scheme 82). Condensation of **673** and **674** led to **675** and careful ozonolysis gave the unstable aldehyde **676**. Treatment with DBU

converted **676** into a 1:1 *Z*/*E* mixture of unsaturated aldehydes **677**, which on brief warming in formic acid underwent the critical double cyclization to give **678** exclusively in good yield. The stereochemistry was based on an independent synthesis by a piperazinedione route.[362] Hydrogenation of **678** on the less-hindered face also cleaved the protecting groups and was followed by reductive methylation to the *N*-methyl derivative and further reduction of the lactam function to an amine. Ring closure of the phenolic amine **679** to



Scheme 82



679

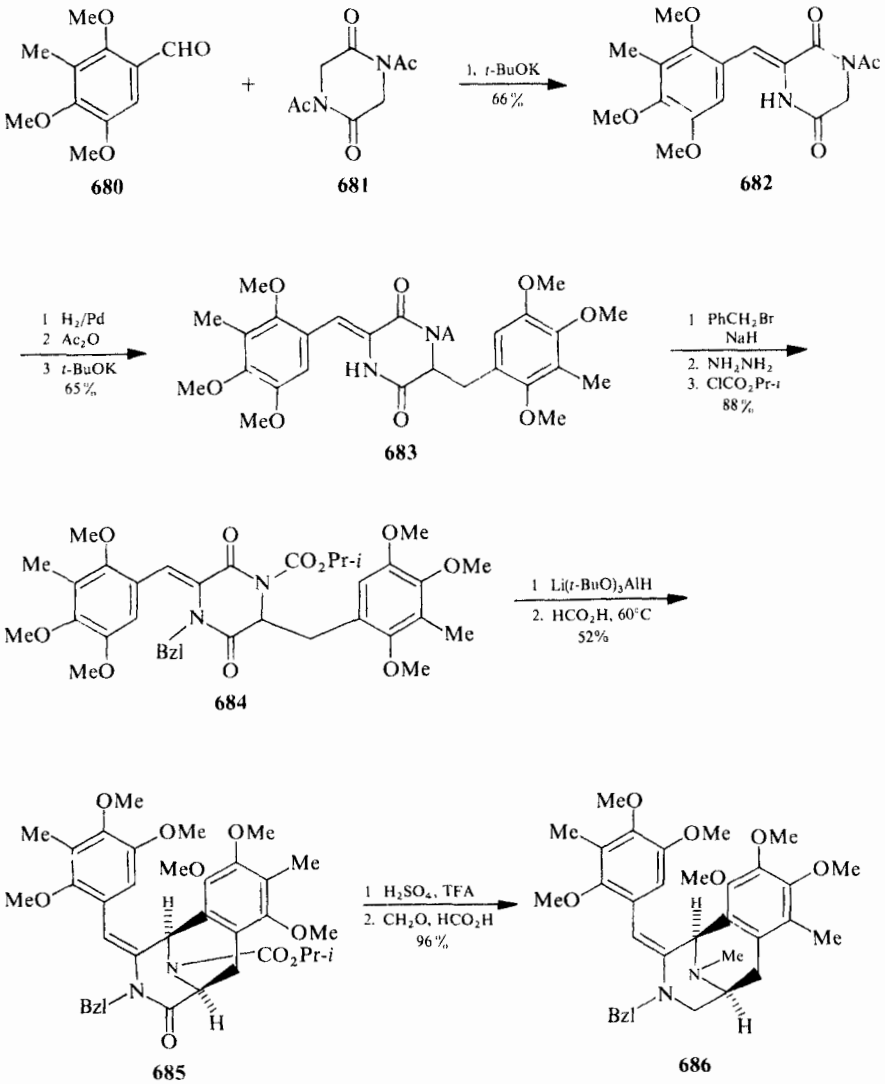
671

Scheme 82 (*continued*)

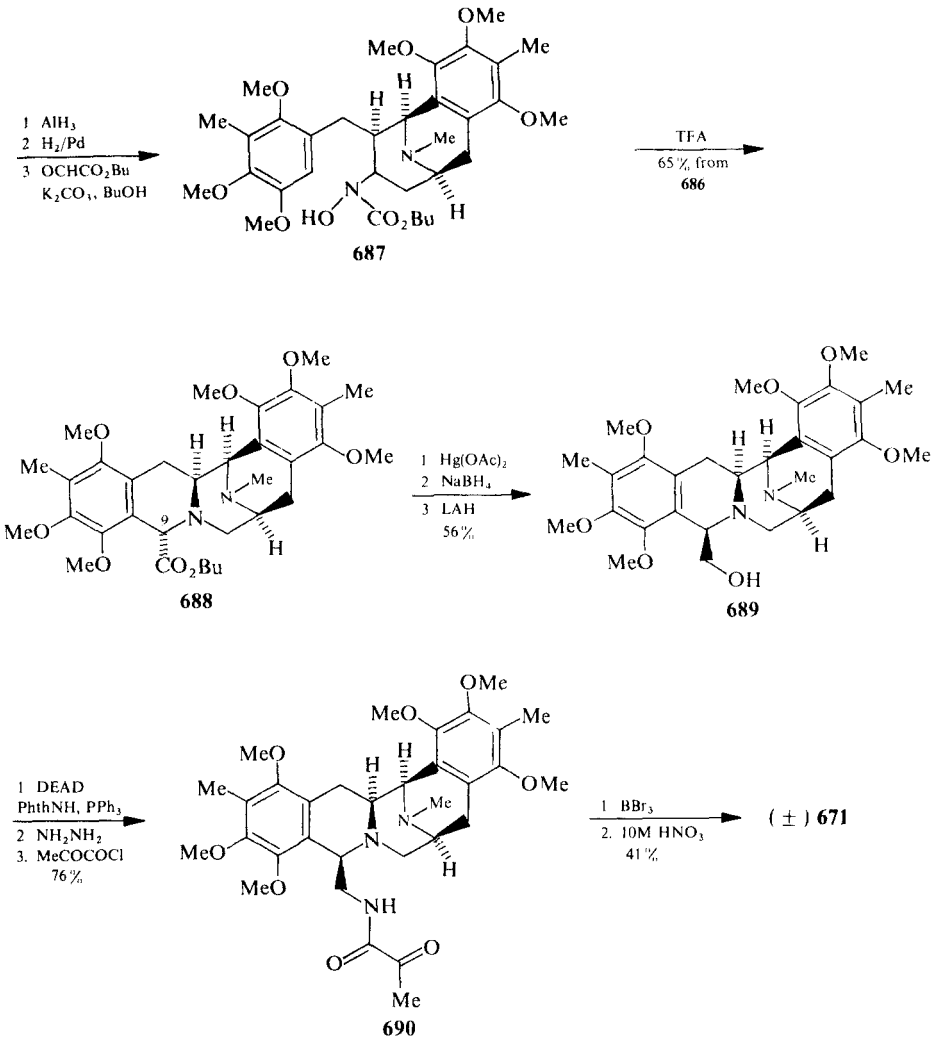
the pentacyclic system was achieved by Kametani's[363] phenolic cyclization method of isoquinoline synthesis. Insertion of the pyruvamide side chain and final CAN oxidation completed the synthesis of (±)-saframycin B.

Kubo[364] tackled the synthesis (Scheme 83) by rapidly assembling the central and two outer rings in the form of the piperazinedione **683** followed by two separate ring closures, the first of which gave **685** analogous to Fukuyama's lactam **678**. Aldehyde **680** was condensed with the piperazinedione **681** to give the *Z*-arylidene **682**, and after hydrogenation and reacetylation the condensation was repeated. The resulting **683** was then converted to **684**. Next the conjugated carbonyl group was reduced with sodium tri-*t*-butoxyaluminum hydride and the allylic alcohol so obtained was cyclized by warming in formic acid to give **685** with a change in stereochemistry around the double bond. Replacing the ester in **685** by a methyl group afforded **686**, whose structure and stereochemistry were established by X-ray analysis. Lactam **686** was then reduced to the amine with aluminum hydride, and hydrogenated, and to effect the final ring closure it was treated with butyl glyoxylate in butanol to provide the aminoacetal **687**, which afforded the pentacyclic compound **688** on stirring in trifluoroacetic acid.[365] Another

X-ray analysis of the corresponding ethyl ester revealed that the stereochemistry, as shown, was epimeric at C-9 to that in saframycin B. It was epimerized by oxidation[366] with mercuric acetate followed by reduction with sodium borohydride (hydride attack exclusively from the less-hindered side), and the ester function was reduced to the alcohol **689**. That was then transformed to



Scheme 83

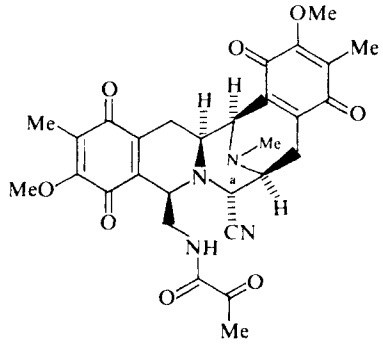


Scheme 83 (*continued*)

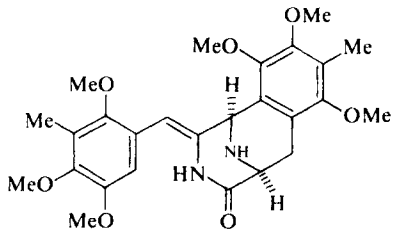
the amine by Mitsunobo's[217] procedure, acylated, and with some difficulty the amido side chain was added. The final oxidation to (±)-saframycin B was also difficult, and after much experimentation it was found best to partially demethylate **690** and then oxidize with nitric acid.

In the synthesis of other saframycins there are further problems arising from the presence of substituents in the nitrogenous rings. In saframycin A

691 the most potent antitumor member of the group,[367] the nitrile substituent at C_a requires the presence of a functional group at that position at some stage prior to the final ring closure, for example, the amide carbonyl group in **685**. In the previous work it was found impossible to remove the benzyl group in **685** until the amide carbonyl had been eliminated by aluminum hydride reduction. Kubo[368] has now found that if the benzyl group in **685** is replaced by *p*-methoxybenzyl, it is removed on treatment with trifluoroacetic acid–sulfuric acid together with the *N*-ester group to give **692** (there is also a change from *E* to *Z* stereochemistry). The way now seems open for a total synthesis of (±)-saframycin A.

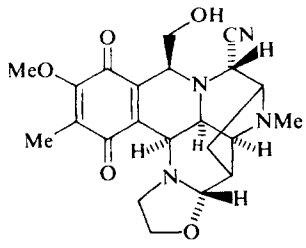


691



692

Cyanocycline A. This alkaloid **693** is distinct from the foregoing saframycins and their relatives, but for the purpose of this review it belongs to the "isoquinolinequinone" group. (Cervinomycin A_2 was arbitrarily included in the polycyclic quinone section of this chapter.) It was isolated from *Streptomyces flavogriseus*[162] and has also been obtained from naphthyridinomycin (**693**, OH in place of CN), a metabolite of *Strep. lusitanicus*,[369] by adding sodium cyanide to cultures of *Strep. flavogriseus* at pH 8.0.[370] Hence the alternative name cyanonaphthyridinomycin. It shows antibiotic and antitumor activity but is also toxic. The structure, established by X-ray ana-

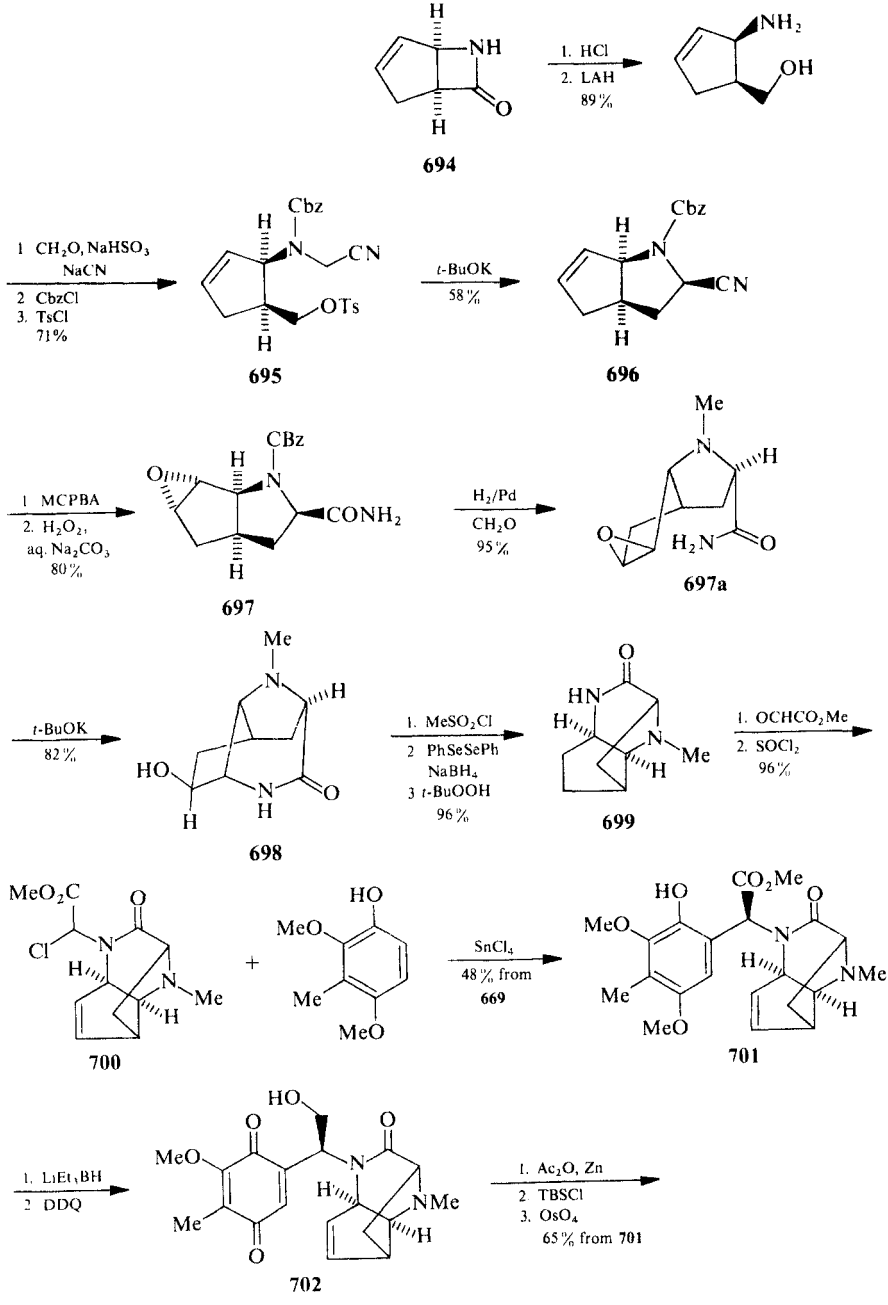


693

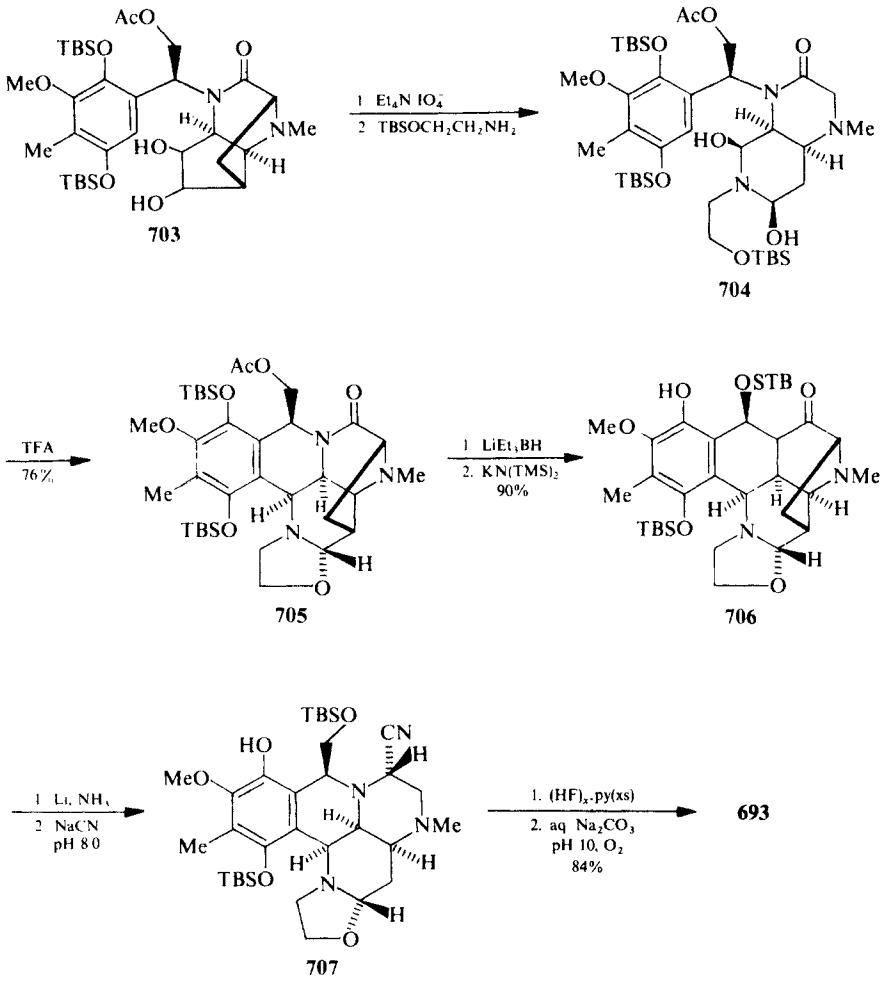
lysis,[371] is a formidable synthetic challenge comprising a highly condensed hexacyclic system with eight chiral centers. Two syntheses have been published.

The Evans[372] synthesis proceeded in three stages. The first objective was the tricyclic lactam **698**; that was then extended by addition of an aromatic moiety to form **701**, which was ingeniously elaborated to the hexacyclic system (Scheme 84). The initial target was the construction of the tricyclic lactam **698**. This was done starting from the β-lactam **694**, which was obtained from cyclopentadiene and chlorosulfonyl isocyanate by an improved procedure.[373] Elaboration by cyclization of **695** gave a mixture of epimeric nitriles, but recycling the unwanted isomer by equilibration with potassium *t*-butoxide gave a 58% yield of **696**. Selective epoxidation on the α face and hydrolysis of the nitrile yielded the epoxyamide **697**, but the subsequent cyclization was not regiospecific. However, after conversion to the *N*-methyl analogue **697a**, it cyclized smoothly to the tricyclic lactam **698** with only traces of the isomeric alcohol, and dehydration via the phenyl selenide gave the key intermediate **699**. The quinone ring synthon 2,4-dimethoxy-3-methylphenol was then linked to the amido nitrogen in two ways, preferably as shown by reaction with methyl glyoxylate followed by treating the aminoacetal with thionyl chloride to form **700**. This was then used in a critical Friedel–Crafts condensation with 2,4-dimethoxy-3-methylphenol. The product was a mixture from which the desired diastereoisomer **701** was best obtained by direct crystallization.

The plan then was to cleave the olefinic double bond to a dialdehyde which would permit ring closure onto the aromatic system and elaboration of the two remaining rings. Much experimentation with related compounds showed that such dialdehydes were exceptionally prone to aldehyde hydration and then ring closure to a dihydroxypyran, a process which could not be reversed. It was therefore essential to trap the dialdehyde from **702** immediately after it was formed. Earlier studies also showed that the aromatic ring precursor to the final quinone should be in the hydroquinone form and that it should be in place before the hexacyclic ring system was assembled. Therefore phenol **701**, after reduction of the ester function, was oxidized to quinone **702** and then reduced and protected, after which diol **703** was formed by osmylation.[374] Periodate oxidation of the diol in nonaqueous solution and trapping the dialdehyde with protected ethanolamine gave the aminodiol **704** as a mixture of diastereomers which cyclized smoothly in neat trifluoroacetic acid to the required hexacyclic lactam **705**. At this stage it seemed that the remainder of the synthesis would be all downhill, but substantial difficulties remained. The lactam carbonyl group was particularly difficult to reduce. Metal–ammonia reduction was possible, but concomitant reduction of the aromatic ring was unavoidable. To suppress that the


1. HCl
2. LAH
89%
694
1. CH2O, NaHSO3
NaCN
2. CbzCl
3. TsCl
71%
t-BuOK
58%
695
696
1. MCPBA
2. H2O2,
aq. Na2CO3
80%
H2/Pd
CH2O
95%
697
697a
t-BuOK
82%
1. MeSO2Cl
2. PhSeSePh
NaBH4
3. t-BuOOH
96%
1. OCHCO2Me
2. SOCl2
96%
698
699
SnCl4
48% from 669
700
701
1. Et3BH
2. DDQ
1. Ac2O, Zn
2. TBSCl
3. OsO4
65% from 701
702

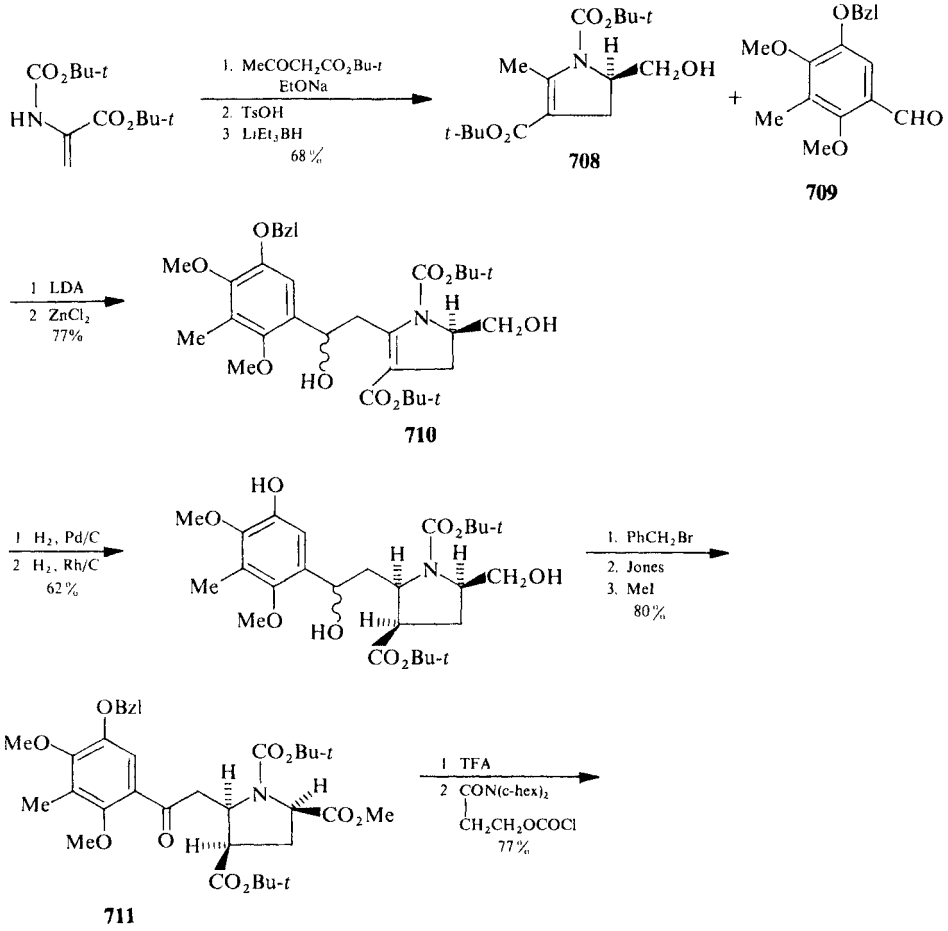
Scheme 84



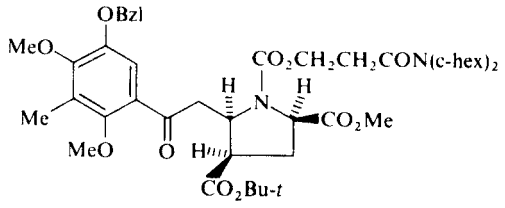
Scheme 84 (*continued*)

protected hydroquinone **705** was converted to the more resistant phenol **706**. That was neatly achieved by reducing the acetate function in **705** to an alcohol, and then transferring to it the silyl group on the adjacent phenolic oxygen. The resulting phenolic lactam **706** could then be reduced with lithium–ammonia, under careful control, to an unstable carbinolamine which was directly converted to the nitrile **707**. Final deprotection with pyridine hydrofluoride and exposure to oxygen at pH 10 yielded synthetic (±)-cyanocycline A **693**.

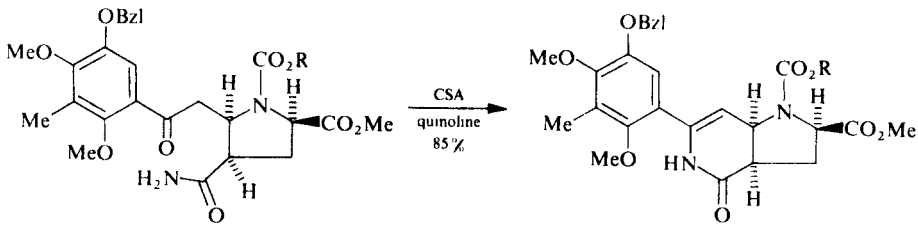
Fukuyama followed his elegant synthesis of saframycin B by synthesizing[375] cyanocycline A. The route chosen proceeded by linking an aromatic ring to a pyrroline to produce **710**, the two central rings were then constructed, leading to **716**, which was efficiently cyclized to a hexacyclic system (Scheme 85). Thus **710** was cleverly obtained by coupling aldehyde **709** with the zinc dienolate of **708** having found previously that use of the lithium dienolate gave predominantly the unwanted cyclic urethane. Earlier experience showed that the *N*-Boc protecting group in **711** was inadequate so, after numerous attempts, it was replaced by the group shown in **712**, which was resistant to the pH changes and reducing conditions encountered at later



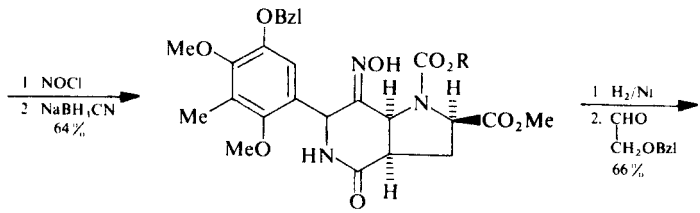
Scheme 85



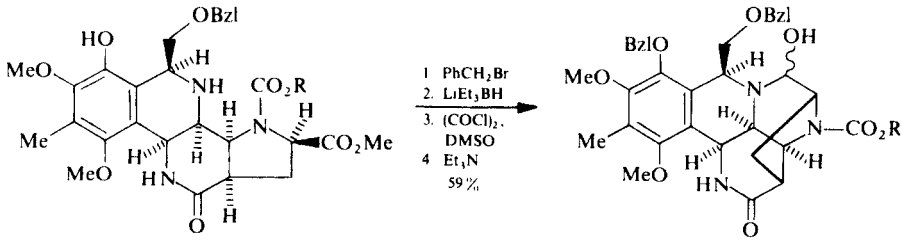
712



713 714

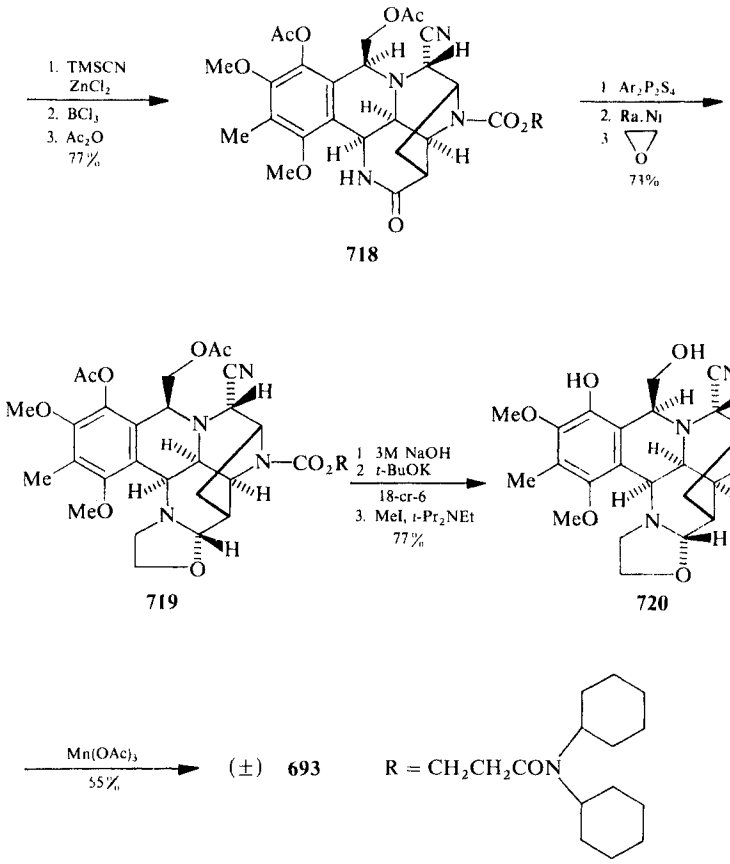


715



716 717

Scheme 85 (*continued*)

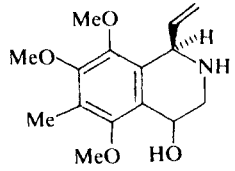


Scheme 85 (*continued*)

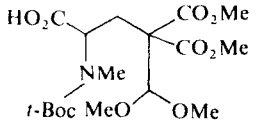
stages. The critical ring closure to the ene lactam **714** was then effected in high yield through the amide **713**. The next step, conversion of the ene lactam **714** to the oxime **715** was crucial, and it was neatly carried out by addition of nitrosyl chloride to the double bond followed by *in situ* reduction of the α-chloro oxime to give predominantly **715**. Catalytic hydrogenation occurred on the less-hindered (convex) face to give an aminophenol which condensed smoothly with glycollic aldehyde benzyl ether to form the tetracyclic phenol **716** exclusively. After reprotection and reduction of the methyl ester, Swern oxidation provided the aldehyde which cyclized efficiently (85%) to the pentacyclic aminoacetal **717**. This epimeric mixture gave a single isomer on cyanation with trimethylsilyl cyanide, and at that stage, based on experience, the benzylic protecting groups were replaced by acetates. The remaining

oxazolidine ring was introduced by converting **718** to the thioamide using Lawesson's reagent,[376] followed by desulfurization to the imine and addition of ethylene oxide to give **719**. After deprotection and *N*-methylation the phenol **720** was finally oxidized to (±)-cyanocycline A.

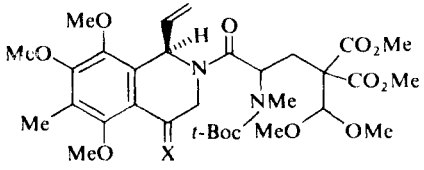
In his approach to the synthesis of naphthyridinomycin **693** (OH in place of CN), Danishefsky[377] succeeded in coupling the two components **721** and **722** to form **723** (X = H, OH) which, after oxidation to the ketone **723** (X = O), was converted to the tetracyclic compound **724** (R = Me) by heating with boron trifluoride. The structure was established by crystallographic analysis of **724** (R = H) obtained by demethylation with boron tribromide. Tetracycle **724** represents a substantial part of the naphthyridinomycin molecule with the correct stereochemistry except at C-13c.



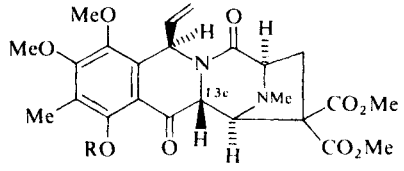
721



722



723



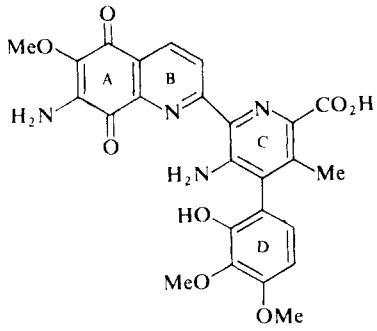
724

D. Quinolinequinones

*Streptonigrin.** Woodward's[378] announcement in 1963 of the structure of streptonigrin **725**, a metabolite of *Streptomyces flocculus*,[379] was later confirmed by an X-ray analysis.[380] The unusual structure, together with its broad spectrum antibiotic activity and initially promising antitumor activity *in vivo*, triggered off extensive studies on its synthesis, biosynthesis,[401] biological activity, and mode of action extending over a period of more than 20 years.[381] Following numerous earlier studies which explored different approaches to the synthesis of streptonigrin, the first total synthesis appeared in 1980.[382]

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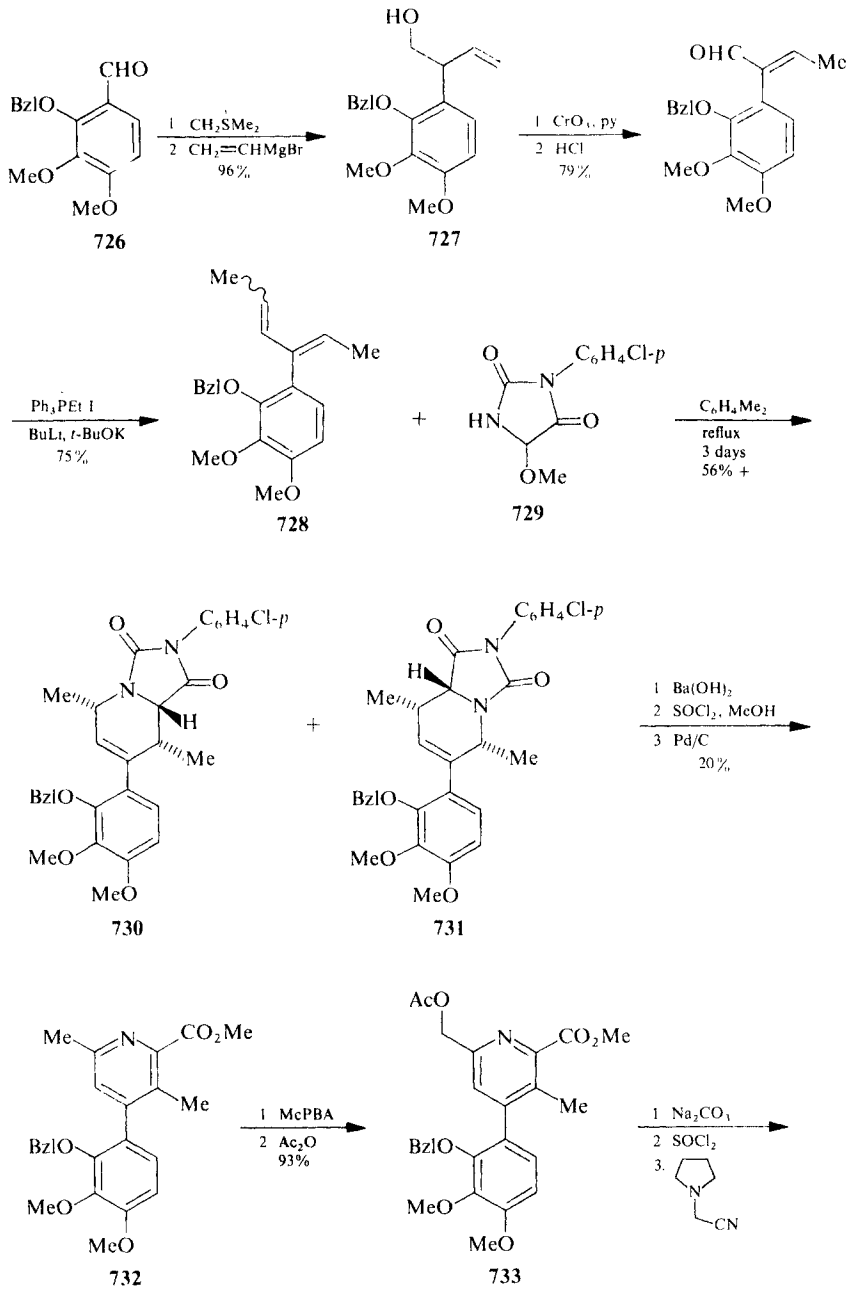
* Identical with bruneomycin[383] and rufochromomycin.[384]



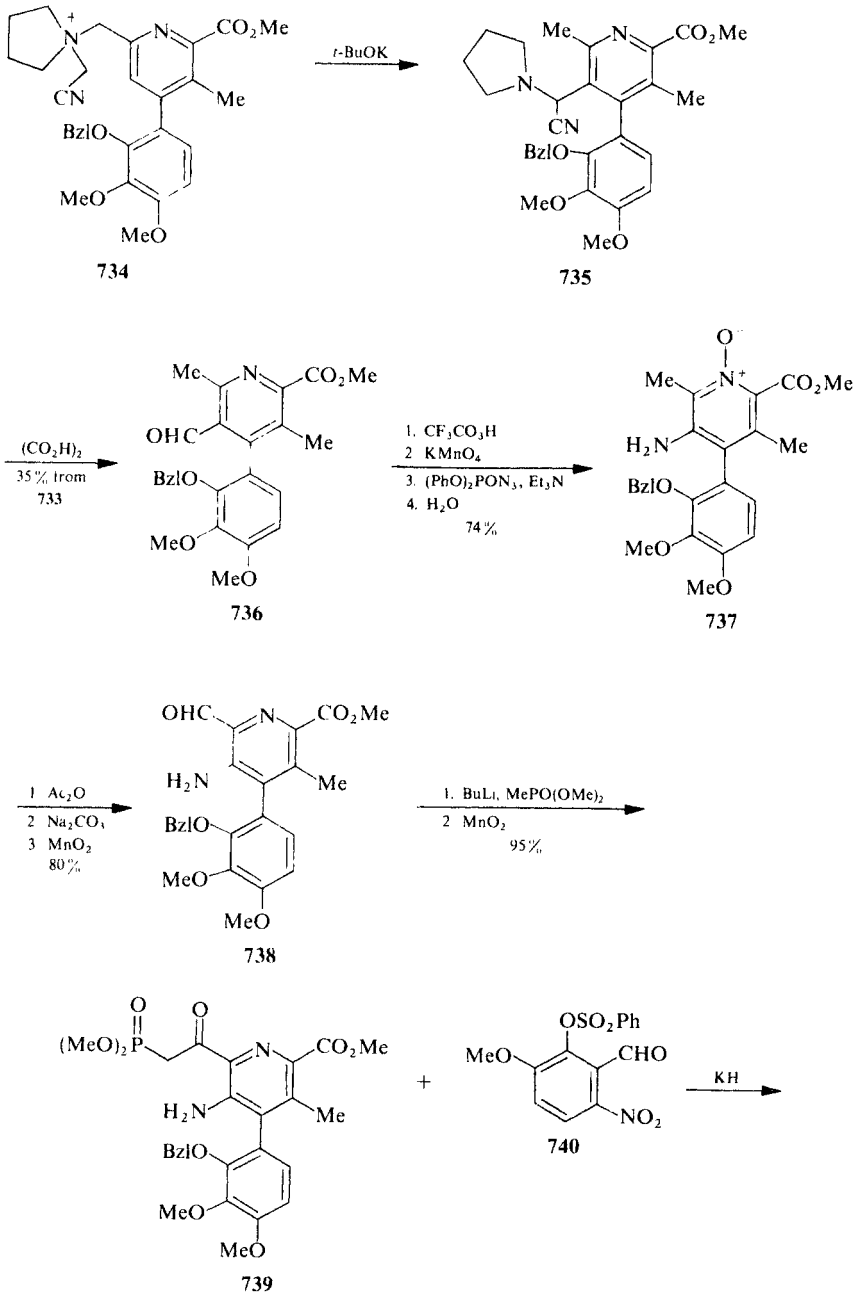
725

After preliminary studies, Weinreb[385] selected the D → DC + A → DCBA route, a particular difficulty being the fully substituted pyridine ring C (Scheme 86). The easily available ring D synthon **726** was converted to the epoxide by Corey's method and then extended to the alcohol **727**. After further extension to the diene **728**, using a modified Wittig reaction, elaboration of ring C began with a hetero-Diels–Alder addition to the methoxyhydantoin **729**. This is an interesting method evaluated in previous studies,[386] but unfortunately is not regiospecific. The reaction produced both regioisomers **730** and **731** (ratio ~ 3:1) and was incomplete after refluxing in xylene for 3 days. Acid catalysis had little effect, but the yield of adducts could be increased by recycling the unreacted diene (56% after one repetition). The major isomer was **730** and after hydrolysis, methylation, and aromatization, pyridine **732** was obtained with very little of the regioisomer. Pyridine **732** still lacks the primary amino group required for ring C of streptonigrin, and it was introduced next by a circuitous route. Converting **732** to the *N*-oxide and reaction with acetic anhydride resulted in rearrangement to **733** which was transformed, as indicated, to the quaternary salt **734**. That, on treatment with potassium *t*-butoxide under carefully controlled conditions developed previously,[387] underwent a [2,3]-sigmatropic rearrangement to aminonitrile **735**, which was at once hydrolyzed with oxalic acid to aldehyde **736**. Following *N*-oxide formation (required later) and oxidation of the aldehyde function, the resulting carboxylic acid was subjected to a Curtius rearrangement, using Yamada's modification, which afforded the amine **737**.

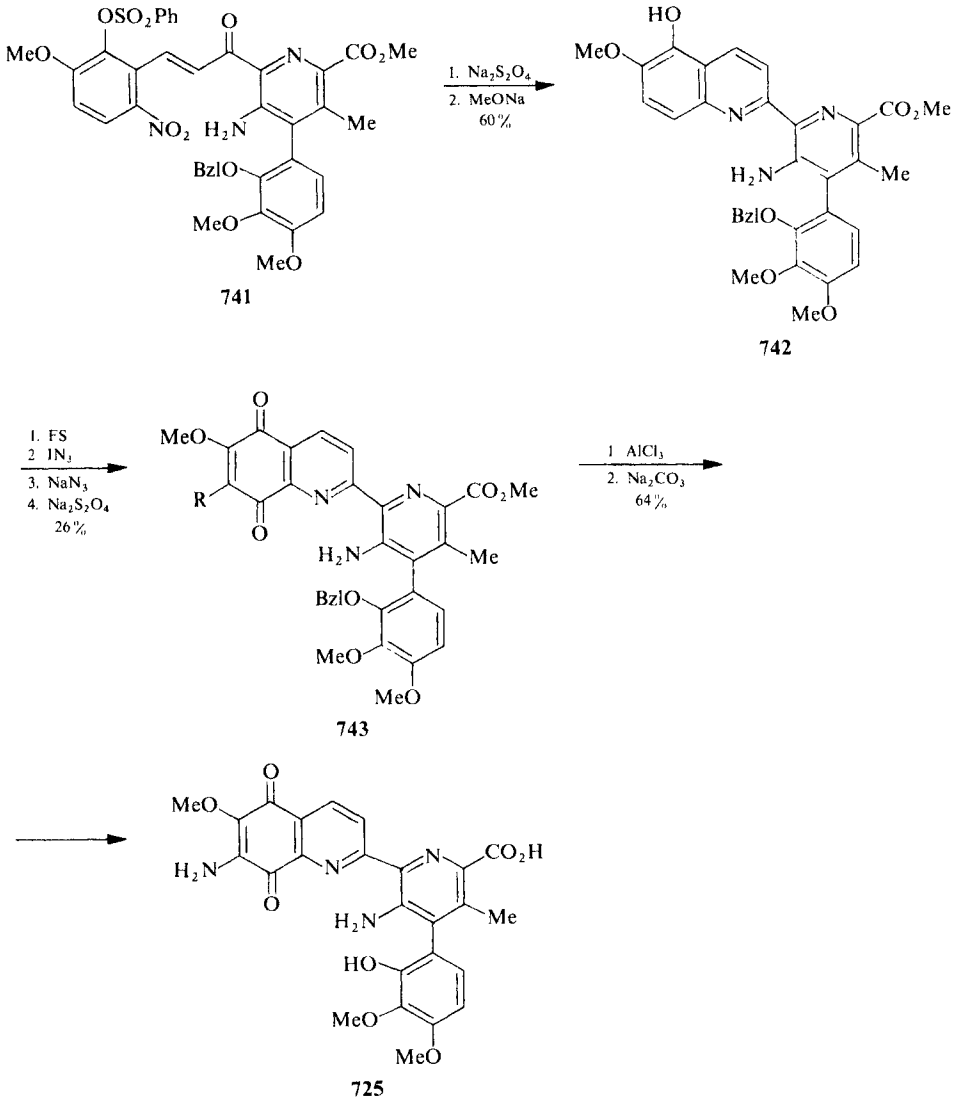
To link this CD-ring moiety to the ring A synthon **740**[388] entails a quinoline synthesis and the route chosen was a modified Friedländer synthesis proceeding via a nitrochalcone intermediate. The *N*-oxide **737** was rearranged with acetic anhydride, as before, and after hydrolysis to the alcohol oxidation with activated manganese dioxide gave the aminoaldehyde


CHO
BzlO
MeO
MeO
726
1 CH_2SMe_2
2 CH_2=CHMgBr
96%
HO
727
1 CrO_3, py
2 HCl
79%
OHC
Me
$Ph_3PEt\ I$
BuLi, t-BuOK
75%
728
729
$C_6H_4Me_2$
reflux
3 days
56% +
730
731
1 $Ba(OH)_2$
2 $SOCl_2$, MeOH
3 Pd/C
20%
CO_2Me
732
1 MCPBA
2 Ac_2O
93%
AcO
733
1 Na_2CO_3
2 $SOCl_2$
3.
CN

Scheme 86



Scheme 86 (*continued*)

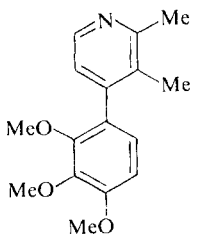


Scheme 86 (*continued*)

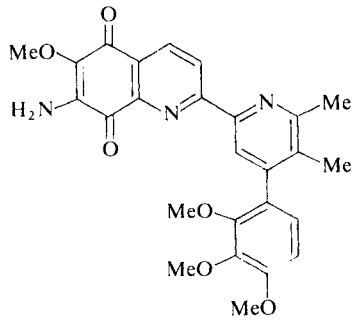
738 in remarkably high yield (88%). Using interesting phosphonate chemistry, addition of dimethyl(lithiomethyl)phosphonate to the aldehyde, and oxidation of the ensuing alcohol gave the β-ketophosphonate **739**, which was condensed by a Wadsworth–Emmons–Horner reaction with the easily accessible[388] nitroaldehyde **740** to give the nitrochalcone **741**. On reduction

with sodium dithionite, the resulting amine underwent a Friedländer condensation to form the desired quinoline, which gave the tetracyclic phenol **742** on hydrolysis. Fremy's salt oxidation of the phenol produced the quinone **743** (R = H), which was converted in three steps via the azide into the aminoquinone **743** ($R = NH_2$), and final deprotection gave the first sample of synthetic streptonigrin.

The Kende[389] synthesis followed essentially the same strategy of coupling a CD bicyclic unit to a ring A synthon by a modified Friedländer cyclization. The route had previously been tested in the synthesis[390] of the analogue **745**, making use of the known 4-arylpyridine **744**.



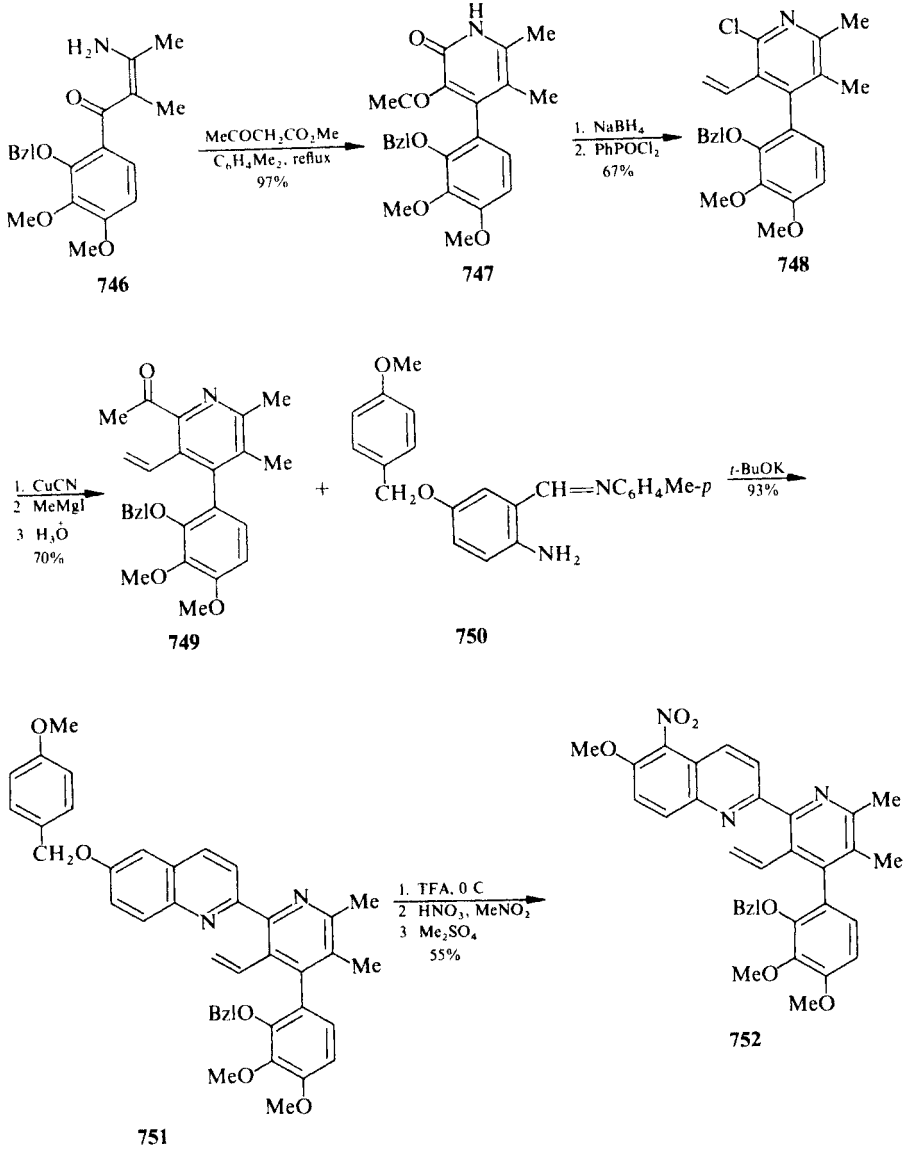
744



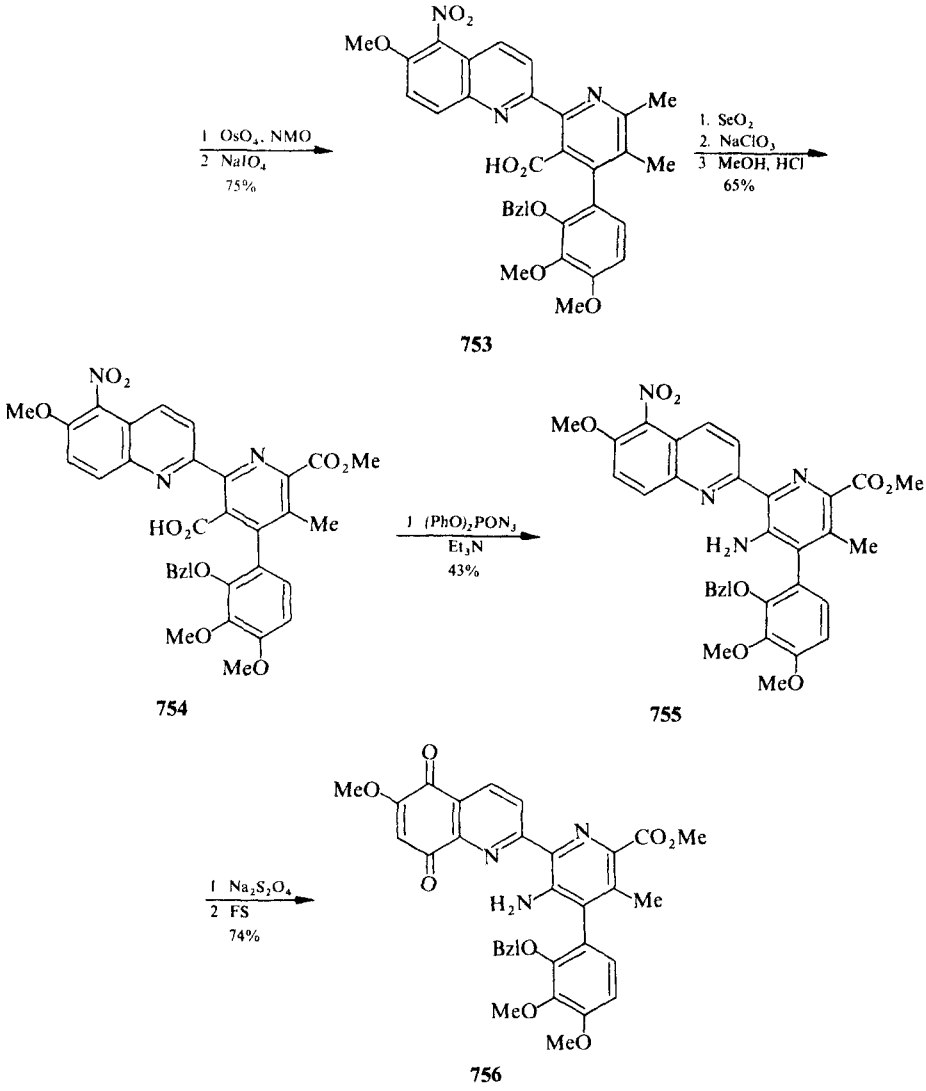
745

The ketoenamine **746**, known[391] from previous investigations, was condensed with methyl acetoacetate very efficiently with remarkable regiospecificity to give the acetylpyridone **747**. After reduction to the alcohol, heating with phenylphosphonic dichloride accomplished two reactions yielding the chlorovinylpyridine **748** leading, as shown (Scheme 87), to the key pyridine **749**, which provides an acetyl group available for quinoline ring formation and a vinyl group for later transformation to an amino group. With both CD **749** and the A-ring component **750** (obtained from 5-hydroxy-2-nitrobenzaldehyde) available, the stage was set for quinoline formation, and after much experimentation the Borsche[392] variation of the Friedländer synthesis gave the tetracyclic **751** in excellent yield. Conversion to **752** by selective debenzylation and further modification of the A ring then followed.

The ring C substituents were next transformed by oxidative cleavage of the vinyl group to give **753**, and selective oxidation of the α-methyl group followed by selective esterification to yield **754**. The Yamada[393] modification of the Curtius rearrangement was used to obtain the primary amine **755**, and after reduction of the nitro group the diamine was oxidized with Fremy's salt to quinone **756**, which had previously been converted by Weinreb to streptonigrin (Scheme 87).


H2N
Me
O
Me
BzlO
MeO
MeO
746
MeCOCH2CO2Me
C6H4Me2, reflux
97%
H
N
Me
O
MeCO
Me
BzlO
MeO
MeO
747
1. NaBH4
2. PhPOCl2
67%
Cl
N
Me
Me
BzlO
MeO
MeO
748
1. CuCN
2 MeMgI
3 H3O
70%
O
Me
N
Me
Me
BzlO
MeO
MeO
749
+
OMe
CH2O
CH=NC6H4Me-p
NH2
t-BuOK
93%
750
OMe
CH2O
N
N
Me
Me
BzlO
MeO
MeO
751
1. TFA, 0 C
2 HNO3, MeNO2
3 Me2SO4
55%
NO2
MeO
N
N
Me
Me
BzlO
MeO
MeO
752

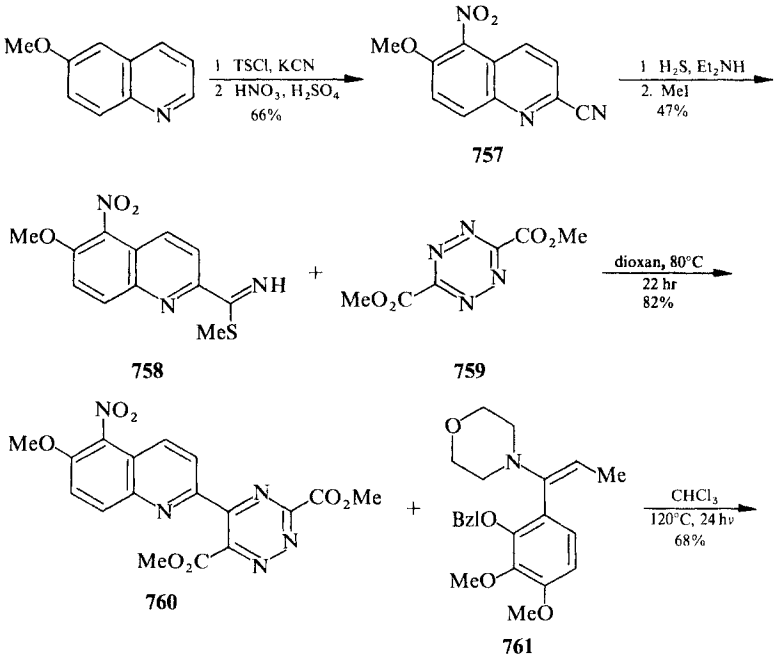
Scheme 87



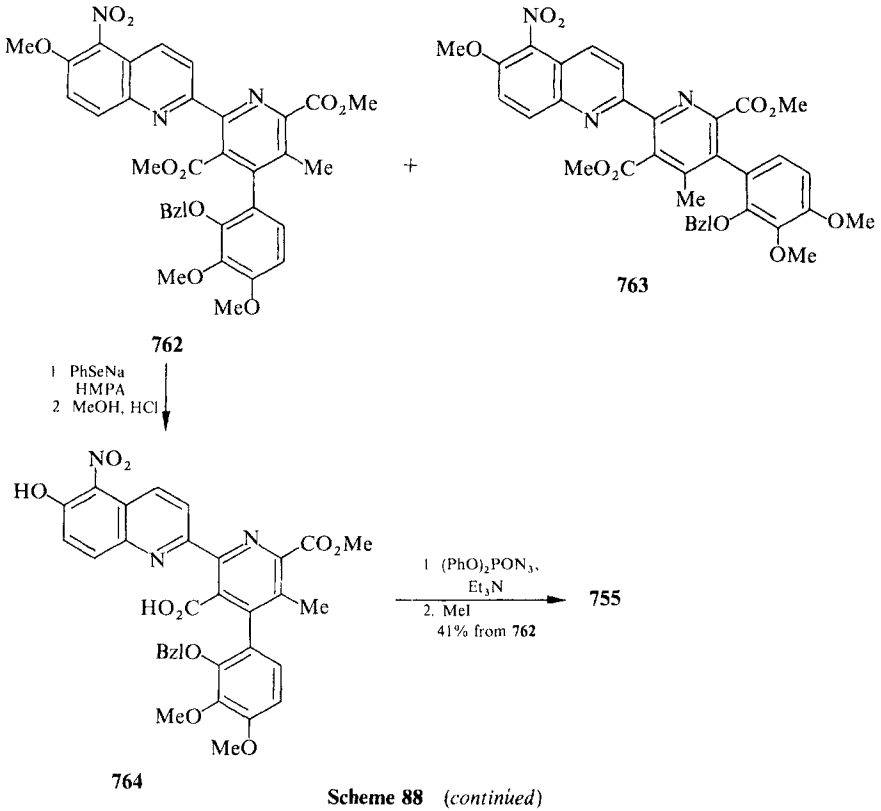
Scheme 87 (*continued*)

The third total synthesis, accomplished by Boger and Panek,[394] again followed extensive preliminary investigations and led to the nitroquinoline **756**, which Kende had previously converted to streptonigrin. A short convergent strategy took the form of an AB + D → ABCD synthesis in which ring C was cleverly elaborated by two successive inverse-electron-demand

Diels–Alder reactions (Scheme 88). The quinoline nitrile **757** was converted to the *S*-methyl thioimidate **758**, which then served as a heterodienophile for cycloaddition of the tetrazine diester **759**. Prolonged heating in dioxan afforded the triazine **760** in good yield. This was utilized as the diene component in the next cycloaddition onto the morpholino enamine of 2-benzyloxy-3,4-dimethoxypropiophenone **761**,[391] which gave a 1:1 mixture of **762** and **763** which were separated chromatographically. This reaction was studied in detail, but whereas the yield could be changed according to the conditions, two isomers were always obtained. In acetonitrile at 80°C the ratio of **762**:**763** improved to 4:1, but the yield fell to 15–26% with 35–45% triazine **760** recovered. Replacement of the hindered β-ester group in **762** by an amino function was not straightforward, as it was remarkably resistant to normal methods of hydrolysis. The problem was overcome by Liotta's[395] method using sodium phenylselenolate, which cleaved both ester methyl groups and the ring A methoxyl. Selective remethylation of the unhindered carboxylic acid gave ester **764**, and a modified Curtius rearrangement and final methylation of the phenol provided the nitroquinoline **755**, identical with that obtained by Kende (Scheme 88).

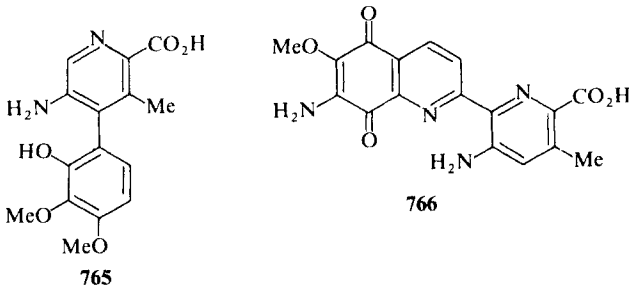


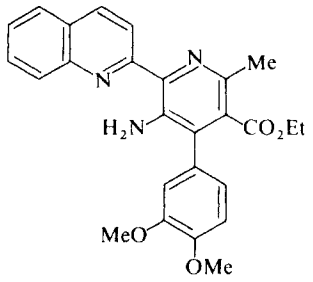
Scheme 88



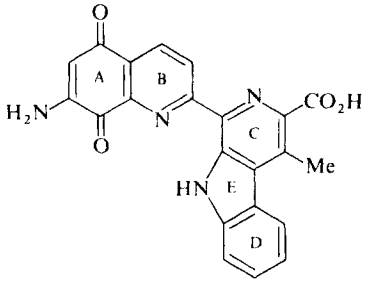
Scheme 88 *(continued)*

The numerous studies published prior to these total syntheses have been summarized.[396] They were concerned mainly with the formation of appropriately substituted quinolinequinones, and construction of highly substituted pyridines and 4-arylpyridines corresponding to rings C and D. Highlights in these investigations were Cheng's[397] synthesis of the CD bicyclic unit **765**, Rao's[398] ABC tricyclic compound **765**, and Kametani's[399] synthesis of the tetracyclic streptonigrin analogue **767**.





767

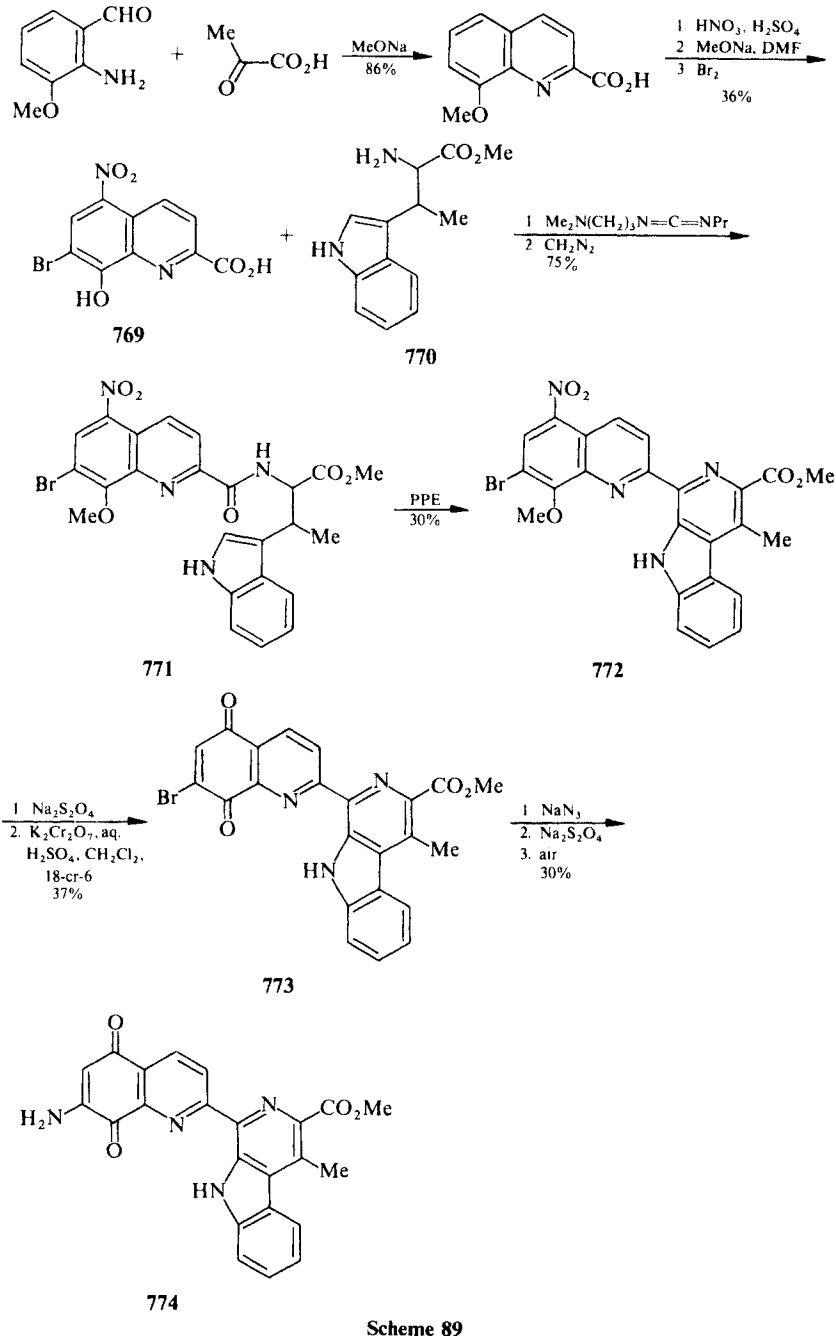


768

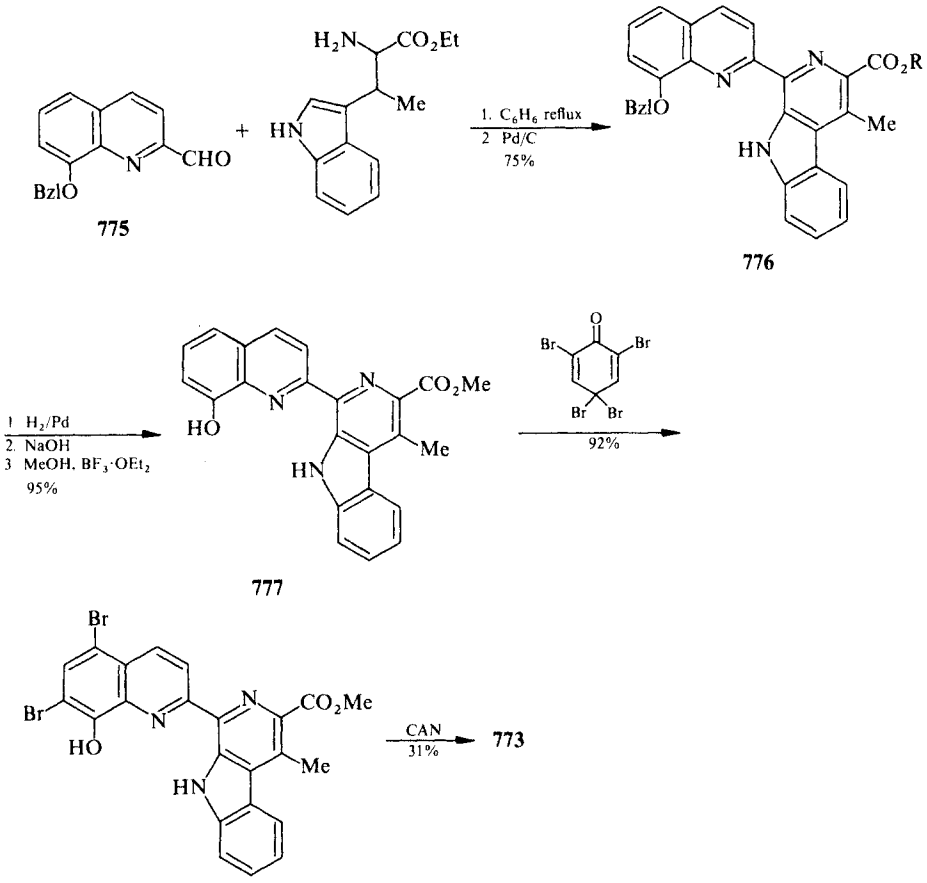
Lavendamycin. This metabolite from *Streptomyces lavendulae*[400] is biogenetically[396] related to streptonigrin and shows biological activity which is generally similar but less potent.[381, 400] Relative to streptonigrin the total synthesis of lavendamycin is an easier task and it has been successfully achieved by four groups. An early suggestion that lavendamycin might be an intermediate in the biosynthesis of streptonigrin, and the demonstration[402] that β-methyltryptophan was incorporated into streptonigrin in cultures of *Strep. flocculus* persuaded Kende[403] to adopt that presumptive biogenetic precursor as the basis for his short total synthesis of lavendamycin methyl ester **774** (Scheme 89). Condensation of the quinoline carboxylic acid **769** with β-methyltryptophan methyl ester[404] **770**, using a basic carbodiimide, gave the amide **771**, after methylation, as a mixture of diastereomers, which cyclized on heating in polyphosphate ester to the β-carboline ester **772**. The remaining stages to **774** followed standard practice except that, owing to the insolubility of the methoxyamine derived from **772**, the oxidation step was conducted in a two-phase system.

Hibino's formal synthesis[405] of lavendamycin methyl ester followed a very similar route (Scheme 90). β-Methyltryptophan ethyl ester was condensed with aldehyde **775** and the product was immediately dehydrogenated to the β-carboline ester **776** (R = Et). After debenzylation and conversion to the methyl ester, the phenol **777** was dibrominated and oxidized to the bromoquinone **773**, which Kende had previously transformed to lavendamycin methyl ester **774**.

Boger's[406] approach to the synthesis was to elaborate first the 1-acetyl-β-carboline **785** comprising the CDE component, which was condensed with the aminoaldehyde **786** to form the pentacyclic system (Scheme 91). An interesting route to the required β-carboline was developed beginning with an inverse-electron-demand cycloaddition of the pyrrolidine enamine of *o*-bromopropiophenone **778** to the triazine **779** (cf. Scheme 88), which gave predominantly (85%) the regio isomer **780**. Exhaustive ester hydrolysis followed by Fischer esterification afforded **781**, leaving the hindered carboxyl


CHO
NH2
MeO
Me
CO2H
O
MeONa
86%
N
CO2H
MeO
1 HNO3, H2SO4
2 MeONa, DMF
3 Br2
36%
NO2
Br
N
CO2H
HO
769
H2N
CO2Me
Me
HN
770
1 Me2N(CH2)3N=C=NPr
2 CH2N2
75%
H
N
O
771
PPE
30%
772
1 Na2S2O4
2. K2Cr2O7, aq.
H2SO4, CH2Cl2,
18-cr-6
37%
773
1 NaN3
2. Na2S2O4
3. air
30%
H2N
774

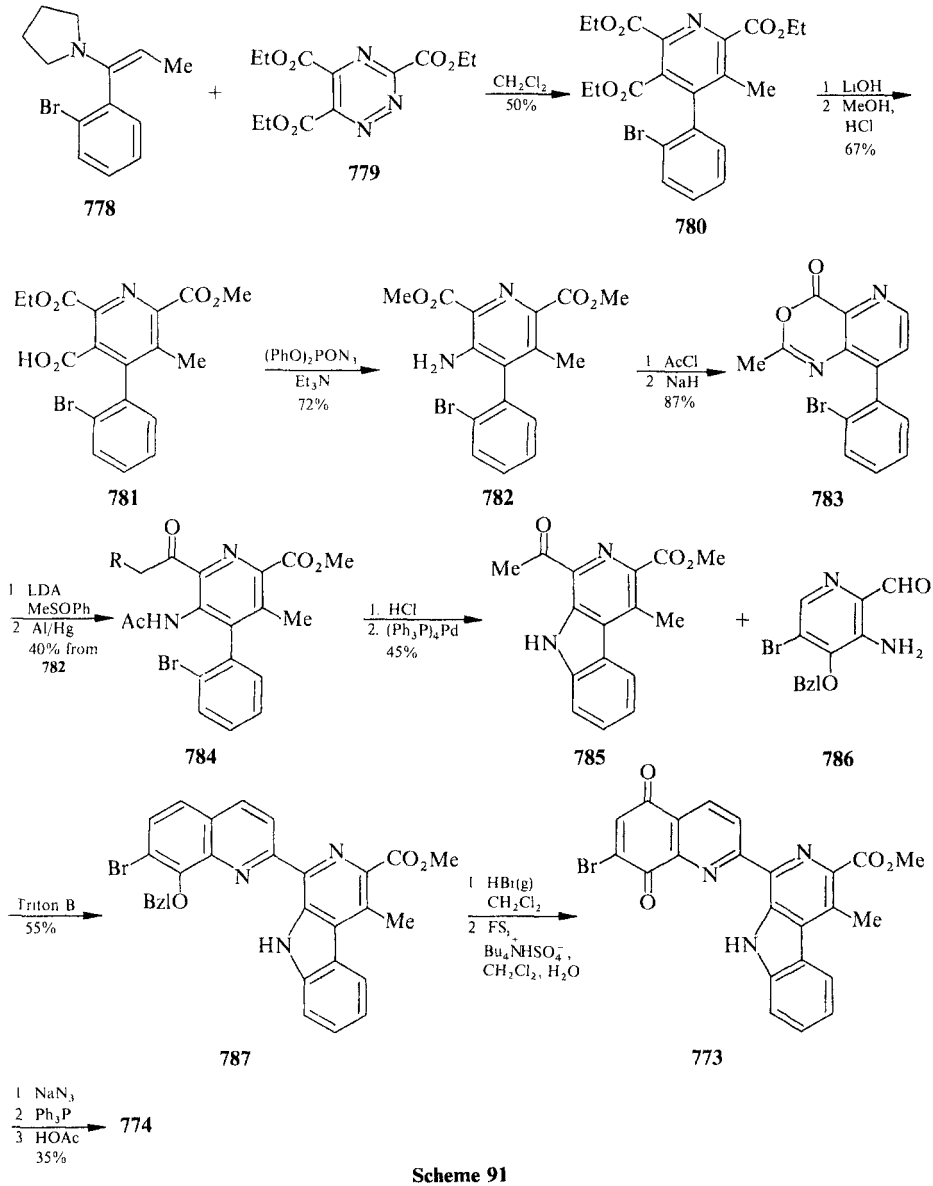
Scheme 89



Scheme 90

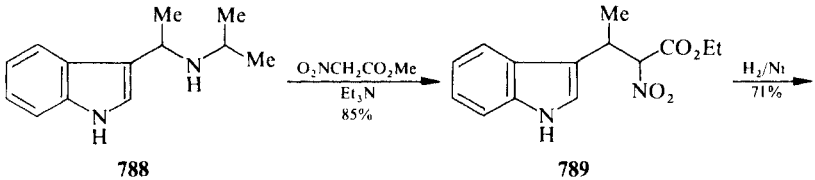
group free for conversion to amine **782** by a modified Curtius–Yamada rearrangement.

The problem then was to distinguish between the two ester groups in **782** in order to effect regiospecific replacement of the C-2 group by an acetyl group. That was accomplished by NH_2-acetylation and ring closure to the oxazinone **783**, followed by treatment with lithiomethyl phenyl sulfoxide to form the β-ketosulfoxide **785** (R = PhSO), which in turn was desulfinated[407] with aluminum amalgam to give the acetylpyridine **784** (R = H). Selective amide hydrolysis of **784** (R = H) afforded the bromo-amine precursor to the β-carboline, but all attempts at ring closure by known methods were unsuccessful. The problem was eventually overcome[408] by palladium(0) mediation, which provided the desired CDE ring component **785**.

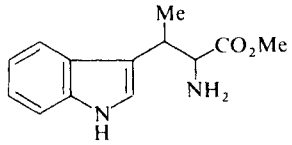


Scheme 91

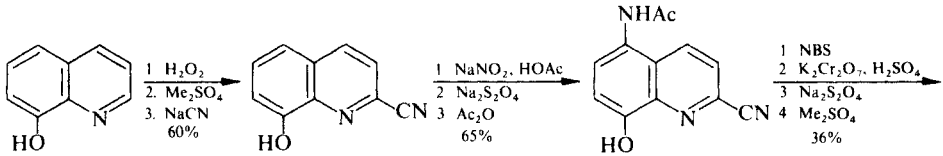
A Friedländer condensation of **785** with the aminoaldehyde **786**, prepared from 3-hydroxybenzoic acid in four steps, yielded the quinoline **787**. The remaining steps to lavendamycin methyl ester **774** proceeded as shown; debenzylation was best carried out using gaseous hydrogen bromide, the

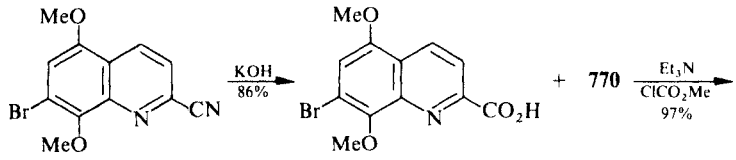


788 **789**

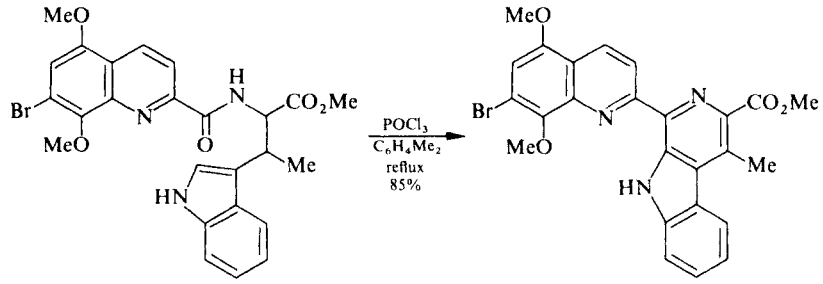


770

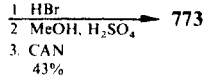




790



791 **792**

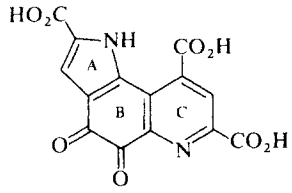


Scheme 92

Fremy's salt oxidation was performed in a two-phase system using a phase transfer reagent, and the final reduction of the azide to an amino group was achieved with triphenylphosphine, which avoids concomitant reduction of quinone to hydroquinone.

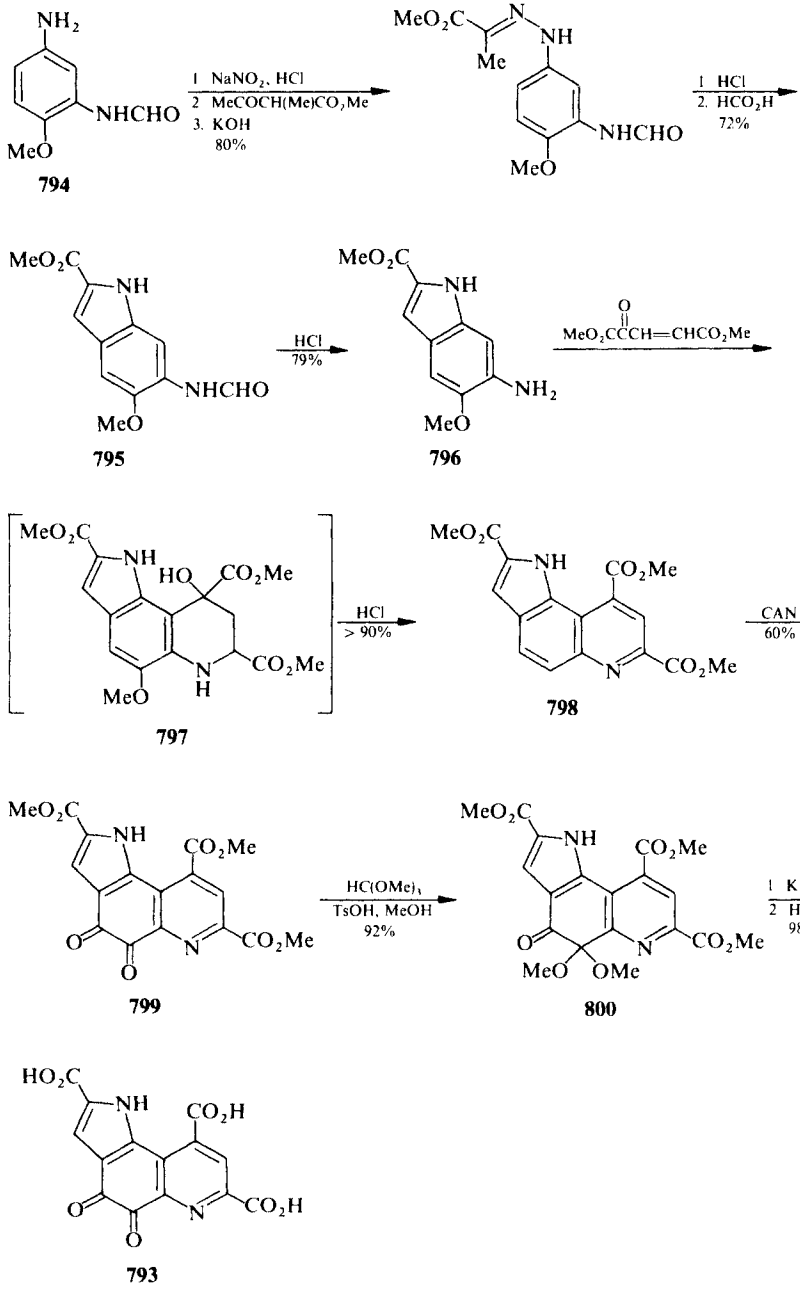
The fourth formal synthesis of lavendamycin methyl ester, devised by Rama Rao,[409] followed the route AB + DE → ABCDE, the pyridine ring C being constructed last. The base from which the β-carboline moiety was elaborated was again β-methyltryptophan methyl ester **770**, for which a new synthesis was developed from the amine **788**[404] easily obtained from indole. The AB synthon **790**, derived from 8-hydroxyquinoline by standard chemistry, was condensed with β-methyltryptophan methyl ester by the mixed anhydride method to give the amide **791** in excellent yield. Cyclization with phosphorus oxychloride provided the pentacyclic structure **792** from which Kende's bromoquinone **773** was obtained in three steps (Scheme 92).

Methoxatin. The bacterial dehydrogenases known as quinoproteins use methoxatin[410] as coenzyme (coenzyme PQQ) which enables methylotrophic bacteria to sustain growth on one-carbon compounds such as methane and methanol as their sole source.[411] It is also a cofactor in ethanol, acetic acid, glycerol, and other dehydrogenases, and indeed in mammalian enzymes, suggesting that it maybe a dietary requirement.[412] The unique pyrroloquinolinequinone structure **793** of methoxatin, and the importance of methylotrophic bacteria in the production of "single-cell protein" stimulated great interest, and six syntheses have been reported using mainly updated classical reactions for quinoline and indole synthesis. It is now commercially available.



793

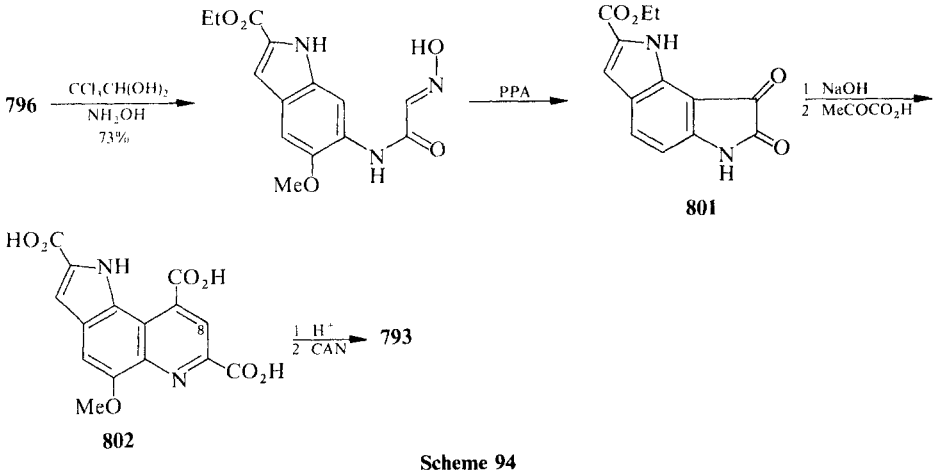
The Corey[413] synthesis proceeded by the B → AB → ABC route starting from the aniline **794**, which was easily derived from 2-methoxy-5-nitroaniline. A Japp–Klingemann reaction with methyl α-methylacetoacetate followed by a Fischer cyclization yielded the indole **795** with < 3% of the regioisomer. After selective hydrolysis to the aminoindole **796**, addition of the C ring then followed by a very efficient Doebner–Miller type reaction with dimethyl 2-oxoglutaconate, which yielded the pyrroloquinoline **798** (intermediate **797** could also be isolated). An unusual CAN oxidation then provided


NH2
NHCHO
MeO
794
1. NaNO2, HCl
2. MeCOCH(Me)CO2Me
3. KOH
80%
MeO2C
N
NH
Me
NHCHO
MeO
1. HCl
2. HCO2H
72%
MeO2C
NH
NHCHO
MeO
795
HCl
79%
MeO2C
NH
NH2
MeO
796
O
MeO2CCCH=CHCO2Me
MeO2C
NH
HO
CO2Me
CO2Me
N
H
MeO
797
HCl
> 90%
MeO2C
NH
CO2Me
CO2Me
N
798
CAN
60%
MeO2C
NH
CO2Me
O
O
N
CO2Me
799
HC(OMe)3
TsOH, MeOH
92%
MeO2C
NH
CO2Me
O
N
CO2Me
MeO
OMe
800
1. K2CO3
2. HCl
98%
HO2C
NH
CO2H
O
O
N
CO2H
793

Scheme 93

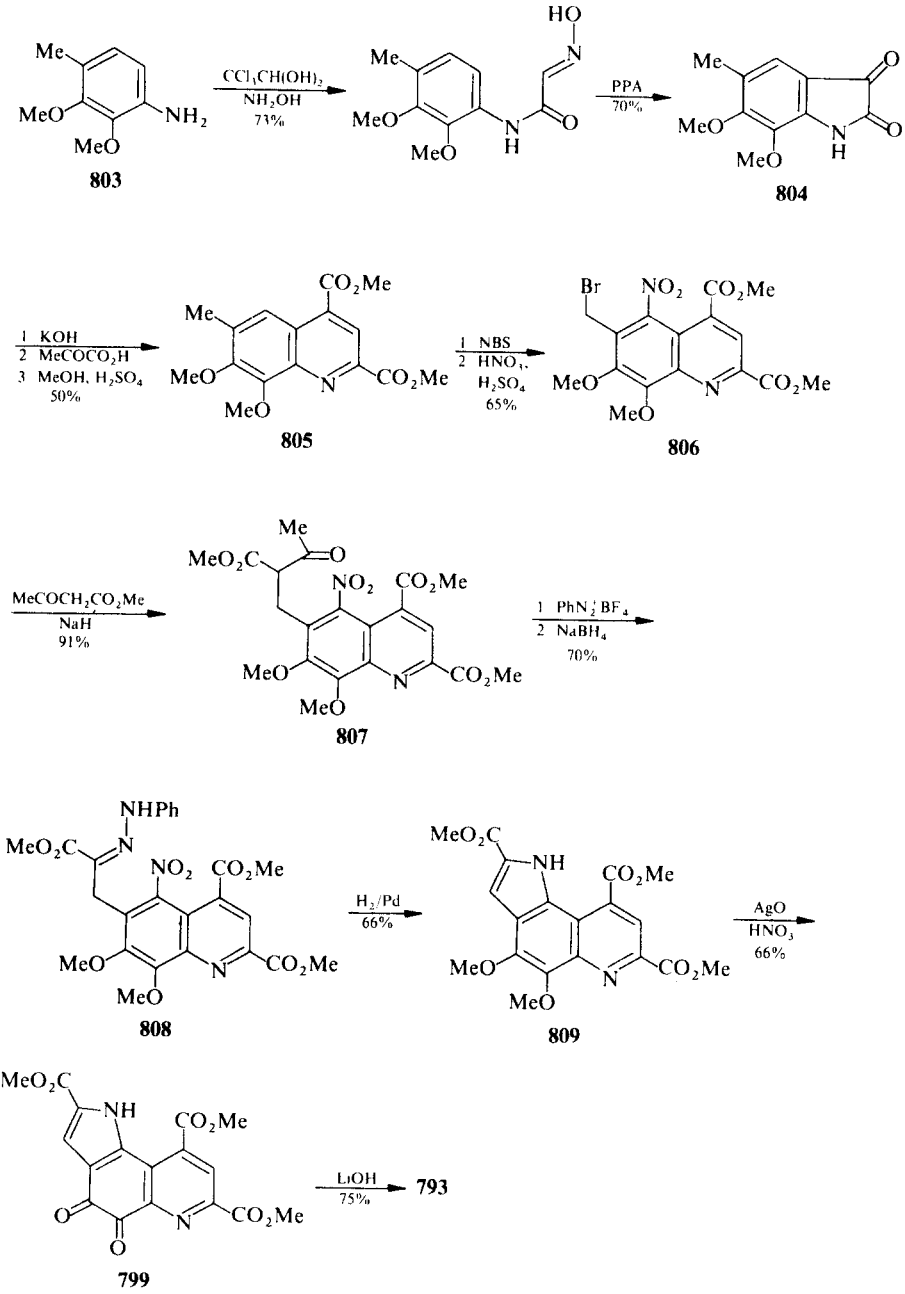
methoxatin trimethyl ester **799** directly. Complete hydrolysis of the ester groups in **799** proved to be difficult under acidic conditions, but a solution to the problem was found by reaction with methyl orthoformate, which afforded the monoketal **800**. Complete hydrolysis could then be effected very efficiently with hot aqueous potassium carbonate, whence acidification to pH 2.5 gave synthetic methoxatin **793** (Scheme 93).

Jongejan[414] has prepared labelled methoxatin for use in studies on its biosynthesis and mode of action. Using methyl α-methylacetoacetate labelled with ^{13}C and with ^{2}H in the α-methyl group, and following Corey's route, under optimized conditions they succeeded in preparing methoxatin labelled in the A ring in an overall yield of > 40%. This is much the most efficient synthesis achieved so far. An alternative synthesis was also devised[414] (Scheme 94). The aminoindole **796** was converted to the isatin **801**, which was used in a Pfitzinger synthesis to secure the acid **802**. By conducting the ring opening of **801** and the condensation with pyruvic acid in $NaO^2H/^2H_2O$ **802** deuterium-labelled at C-8 could be obtained in 70% yield.



Scheme 94

The Weinreb[415] synthesis of methoxatin, contemporaneous with Corey's, followed a B → BC → ABC pathway (Scheme 95). 2,3-Dimethoxytoluene was converted to the amine **803** and then by the Sandmeyer route to the isatin **804**, whence a Pfitzinger synthesis afforded the quinoline **805**. The pyrrole ring was then constructed by first alkylating methyl acetoacetate with the bromomethyl derivative **806** giving **807**, followed by a modified[416] Japp–Klingemann reaction which produced the hydrazone **808**, and finally, after this roll call of classical reactions, hydrogenation of **808** gave, directly,

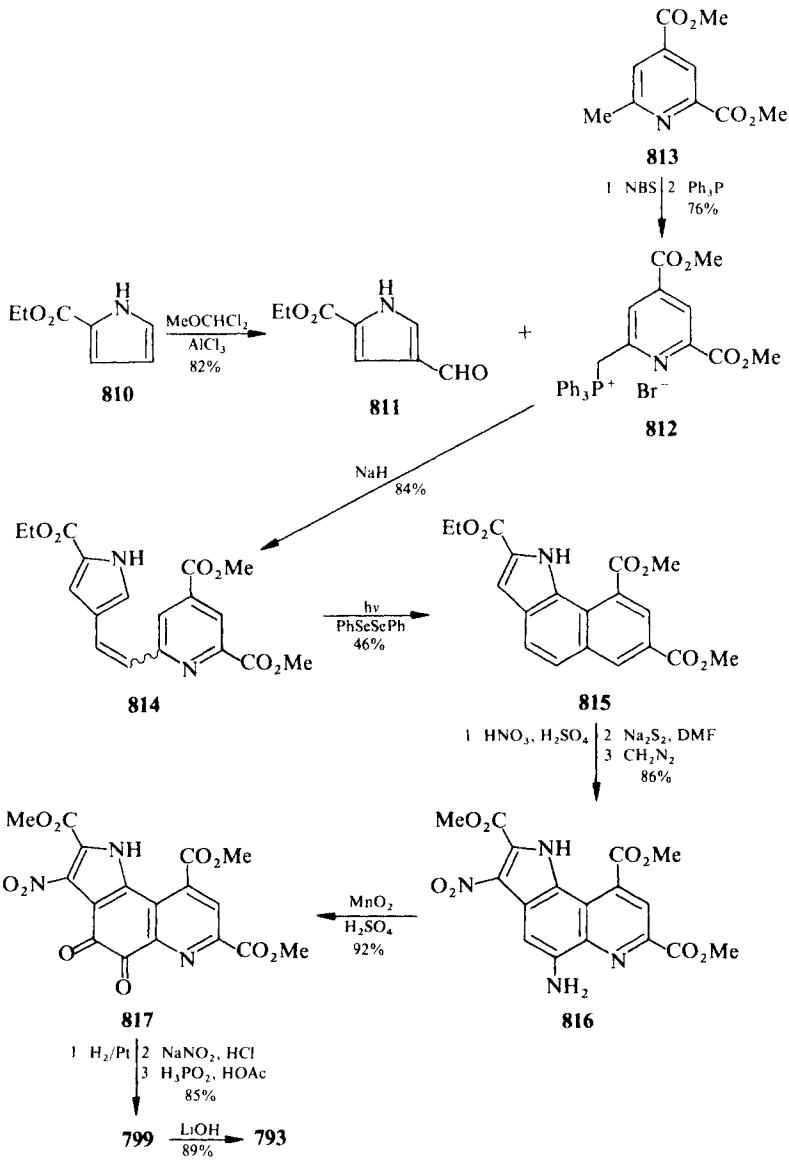


Scheme 95

the pyrroloquinoline **809**. Oxidation with silver(II) oxide yielded methoxatin triester **799**. Ester hydrolysis again proved to be difficult, but eventually it was successfully achieved using aqueous lithium hydroxide.

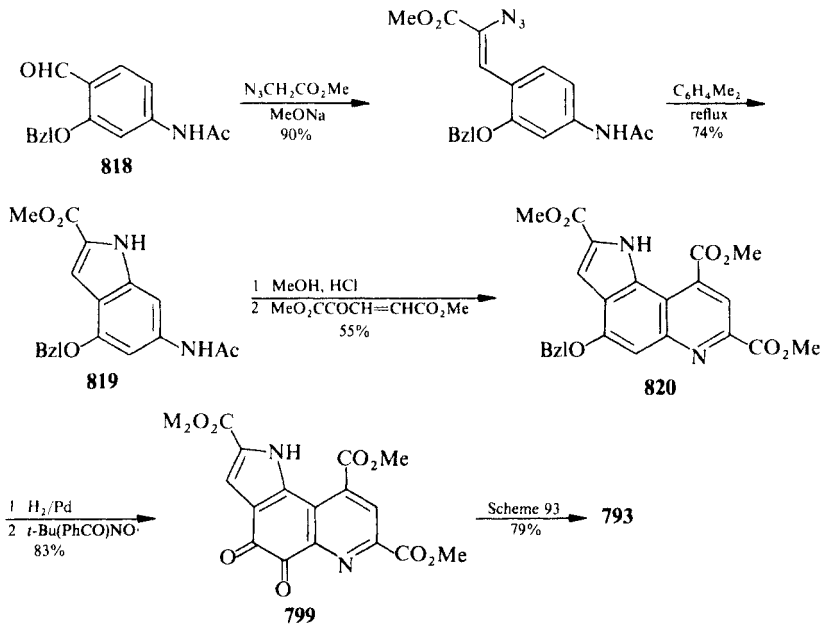
Whereas all the foregoing syntheses start with ring B and build on A and C, Hendrickson[417] devised a convergent strategy in which ring A and C synthons were linked in the form of a "stilbene" **814** which was then cyclized to the ABC system (Scheme 96). The starting components were easily assembled. The ring A synthon **811** had previously been prepared[418] by a Friedel–Crafts formylation of ethyl pyrrole-2-carboxylate **810** with remarkable regiospecificity, and the C ring synthon was secured from 2-methylpyridine-4,6-dicarboxylic acid (obtained from pyruvic acid and ammonia in one step[419]) by esterification, bromination, and conversion to the phosphonium bromide **812**. Monobromination of **813** without dibromination was difficult to achieve and in practice a limited amount of *N*-bromosuccinimide was used and unreacted diester was recovered. Wittig coupling of **811** and **812** proceeded smoothly to give the *trans* isomer ($\sim 95\%$) which rearranged to the *cis* isomer **814** under UV radiation. However, much longer photolysis (3–4 weeks) in the presence of diphenyl diselenide resulted in ring closure to the tricyclic compound **815**. It was hoped that **815** would behave like a phenanthrene and permit direct oxidation of the central ring to an *o*-quinone, but all attempts to do so were unsuccessful. A more circuitous route was therefore necessary. It was found impossible to nitrate the benzene ring without also nitrating the pyrrole ring even when the 3-position was blocked by halogen. Accordingly, the dinitro compound was accepted and fortunately partial reduction with sodium disulfide in cold aqueous dimethylformamide gave the nitro-amine **816** quantitatively and with complete regiospecificity. At the same time the pyrrolic ester group at C-2 was hydrolyzed and was remethylated before workup. Oxidation of **816** to quinone **817** was not easy, but activated manganese dioxide in sulfuric acid proved to be remarkably effective. Finally the nitro group was eliminated by reduction to the amine and deamination with hypophosphorous acid to give the triester **799**, which was hydrolyzed to methoxatin by Weinreb's procedure.

Later Rees[420] completed an efficient, short synthesis of methoxatin in six steps from the aldehyde **818** readily obtained from 4-amino-salicylic acid (27% overall yield). It followed the general plan of Corey's synthesis (Scheme 93), but used the high-yielding azidocinnamate route[421] to form the indole **819** with complete regiospecificity. As oxidation of the phenol resulting from debenzylation of **820** with Fremy's salt was disappointing, owing to poor solubility in aqueous media, it was replaced by benzoyl *t*-butyl nitroxide which in methanol–chloroform gave methoxatin triester **799** in excellent yield (Scheme 97).



Scheme 96

Büchi[422] has devised an interesting biomimetic synthesis of methoxatin based on the hypothesis (since established[423]) that the quinone originates from *o*-tyrosine and glutamic acid. It was found that the AB unit **822** could be obtained directly from *o*-tyrosine by a Fremy's salt oxidation but the yield

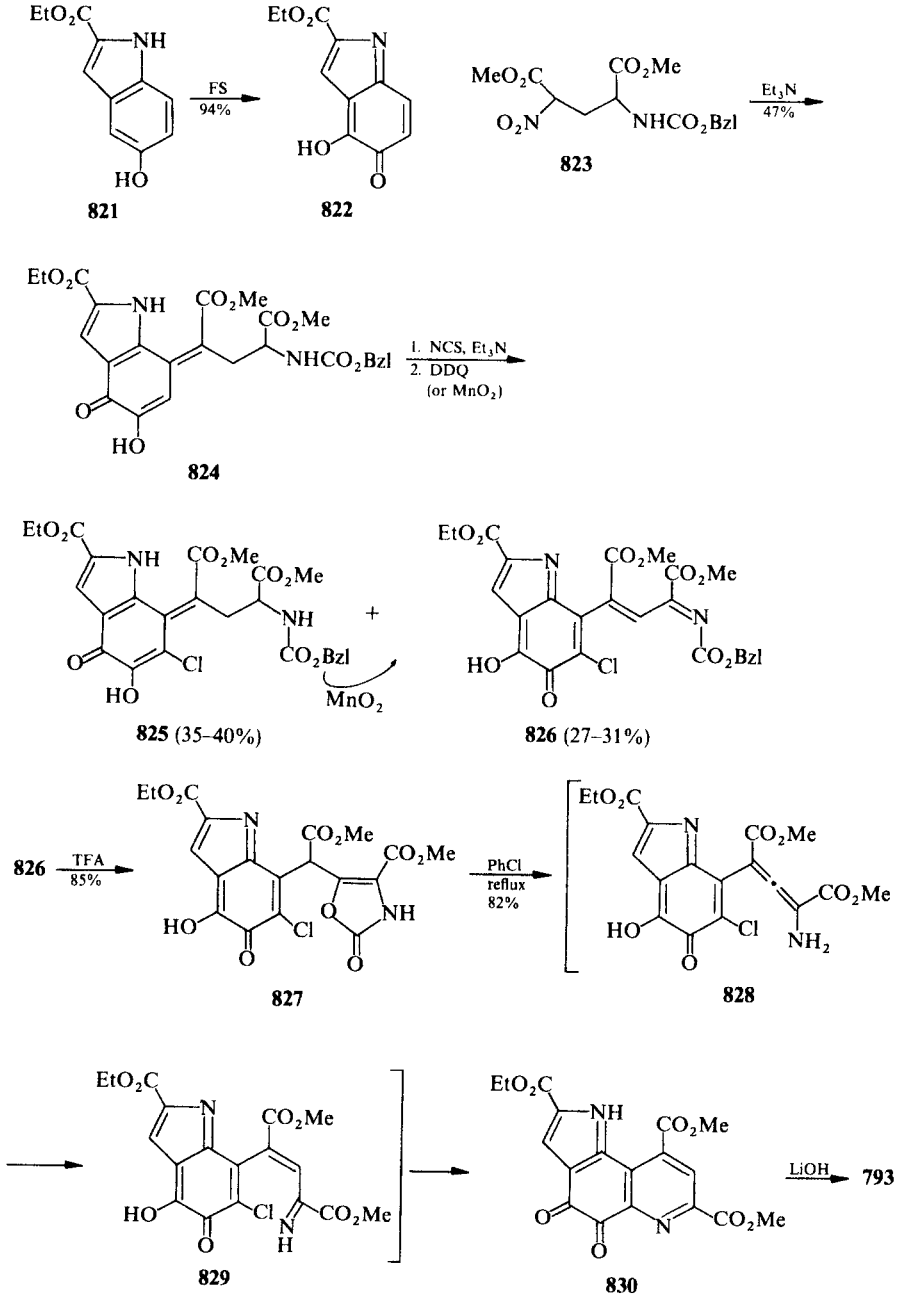


Scheme 97

was poor, and it was more conveniently prepared by oxidation of the indole ester **821** (the benzyl ether is commercially available). The synthesis proceeded by annulation with glutamate using the derivative **823** which was made, as a mixture of diastereomers, by conjugate addition of methyl nitroacetate to *N*-(benzyloxycarbonyl)dehydroalanine.[424] Michael addition of **823** to **822** and immediate elimination of the nitro group gave the quinone methide **824**. Treatment of that with *N*-chlorosuccinimide, followed by oxidation, gave the quinonemethide **825** (two diastereomers) and the diimine **826**. More of **826** could be obtained by further oxidation of **825**. Debenzylation of **826** in trifluoroacetic acid led to the formation of the oxazolinone **827**, and when that was heated in refluxing chlorobenzene it cyclized, probably via the allene **828** and the imine **829**, to the methoxatin triester **830** in good yield (Scheme 98).

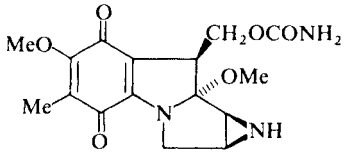
E. Mitomycins

The mitomycins comprise a small group of quinones isolated from cultures of *Streptomyces caespitosus*[15] and other *Strep.* spp.[425,426] which are active against a wide spectrum of bacteria and tumors. The most important are

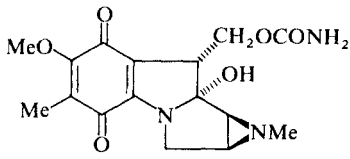

EtO2C
NH
HO
821
FS
94%
EtO2C
N
HO
O
822
MeO2C
CO2Me
O2N
NHCO2Bzl
823
Et3N
47%
CO2Me
CO2Me
NHCO2Bzl
1. NCS, Et3N
2. DDQ
(or MnO2)
824
Cl
NH
CO2Bzl
MnO2
825 (35–40%)
826 (27–31%)
826
TFA
85%
827
PhCl
reflux
82%
828
829
LiOH
793
830

Scheme 98

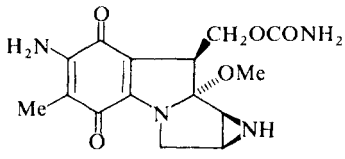
mitomycin A **831**, B **832**, C **833**, and porfiromycin **834**. Mitomycin C is probably the most active antitumor antibiotic known, and is used in cancer therapy.[427] Although the unique mitomycin structures posed a formidable challenge to synthetic chemists, having regard of their powerful biological activity it was taken up with enthusiasm, and approaches to mitomycin synthesis became a growth industry in the years following the initial structural elucidation in 1962,[428] (the stereochemistry was revised later[15]). These studies, which have added substantially to our knowledge of [1,2a]-pyrroloindole chemistry, have been extensively reviewed.[12,429] In 1977 Kishi published brilliant syntheses of (±)-mitomycins A and C, and porfiromycin, B followed a little later, and in 1987 Fukuyama reported a total synthesis of (±) isomitomycin A.



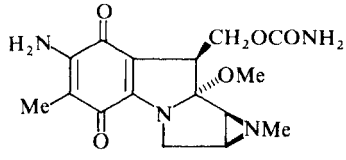
831



832

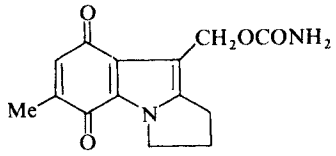


833

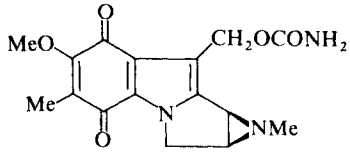


834

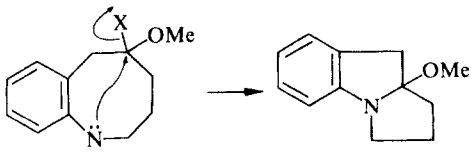
Porfiromycin. Many early studies were directed toward the synthesis of indoles of type **835** (mitosenes), which are not only less complex target molecules, but the particular difficulties associated with the C-9a substituent are avoided. This is very sensitive to acidic conditions and elimination of water or methanol occurs very readily to form, for example, the mitosene **836** from mitomycin A. The same product is formed even on catalytic hydrogenation under mild conditions. This dictates that in any mitomycin synthesis the C-9a function should be introduced at as late a stage as possible, following which reducing conditions must be avoided. With that in mind Kishi[430] planned a synthesis in which an appropriately substituted benzazocine would undergo a transannular reaction to form a dihydropyrroloindole carrying a methoxyl group at C-9a (e.g., **837** → **838**). Despite the difficulties in elaborating the required benzazocine, and although previous transannular reactions[431] of this type had failed to retain the oxygen function at C-9a, Kishi successfully synthesized[430] deiminomitomycin A **839** by this route.



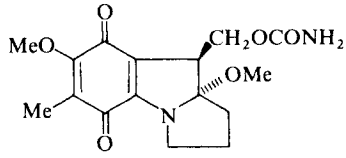
835



836



837 838

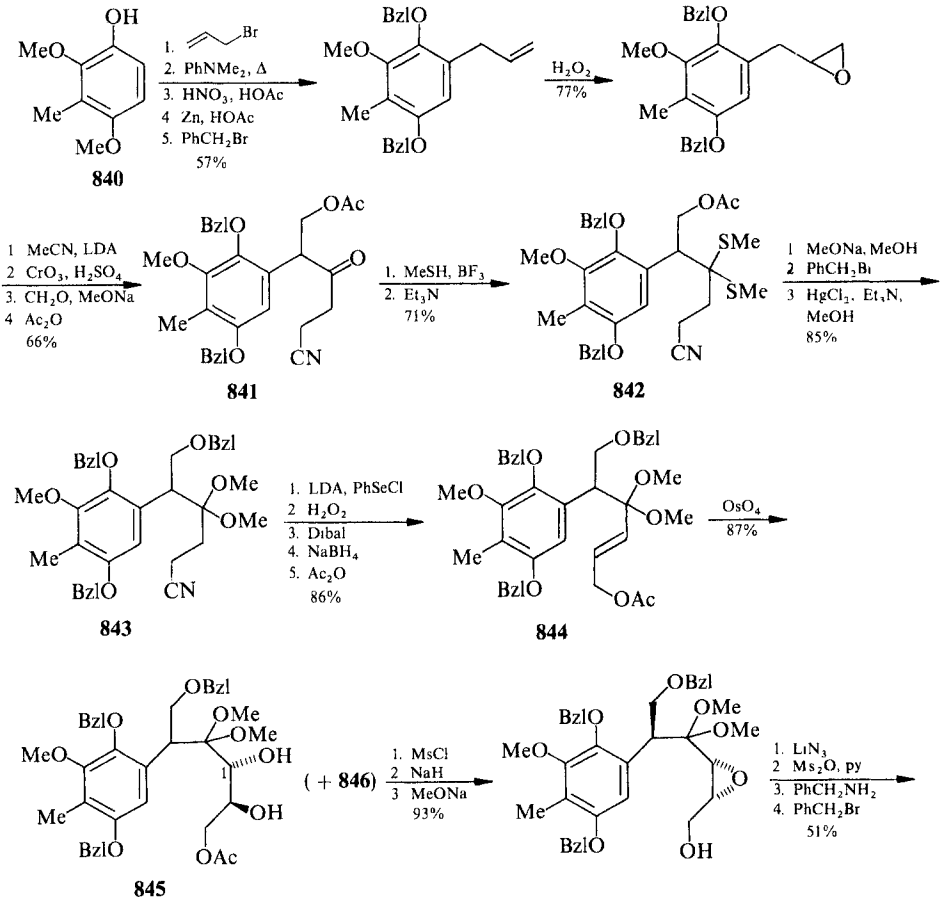


839

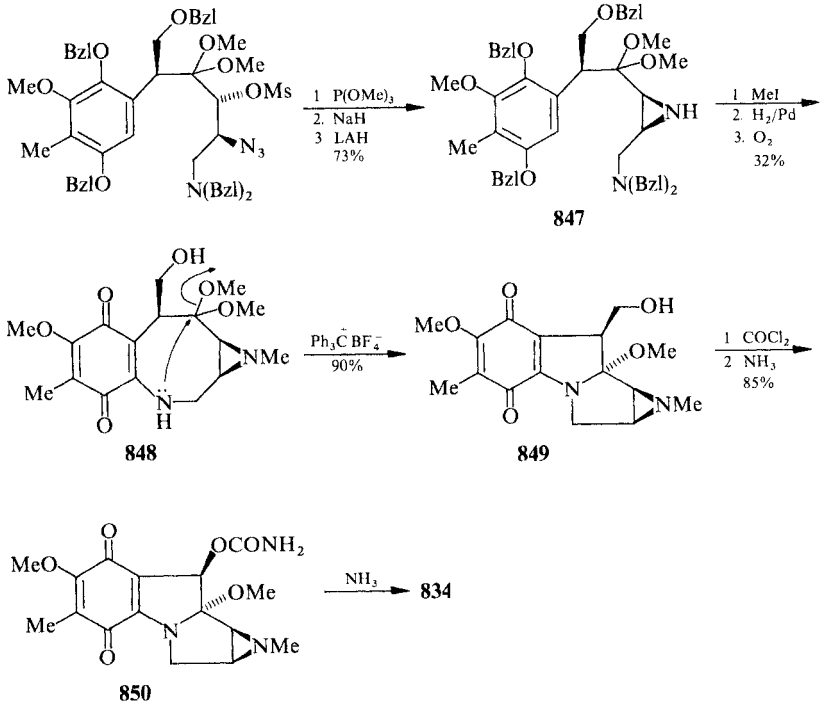
Having demonstrated the feasibility of both benzazocine formation and the transannular cyclization, Kishi[432] tackled the more difficult task of synthesizing the natural quinones **831–834**. The route to porfiromycin **834** is shown in Scheme 99. 2,6-Dimethoxytoluene was converted in three steps very efficiently to the phenol **840**, and after allylation the side chain was extended, as shown, to the ketonitrile **841**. Direct ketalization of **841** was difficult as elimination of acetic acid could not be avoided, and it was achieved eventually through the dithioketal **841** → **843**. In the process methanethiol also adds to the nitrile function and was removed by treatment with triethylamine. As a first step toward introduction of the aziridine ring, a double bond was next introduced via selenoxide elimination giving, after further elaboration, the unsaturated acetate **844**. Osmylation of **844** provided **845** and the diastereomeric diol **846** in equal amounts, which could be separated chromatographically. The next sequence of reactions leading to the aziridine **847** proceeded with high regio- and stereoselectivity due largely to the hindered position of C-1 (mitomycin numbering) adjacent to the dimethyl ketal function. Continuing toward porfiromycin, *N*-methylation of **847** was followed by deprotection, and the resultant ω-aminohydroquinone oxidized to the quinone on exposure to air, followed by intramolecular nucleophilic addition and then further oxidation to the quinone level to form the desired benzazocinequinone **848**. Transannular reaction of **848** was effected very efficiently and stereospecifically using trityl tetrafluoroborate[435] to give mitomycin **849** exclusively, which was converted to ($\pm$)-*N*-methylmitomycin A **850**.[433] The transformation to porfiromycin **834** had been carried out previously by Webb et al.[428]

Mitomycins A and C. The syntheses of mitomycin A and C were accomplished[434] next. That entailed conversion of **847** by deprotection and oxidation into the *N*-demethyl analogue of **848**, but in practice the yield was poor,

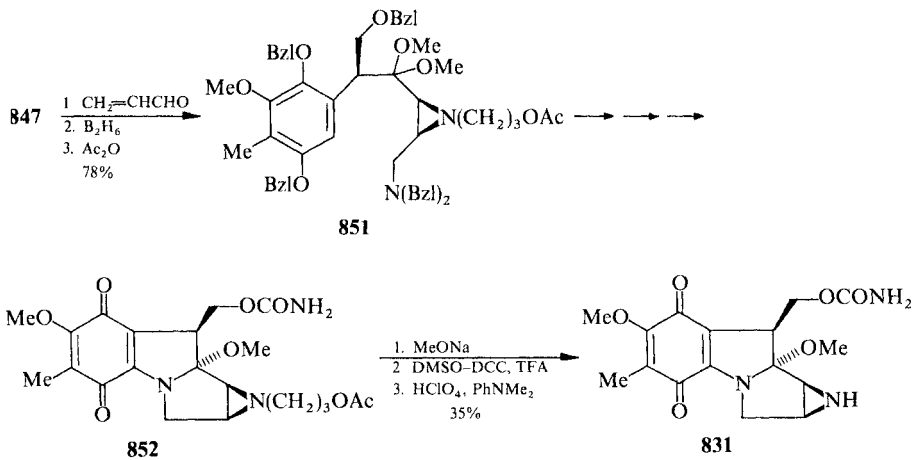
the major compound arising, it was suggested,[434] by interaction of the azidiridine nitrogen and the C-8 carbonyl group. Protection of the aziridino nitrogen was therefore essential, and as all the conventional protecting groups were found to be inadequate at some later stage in the synthesis a new one was devised, the 3-acetoxypropyl group. It was introduced to **847** by a Michael addition to acrolein, diborane reduction, and acetylation to give **851**. This intermediate was then carried through the same reaction sequence as before (Scheme 99), and finally **852** was deprotected in three steps by ester cleavage, oxidation of the alcohol, and a retro-Michael addition which afforded (±)-mitomycin A **831** (Scheme 100). Transformation to mitomycin C **833** (and porfiromycin) had been reported previously.[428]



Scheme 99

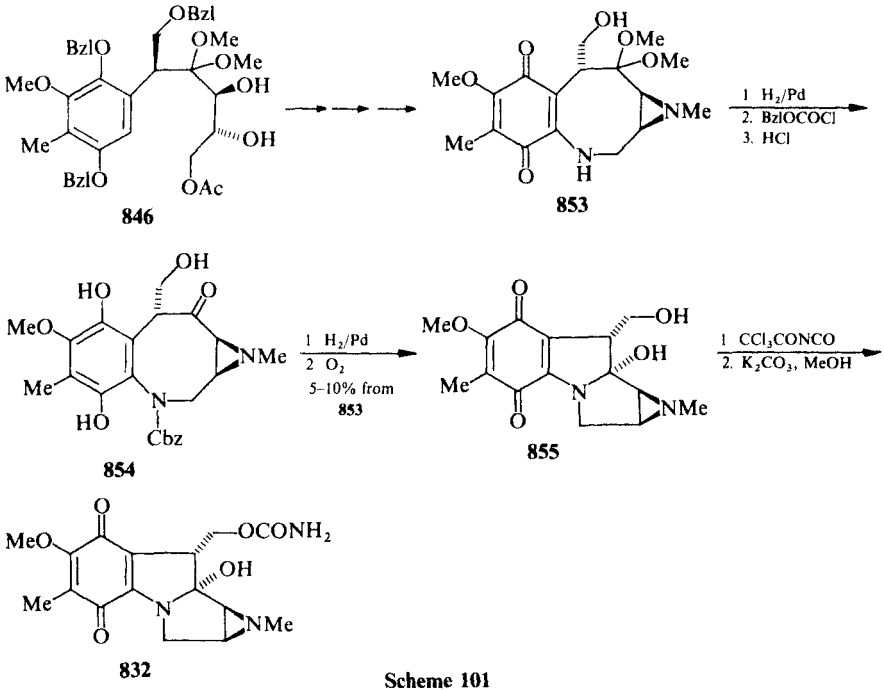


Scheme 99 (*continued*)



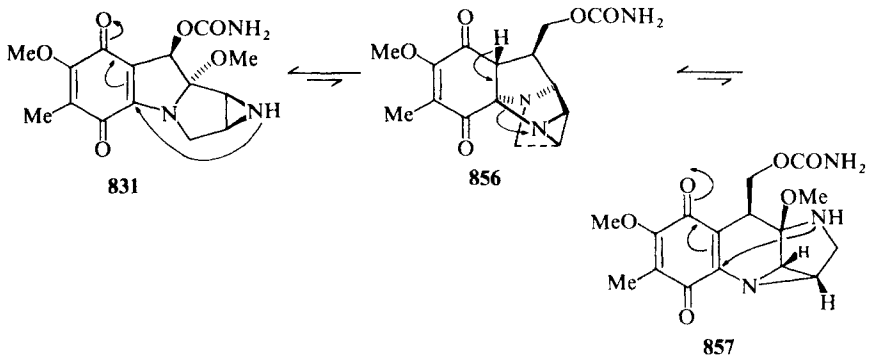
Scheme 100

Mitomycin B. The stereochemistry of mitomycin B **832** is different from the others and there is a hydroxyl group at C-9a. It was noted in Scheme 99 that osmylation of **844** gave diol **845** and its diastereomer **846**. The latter was also transformed into a benzazocinequinone **853**, and Kishi[432] planned to approach mitomycin B by hydrolysis of **853** to the ketone followed by transannulation. In order to prevent premature cyclization during the hydrolysis, the NH group was protected by carbobenzoxylation. Ketone **854** thus obtained, was then deprotected and exposed to air, which resulted in transannulation to the desired mitomycin **855**. Conversion to the carbamate (i.e., mitomycin B) by the standard method failed, probably on account of cyclic carbonate formation, but the problem was neatly overcome by treating **855** with trichloroacetyl isocyanate followed by hydrolysis of the urethane with potassium carbonate in cold methanol (Scheme 101).



Scheme 101

Isomitomycin A. Mitomycins A and B were first isolated[436] in the Kyowa Hakko laboratories in 1956 from cultures of *Streptomyces caespitosus.* A group from the same company, investigating the minor constituents of the fermentation broth of the same organism reported[437] in 1987 the isolation of two new metabolites, albomitomycin A **856** and isomitomycin A **857**, which

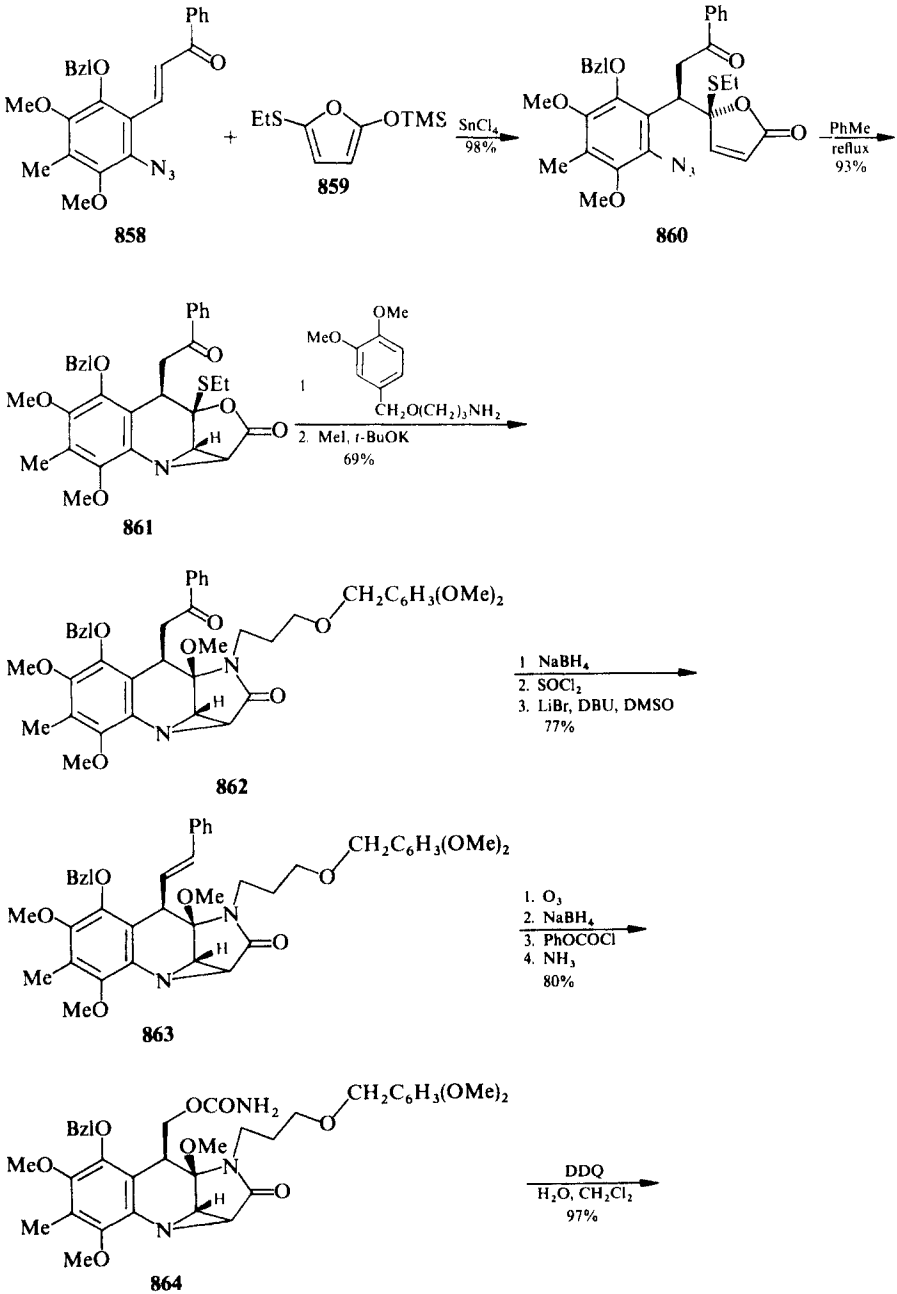


831 856 857

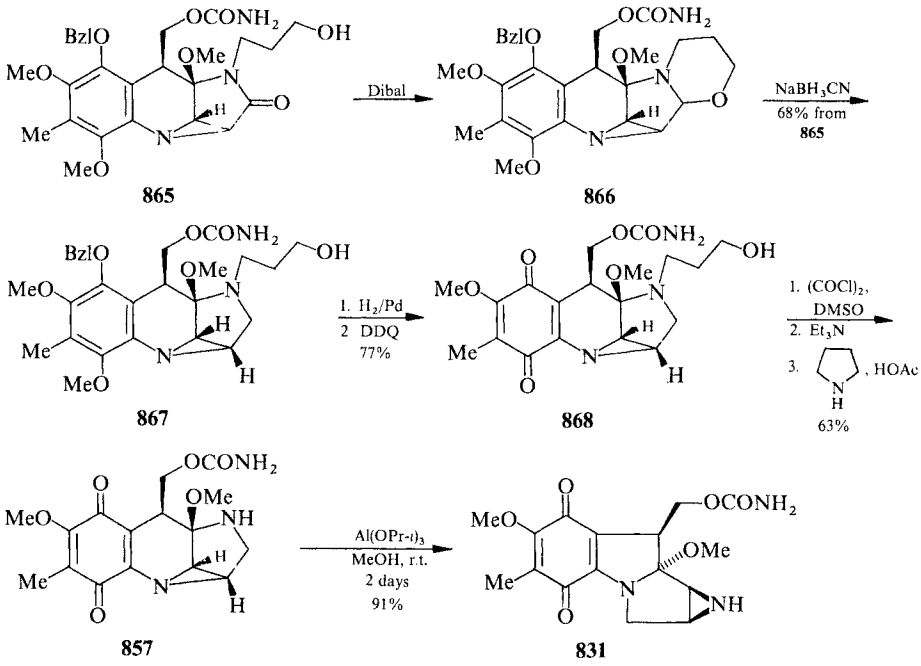
are isomers of mitomycin A **831**. Astonishingly, all three form an equilibrium mixture in methanol with mitomycin A predominating. They are more stable in aprotic solvents, but the rate of equilibration in all solvents is increased in the presence of certain Lewis acids, for example, aluminum triisopropoxide. This "mitomycin rearrangement" evidently proceeds by intramolecular Michael and retro-Michael reactions. Fukuyama and Yang[438] have accomplished an ingenious and very efficient total synthesis of (±)-isomitomycin A **857** which opens a new route to mitomycins A and C. The synthesis introduces the aziridine ring in one step at an early stage and the troublesome acid sensitivity of the C-9a methoxyl group encountered in previous mitomycin synthetic work is avoided. It also is introduced at an early stage (**862**), but in a more stable bridgehead position (Scheme 102).

Starting from chalcone **858**, previously prepared[439] from 2,6-dimethoxytoluene in 13 steps (45% overall), addition of furan **859** (available from 5-ethylthiobutenolide by silylation) gave the azidobutenolide **860** with remarkably high stereoselectivity. On thermolysis of the azide, cycloaddition[440] to the olefinic double bond afforded exclusively the tetracyclic aziridine **861** in excellent yield. The lactone ring in **861** was then converted to a lactam **862** in which the nitrogen was protected by a 3-(3,4-dimethoxybenzyloxy)propyl group, the required amine being prepared by conjugate addition of 3,4-dimethoxybenzyl alcohol to acrylonitrile, followed by hydrogenation (81%). Conventional *N*-protecting groups did not survive the ensuing reaction conditions. The ketonic side chain was next reduced to the styrene **863**, which was cleaved by ozonolysis and transformed to the carbamate **864**. As model studies showed that the isomitomycin A system was unstable in acidic conditions, the veratryl group was removed selectively at that stage by oxidative hydrolysis[441] under neutral conditions, which provided **865** almost quantitatively.

The later stages of the synthesis dealt with the elimination of the lactam oxygen and, after oxidation to the quinone level, removal of the nitrogen


Ph
BzlO
MeO
Me
MeO
N3
O
858
EtS
OTMS
859
SnCl4
98%
SEt
860
PhMe
reflux
93%
OMe
CH2O(CH2)3NH2
1
2. MeI, t-BuOK
69%
861
CH2C6H3(OMe)2
862
1 NaBH4
2. SOCl2
3. LiBr, DBU, DMSO
77%
863
1. O3
2. NaBH4
3. PhOCOCl
4. NH3
80%
OCONH2
864
DDQ
H2O, CH2Cl2
97%

Scheme 102



Scheme 102 (*continued*)

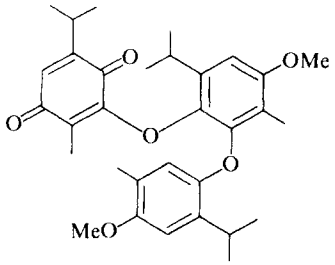
protecting group. Reduction of the lactam **865** to the amine **867** was effected in a one-pot two-stage sequence via the oxazine **866**. Hydrogenolysis followed by DDQ oxidation then gave the quinone **868**, and finally the hydroxypropyl group was removed by Swern oxidation to the aldehyde and a retro-Michael reaction to yield (±)-isomitomycin A **857**. On equilibration for two days in methanol in the presence of aluminum isopropoxide it yielded (±)-mitomycin A **831** in 91% yield.

8. TERPENOID QUINONES

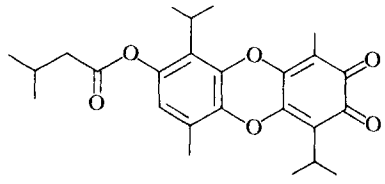
There are about 90 quinones[14, 15] whose carbon skeleton is wholly of mevalonate origin. About two-thirds of these are diterpenoid, six are monoterpenoid, and the remainder sesquiterpenoid.

A. Monoterpenoids

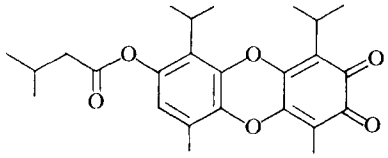
These are related to thymol including thymoquinone itself, its hydroxy derivatives, and the more interesting 3-libocedroxythymoquinone **869**, from



869



870

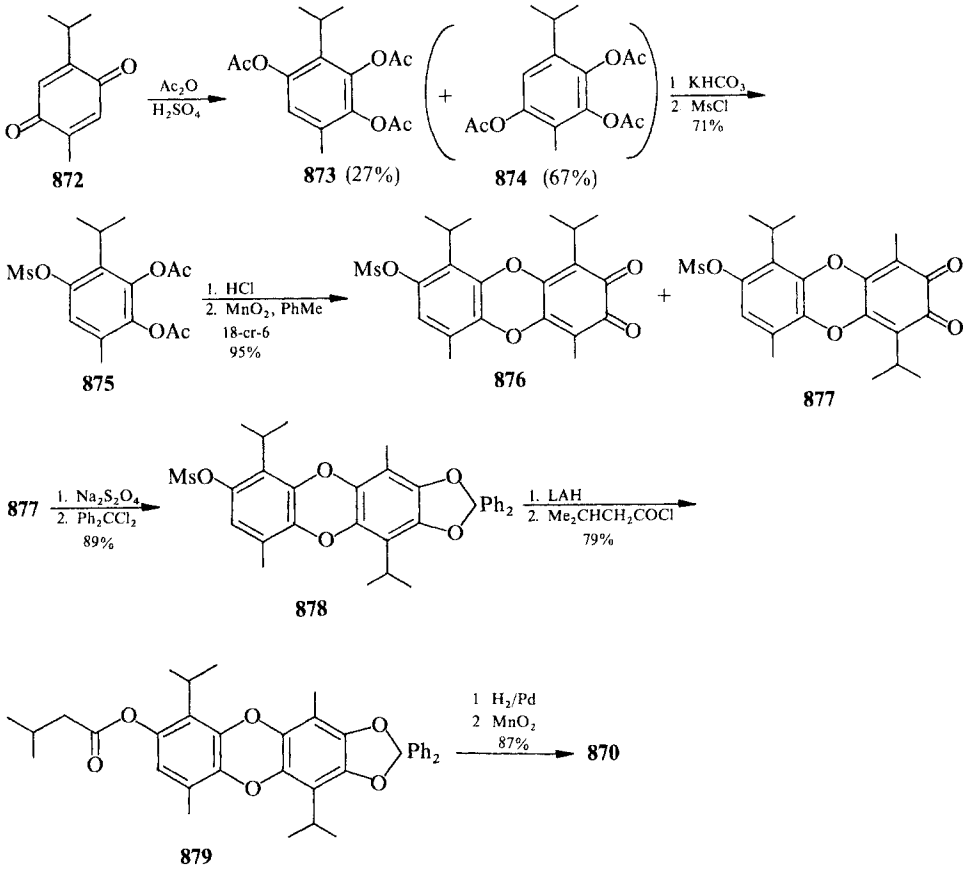


871

Heyderia decurrens[14] and ecklonoquinones A **870** and B **871**, isolated[442] from the leaf glands of *Plectranthus ecklonii*. *o*-Benzoquinones are rare natural products and these two dibenzodioxinquinones are unique. They have been synthesized by Eugster,[443] the key step being the oxidative dimerization of a catechol which mimics the biosynthetic process.[444] Thiele acetylation[445] of thymoquinone **872** gave the isomeric triacetates **873** and **874** which were separated; synthesis of the ecklonoquinones then proceeded from **873** and the same reaction sequence was carried through from **874** to give the isomeric isoecklonoquinones, which may be regarded as potential natural products. Selective hydrolysis of the least-hindered acetate group in **873** gave a phenol which was protected as the mesylate **875**. After hydrolysis of the remaining acetate functions, the catechol was oxidized by manganese dioxide to the isomeric dibenzodioxinquinones **876** and **877** in high yield. After chromatographic separation isomer **877** was reduced to a tricyclic catechol, protected as the diphenylmethylene ether **878**, and the mesylate exchanged for an isovalerate ester **879**. Deprotection and final oxidation gave ecklonoquinone A **870** (Scheme 103). A similar reaction sequence starting from **876** afforded ecklonoquinone B. The structures were confirmed by an X-ray analysis of the leucodiacetate of **870**.

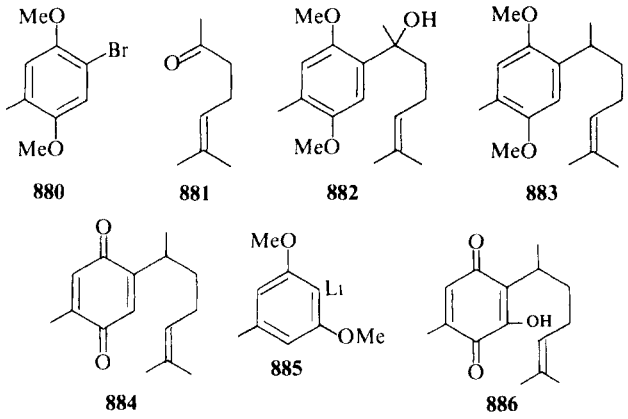
B. Sesquiterpenoids

The benzoquinones in this group have either a cuparane or a bisabolane skeleton. None of the former have been synthesized. The latter group includes

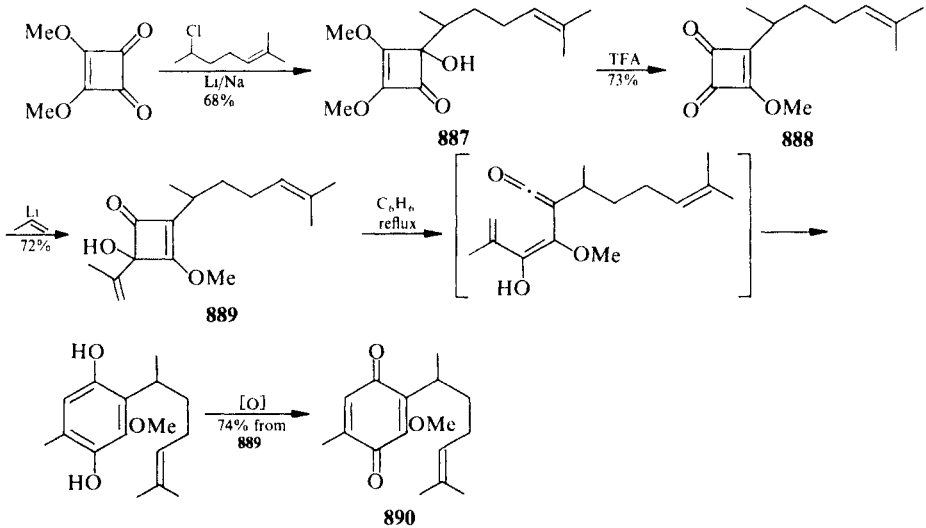


Scheme 103

perezone **886**, first studied in 1852, found in *Perezia* and other Compositae genera,[14, 15] and the simplest curcuquinone **884**, found in the coral *Pseudopterogorgia rigida*.[15] They have been synthesized by standard methods. Thus the carbon skeleton of curcuquinone was assembled by interaction of the commercially available methyl heptenone **881** with the Grignard reagent from **880** to give **882**. Dehydration and sodium–ammonia reduction of the conjugated olefinic bond led to **883**, from which (±)-curcuquinone **884** was derived by oxidation with silver(II) oxide.[446] Earlier, another Mexican group[447] had synthesized (±)-perezone **886** by essentially the same route, starting from **885**, but the final Jones oxidation was poor. Several similar syntheses of (±)-perezone and its methyl ether, also a natural product,[15] have been reported.[448]

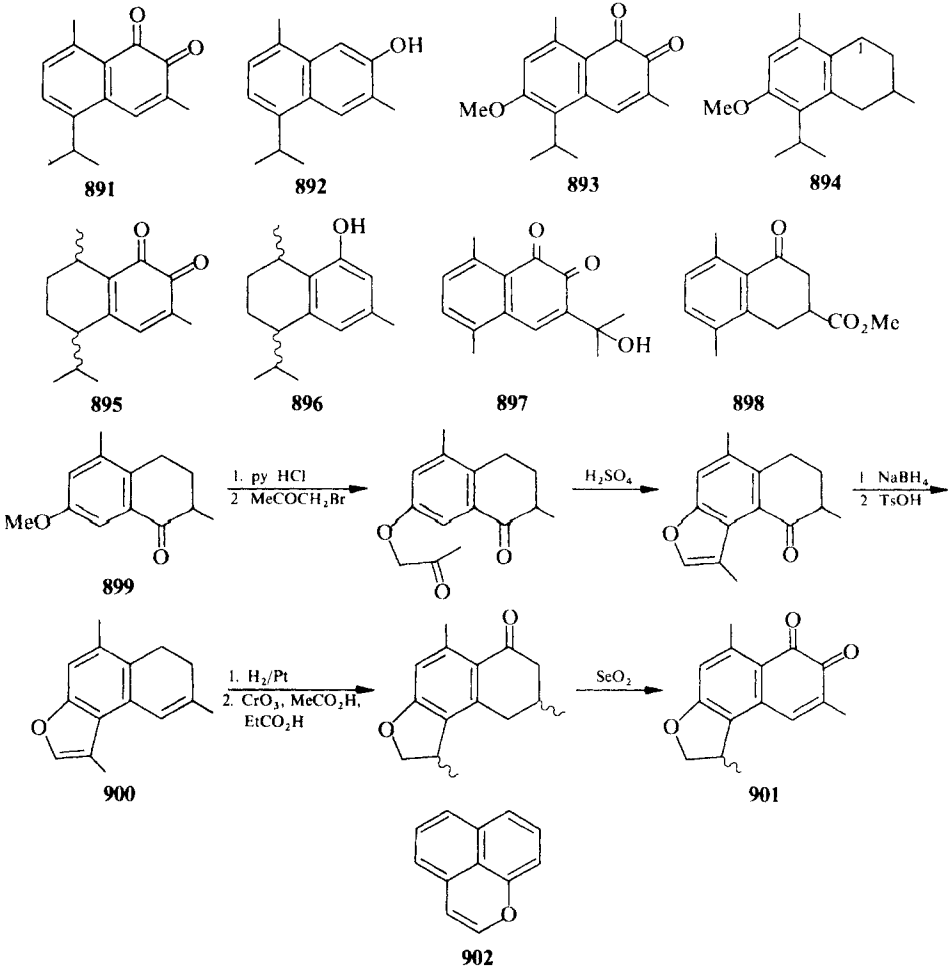


Moore[449] has recently devised an efficient short route to perezone methyl ether making use of his hydroxycyclobutenone thermal rearrangement procedure. Starting from dimethyl squarate, treatment with 6-lithio-2-methylhep-2-ene, prepared under specific conditions,[450] afforded hydroxycyclobutenone **887**, and after conversion to the dione **888**, further reaction with 2-lithiopropene provided the hydroxycyclobutenone **889**, reaction occurring at the more electron-deficient carbonyl group. Thermolysis of **889** followed by oxidation gave (±)-perezone methyl ether **890** in 27% overall yield (Scheme 104).



Scheme 104

Most of the sesquiterpenoid naphthoquinones, occurring chiefly in the wood of *Mansonia altissima*[14] and *Ulmus* spp.,[14, 15] are related to cadalene and several have been prepared by manipulation of related naphthalene and tetralin derivatives. Mansone C **891** is accessible simply by leaving 7-hydroxycadalene **892** (which has been synthesized) on layers of silica gel, even under argon.[451] Krishna Rao[452] obtained mansonone G methyl ether **893**[452] by oxidizing the tetralin **894** first with chromic acid in acetic acid–propionic acid to the 1-tetralone, followed by further oxidation with selenium dioxide, and mansonone A **895**[453] by oxidation of 8-hydroxycalamene **896** with iodoxybenzene (some of the *p*-isomer was also formed). Emmotin H **897** was prepared[454] similarly from the tetralone **898** followed by a Grignard reaction.



891 **892** **893** **894**

895 **896** **897** **898**

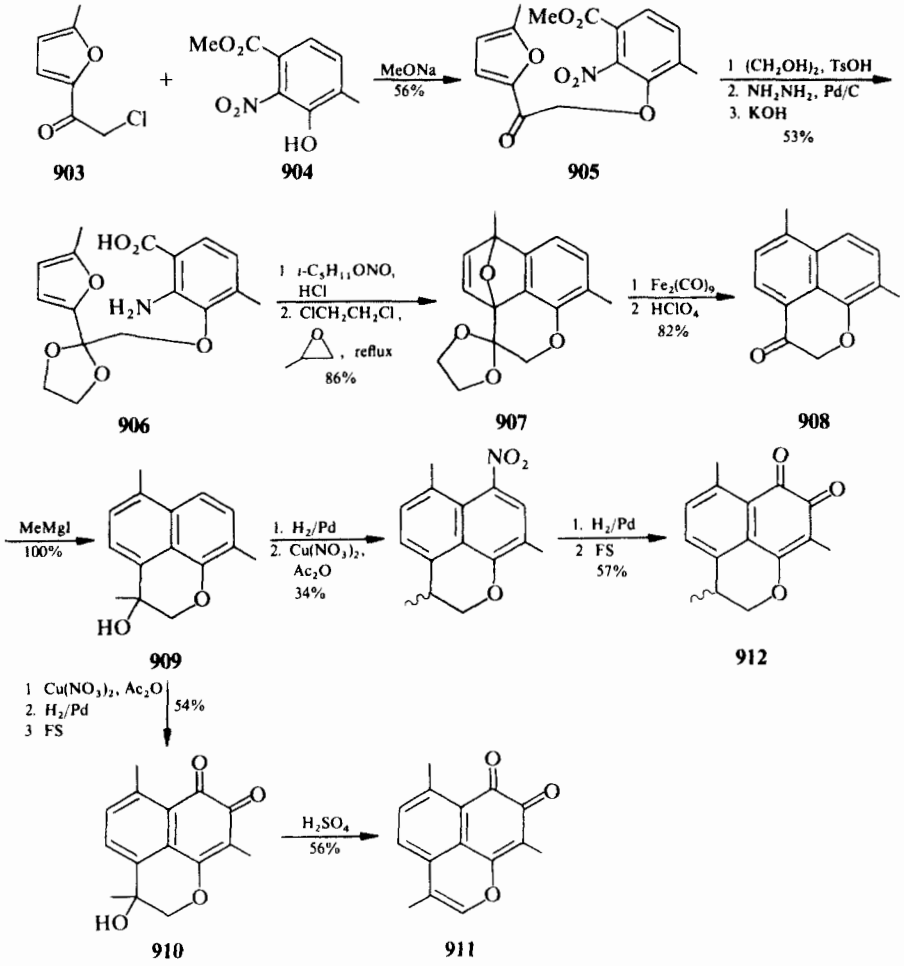
899

900 **901**

902

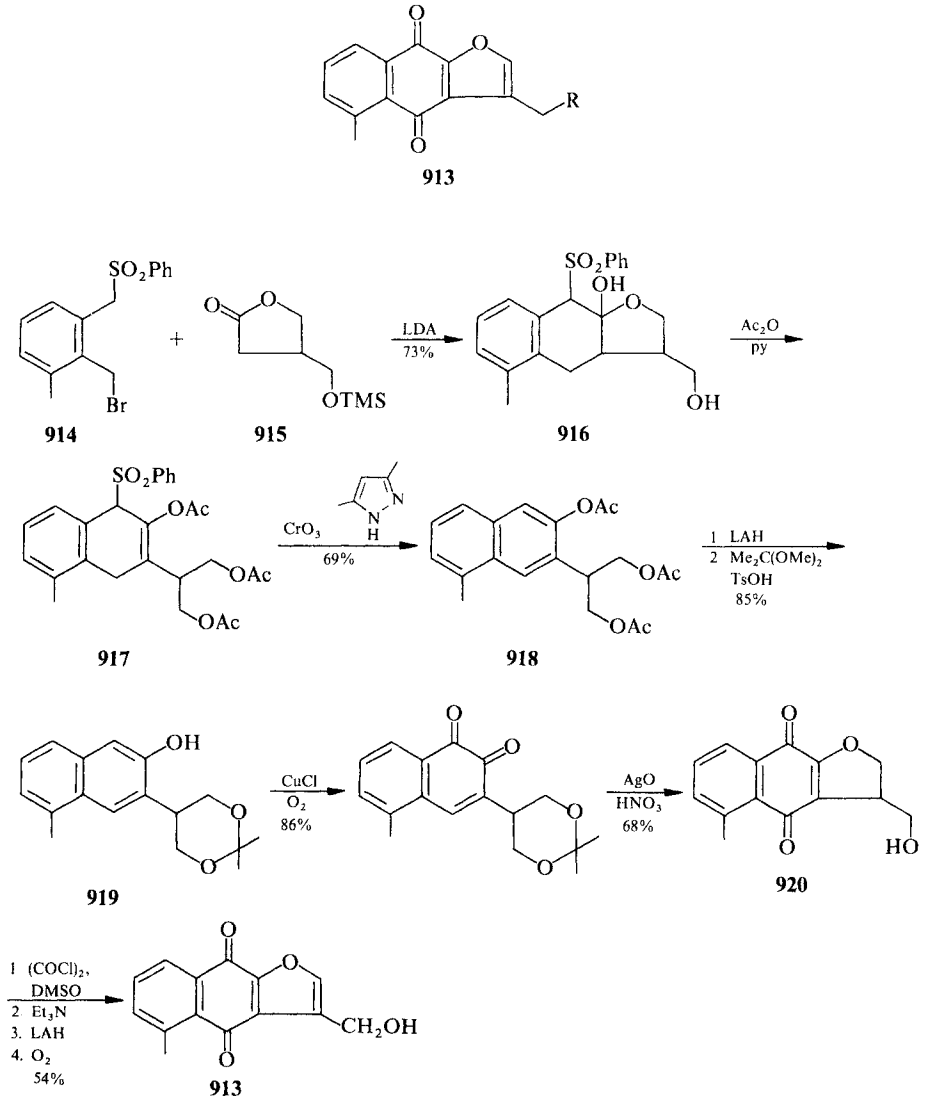
The furano-*o*-naphthoquinone, mansonone D **901**, was derived from the tetralone **899** via pyrocurzerenone **900** as indicated.[455]

Three of the mansonone group are derivatives of the oxaphenalene system **902**, and Best and Wege[456] devised a novel convergent approach to these compounds whereby the tricyclic structure was assembled by an intramolecular Diels–Alder reaction (Scheme 105). Coupling furan **903** with the known phenol **904** gave the ester **905**, and hence the anthranilic acid **906**. Thermolysis of the diazonium salt derived from **906** in boiling 1,2-dichloroethane, containing propene epoxide as scavenger for any liberated hydrochloric acid,



Scheme 105

generated a benzyne which was efficiently trapped by the furan to form the tetracyclic adduct **907** in 86% yield. Deoxygenation with enneacarbonyldiiron and deprotection afforded the naphthalene **908**, which was converted via **909** by straightforward steps into (±)-mansonone E **912**. The tertiary alcohol **909** was also converted in the same way to the corresponding



Scheme 106

quinone **910**, which is (±)-mansonone I, and then after dehydration into mansonone F **911**.

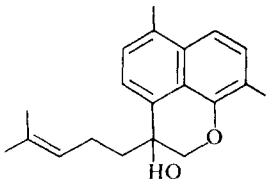
Two other sesquiterpenoid quinones, maturone **913** (R = OH) and maturinone **913** (R = H) have a degraded eremophilane skeleton. They occur with related C_{15} terpenes in *Cacalia* spp.[14, 15] Ghere[457] has synthesized maturone in an interesting way by annulating the enolate of lactone **915** with the bifunctional bromosulphone **914** (prepared from methyl 2,6-dimethylbenzoate in four steps) to give the tricyclic product **916** as a stereoisomeric mixture. Acetylation to the triacetate **917** was followed by aromatization using the chromium trioxide-3,5-dimethylpyrazine complex.[458] Triacetate **918** was transformed to the acetonide **919** and then oxidized in two stages, the second forming **920** and a small amount (8%) of the angular isomer. Final conversion to maturone was effected by Swern oxidation to the furanoaldehyde and LAH reduction (Scheme 106).

Several poor-yield syntheses of maturinone by conventional methods have been reported.[459]

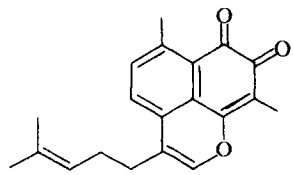
C. Diterpenoids

Nearly all of these belong to the abietane group of diterpenes. Ring C is always quinonoid, and rings A and B may be aromatic. They are found[14, 15] mainly in *Salvia* plants and in the leaf glands of *Coleus* and *Plectranthus* spp.

An exception is biflorin **922**, from *Capraria biflora*,[14] the first oxaphenalene quinone to be discovered. It was obtained[456] synthetically from ketone **908** by reaction with 4-methylpent-3-enylmagnesium iodide to give the C_{20} alcohol **921**, which was then converted to biflorin **922** following the route used for mansonone F (Scheme 105).

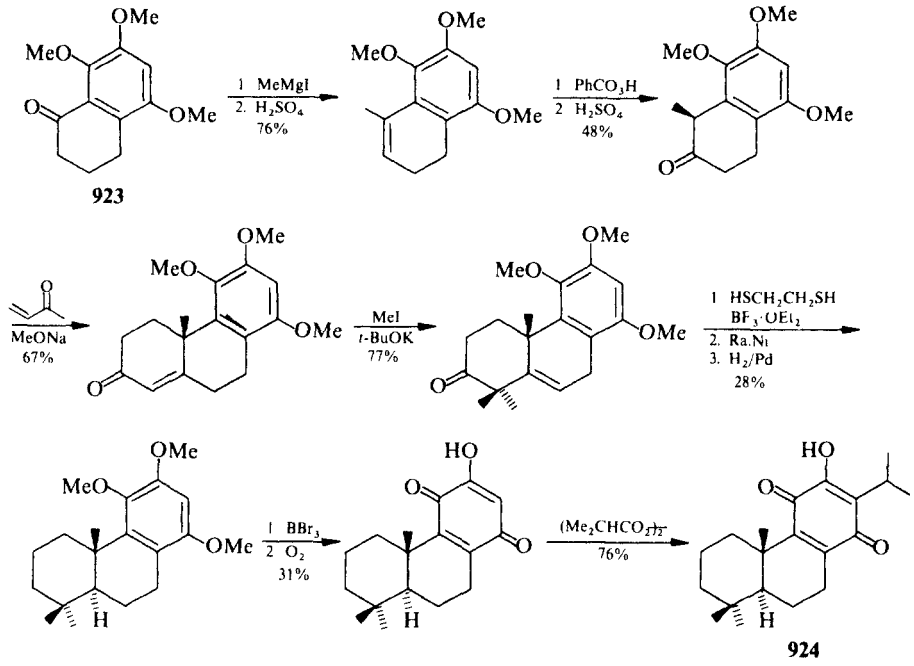


921



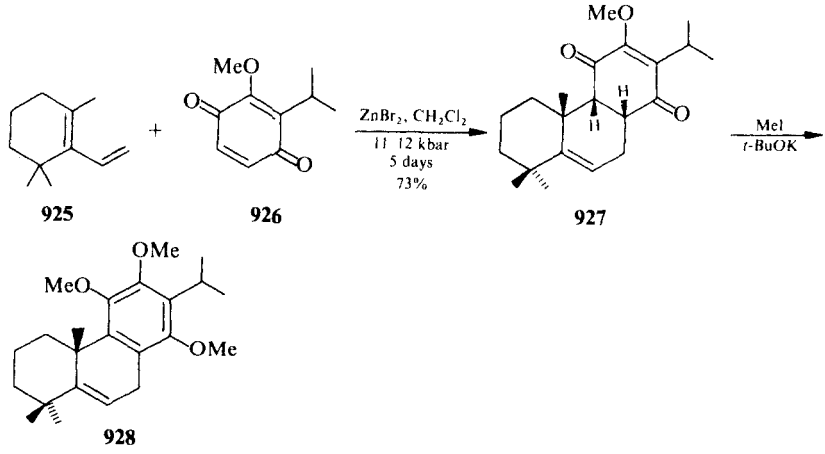
922

Royleanone **924**, probably the best known of the nonaromatic abietane-type quinones, shows some cytotoxic activity. It was first synthesized by a Japanese group[460] using conventional methods starting from the BC synthon **923** and adding ring C by Robinson annulation (Scheme 107).



Scheme 107

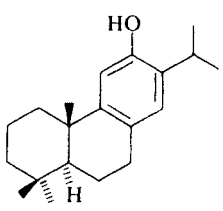
In a convergent approach Engler et al.[461] made use of a Diels–Alder cycloaddition to produce ring B (Scheme 108). Addition of the known[462] diene **925** to the benzoquinone **926** (from 1,3-dimethoxybenzene in four steps) was carried out under pressure in the presence of zinc bromide to form **927**



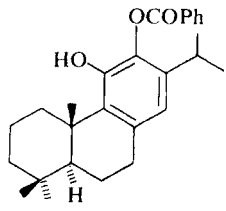
Scheme 108

and its 8,9-epimer together with 10% of the regioisomer. The regiospecificity was improved by the combined use of a mild Lewis acid and high pressure. The mixture was converted to **928**, which constitutes a formal synthesis of (±)-royleanone (see Scheme 107).

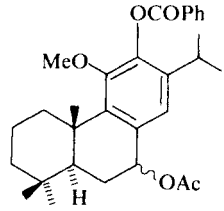
Royleanone[463, 464] and certain natural derivatives have also been derived from abietic acid and ferruginol by manipulation of ring C. Thus Matsumoto[464, 466] oxidized (±)-ferruginol **929**, previously synthesized,[465] with benzoyl peroxide and obtained *inter alia* the phenol **930** (44%). After methylation, treatment with lead tetraacetate gave an epimeric mixture of the 7-acetates **931** which were separated, the β isomer with some difficulty. Chromic acid oxidation of the 7-β-acetate yielded a quinone which, on hydrolysis, provided taxoquinone **932**, and dehydroroyleanone **933** after dehydration. Both are natural compounds. Similar treatment of the 7-α-acetate **931** led to the 7-α isomer of **932** (horminone), which could be oxidized to 7-oxoroyleanone **934**, another natural compound.



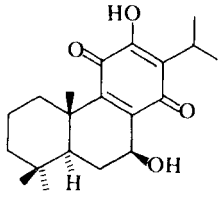
929



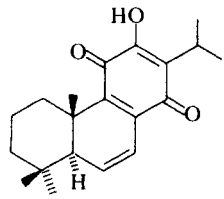
930



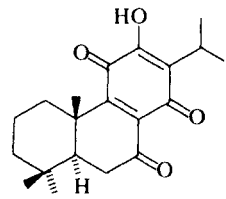
931



932

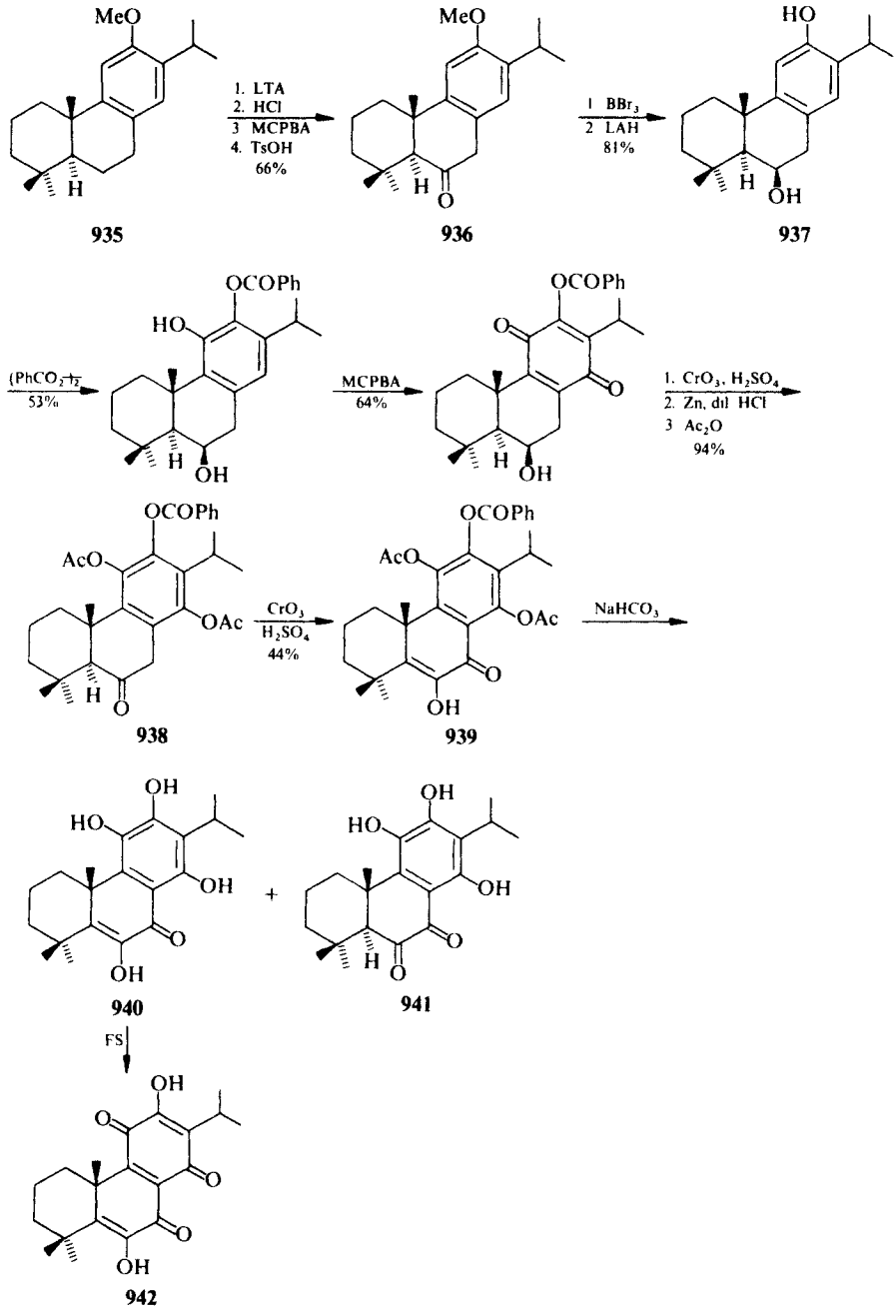


933



934

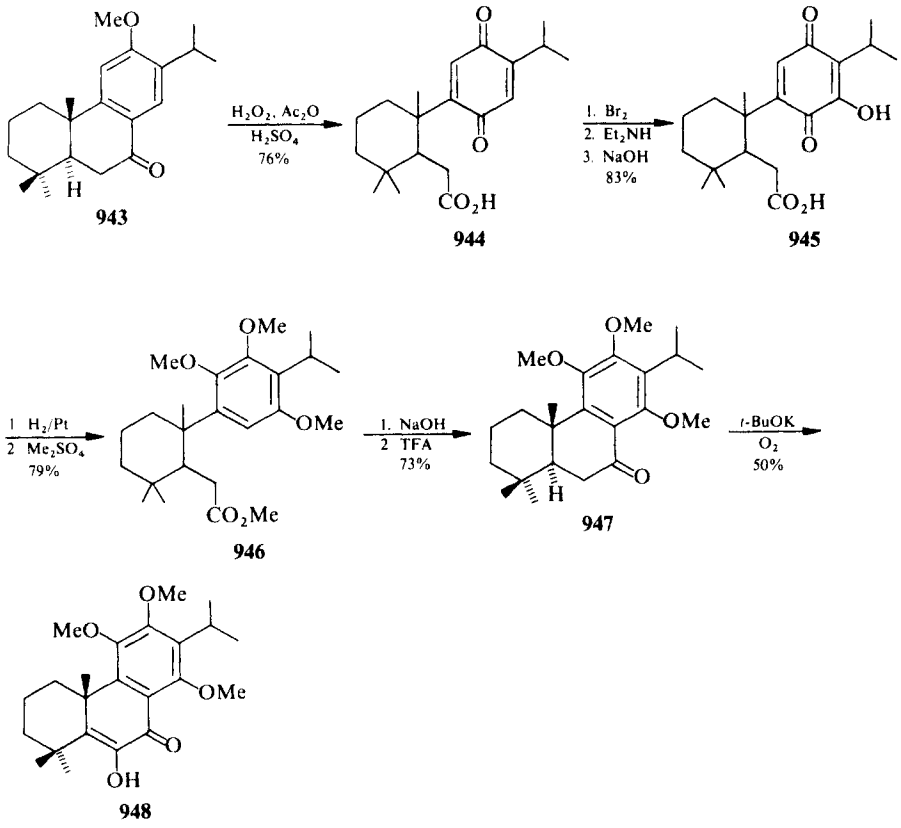
In the course of very extensive studies Eugster[467] has isolated a large number of diterpenoids, related to abietane and totarane, from the leaves and leaf glands of *Coleus* and other Labiatae. They are highly oxygenated and dehydrogenated derivatives including quinone-methides and a few quinones. Two of the latter have been synthesized. Continuing his work in this area Matsumoto[468] proceeded to synthesize coleone U quinone **942** starting from (+)-ferruginol methyl ether **935** (Scheme 109). Oxygenation at C-6 was achieved by acetoxylation at C-7 followed by elimination, epoxidation of the 6,7-double bond, and rearrangement to ketone **936**. After demethylation, reduction gave predominantly the β alcohol **937**. A sequence of oxidations


MeO
1. LTA
2. HCl
3 MCPBA
4. TsOH
66%
935
936
1 BBr3
2 LAH
81%
HO
937
OCOPh
HO
(PhCO2)2
53%
MCPBA
64%
O
1. CrO3, H2SO4
2. Zn, dil HCl
3 Ac2O
94%
AcO
OAc
CrO3
H2SO4
44%
NaHCO3
938
939
940
941
FS
942

Scheme 109

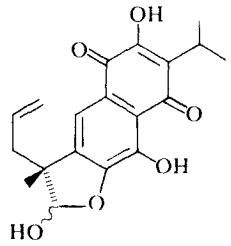
followed by reduction and acetylation led to the ketone **938**, and then another Jones oxidation afforded the diosphenol **939**. Mild hydrolysis of **939** then gave a 1:1 mixture of **940** (coleone U) and **941** (coleone V). Coleone U had previously been oxidized[469] to coleone U quinone **942**.

Burnell[470] has synthesized the trimethyl ether **948** of coleone U, again starting from (+)-ferruginol, but thereafter following a completely different route (Scheme 110). Benzylic oxidation of **935** gave the ketone **943**. When that was subjected to a Baeyer–Villiger oxidation, ring opening produced a phenolic acid which was further oxidized *in situ* to the quinone acid **944** directly. After conversion to the hydroxyquinone **945** via selective bromine addition on the less hindered side of the quinone, reductive methylation afforded **946**. Cyclization to ketone **947** and then oxygenation in strong base produced the diosphenol **948**.

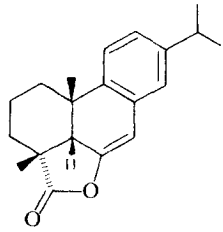


Scheme 110

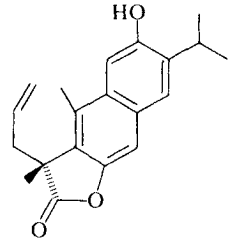
Coleone A. After extensive investigation Eugster[471] established that coleone A, from the leaves of *Coleus ignarius*, had the unusual 1,10-secoabietane structure **949**. He suggested that it might originate *in vivo* from ferruginol by a series of oxygenations and aromatization of ring B, followed by a 1–10 bond cleavage, and Matsumoto[472] has demonstrated how this can be done *in vitro*. Lactones of type **950** on fusion with potassium hydrogen sulfate at 220°C, or heating with sulfuric acid, undergo aromatization and ring cleavage to form *inter alia* **951** in low yield. Specifically lactone **952**, derived from (+)-dehydroabietic acid, on refluxing with sulfuric acid in acetic acid gave the 1,10-seco derivative **953** (23%), which has the coleone A skeleton and ring C is phenolic, and from that (+)-coleone A was synthesized (Scheme 111). After protecting **953** as **954**, the lactone was reduced to a mixture of epimeric



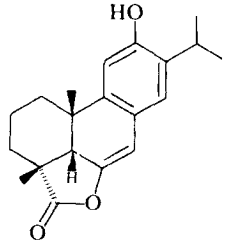
949



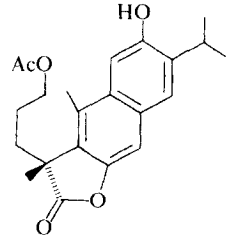
950



951

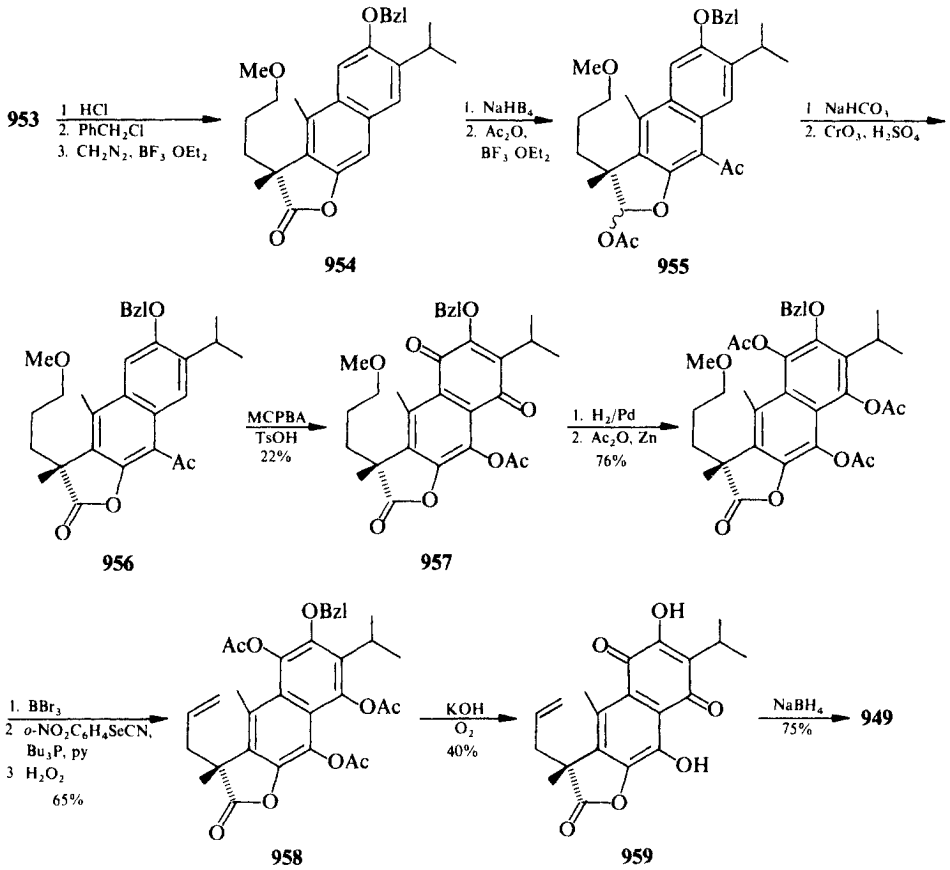


952



953

lactols which were *C*-acetylated at C-7 (**955**). After reforming the lactone ring, giving **956** (42% from **953**), Baeyer–Villiger reaction then converted the acetyl function to acetoxyl with concomitant oxidation of ring C to a quinone **957**, albeit in low yield. Following reductive acetylation and demethylation, the side-chain double bond was introduced by the selenoxide method.[292] Finally, **958** was converted to quinone **959** and reduced to the epimeric lactols **949** identical with (+)-coleone A.

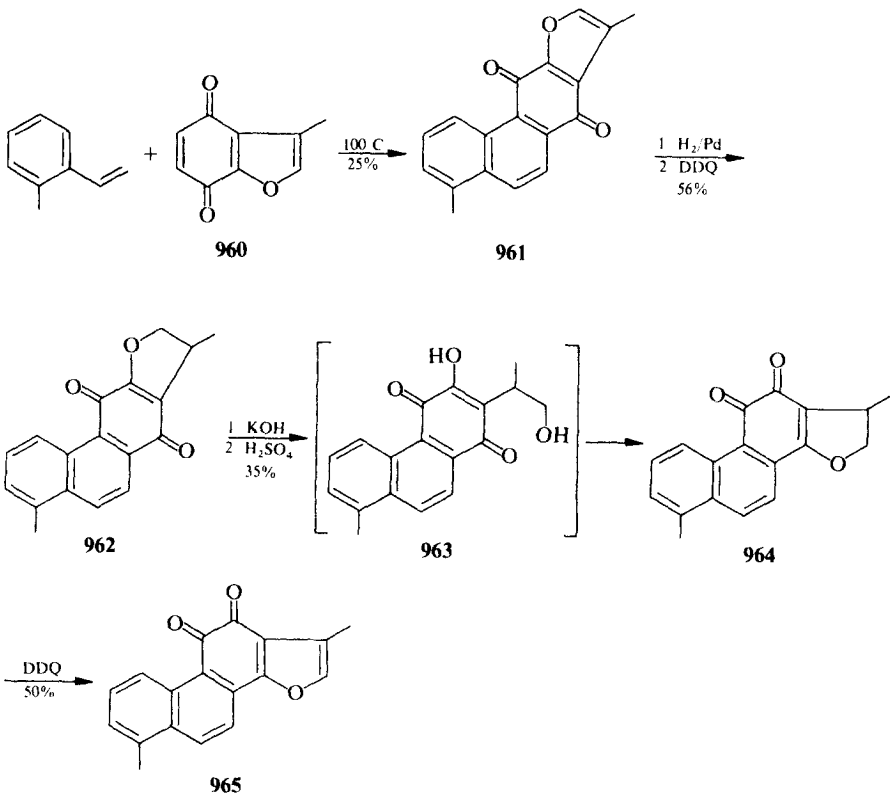


Scheme 111

Tanshinones. A range of curative properties[473,476] are attributed to the ancient Chinese medicine Dan Shen prepared from the roots of *Salvia miltiorrhiza.* Some 30 diterpenoids, mostly *o*-quinones, have been isolated and it is likely that more will be discovered. The activities of the total drug

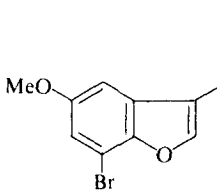
appear to far exceed those of individual metabolites, which are often present in very small amounts.

The fully aromatic pigment tanshinone I **965** is a furanophenanthraquinone with a dinorabietane skeleton. Several syntheses have been reported, mainly by older methods, two of which started from known hydroxy- or methoxyphenanthrenes.[477] A Diels–Alder approach by Kakisawa[478] was disappointing, as the yield was low at the first stage (Scheme 112). Addition of *o*-methylstyrene to the quinone **960** gave an adduct which, after chromatography and crystallization, proved to be the *p*-quinone isomer **961**, of tanshinone I. It is known as isotanshinone I, and is also present in Dan Shen.[15] The dihydro derivatives **962** was converted to its *o*-quinone isomer **964** by hydrolytic ring opening in alkaline solution and ring closure with sulfuric acid. Dehydrogenation of **964** yielded tanshinone I **965**. The intermediate compound **963** is identical with danshexinkun A found[479] in *S. miltiorrhiza*.

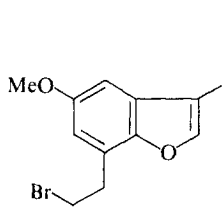


Scheme 112

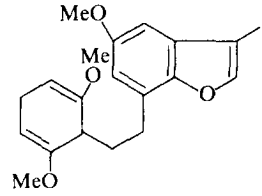
In a longer and poor-yielding synthesis, Imai[480] prepared the benzofuran **966** by a standard method, added a side chain in two steps, and then coupled the bromide **967** to dihydroresorcinol dimethyl ether to form **968**. After enolic hydrolysis the β-diketone was cyclized to **969** in polyphosphoric acid. A Grignard reaction, followed by aromatization, afforded the phenanthrene **970**, whence demethylation and Fremy's salt oxidation yielded tanshinone I **965**. The same reaction sequence was also completed starting from the benzofuran **971**.



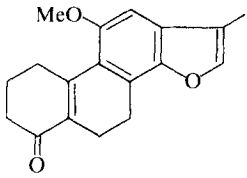
966



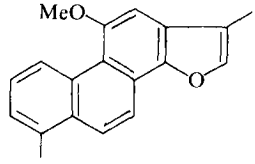
967



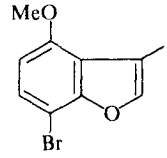
968



969

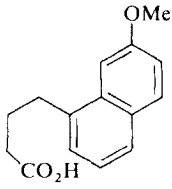


970

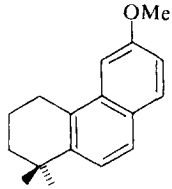


971

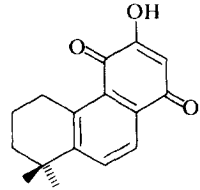
The norabietanoid quinones cryptotanshinone **975** and tanshinone IIA **976** were first obtained[477] by a linear synthesis using standard methods. 7-Methoxy-1-tetralone was transformed via a Reformatsky reaction into acid **972**, which was converted by a Grignard reaction into a tertiary alcohol and then cyclized to **973**. Quinone **974** derived from the corresponding phenol, on treatment with 3-chloro-2-methylpropionyl peroxide, gave ($\pm$)-cryptotanshinone **975**, which was dehydrogenated with DDQ to tanshinone IIA **976**.



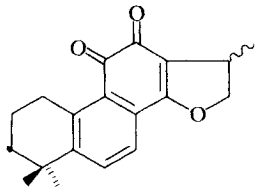
972



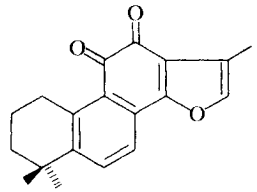
973



974

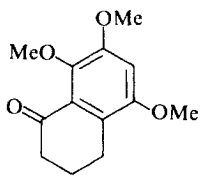


975

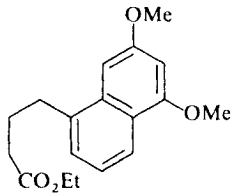


976

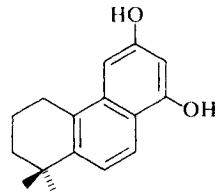
Kakisawa[481] planned a synthesis of tanshinone IIA starting from a tetralone, but ran into two unexpected difficulties. Annulation of the trimethoxytetralone **923**, commenced with a Reformatsky reaction using zinc and ethyl γ-bromocrotonate followed by heating with palladized charcoal; surprisingly the product was the dimethoxy ester **977** (yield not stated). It was transformed by standard procedures to the dihydroxyphenanthrene **978**, which was converted into the hydroxyquinone **979** by autoxidation in strong base (Fremy's salt failed). The intention at that stage was to treat the acetate of **979** with *N*-propenylmorpholine to give tanshinone IIA **976** directly or the *p*-isomer. This method gave modest results[482] with 2-acetoxy-1,4-naphthoquinone, but with the acetate of **979** it afforded the ethylquinone **980** (80%) in another unexplained reaction. That approach was therefore abandoned and the furan ring was constructed starting from the dimethyl ether of **978**. Elaboration in seven steps led to the keto acid **981**, which was cyclized to the furan and finally converted into tanshinone IIA **976** by demethylation and a difficult Fremy's salt oxidation.



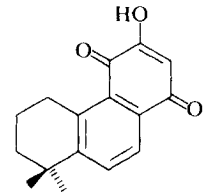
923



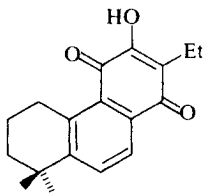
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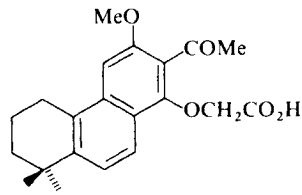
978



979

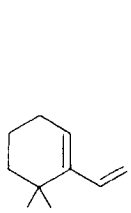


980

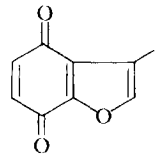


981

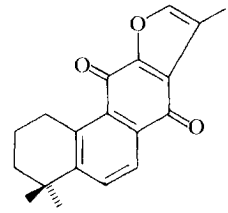
Kakisawa[478] also carried out a convergent synthesis of tanshinone IIA by cycloaddition of the diene **982** to quinone **960**. After oxidation the resulting quinone **983**, isotanshinone IIA (present in Dan Shen), was converted into tanshinone IIa following the sequence **962** → **965** used for the synthesis of tanshinone I (Scheme 112).



982



960

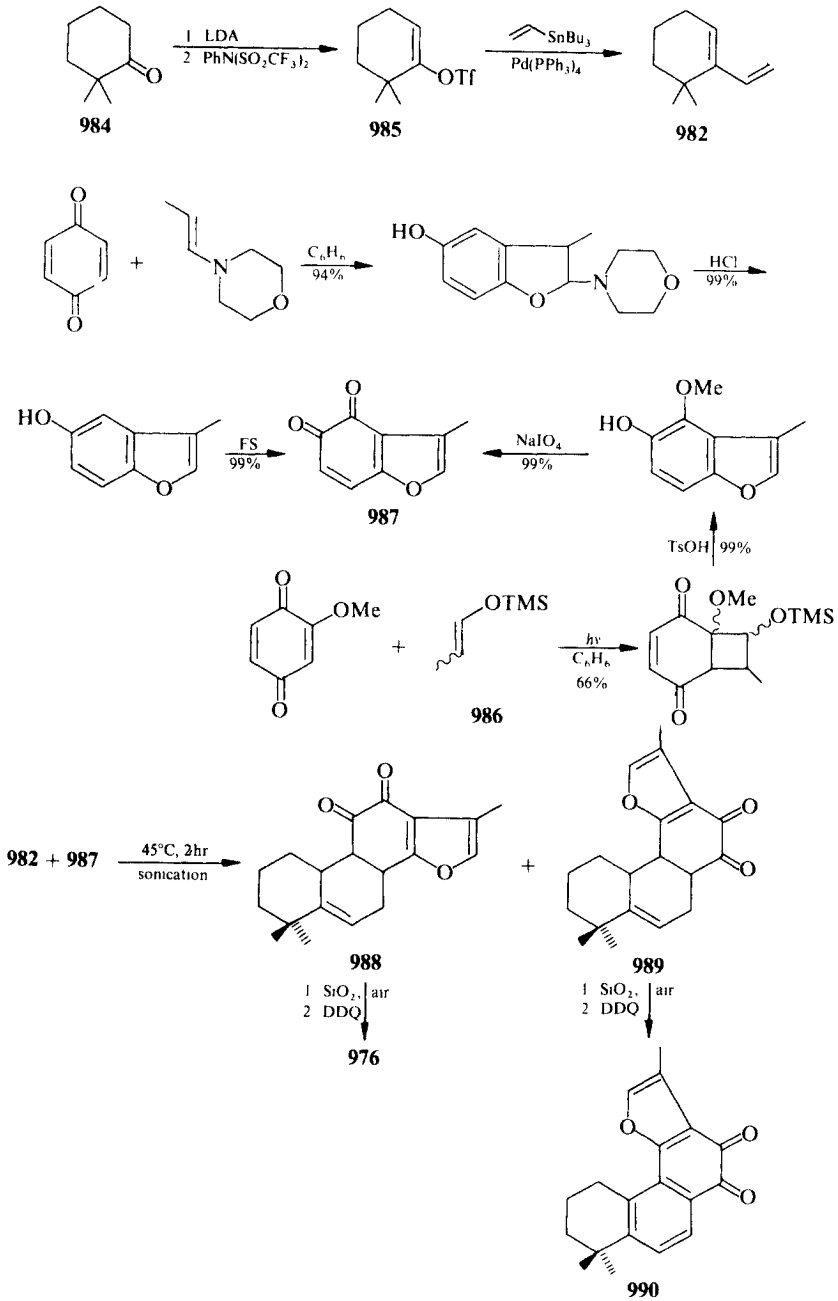


983

However, a much superior and more direct route to tanshinone IIA **976** is that due to Snyder,[483] starting from diene **982** and the *o*-quinone **987**. The diene **982** was prepared from the cyclohexanone **984** using Stille's[484] method of palladium-catalyzed vinyl coupling to enol triflates, and the *o*-quinone **987** via addition of *N*-propenylmorpholine to benzoquinone. A slightly less efficient route proceeded by photo-cycloaddition[485] of the silyl enol ether **986** to methoxybenzoquinone and rearrangement–elimination of the adduct (Scheme 113). In previous studies[486] it was observed that yields obtained in the cycloaddition of less-reactive dienes, such as vinylcyclohexenes, to the *o*-quinone **987** could be substantially increased under pressure. It was subsequently found[483] that cycloaddition could also be promoted by sonication in the absence of solvent and with improved regioselectivity. Thus addition of diene **982** to *o*-quinone **987** in refluxing benzene gave, after aromatization, quinones **976** (tanshinone IIA) and **990** in 53% yield (ratio 54:45), but after sonication, neat, the combined yield improved to 76% (ratio 10:3).

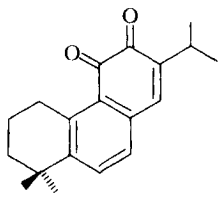
It is of interest that diene **982** was used in the synthesis[487] of miltirone (= rosmariquinone) **991**, but under normal conditions addition to 3-isopropyl-*o*-benzoquinone never exceeded 30%. Miltirone, found in *Salvia drobovii*[14] and *Rosmarinus officinalis*[474] but not in Dan Shen, has significant antioxidant properties.[474] It was previously synthesized[475] by the linear tetralone route.

Returning to the tanshinone group, Snyder[483] also secured nortanshinone **993** by cycloaddition of diene **992** to quinone **987**, followed by oxidation and deprotection. In refluxing benzene the yield was 18% [ratio of adduct (**993** precursor) to its regioisomer 1:1], under pressure (10 kBar) in toluene 75%

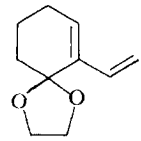

1 LDA
2 PhN(SO2CF3)2
SnBu3
Pd(PPh3)4
OTf
984
985
982
C6H6
94%
HCl
99%
HO
FS
99%
NaIO4
99%
OMe
987
TsOH 99%
OTMS
986
hν
C6H6
66%
982 + 987
45°C, 2hr
sonication
988
989
1 SiO2, air
2 DDQ
976
990

Scheme 113

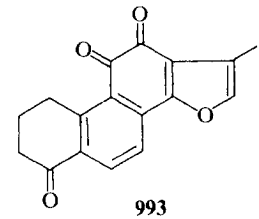
(5:2), and with ultrasound and no solvent 65% (8:1). Similarly (±)-tanshindiol B **995** was obtained by addition of diene **994** to quinone **987**, dehydrogenation, and deprotection. The initial mixture of adducts was obtained in 73% yield (ratio 7:1) under pressure and in 76% (5:1) yield when exposed to sonication. It appears that tanshindiol B is the *cis*-diol **995** and C is the *trans*-diol, and not the reverse as originally suggested.[488]



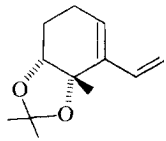
991



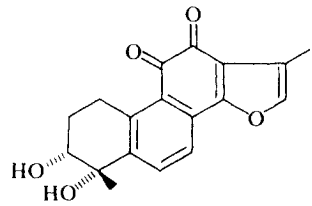
992



993



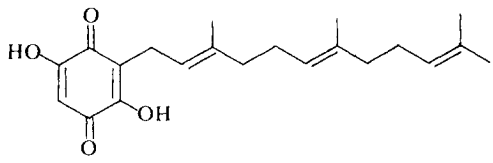
994



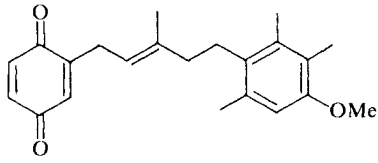
995

9. MEROTERPENOID QUINONES

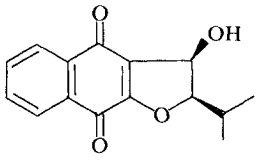
These are quinones which are partially derived from mevalonic acid; simple examples are **40** and **111**. They can be divided for convenience, into (a) benzoquinones and naphthoquinones which carry prenyl or polyprenyl side chains, occasionally cyclized at the terminus (e.g., boviquinone-3 **996** and panicein A **997**), (b) benzoquinones and naphthoquinones in which a terpenoid side chain is incorporated into an *O*-heterocycle (e.g., **998**), and (c) benzoquinones linked by a C–C bond or fused to a cyclic terpenoid system (e.g., cordiachrome G **1000** and ilimaquinone **999**). None of these examples have been synthesized.



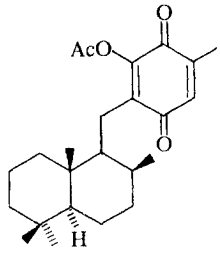
996



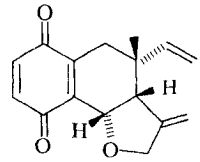
997



998

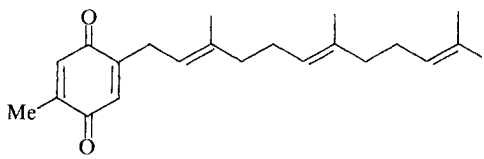


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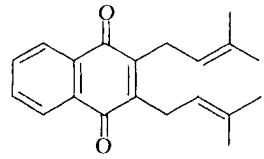


1000

Simple prenylation of benzenoid compounds is a straightforward process and formerly it was standard practice to obtain prenylated quinones by acid-catalyzed reaction of a hydroquinone and a prenyl alcohol or halide. Thus quinone **1001**, present in the roots of several Umbelliferae,[15] was prepared[489] by condensing toluhydroquinone with farnesol in the presence of boron trifluoride, followed by oxidation, and the diprenylnaphthoquinone **1002**, found in the heartwood of *Tabebuia guayacan*,[15] by reaction of naphthohydroquinone with 2-methylbut-3-en-2-ol catalyzed by citric acid, oxidation occurring during workup.[490] However, such methods are not particularly efficient, the instability of allyl alcohols under acidic conditions being a recurrent problem, although numerous variations have been devised and continue to appear.[491] The need arose for better procedures following the discovery that the so-called bioquinones,[492] present in virtually all forms of life, play a significant role in cellular energy metabolism and in photosynthesis.[493]

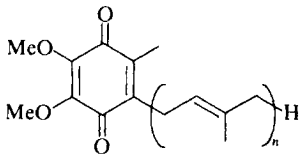


1001

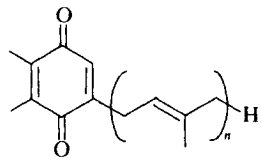


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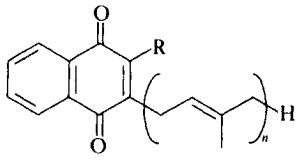
Bioquinones. The ubiquinones (coenzymes Q) **1003**, plastoquinones **1004**, and menaquinones **1005** (R = Me or H) have side chains containing up to 10 or more isoprene units with all-*trans* geometry, various degrees of unsaturation, and occasionally a cyclic terminus. Phylloquinone (vitamin K) is **1006** and the side chain may be hydroxylated. In the synthesis of such molecules it is particularly important to maintain *E*-geometry at C-2′ and avoid cyclization onto the adjacent oxygen. Numerous procedures have been described,[494,495] the most useful employing organometallic intermediates. Regiospecificity is also required to avoid ipso substitution and consequent loss of yield.



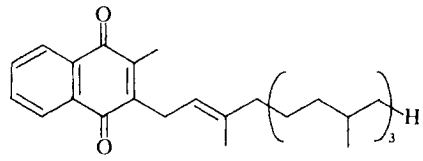
1003



1004

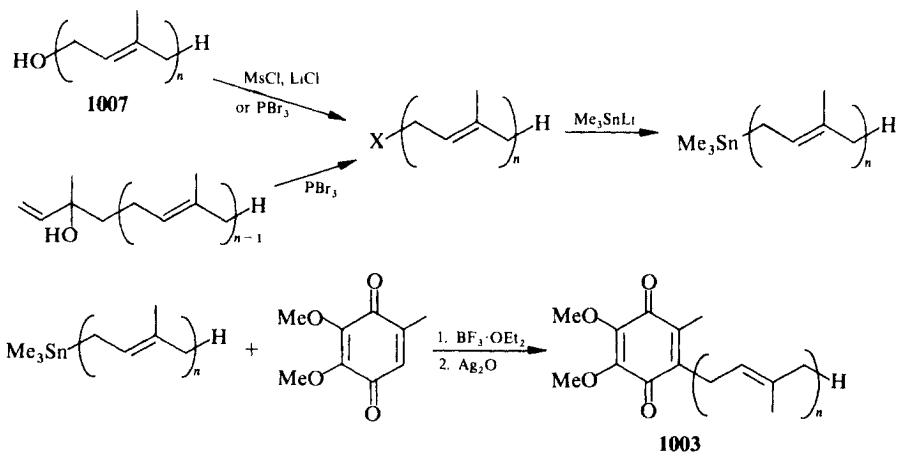


1005



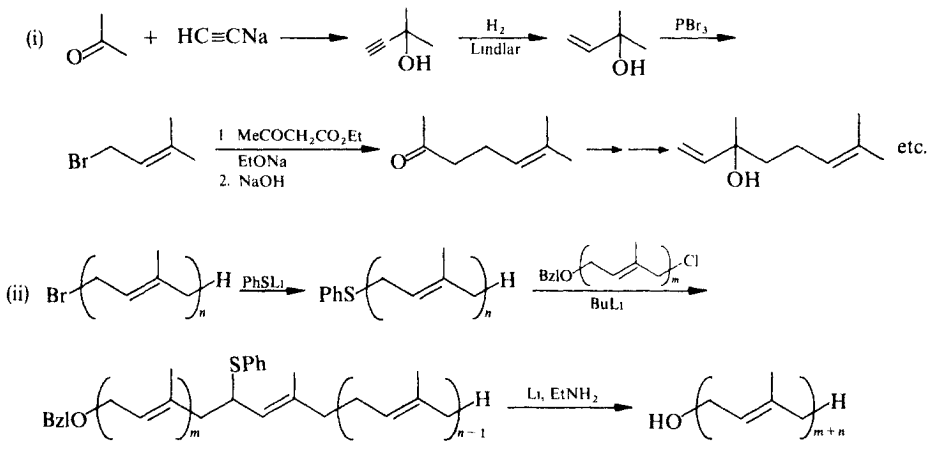
1006

Direct prenylation of quinones is obviously the most attractive method, and this was achieved effectively by Naruta and Maruyama[496] using polyprenyltrialkylstannanes and a Lewis acid. Yields of 50–95% were obtained in the ubiquinone series with virtually 100% *trans* stereochemistry at C-2′ (Scheme 114). Phylloquinone and plastoquinone-2 (not natural) were also prepared and other bioquinones should be accessible by this route. The all-*trans* alcohols **1007** can be derived from acetone by a general procedure,[497] as indicated [Scheme 115(i)] and methods are known[496c, 498, 510] for the extension of polyprenyl chains [see Scheme 115(ii)[496c]].



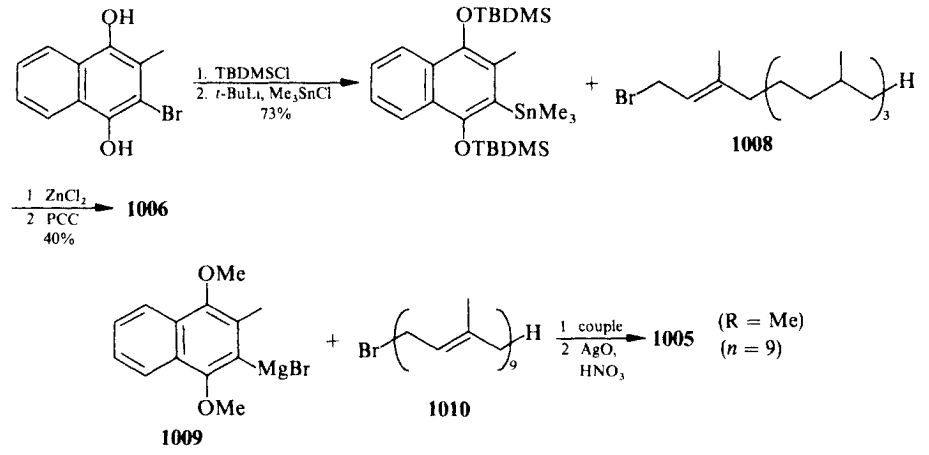
1007 1003

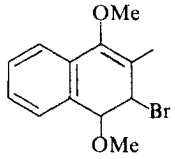
Scheme 114



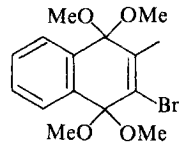
Scheme 115

Reversing this procedure phylloquinone **1006** was derived[499] in moderate yield from an aryltrialkylstannane and phytyl bromide **1008** as shown. This involves prenylation of a hydroquinone derivative and other arylmetal reagents have been used successfully. Snyder and Rapoport[500] coupled the Grignard reagent **1009** with solanesyl bromide **1010** and obtained menaquinone-9 **1005** (R = Me, $n = 9$) in 73% overall yield with 98% *trans* C-2′ geometry, and the method should be generally applicable. Excellent yields of phylloquinone and ubiquinones were obtained similarly using polyprenyl phosphates.[501] A variation[502] is the use of the lithium organocuprate prepared from the quinone bisketal **1012**, itself obtained from **1011** by anodic





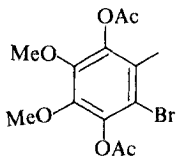
1011



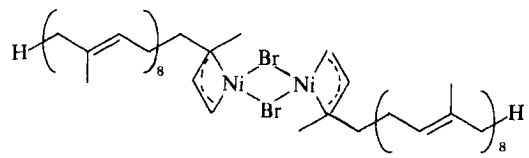
1012

oxidation. Coupling with phytyl bromide led to phylloquinone **1006** in excellent yield (93%), with complete retention of *trans* geometry. However, no other bioquinones have been made in this way.

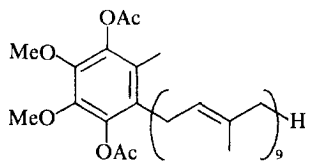
Polyprenylation has also been achieved[503] using π-allylnickel bromide complexes; ubiquinone-9, **1003** ($n = 9$), for example, was obtained by coupling the diacetate **1013** with complex **1014**, followed by deacetylation (LAH) of the product **1015** and oxidation with ferric chloride. Several ubiquinones were prepared thus, but the method is not stereospecific, the *trans*:*cis* ratio at C-2′ being 3:1. Menaquinone-9, **1005** (R = Me, $n = 9$), was prepared[504] in similar fashion as a 7:3 *trans*:*cis* mixture. π-Allylnickel bromides will actually react with quinones, attacking initially a carbonyl group followed by rearrangement. However, only monoprenylation has been achieved and ipso substitution was observed.[505]



1013



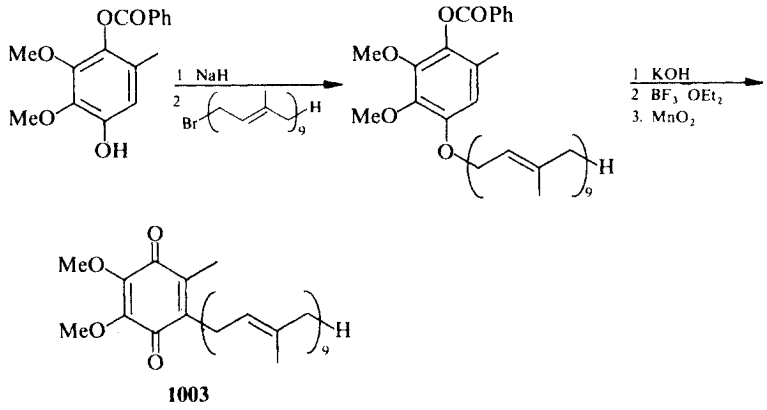
1014



1015

A Japanese group[506] has obtained ubiquinones in good yields and with complete retention of *trans* stereochemistry by Claisen-type rearrangement of polyprenyl aryl ethers in the presence of Lewis acids (Scheme 116) but none of these methods match the convenience of Scheme 114.

Several multistep procedures have been developed[507] for the elongation of polyprenyl chains attached to a quinone. Of these, much the most impressive is the palladium-catalyzed oligomerization of monoterpenes devised by Eren

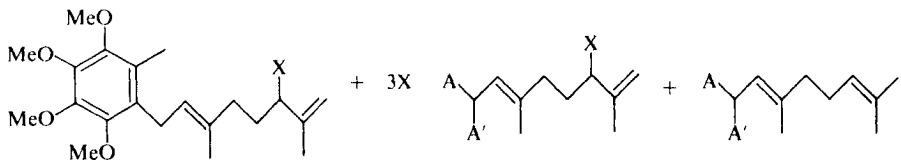


1003

Scheme 116

and Keinan[508] which resulted in highly efficient regio- and stereoselective syntheses of several ubiquinones, and the first practical total synthesis of ubiquinone-10 (Q10), which is used clinically as a cardiovascular agent.

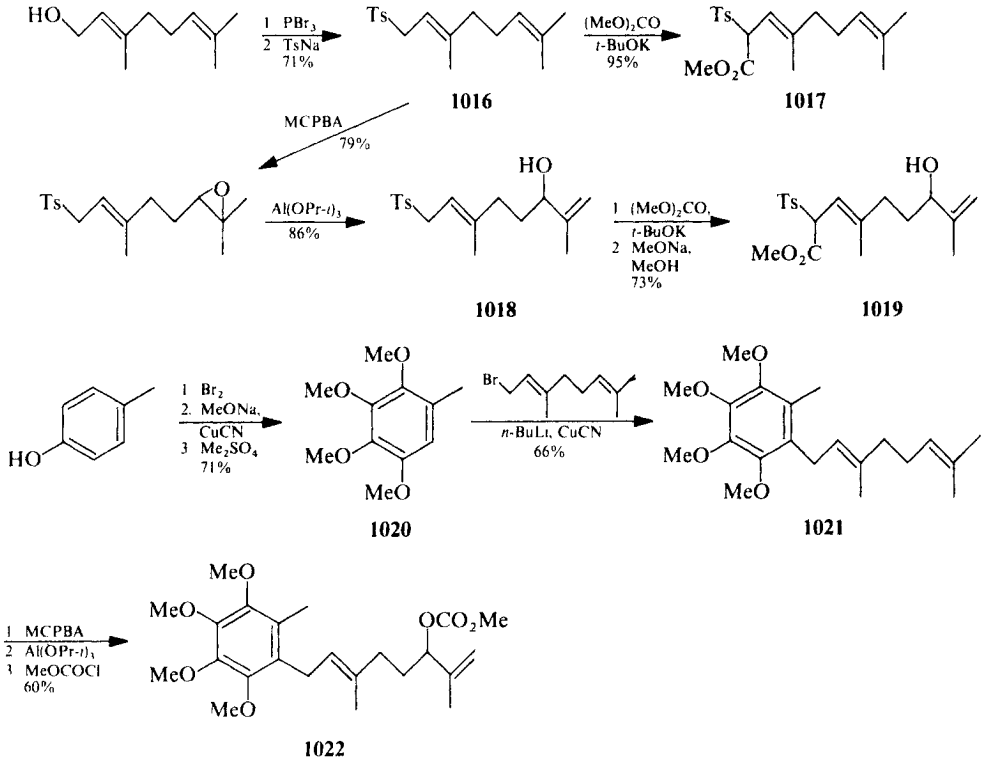
Ubiquinone-10 was synthesized by linking together the monoterpene "monomers" I, II, and III, each derived from geraniol, and equipped with appropriate functional groups. The leaving group X was designed to provide an electrophilic terminus for I and II to be activated by a Pd(0) catalyst. From model studies the methyl carbonate group was selected as offering high yields and almost complete retention of all *trans* geometry. The groups A and A′ are electron-withdrawing functions, methoxycarbonyl and tosyl, which provide the nucleophilic terminus of II and III when activated by a base. They were used successfully by Trost[510] in converting lower to higher terpenes by palladium-catalyzed allylic alkylations, and have the advantage of easy removal later in the synthesis.



I II III

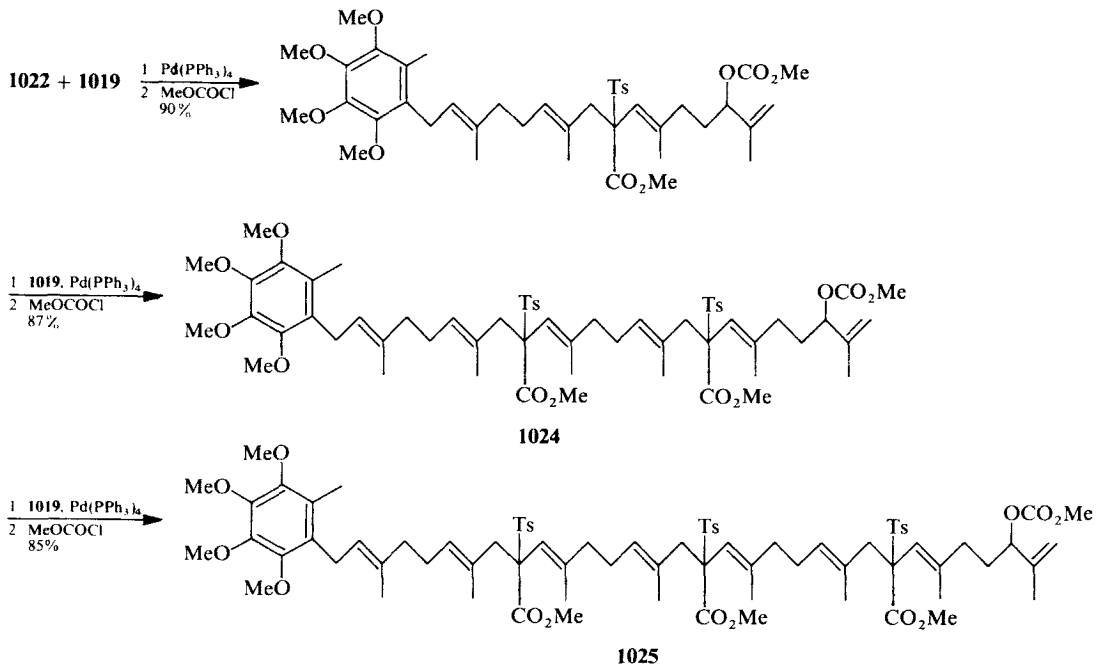
The preparation of the "monomers" is shown in Scheme 117. The tolylsulfone **1016** served as precursor for **1017** and also for **1019** by selective epoxidation and rearrangement with aluminum isopropoxide[511] to the allylic alcohol **1018**. In the final assembly of the decaprenyl chain, the hydroxyl

group in **1019** was converted to the methyl carbonate (equivalent to II, X = OCO_2Me) when required. For the aryl monoterpene unit I tetramethoxytoluene **1020**, obtained[509] in good yield by tribromination of *p*-cresol followed by one-pot methoxylation–methylation, was coupled via the cuprate with geranyl bromide to give **1021**. Conversion to the methyl carbonate **1022** proceeded by way of the epoxide as for **1018**.

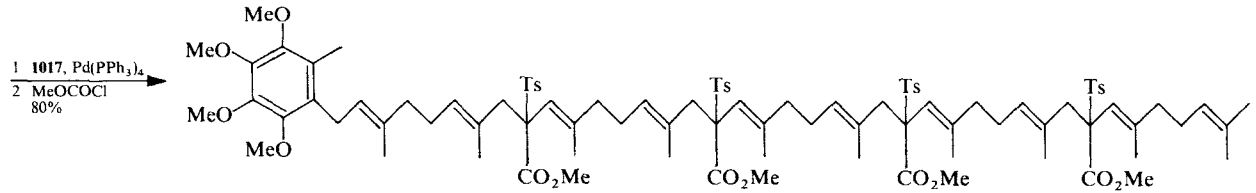


Scheme 117

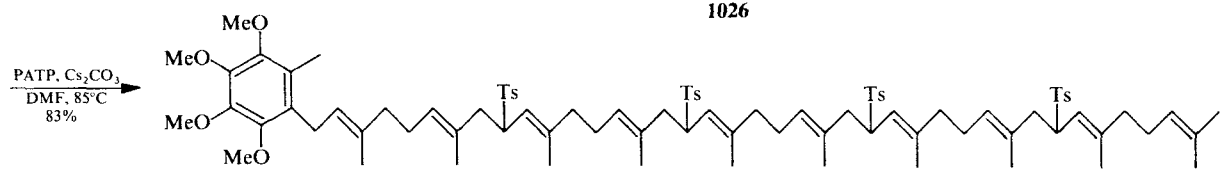
The complete synthesis of ubiquinone-10 was then achieved as shown in Scheme 118. Palladium-catalyzed coupling of **1022** and **1019** gave, after treatment with methyl chloroformate, the tetraprenyl intermediate **1023**. Repeating the process yielded **1024** and then **1025**, and a final coupling with **1017** provided **1026** with the required decaprenyl chain. The methoxycarbonyl groups were then removed using a stoichiometric amount of *p*-aminothiophenol (PATP), catalyzed by cesium carbonate in hot dimethylformamide, an effective method discovered earlier,[512] and the tosyl groups


1022 + 1019
1 Pd(PPh3)4
2 MeOCOCl
90%
MeO
MeO
MeO
MeO
Ts
OCO2Me
CO2Me
1 1019, Pd(PPh3)4
2 MeOCOCl
87%
Ts
Ts
CO2Me
CO2Me
1024
1 1019, Pd(PPh3)4
2 MeOCOCl
85%
Ts
Ts
Ts
CO2Me
CO2Me
CO2Me
1025

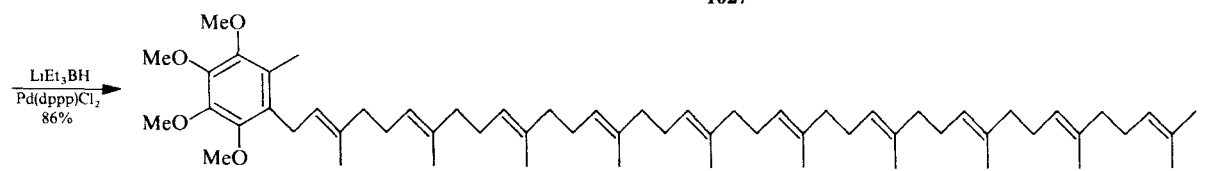
Scheme 118



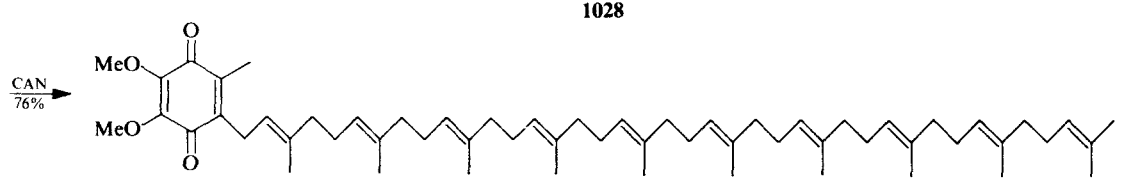
1026



1027



1028

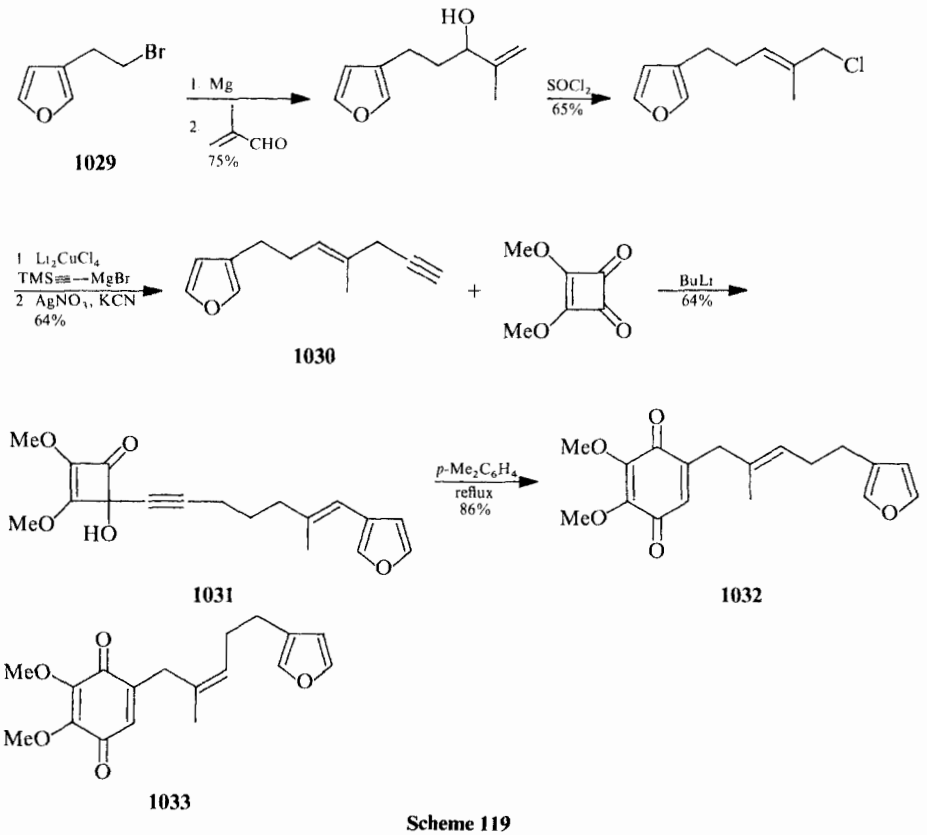


1003

Scheme 118 (*continued*)

were eliminated by reductive cleavage with lithium triethylborohydride catalyzed by $Pd(dppp)Cl_2$.[513] Finally oxidation of **1028** provided ubiquinone-10 **1003**, identical with natural material, in overall yield of 27.4% for the seven steps in Scheme 118. Most of the bioquinones should be accessible by the Eren–Keinan route.

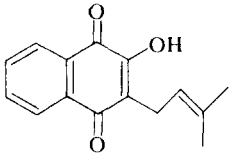
Arnebifuranone. This prenylated benzoquinone, previously regarded as **1032**, occurs in the root of *Arnebia euchroma*,[515] an oriental medicinal drug. The monoterpenoid side chain terminates in a furan ring and in Moore's[514] synthesis the side chain was constructed first, then attached to a cyclobutenedione and rearranged. The bromide **1029** was extended to the acetylene **1030**, the lithium salt of which was added to dimethyl squarate to give the required alkynylhydroxycyclobutenone **1031**. On thermolysis it rearranged smoothly to give the benzoquinone **1032** in excellent yield (Scheme 119). However, the product was not the same as the natural compound. Comparison of the



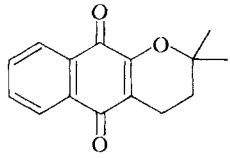
Scheme 119

spectra of the two quinones confirmed that the synthetic product **1032** (isoarnebifuranone) has *E* stereochemistry while natural arnebifuranone is actually the *Z* isomer **1033**. The latter is ustable and gradually isomerizes to isoarnebifuranone.

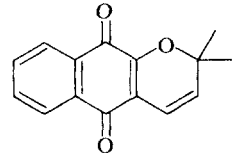
Of the O-heterocyclic quinones the majority contain only one prenyl unit and many have been synthesized by straightforward methods.[14, 15] For instance lapachol **1034** can be prepared *inter alia* by alkylation of 2-methoxy-1,4-naphthoquinone with 2-methylbut-3-en-2-ol, cyclized to α-lapachone **1035**, and then dehydrogenated (*DDQ*) to the dehydro compound **1036**. Epoxidation of lapachol leads directly to (±)-stenocarpoquinones A **1037** and B **1038**. These compounds and others are found in Bignoniaceae and Proteaceae heartwoods. Where the chromene ring is fused to the benzenoid ring, as in teretifolione B **1039**, the starting point is a naphthol. Condensation of 2,7-dihydroxynaphthalene with citral affords **1040**, which is easily converted into **1039**. More recent papers in this area are cited in reference 515.



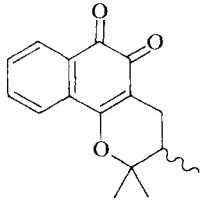
1034



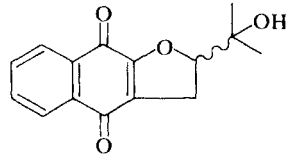
1035



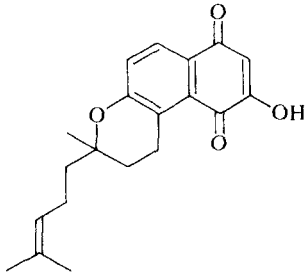
1036



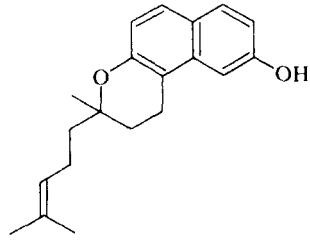
1037



1038

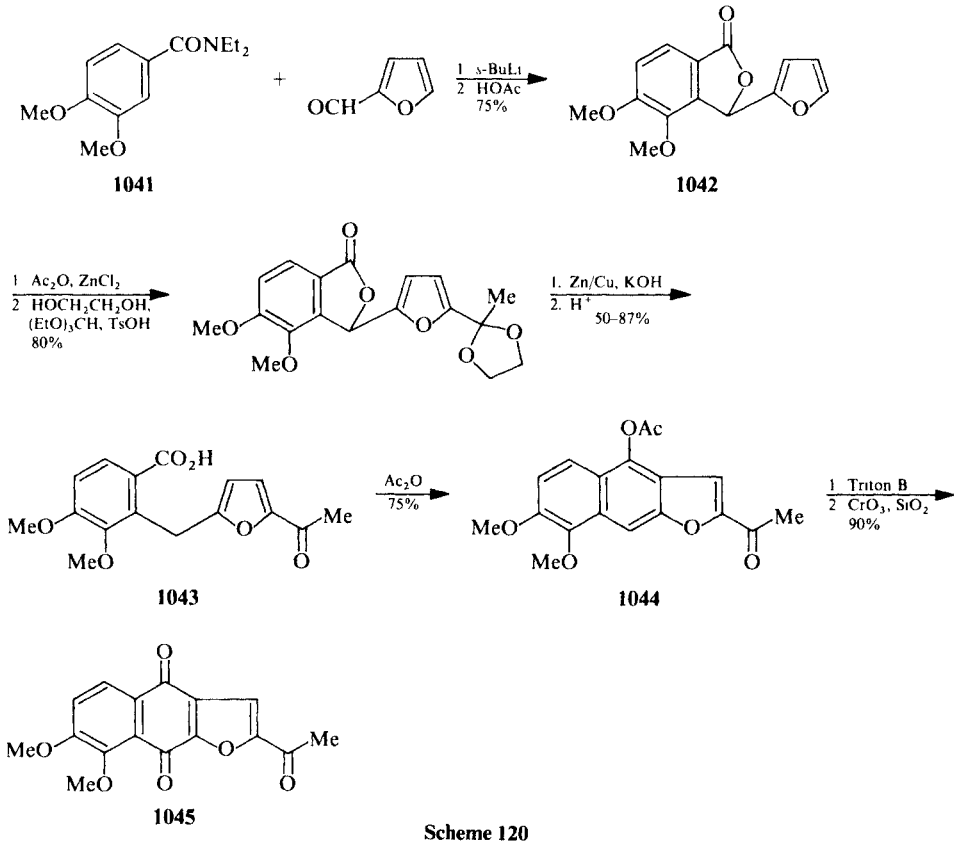


1039



1040

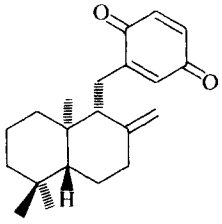
The small group of naturally occurring furanonaphthoquinones has aroused little synthetic interest, but a regiospecific synthesis of the acetyldimethoxy derivative[516] **1045** (from *Tabebuia ochracea*) should pave the way for other endeavors. Following an anthraquinone route Snieckus[517] coupled furfuraldehyde with metalated amide **1041** to obtain the phthalide **1042**. A Friedel–Crafts acetylation of the furan ring followed by reductive cleavage of the phthalide afforded the acid **1043**, which underwent Friedel–Crafts cyclization to the aromatic acetate **1044**. After hydrolysis, final oxidation on silica gel gave the desired quinone **1045** (Scheme 120).



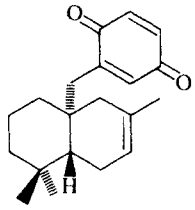
Scheme 120

A small group of quinones, all isolated from marine sources, comprise a simple benzoquinone moiety linked to a bicyclic sesquiterpenoid system. They have not attracted great interest and so far only the zonarol–zonarone pair and their isomers have been synthesized. The hydroquinones zonarol

1053 (R = H) and isozonarol **1054** (R = H) were found[518] separately, in samples of the brown alga *Dictyopteris zonaroides* collected in different locations. Small amounts of the corresponding quinones, zonarone **1046** and isozonarone **1047**, were also present.



1046

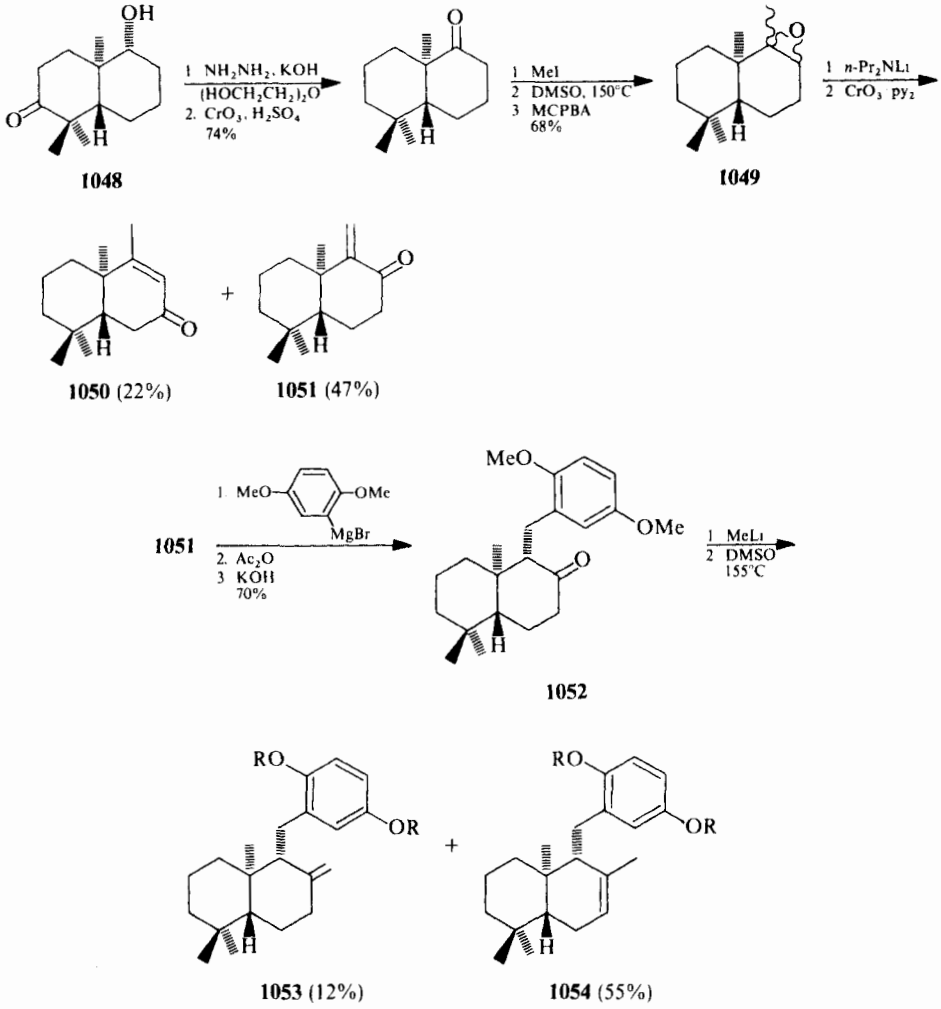


1047

Welch and Rao[519] chose to start their synthesis from the readily available ketol **1048**;[520] it was modified in seven steps to the enone **1051** to which a benzenoid side chain was added (Scheme 121). Rearrangement of the epoxides **1049** with lithium di-*n*-propylamide gave a mixture of allylic alcohols[521] which on oxidation with Collins' reagent afforded the easily separated enones **1050** and **1051**. Conjugate addition of 2,5-dimethoxyphenylmagnesium bromide to **1051** and quenching with acetic anhydride produced an enol acetate from which ketone **1052** was obtained on hydrolysis. A Wittig reaction on **1052** afforded (±)-zonarol dimethyl ether **1053** (R = Me), and treatment of **1052** with methyl lithium followed by dehydration provided both **1053** (R = Me) (±)-isozonarol dimethyl ether **1054** (R = Me), which were demethylated (*n*-BuSLi, HMPT) separately (Scheme 121).

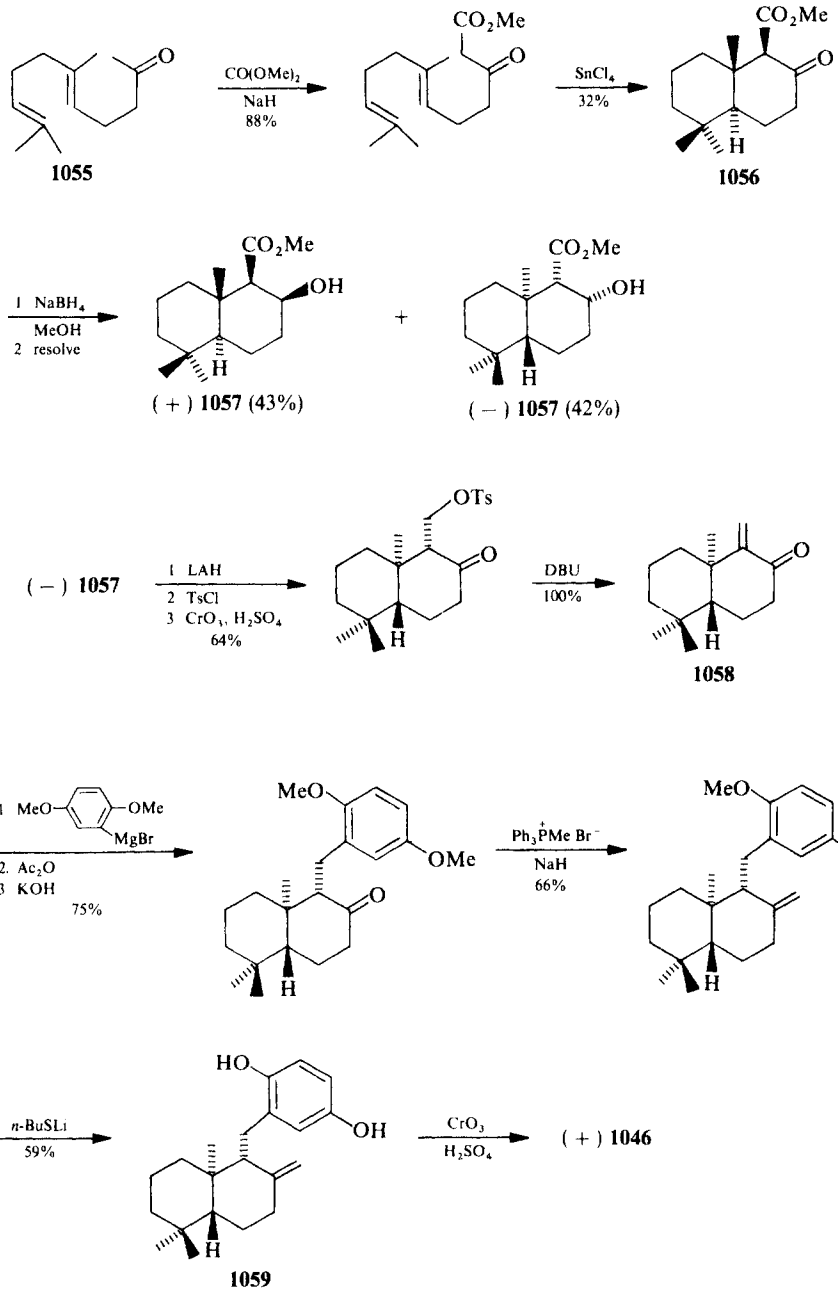
Following that work Mori and Komatsu[522] reported a total synthesis of (+)-zonarol and (+)-zonarone which established the absolute configuration (Scheme 122). The key intermediate was the optically active hydroxyester **1057**, which was prepared from geranylacetone **1055** by transformation into the known keto ester **1056**, which was reduced to the alcohol (±)-**1057**. Resolution of **1057** was achieved through the (*R*)-1-(1-naphthyl)ethylcarbamates which were easily separated by chromatography. The (−)-enantiomer of **1057** thus obtained was converted, as indicated, into (+)-**1058** and the synthesis was completed, following Welch and Rao (Scheme 121), to give (+)-zonarol **1059** and (+)-zonarone **1046** identical with the natural materials. In the same way (−)-zonarol and (−)-zonarone were derived from (+)-**1057**. The absolute configurations of the natural compounds, hitherto unknown, were deduced from their ORD–CD spectra.

Benzoquinones fused to a terpenoid ring system are rare. One of these is cordiachrome B **1063**, a member of a small group of compounds found in the

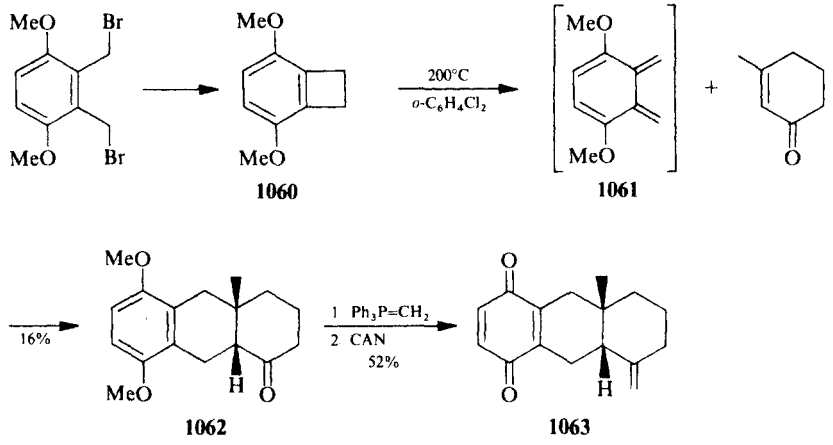


Scheme 121

heartwood of *Cordia* spp.[15] In a short synthesis Oda[523] took advantage of the fact that benzocyclobutenes undergo thermal electrocyclic ring opening to *o*-quinodimethanes which can be trapped by dienophiles. On heating **1060**[524] in the presence of a large excess of 3-methylcyclohex-2-en-1-one the quinodimethane **1061** was trapped, but only 16% of the desired ketone **1062** was isolated together with 40% of the *trans* epimer. A Wittig reaction on **1062** followed by oxidation yielded (±)-cordiachrome B **1063** (Scheme 123).

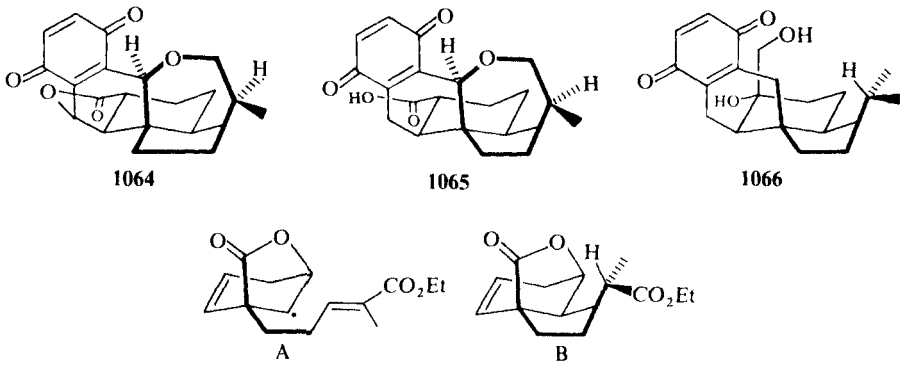

1055
CO(OMe)2
NaH
88%
CO2Me
SnCl4
32%
1056
1 NaBH4
MeOH
2 resolve
OH
(+) 1057 (43%)
(−) 1057 (42%)
(−) 1057
1 LAH
2 TsCl
3 CrO3, H2SO4
64%
OTs
DBU
100%
1058
1 MeO
OMe
MgBr
2. Ac2O
3 KOH
75%
MeO
OMe
Ph3PMe Br−
NaH
66%
n-BuSLi
59%
HO
OH
CrO3
H2SO4
(+) 1046
1059

Scheme 122



Scheme 123

Pleurotin. In contrast to cordiachrome B, in the fungal metabolite pleurotin **1064** the sesquiterpenoid system fused to the quinone ring is a complex polycyclic structure. It was first isolated from *Pleurotus griseus*[525] and later from *Hohenbuehelia geogenius*[526] (and named géogénine), and displays antibiotic and antitumor activity. Two related fungal metabolites[527] are dihydropleurotin acid **1065** and pleurogrisein **1066**. An impressive synthesis of this formidable molecule has been successfully achieved by Hart[528] and his colleagues. Analysis of the structure reveals a *trans*-perhydroindane subunit, and it was planned to construct that first in the form of the lactonic ester B, which it was expected[529] could be derived from the radical A by cyclization. The double bond in B could then be utilized to attach the quinone unit, and the ether bridge inserted in due course. It was possible to accomplish all of this with remarkable efficiency (Scheme 124).

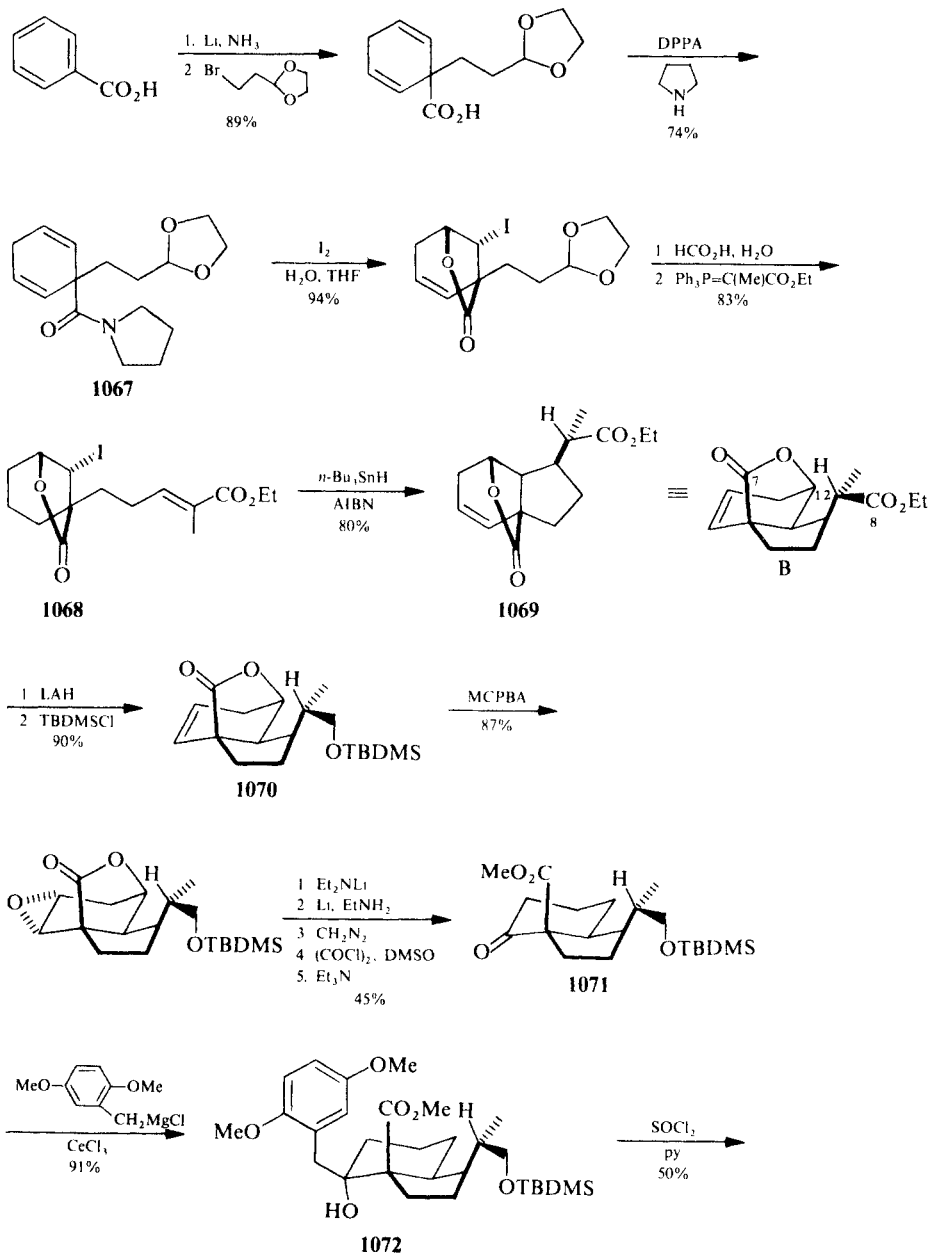


Birch reduction of benzoic acid followed by alkylation with 2-(2-bromoethyl)-1,3-dioxan gave an acid which was converted to amide **1067** using pyrrolidine and diphenylphosphoryl azide,[530] and three more steps, iodolactonization, deprotection, and a Wittig reaction produced the unsaturated ester **1068** (cf. A). On treating **1068** with tributyltin hydride, the resulting radical added to the double bond to form a mixture of four separable diastereomers, but with surprising stereoselectivity as the desired tetrahydroindane **1069** (= B) was obtained in 80% yield. The structure of **1069** was established by X-ray crystallography.

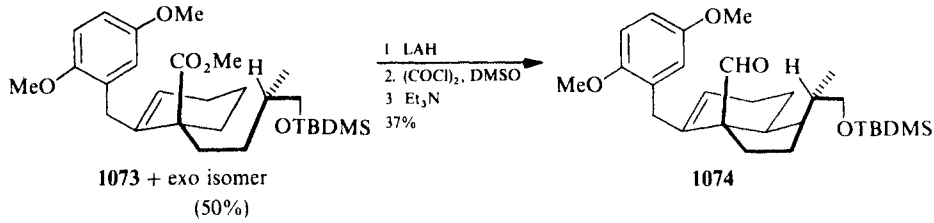
At that point the oxidation states of C-7 and C-8 were differentiated by a standard sequence of reactions on the ester function. However, it was found later that the lactone-ester **1069** could be reduced exclusively with lithium aluminum hydride to the lactone-alcohol (**1070** after protection) (95%), which can be attributed to steric effects. Further progress toward pleurotin then required reduction of the C-12–oxygen bond, which was achieved in one-pot by epoxidation of **1070**, rearrangement to an allylic alcohol with lithium diethylamide[531] in ether, and reduction with lithium ethylamine[532] to give a hydroxyperhydroindane carboxylic acid. Methylation with diazomethane and a Swern oxidation then provided the keto ester **1071**, a key compound in the synthesis.

The quinone synthon was then introduced by exposing **1071** to a Grignard–cerium(III) chloride reagent[532] which provided the alcohol **1072**. Dehydration with thionyl chloride was quantitative, but unfortunately olefin **1073** and the unwanted *exo* isomer were formed in a 1:1 ratio. Reduction of the mixture with lithium aluminum hydride gave a pair of alcohols which were separated and the *endo* isomer was converted to aldehyde **1074** by Swern oxidation. Two crucial steps then followed. Treating aldehyde **1074** with acidic Dowex-50 in methanol resulted in formation of the ether bridge linking C-7 and C-8. An electrophilic aromatic substitution was then effected by treating the acetals **1075** with boron trifluoride to give **1076** (52%) with 11% of recovered starting material.

Conversion of **1076** to dihydropleurotin acid entails saturation of the double bond and carboxylation at C-14. That was done by oxidative hydroboration and Swern oxidation of the resulting alcohol to ketone **1077**, then successive conversion to a nitrile,[533] aldehyde, and oxidation with alkaline silver oxide to yield the acid **1078**. A final CAN oxidation of **1078** provided dihydropleurotin acid **1065**. Conversion of dihydropleurotin acid to pleurotin requires nucleophilic addition of the carboxyl anion to a quinone–methide tautomer and reoxidation. Experimentally that proved to be difficult. It was eventually achieved by stirring with excess of manganese dioxide in dichloromethane to give (±)-pleurotin **1064** in 32% yield with

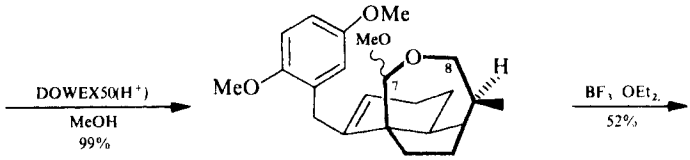

1. Li, NH3
2 Br
89%
DPPA
74%
1067
I2
H2O, THF
94%
1 HCO2H, H2O
2 Ph3P=C(Me)CO2Et
83%
n-Bu3SnH
AIBN
80%
1068
1069
B
1 LAH
2 TBDMSCl
90%
OTBDMS
1070
MCPBA
87%
1 Et2NLi
2 Li, EtNH2
3 CH2N2
4 (COCl)2, DMSO
5. Et3N
45%
1071
CeCl3
91%
1072
SOCl2
py
50%

Scheme 124

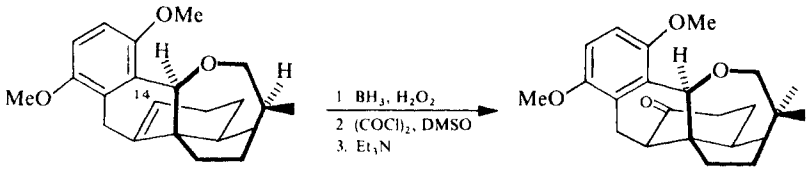


1073 + exo isomer
(50%)

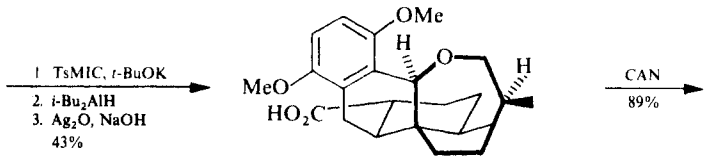
1074



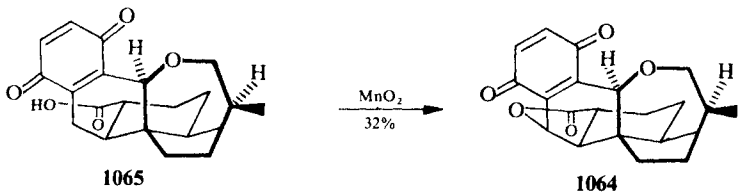
1075



1076 **1077**



1078



1065 **1064**

Scheme 124 *(continued)*

33% recovered acid. In sum, the synthesis of (±)-pleurotin was accomplished in 26 steps from benzoic acid in 0.3% overall yield, a remarkable average of 80% yield per step.

The total synthesis of naturally occurring quinones has come a long way since 1868.

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The Total Synthesis of Spiroketal-Containing Natural Products

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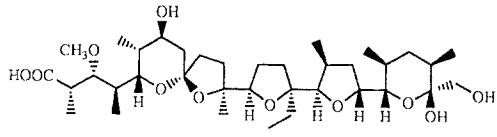
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1. INTRODUCTION

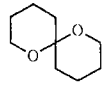
A. General Comments

A large variety of insects, microbes, plants, fungi, and various marine organisms have elaborated spiroketal-containing metabolites. The increasing pharmacological importance of such compounds has generated fervent interest in their synthesis in the chemistry community. This interest did not arise until approximately the mid-1970s, following the isolation and structure elucidation of the polyether antibiotic monensin A (**1**) in 1967.[1] The description of the ionophoric properties of this substance, coupled with the near-simultaneous discovery of crown ether ionophores and the subsequent birth of host–guest chemistry, was sufficient to intensify interest in monensin A and similar substances. The structural complexity of **1**, however, did not attract widespread interest in its synthesis. The description of several structurally simple fly pheromones (**2** and simple analogs)[2] and chalcogran (**3**)[3] in the mid-to-late 1970s provided simple target molecules around which synthetic methodology could be designed and explored.



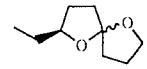
1

Monensin A
Streptomyces cinnamonensis



2

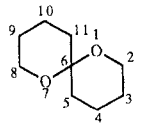
1,7-Dioxaspiro[5.5]undecane
Dacus oleae



3

E and *Z*-2-Ethyl-1,6-dioxaspiro[4.4]nonane
(Chalcogran)
Pityogenes chalcographus

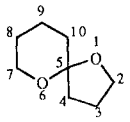
The vast majority of the synthesis in this area has been focussed on the spiroketal general ring systems shown in Scheme 1, presumably because most natural product substructures fall into one of these categories.



4

1,7-Dioxaspiro[5.5]undecane

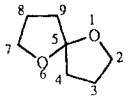
Milbemycins
Avermectins
Insect Pheromones
Aplysiatoxin
Calcimycin
Talaromycins
Okadaic Acid
Sapogenins (mainly)



5

1,6-Dioxaspiro[4.5]decane

Phyllanthocin
Monensin
Insect Pheromones



6

1,6-Dioxaspiro[4.4]nonane

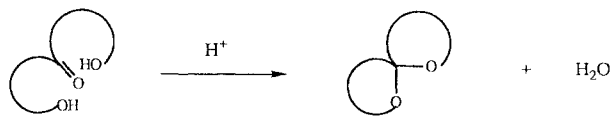
Chalcogran
Asteraceae metabolites
Insect Pheromones

SCHEME 1. Parent spiroketals.

Various aspects of spiroketal synthesis have been previously reviewed.[4] The scope of this chapter will be more extensive and will cover the literature comprehensively (with respect to referencing) from 1970 to mid-1989, although a small amount of work published before 1970 is included. We have taken a more analytical approach to the syntheses of the more structurally complex metabolites than with the simple spiroketals discussed in Sections 2 and 3. However, we have strived to present a critical treatment of the information, as opposed to a simple compilation of what has been accomplished. We have omitted coverage of monensin total synthesis because this has been fully reviewed in an earlier volume of this series.[5]

B. Conformational Aspects

Several conformational factors have led to synthetic simplification in the construction of spiroketals, especially those derived from the parent ring system **2**. In a great majority of the syntheses, the relative configuration of the spiro carbon was determined in an acid-promoted thermodynamic spiroketalization of a dihydroxyketone precursor or an equivalent thereof (Scheme 2).

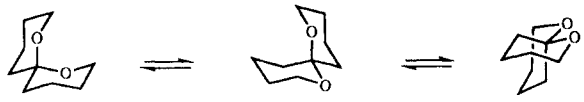


7 8

SCHEME 2

In complex syntheses an assumption was usually made that the natural configuration of the spiroketal ring system, and the configuration of the spiro carbon in particular, was the thermodynamically favored isomer. As will be seen, these assumptions have been borne out quite nicely, especially in the more highly substituted cases.

The preferred conformation of a spiroketal of the [5.5] variety (and presumably the [4.5] and [4.4] as well) is determined primarily by three factors: (1) steric influences, (2) anomeric and related effects, and (3) intramolecular hydrogen bonding and other chelation effects. In the parent ring system **2**, there are three possible all-chair conformers (**9–11**). Deslongchamps[6] has shown by ^{13}C NMR that **2** exists predominantly, if not exclusively, in the bis-diaxial C–O arrangement **9** in solution. This has been ascribed to a maximization of thermodynamic anomeric effects when the spiro C–O bonds are axially oriented. Although there are several hypotheses as to the origin of the anomeric effect,[7] it is clear that there is a strong preference for a carbon–oxygen bond at the 2-position of a tetrahydropyran ring to reside in an axial orientation and that this has a profound influence on the conformation of spiroketals. This is evident in the conformations of both naturally occurring and synthetic spiroketals and in the thermodynamic acid-catalyzed spirocyclizations of dihydroxyketone equivalents. However, the typical preference for substituents to reside in equatorial positions is also important and in carbocyclic systems is normally an overriding factor. As will become evident, this must be balanced against the stabilizing consequences of the anomeric and related effects in tetrahydropyrans. There are cases in which the anomeric effect outweighs the equatorial preference of alkyl substituents. However, when the two factors are reinforcing, that is, when anomeric effects are maximized and 1,3-diaxial interactions are minimized, one can make a confident prediction of molecular conformation. Predictions are more tenuous when one of the preferences must be compromised.

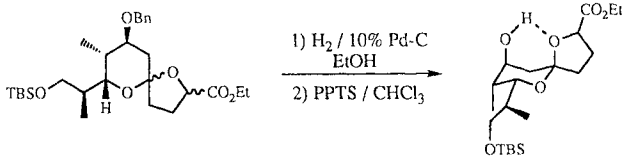


9 10 11

2 anomeric effects 1 anomeric effect no anomeric effects

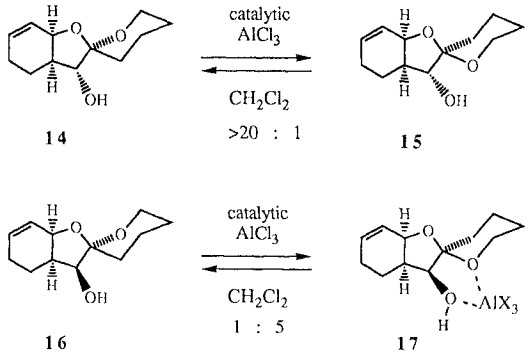
Intramolecular hydrogen bonding and related chelation phenomena have been shown to be important influences on conformer stability and on product ratios in thermodynamic spiroketalizations. Hydrogen bonding is especially

prevalent between axial hydroxy groups and a 1,3-diaxial C–O spiro bond. Several examples of this phenomenon have been characterized. Ireland[8] found that each of the four isomers of the spiroketal **12** isomerized to one of two compounds (**13**), both of which possessed the same configuration at the spirocenter and are epimeric only at the carboethoxy-bearing carbon. There are other examples of similar hydrogen-bonding phenomena.[9]



12 13

Related to intramolecular hydrogen bonding in these systems is a metal chelation phenomenon reported by various workers. Kurth[10] described Lewis acid-promoted isomerizations in a tricyclic system which could be rationalized by a complexation phenomena (Scheme 3). Compound **16** was isomerized to a mixture in which **17** predominated and **15** isomerized almost exclusively to **14**. In both cases, the isomer in which the hydroxyl is *cis* to the spiro C–O bond was favored, suggesting a stabilizing chelation of the metal between the two oxygen atoms (see **17**). Williams[11] described an occurrence in a similar, but more highly functionalized, ring system, while an observation by Descotes in a simpler system[12] pre-dates the observations of both Kurth and Williams.



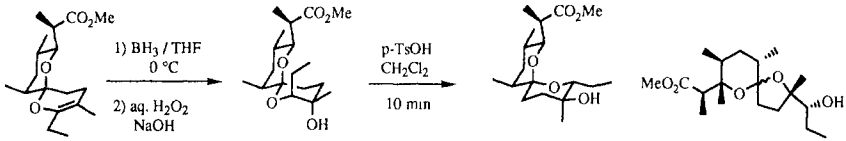
14 15

16 17

SCHEME 3

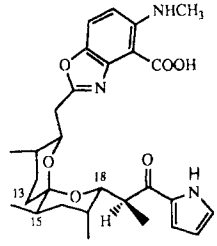
One can take advantage of these factors synthetically and effect a spiro-epimerization of a kinetically produced spiroketal. For example, Ireland[13] found that hydroboration–oxidation of the anomerically disfavored **18**

resulted in **19** possessing an ethyl group which was syn-diaxial with a spiro C–O bond. Since **19** is not anomerically maximized *and* experiences 1,3-diaxial interactions, it is not surprising that spiroepimerization occurs easily to give **20** and a mixture of [4.5] spiroketals **21**. There are other examples of similar phenomena.[14]

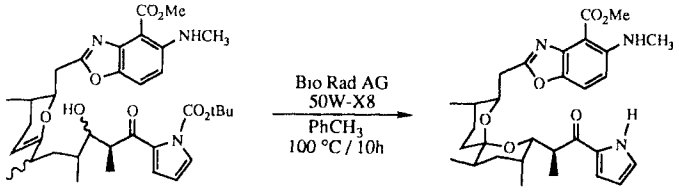


18 19 20 53% 21 47%

A final epimerization process frequently utilized in spiroketal synthesis design is the ready epimerization of stereogenic centers α to the spiro carbon. Evans found that the deuterium exchange occurs at the C-13 and C-15 positions of calcimycin (**22**) when treated with DCl in dioxane.[15] This led to the synthetic simplification that the methyl group at C-15 need not be introduced stereospecifically, since it appeared to occupy the more stable equatorial position in the natural product. This was indeed the case, as the intermediate **23** (as a mixture of diastereomers at C-15 and C-18) equilibrated at C-15 to a single equatorial methyl isomer **24** at C-15 of the spirocyclic system. This simplification was later utilized by Nakahara in another calcimycin synthesis.[16] A similar tactic was used by both Hoye[17] and Schreiber[18] in the course of invictolide syntheses.



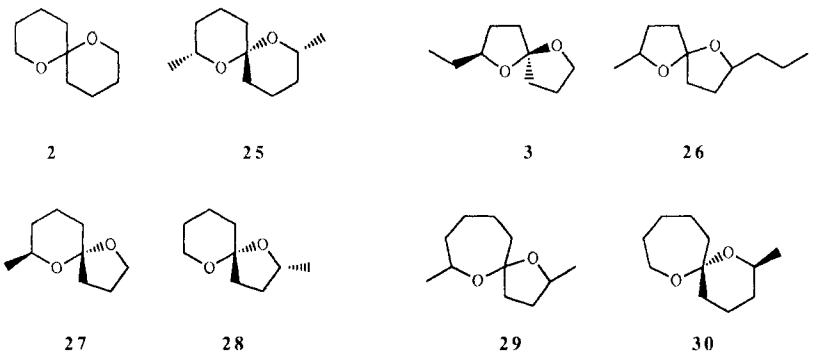
22



23 24

2. INSECT PHEROMONES

A number of insect species utilize simple spiroketals as pheromonal components.[2] These metabolites possess unbranched carbon skeleta and are usually devoid of further functionality. Frequently, several stereo- and structural isomers of one formula are found in the same organism. Insects elaborate the only known examples of naturally occurring spiroketals containing seven-membered rings. A few representative examples are shown in Scheme 4. The parent compound **2** as well as some others have been synthesized several times. These compounds played important roles in the early synthetic work, providing simple target molecules with which to evaluate synthetic methodology. As a result, several general routes to spiroketals were developed, with the typical method for ring closure being the usual acid-promoted spirocyclization of a dihydroxyketone or an equivalent thereof. Because a particular method may be used to synthesize several pheromones, this section was not organized according to structure. Instead, the section is organized methodologically, with similar methods being grouped together. The insect pheromone chalcogran is treated in the next section.

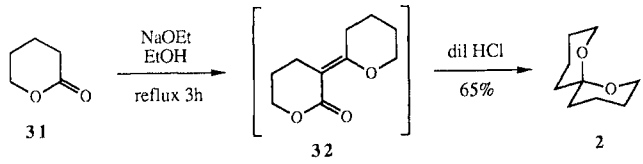


SCHEME 4. Spiroketal insect pheromones.

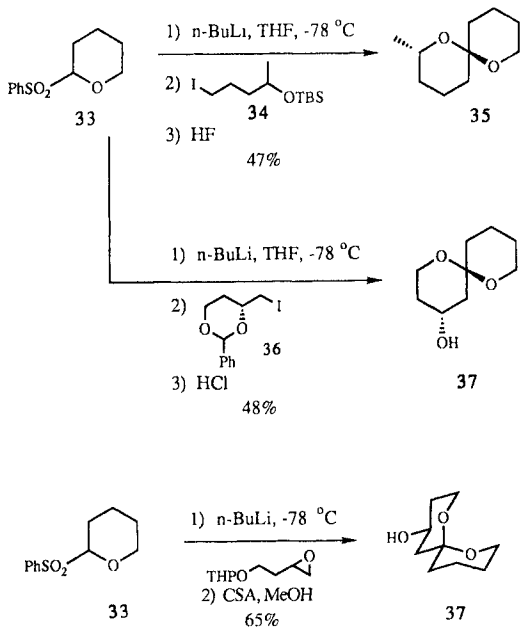
A. Miscellaneous Spiro[n.5] and [n.6] Pheromones

Other than chalcogran, the only insect pheromone to receive extensive synthetic attention is 1,7-dioxaspiro[5.5]undecane **2**, the major component of the sex pheromone of *Dacus oleae* (olive fruit fly).[2e] The synthetic attention stems from the simplicity of its structure and the damage caused by this insect. The compound was first synthesized by Erdmann in 1885.[19] The reaction sequence involved condensation of two δ-valerolactones in refluxing

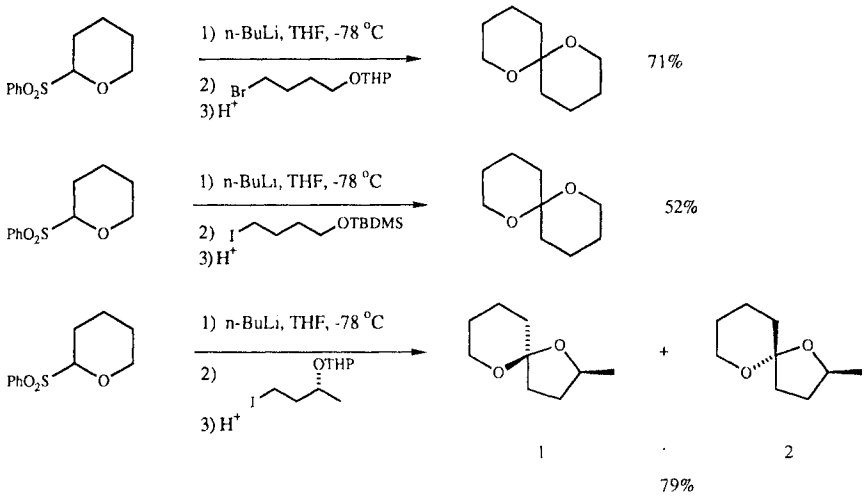
sodium ethoxide–ethanol to give the lactone dimer **32** followed by treatment with dilute HCl to yield the parent spiroketal **2**. This same reaction sequence was later reported by Baker[2e] and by Gariboldi[20] as part of the structure elucidation process.



Ley described a general approach to a variety of [5.5] and [4.5] spiro systems by alkylation of the tetrahydropyran sulfone **33**.[21] Two typical examples are shown in Scheme 5. Deprotonation and alkylation with iodide **34** furnished 2-methyl-1,7-dioxaspiro[5.5]undecane **35** in 47% yield. Alkylation of the sulphone with a optically active iodo compound **36** afforded the hydroxyspiroketal **37**. By using various alkylating agents, a number of other insect pheromones were also produced, as summarized in Scheme 6. Epoxides could also be used as alkylating agents, leading to hydroxylated spiroketals.

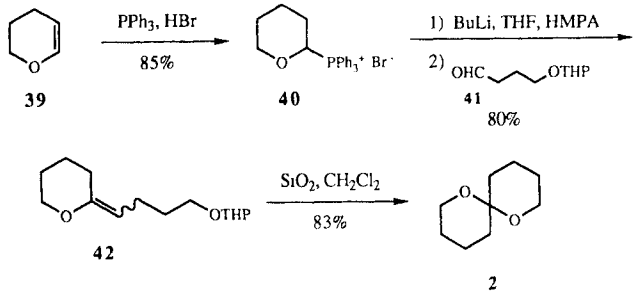


SCHEME 5. Ley sulfone alkylation method.



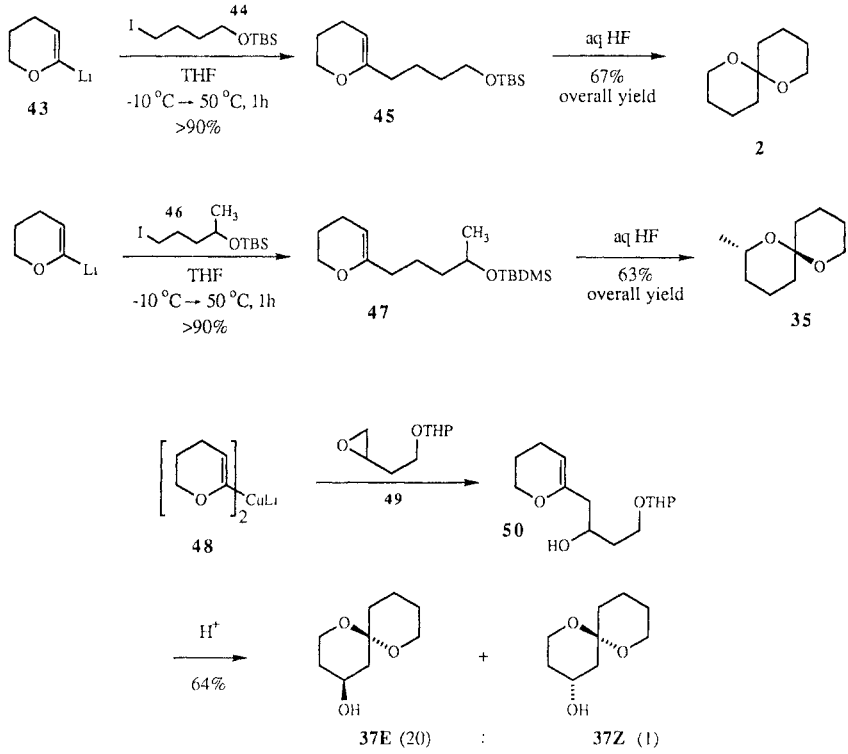
SCHEME 6. Ley sulfone alkylation route to spiroketals.

Mioskowski and Falck[22] described a Wittig-based approach using the phosphonium salt **40**. This method was developed as a general approach to insect pheromones and tetrahydropyrans. Dihydropyran was transformed into **40** by treatment with triphenylphosphine and HBr. Reaction of the ylide from **40** with the aldehyde **41** resulted in olefination to a mixture of isomers **42**. Cyclization in the presence of silica gel formed racemic **2** in an overall 56% yield (Scheme 7).



SCHEME 7. Mioskowski–Falck synthesis of **2**.

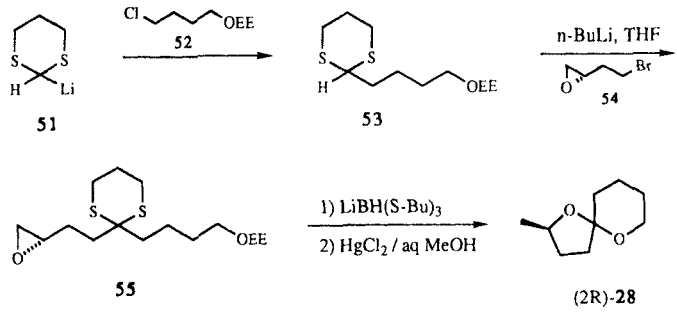
Alkylation of metallated dihydropyrans has been utilized by a number of workers (Scheme 8). Amoroux[23] described a general method for the synthesis of the dioxaspiro[5.5]undecanes that led to the synthesis of two pheromones.



SCHEME 8. Metallated dihydropyran routes to spiroketals.

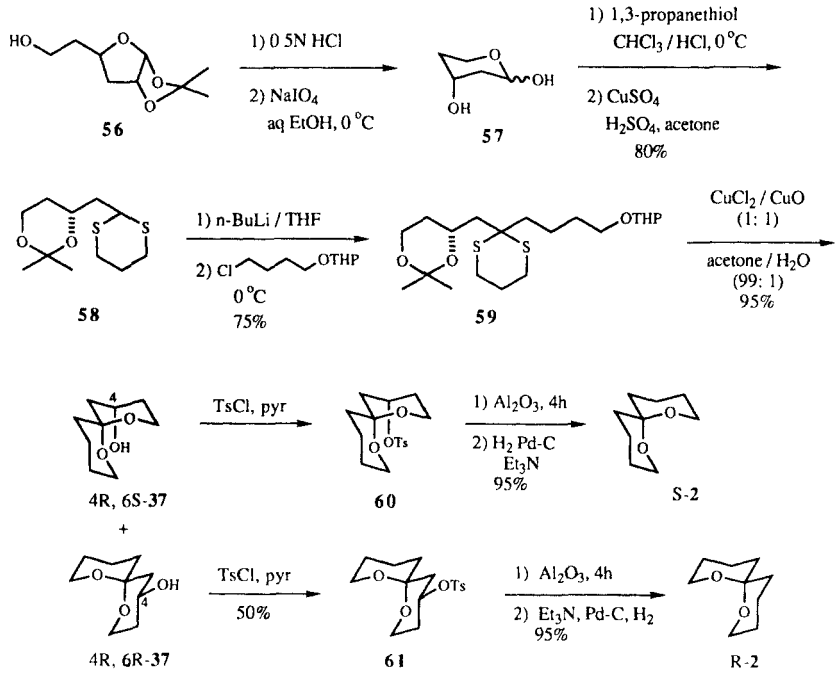
Dihydropyran was lithiated and alkylated with the TBS ether of 3-iodobutanol (**44**), eventually affording **2** in 67% overall yield. In the same manner, dihydropyran was also alkylated with the TBS ether of iodo compound **46** to yield 2-methyl-1,7-dioxaspiro[5.5]undecane (**35**) in 63% overall yield. Kocienski[24] converted the lithium reagent **43** to the cuprate **48** to facilitate epoxide opening to provide hydroxylated spiroketals. Addition of **48** to the protected epoxide **49** afforded a single major component **50**, which was cyclized under acid catalysis to a 20:1 mixture of *E* and *Z* spiroketals **37**.

Dithiane alkylation has been used to stitch together hydroxyalkyl components prior to a deprotection–cyclization sequence. Seebach's group has synthesized 2R-methyl-1,6-dioxaspiro[4.5]decane (**28**, Scheme 9) in a manner similar to their chalcogran synthesis.[25] Sequential alkylation of 1,3-dithiane first with a protected 3-chlorobutanol **52** and then with S-4-bromo-1,2-epoxybutane **54** furnished the open chain intermediate **55**. The epoxide was then opened with L-selectride followed by mercuric ion-induced dethioketalization and cyclization to afford **28** as a mixture of isomers at the spiro center.

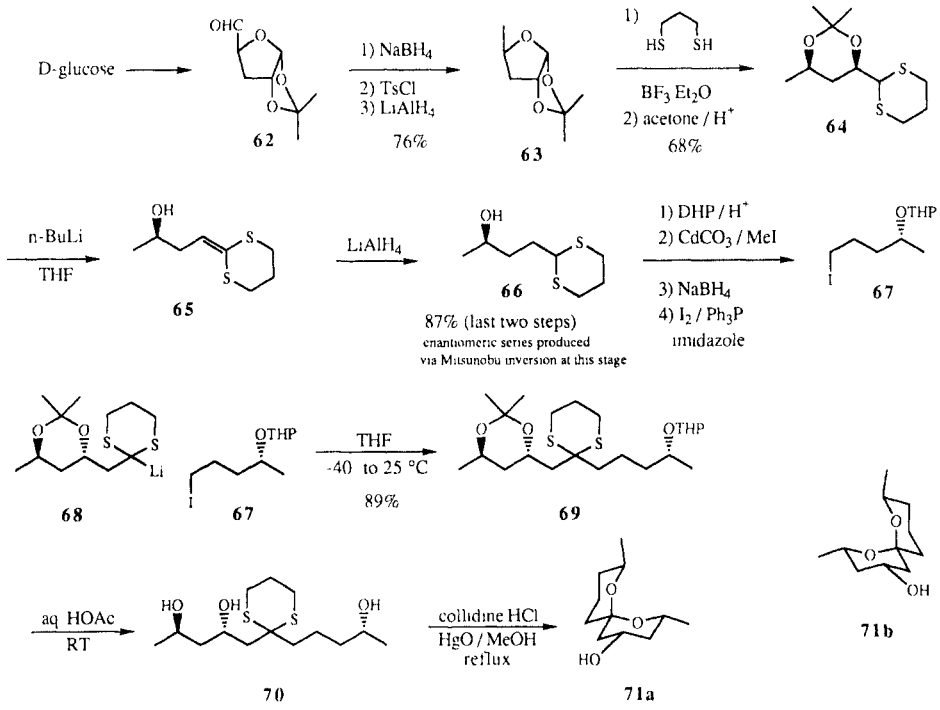


SCHEME 9. Seebach dithiane synthesis of **28**.

Redlich's general approach to enantioselective synthesis of insect pheromones of the [5.5] variety involves initial conversion of glucose to optically pure dithianes (Schemes 10 and 11).[26] Alkylation of the sugar-derived **58** with THP-protected 4-chlorobutanol followed by Cu^{2+}-catalyzed deprotection



SCHEME 10. Redlich synthesis of (*R*)- and (*S*)-**2**.

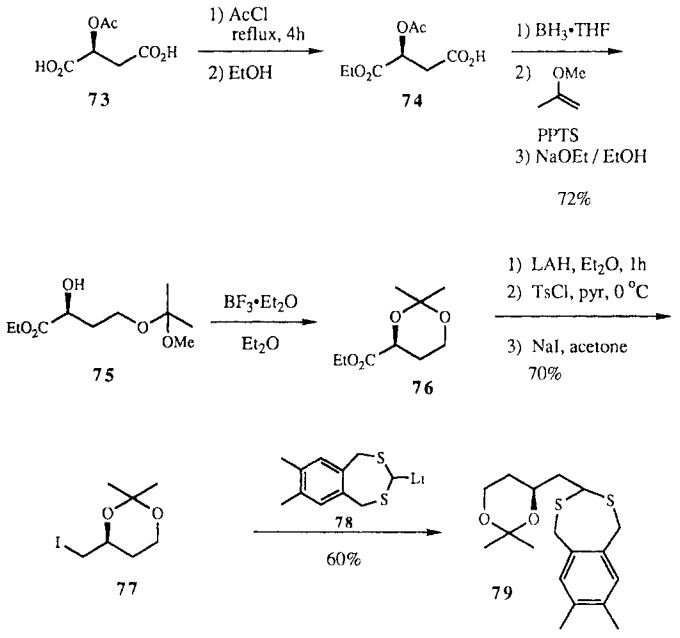


SCHEME 11. Redlich syntheses of **71** and its enantiomer.

and cyclization afforded a 35:65 mixture of the 4R,6S- and 4R,6R-4-hydroxy-1,7-dioxaspiro[5.5]undecanes, respectively. Separation and removal of the hydroxy groups by standard procedures yielded both (*R*)- and (*S*)-**2**. Redlich also accomplished syntheses of the two enantiomers of 4-hydroxy-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane **71** by coupling the appropriate chiral dithianes and alkyl halides.[27] The chiral dithiane **64** was made from D-glucose (Scheme 11). Elimination and LAH reduction of the newly formed alkene afforded the chiral alcohol **66**. The enantiomeric series was entered at this point by Mitsunobu inversion of the alcohol. Conversion of **66** to the corresponding iodide **67** was straightforward. The iodide was then used to alkylate the chiral dithiane **68**. Deprotection of the resulting displacement product **69** and concomitant cyclization yielded **71a**. The isomer **71b** was also produced using enantiomeric technology.

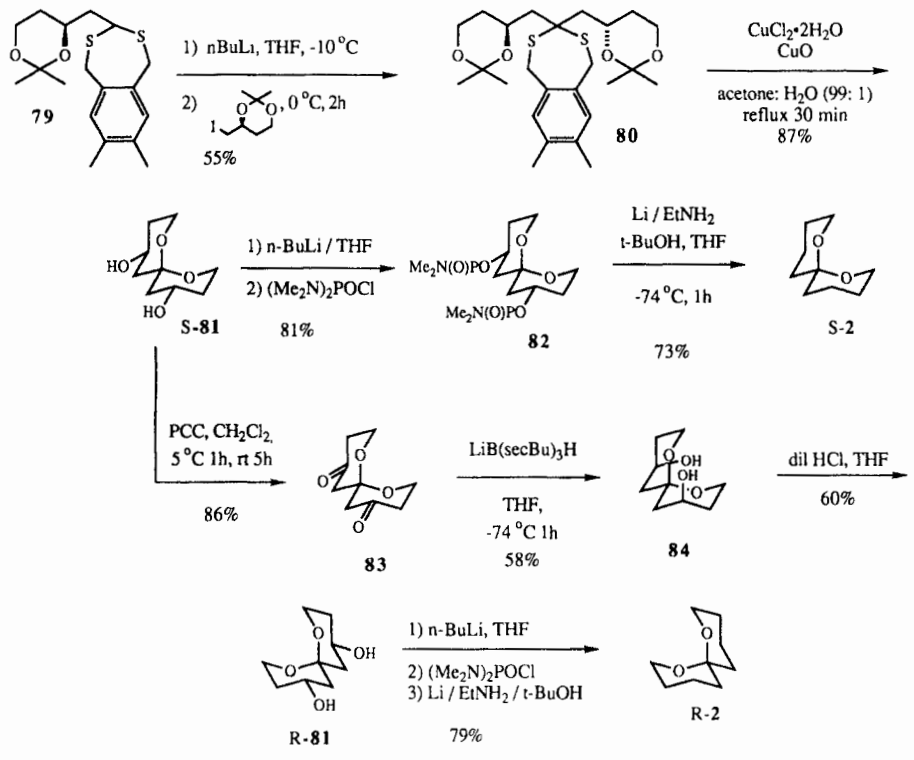
Dithiane alkylation with optically active halides was also exploited by Mori, who achieved an enantioselective synthesis of both enantiomers of 1,7-dioxaspiro[5.5]undecane in a manner analogous to Redlich.[28] The optically active alkylating agent **77** was prepared from (*S*)-(−)-malic acid by conven-

tional methods (Scheme 12). This iodide was then used to alkylate the dithiane **78** providing **79**. A second alkylation with the same iodide produced **80** (Scheme 13). Deprotection and subsequent spirocyclization gave the bis-equatorial dihydroxy spiroketal **81**, possessing full anomeric stabilization. Reductive removal of the hydroxyls provided the *S*-enantiomer of **2**. Oxidation of the diol *S*-**81** to the diketone and hydride reduction gave the bis-axial isomer **84**. Isomerization at the spiro center is the only way in which an epimer can be produced which contains full anomeric stabilization and equatorial hydroxyl groups on two chair-like rings. On treatment of **84** with dilute HCl, isomerization to *R*-**81** occurred in 60% yield. Reductive deoxygenation as before led to (*R*)-**2**. A second route to both of these enantiomers was also described that was analogous to that shown in Scheme 13 along the same lines as the Redlich synthesis (Scheme 10).

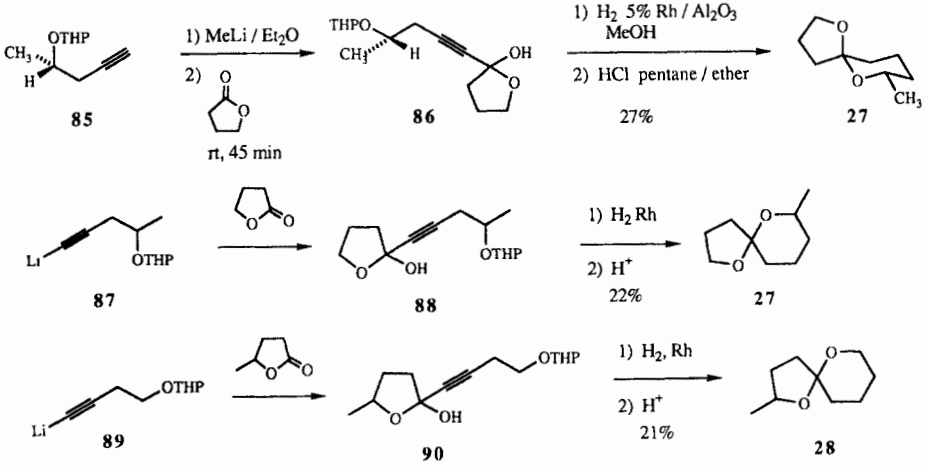


SCHEME 12. Mori Synthesis of chiral dithiane **79**.

Addition of acetylide anions to lactones was the general method that Smith used to prepare many of the [4.4], [4.5], and [5.5] spiroketals (Scheme 14).[29] Deprotonation of the chiral acetylene **85** and addition to γ-butyrolactone afforded the acetylene **86**. Hydrogenation and acid catalyzed deprotection–cyclization yielded 2-methyl-1,6-dioxaspiro[4.5]decane **27** in



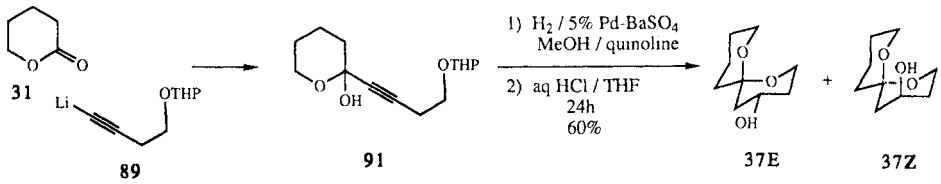
SCHEME 13. Mori synthesis of the enantiomers of **2**.



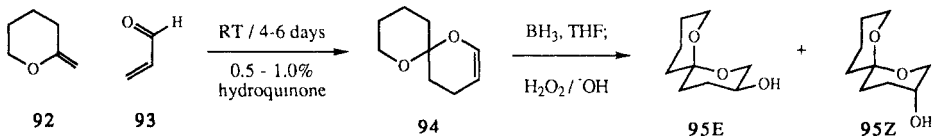
SCHEME 14. Smith lactone addition approach to spiroketals.

27% overall yield. This method has also been applied to the synthesis of racemic **27** and **28**. The manuscript describing this work provides only general experimental detail and no information was given concerning the composition of diastereomeric mixtures.

As part of the structure elucidation of minor components of the olive fly sex pheromone, Baker used essentially an equivalent approach (Scheme 15).[30] Hydrogenation of the acetylene **91** with Lindlar catalyst gave (presumably) a *cis* alkene. Reaction of this alkene with dilute HCl effected spiroketalization and regiospecific hydration of the olefin to provide a mixture of the *E* and *Z* spiroketals **37**. To synthesize the 3-hydroxy-isomers **95Z** and **-E**, also found in this species, the hetero-Diels–Alder adduct **94** was prepared from acrolein and the vinyl ether **92** (Scheme 16). Hydroboration and oxidation of the alkene **94** furnished 3-hydroxy-1,7-dioxaspiro[5.5]-undecane (**95**) as a mixture of the *E* and *Z* isomers.

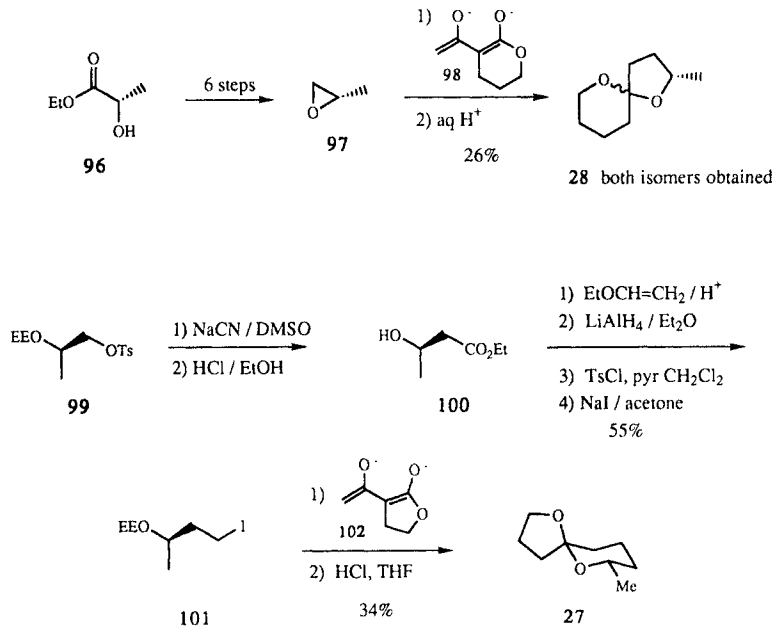


SCHEME 15. Baker lactone–alkyne approach.



SCHEME 16. Baker hetero Diels–Alder synthesis of **95**.

Schurig, and to a greater extent, Mori have utilized β-keto ester and lactone dianions as ω-hydroxyketone equivalents for spiroketal construction. Schurig described syntheses of 2*S*- and 7*S*-methyl-1,6-dioxaspiro[4.5]decane (**28** and **27**) using optically active alkylating agents to control absolute stereochemistry.[31] The two syntheses are shown in Scheme 17. Alkylation of the ketolactone dianion **98** with epoxide **97** derived from *S*-ethyl lactate **96** gave rise to the optically active 2*S*-methyl spiroketal **28**. The course of events following alkylation includes lactone hydrolysis and decarboxylation as well as acidic spiroketalization in undetermined order. Alkylation of the ketovalerolactone dianion **102** with the chiral iodide **101** (also derived from *S*-ethyl

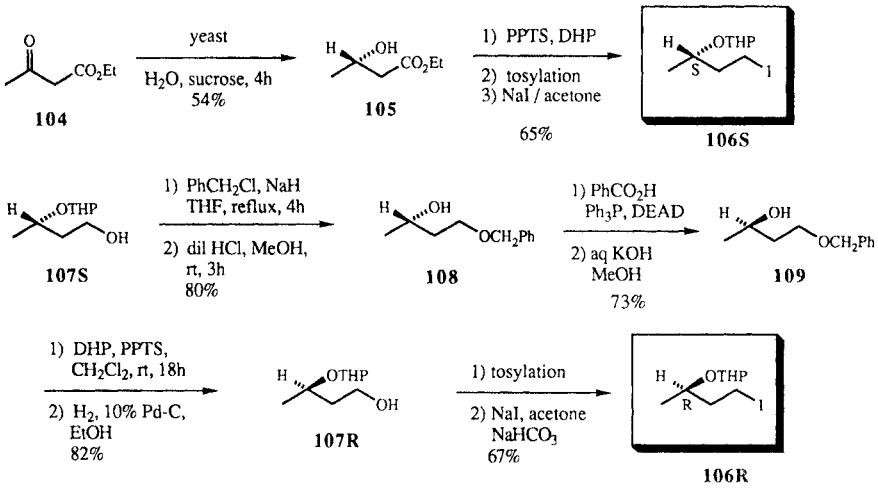


SCHEME 17. Schurig β-keto lactone dianion alkylation method.

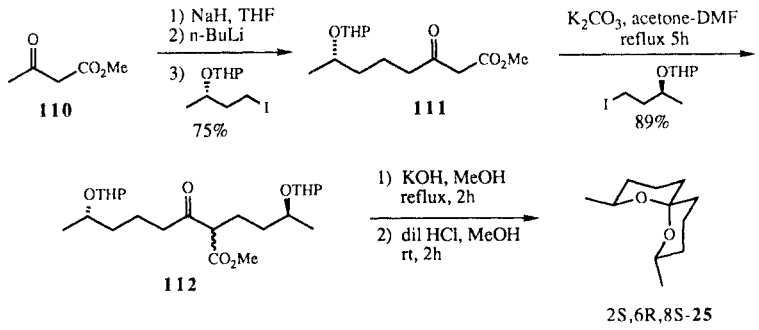
lactate **96**) afforded (7*S*)-7-methyl-1,6-dioxaspiro[4.5]decane in an overall 34% yield.

Mori has developed perhaps the most general method for the synthesis of simple spiroketals in optically active form. Using an approach analogous to Schurig, it was possible to synthesize many isomers of substituted [4.6], [4.5], [5.5], and [5.6] systems. Both enantiomers of the iodide **106** (Scheme 18) were prepared from ethyl acetoacetate. Formation of the *S*-alcohol **105** was accomplished by microbial reduction and the enantiomeric series was prepared by Mitsunobu inversion. These chiral iodides were then used to alkylate various β-keto esters. For example, alkylation of **110** with the *S*-iodide twice, followed by decarboxylation and acid-promoted spirocyclization produces the spiro[5.5] compound **25**.[32] Other combinations of iodides can be used to prepare diastereomers of this system. Analogously, a variety of substituted spiro[4.5] systems were prepared using a combination of a chiral lactone **113** and a chiral alkyl iodide (Scheme 19) via the same strategy.[33] Mori has reported the only syntheses of spiroketals containing seven-membered rings by simply altering the lactone and alkyl halide fragments, providing a variety of pheromone isomers (Schemes 20 and 21).[34]

Enders synthesized several of the 1,6-dioxaspiro[4.4]nonane pheromones (including chalcogran) by dimethylhydrazone alkylation (Scheme 22).[35]

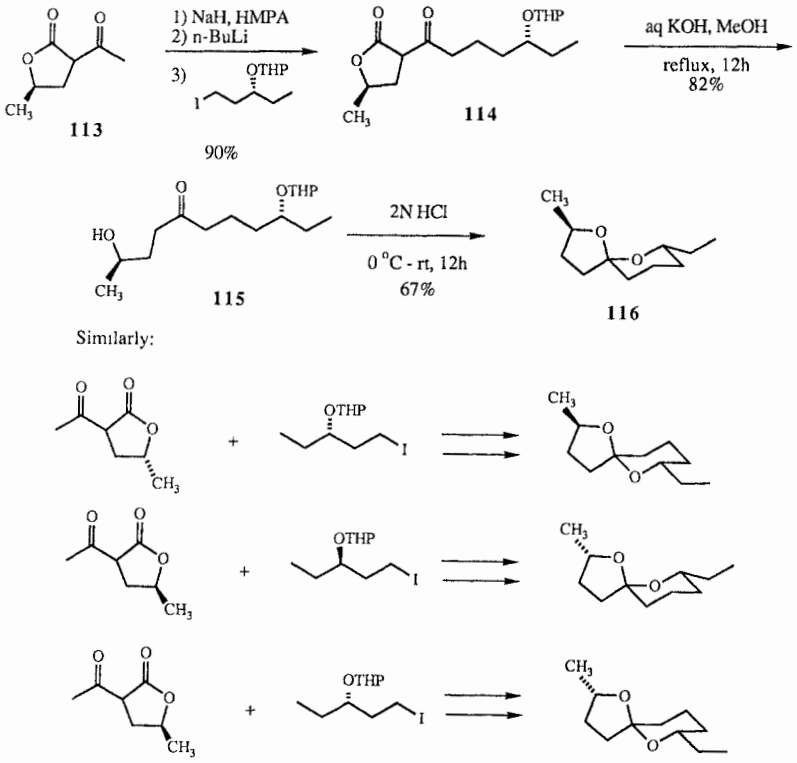


SCHEME 18. Mori synthesis of enantiomeric iodides **106** *R* and *S*.

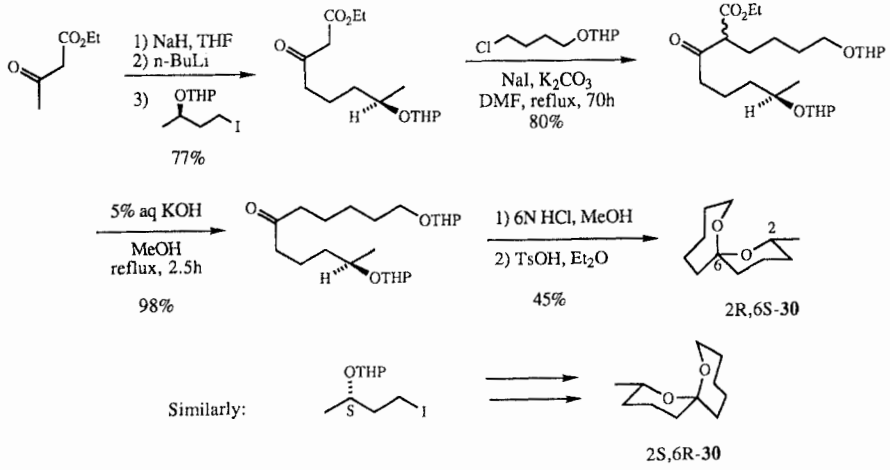


Sequential dialkylation of acetone dimethyl hydrazone **113** with 1,2-epoxybutane furnished the open-chain precursor **115**. Acid-catalyzed cyclization yielded 2,7-diethyl-1,6-dioxaspiro[4.4]nonane **116** as a mixture of isomers in 65% yield. Similarly, dialkylation of **113** with 1,2-epoxypentane furnished 2,7-di-*n*-propyl-1,6-dioxaspiro[4.4]nonane in 75% yield upon cyclization. Three years later, Mitra described a synthesis of 1,7-dioxaspiro[5.5]undecane using an essentially identical approach (Scheme 23).[36] Sequential dialkylation of **113** with the bromide **118** followed by acid-catalyzed deprotection and cyclization furnished the parent spiroketal **2** as a racemic mixture.

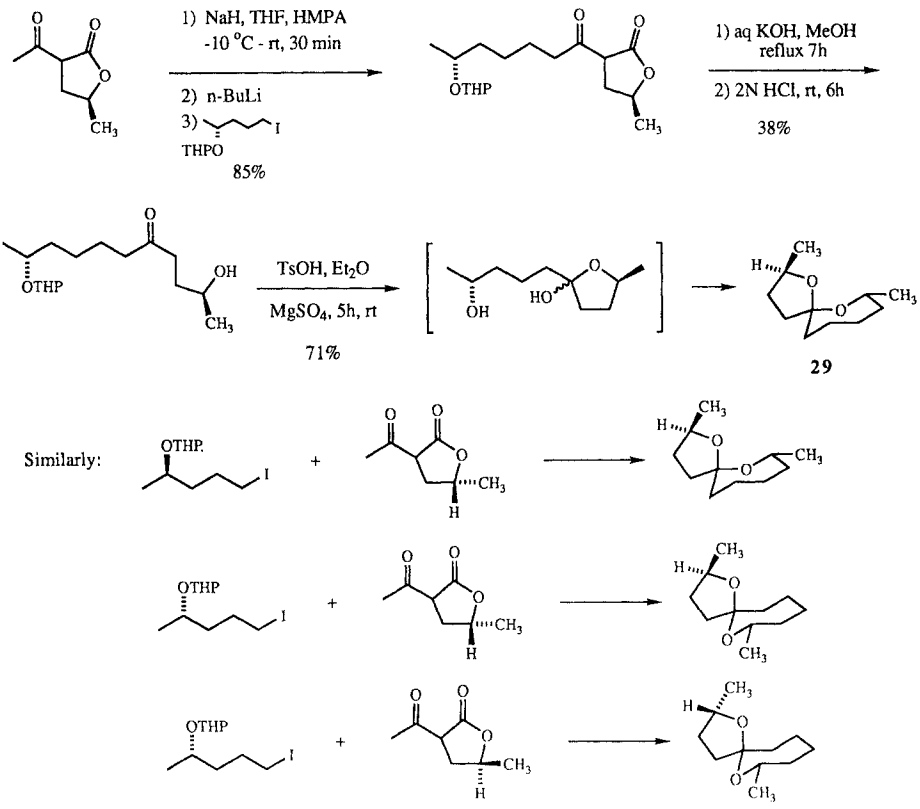
Ley developed a method based on phenylselenoetherification using *N*-phenylselenopthalimide (NPSP) to synthesize several spiro[5.5] and [4.5] insect pheromones (Scheme 24).[37] For example, reaction of δ-valerolactone



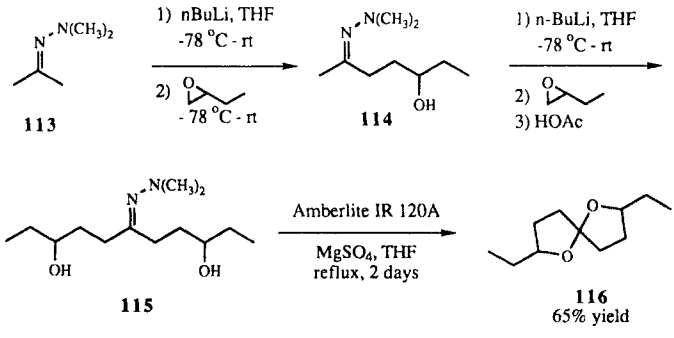
SCHEME 19. Mori synthesis of 1,6-dioxaspiro[4.5]decanes.



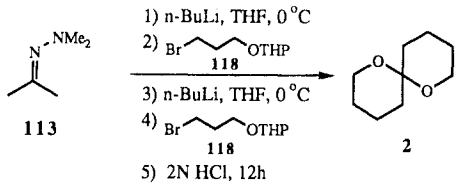
SCHEME 20. Mori synthesis of 1,7-dioxaspiro[5.6]dodecanes.



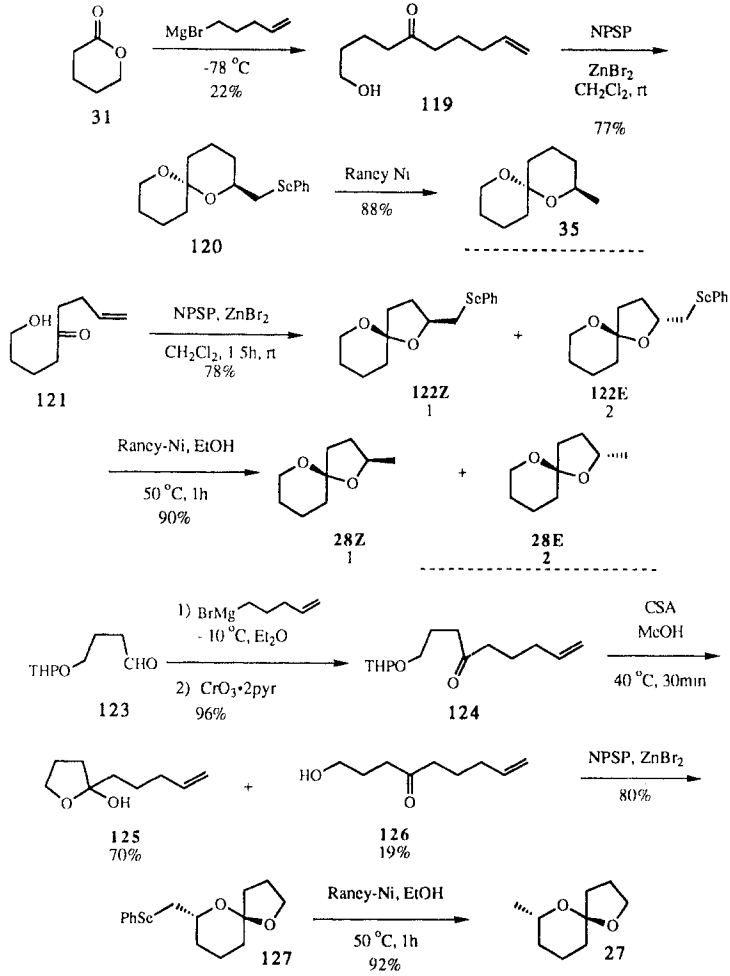
SCHEME 21. Mori synthesis of 1,6-dioxaspiro[5.6]undecanes.



SCHEME 22. Enders' dimethylhydrazone bis-alkylation method.



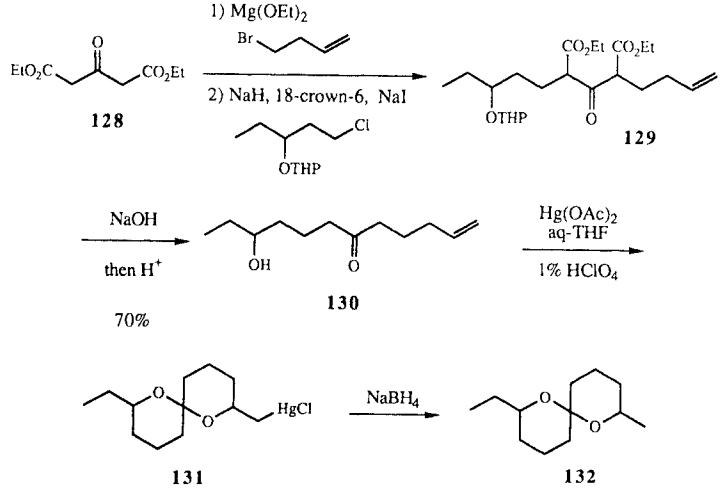
SCHEME 23. Mitra synthesis of racemic **2**.



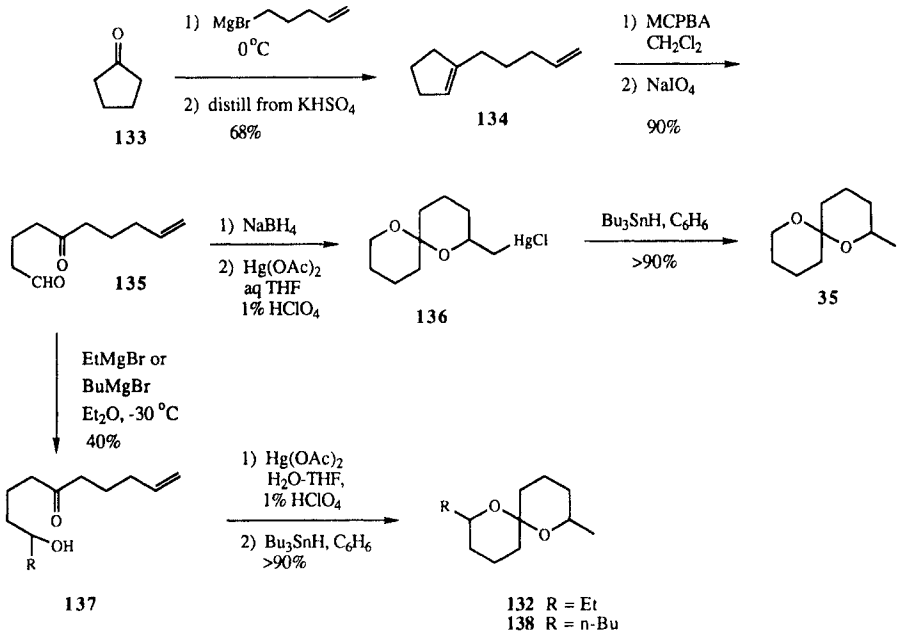
SCHEME 24. Ley phenylselenoetherification method.

with 4-pentenylmagnesium bromide provided the enone intermediate **119**. Cyclization with NPSP in the presence of zinc bromide and subsequent reductive removal of the phenyl selenide yielded 2-methyl-1,7-dioxaspiro[5.5]undecane **35**. In a similar manner, the enone precursor **121** gave rise to a mixture of *E* and *Z*-2-methyl-1,6-dioxaspiro[4.5]decanes (**28**) upon treatment with NPSP and removal of SePh; *E*-7-methyl-1,6-dioxaspiro[4.5]decane **27** was also made by this method. It should be noted that Sharpless observed a similar cyclization several years earlier.[38]

Kitching[39] described a cyclization initiated by mercuric acetate. Two variations were reported, the first (Scheme 25) being analogous to that reported by Ley. Using diethyl acetonedicarboxylate **128** as an acetone anion equivalent, the cyclization substrate **130** was prepared. Treatment with mercuric acetate under acidic conditions leads to organomercurial **131** as a mixture of isomers. Reductive demercuration provided the spiroketal mixture **132**. A more versatile variant of this process is shown in Scheme 26, in which the cyclization substrates are produced in such a way as to control the identity of the substituent at the 2-position, the point at which most structural variation in this class occurs. Oxidation of the cyclopentene **134** provided a keto aldehyde (**135**) which regioselectively adds Grignard reagents to provide the hydroxyketone cyclization substrates **137**. Oxymercuration–demercuration as before leads nonstereoselectively to spiroketals **132** and **138**. A further variant was described by Kitching which was similar to work reported several years earlier by Sondheimer[40] and by Evans.[41] Two examples of this process are shown in Scheme 27. Treatment of



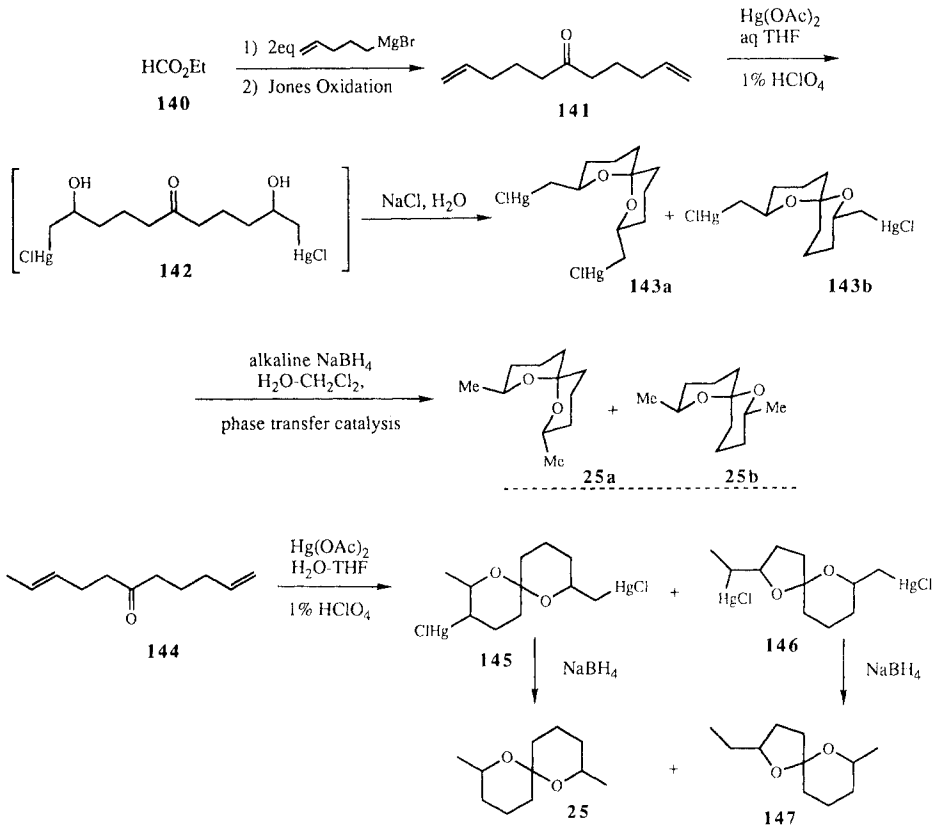
SCHEME 25. Kitching oxymercuration cyclization method.



SCHEME 26. Kitching alternate synthesis of substituted spiro[5.5] systems.

the dienone **141** with mercuric acetate in a THF–water mixture followed by brine afforded the cyclic organomercurials **143a** and **143b**. This reaction presumably proceeds via nonstereoselective bis-oxymercuration of the remote olefins providing an intermediate ketone **142** which undergoes spirocyclization under the acidic reaction conditions providing the two spiroketals **143a** and **b**. Demercuration of this mixture provides the corresponding mixture of pheromones. Similar treatment of the ketodiene **144** leads to two classes of spiroketals (**145** and **146**), which is expected since oxymercuration of the disubstituted olefin of **144** should exhibit low regiospecificity. Again, reductive demercuration of the mixture leads to the two pheromones **25** and **147**.

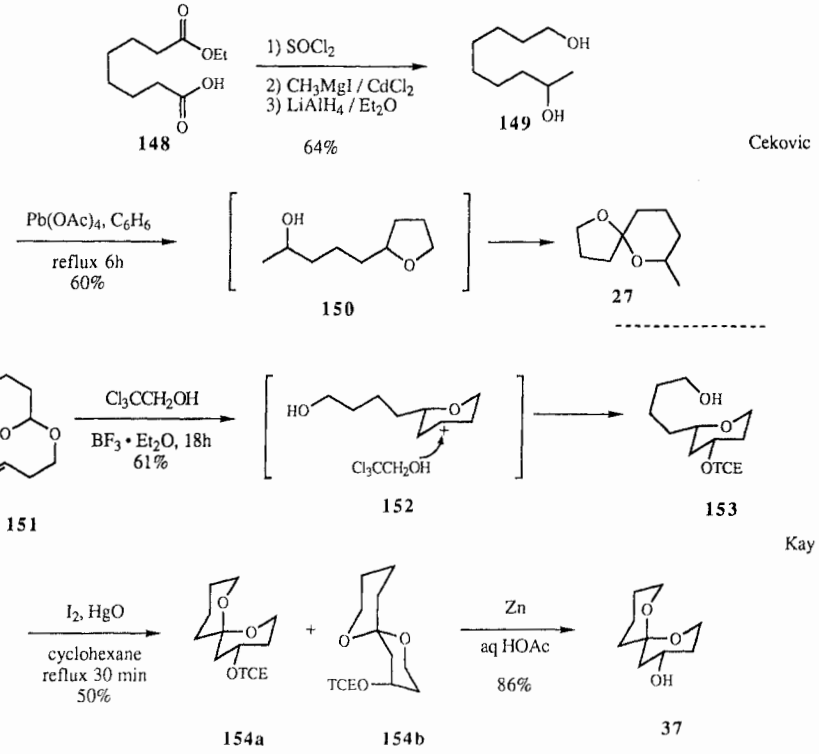
Cekovic applied the same remote oxidation method that was used for a synthesis of chalcogran to the synthesis of 7-methyl-1,6-dioxaspiro[4.5]-decane **27** (Scheme 28).[42] The desired diol **149** was formed from ethyl hydrogen suberate **148** via a standard sequence. Lead tetraacetate oxidation furnished 7-methyl-1,6-dioxaspiro[4.5]decane in 60% yield. The reaction probably proceeds in two stages involving consecutive free radical abstraction–cyclization reactions. In separate studies, several reagents were found to provide varying yields of cyclization products.[43]



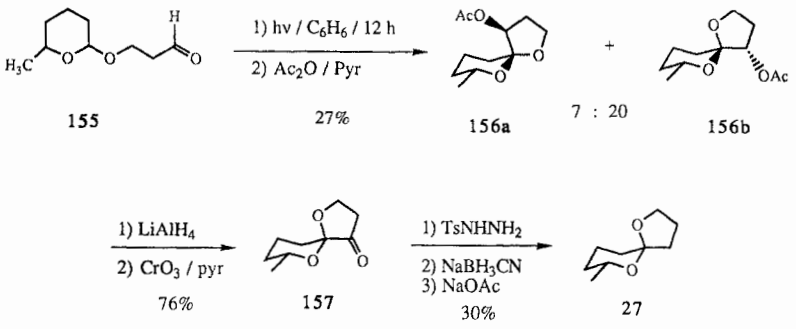
SCHEME 27. Kitching cationic cyclization of keto dienes.

Kay[44] described the synthesis of the hydroxy pheromone **37** using a similar process in a more controlled fashion. An intermediate tetrahydropyran (**153**) was produced first with radical abstraction–cyclization taking place in a subsequent step. In this way, one level of difficulty was circumvented and the method was much more selective.[45] In the Kay approach (Scheme 28) cation–olefin cyclization of the simple THP ether **151** leads to tetrahydropyran **153**. This substance was then heated in the presence of mercuric oxide and iodine to form an intermediate hypoiodite (not shown) which proceeds to a mixture of **154a** and **154b** via an alkoxy radical. Reductive removal of the protecting group afforded the single spiroketal **37** via an equilibration process in an overall 26% yield.

Related phenomologically to the two prior methods is the work of Descotes[46] involving Norrish Type II photochemical processes (Scheme 29).

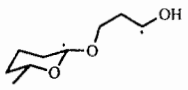


SCHEME 28. Radical abstraction–cyclization methods (Kay and Cekovic).



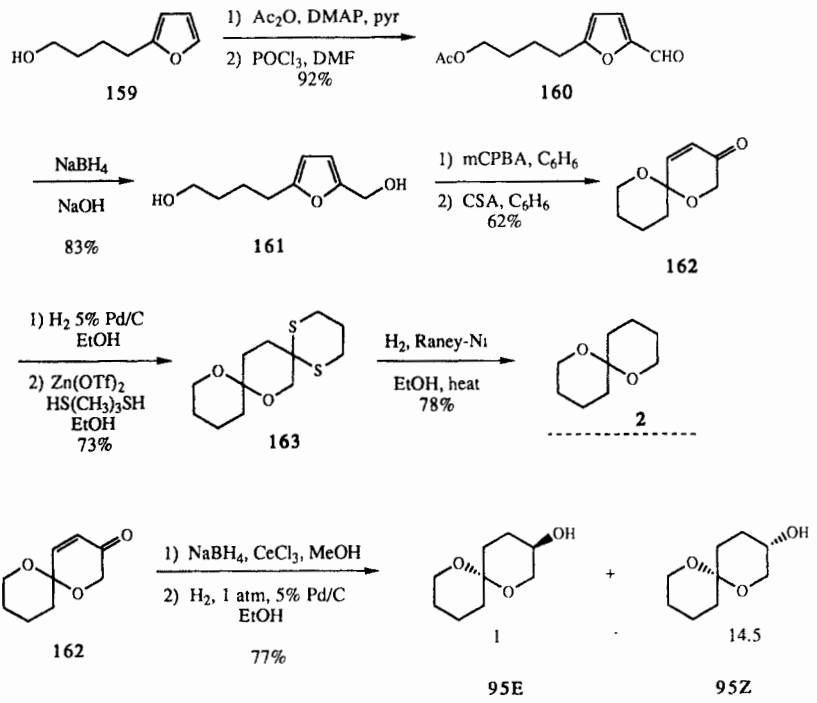
SCHEME 29. Descotes' photochemical synthesis of **27**.

The tetrahydropyran–aldehyde **155** was irradiated and the resulting products were acetylated to provide **156a** and **156b** in 27% yield. The process appears to involve a hydrogen atom abstraction producing diradical **158** which cyclizes to the spiroketals **156a** and **156b**. Separation of the major product and reductive removal of the acetoxy group provides the spiro[4.5]pheromone **27**.



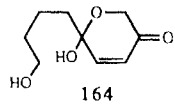
158

DeShong described a general synthesis of highly functionalized spiroketals involving the well-known oxidation of 2-furylcarbinols (Scheme 30).[47] Acylation of the alcohol **159** followed by Vilsmeier–Haack formylation and reduction yielded the desired furan diol intermediate **161**. Oxidation with MCPBA and acid-catalyzed spiroketalization afforded the 1,7-



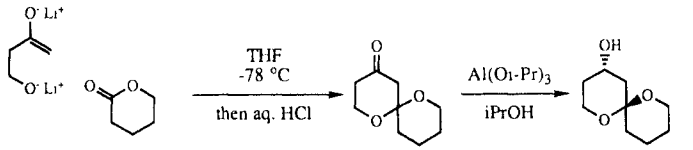
SCHEME 30. DeShong furan oxidation route to insect pheromones.

dioxaspiro[5.5]undecene intermediate **162**. This process presumably proceeds via an intermediate pyranone **164**, the normally observed product of 2-furylcarbinol oxidation. Complete defunctionalization of **163** produces the parent pheromone **2**. However, the strength of this method lies in the production of functionalized systems. Carbonyl reduction of **162** followed by hydrogenation of the alkene afforded 3-hydroxy-1,7-dioxaspiro[5.5]-undecane (**95**) as a 14.5:1 mixture of the *Z* and *E* isomers.



164

Martin and Albizati have synthesized *E*-4-hydroxy-1,7-dioxaspiro[5.5]-undecane **37** using aldolate dianion chemistry (Scheme 31). Reaction of the dianion **165** generated from 4-hydroxy-2-butanone and 2 equiv of LDA with δ-valerolactone furnished the spiroketone intermediate **166**. Meerwein–Pondorff–Verley reduction of the ketone afforded *E*-4-hydroxy-1,7-dioxaspiro[5.5]undecane (**37**) in 20–30% overall yield. The *Z* isomer of **37** could be obtained by hydride reduction of **166**.[48]



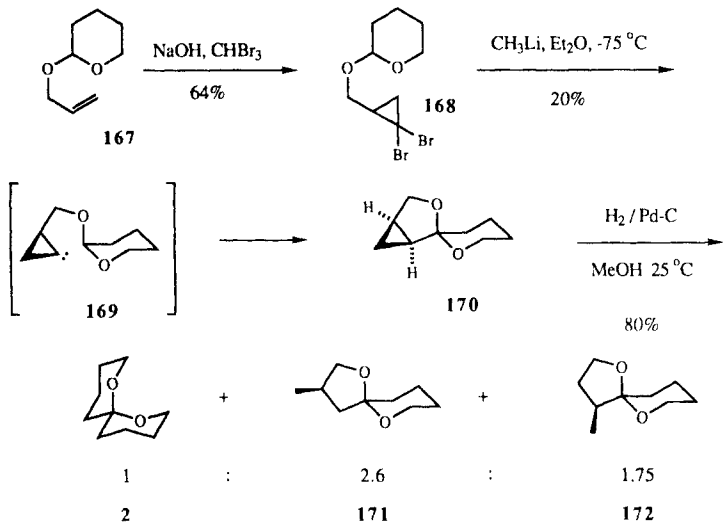
165 31 166 37

ca. 20-30% overall

SCHEME 31. Synthesis of *Dacus* metabolite **37**.

In 1985, Brinker[49] demonstrated a clever but low-yielding approach to spiroketal systems involving carbenes (Scheme 32). Dihydropyran was transformed into the dibromocyclopropane **168**. Treatment of **168** with MeLi produced the spiroketal **170** in 20% yield, probably by way of carbene insertion into the acetal C–H bond. Reductive cleavage of the cyclopropane ring was accomplished by hydrogenation leading to a mixture of **2**, **171**, and **172**.

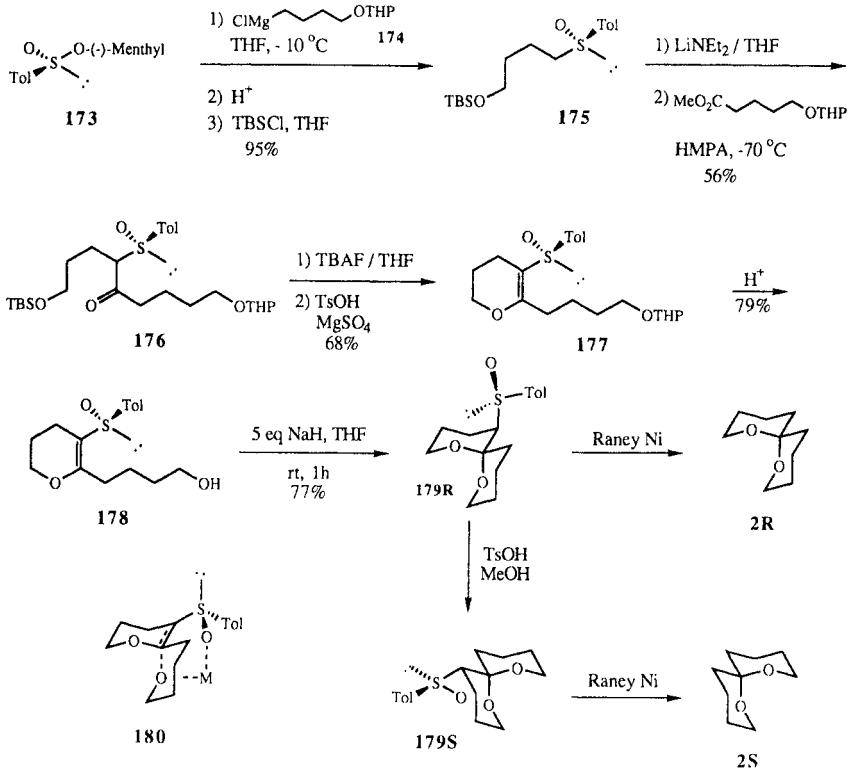
Intramolecular conjugate addition of alkoxides to unsaturated sulfoxides has been developed by Iwata and co-workers into a highly selective general synthesis of spiroketals which has been applied to the production of several natural products. Using chiral vinyl sulfoxides, Iwata enantioselectively



SCHEME 32. Brinker carbene insertion route to spiroketals.

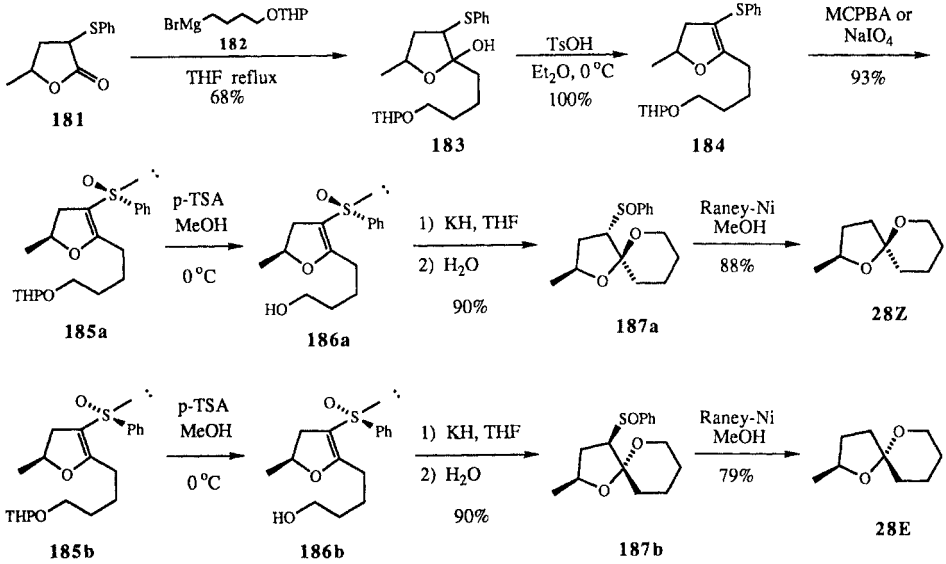
synthesized the two enantiomers of **2** (Scheme 33).[50] Alkylation of the chiral sulfoxide **173** with the Grignard reagent **174** gave rise eventually to the sulfoxide **175** which was α-deprotonated and acylated to yield **176**. Desilylation followed by acid-catalyzed cyclization gave rise to the chiral vinyl sulfoxide **177**, which was deprotected to give the cyclization substrate **178**. Treatment with NaH in THF gave the single diastereomeric spiroketal **179R**. The course of events was rationalized to proceed via a chelated transition state **180** in which axial addition of the alkoxide is assisted by the sulfoxide oxygen. Stereospecific equatorial protonation leads to the axial sulfoxide diastereomer **179R**. Desulfurization of this substance leads to **(R)-2**. Epimerization of the spiro center of **179R** occurred on treatment with acid to provide the thermodynamic isomer **179S** possessing full anomeric stabilization and an equatorial sulfoxide. Desulfurization of this material provided the parent spiroketal **2S**.

Iwata also described two syntheses of 2-methyl-1,6-dioxaspiro[4.5]decane isomers using the same technology. The first synthesis[51] involved alkylation of 5-methyl-3-phenylthiotetrahydrofuran-2-one **181** with the Grignard reagent **182** (Scheme 34). Dehydration followed by oxidation of the sulfide gave rise to the key chiral vinyl sulfoxide diastereomers **185a** and **185b** in a 1:1 ratio. The diastereomers were separated and individually carried on to the two isomers of **28**. Deprotection and base-promoted spiroketalization followed by desulfurization afforded both *E* and *Z*-2-methyl-1,6-dioxaspiro-[4.5]decane as racemic mixtures.

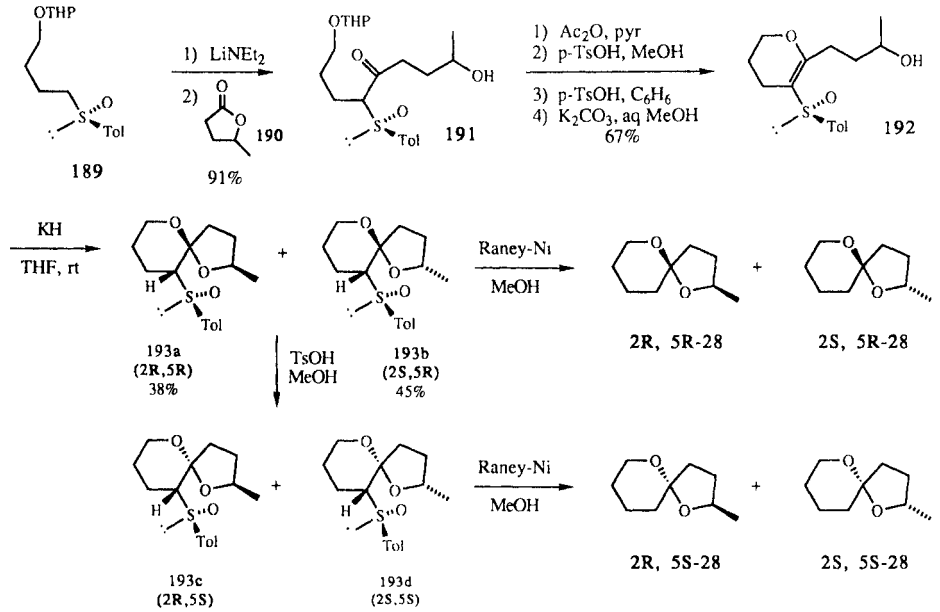


SCHEME 33. Iwata sulfoxide-directed synthesis of the enantiomers of **2**.

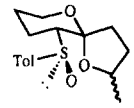
Iwata's second synthesis[52] provided the four stereoisomers enantioselectively starting from the stereogenically pure sulfoxide **189** (Scheme 35). Alkylation of **189** with racemic γ-valerolactone **190** afforded the chiral sulfoxide **191** in 91% yield as a mixture of isomers at the carbinol center. Acid-catalyzed closure to the dihydropyran derivative and further manipulation afforded the key vinyl sulfoxide intermediate **192**. Sulfoxide-directed spiroketalization in basic conditions afforded a mixture of the (2*R*, 5*R*) and (2*S*, 5*R*) spiro sulfoxides of **193**. Desulfurization of these intermediates afforded (2*R*, 5*R*)- and (2*S*, 5*R*)-**28**. As before (Scheme 33), the spiro center of **193a** and **b** could be epimerized with acid to give **193c** and **d**, both of which can reside in a conformation (**194**) with an equatorial sulfoxide and an axial C–O bond at the spiro center. Desulfurization affords (2*R*, 5*S*)- and (2*S*, 5*S*)-**28**.



SCHEME 34. Iwata synthesis of **28*E*** and ***Z***.



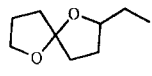
SCHEME 35. Iwata enantioselective synthesis of the isomers of **28**.



194

B. Chalcogran

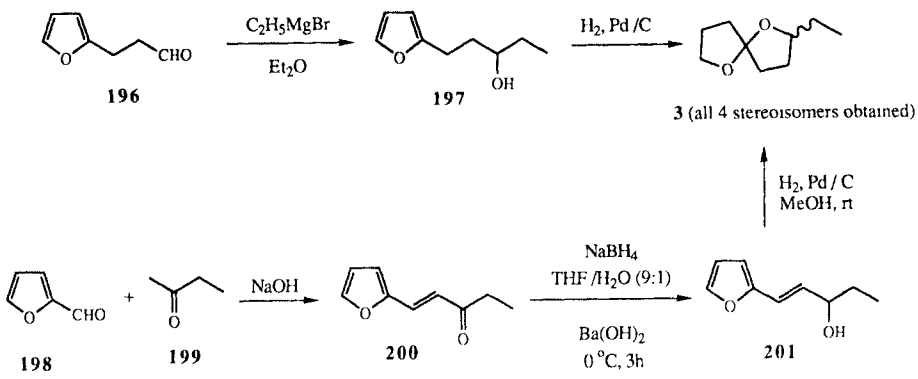
A mixture of spiro[4.4]ketal isomers was isolated by Francke[3] in 1977 as the major components of the aggregation pheromone of the beetle *Pityogenes chalcographus*. This pheromone mixture, collectively known as chalcogran, was shown to be a mixture of the four diastereomers of 2-ethyl-1,6-dioxaspiro[4.4]nonane **3**. These isomers have received more attention from the synthesis community than any other spiroketal due to both the simplicity of the structure and the damage inflicted by this beetle on Norwegian spruce trees. Chalcogran lends itself quite well to methodology development as the following variety of approaches will attest. The majority of the syntheses establish the absolute configuration of ethyl-bearing C-2 in an acyclic precursor and then allow the spiro carbon to be determined in a classical acid-promoted spiroketalization, invariably producing chalcogran isomers.



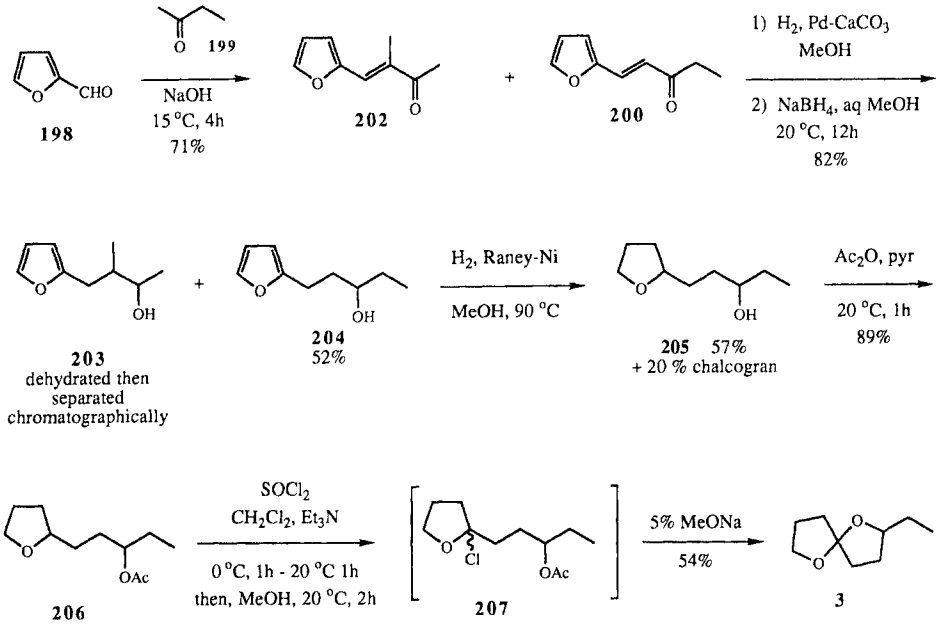
3

Francke reported the first synthesis[3] of chalcogran as part of the structure elucidation process (Scheme 37). Grignard coupling of 3-(2-furyl)-propionaldehyde **196** with ethylmagnesium bromide formed the intermediate **197**. Reductive cyclization of this intermediate gave rise to a mixture of chalcogran isomers. Later, Francke described a general route into the [4.4] spiro systems[53] based on aldol condensations of partners with varying substituents. An aldol condensation between 2-furaldehyde and 2-butanone furnished the intermediate **200**. Reduction of the ketone followed by reductive cyclization yielded chalcogran, again as a mixture of the four possible stereoisomers.

Another furan-based approach was described by Torgov[54] culminating in racemic chalcogran (Scheme 38). As in the Francke synthesis, aldol condensation of 2-furaldehyde with 2-butanone furnished the two enones **200** and **202**, which were not readily separable. Hydrogenation and reduction afforded the mixture of alcohols **203** and **204**. Isomer **203** could be readily dehydrated and



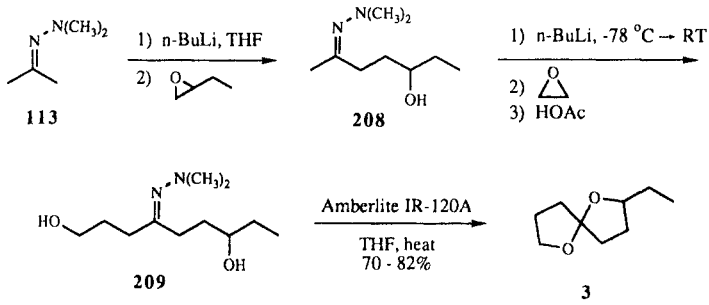
SCHEME 37. Francke syntheses of chalcogran and isomers by reductive cyclization.



SCHEME 38. Torgov synthesis of chalcogran isomers.

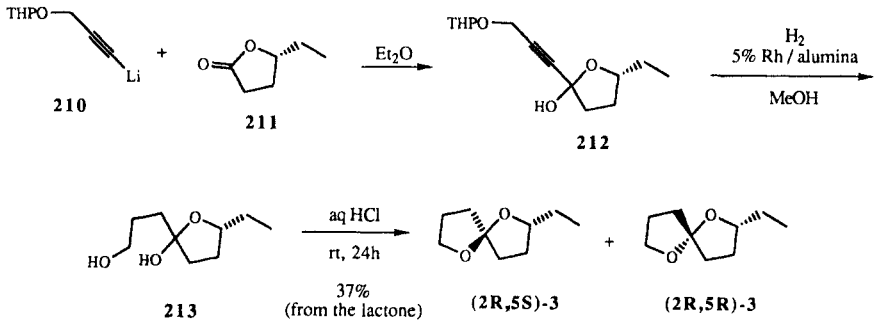
chromatographically separated. Hydrogenation of the furan ring of **204** furnished only 20% of the desired chalcogran. The major product was the open-chain precursor **205**. Acylation and chlorination followed by base-catalyzed cyclization yielded racemic chalcogran.

Enders[35] developed a general method of acetone dimethylhydrazone alkylation for preparing spiroketals which was employed for chalcogran synthesis. Alkylation of **113** with 1,2-epoxybutane followed by subsequent alkylation with ethylene oxide afforded the open-chain precursor **209** (Scheme 39). Acid-catalyzed cyclization furnished racemic chalcogran isomers. It was also found that optically active chalcogran could be synthesized by the use of chiral epoxides as alkylating agents.

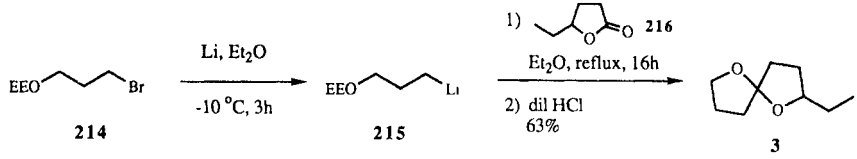


SCHEME 39. Enders synthesis of **3**.

Silverstein[55] described the first optical synthesis of chalcogran isomers the year following the structure description. Addition of THP-protected propargyl alcohol anion **210** to the readily available (+)-γ-caprolactone (**211**) yielded the intermediate **212**. Reduction of the alkyne and acid-catalyzed cyclization gave rise to two diastereomers of **3**, enantiomerically pure at C-2 (Scheme 40). Complete separation, however, could not be achieved. The addition of an alkyllithium to a lactone was used again by Smith[29a] in 1980 (Scheme 41). The desired organometallic (**215**) was formed by



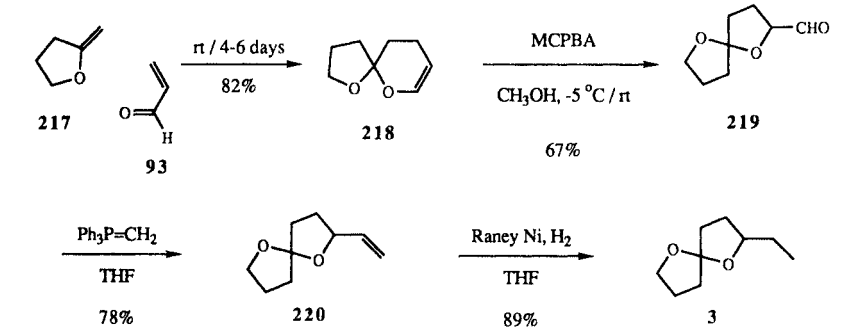
SCHEME 40. Silverstein synthesis of chalcogran.



SCHEME 41. Smith synthesis of chalcogran isomers.

halogen–lithium exchange of a protected 3-bromopropanol. Addition to the racemic lactone **216** and acid-catalyzed cyclization furnished racemic chalcogran isomers.

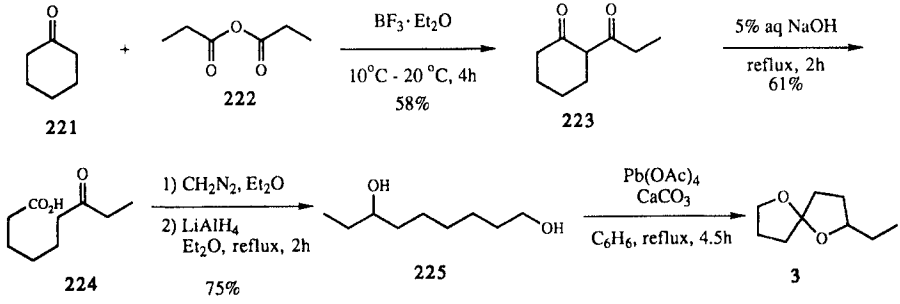
Using a hetero-Diels–Alder reaction first described by Paul and Tchelitcheff,[56] Ireland[57] formed the intermediate **218** (Scheme 42). Epoxidation gave rise to the aldehyde **219**, which was olefinated to **220**. Reduction of the newly formed alkene furnished racemic chalcogran isomers.



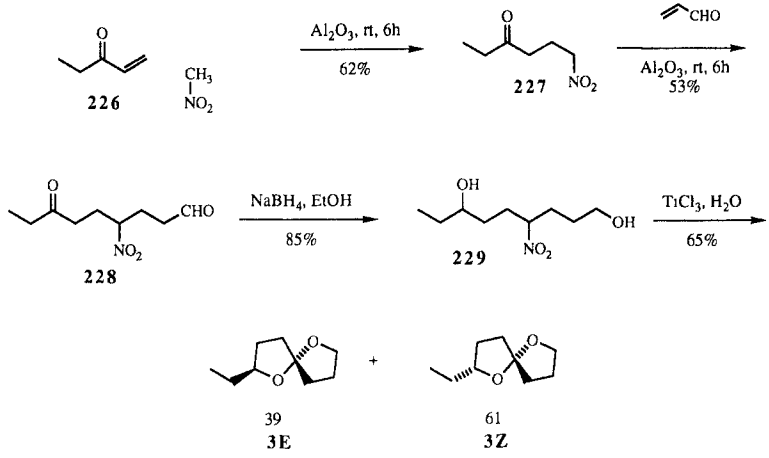
SCHEME 42. Ireland hetero Diels–Alder synthesis of chalcogran isomers.

In 1985 Cekovic[42] described a synthesis of chalcogran that was based on general methodology involving oxidative cyclization of diols (Scheme 43). Acylation of cyclohexanone with propionic anhydride gave rise to the dione **223**. Base-catalyzed ring opening and reduction furnished 1,7-nonanediol (**225**), which was subsequently oxidized with $Pb(OAc)_4$ to afford the chalcogran mixture.

A recent synthesis of chalcogran reported in 1986 by Rosini[58] employed nitromethane as a carbonyl dianion synthon. Conjugate addition of nitromethane to 1-penten-3-one **226** in the presence of alumina afforded **227**. Conjugate addition of **227** to acrolein furnished the ketoaldehyde **228**. Reduction to the diol was followed by Nef-type reaction with concomitant spiroketalization yielded a mixture of both sets of chalcogran diastereomers (Scheme 44).



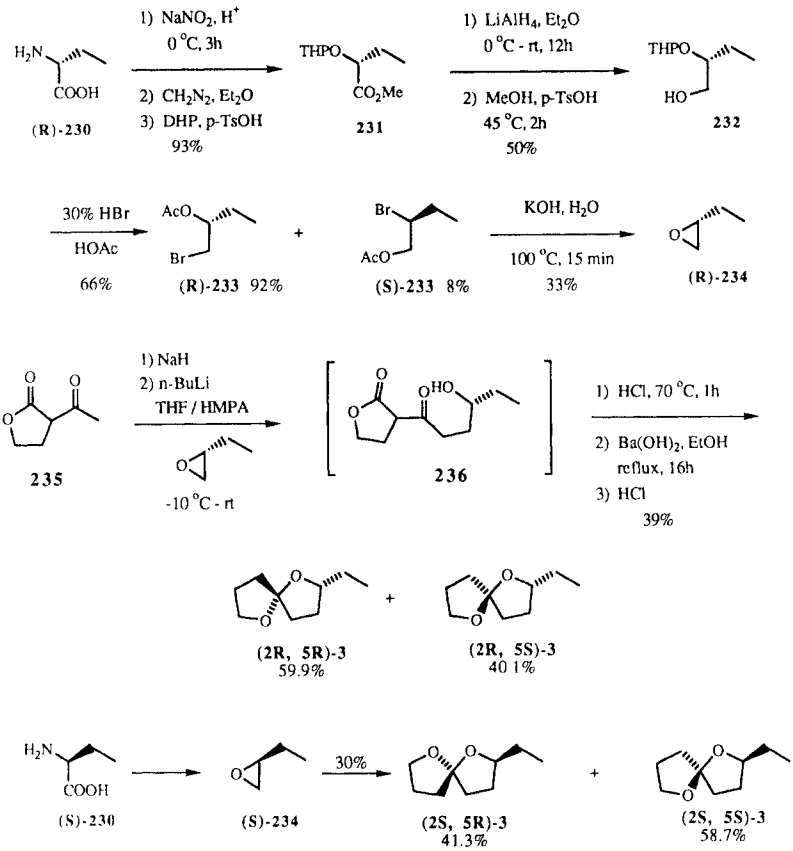
SCHEME 43. Cekovic free-radical cyclization of diols



SCHEME 44. Rosini synthesis of chalcogran isomers.

Mori has used a β-ketoester dianion alkylation approach extensively in spiroketal synthesis. His approach to chalcogran[59] (Scheme 45) involved preparing *R*-1,2-epoxybutane **234** from the optically active amino acid **230**. This epoxide was used to alkylate the achiral β-ketolactone **235**. Decarboxylation and acid promoted cyclization furnished (**2R**, **5R**)-**3** and (**2R**, **5S**)-**3** as a 60:40 mixture of diastereomers. Similarly, L-(+)-α-amino-butyric acid (**S**)-**230** provided a mixture of (**2S**, **5R**)-**3** and (**2S**, **5S**)-**3** as a 60:40 mixture of diastereomers using the same method.

Using a chiral reducing agent to reduce an yne-one, Utimoto[60] created the chalcogran diastereomers (Scheme 46). The internal alkyne was then translocated to a terminal alkyne and deprotonated. Alkylation with ethylene

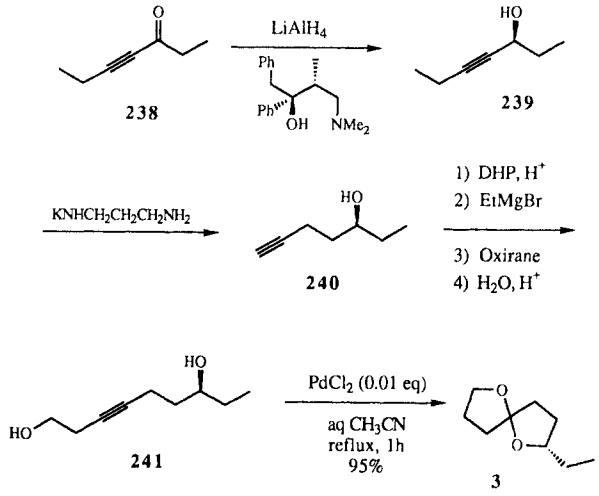


SCHEME 45. Mori chalcogran synthesis.

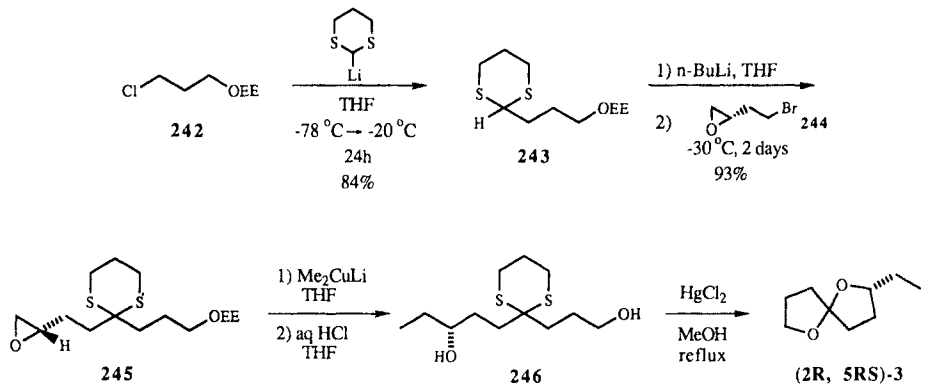
oxide afforded the diol **241**. Treatment of this diol with catalytic palladium(II)chloride furnished the chalcogran mixture.

Seebach and Redlich both used dithiane alkylation to synthesize optically active chalcogran. Seebach[25] formed the dithiane **243** by chloride displacement on **242** (Scheme 47). Deprotonation of **243** and alkylation with the chirally pure bromide **244** led to **245**. Opening of the epoxide with lithium dimethylcuprate and removal of the ethoxyethyl group generated the open-chain dithiane **246**. Deprotection and cyclization yielded 2R-chalcogran as a 3:2 mixture of isomers at the spiro center.

Using the converse approach, Francke and Redlich[61] created an optically active dithiane derivative and coupled it to an achiral bromide (Scheme 48). The chiral carbon at C-2 originated from D-glucose, which was transformed



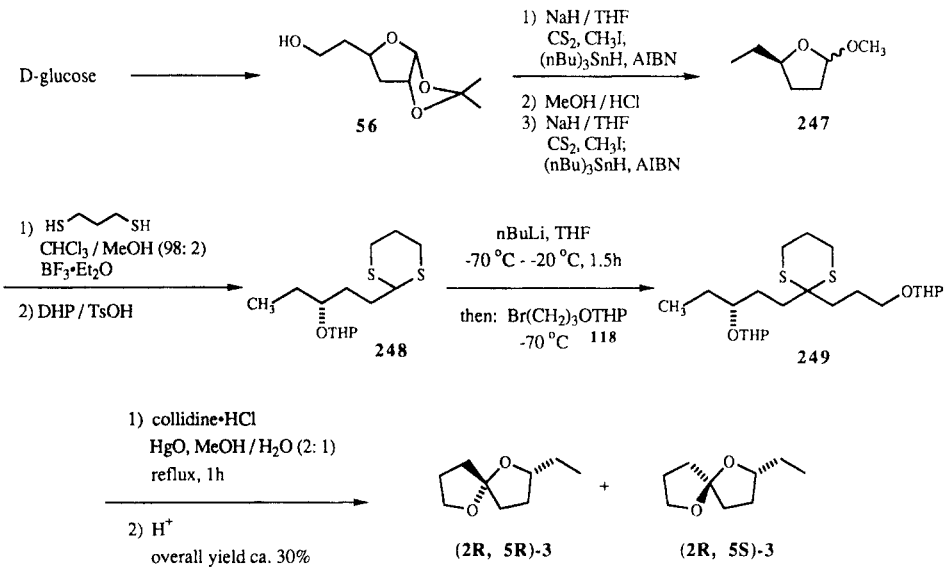
SCHEME 46. Utimoto Pd-based chalcogran synthesis.



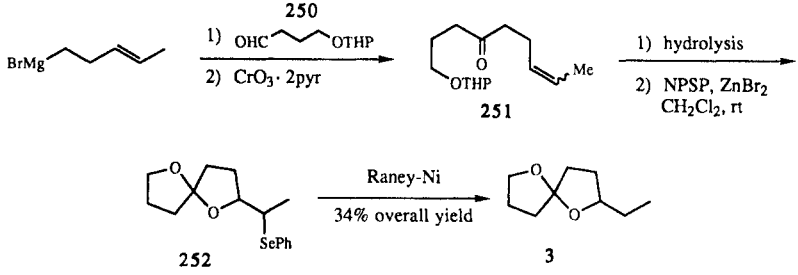
SCHEME 47. Seebach dithiane-based synthesis of chalcogran.

to **56** by known carbohydrate chemistry. The two excess hydroxyls were removed by radical cleavage of the corresponding xanthates. The resulting cyclic acetal **247** was doubly blocked and the newly formed dithiane **248** was lithiated and alkylated with bromide **118**. Deprotection and acid-catalyzed cyclization afforded the usual mixture of (2*R*, 5*R*) and (2*R*, 5*S*) chalcogran.

In 1984, Ley[9b] described one in a series of general approaches to the synthesis of spiroketals. This approach utilized cation–olefin cyclization initiated by $PhSe^+$. Addition of 3-pentenylmagnesium bromide to the aldehyde **250** afforded the enone intermediate **251**. Hydrolysis of the THP and



SCHEME 48. Francke–Redlich dithiane-based synthesis of chalcogran.

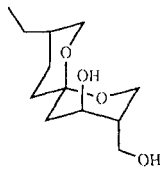


SCHEME 49. Ley synthesis of chalcogran isomers.

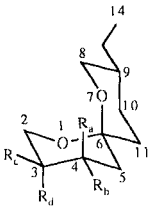
treatment with *N*-phenylselenophthalamide (NPSP) furnished the cyclized product **252** (Scheme 49). Removal of the phenyl selenide with Raney nickel yielded chalcogran isomers.

3. TALAROMYCINS

Talaromycins A and B (Scheme 50) were isolated from the toxicogenic fungus *Talaromyces stipitatus* found in chicken litter in 1982 by Lynn and co-workers.[62] This was followed by the isolation of the structurally similar



257 talaromycin D



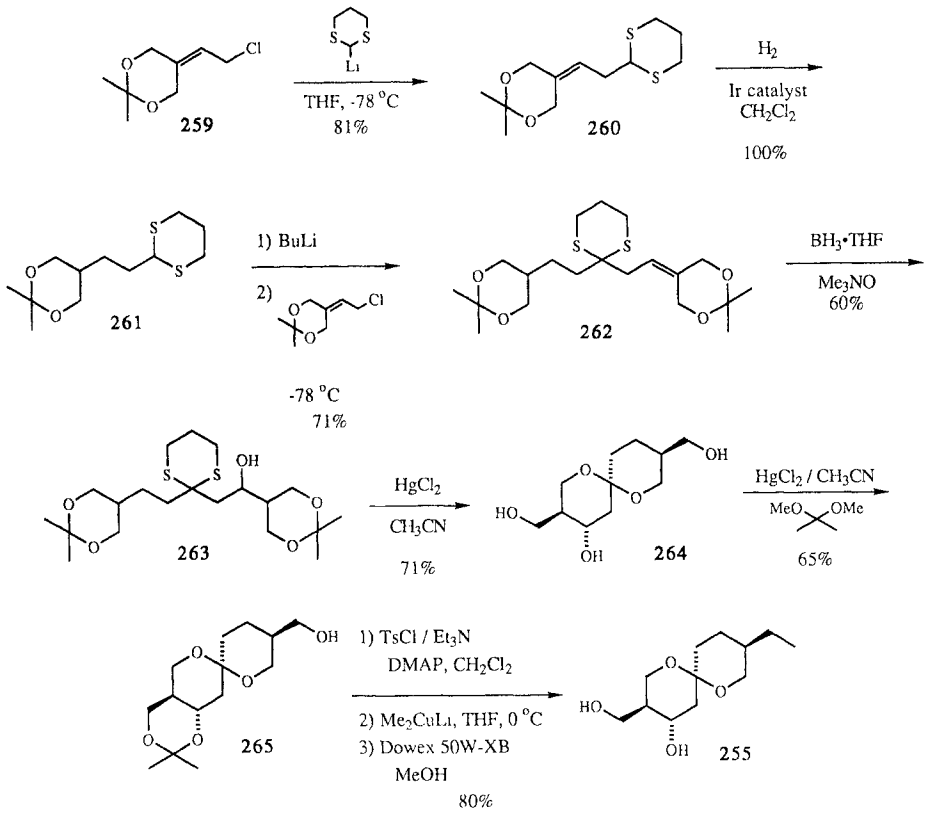
talaromycin		R_a	R_b	R_c	R_d
A	**254**	H	OH	H	CH_2OH
B	**255**	H	OH	CH_2OH	H
C	**256**	OH	H	H	CH_2OH
E	**258**	OH	H	CH_2OH	H

SCHEME 50. Talaromycins structure.

minor metabolites talaromycins C, D, E, and F in 1987.[63] At present, the only reported syntheses concern the major metabolites talaromycins A and B, although other talaromycins were produced before they were described from the natural source. Talaromycin B is the more thermodynamically stable of the two major metabolites, attributable to the all equatorial arrangement of the C-9 ethyl, C-4 hydroxyl and C-3 hydroxymethyl groups. Not surprisingly, racemic syntheses of talaromycin B appeared first in early literature in this area.

In 1983, the first synthesis of racemic talaromycin B appeared (Scheme 51).[64] Schreiber and many other workers took advantage of the symmetry elements present in **255** in planning strategies and designing intermediates. The key steps of the Schreiber synthesis included dithiane alkylation with the protected allylic chloride **259**, reduction of the olefin, and a second alkylation with **259** giving **262**. Hydroboration–oxidation of the olefin followed by deprotection and thermodynamic cyclization afforded the spiroketal triol **264**. Methyl cuprate displacement of the unprotected primary alcohol **265** via its tosylate gave rise to racemic talaromycin B in approximately 13% overall yield for the nine steps from the chloride **259**. A similar approach was subsequently used in the synthesis of talaromycin A by this group, which will be described later.

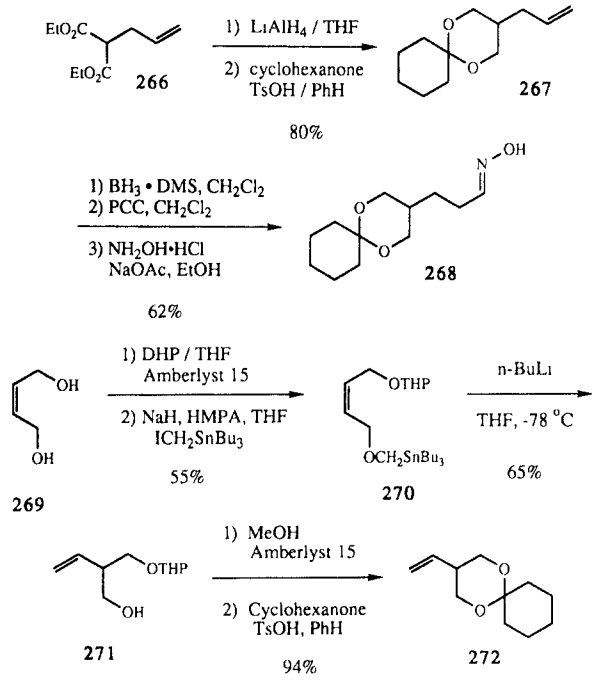
In 1984, Kozikowski[65] described a synthesis based on the coupling of two protected diols via nitrile–oxide cycloaddition. The cycloaddition partners **268** and **272** were prepared *via* straightforward chemistry shown without comment in Scheme 52. Cycloaddition and cleavage of the N–O bond (Scheme 53) gave rise to an open-chain protected intermediate **274**. The synthesis from this point was a variation of that in Scheme 51. Deprotection and acid-catalyzed spiroketalization yielded the basic talaromycin skeleton. Cuprate displacement of the primary alcohol as its mesylate afforded racemic talaromycin B in 13 steps with an overall yield of about 12%.



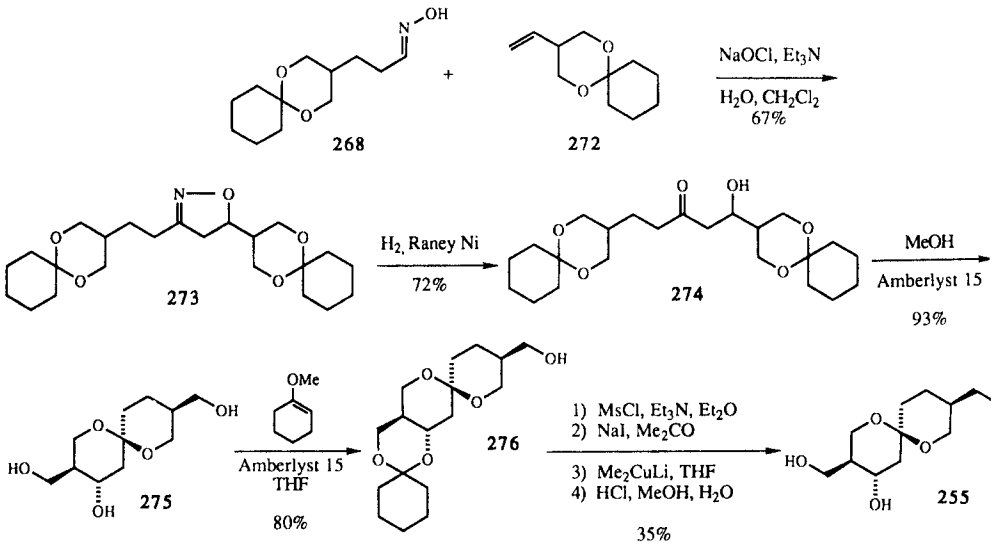
SCHEME 51. Schreiber synthesis of racemic talaromycin B.

Kay[66] prepared racemic talaromycin B by a synthesis that initially involved cation–olefination cyclization to form one ring with the correct stereocenters at C-3 and C-4 (Scheme 54). Radical spirocyclization of **282** using mercuric oxide and iodine provided the isomers **283** and **284** in a 1:3 ratio. This method was later utilized by Danishefsky in the synthesis of the avermectin A_{1a} spiroketal. The route provided no stereocontrol at ethyl-bearing C-9 and afforded a mixture of diastereomers which were separated. Deprotection of the desired diastereomer **284** yielded talaromycin B (**255**). Acid deprotection of the other diastereomer (**283**) gave rise to a mixture of talaromycin D (**257**) and 2 diastereomers **285** and **286**.

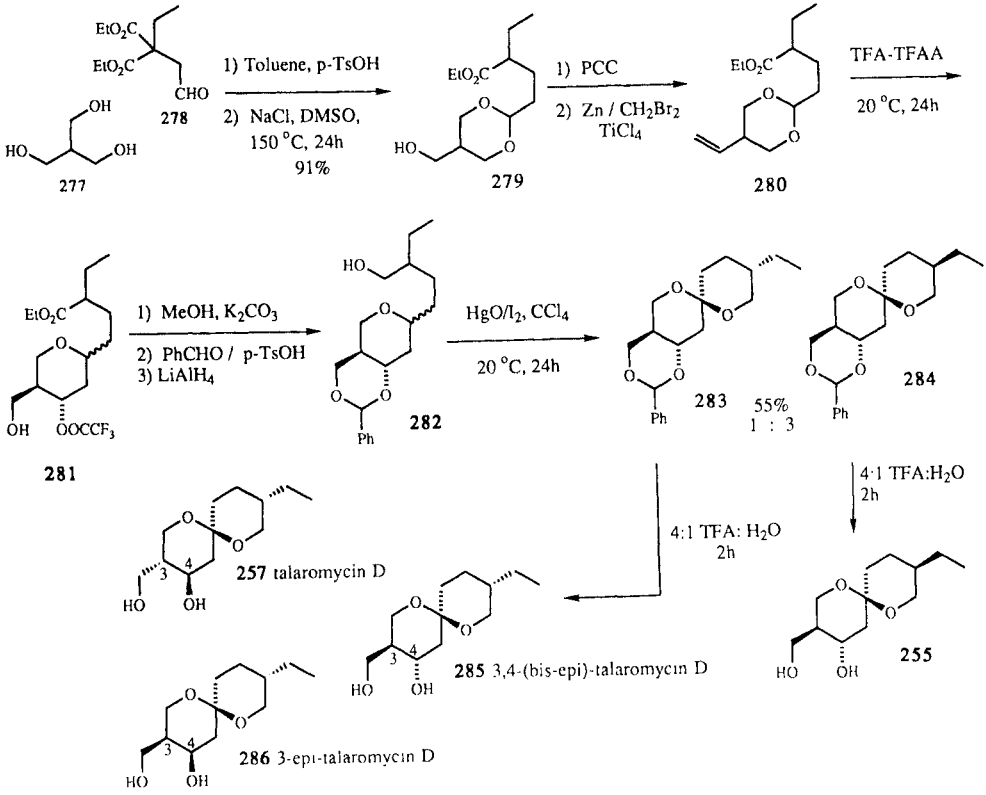
Kocienski[67] reported a synthesis of racemic talaromycin B using a metallated vinyl ether intermediate (Scheme 55). The racemic epoxide **289** was produced via standard chemistry from the selenide **287**. This epoxide was



SCHEME 52. Synthesis of talaromycin B precursors (Kozikowski).



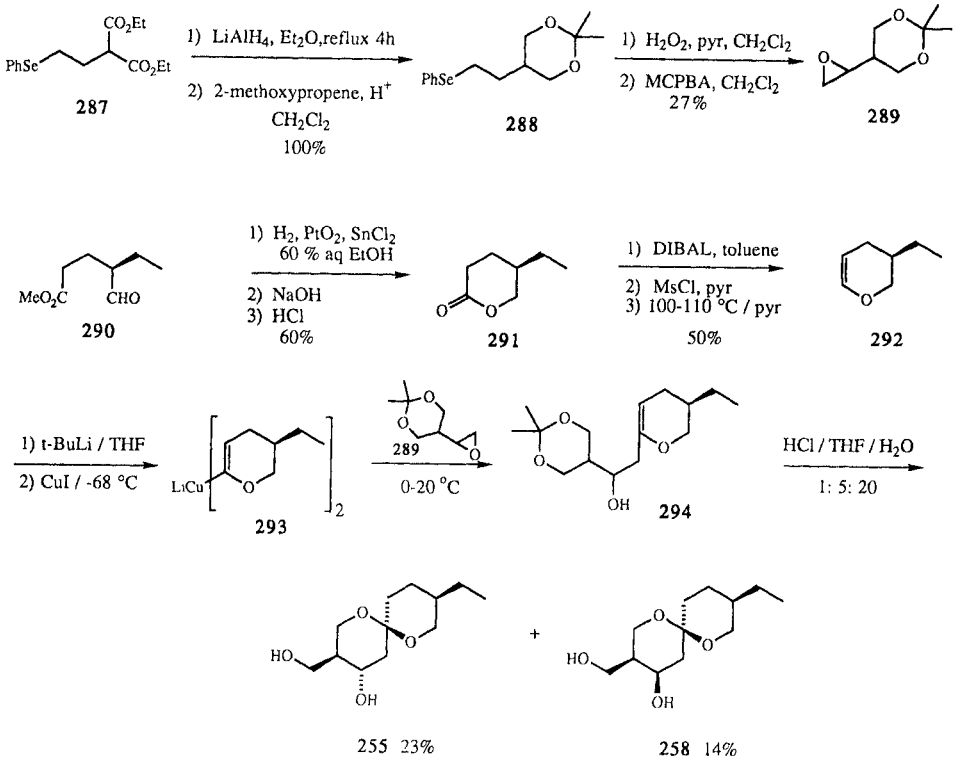
SCHEME 53. Nitrile–oxide cycloaddition approach to talaromycin B (Kozikowski).



SCHEME 54. Kay synthesis of talaromycin B.

then opened by the optically active cuprate **293** that had been prepared from the known aldehyde **290**. The resulting product was a diastereomeric mixture which was subjected to acid-catalyzed spiroketalization to afford a mixture of talaromycin B (**255**) and E (**258**). The overall yield of talaromycins was about 3% for the 12 steps.

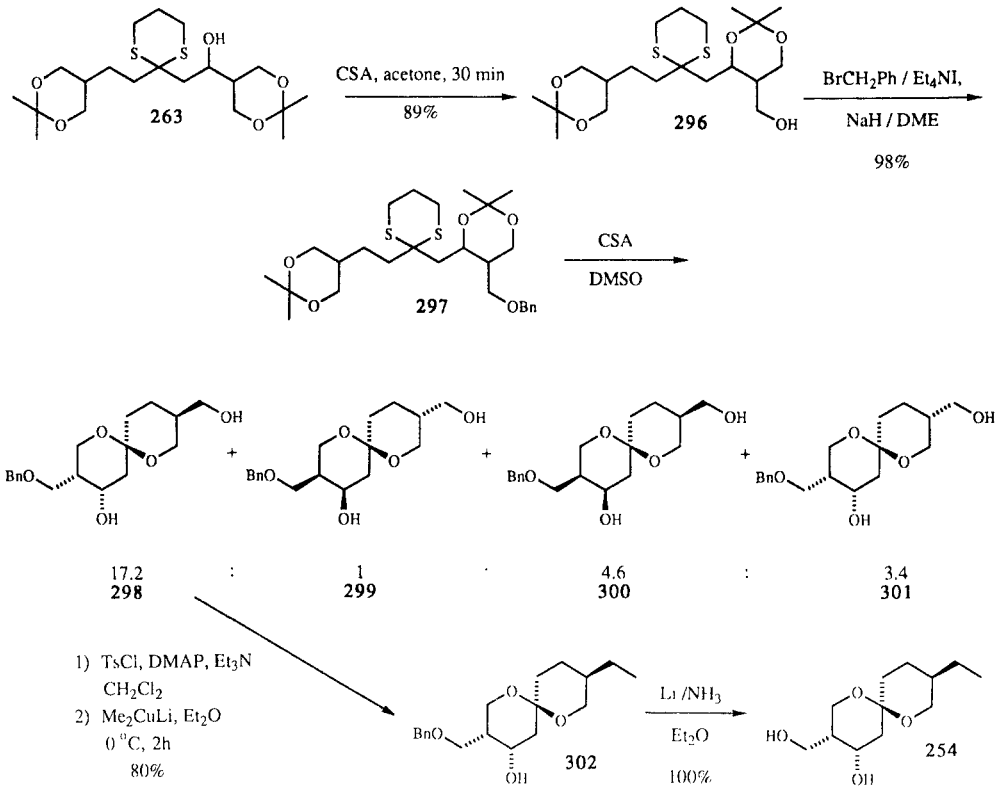
Schreiber also reported the only racemic synthesis of talaromycin A.[68] This synthesis utilized the same intermediate (**263**) as in their talaromycin B synthesis that was prepared by dithiane alkylation (see Scheme 51). Regioisomerization of the acetonide **263** provided **296**. Benzylation of the secondary alcohol gave the cyclization substrate **297**. A variety of cyclization conditions were then examined with the best results realized by the use of camphorsulfonic acid in DMSO. This yielded about a 2:1 ratio of the desired cyclization product **298** to other isomers. The primary alcohol of **298** was



SCHEME 55. Kocienski synthesis of talaromycins B and E.

then tosylated and displaced by methyl cuprate, and the product deprotected to afford racemic talaromycin A in a 38% overall yield from **263** (Scheme 56).

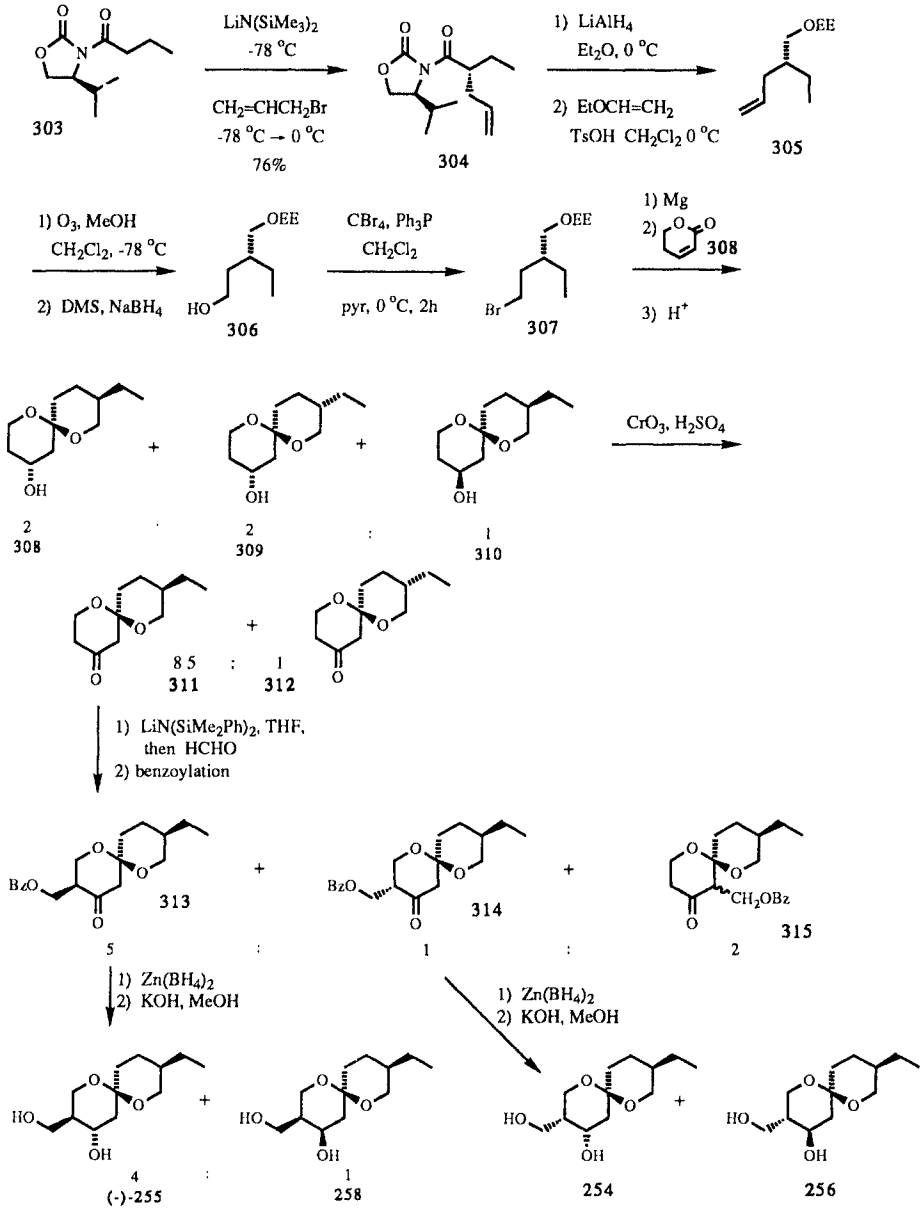
The Smith group reported the first enantioselective syntheses of talaromycins A and B in 1984.[69] Their synthetic pathway used a chiral auxiliary to induce the proper stereochemistry at C-9 (**304**). This optically active piece was then transformed in a 40% overall yield into the Grignard reagent of **307** and added to the unsaturated lactone **308**. Hydrolysis of the addition product gave a mixture of three cyclized alcohols **308–310** in a 2:2:1 ratio. Oxidation of the alcohols gave a 8.5:1 mixture of the corresponding ketones, which were then separated. The major ketone (**311**) was deprotonated and treated with formaldehyde to afford a 60% yield of a product mixture containing 75% of a 5:1 mixture of the desired alkylation products and 25% of the product (**315**) with incorrect regiochemistry. The respective ketones were then reduced and deprotected to afford (−)-talaromycin A (**254**) and (−)-talaromycin B (**255**).



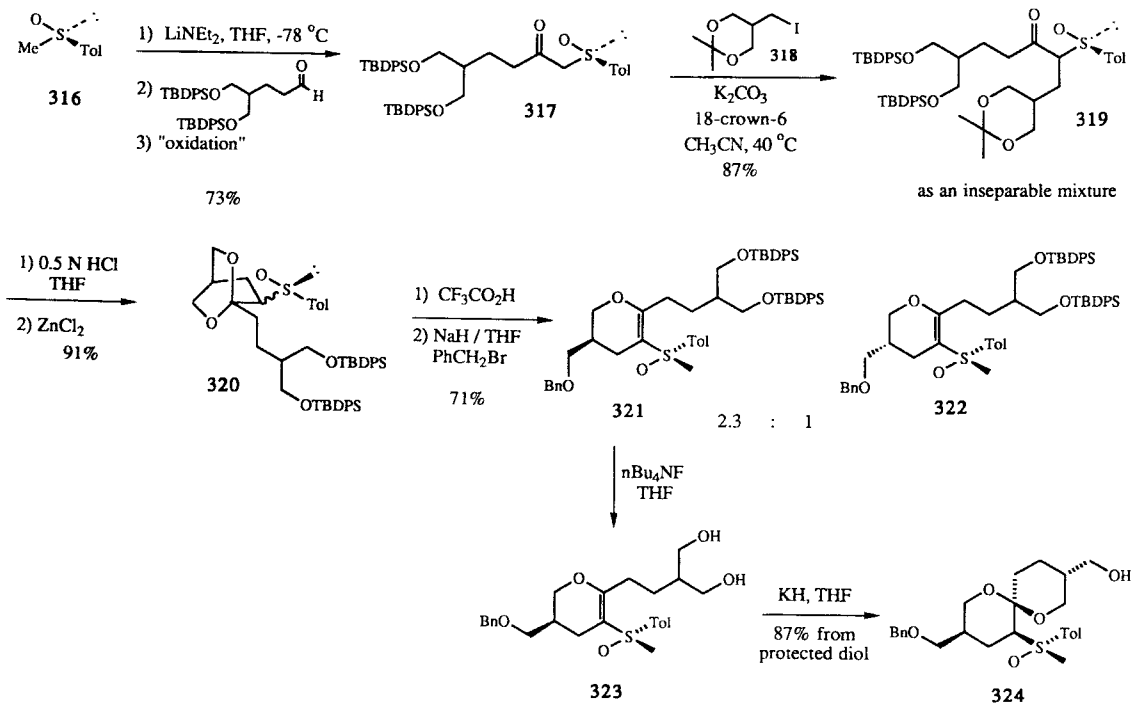
SCHEME 56. Synthesis of racemic talaromycin A (Schreiber).

The minor isomers of the reductions were talaromycins E (**258**) and C (**256**) which had not been isolated at that point (Scheme 57).

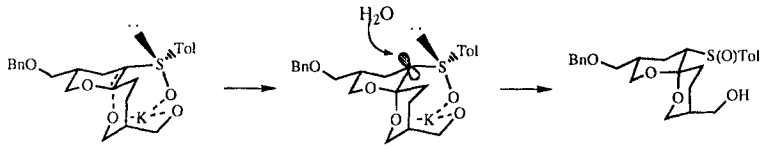
Iwata[70] reported enantioselective syntheses of (+)-talromycin A and (−)-talaromycin B using a divergent route employing a chiral sulfinyl group. Sequential alkylation of the chiral sulfoxide **316** (Scheme 58) furnished the fully protected intermediate **319**. Deprotection of **319** and Lewis acid-catalyzed cyclization afforded the bicyclic ketal **320**. Treatment with acid and benzylation of the resulting alcohol gave rise to the chiral sulfinyl precursor **321** as a 2.3:1 mixture of diastereomers. Fluoride deprotection of the silyl protecting groups led from **321** → **323**. Treatment with KH resulted in conjugate addition proving spiroketal **324**. This transformation was stereospecific and was rationalized by chelation-assisted addition of the alkoxide to the α,β-unsaturated sulfoxide via transition state **325**. Stereospecific protonation of the resultant intermediate was also rationalized with a chelated



SCHEME 57. Smith synthesis of (−)-talaromycin B.



SCHEME 58. Iwata convergent synthesis of talaromycins A and B.

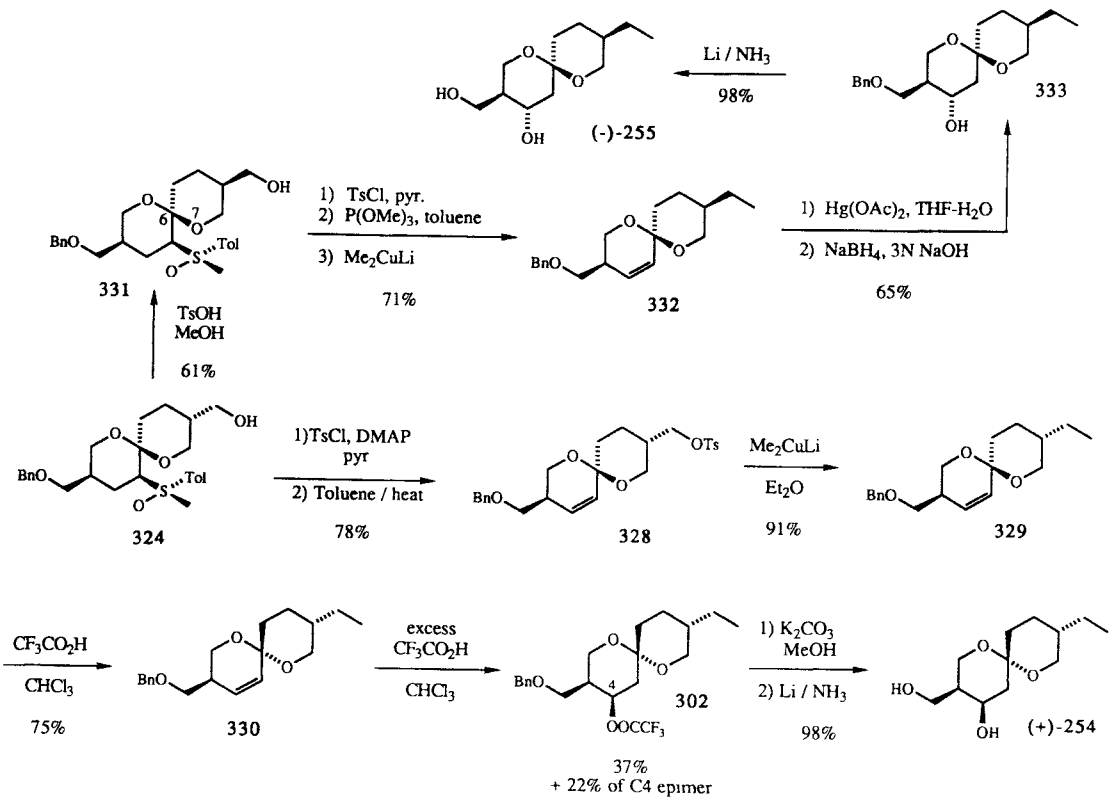


transition state (**326**) providing the observed product **324** containing an axial hydroxymethyl group at C-3.

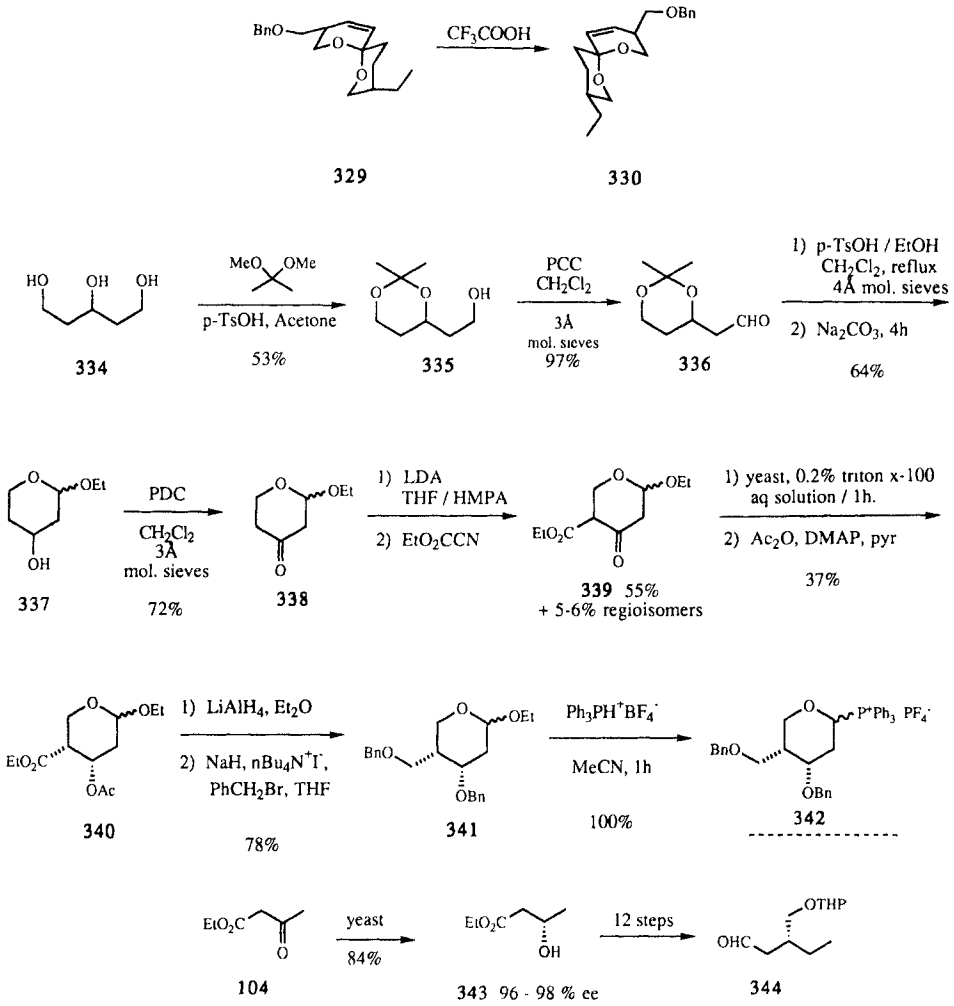
Compound **324** served as a branchpoint intermediate. At this point the route diverged (Scheme 59). Tosylation of the primary alcohol and methyl cuprate displacement of the tosylate was used to introduce the ethyl group in **329**. Treatment with catalytic trifluoroacetic acid caused spiroepimerization to **330**. Inversion of the spirocenter (**329** → **330**) can provide a spiroketal in a conformation in which the ethyl group has attained an equatorial configuration in exchange for a pseudoaxial disposition for the benzyloxymethyl group. Note that anomeric effects have not been compromised and that this constitutes a further example of the importance of the anomeric effect in spiroketal structure. Treatment of **330** with excess trifluoroacetic acid regiospecifically provided the trifluoroacetate **302** as a mixture of C-4 epimers. The regioselectivity of electrophilic addition to olefins in this position of a [5.5] spiroketal has been noted many times (see later) and is thought to be due to better positive charge stabilization at the carbon farthest away from the inductively electron withdrawing C–O bonds. The major isomer **302** was converted to (+)-**254**.

Alternatively, the branchpoint intermediate **324** can be isomerized by ionization (TsOH) of the C-6–O-7 bond and reclosure of the resulting oxenium ion onto the diastereomeric hydroxyl. This can also be accounted for on the basis of anomeric stabilization balanced with equatorial placement of substituents because the only change is switching from an axial hydroxymethyl to one which is equatorial. Tosylation, sulfoxide elimination, and methyl cuprate displacement afforded the intermediate **332**. Stereoselective oxymercuration of the olefin and removal of the benzyl group yielded (−)-**255**.

Enantioselective syntheses of (−)-talaromycin A and (−)-talaromycin B were also accomplished by Mori and co-workers[71] using a Wittig approach in which two optically enriched coupling partners were produced via microbial reduction. The triol **334** was converted to ketone **338** via standard operations (Scheme 60). Compound **339** was subjected to microbial reduction and acetylation to yield the enantiomerically pure intermediate **340**. Formation of the desired Wittig partner was completed by treatment of **341** with triphenylphosphonium tetrafluoroborate yielding the phosphonium salt **342**.

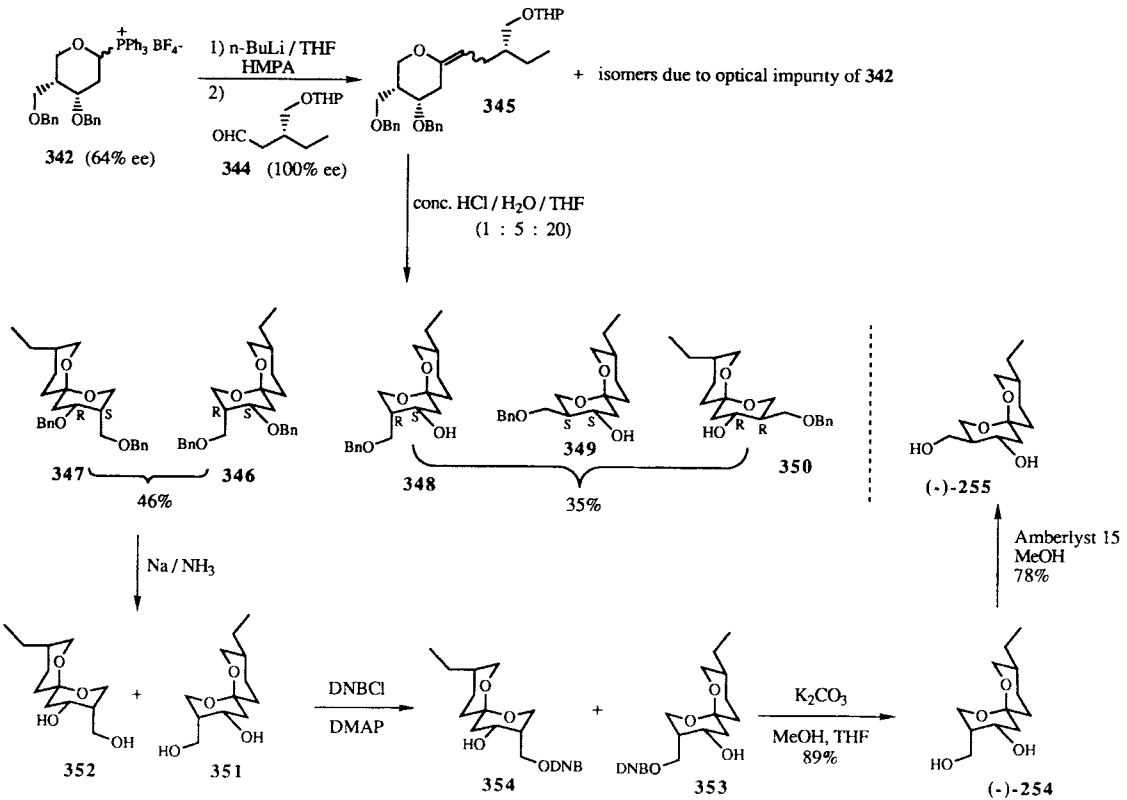


SCHEME 59. Divergence of intermediate **324** to talaromycins A and B (Iwata).

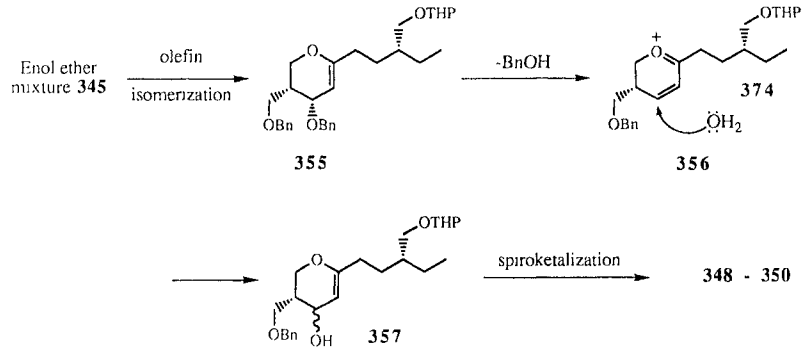


SCHEME 60. Synthesis of optically pure Wittig reaction partners (Mori).

The aldehyde component **344** was produced in a 13-step process from ethyl acetoacetate, also involving microbial reduction. Wittig reaction of **342** with **344** (Scheme 61) gave a mixture of olefin isomers **345**. Acid-catalyzed spiroketalization, however, was complicated by the optical impurity of **342** and also by a C-4 epimerization process leading to the five products **346–350**. It was postulated that the monobenzylated compounds arose via ionization of the benzyloxy group to the cation **356** which suffered nonspecific addition

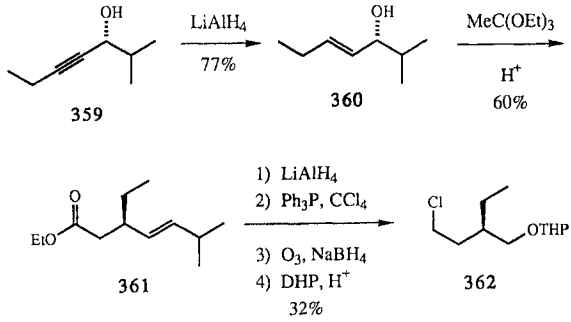


SCHEME 61. Coupling of Wittig partners leading to talaromycins (Mori).

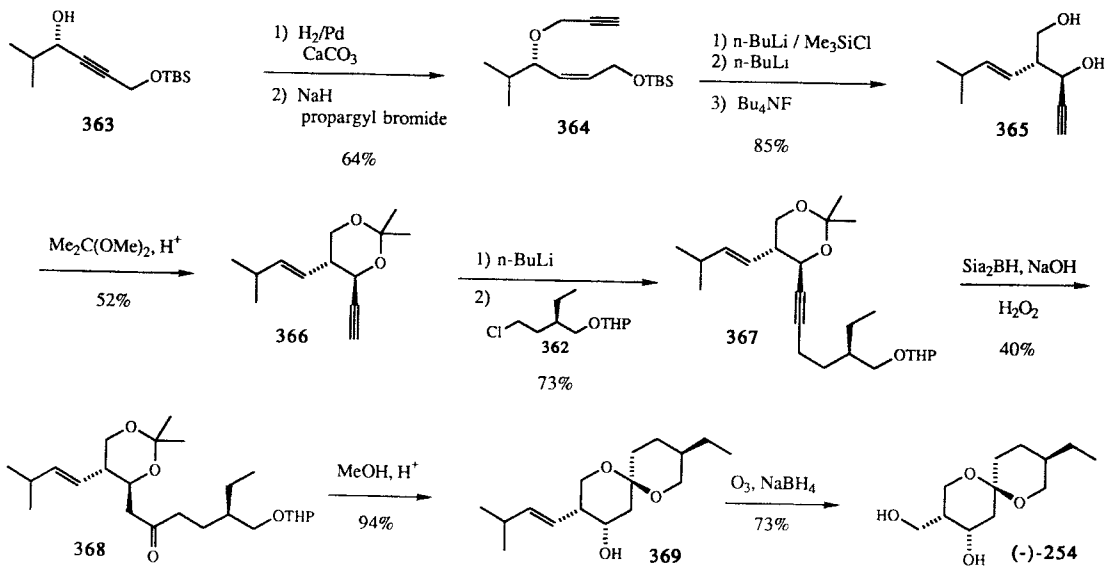


of water to provide the monobenzylated products **348–350**. The mixture of dibenzyl ethers (**346–347**) was separated and deprotected. Purification was achieved by transformation to the primary dinitrobenzoate and recrystallization. The DNB ester **353** was then hydrolyzed to yield enantiomerically pure (−)-talaromycin A. Treatment of this with Amberlyst-15 isomerized **254** to enantiomerically pure (−)-talaromycin B (**255**).

Another synthesis of (−)-talaromycin A was reported by Midland.[72] The approach involved the coupling of an alkyne with an alkyl chloride, both of which were stereogenically pure. The chloride **362** was made from the propargylic alcohol **359** in 6 steps (Scheme 62). Hydrogenation of **363** to the *cis* alkene and *O*-alkylation with propargyl bromide furnished **364**. Alkyne silylation followed by [2,3] sigmatropic rearrangement proceeded with chirality transfer to give diol **365**. Further down the line, alkyne **366** was joined to **362**, providing **367**. In a key transformation, hydroboration–oxidation of the unsymmetrical alkyne **367** proceeded to ketone **368**, which was spirocyclized to **369**. Ozonolysis of **369** with a reductive workup furnished (−)-talaromycin A (Scheme 63).

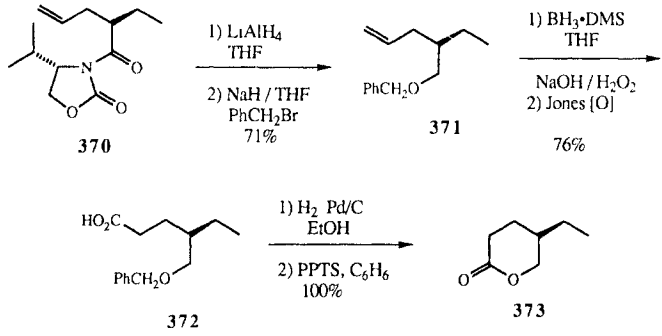


SCHEME 62. Synthesis of chloride **362** (Midland).



SCHEME 63. Midland synthesis of (−)-talaromycin A.

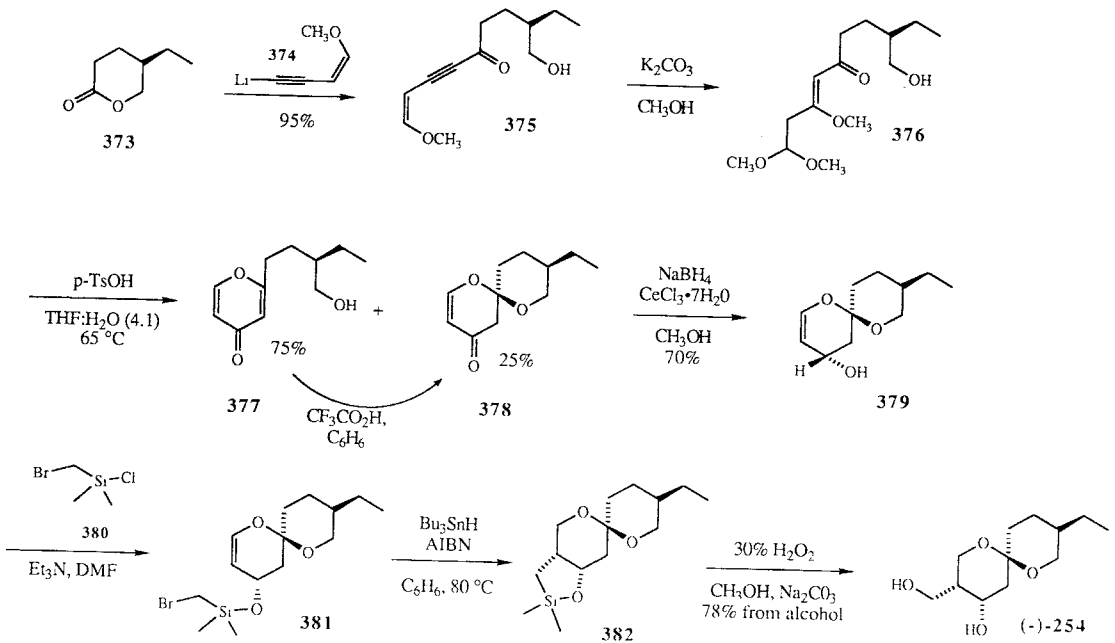
The most recent synthesis of (−)-talaromycin A was described in 1988 by Crimmins.[73] Using the Evans chiral auxiliary, the optically active lactone **373** was produced in six steps (see Scheme 64). Using general technology developed in this group for spiroketal synthesis,[74] the lithiated enyne **374** was added to the lactone producing **375** (Scheme 65). Base-catalyzed methanolysis followed by acid-catalyzed cyclization afforded the spiroketal **378** and dihydropyrone **377**. Trifluoroacetic acid treatment cyclized **377** → **378**. Luche reduction of **378** afforded a 2.4:1 mixture of alcohols. The minor isomer could be recycled to the desired isomer (**379**) by reoxidation. To establish the *cis*-relationship between the C-3 hydroxymethyl and the C-4 hydroxyl, the alcohol **379** was silylated with **380**. Radical cyclization gave the *cis*-fused siloxacyclopentane **382** which upon treatment with H_2O_2 yielded (−)-talaromycin A.



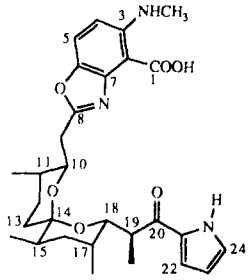
SCHEME 64. Synthesis of lactone **373** (Crimmins).

4. CALCIMYCIN (A-23187)

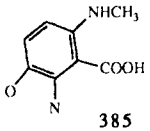
The divalent cation ionophore calcimycin (also known as A-23187) was isolated from *Streptomyces chartreusensis* in 1974 by Chaney and co-workers.[75] An X-ray crystallographic study revealed the molecule to have the solid-state structure shown in **22**, possessing full anomeric stabilization. The ability of calcimycin to selectively complex and transport divalent over monovalent cations has attracted much interest in its chemistry and biology.[76] Six complete or nearly complete syntheses have been reported for this substance. The first synthesis, by Evans, described a simple solution to the problem of stereocontrol of the methyl group at C-15, which was described earlier in the section on spiroketal conformation. Some of the subsequent syntheses used this simplification, while others opted for rigorous stereocontrol. A common strategy for construction of **22** was the assembly of a



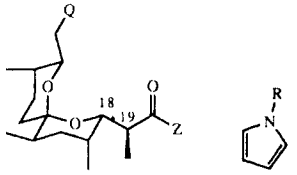
SCHEME 65. Crimmins synthesis of (−)-talaromycin A.



22 Calcimycin (A23187)



385

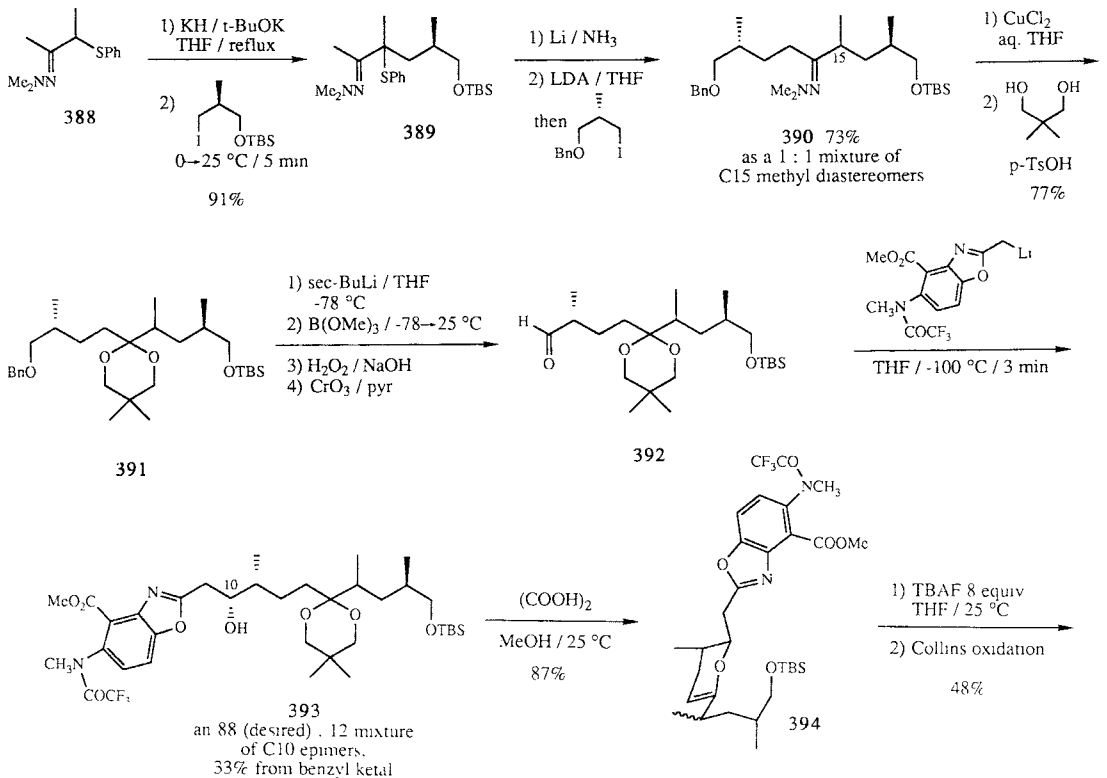


386 **387**

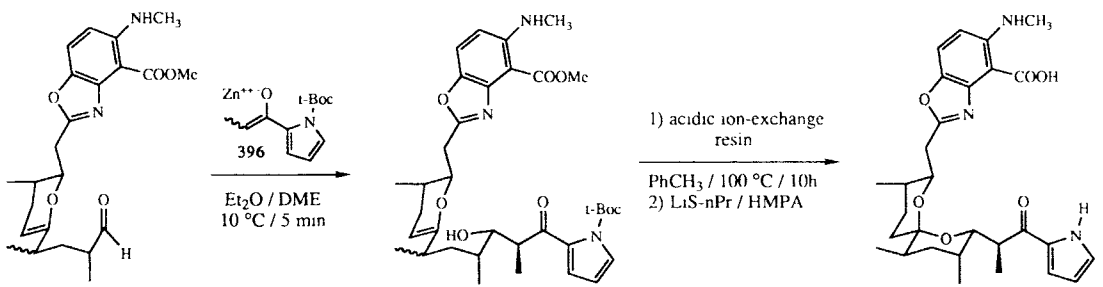
SCHEME 67. Common strategy for calcimycin synthesis.

spiroketal (or an open-chain derivative) which was then coupled sequentially to a pyrrole fragment, usually as an anion, and a benzoxazole fragment as shown in Scheme 67. One approach utilized an aldol condensation to form the C-18–C-19 bond while adding the pyrrole fragment. Finally, only one approach spirocyclized a fully functionalized acyclic precursor to **22**.

The Evans approach had been carefully modelled[41] and stands as a pioneering work in spiroketal synthesis (Scheme 68).[15] The dimethylhydrazone **388** was used as a rivetting agent to sequentially connect an optically active iodide at both ends. Compound **390** was obtained as a set of C-15 diastereomers. This intermediate was manipulated to **392**, whereupon the benzoxazole unit was coupled via an anionic process leading to **393**. Compound **393** was partially cyclized to the dihydropyran **394**. Functional group manipulation led to **395**, which was then aldol condensed with **396** giving rise to the diastereomers **397**. In the key transformation, **397** was treated with an



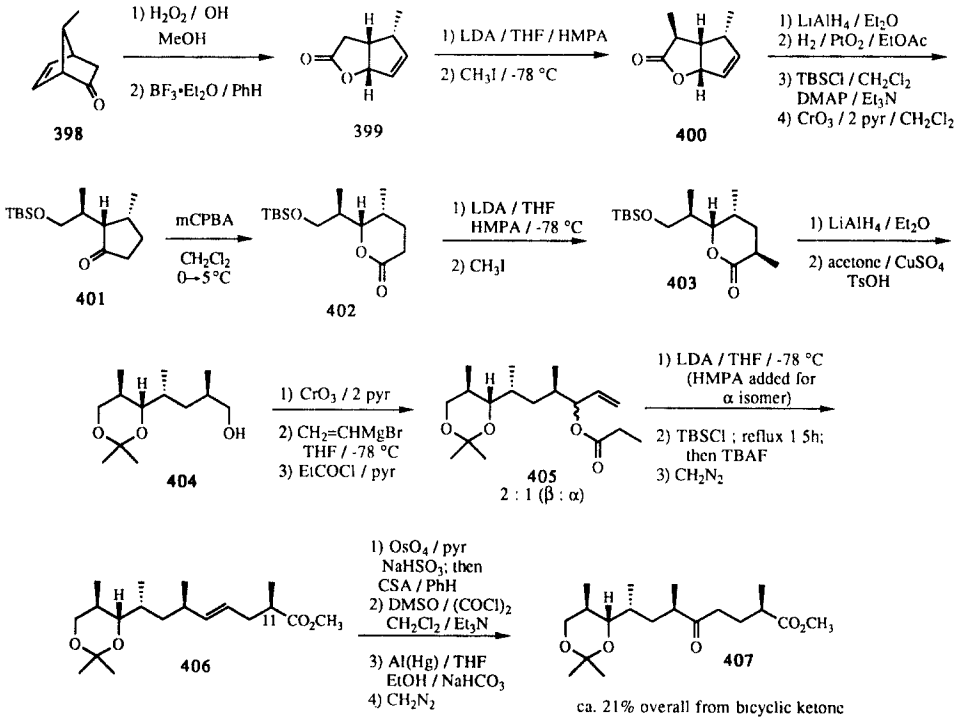
SCHEME 68. Evans calcimycin synthesis.



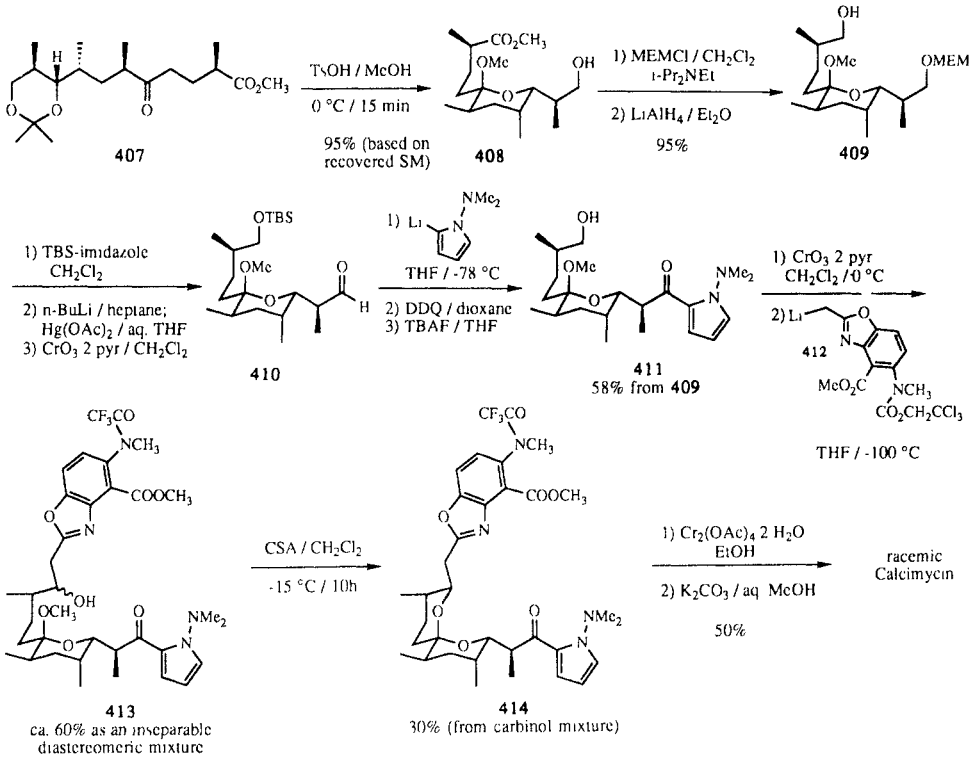
SCHEME 68. Evans calcimycin synthesis (*continued*).

acidic ion-exchange resin at 100°C which caused spiroketalization, equilibration of the C-15 methyl group to an equatorial orientation, and removal of the *t*-BOC protecting group from the pyrrole nitrogen. Demethylation led to (−)-calcimycin. Although the overall yield was < 1%, the approach was only 15 steps and established the absolute configuration of **22**.

The next synthesis was reported in 1982 by Grieco and embodies a conceptually different approach to the problem (Scheme 69).[77] A linear sequence was used to assemble an acyclic precursor in which the relative stereochemistry of the six nonspiro asymmetric carbons was rigorously established prior to final closure of the spiroketal. Equilibration was not utilized to establish the stereochemistry of the methyl group at C-15. Bicyclic ketone **398** was converted by a standard series of manipulations to a 2:1 mixture of the allylic propionate esters **405**. This substance contains three methyl groups at asymmetric carbons, two of which were created by methylation of enolate anions, with the third being present in the original "starting material" **398**. It was found that each of the isomers of **405** could be converted

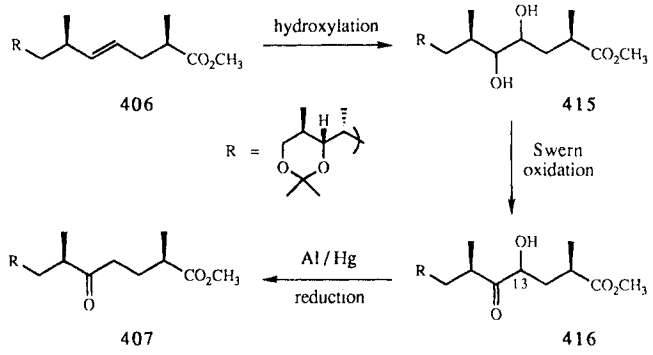


SCHEME 69. Grieco synthesis of **22**.



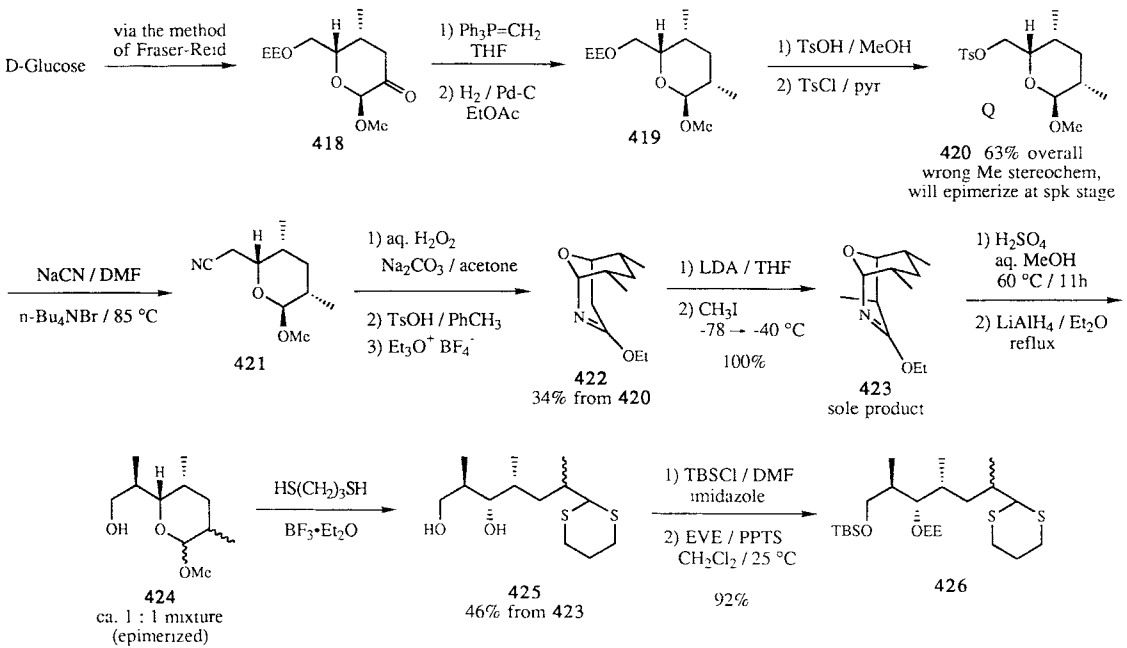
SCHEME 69. Grieco calcimycin synthesis (*continued*).

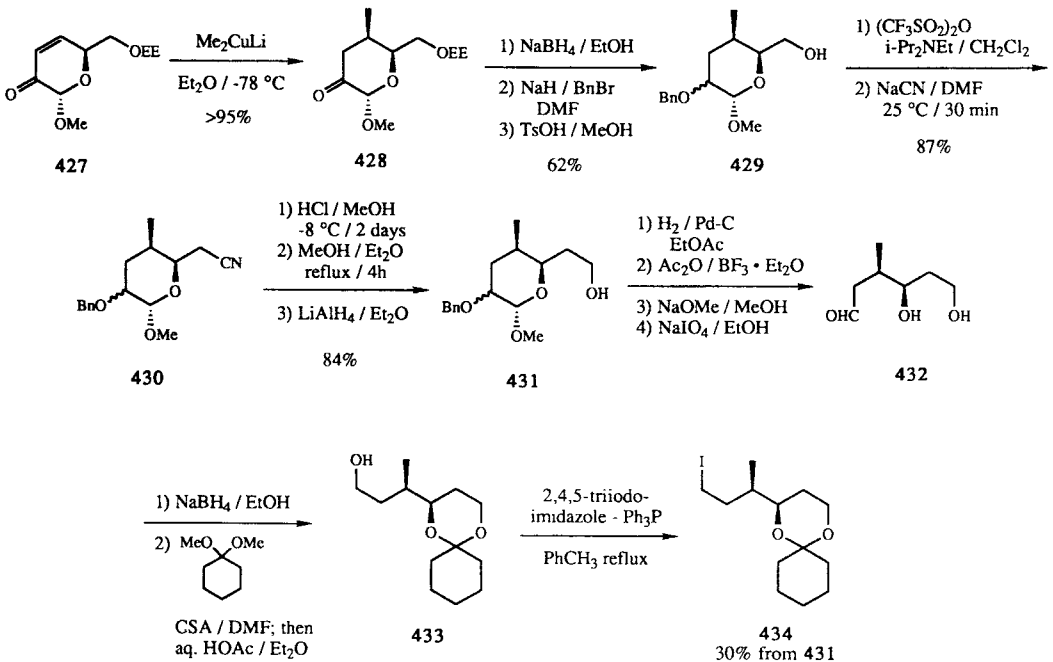
to **406** by controlling the geometry of the ester enolate intermediate in the Ireland–Claisen rearrangement process. In this manner, 1,5-asymmetric induction in a relative sense fixed the stereochemistry of the methyl group at C-11 providing **406**. OsO_4 oxidation of the olefin to the diol followed by Swern oxidation and reduction with aluminum amalgam provided the ketone **407**. Presumably, the intermediate diol **415** was regiospecifically oxidized by the Swern reagent to the α-hydroxyketone **416**, which was then reduced at C-13, providing the observed product **407**. At this point a standard nine-step sequence was used to attach the terminal pyrrole ring eventually leading to ketone **411**. Addition of the anion **412** to **411** resulted in an inseparable diastereomeric mixture of alcohols **413**, which was carried on to the spiroketal **414** in 30% yield. Deprotection of the nitrogens and saponification of the methyl ester provided racemic calcimycin. Starting from the bicylic ketone **398**, the synthesis required > 30 steps, of which 8–9 steps involved protection and deprotection of functionality. The overall yield was approximately 1–2%.



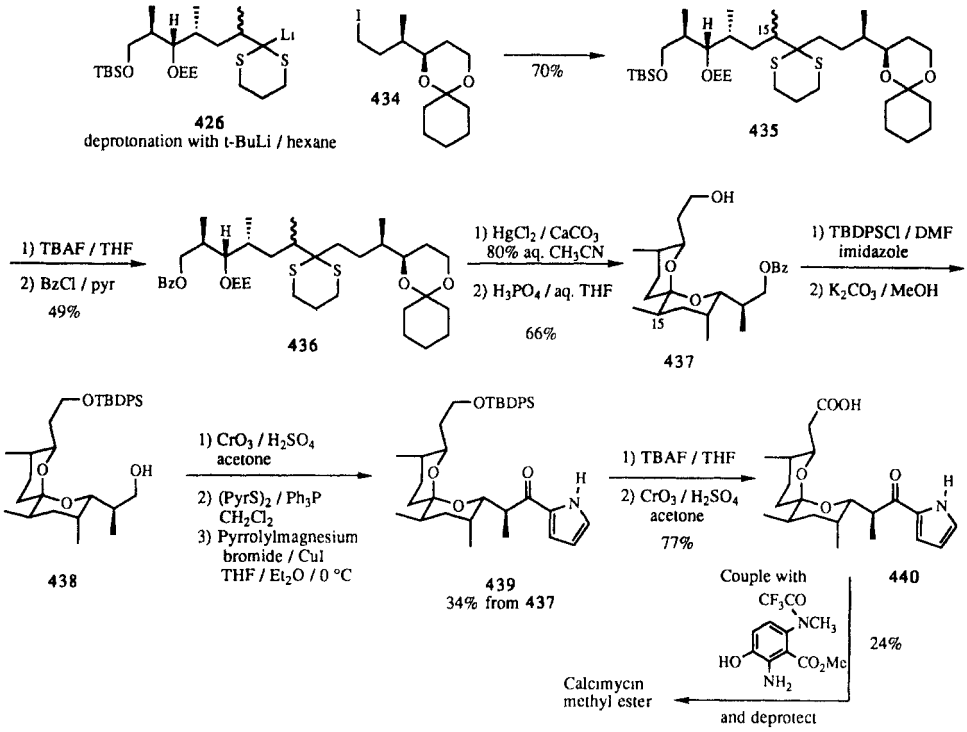
Nakahara's approach[78] is characterized by the use of dithiane chemistry to join two optically active fragments which were synthesized from carbohydrate precursors. The 2-lithio-1,3-dithiane **426** was coupled with the iodide **434** (Scheme 71) which resulted in a mixture of isomers at C-15 (**435**). Compound **436** was converted to the spiroketal **437** in which the primary alcohols at the termini were differentiated. The pyrrole and benzoxazole fragments were attached sequentially using standard methodology eventually resulting in calcimycin methyl ester. The syntheses of the two fragments for the dithiane coupling are shown in Scheme 70. D-Glucose was converted to methyl glycoside **418**, which was methylenated and reduced at C-19 to give **419**, containing the correct absolute configuration at C-19, C-18, and C-17, but incorrect at C-15. This center epimerized to a 1 : 1 diastereomeric mixture at C-15 during acidic hydrolysis of the imidate. The mixture was carried through the synthesis until the spiroketalization step where the problem was corrected using the Evans simplification. The iodide fragment **434** was produced from **427** in an unremarkable 16-step pathway. The overall synthesis was approximately 30 steps in the longest linear sequence.

Two aspects distinguish the Kishi strategy:[79] use of the classical Barbier–Wieland degradation and the spirocyclization of a fully functionalized intermediate in the final steps (Schemes 72 and 73). Optically pure enone **441** was manipulated in two directions to give the fragments **446** and **450**, which were combined to give **451**. In the conversion of **441** to **446**, one carbon was excised via the Barbier–Wieland degradation. The lactone **443** was treated with excess PhMgBr to give a diphenylcarbinol which was dehydrated to **444**. The olefin of **445** served as a protecting group for an aldehyde, which was produced via ozonolysis. Likewise, enone **441** was converted to olefin **450**, which served as the protecting group for the eventual aldehyde in **452**. The termini of compound **452** were combined with the heterocyclic units producing the key intermediate **455**. Sequential treatment


D-Glucose
via the method of Fraser-Reid
418
1) Ph3P=CH2 THF
2) H2 / Pd-C EtOAc
419
1) TsOH / MeOH
2) TsCl / pyr
Q
420 63% overall
wrong Me stereochem, will epimerize at spk stage
NaCN / DMF
n-Bu4NBr / 85 °C
421
1) aq. H2O2 Na2CO3 / acetone
2) TsOH / PhCH3
3) Et3O+ BF4-
422
34% from 420
1) LDA / THF
2) CH3I -78 → -40 °C
100%
423
sole product
1) H2SO4 aq. MeOH 60 °C / 11h
2) LiAlH4 / Et2O reflux
424
ca. 1 : 1 mixture
(epimerized)
HS(CH2)3SH
BF3•Et2O
425
46% from 423
1) TBSCl / DMF imidazole
2) EVE / PPTS CH2Cl2 / 25 °C
92%
426



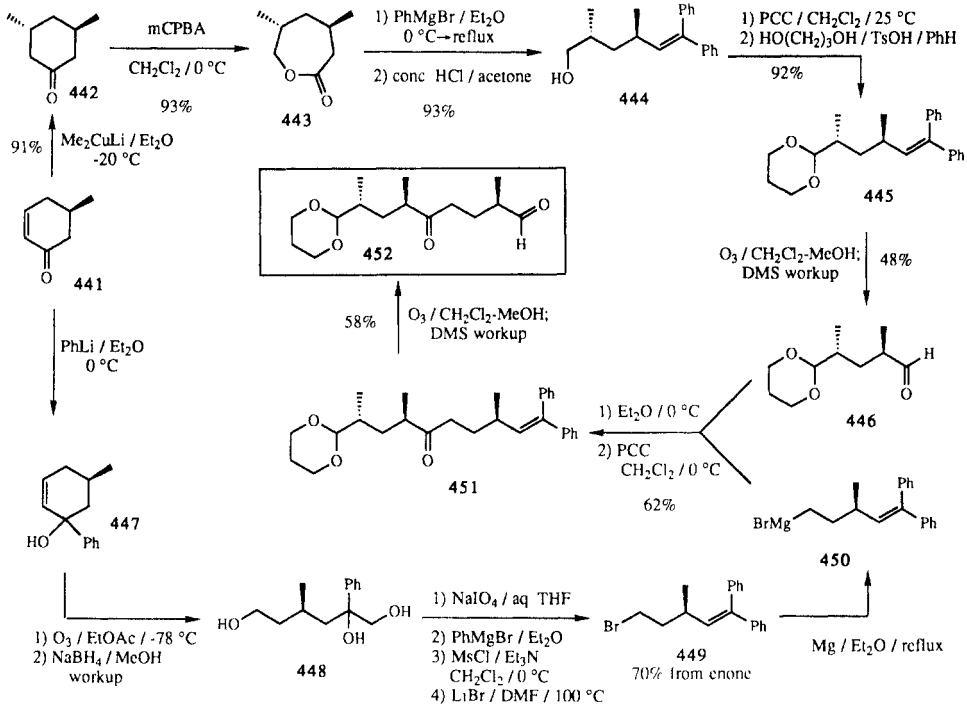
SCHEME 70. Calcimycin fragment synthesis (Nakahara).



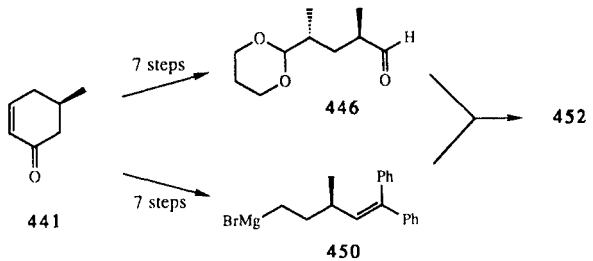
SCHEME 71. Combination of calcimycin fragments (Nakahara).

of **455** with catalytic NaOMe/MeOH/CH_2Cl_2 followed by Zn/HOAc/THF/HCl resulted in calcimycin methyl ester in 42% yield. It was theorized that the cyclization was occurring in the first step (NaOMe/MeOH) via the stereoelectronically-controlled formation of the alkoxide **456** (Scheme 74) which formed the second ring in a conjugate addition to the α,β-unsaturated benzoxazole. However, it is not clear that this was the course of events. It was reported that only "one cyclization product was observed" by thin-layer chromatography *after* treatment with NaOMe and *before* treatment with Zn/HOAc. While it seems plausible that the predicted course of events was indeed taking place, the structure of the intermediate(s) between the two steps was not discussed. Without further data, one cannot rule out spiroepimerization during the subsequent Zn/HOAc/HCl step. The mechanistic details of this cyclization[80] remain uncertain.

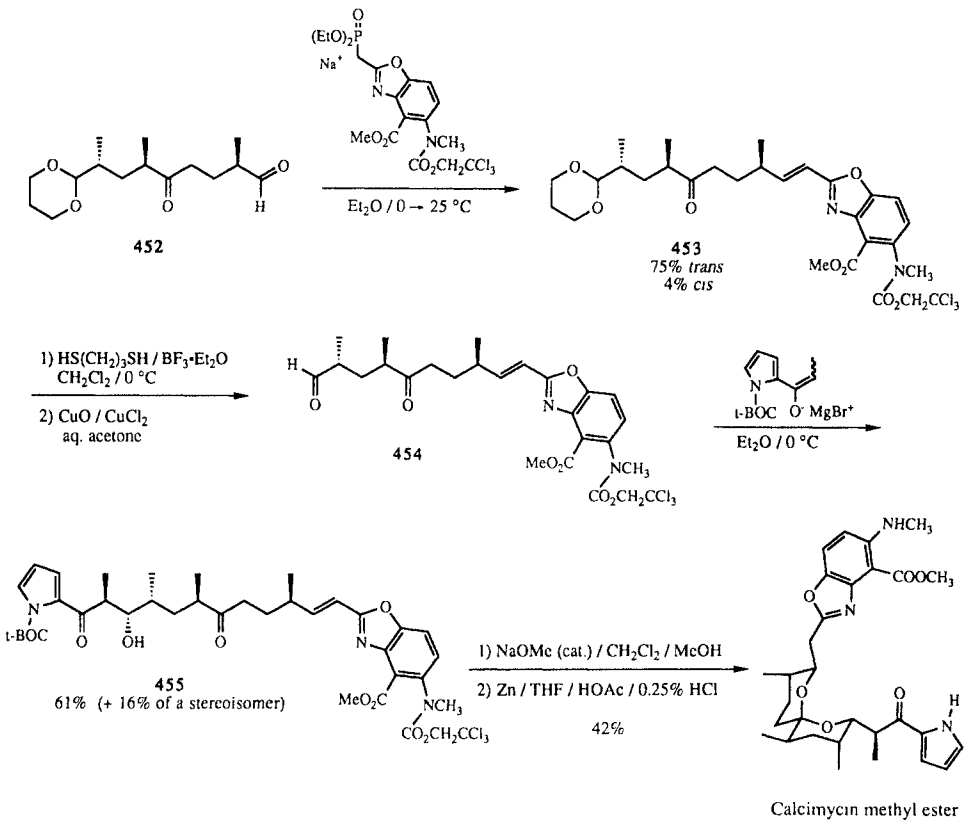
Boeckman[81] also took the approach of coupling two optically active fragments, except that the stereochemistry of the C-15 methyl group was established in an ingenious way. The coupling of the lithium reagent **462** to



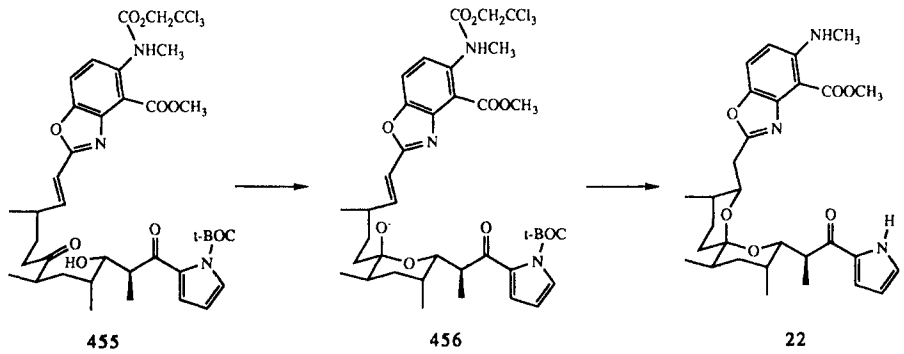
SCHEME 72. Kishi calcimycin synthesis.



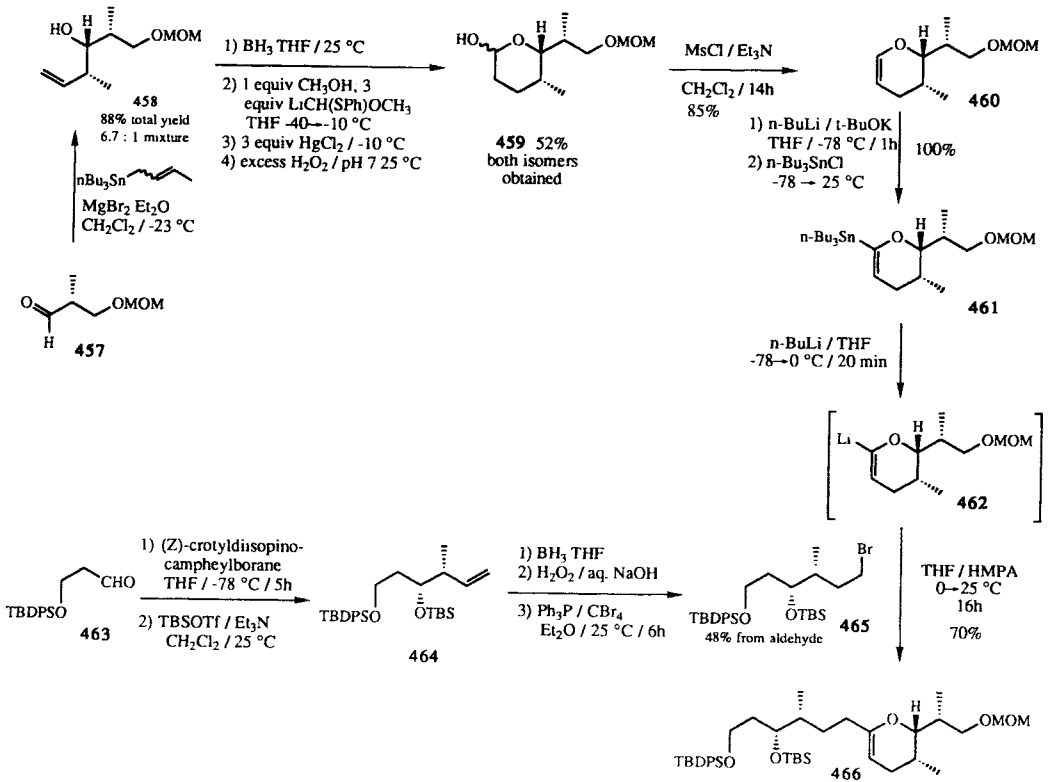
the bromide **465** resulted in the dihydropyran **466** (Scheme 75). The two fragments were synthesized using enantio- and diastereoselective addition of allylic organometallics to β-oxygenated aldehydes. The dihydropyran **466** was converted to the cyclopropane **467** nonstereoselectively. The carbon atom added via this process was destined to become the methyl group at C-15. Treatment of the mixture **467** with TsOH/PhH resulted in protonation of the cyclopropanes presumably to oxenium ions which then cyclized.



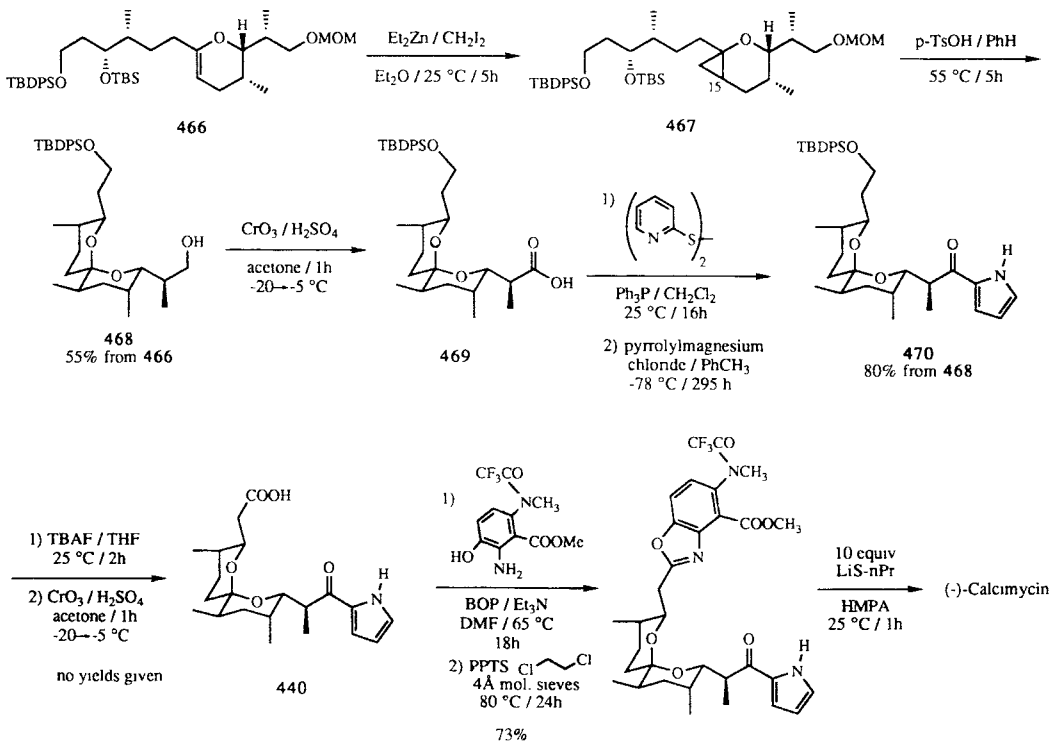
SCHEME 73. Kishi calcimycin synthesis (continued).



SCHEME 74. Predicted cyclization mechanism for the **455** → **22** conversion (Kishi).



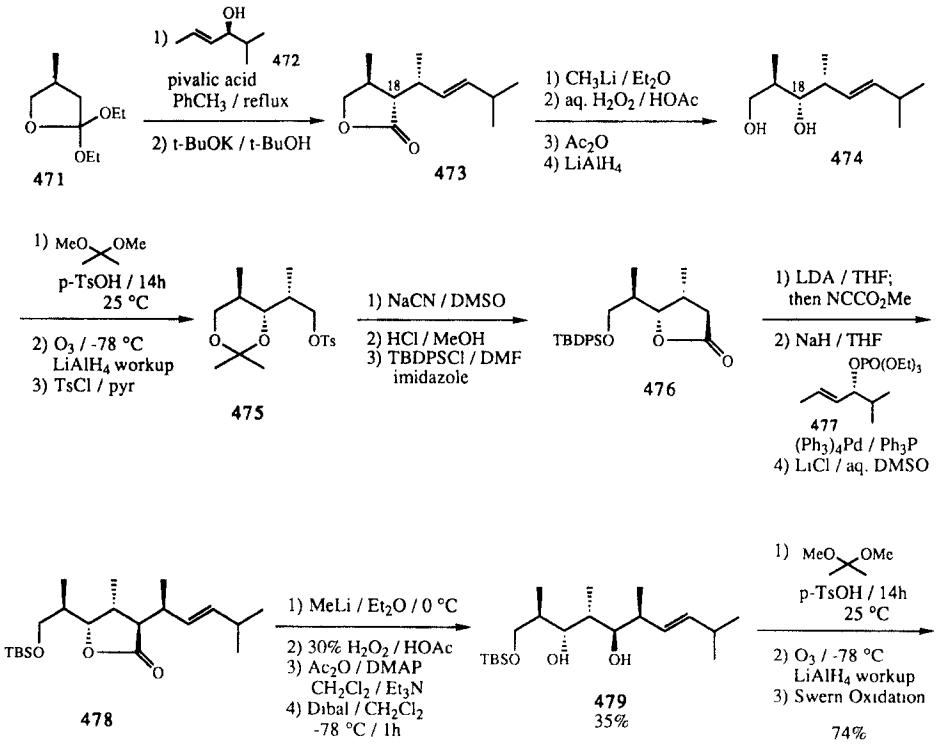
SCHEME 75. Boeckman calcimycin synthesis.



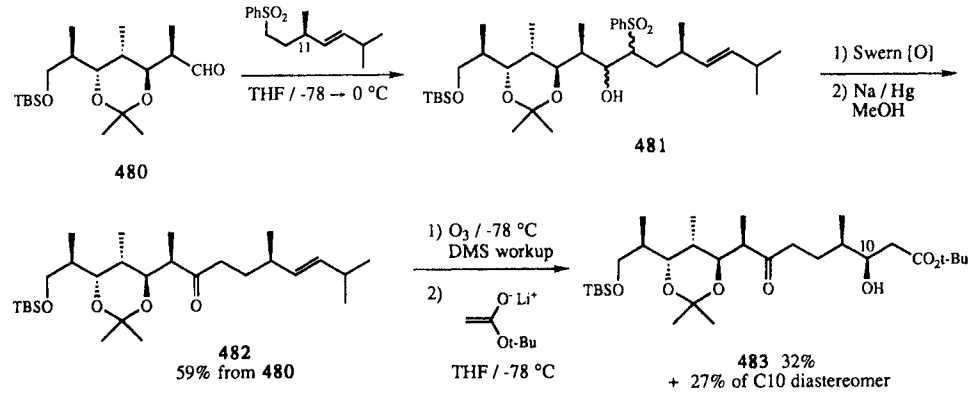
SCHEME 75. Boeckman calcimycin synthesis (*continued*).

Epimerization at C-15 under the acidic conditions occurred as before, leading to the spiroketal **468** in 55% yield from the vinyl ether **466**. A sequence similar to that employed by Nakahara was used to convert **468** to (−)-calcimycin. The synthesis, comprised of about 17 operations, was clearly simplified by the **467** → **468** transformation.

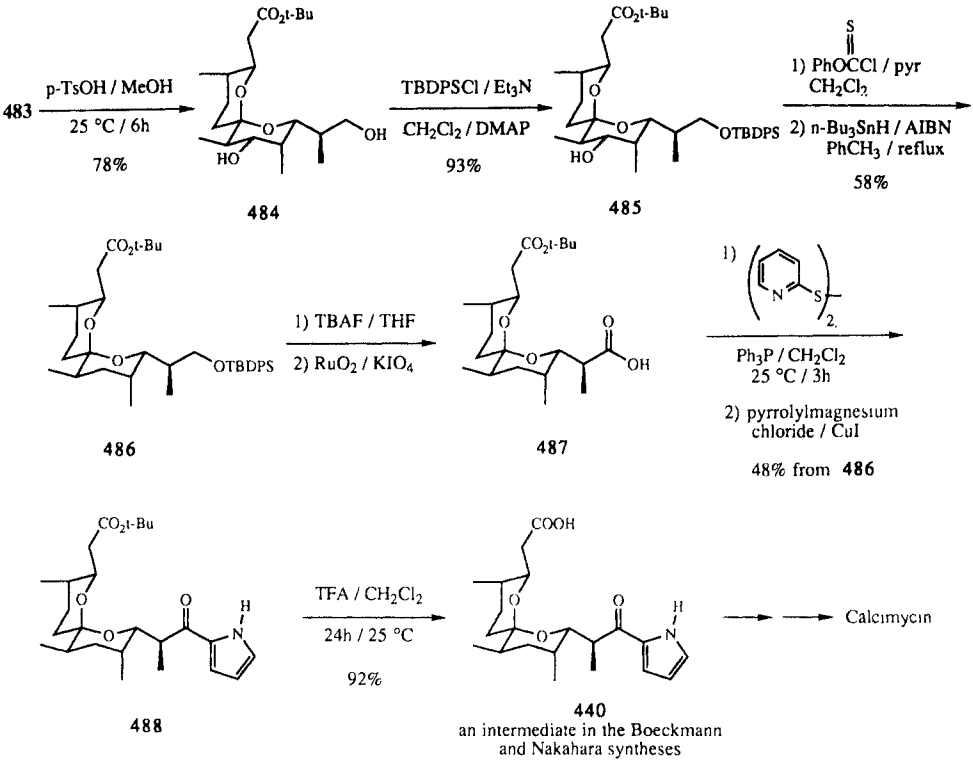
Although only a formal synthesis, Ziegler's construction of the Boeckman and Nakahara intermediate **440** bears analysis.[82] An iterative sequence was used to establish the stereochemistry of alternating methyl- and hydroxy-bearing carbons. Claisen rearrangement of the optically active ortholactone **471** and allylic alcohol **472** followed by epimerization of the α-position led to lactone **473** (Scheme 76 and 77). Baeyer–Villiger oxidation proceeded to **474**, forming the C-18–O bond present in the natural product. To repeat the sequence, **475** was converted to lactone **476**. Enolate alkylation was used to join **476** to the optically active allylic phosphate **477**, forming **478**. A four-reaction sequence (analogous to **473** → **474**) was used to convert **478** → **479**. The remote stereocenter at C-11 was unequivocally controlled by coupling



SCHEME 76. Ziegler synthesis of calcimycin.



SCHEME 76. Ziegler synthesis of calcimycin (*continued*).

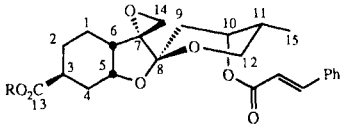


SCHEME 77. Ziegler synthesis of calcimycin (*continued*).

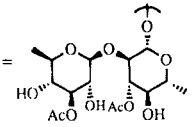
aldehyde **480** with an optically active sulfone resulting in **481**. However, the C-10 stereocenter constructed by addition of lithio-*t*-butylacetate addition to an aldehyde which proceeded with only 1.2:1 (desired:undesired) selectivity providing **483**. Spiroketalization of **483** resulted in **484** which was converted to the Boeckman–Nakahara intermediate **440** in 8 steps.

5. PHYLLANTHOCIN AND PHYLLANTHOSIDE

Phyllanthocin (**489**, R = CH_3) is the aglycone of the potent antileukemic compound phyllanthoside (**490**) which originates from *Phyllanthus acuminatus*. Phyllanthocin was isolated by Kupchan and co-workers in 1977[83] by methanolysis of **490** and its structure was elucidated by X-ray crystallography. Five syntheses of **489** have been described, as well as a synthesis of phyllanthoside by Smith.

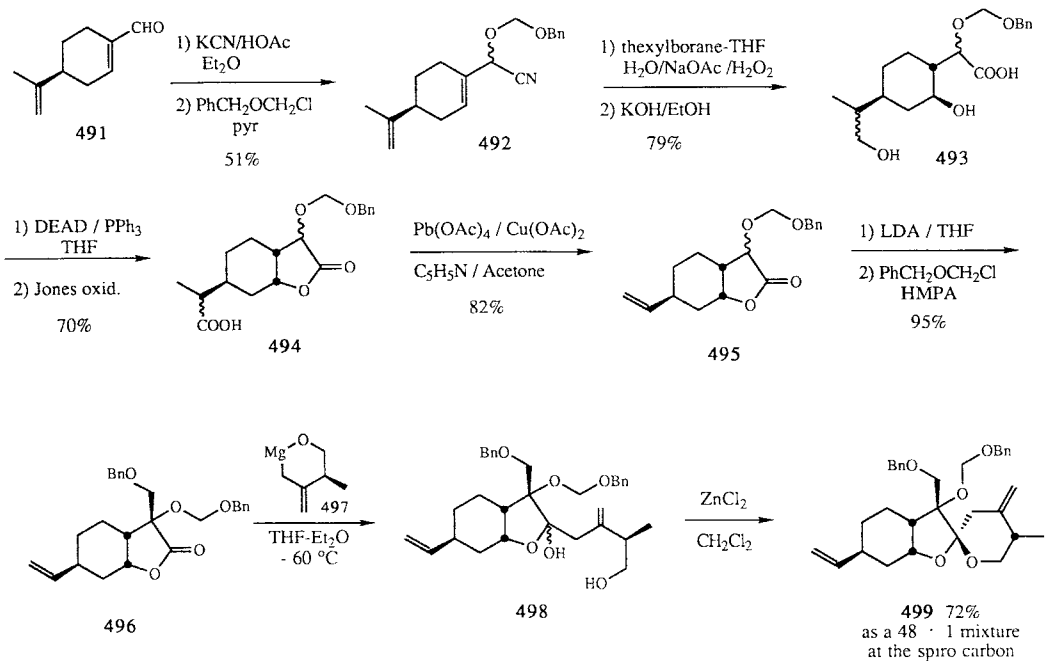


489 R = Me phyllanthocin

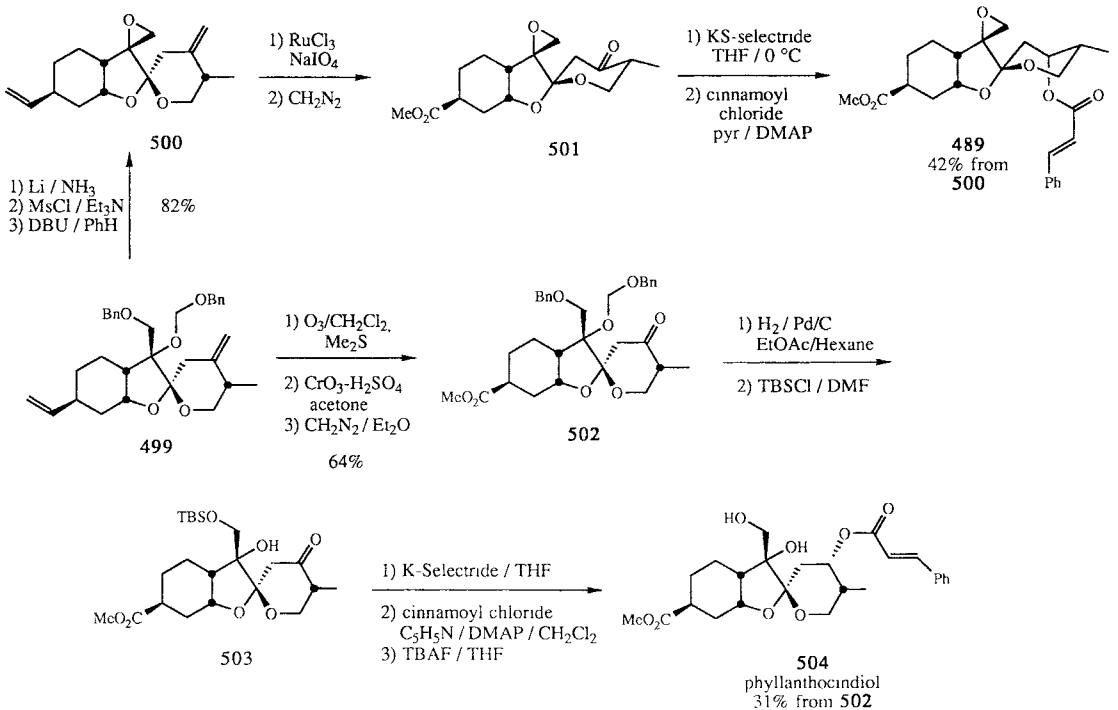
490 R =  phyllanthoside

A key synthetic challenge is communication of asymmetry between C-3, C-5, and C-6 of the *cis*-fused oxabicyclononane and C-10 and C-11 of the spiroketal. In four of the five syntheses this problem was solved by coupling optically active fragments with some or all of these stereocenters intact. All of the syntheses utilized acid-promoted spiroketalization to fix the stereochemistry at C-8.

The first synthesis of phyllanthocin was reported in 1982 by Collum[84] (Scheme 78) which established the absolute stereochemistry of the aglycone. The stereogenic carbon of (*S*)-perillaldehyde was used to control the stereochemistry at C-5, C-6, and C-7. The remote C-11 stereochemistry originated from the optically active organomagnesium compound **497** which was prepared from (*S*)-(+)-3-hydroxy-2-methylpropanoic acid (**505**, Scheme 80). The stereochemistry at C-11, along with the conformation of a spiroketal intermediate, was enough to allow establishment of the correct stereochemistry at C-10 by reduction of a ketone.

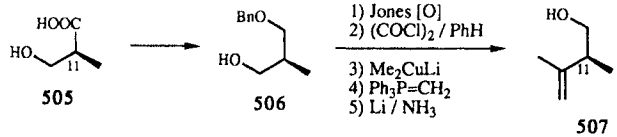


SCHEME 78. Collum synthesis of (+)-phyllanthocin.

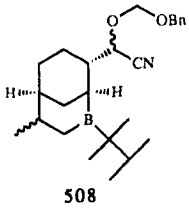


SCHEME 79. Divergent pathways from intermediate **499** (Collum).

(*S*)-Perillaldehyde was converted to the blocked cyanohydrin **492**, which underwent stereoselective hydroboration of the isolated olefins by thexylborane, producing cyclic borane **508**. This was modeled after a stereospecific hydroboration of limonene.[85] Standard H_2O_2 oxidation followed by basic hydrolysis of the nitrile gave the dihydroxyacid **493**, stereochemically defined at C-3, C-5, and C-6. Formation of the desired lactone **494** was accomplished by the Mitsunobu process, thus inverting the C-5 stereochemistry. Oxidative decarboxylation of **494** → **495** removed the unwanted branchpoint carbon present in the isopropenyl group of **491**. Alkylation of the lactone **495** with chloromethyl benzyl ether produced **496** with ⩾ 95% stereoselectivity. Addition of the organomagnesium reagent, tentatively formulated as **497**, gave rise to lactol **498**, which was cyclized with 3 equiv $ZnCl_2$ in CH_2Cl_2 at − 20°C to give spiroketal **499** as a 48:1 epimeric mixture at the spiro carbon. It was determined by equilibration experiments that this was a thermodynamically determined product ratio. Intermediate **499** was carried on to both phyllanthocin and phyllanthocindiol (**504**) by similar routes (Scheme 79). The epoxide was generated by double debenzylation to the diol, followed by mesylation and ring closure. Intermediate **499** (or its counterpart **500**) was oxidatively cleaved to intermediates containing C-13 ester and C-10 ketone functionalities. Reduction of ketones **501** and **503** proceeded to axial alcohols, which were converted to the required cinnamate esters. The first synthesis of phyllanthocin (**489**) was thus completed in 17 steps.

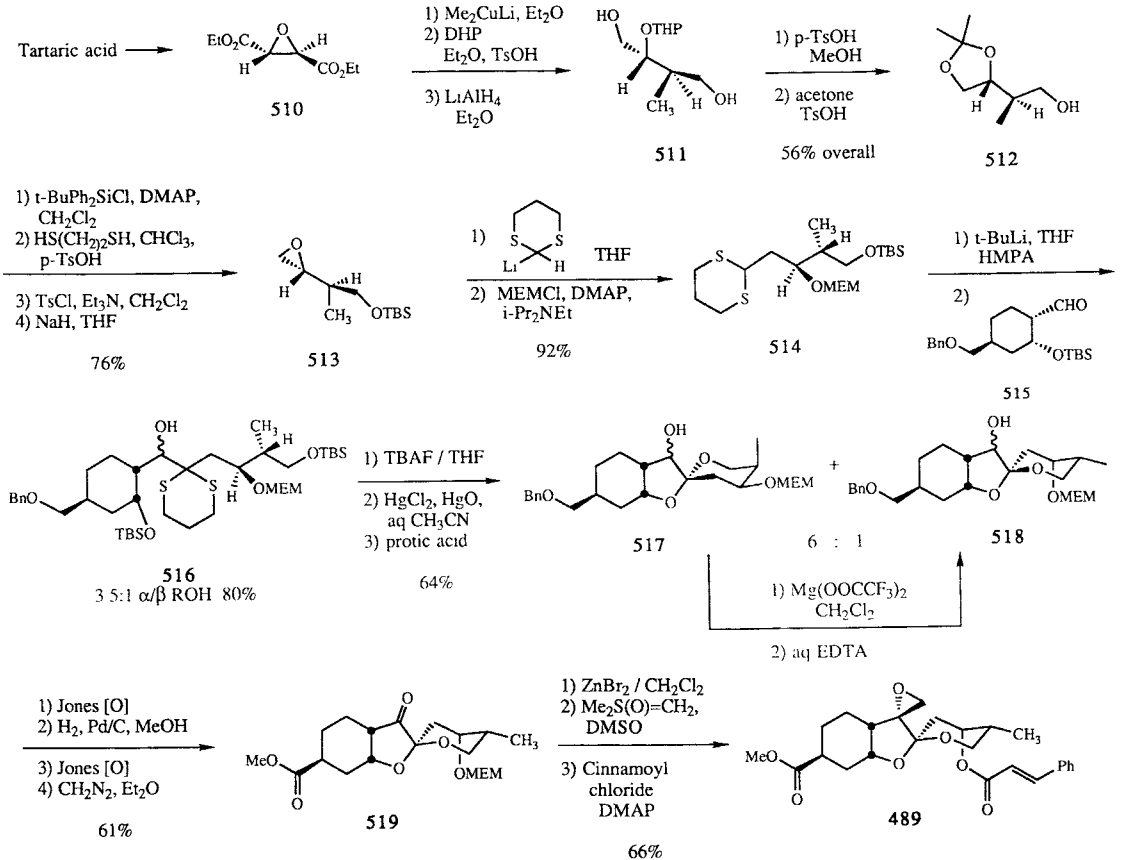


SCHEME 80. Synthesis of fragment **507** (Collum).

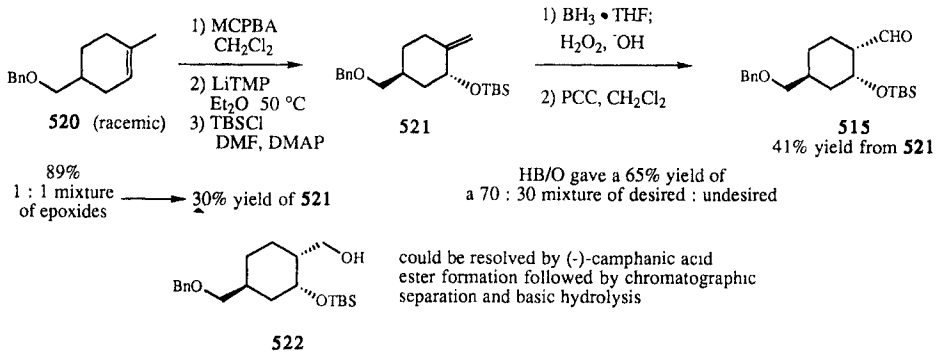


508

The focal point of a synthesis by Williams[11] (Scheme 81) is the addition of the dithiane **514** to the aldehyde **515** (see Scheme 82 for synthesis) as optically active partners giving a mixture of carbinols **516**. Spiroketalization under protic conditions led to a 6:1 mixture of isomers **517** and **518**, in contrast to



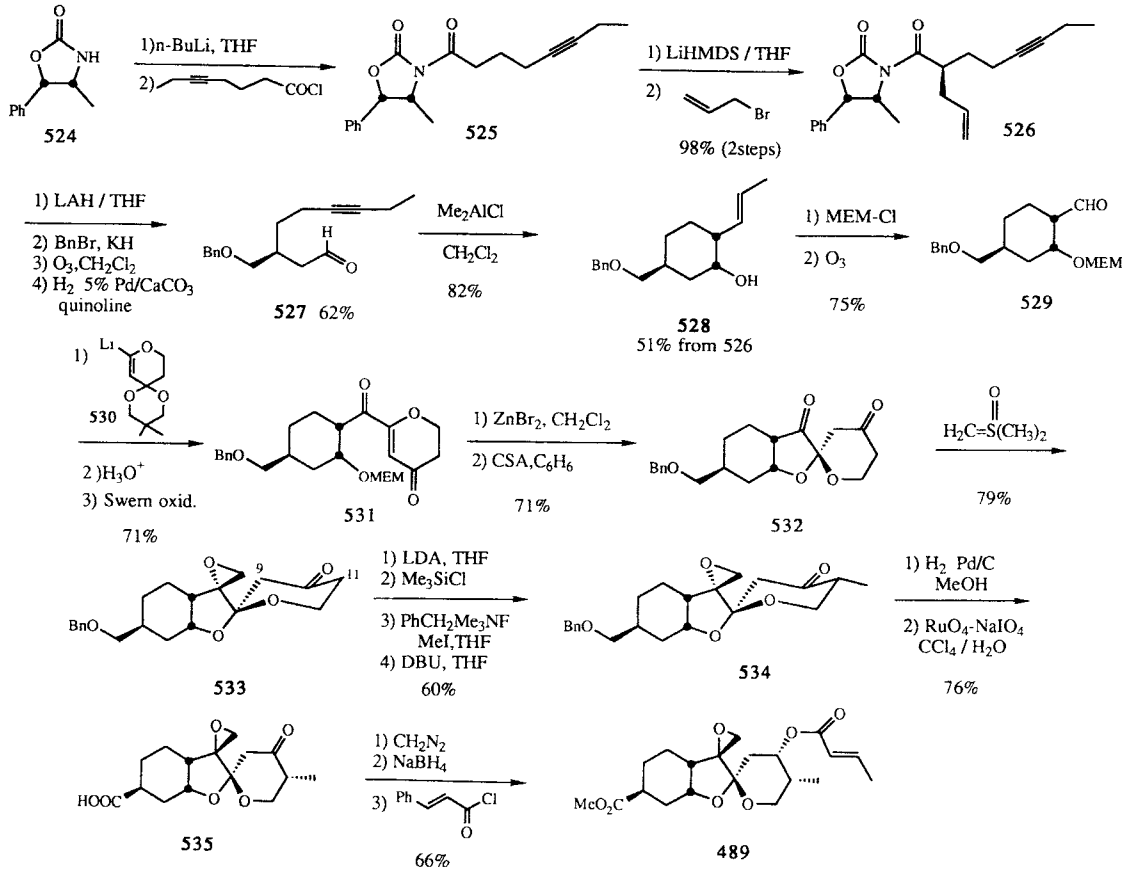
SCHEME 81. Williams synthesis of (+)-phyllanthocin.



SCHEME 82. Synthesis of **515** (Williams).

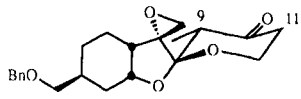
the results of Collum. It was found that resubmission of **517** to the cyclization conditions did not result in equilibration to **518**. This suggests that under these conditions **517** and **518** are formed in a kinetically-controlled cyclization. In attempting to optimize the formation of the desired isomer **518**, compound **517** was found to isomerize to **518** when treated with a variety of Lewis acids, including $ZnBr_2$, $TiCl_4$, and $SnCl_4$. This phenomenon was independent of the configuration at C-7, suggesting that the hydroxyl group on this carbon is not involved in the isomerization. When **517** was treated with magnesium trifluoroacetate, isomerization was accompanied by the production of a stable magnesium chelate. The complex could be isolated by chromatography on silica and was found to be spectrally similar to free **518** except for broadening of the ^1H NMR signals. The complex was freed of magnesium by addition of buffered EDTA. Kurth[10] reported a similar occurrence in model studies directed toward phyllanthocin. From this point the synthesis was anticlimactic, proceeding from **518** (+)-phyllanthocin in seven steps in 40% yield. However, a second strategy for the formation of the C-7 to C-14 epoxide had emerged. Addition of $Me_2S(O)=CH_2$ to a C-7 ketone proceeded with 30:1 stereoselectivity for the desired configuration. Overall, the synthesis required approximately 22 steps from **510**.

Smith's group reported the first synthesis of (+)-phyllanthoside[86] by way of a synthesis of (+)-phyllanthocin[87] (Scheme 83). This synthesis differed from the others in that the chiral centers were controlled in a linear manner, that is, without coupling together optically active fragments. The initial chiral carbon was induced by an alkylation process using the Evans chiral auxiliary **524**, eventually leading to the chiral *cis*-olefinic aldehyde **527**. In one of many key transformations, treatment of **527** with dimethylaluminum chloride promoted an intramolecular ene reaction proceeding stereoselectively to **528**, in which the C-3 chiral center induced the centers at C-5 and C-6. The



SCHEME 83. Smith synthesis of (+)-phyllanthoside.

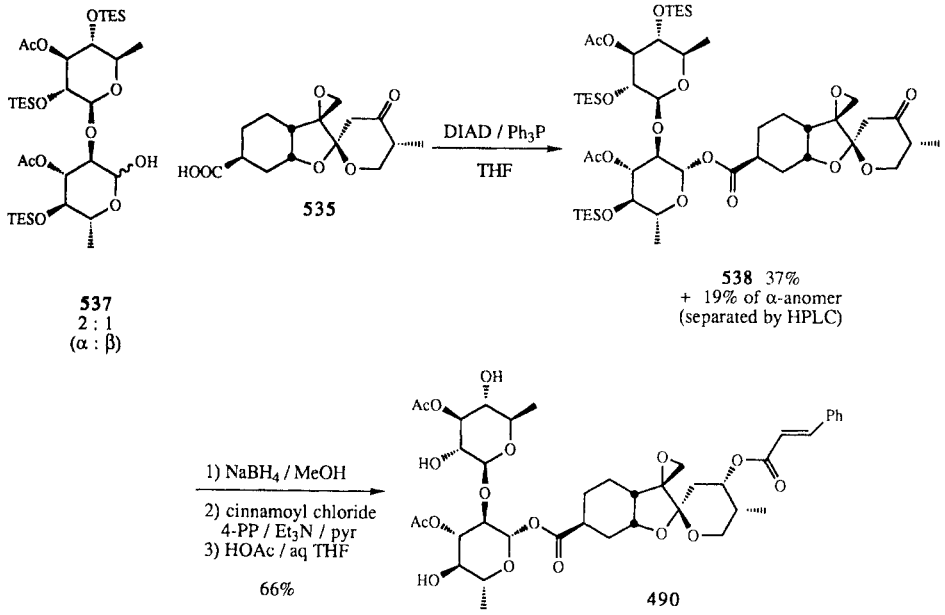
tetrahydropyran ring of the spiroketal was incorporated in one piece, devoid of stereocenters, by addition of the alkyllithium reagent **530** to the aldehyde **529**. Hydrolysis of the ketal and oxidation gave rise to diketone **531**. The MEM ether was removed and spirocyclization using catalytic CSA in benzene led in 71% yield to the spiroketal **532** along with 2% of the C-8 epimer. It was determined that while **532** is the thermodynamic product, the reaction product ratio (ca. 35:1) reflects a kinetic cyclization instead of an equilibrium process. Treatment of the diketone with dimethylsulfoxonium methylide proceeded regio- and stereospecifically to epoxide **533**. Two chiral centers were yet to be established at C-10 and C-11. These were cleverly introduced using the specific conformation of the spiroketal ring system. Standard kinetic alkylation of **533** occurred at the undesired C-9 position. However, when **533** was added to an LDA–TMSCl mixture, an 85:15 ($\Delta^{10,11}$:$\Delta^{9,10}$) mixture of silyl ethers were formed. Enolate regeneration from these and alkylation with MeI afforded a 5:1 mixture of C-11:C-9 methylated products. The mixture was treated with DBU to equilibrate–epimerize the C-11 (C-9) position resulting in a 60% overall yield of **534** containing the desired C-11 equatorially oriented methyl group. This three-step sequence also gave 17% of the starting ketone **533** and 12% of the isomeric substance **536**. The final C-10 stereocenter was produced by reduction of the ketone, among other functional group manipulations in the final stages of the synthesis. The synthesis took approximately 23 steps, proceeding in 4–5% overall yield.



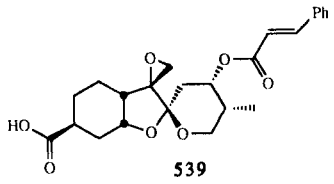
536

The conversion to phyllanthoside (Scheme 84) did not occur from **489**, but instead proceeded from keto acid **535**. Coupling was effected by the Mitsunobu process resulting in a 2:1 (β:α) anomeric mixture. The desired β isomer was isolated and reduced with $NaBH_4$ to a 6:1 (axial:equatorial) mixture of alcohols. The desired axial alcohol was isolated and cinnamoylated under the usual conditions. Removal of the TES groups on the disaccharide produced (+)-phyllanthoside (**490**). In subsequent manuscripts, the Smith group reported syntheses of the related phyllanthostatins-1[88] and -2[89] using the same coupling reagents, by joining the fully functionalized acid **539** with the appropriate disaccharides via more convergent routes.

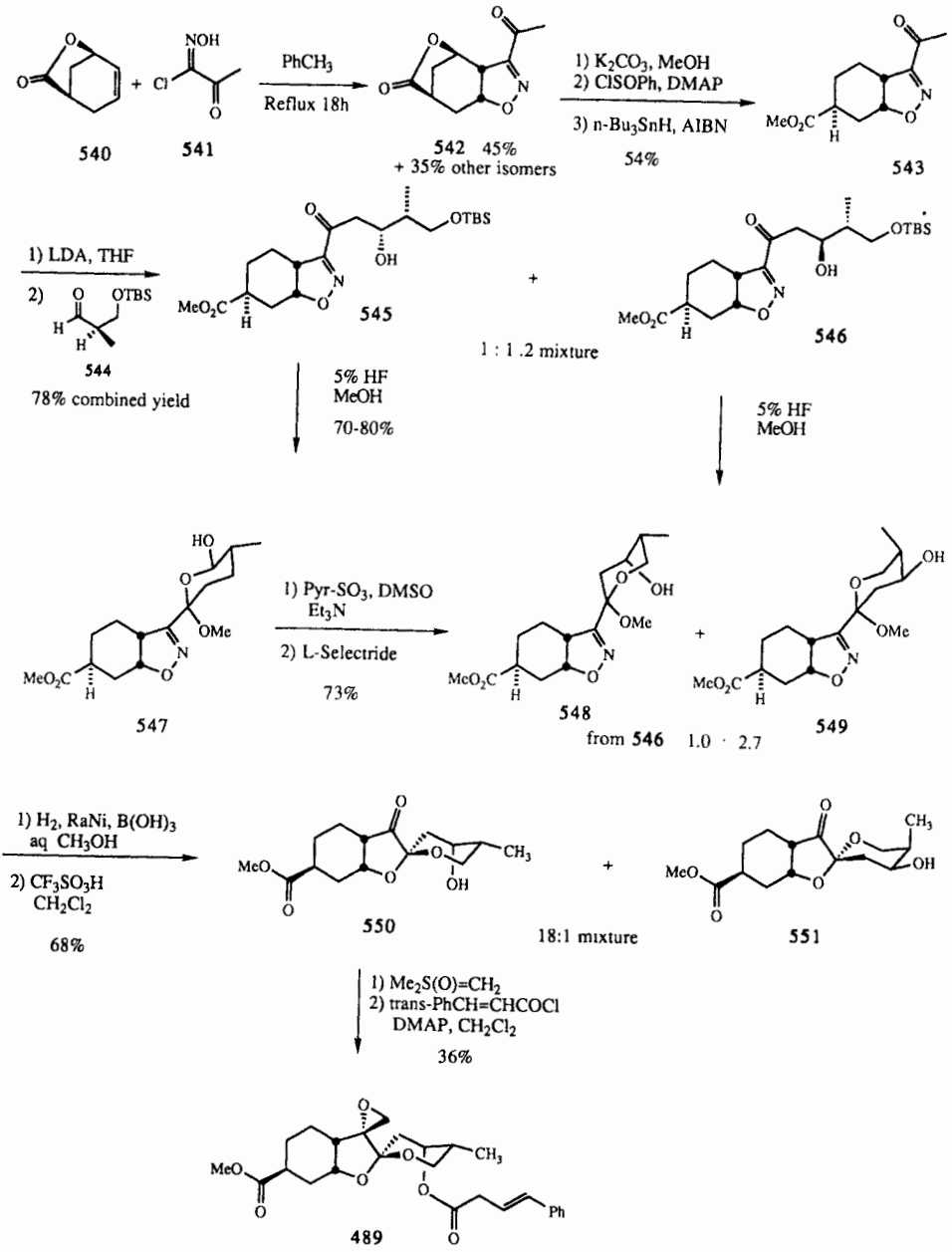
Martin[90] reported an approach using 1,3-dipolar cycloaddition to establish the *cis* relationship between C-5 and C-6. The nitrile–oxide thermally



SCHEME 84. Addition of the disaccharide unit completing phyllanthoside (Smith).

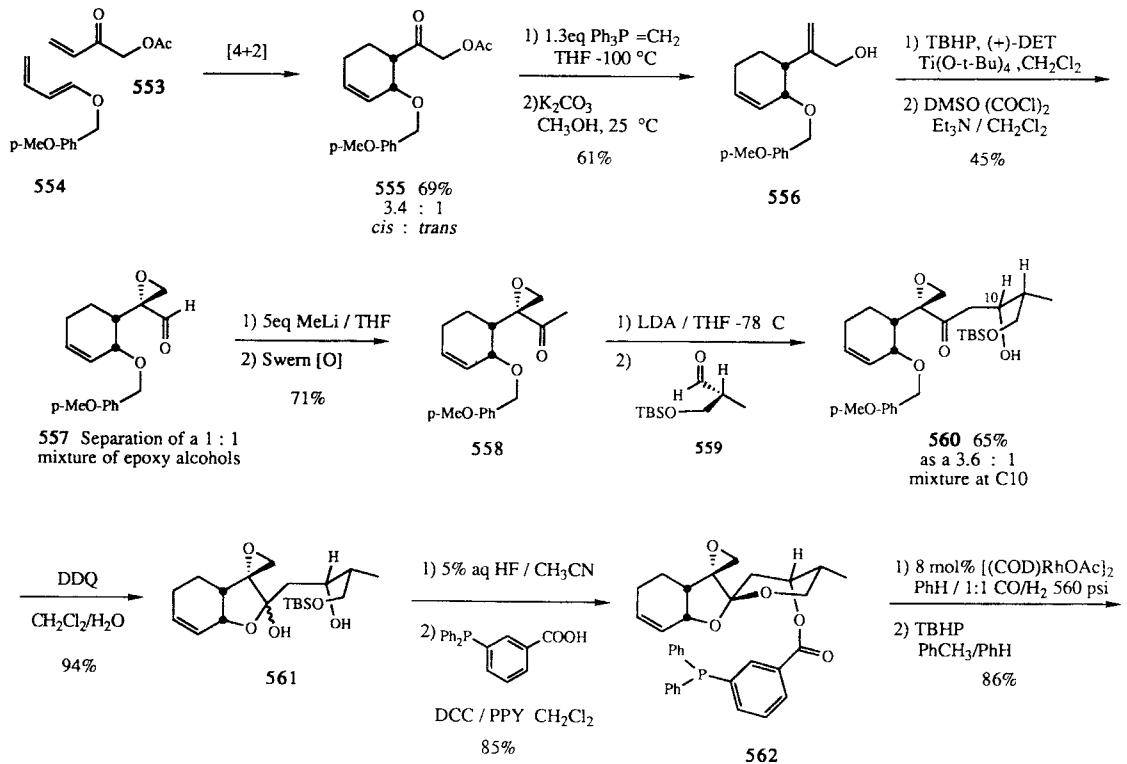


generated from **541** underwent relatively nonselective cycloaddition to **540** giving adduct **542** in 45% yield along with 35% of other, presumably unwanted, isomers. Defunctionalization of C-1 of **542** required three steps, giving **543**, wherein the three stereocenters at C-3, C-5, and C-6 were established. Enolate formation and quenching with the known optically active aldehyde **544** produced a 1 : 1.2 mixture of aldol adducts **545** and **546**. Fortunately, both isomers could be converted to useful adducts. The "major" isomer was converted to the **548–549** glycoside mixture with HF–MeOH (Scheme 85). The unwanted product **545** could be converted to **548** by glycosidation and a standard oxidation–reduction sequence, such that all of the aldol adduct material was usable. Hydrogenolysis of the N–O bond and acid treatment of **548–549** resulted in an 18 : 1 mixture of spiroketals **550** and **551**. It was believed that this was a kinetically generated mixture; however,

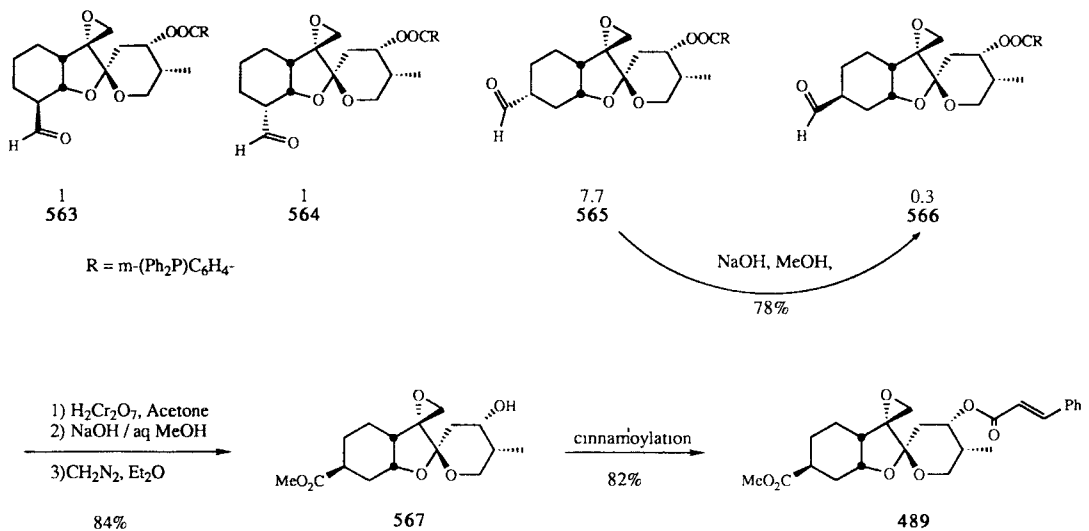


540 541 542 45% + 35% other isomers 543 544 545 546 547 548 549 550 551 489

SCHEME 85. Martin phyllanthocin synthesis.

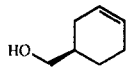


SCHEME 86. Burke phyllanthocin synthesis.



SCHEME 86. Burke phyllanthocin synthesis (*continued*).

the reasons given for this belief were not stated. The major isomer could be treated with $Me_2S(O)=CH_2$ as described by Williams to install the epoxide, eventually culminating in (+)-phyllanthocin. While the sequence required only 10–12 steps from known lactone **540** (which requires three steps for its preparation from **552**), the mild selectivity of the dipolar cycloaddition step indicates that the lactone bridge in **540** is only fair in its ability to serve as a regio- and stereocontrol element.

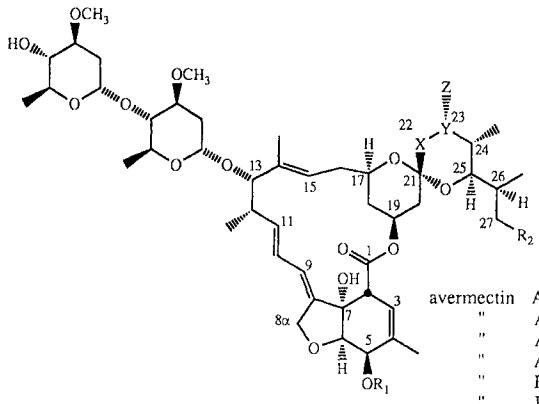


552

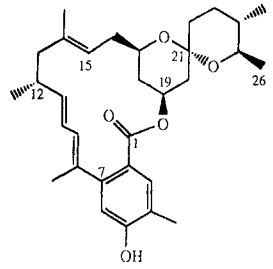
In the Burke approach[91] the *cis* stereochemistry at C-5 and C-6 was determined by the *endo* specificity of the Diels–Alder reaction between **553** and **554** resulting in **555**. By not utilizing a C-3-substituted diene, the problem of the stereochemistry of the C-3 carbomethoxy group was postponed until later in the synthesis. Compound **555** was converted to the racemic allylic alcohol **556**, which was resolved using the Sharpless asymmetric epoxidation. The enolate of methyl ketone **558** was combined with optically active aldehyde **559** and led to a 3.6:1 (desired:undesired) mixture at C-10. Spiroketalization of **561** mediated by 5% aqueous HF led in 95% yield to the correct configuration at the spiro carbon. At this point, regioselective introduction of the carbomethoxy group could be accomplished via hydroformylation of the C-3–C-4 olefin. By use of intramolecular phosphine[92] coordination, a mixture of all possible isomers was obtained (**563–566**) in the indicated ratios, with the α orientation at C-3 (**565**) predominating. Using this strategy, the regioselectivity reached an 8:2 level (C-3:C-4). Fortunately, the aldehyde substituent could be equilibrated to the desired β orientation (**566**) with base. Standard manipulations then led from **566** to (+)-phyllanthocin.

6. MILBEMYCIN–AVERMECTINS

The milbemycins and the structurally more complex avermectins possess 16-membered ring macrolides bridging one ring of a 1,7-dioxaspiro[5.5]undecane (Scheme 87). First isolated from Streptomycetes,[93] these relatively rigid molecules were structurally assigned on the basis of X-ray crystallographic analyses of milbemycin β_1 (*p*-bromophenylurethane derivative),[94] avermectin B_{1a}, and avermectin B_{2a} aglycone[95] combined with chemical degradation and spectroscopic analysis. The synthetic interest in these metabolites arises from their unique architecture as well as their extraordin-



		R_1	R_2	X——Y	Z	
avermectin	A_{1a}	CH_3	CH_3	CH=C	H	569
"	A_{1b}	CH_3	H	CH=C	H	
"	A_{2a}	CH_3	CH_3	CH_2—CH	OH	
"	A_{1b}	CH_3	H	CH_2—CH	OH	
"	B_{1a}	H	CH_3	CH=C	H	570
"	B_{1b}	H	H	CH=C	H	
"	B_{2a}	H	CH_3	CH_2—CH	OH	
"	B_{2b}	H	H	CH_2—CH	OH	



571 milbemycin β_3

SCHEME 87. Structural summary of the avermectins and milbemycin β_3.

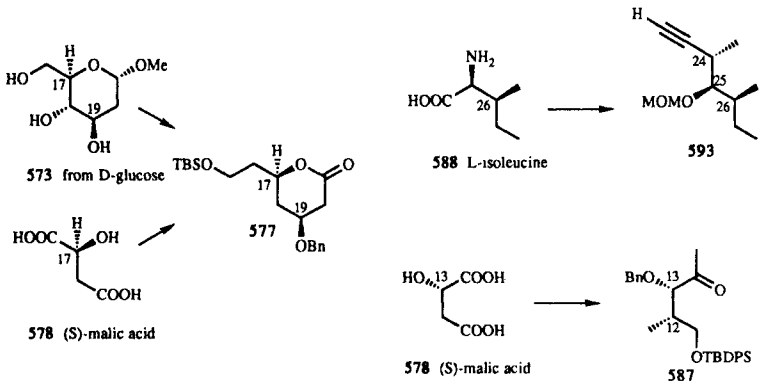
ary antihelmintic properties. As a class, these metabolites exhibit medicinally significant insecticidal and acaricidal activity.[96] Coupled with low mammalian toxicity, the compounds hold enormous potential for the treatment of parasitic infections. The isolation, structure determination, biosynthesis, as well as some of the early chemistry in this area have been reviewed.[97]

Most of the synthetic attention in the milbemycin series has been directed at milbemycin β_3 (**571**), one of the structurally simplest members containing an aromatic C-1–C-8 moiety. Five complete syntheses of **571** have been reported as well as several additional approaches to milbemycin spiroketal subunits. Two syntheses have been recorded in the avermectin series, both of which use chemical degradation to obtain relay compounds which were then carried on to avermectin A_{1a} (**569**) and B_{1a} (**570**).

A. Avermectins

Consideration of the synthetic problem posed by the avermectins reveals four areas of remote stereocenters on the aglycone consisting of sets at C-24–C-27, C-17–C-19, C-12–C-13, and C-2–C-7. The spiroketal rings exist in the favored bis-diaxial C–O arrangement with all ring substituents occupying equatorial positions. Therefore, the spiro stereocenter should be easily established in a thermodynamic process. There have been many approaches to the upper spiroketal portion[98] and the lower "oxahydrindene" portion.[99] However, only two complete syntheses have been reported in this area (avermectin B_{1a} by Hanessian[100] and avermectin A_{1a} by Danishefsky[101]) and both utilize the most common method for solving the remote stereocenter problem—combination of stereogenically pure building blocks. However, Danishefsky also used a chiral auxiliary to induce the stereocenters at C-12 and C-13.[102] Both sets of workers also closed the 16-membered ring by macrolactonization as opposed to C–C bond formation. Further, both syntheses focus on separately constructing the aglycone and the L-oleandrosyl-L-oleandrose disaccharide substructures, although the Hanessian group incorporates the disaccharides before macrolactonization, while the Danishefsky group attaches the sugars in the final stage of the synthesis.

Hanessian naturally took the chiral pool approach in assembling the main components in the synthesis of the aglycone, as outlined in Scheme 89. The stereogenic centers at C-13, C-17, C-19, and C-26 were directly derived from the chiral pool. The entire oxahydrindene component was derived by ozonolysis of the C-10–C-11 olefin of a derivative of natural avermectin B_{1a}.

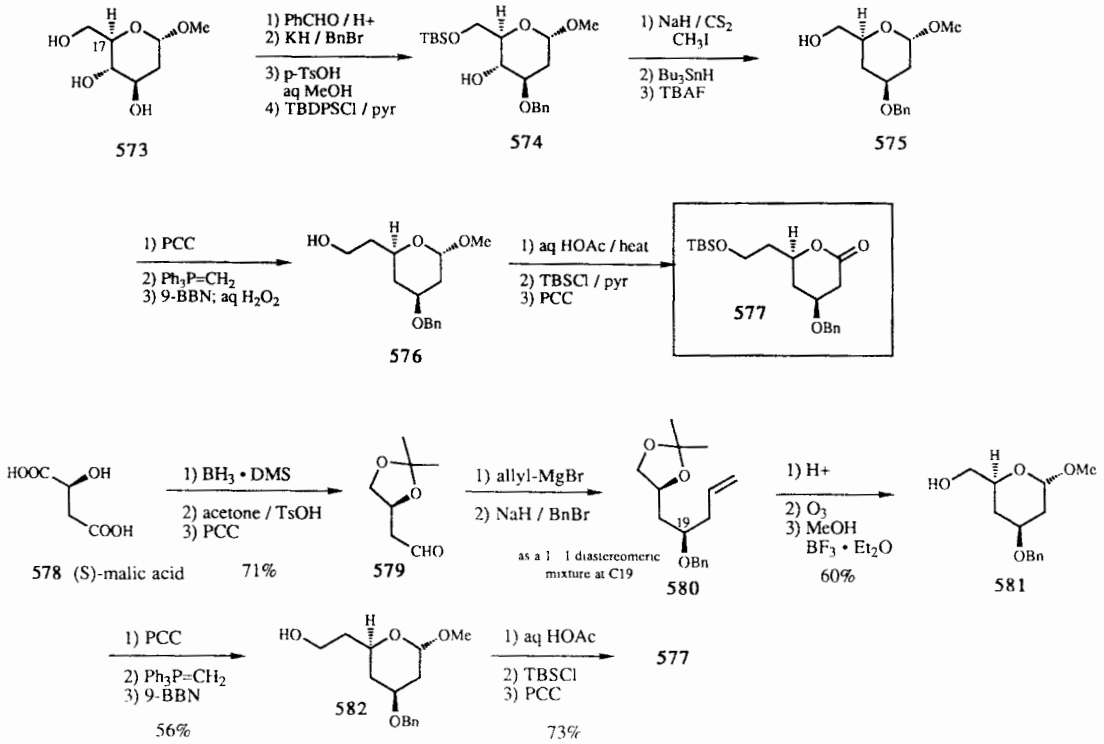


SCHEME 89. Chiral pool synthons used in the assembly of avermectin B_{1a} (Hanessian).

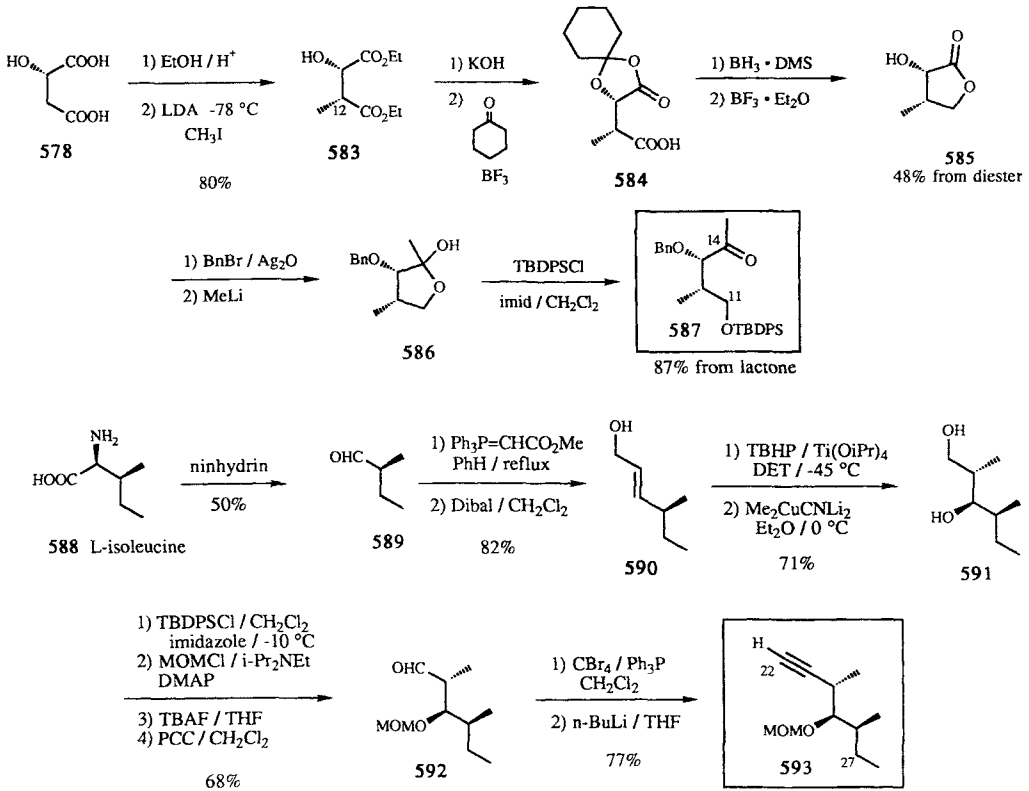
Two approaches to the assembly of the lactone fragment **577** are shown in Scheme 90. Compound **577** has been an attractive intermediate for the synthesis of various milbemycin–avermectin spiroketal units. In the first approach starting from the glucose derivative **573**, both stereogenic centers were incorporated from the chiral pool synthon and only one C–C bond needed to be made, extending the side chain at C-17 by one. The remainder of the steps were unexceptional functional group manipulations. The second synthesis was of approximately the same length, except the chiral center at C-19 had to be induced. This was accomplished by conversion of (*S*)-malic acid **578** to the known aldehyde **579**, which underwent nonstereoselective addition of allylmagnesium bromide, resulting in a mixture of **580** and its C-19 epimer. Intermediate **580** was converted to the lactone **577** in a further nine steps.

The synthesis of fragments **587** and **593** are shown in Scheme 91. (*S*)-Malic acid was again utilized, this time in the production of **587**. The methyl group at C-12 was introduced via alkylation of the chiral dianion of diethyl malate giving **583**. After this point, it was a matter of adjusting functionality and adding the last carbon by methyllithium addition to the lactone **585**, eventually resulting in fragment **587**. The alkyne **593** was also a popular intermediate for milbemycin–avermectin spiroketal synthesis, which was invariably coupled to lactone **577** or a similarly protected derivative. L-Isoleucine was degraded to aldehyde **589** and chain-extended to allylic alcohol **590**. Sharpless epoxidation of this substance led to an epoxyalcohol which was opened with a methyl cuprate reagent to **591**, completing the construction of the three contiguous stereogenic centers of this fragment. Six additional steps were required to differentiate the alcohols and extend the chain by one to the desired alkyne **593**.

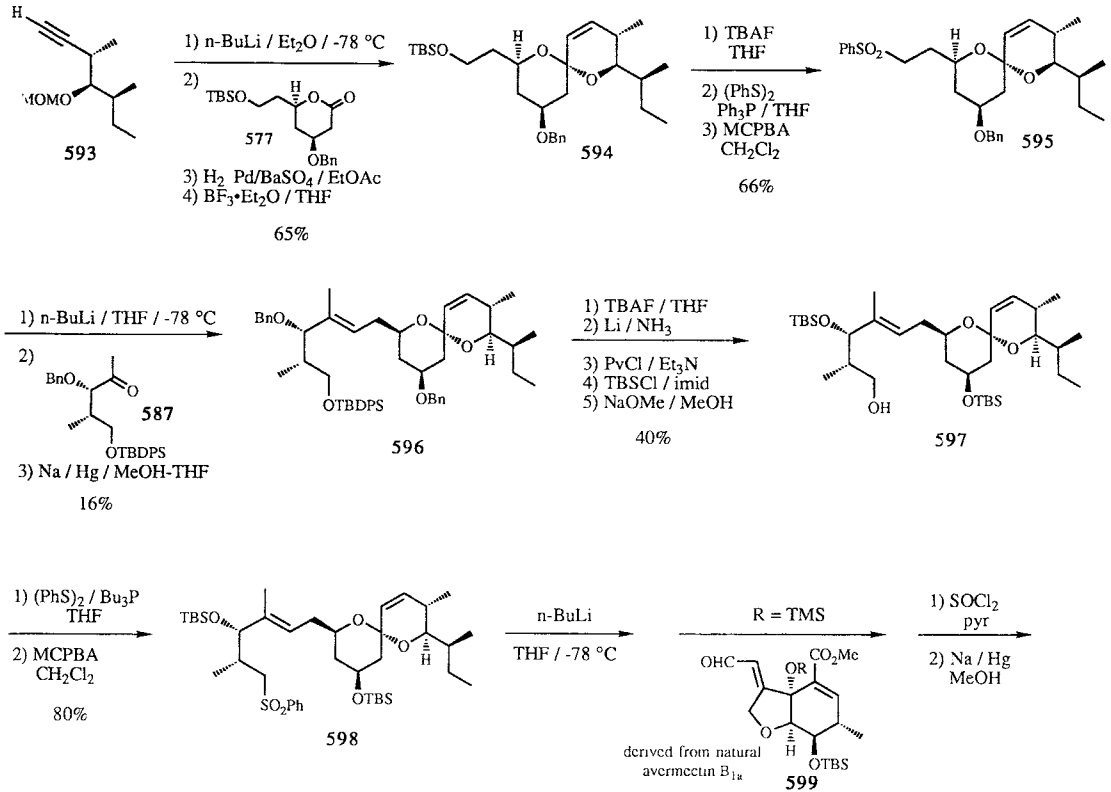
Assembly of the various fragments is shown in Scheme 92. The spiroketal was constructed by lithiation of **593** and alkylation with lactone **577**. This presumably resulted in a lactol which was hydrogenated to a *cis* alkene and spirocyclized to **594**. This sequence should be quite familiar to many workers in this area. As expected, the cyclization provided the desired relative configuration at the spiro carbon. Compound **594** was manipulated to sulfone **595**, which was then deprotonated and added to the methyl ketone fragment **587**. Eliminative desulfonation resulted in the *E*-trisubstituted alkene **596**. Another sulfone anion–carbonyl addition was utilized to hook on the oxahydrindene component. Deprotonation of **598**, followed by addition to the naturally derived oxahydrindene component **599**, followed by elimination resulted in the desired C-1–C-11 *trans* alkene of seco-compound **600**. The carboxylic acid and alcohols were freed and the macrocycle was closed by the DCC–DMAP method in 30% yield. Specific silylation of the C-5 alcohol gave **601**, which required attachment of the disaccharide and deconjugation



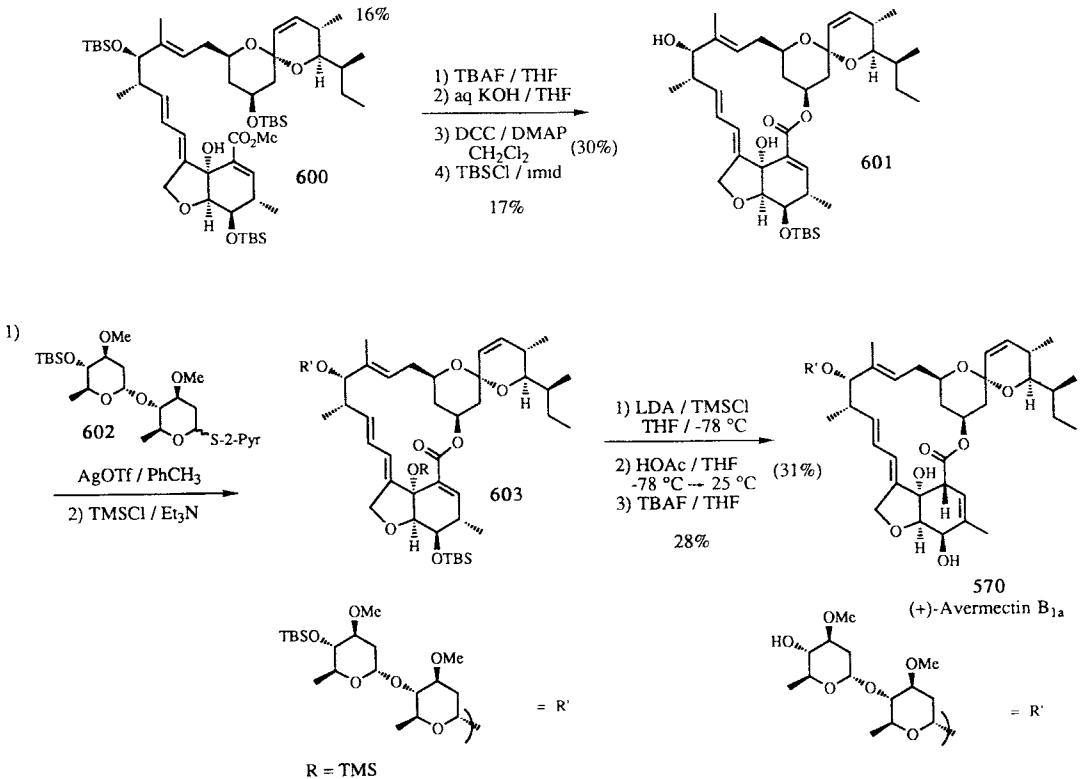
SCHEME 90. Two syntheses of the C-15–C-21 subunit (Hanessian).



SCHEME 91. Syntheses of the C-11–C-14 and C-22–C-27 subunits (Hanessian).

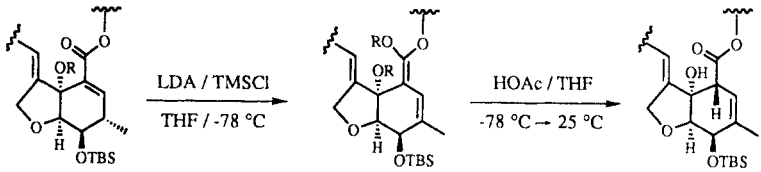


SCHEME 92. Combination of the optically active segments (Hanessian).



SCHEME 92. Combination of the optically active segments (Hanessian) (*continued*).

to complete the synthesis. The disaccharide was installed by coupling the alcohol at C-15 with the protected sugar **602**, followed by silylation of the C-7 alcohol giving **603**. The crucial deconjugation has been a subject of controversy. This was accomplished by deprotonation of the α,β-unsaturated ester with LDA and trapping of the anion with TMSCl, resulting in a silyl ketene acetal (**604**, Scheme 93). It was reasoned that controlled protonation of **604** would lead to β-proton addition, resulting in the desired stereochemistry at C-2. In the original communication[100b] and a subsequent full report[100d] of this work, protonation of **604** by HOAc was reported to proceed in 31 and 72% yields, respectively. Final desilylation led to avermectin B_{1a}.



603 **604**

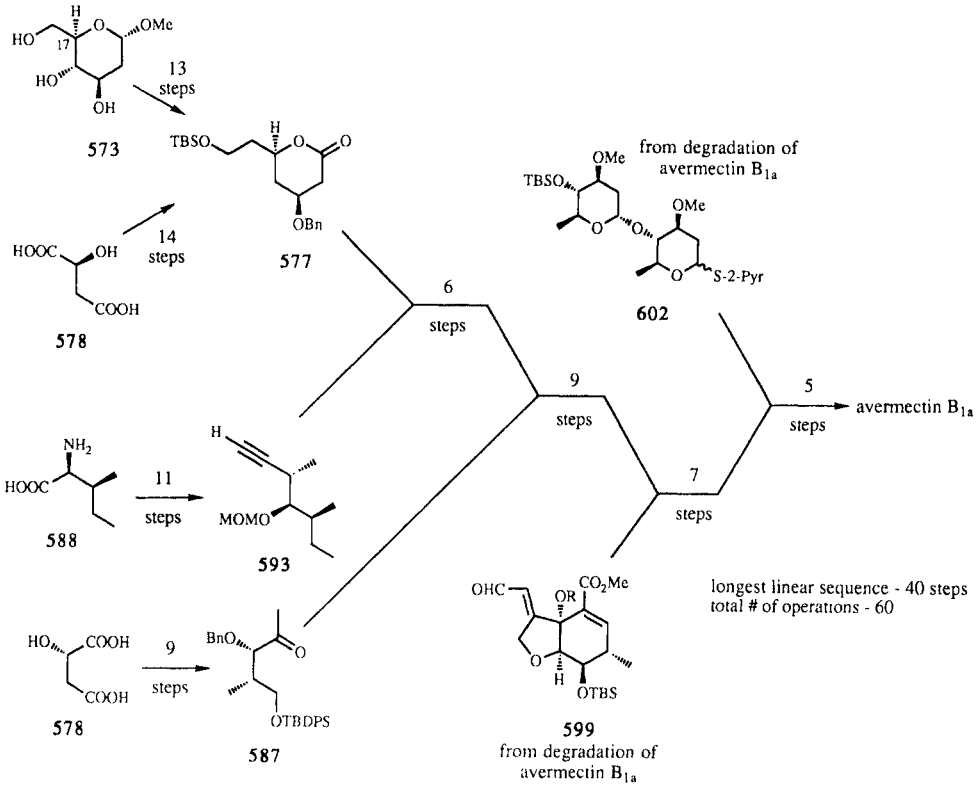
R = TMS

SCHEME 93. Deconjugation of **603** (Hanessian).

The aforementioned deconjugation results were questioned in a study by Fraser-Reid,[103] who concluded that C-3, C-4 alkenes must be viewed as "unreliable synthons" for the oxahydrindene portion of the avermectins. The deconjugation was further studied by the Hanessian group[104] and concluded that "the original material produced in (the) original deconjugation was not the primary product of deconjugation, but possibly the results of a subsequent epimerization of an initially formed 2-epi isomer." They additionally reported that a deconjugation–epimerization protocol employing imidazole in benzene was an effective method for converting C-2–C-3 alkene intermediates to the desired C-3–C-4 compounds with the natural configuration at C-2.

A summary of the Hanessian pathway is shown in Scheme 94. Since both the disaccharide and the oxahydrindene components were obtained from natural avermectin, it can be argued that this was a "partial synthesis." However, crucial technology and information which will prove useful in subsequent study was uncovered in the course of this work.

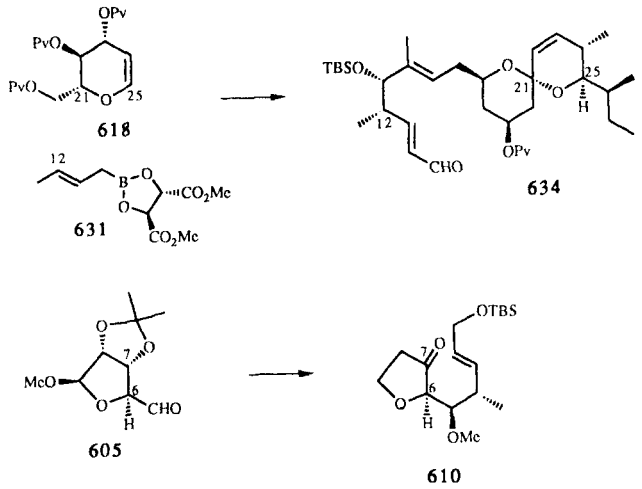
The Danishefsky approach focussed on preparing the spiroketal fragment and the protooxahydrindene fragment via linear sequences. The fragments used for assembly are shown in Scheme 95. Interestingly, none of the chiral



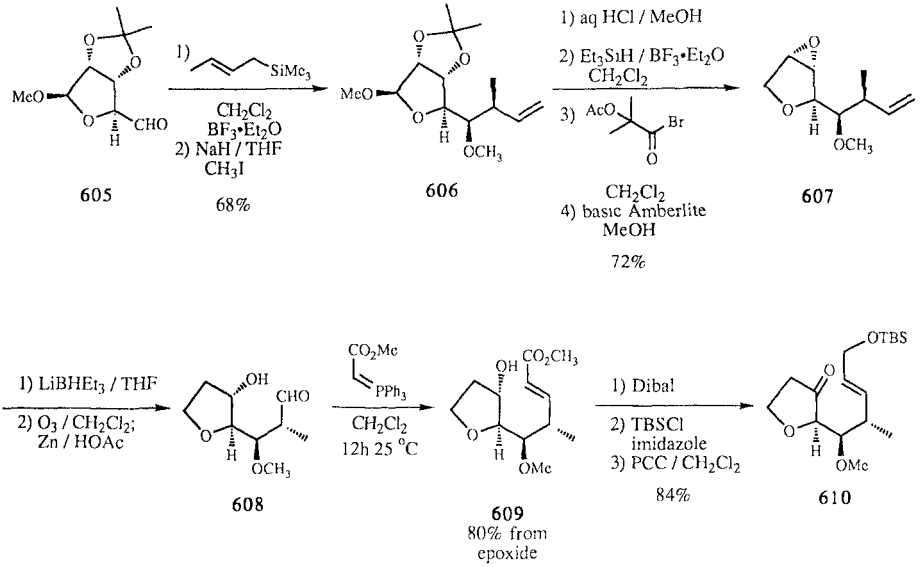
SCHEME 94. Summary of avermectin B_{1a} synthesis (Hanessian).

carbons in the glucal starting material for the spiroketal fragment were incorporated intact into **634**. The construction of the oxahydrindene fragment proceeded along classical lines, wherein the C-6 stereogenic center of the sugar derivative **605** was parlayed into chirality at C-5 in **610**. A noteworthy difference from Hanessian's approach is that an unfinished oxahydrindene fragment was combined with **634**.

The synthesis of the oxahydrindene precursor **610** is shown in Scheme 96. Addition of crotyl trimethylsilane proceeded selectively, giving **606** after methylation and separation of unwanted isomers. Defunctionalization at C-8α and conversion of C-7–C-8 to an epoxide gave **607**. Regiospecific reduction of the epoxide and ozonolysis gave the aldehyde **608**. The chain was extended via Wittig methodology and the functional groups modified to give the targeted tetrahydrofuranone **610** in a total of 12 steps from **605**.

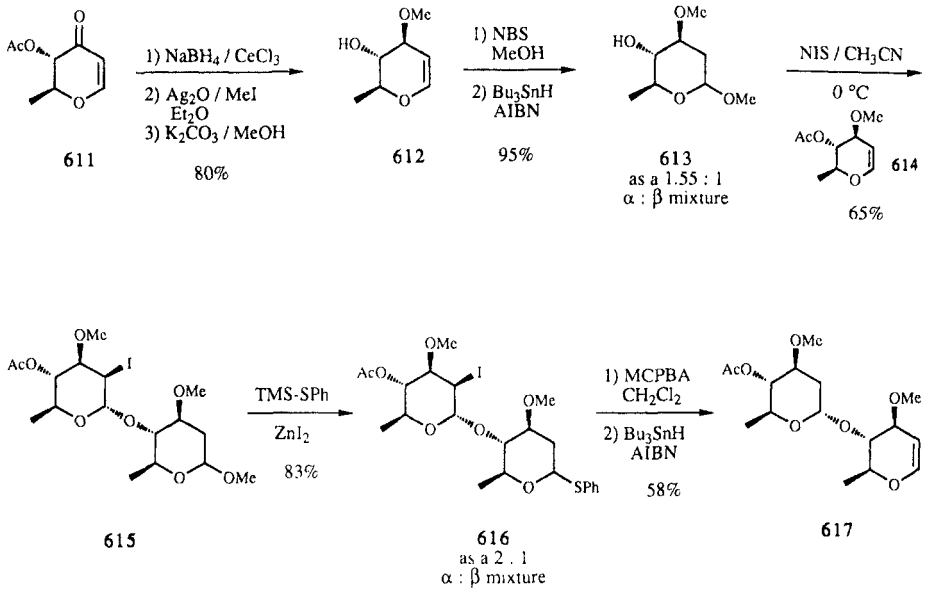


SCHEME 95. Fragments for assembly of avermectin A_{1a} (Danishefsky).



SCHEME 96. Synthesis of avermectin oxahydrindene precursor (Danishefsky).

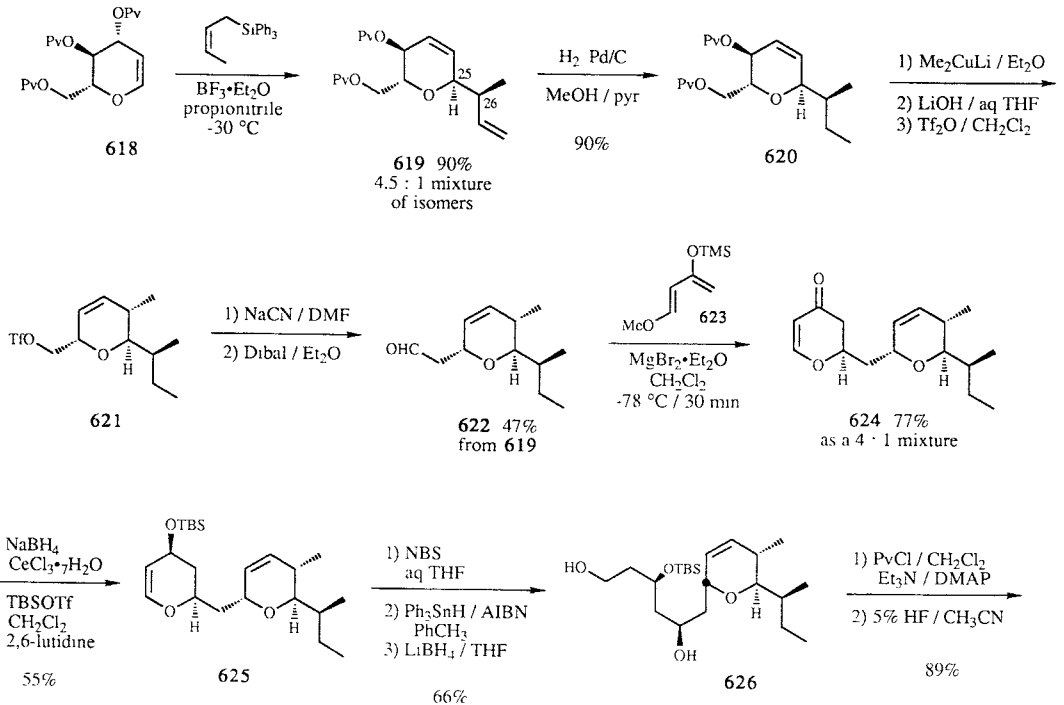
The disaccharide fragment was synthesized beginning with the optically active dihydro-2-pyrone **611** (Scheme 97). Reduction proceeded stereospecifically, producing compound **612** after methylation and ester saponification. The methyl glycoside mixture derived from **612** was connected to the glycal



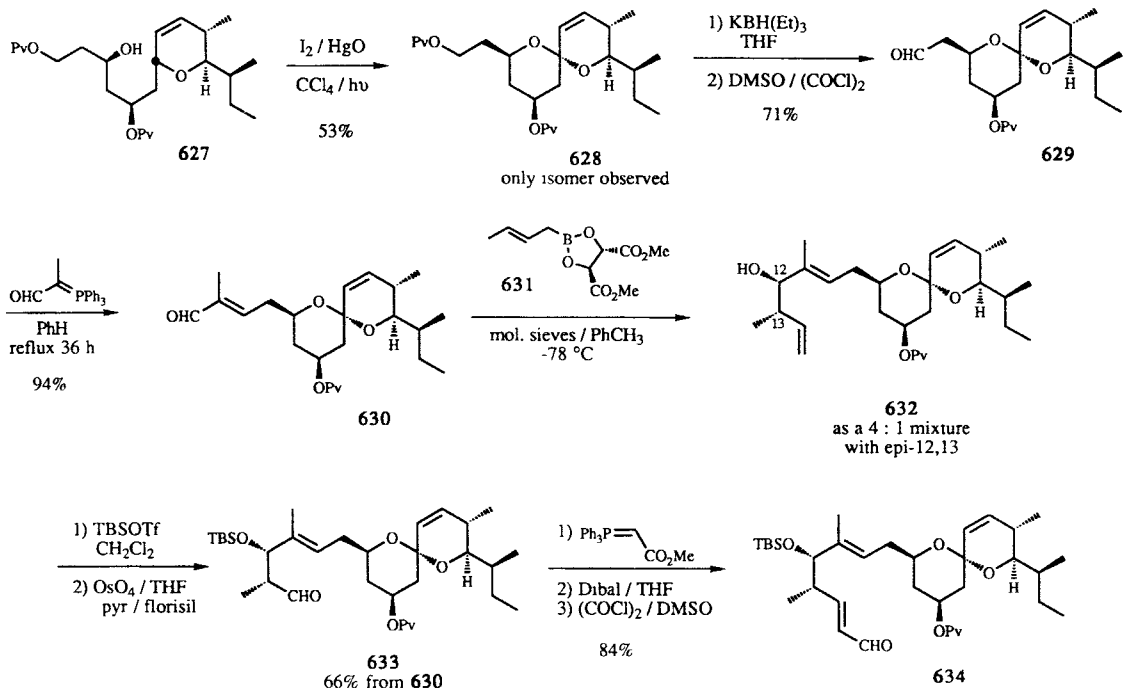
SCHEME 97. Synthesis of disaccharide glycal **617** (Danishefsky).

614 using the NIS method, producing iododisaccharide **615** in which an axial glycosidic bond was produced stereospecifically. Elimination of PhSOH and reductive deiodination led to the desired glycal disaccharide **617**.

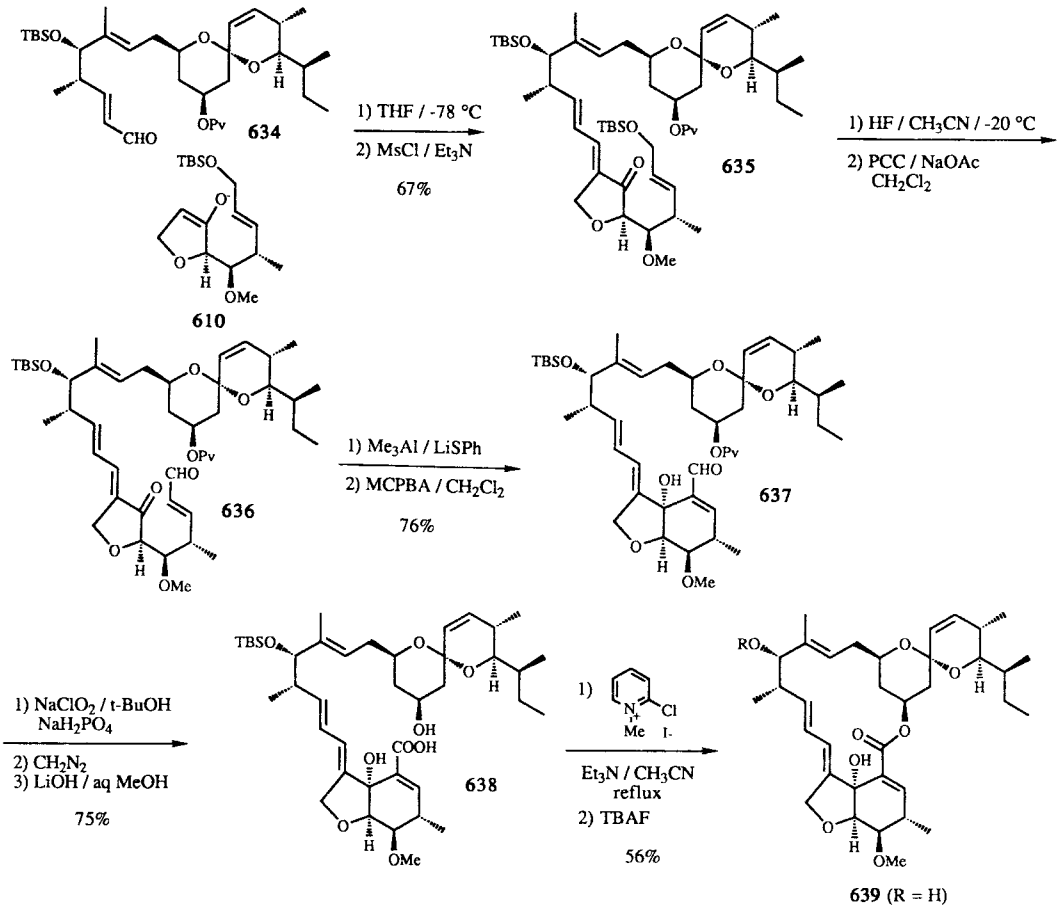
The synthesis of the spiroketal fragment **634** was much more interesting (Scheme 98). The glucal **618** was treated with *Z*-crotyltriphenylsilane to give **619** in 90% yield as a 4.5:1 mixture of desired:undesired isomers, successfully generating the correct relative and absolute configuration at C-25 and C-26. The adjoining stereocenter at C-24 was constructed by *anti*-displacement of the allylic pivaloate of **620** by lithium dimethylcuprate, eventually resulting in **621**. In the next series of key steps, aldehyde **622** was treated with diene **623** in the presence of $MgBr_2$ etherate, giving the cycloadduct **624** as a 4:1 mixture. The dihydro-4-pyrone **624** was reduced with the Luche reagent and silylated to give **625**. Thus, the transfer of chirality from C-21 of the original sugar to C-19 and thence to C-17 was completed. The functionality of compound **625** was adjusted to **627** in a five-step sequence. The crucial closure of the spiroketal (**627** → **628**) using the photochemical hypoiodite method, although precedented and predictable, was accomplished in 53% yield and is noteworthy for the functionality which is tolerated in the process. Functionality was adjusted, leading to aldehyde **629**. In a perceptive use of current technology, the remote stereocenters at C-12 and C-13 were induced by the reaction of **630** with the chiral crotyl boronate **631** resulting in the desired



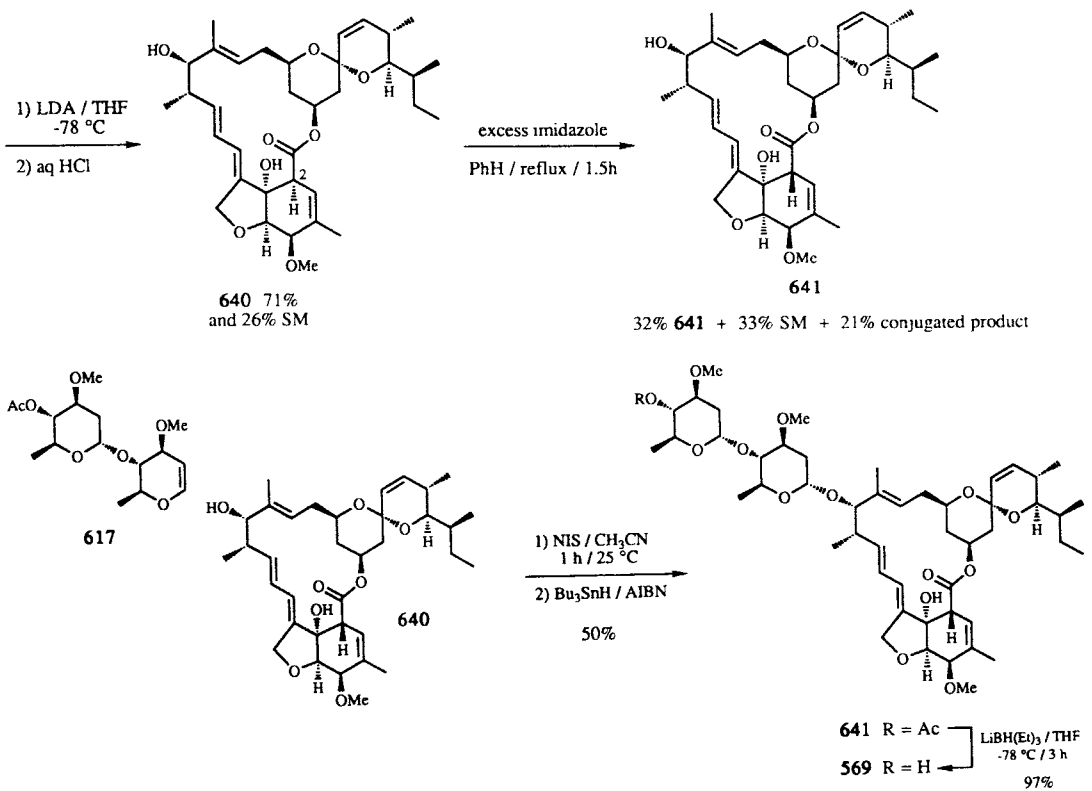
SCHEME 98. Synthesis of the spiroketal fragment **634** (Danishefsky).



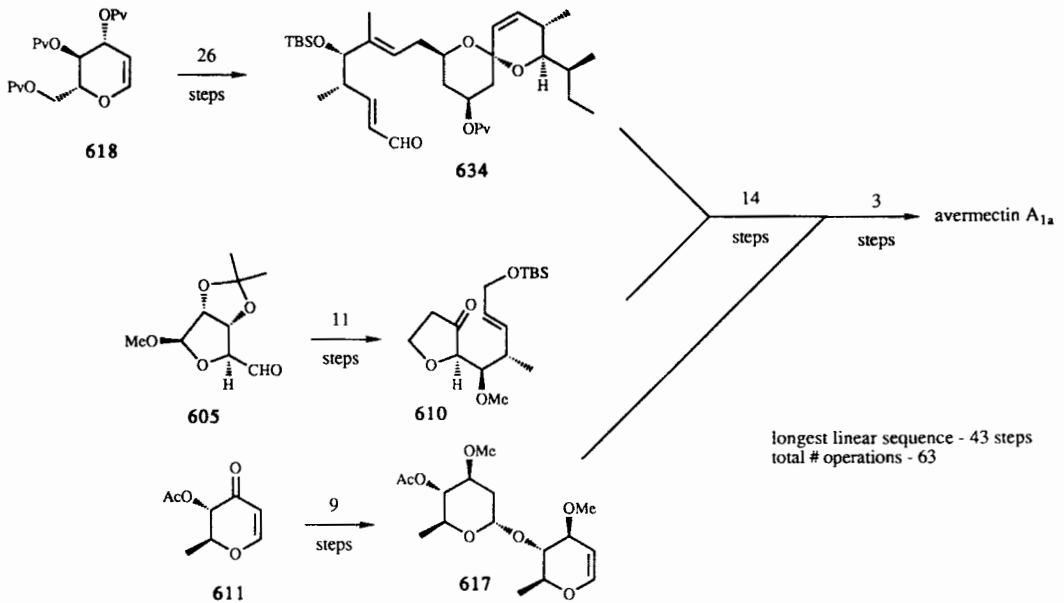
SCHEME 98. Synthesis of the spiroketal fragment **634** (Danishefsky) (*continued*).



SCHEME 99. Coupling of avermectin fragments (Danishefsky).



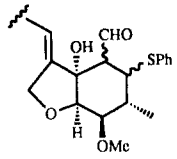
SCHEME 99. Coupling of avermectin fragments (Danishefsky) (*continued*).



SCHEME 100. Summary of avermectin A_{1a} synthesis (Danishefsky).

absolute stereochemistry as a 4:1 mixture. Standard transformations were used to convert **632** to the α,β-unsaturated aldehyde **634**, ready for connection to the oxahydrindene segment.

In a bold strategic move (Scheme 99), the spiroketal fragment **634** was attached to the proto-oxahydrindene fragment **610** via condensation of the enolate of the latter onto the aldehyde of **634**, producing in the process the *E* C-8–C-9 olefin (Scheme 99). Attention was next turned to completing the construction of the oxahydrindene ring system. Regiospecific desilylation and oxidation of **635** led to aldehyde **636**. Treatment of this substance with Me_3Al and LiSPh effects an intramolecular Nozaki reaction[105] via conjugate addition to the enal followed by intramolecular trapping of the enolate, producing the presumed intermediate **642** which was oxidatively eliminated to give the observed product **637**. The functionality of **637** was adjusted to prepare for macrolactonization, which was carried out using the method of Mukaiyama resulting in **639**. At this point in the synthesis, the supply of intermediate **639** (R = TBS) was supplemented with material obtained by degradation of natural avermectin, as described by Hanessian.[100d] Remaining tasks included the troublesome deconjugation and attachment of the disaccharide. Deconjugation led to the 2-epi compound **640**, which was followed by epimerization with excess imidazole in benzene as described by Hanessian to give a three-component mixture containing 33% starting material (2-epi), 21% conjugated product, and 32% of the desired 2 α-H compound aglycone **641**. The disaccharide units were then attached via the glycal **617**. Final deprotection was accomplished reductively, resulting in (+)-avermectin A_{1a}.



642

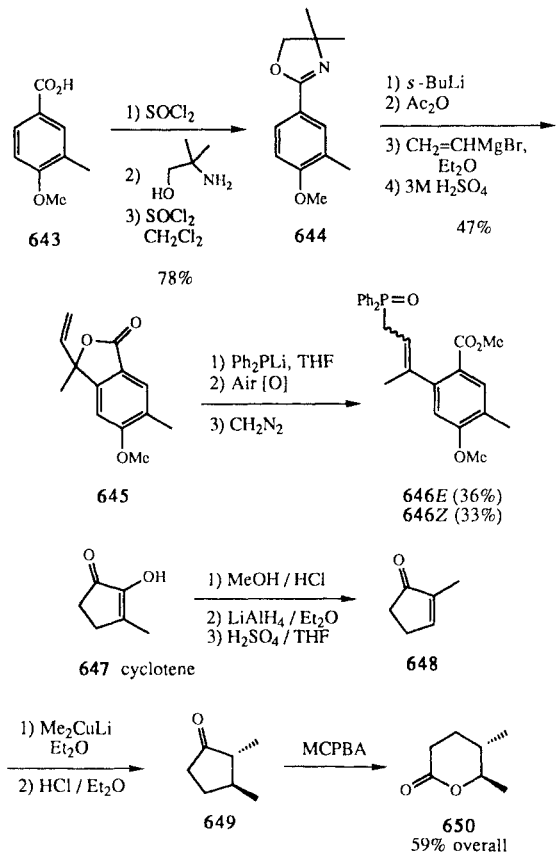
A summary of the Danishefsky approach is shown in Scheme 100. The synthesis required approximately 43 steps in the longest linear sequence and represents the first totally synthetic route in the avermectin series.

B. Milbemycin β_3

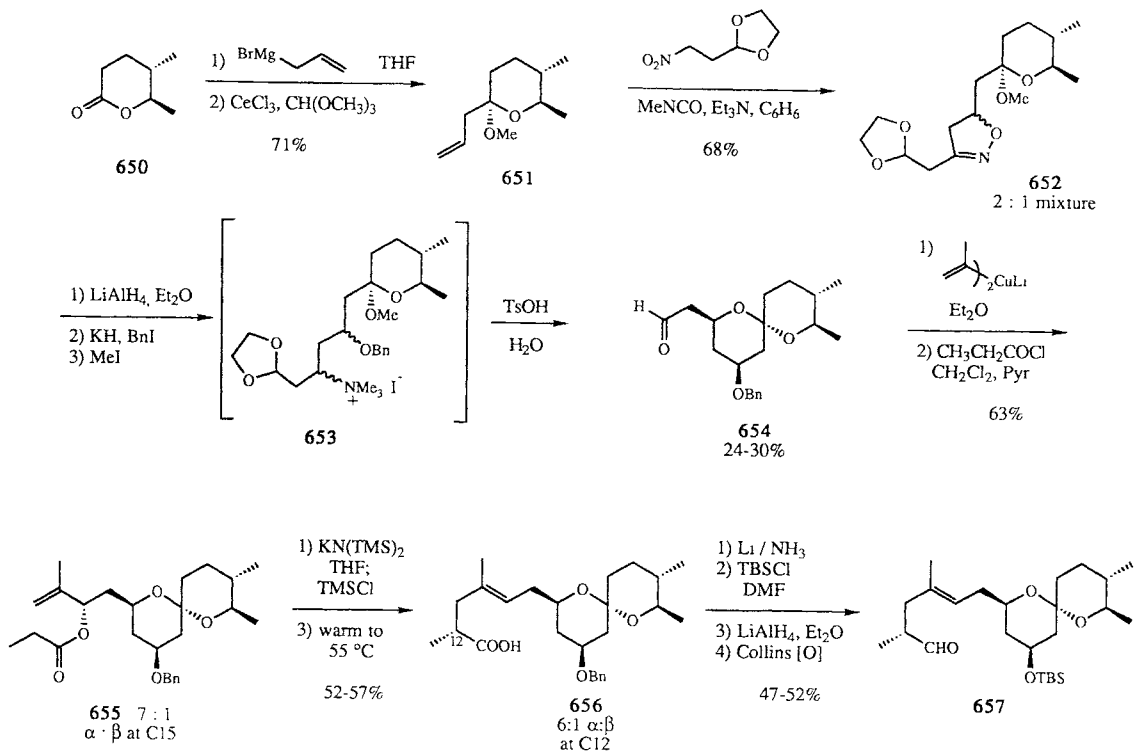
Milbemycin β_3 is one of the structurally simplest members of this class and was the first to draw a large amount of attention from the synthesis community. Several syntheses have been described, all of which assemble an

intact spiroketal fragment prior to connection to other fragments, as might be expected. The first syntheses were reported by Smith and by Williams in 1982. Subsequent syntheses reflect several of the elements of these two pioneering works.

The strategy for establishing the two remote sets of stereocenters (C-12 and the spiroketal region) generally involved coupling optically active fragments; the Smith group, however, used chelation-controlled organometallic addition to establish stereochemistry at C-15, which was then transferred to C-12 by [3,3] sigmatropic rearrangement. All of the syntheses, except for that of Baker, utilized organometallic addition to the optically active lactone **650** as a main bond-forming step in the synthesis of a spiroketal fragment. As with the avermectins, sulfone anion additions to aldehydes was a common method to link two fragments together, generating an olefin in the process.



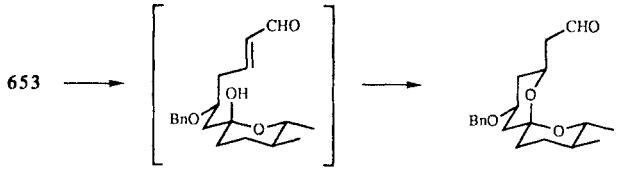
SCHEME 101. Smith synthesis of milbemycin fragments.



SCHEME 102. Milbemycin β_3 synthesis (Smith).

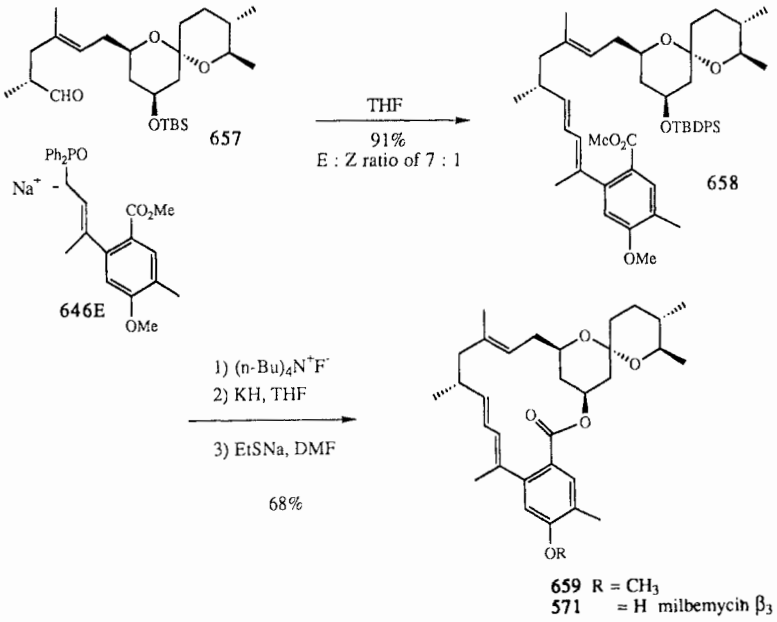
Smith's synthesis[106] began with the preparation of the two segments **646E** and **650** (Scheme 101). This group generated all the stereocenters of milbemycin β_3 from the optically active lactone **650**, which was prepared in racemic form from cyclotene (**647**). The lactone was also made from citronellol in optically active form by this and other groups. The aromatic C-1–C-10 fragment was made via directed lithiation of oxazoline **644**. However, the final set of transformations (**645** → **646**) resulted in a nearly 1:1 mixture of E/Z isomers.

The assembly of the fragments is shown in Scheme 102. The key sequence involved nitrile–oxide cycloaddition giving the isoxazolidine mixture **652**. $LiAlH_4$ reduction of the mixture followed by *O*-benzylation and exhaustive amine methylation gave a mixture of ammonium salts **653**, which was treated with aqueous TsOH, resulting in the desired spiroketal **654** in 24–30% overall yield. The course of events was thought to involve the intermediate enal **658** undergoing conjugate addition of anomeric hydroxyl via a chair-like transition state providing the observed product (see Kishi calcimycin synthesis). Chelation-controlled cuprate addition to the aldehyde provided a 7:1 (desired:undesired) mixture of allylic alcohols which was acylated to the allylic propionate **655**. Ireland Claisen rearrangement of the derived *Z* ester enolate occurred with good chirality transfer, providing the acid **656** with the correct configuration at both C-12 and the C-14–C-15 trisubstituted olefin. Conversion of **656** to the aldehyde (**657**) and coupling with the aromatic fragment **646E** provided **658** in an E/Z ratio of 7:1 (Scheme 103). The route was finished off by macrolactonization via treatment of the derived hydroxy-ester with KH giving milbemycin β_3 methyl ether (**659**), which was demethylated by sodium ethanethiolate providing milbemycin β_3. The synthesis took 26 steps (longest path) and set the stage for much of the subsequent work in this area.

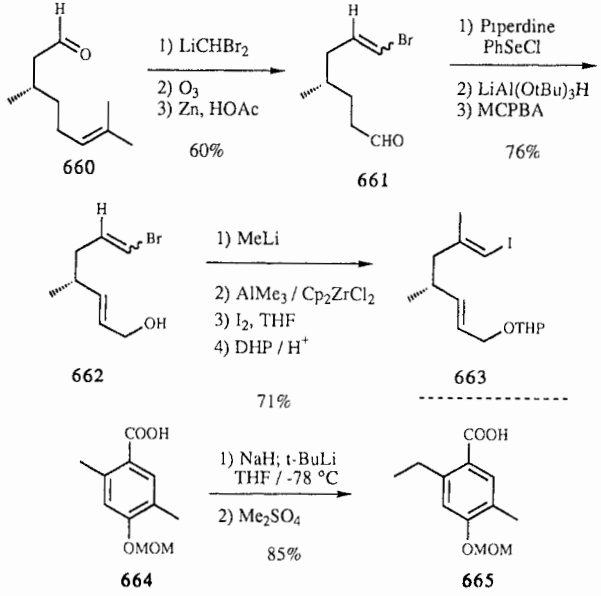


658 654

The Williams group reported a second synthesis later in the same year using a somewhat different strategy.[107] Three fragments were produced and joined to provide the target molecule. Scheme 104 shows the synthesis of two of these fragments. *S*-Citronellal was elongated at one end and shortened at the other via a seven-step process. The required *E* configuration of the C-14–



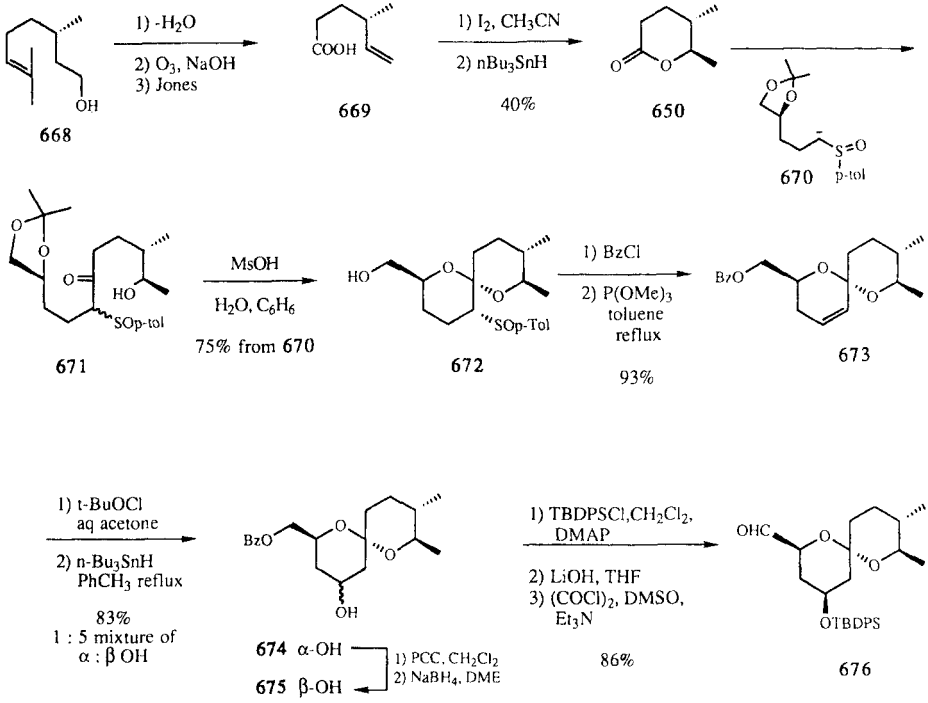
SCHEME 103. Combination of milbemycin β_3 fragments (Smith).



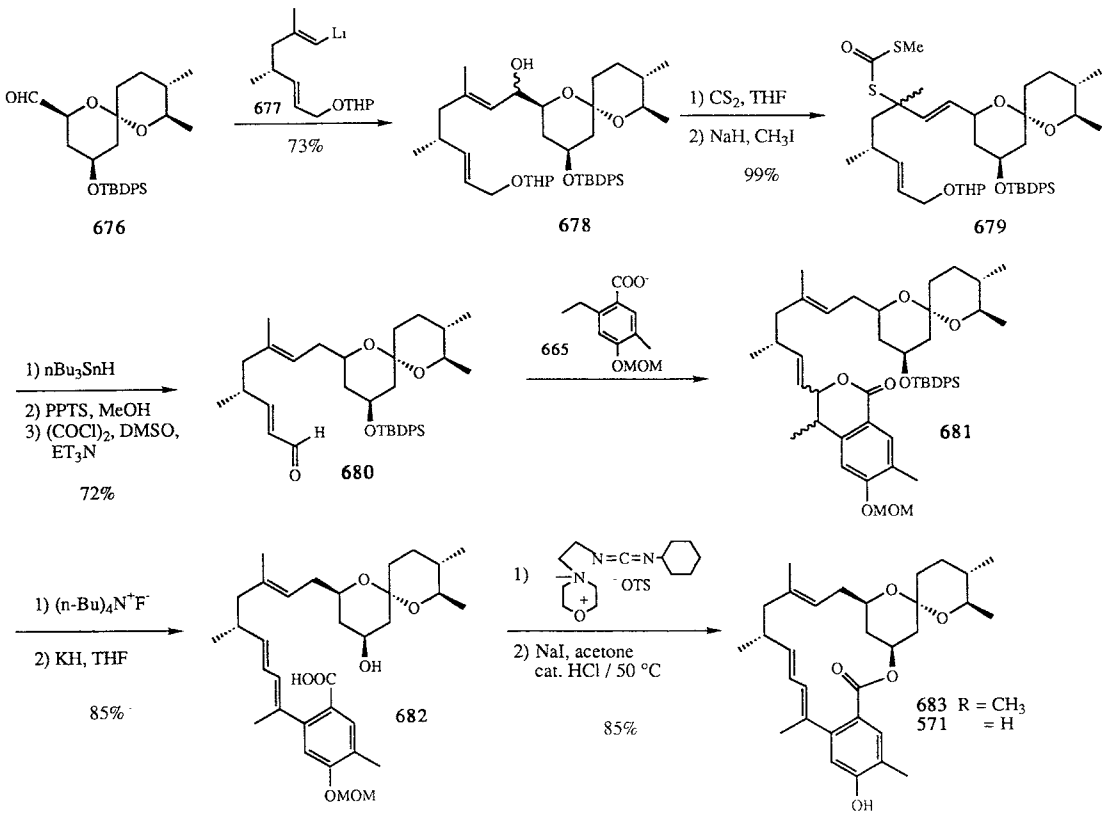
SCHEME 104. Synthesis of C-1–C-8 and C-9–C-15 fragments (Williams).

C-15 olefin was established by stereospecific *cis* addition of a mixed metal Negishi reagent to a terminal alkyne followed by reaction with iodine to give **663**. The aromatic fragment **665** was made by methylation of the known acid **664** via its dianion.

The spiroketal fragment consisted of carbons 16–26 with the connection point being a C-16 aldehyde. Beginning from S-citronellene, the lactone **650** was produced utilizing a stereoselective (15:1) iodolactonization (Scheme 105). Addition of the sulfoxide anion **670** to the lactone gave rise to the ketone **671**, which was closed with acid. The favored bis-diaxial C–O arrangement could be attained with all substituents in equatorial positions. Partial equilibration of the sulfoxide to an equatorial position was observed as well. Sulfoxide elimination produced the unsaturated spiroketal **673**. Hypochlorination of the olefin led to a mixture of chloroalcohols, which was dechlorinated, resulting in the α–β alcohols **674–675**. The regiochemistry of hypochlorination can be rationalized by the greater carbocationic character expected at C-19 over C-20, which is closer to the two spiro C–O bonds and their inductive electron-withdrawing effects. The unwanted α alcohol could



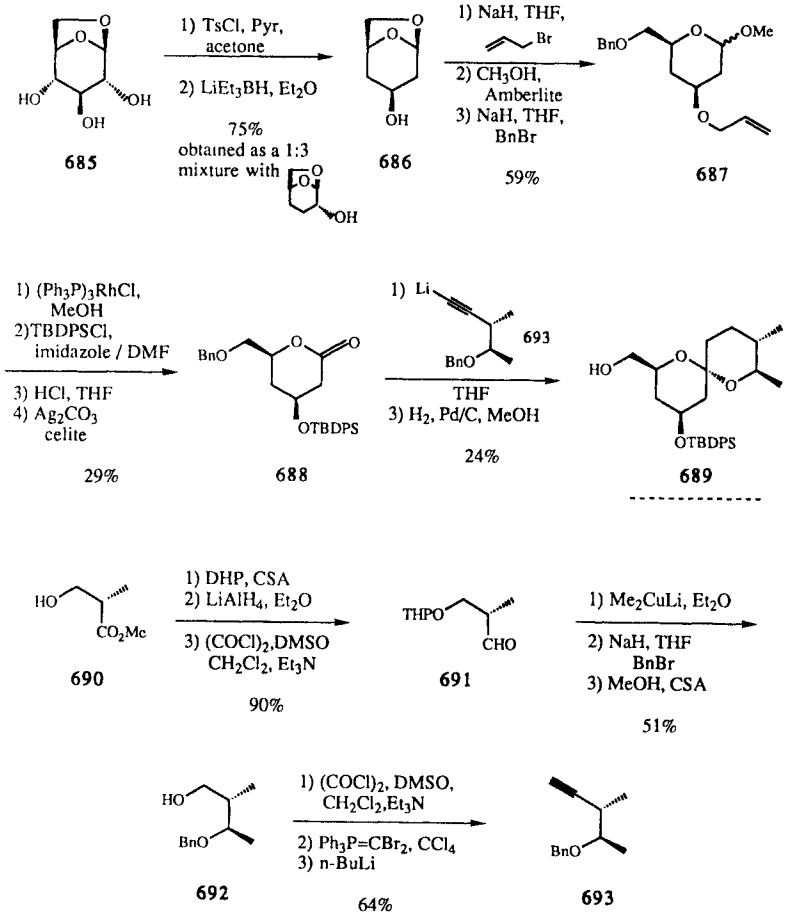
SCHEME 105. Synthesis of the milbemycin β_3 spiroketal fragment (Williams).



SCHEME 106. Connection of milbemycin β_3 fragments (Williams).

be recycled via a standard oxidation–reduction sequence. Functional group manipulation led from **675** → **676**.

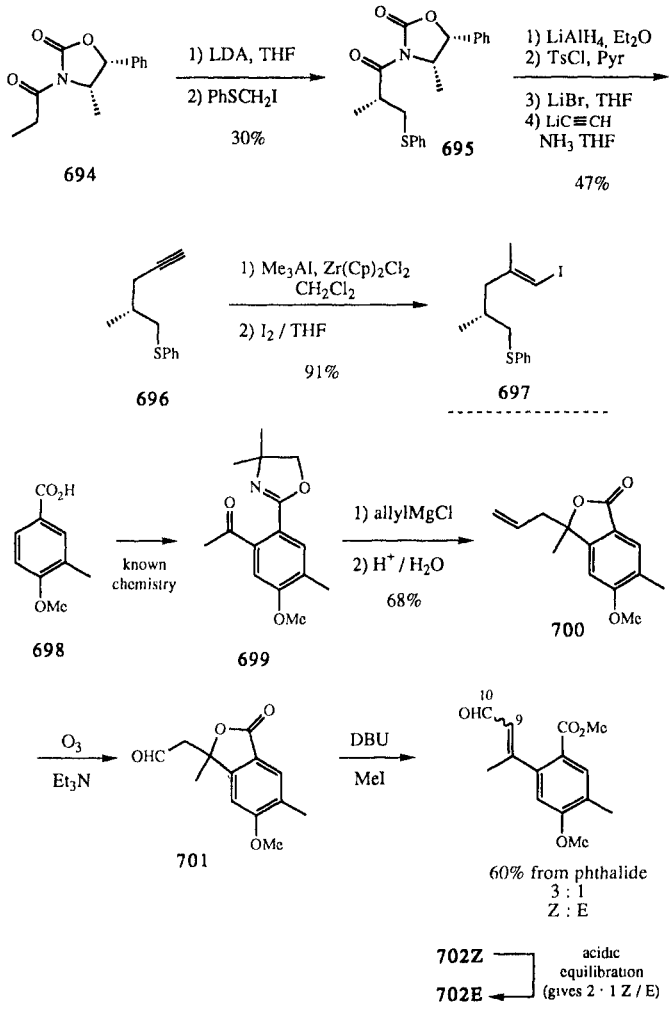
The combination of fragments **663**, **665**, and **676** is shown in Scheme 106. The lithium reagent was added to the aldehyde **676**, producing a mixture of carbinols. Xanthate formation and [3,3] sigmatropic rearrangement led to the *trans*-olefin isomer **679**. Free radical reduction of the dithiocarbonates led selectively to the desired C-14–C-15 *E* olefin **680** along with 25% of other olefin isomers. The aromatic fragment was attached via its benzylic anion to **680**, producing a diastereomeric pair of lactones **681**. Desilylation and treatment with KH induced elimination of each separated isomer to the same



SCHEME 107. Synthesis of the milbemycin spiroketal (Baker).

E olefin **682**. Macrolactonization was accomplished using a modified DCC reagent giving **683**, which was demethylated to give milbemycin β_3. The route was approximately 23 steps, including 10 steps from the point of first convergence.

The Baker synthesis approached the construction of the spiroketal portion from a different perspective (Scheme 107).[108] Glucose was used as the chiral pool starting material and the C-3 and C-6 asymmetric carbons of glucose



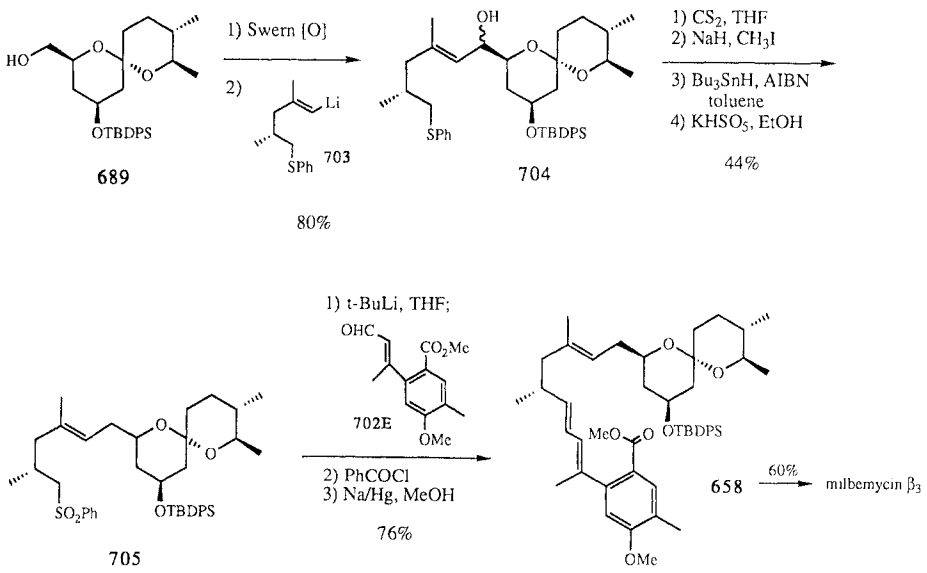
SCHEME 108. Synthesis of the C-11–C-15 and C-1–C-10 fragments (Baker).

were transformed into C-19 and C-17 of milbemycin β_3. In this strategy a C-22–C-26 alkynyl unit (**693**) was added to a C-16–C-21 lactone piece (**688**), leading to the spiroketal **689** after thermodynamic cyclization. The alkyne **693** was derived from the popular chiral pool element **690**.

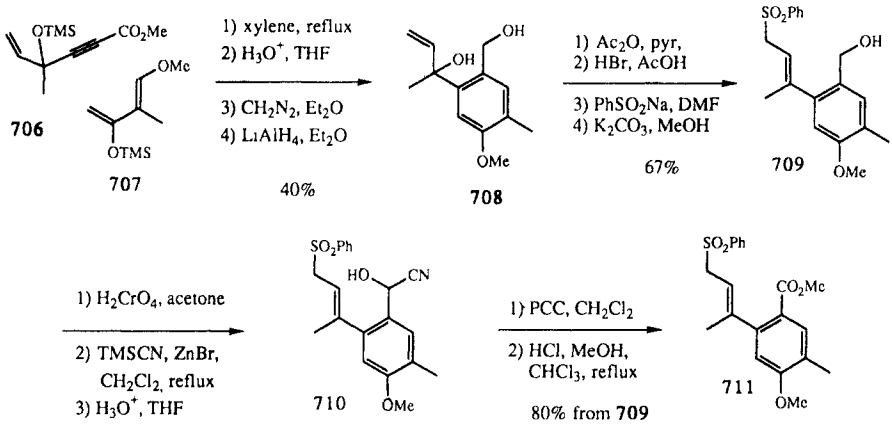
Syntheses of the two other segments are shown in Scheme 108. The aromatic fragment was made in a manner similar to the Smith synthesis, although the Baker fragment was two carbons larger (C-9–C-10). Unfortunately, formation of the *E*-trisubstituted olefin (**701** → **702E**) was not controlled. The C-11–C-15 piece **697** was made in an efficient six-step process using the Evans chiral auxiliary to establish the absolute stereochemistry at C-12.

Combination of the three fragments is shown in Scheme 109. Oxidation of **689** to the aldehyde and combination with the organolithium **703** joined C-15 and C-16, giving the allylic alcohol **704** as a mixture of isomers. Deoxygenation of C-16 was accomplished using the Williams protocol. Sulfone anion–aldehyde addition was used to connect C-11 to C-10, giving the *trans* olefin **658**. This intermediate was identical to a Smith intermediate and the Smith protocol was used to convert **658** to milbemycin β_3 in 60% yield. Twenty-two steps comprised the longest sequence.

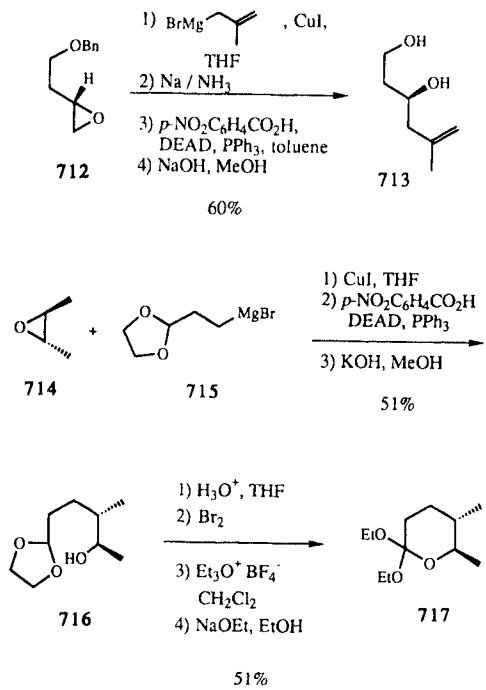
The Kocienski group took a novel approach to both the aromatic and spiroketal fragments (Schemes 110 and 111).[109] Diels–Alder cycloaddition



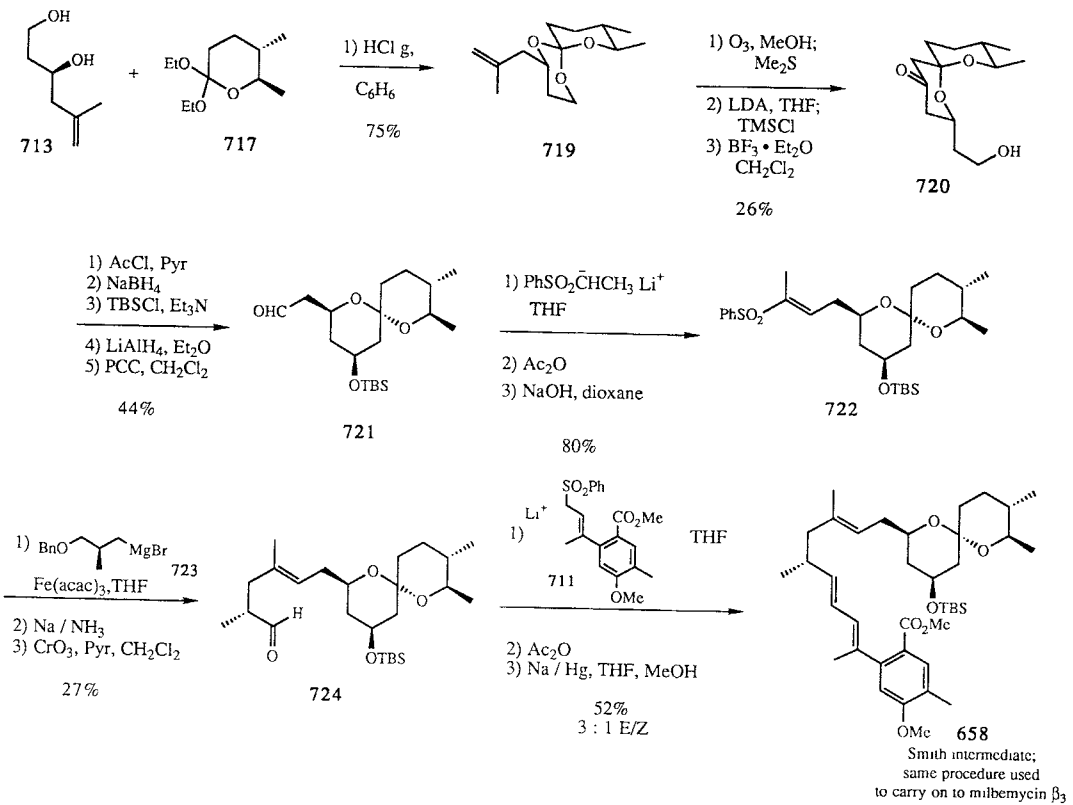
SCHEME 109. Combination of milbemycin β_3 fragments (Baker).



SCHEME 110. Synthesis of milbemycin β_3 aromatic fragment (Kocienski).



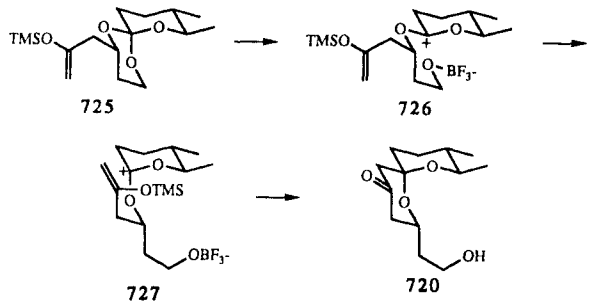
SCHEME 111. Synthesis of two segments used to construct the spiroketal fragment (Kocienski).



SCHEME 112. Assembly of milbemycin β_3 (Kocienski).

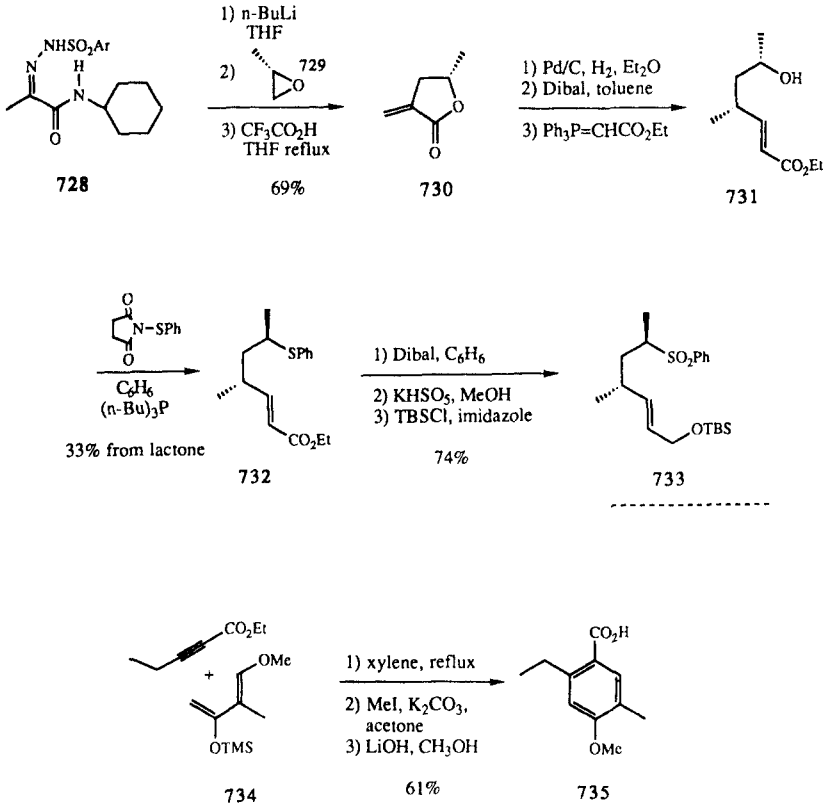
was used to assemble an aromatic ring precursor **711**. It required nine steps to adjust the functionality in **708** to that of the desired fragment **711**. However, the overall yield of the 13 steps was 21%.

Two stereogenic segments were needed for the spiroketal. They were produced in straightforward sequences (Scheme 111) from optically active epoxides. The ortholactone **717** was transorthoesterified with the diol **713**, producing **719** (Scheme 112). Ozonolysis and enolate formation led to the silyl ether **725**. Treatment of **725** with Lewis acid led to the desired spiroketal **720** in 26% yield from the ortholactone **719**. One mechanistic rationale invokes production of a dioxenium cation **726** by ionization of **725** followed by cyclization onto the enol ether producing the observed product. Functional group manipulation and elongation at C-15 produced the *E* α,β-unsaturated sulfone **722**. This was coupled to the optically active 3-carbon (C-13–C-11) Grignard reagent **723** and oxidized to give the aldehyde **724**. Sulfone anion-aldehyde addition was used to connect **724** to the aromatic fragment **711** producing the *trans* C-10–C-11 (3:1 *trans/cis*) bond producing the Smith intermediate **658**, which was carried onto milbemycin β_3 using Smith's procedure in 60% yield for the final three steps. The longest sequence (from *trans* epoxide **714**) was approximately 28 steps.



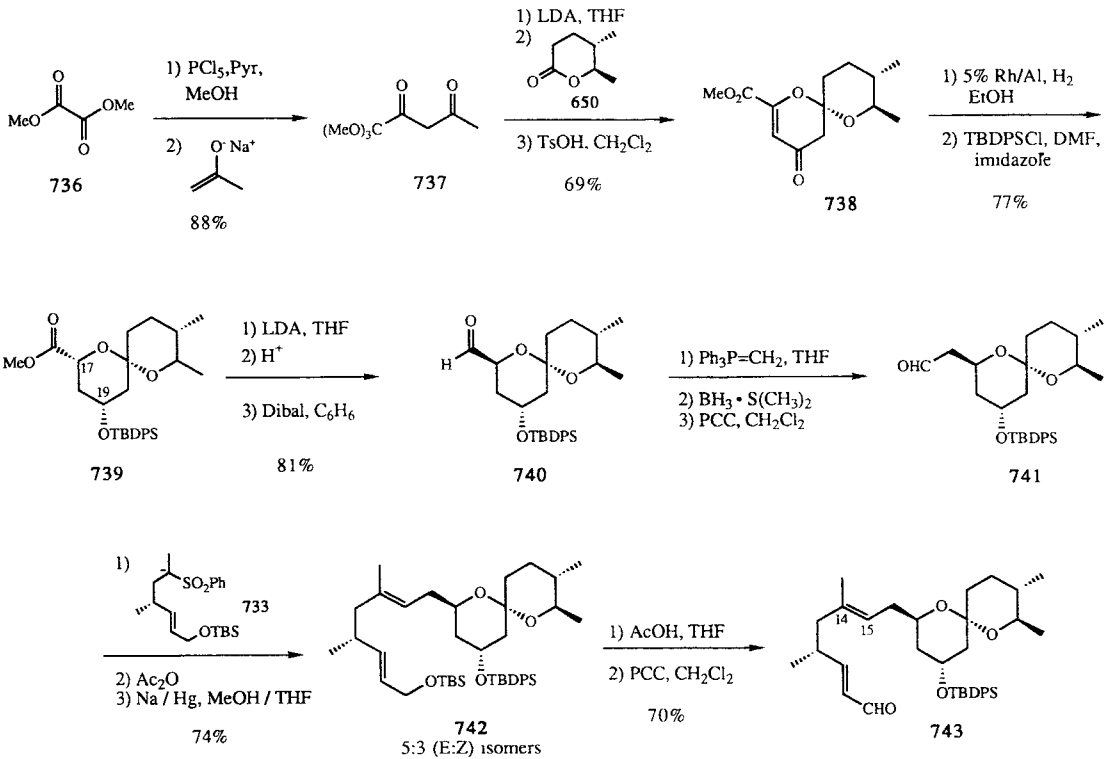
The most recent approach was described by Barrett.[110] The unique feature of this approach was the use of Mitsunobu macrolactonization to close the 16-membered ring with inversion at C-19. The synthesis of the aromatic fragment followed from a Diels–Alder strategy similar to Kocienski's approach, resulting in the acid **735** (Scheme 113). The C-9–C-14 fragment **733** was prepared from *S*-propylene oxide **729** proceeding in nine steps. A transient stereogenic carbon at C-14 was used to induce asymmetry at C-12 via catalytic hydrogenation of the α,β-unsaturated lactone **730**.

The spiroketal fragment was fashioned using technology developed by this group (Scheme 114). The diketo-orthoester **737** was deprotonated and added to the lactone **650** and cyclized to the dihydro-4-pyrone **739**. Hydrogenation

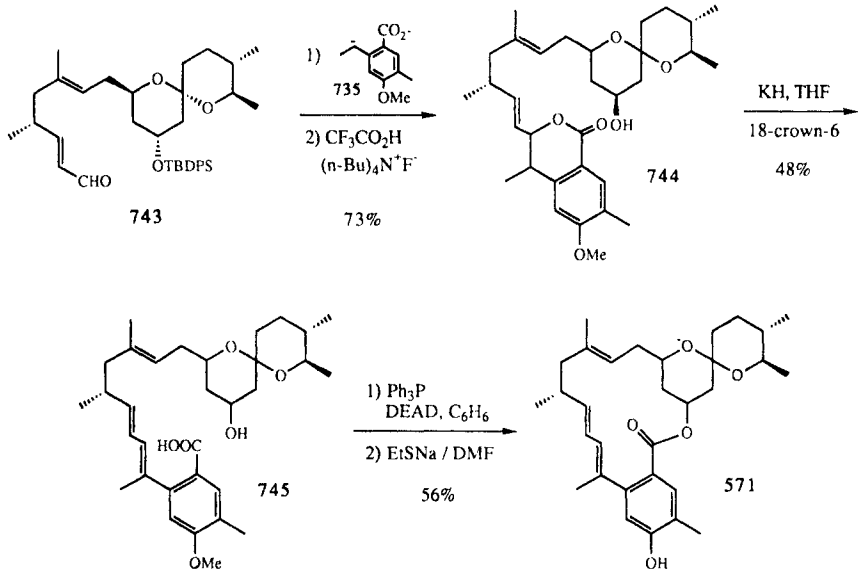


SCHEME 113. Synthesis of the aromatic and C-9–C-14 fragments (Barrett).

of both the olefin and ketone carbonyl gave rise to the C-17 and C-19 bis-*epi* compound **739**. Epimerization of C-17 by base corrected the stereochemistry at this position, leading to **676**. The sulfone anion **733** was added to the elongated aldehyde **740** in a typical three-step Julia olefination. The trisubstituted olefin formed (**742**) was a 5:3 (*E*/*Z*) mixture. A sequence very similar to one in the Williams synthesis was used at this point to convert **742** to the carboxylic acid **745**. Functional group manipulation of **742** led to **743**, which was coupled to the Williams benzylic dianion **735** giving lactone **744** (see Schemes 106 and 115). Base-induced elimination led to *E*-trisubstituted olefinic acid **745**. Finally, Mitsunobu macrolactonization and demethylation using conditions developed by Smith gave milbemycin β_3 in an overall 22-step process.



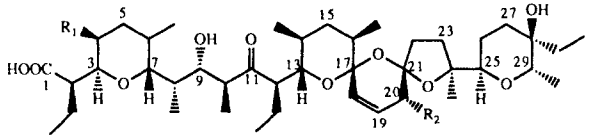
SCHEME 114. Milbemycin β_3 spiroketal synthesis (Barrett).



SCHEME 115. Combination of milbemycin β_3 fragments (Barrett).

7. NARASIN–SALINOMYCIN (TRIOXADISPIROKETALS)

A small number of polyether ionophores contain trioxadispiroketal ring systems—a unique functional arrangement of three rings linked in a spiro fashion at two ketal carbons. Two members of this small family have been synthesized. Narasin[111] and salinomycin[112] possess structures **747** and **748**, differing only trivially at the C-4 position. Despite the complexity of the heavily functionalized trioxadispiroketal embedded in **747** and **748**, these substructures are only one challenge in an extremely provocative molecular arrangement. Not surprisingly, a fair amount of technology was developed

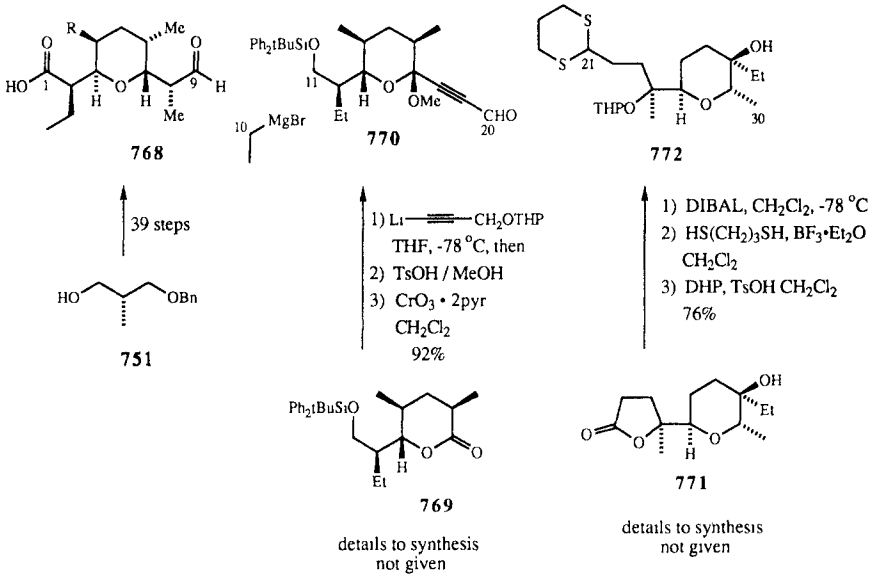


		R_1	R_2	
747	narasin	CH_3	OH	
748	salinomycin	H	OH	
749	deoxy (O-8)-epi-17-salinomycin	H	H	(epi C-17)
750	deoxy (O-8) salinomycin	H	H	

concerning the stereoselective formation of C–O bonds during the course of work on these molecules.

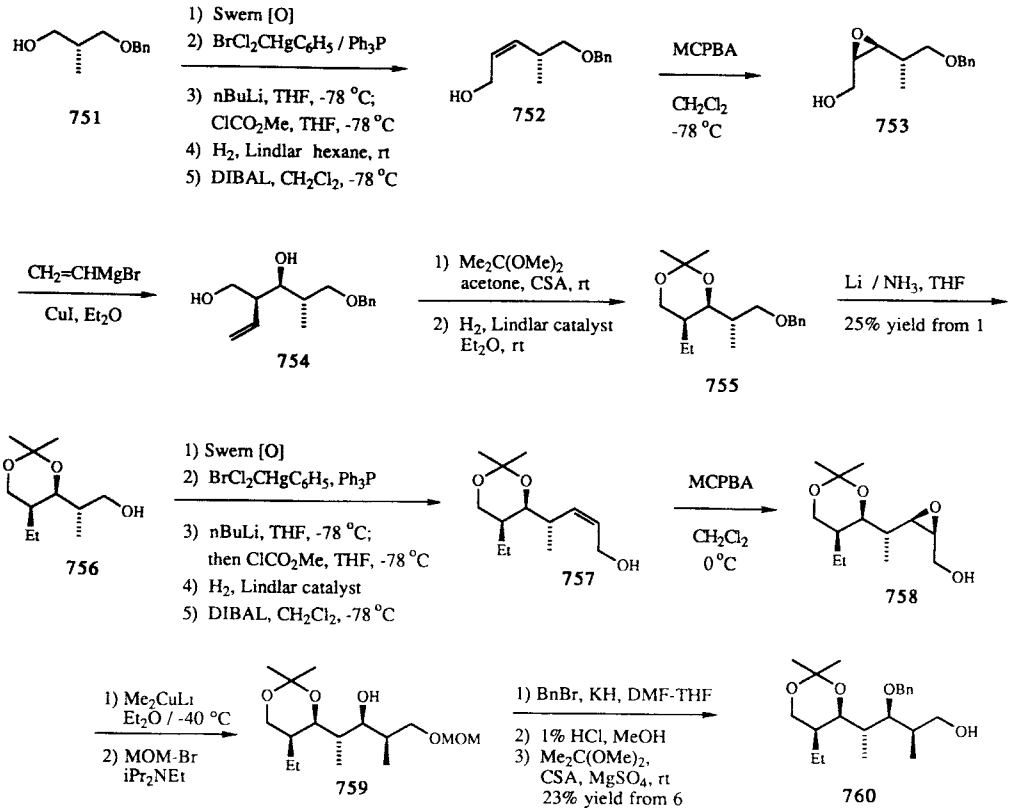
The first syntheses in this series were reported by Kishi in 1981[113] (narasin, salinomycin), which laid the groundwork for subsequent work in this area by Yonemitsu (salinomycin).[114] Both groups constructed the molecules using basically the same strategy and disconnections. Each group divided the problem into construction of three fragments, which were then assembled. The Kishi connections occurred at C-9–C-10 and C-20–C-21. The Yonemitsu group connections were slightly different, occurring at C-9–C-10 and C-17–C-18. Both groups synthesized the same C-1–C-9 end fragment and connected this fragment by aldol reaction to a C-10–C-30 fragment, establishing two new stereocenters at C-9 and C-10 in the process.

The three segments the Kishi group coupled together are shown in Scheme 116. The C-1–C-9 fragment was synthesized in 39 steps from the alcohol **751**, while partial syntheses of the other two fragments **770** and **772** proceeded from **769** and **771**, respectively. No details have yet been divulged for the production of these latter two compounds.

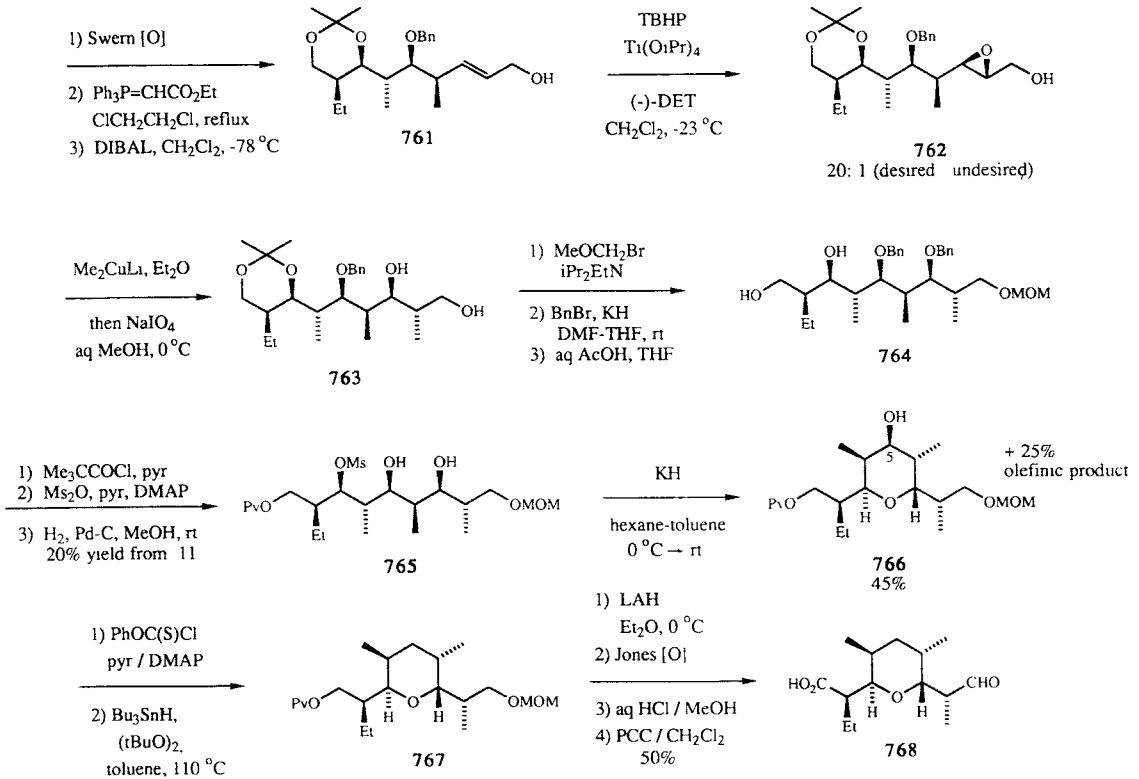


SCHEME 116. Fragments used in the Kishi assembly of narasin and salinomycin.

The synthesis of **768** is shown in Scheme 117 and is the product of a number of systematic studies centered around the production of polyketide units developed in these laboratories. The six chiral carbons of **768** were produced by 3 hydroxyl-directed epoxidation reactions guided additionally

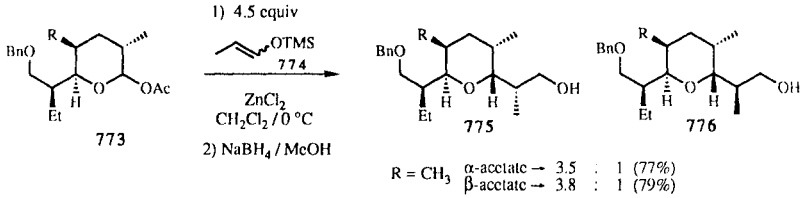


SCHEME 117. Synthesis of narasin–salinomycin C-1–C-9 fragment (Kishi).

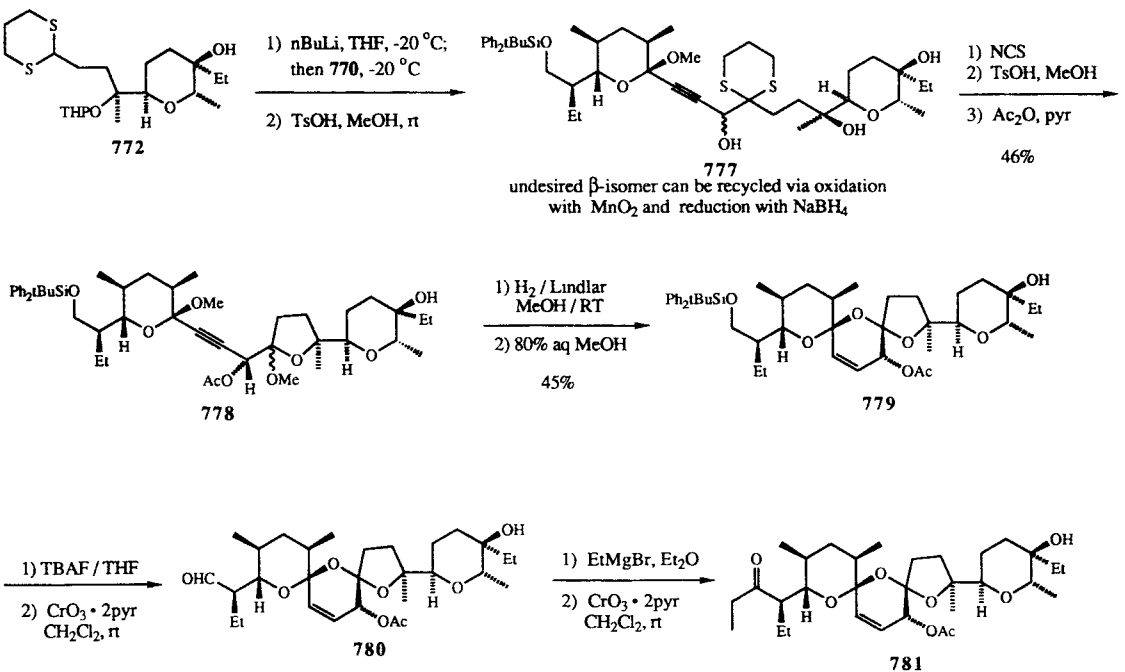


SCHEME 117. Synthesis of narasin–palnomycin C-1–C-9 fragment (Kishi) (*continued*).

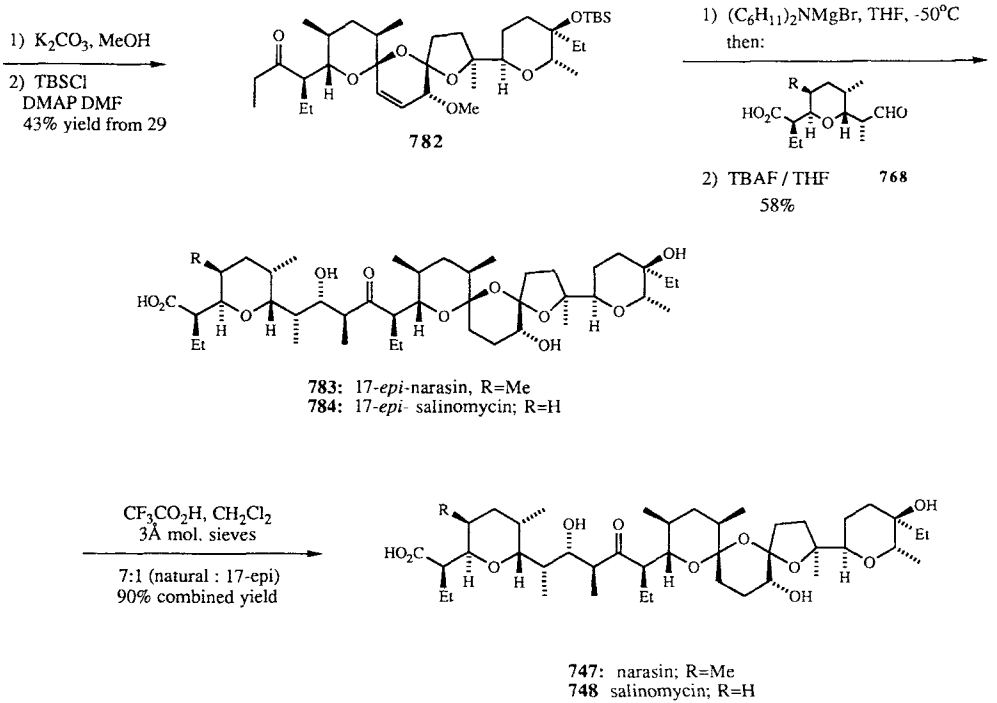
by the presence of allylic methyl groups. Allylic alcohols **752**, **757**, and **761** underwent stereoselective epoxidations, eventually producing a substance **765** which was cyclized by displacement to form the tetrahydropyran **766**. C-5 of this compound contained excess functionality, which was subsequently removed. The overall yield for the 39 steps leading to **768** was a maximum of 0.25%, not counting the **766** → **767** conversion (free-radical defunctionalization) which was a task ". . . which proved to be very difficult. . . ." There were many repetitive sequences, and the route is actually quite systematic despite its length. The use of seven protecting groups accounts for 13 of the 39 steps. An alternate synthesis of **768** has been worked out by the Kishi group,[115] involving as a key step the addition of the silyl ether mixture **774** to either anomeric isomer of acetate **773**. A favorable ratio of desired (3.5):undesired (1) diastereomers was obtained. The undesired isomer **776** could be converted to **775** in a two-step process.



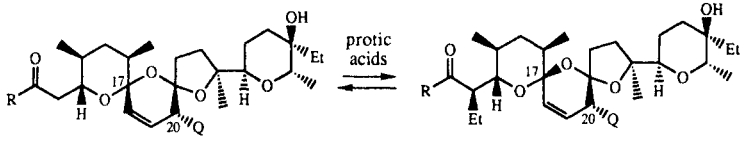
The combination of the three major fragments is shown in Scheme 118. The C-21–C-30 fragment was connected to the C-11–C-30 fragment by dithiane addition to an aldehyde. The crucial spirocyclization of **778** gave the C-17 *epi* compound **779**, which was carried through to aldehyde **780**. The final two carbons (C-10 and its attached methyl group) were added to **780** and oxidized to the desired ethyl ketone **781**. Enolate formation and reaction with the appropriate C-1–C-9 aldehyde fragment **768** produced 17-*epi*-narasin **783**. A key fundamental observation of C-17 epimerizations in these systems is diagrammed in Scheme 119. In synthetic intermediates (where R = Et), protic acid-catalyzed equilibration of the trioxadispiroketal ring system reveals that the C-17 *epi* isomers are favored, regardless of the nature of the group Q. This holds true with the natural-product C-20 acetates **785**. However, when the natural products themselves are equilibrated, the natural configuration and not the C-17 *epi* configuration is favored in both the narasin and salinomycin series. This indicates that the C-20 hydroxyl group and some other factor involving the left-hand portion of the molecules are somehow involved in determining the thermodynamically preferred configuration and conformation of the trioxadispiroketal ring system. In any case, 17-*epi*-narasin could be readily epimerized to narasin, thus completing the pathway.



772 777 778 779 780 781



SCHEME 118. Combination of fragments (Kishi).



747 Q = OH, narasin
748 Q = OH, salinomycin

>7 : 1

783 Q = OH, 17-*epi*-narasin
784 Q = OH, 17-*epi*-salinomycin

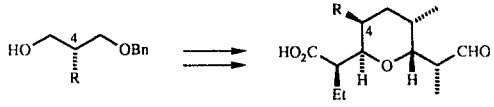
785a Q = OAc, narasin-20-acetate
785b Q = OAc, salinomycin-20-acetate

0 : 100

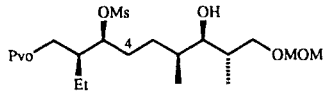
786a Q = OAc, 17-*epi*-narasin-20-acetate
786b Q = OAc, 17-*epi*-salinomycin-20-acetate

SCHEME 119. Spiroepimerization of trioxadispiroketals.

The synthesis of the closely related salinomycin required the fragment **768b** were R = H, and presumably similar chemistry for the remainder of the route resulted in **748**. All of the stereogenic carbons of **768b** originated from the chirality of the starting material **765b** containing the pro-C-4 stereocenter. Details of the synthesis of **765b** were not given.

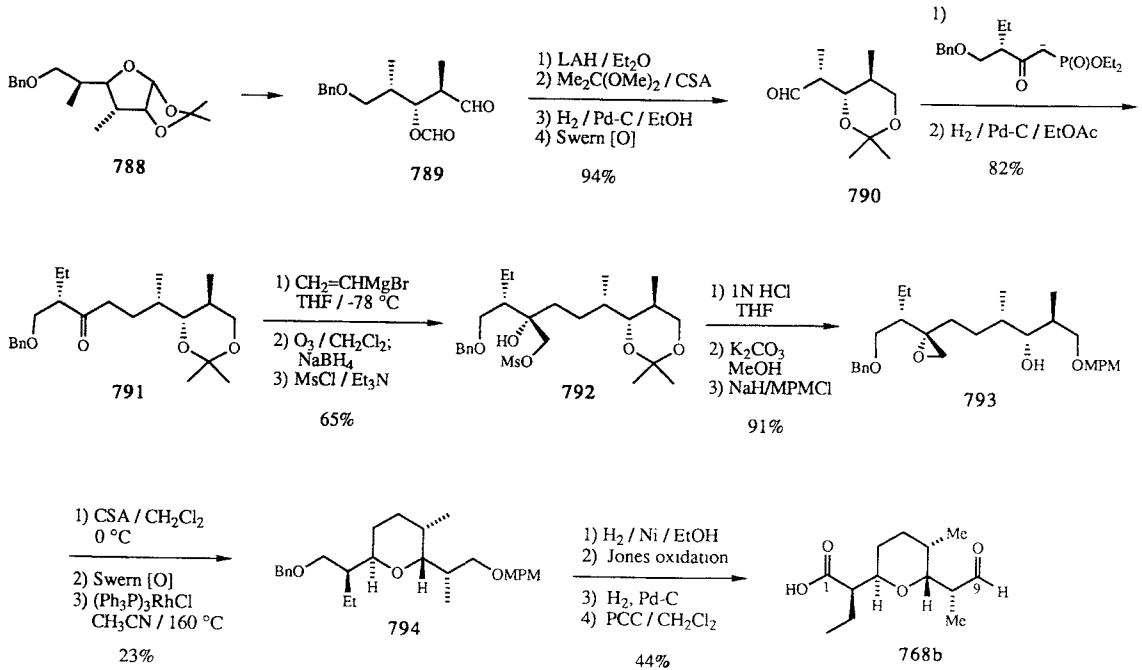


751a R = CH_3 narasin series **768a** R = CH_3
751b R = H salinomycin series **768b** R = H

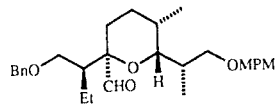


765b

The Yonemitsu group's approach to salinomycin also used the C-1–C-9 fragment **768b**. Their synthesis is shown in Scheme 120. D-Glucose was converted to **788** and then to the aldehyde **789** using an unpublished procedure. Standard chemistry led to the epoxide **793**. While the Kishi group closed the tetrahydropyran ring using an intramolecular displacement reaction, the Yonemitsu approach utilized an intramolecular epoxide opening which, after Swern oxidation, gave the overly functionalized aldehyde **787**. Decarbonylation of **787** with Wilkinson's catalyst, known to procede with



SCHEME 120. Synthesis of C-1–C-9 fragment **768** (Yonemitsu).



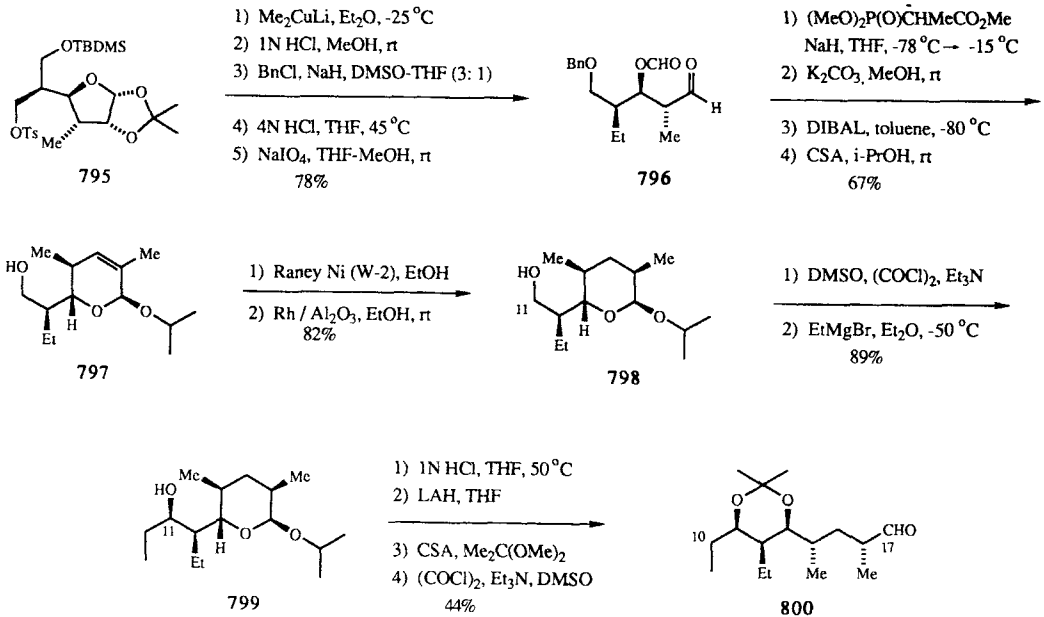
787

retention, provided **794** in 28% yield, which was manipulated to the desired fragment **768b**. The synthesis of **768b** from aldehyde **789** required 19 steps in 4–5% overall yield.

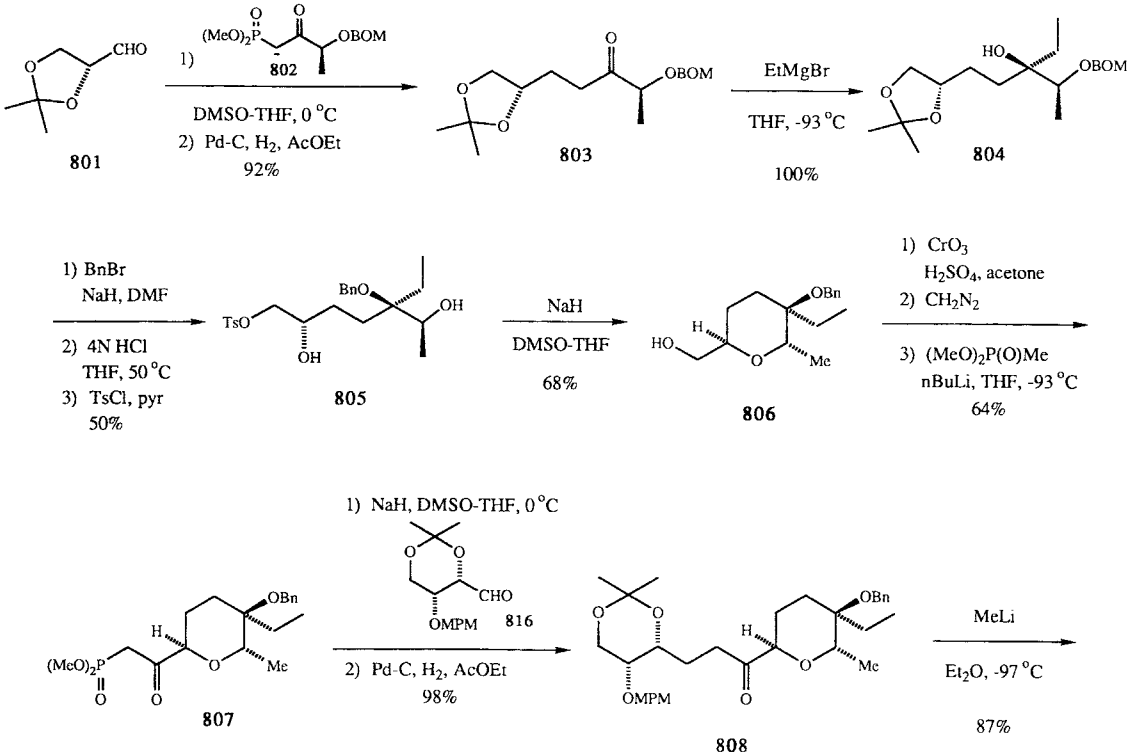
The synthesis of the C-10–C-17 fragment (Scheme 121) began from the previously synthesized **795**, in which three of the five chiral carbons were already established. The fourth and fifth centers were established by hydrogenation of the tetrahydropyranoside **797**, and by stereocontrolled addition of ethylmagnesium bromide to a C-11 aldehyde, resulting in the Cram adduct **799**. This irrelevant stereocenter was eventually converted to the C-11 carbonyl group. Four steps converted **799** to the desired fragment, completing the 17-step pathway (from **795**) to **800**.

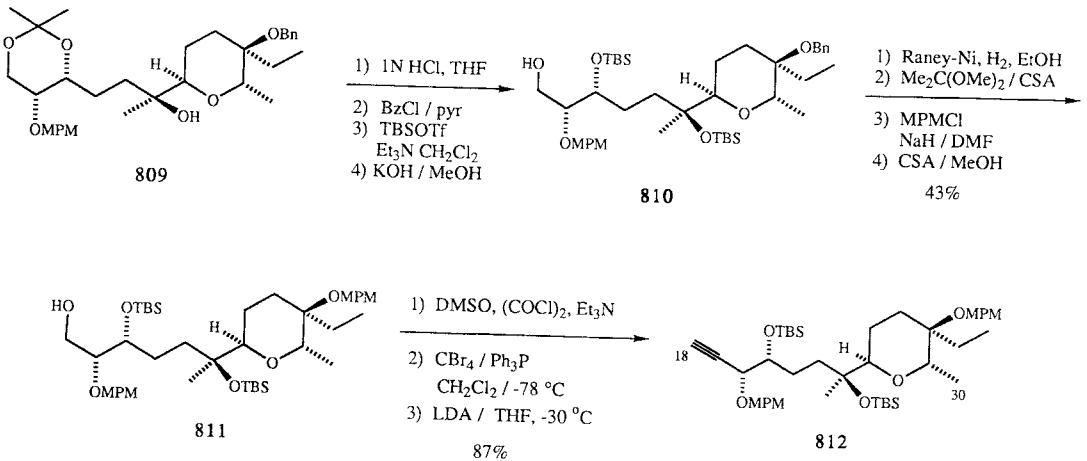
The synthesis of the C-18–C-30 right-hand fragment is shown in Scheme 122, beginning with the ubiquitous aldehyde **801**. Coupling with the optically active phosphonate **802** and hydrogenation gave **803** with two remote stereocenters. Chelation-controlled addition led to a third stereocenter (**804**), which was manipulated to tosylate **805**. Closure of the tetrahydropyran ring occurred via intramolecular epoxide opening, giving **806**. Standard chemistry led to the Wadsworth–Emmons reagent **807**, which was coupled to the optically active aldehyde **816**, the synthesis of which is shown in Scheme 123 without comment. Addition of MeLi to **808** proceeded in 33:1 stereoselectivity to **809**, rationalized as a chelation-controlled addition. It then took eight steps to adjust the protecting groups to give **811**. This change of the benzyl to methoxyphenylmethyl (MPM) at the C-28 position was found to be crucial in the last stages of the synthesis. Deprotection of a C-28 benzyl group with DDQ was slow, allowing a C-20–C-21 cleavage reaction to compete. A C-28 MPM group, however, was quickly and efficiently removed later in the synthesis, thus justifying the exchange of protecting groups. Compound **811** was then chain-extended to **812**, completing the 24-step pathway.

The combination of the fragments is shown in Scheme 124 and required only 10 steps from the first point of convergence. As in the Kishi synthesis, the connecting reactions were the addition of a lithiated alkyne (**812**) to an aldehyde (**800**) and aldol reaction of **819** with **768**. Trioxadispiroketalization led to two isomers (**819** and **820**) in a combined 45% yield. Although it was stated that both of these isomers could be converted to **748**, only the conversion of the major product **819** was described. Again, the final step was acid-promoted epimerization of 17-*epi* salinomycin to salinomycin (**748**).

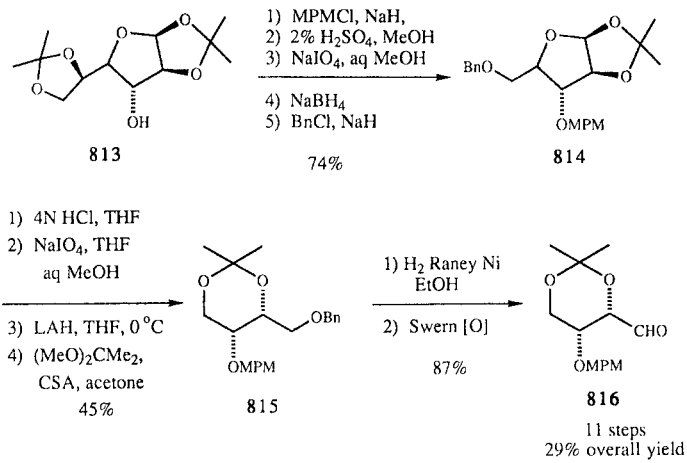


SCHEME 121. Synthesis of C-10–C-17 fragment (Yonemitsu).

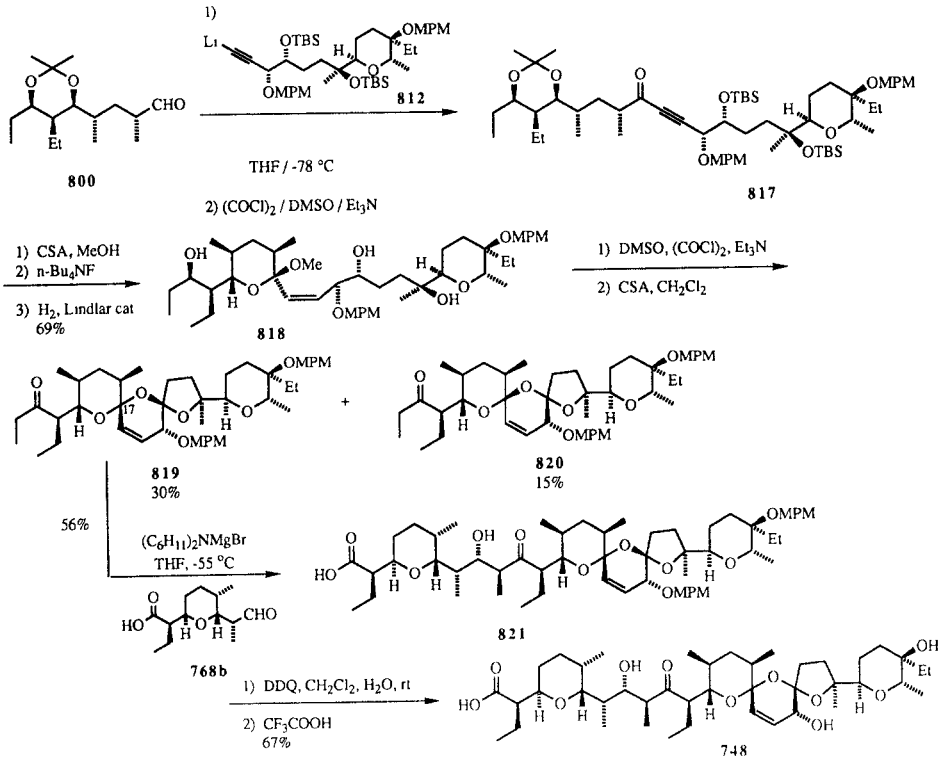

801
1)
802
DMSO-THF, 0 °C
2) Pd-C, H2, AcOEt
92%
803
EtMgBr
THF, -93 °C
100%
804
1) BnBr
NaH, DMF
2) 4N HCl
THF, 50 °C
3) TsCl, pyr
50%
805
NaH
DMSO-THF
68%
806
1) CrO3
H2SO4, acetone
2) CH2N2
3) (MeO)2P(O)Me
nBuLi, THF, -93 °C
64%
807
1) NaH, DMSO-THF, 0 °C
816
2) Pd-C, H2, AcOEt
98%
808
MeLi
Et2O, -97 °C
87%



SCHEME 122. Synthesis of C-18–C-30 fragment **812** (Yonemitsu).



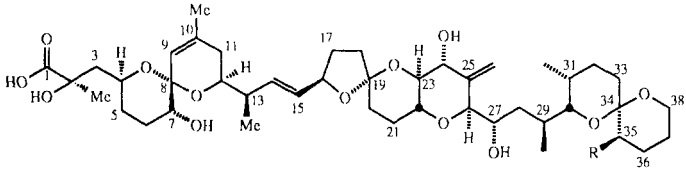
SCHEME 123. Fragment synthesis (Yonemitsu).



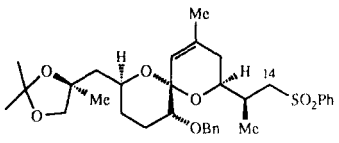
SCHEME 124. Combination of fragments (Yonemitsu).

8. OKADAIC ACID

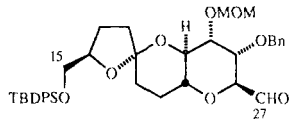
The potent antitumor agent okadaic acid (Scheme 126) was first isolated from sponges of the genus *Halichondria* and was shown to possess structure **823** by X-ray crystallography.[116] The structurally similar metabolites acanthafolicin[117] and dinophysistoxins 1–3,[118] as well as **823**, have been isolated from other organisms including dinoflagellates, suggesting that these metabolites may be synthesized by symbiotic microorganisms. Metabolites **823–825** are unique in that they possess three spiroketal arrangements within their complex skeleta. In the solid state, each of the three spiroketals appear to be anomerically maximized (axial spiro C–O bonds), suggesting that the relative stereochemistry of the spiro carbons might be established in acid-promoted thermodynamic spirocyclizations.



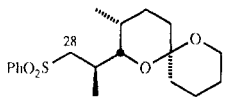
823 okadaic acid R = H
824 dinophysistoxin-3 (R = CH_3)
825 acanthafolicin (R = H, 9,10-α-episulfide)



835



847

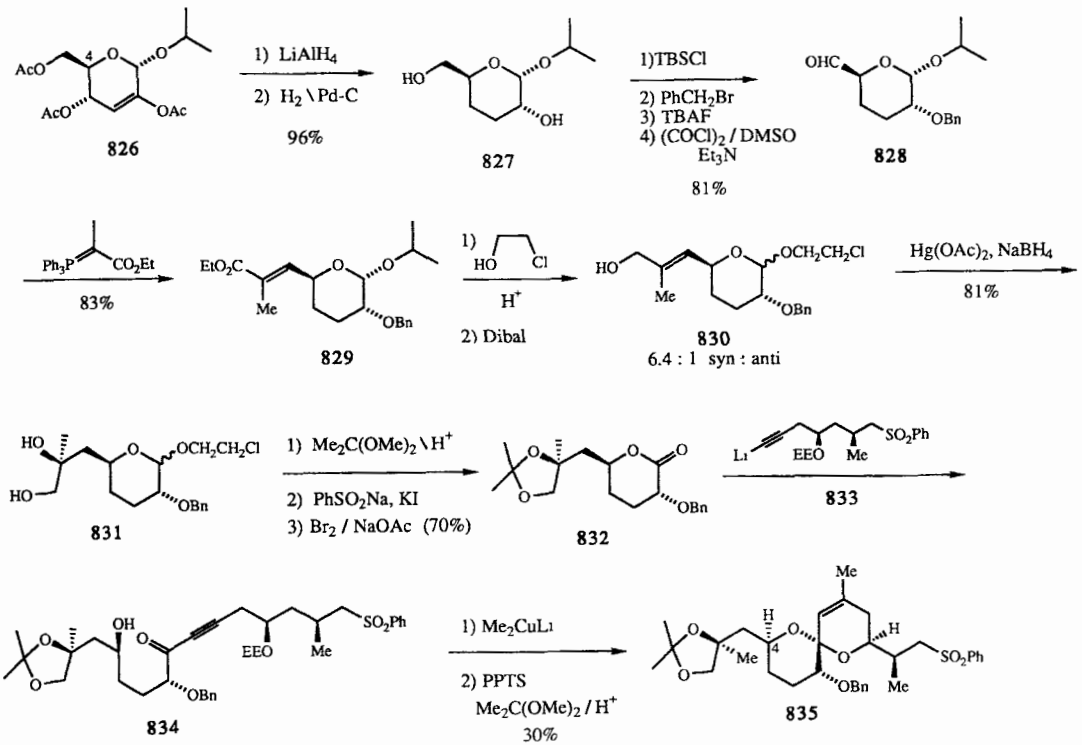


858

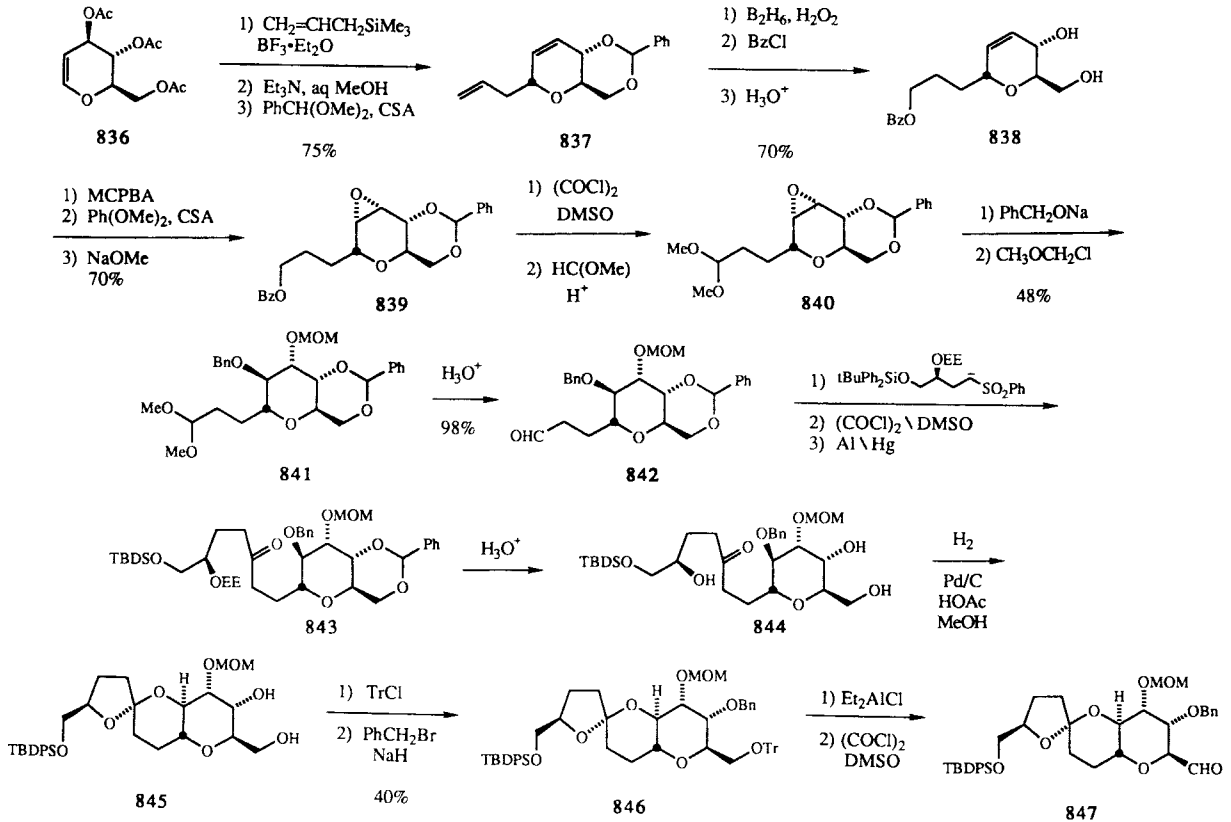
SCHEME 126. Okadaic acid synthesis strategy (Isobe).

Isobe and co-workers took a classical approach to the problem,[119] culminating in the only synthesis of okadaic acid. The molecule was divided into three segments (**835**, **847**, and **858**) which were synthesized in optically pure form using chiral pool elements and then coupled using sulfone anion additions to aldehydes.

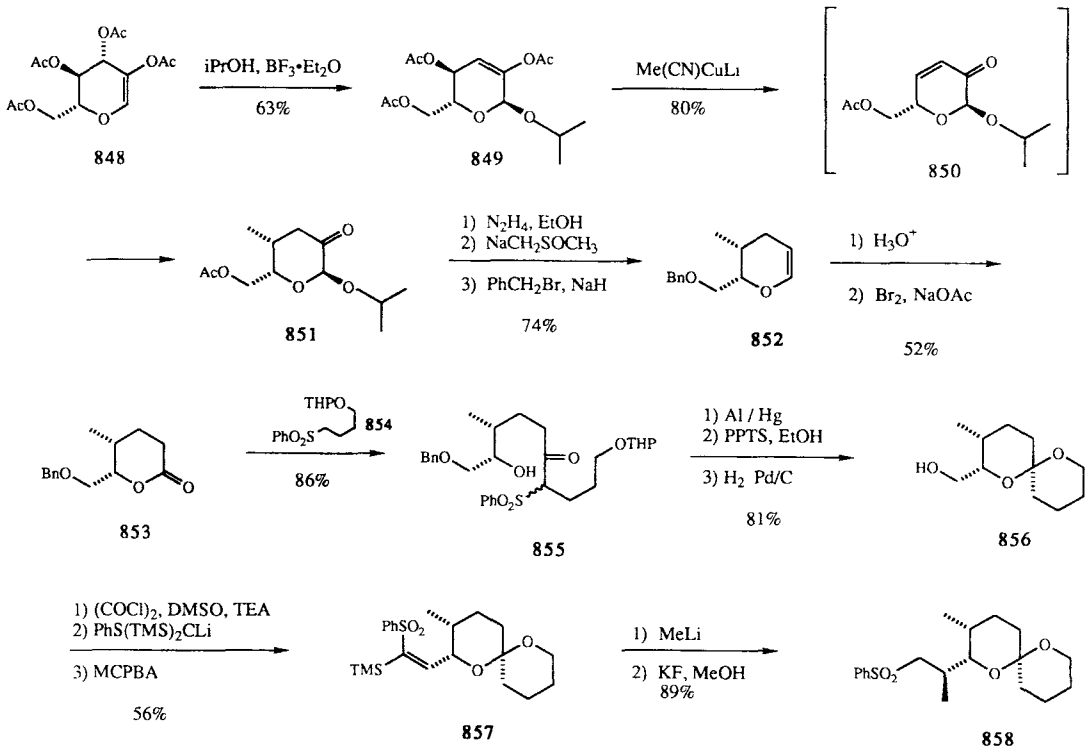
Segment **835** was assembled in 15 steps from the sugar derivative **826** (Scheme 127). Although **826** contains three stereogenic centers, only the one at C-4 was incorporated into **835**. The exocyclic stereocenter at C-2 was established via diastereoselective oxymercuration of the *E*-alkene **830** giving **831**. This was converted to lactone **832**, which was combined with the



SCHEME 127. Synthesis of okadaic acid segment **835** (Isobe).



SCHEME 128. Synthesis of okadaic acid fragment **847** (Isobe).



SCHEME 129. Synthesis of okadaic acid fragment **858** (Isobe).

optically pure acetylide anion **833**, giving ketone **834**. Conjugate addition of methyl cuprate to the alkyne results in a (*Z*)-α,β-unsaturated ketone which is spirocyclized to the key segment **835**.

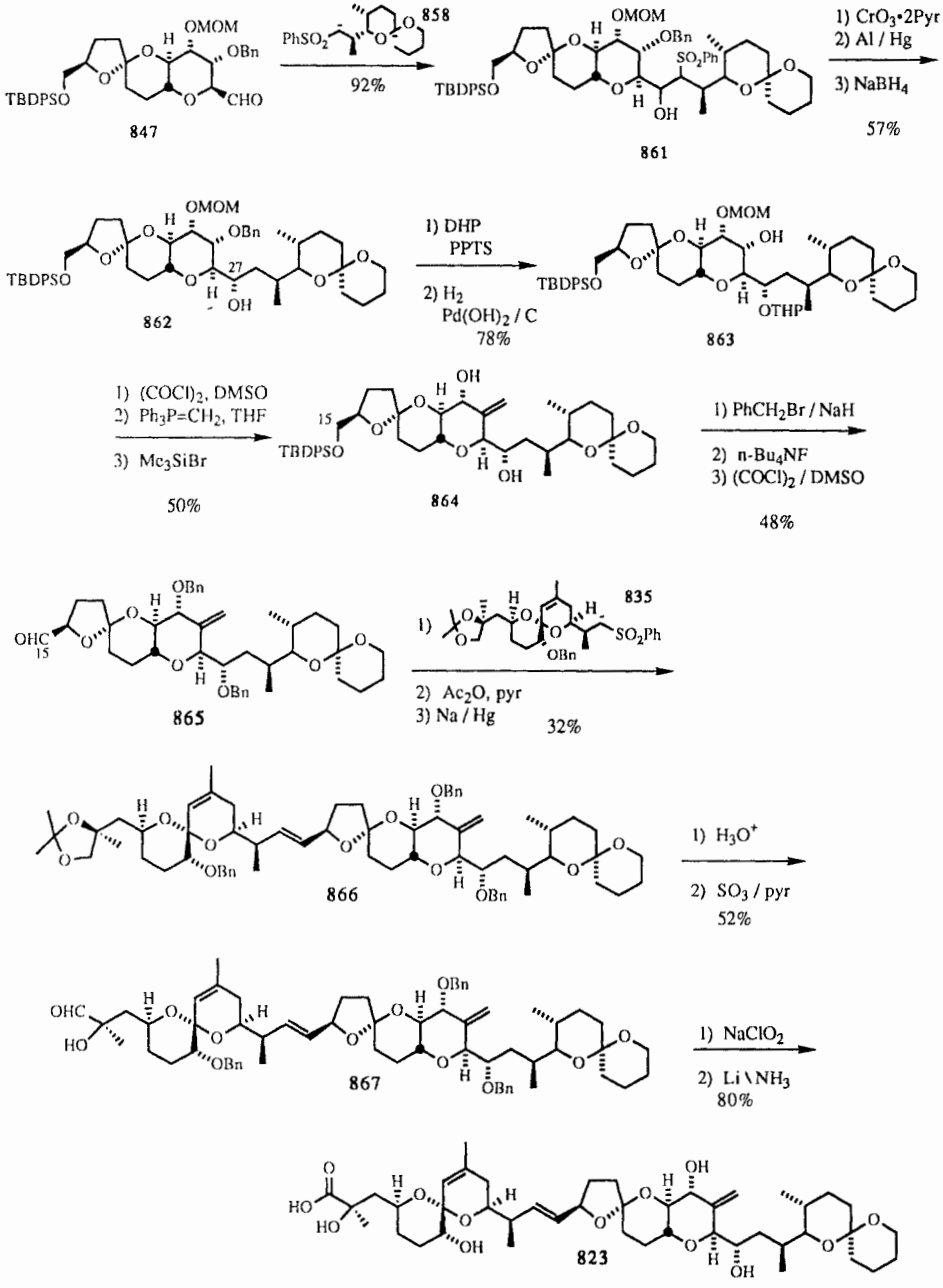
Segment **847** (Scheme 128) is characterized by the presence of five contiguous stereocenters bearing C–O bonds (C-22–C-26). Carbon Ferrier rearrangement of the glucal **836** followed by ester saponification and acetalization led to **837**, in which three of these C–O stereocenters were established. The C-23–C-24 olefin was eventually epoxidized and opened with sodium phenylmethanolate to establish the stereocenters at these two carbons, resulting in **841** after protection. Again, an optically active sulfone was added to an aldehyde (**842**), leading to the cyclization precursor **844**. Closure was achieved by hydrogenolysis of the benzyl ether in the presence of catalytic HOAc. Functional group manipulation led from **845** to aldehyde segment **847**.

Segment **858** was also assembled from a carbohydrate (Scheme 129). D-Glucose led in three steps to tetraacetate **848**. Ferrier rearrangement led to **849** which, when treated with a methyl cuprate reagent, led to **851**. This isomer arises via elimination to enone **850**, which then underwent axial addition of the cuprate reagent giving **851**. Five steps led to lactone **853**, which was combined with sulfone **854**, leading to **855**. Further manipulation led to **857**. Addition of MeLi to the α,β-unsaturated sulfone led eventually to **858**. The stereocontrol in this reaction is thought to be due to chelation of the alkyllithium with a tetrahydropyran oxygen delivering the reagent to one face of the olefin (**859** → **860**). Segment **858** was thus available in 16 steps from **848**.

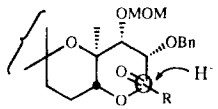


859 **860**

The segments were combined in a B + C → BC → ABC sequence (Scheme 130). The anion of sulfone segment **858** was joined with the aldehyde of segment **847**, generating **861**. The resulting diastereomeric mixture was oxidized to the ketone and the sulfone was reductively removed to give an intermediate ketone which was reduced to give the correct configuration of the alcohol at C-27 (**862**). The reduction proceeded stereospecifically with $NaBH_4$ or $LiAlH_4$; $Zn(BH_4)_2$ (85:15, desired:undesired) and Dibal (70:30) reduced with less selectivity. These results were rationalized via the two transition state models shown in Scheme 131. It was stated that the $NaBH_4$ and $LiAlH_4$ reductions proceeded via **868** while the "low or opposite-

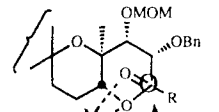


SCHEME 130. Assembly of okadaic acid segments (Isobe).



868

Stereoelectronically-controlled
anti-periplanar addition
($LiAlH_4$, $NaBH_4$)



869

Chelation-controlledaddition
(Dibal, $Zn(BH_4)_2$, B_2H_6)

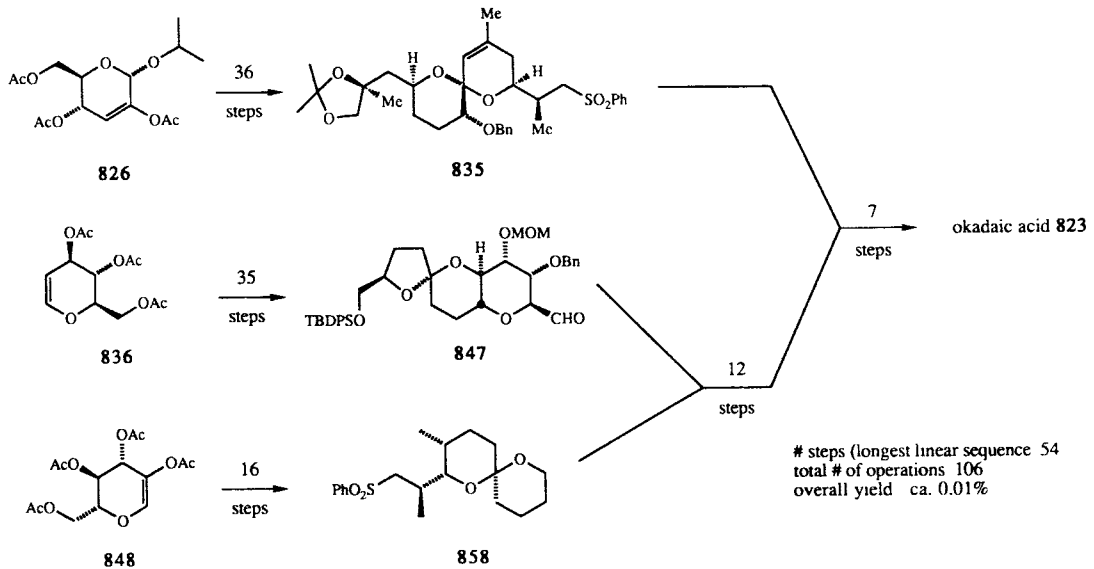
SCHEME 131. Transiton state hypotheses concerning the reduction of the C-27 ketone.

dominant selectivities" were caused by "chelative interaction . . . at the transition state." Experimental support for these hypotheses other than the product structures and ratios was not given. Attention was next turned to adding the C-41 methylene carbon, which was easily accomplished in three steps from **863** with the parent Wittig reagent $Ph_3P{=}CH_2$ performing the methylenation. From here, three steps were required to convert C-15 to an aldehyde, ready for coupling to segment **835**. The reaction sequence used to form the C-14–C-15 olefin entailed sulfone anion addition to the aldehyde, acetylation of the resulting alcohol, and reductive elimination with sodium amalgam, resulting in a *trans* olefin (**866**) in 32% yield for the three steps. At this juncture, the entire carbon skeleton was complete, leaving only the C-1 carboxylic acid terminus to be established. This was accomplished by deprotection of the C-1–C-2 diol and oxidation in two stages to the carboxylic acid via the aldehyde **867**. Final removal of three benzyl groups with Li/NH_3 provided 1.7 mg of crystalline okadaic acid (**823**).

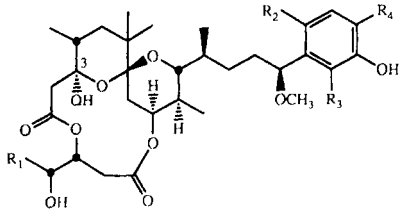
An analysis of the course of the synthesis is shown in Scheme 132. The three starting materials were simple sugar derivatives and led in nearly linear fashion to each of the three main segments **835**, **847**, and **858**. The assembly of the segments took an additional 19 steps, resulting in an overall 54-step process in the longest linear sequence. A total of 106 separate operations (minimum) were required to assemble okadaic acid.

9. APLYSIATOXIN

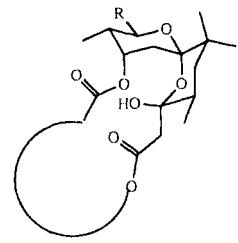
A series of complex hemispiroketals were isolated from the marine aplysiid *Stylocheilus longicauda* by Scheuer in the early 1970s.[120] The aplysiatoxin–oscillatoxin metabolites were eventually traced to the blue-green alga *Lyngbya majuscala* and other sources.[121] A partial listing of the metabolites is shown in Scheme 133. The relative and absolute configurations of this metabolite series was eventually confirmed by Moore and co-workers using



SCHEME 132. Summary of okadaic acid synthesis (Isobe).



		R_1	R_2	R_3	R_4
871	Aplysiatoxin	CH_3	Br	H	H
872	Debromoaplysiatoxin	CH_3	H	H	H
873	Oscillatoxin A	CH_3	Br	Br	Br
874	19,21-dibromaplysiatoxin	H	H	Br	Br



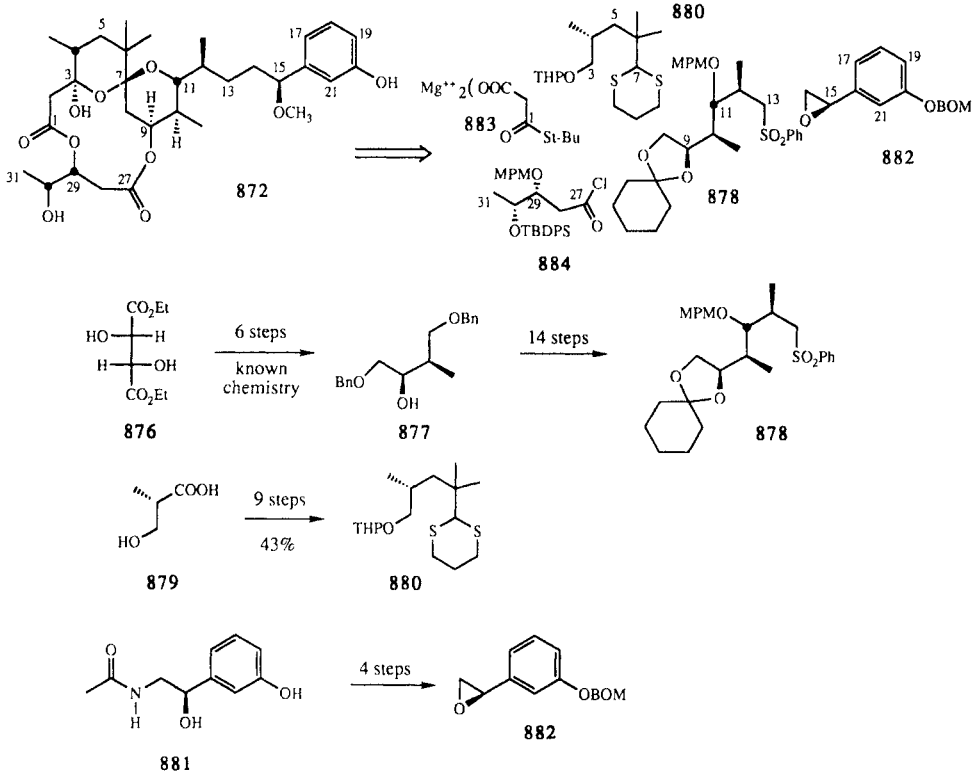
875 solid state spiroketal conformation

SCHEME 133. Some metabolites of *Lyngbya majuscala.*

extensive spectroscopic and chemical degradation techniques, in addition to X-ray crystallography.[122] Compounds in this family exhibit a variety of physiological activities, ranging from tumor promotion to a peculiar form of contact dermatitis.[123] The compounds possess potentially mobile hemispiroketal arrangements due to a hydroxyl at C-3, although open forms of the spiroketal ring system have not been observed. In addition, the spiroketal configurations are not anomerically maximized (see **875**).

The approach of Kishi is the only successful synthesis of a metabolite in this series to date.[124] The fragments used to assemble debromoaplysiatoxin **872** are shown in Scheme 134. The synthesis of fragments **878**, **880**, and **882–884** were straightforward and proceeded from optically active starting materials. Fragment **878** was synthesized from xylose. Fragment **883** is a common reagent. The combining of the fragments is an instructive exercise in manipulation of functional and protecting group technology (Schemes 135 and 136). It is noteworthy that **893** does not exist in a cyclic form. Conversion of **893** → **894** with silver trifluoroacetate suggests that macrocyclization facilitates formation of the hemispiroketal and further suggests that the natural products exist as the most thermodynamically stable isomers at C-3 and C-7. Removal of the protecting groups from **894** produces debromoaplysiatoxin **872**. Aplysiatoxin has already been produced from **872** by bromination. The synthesis of **872** proceeds in 18 steps from the fragments pictured in Scheme 134 in 2–3% overall yield.

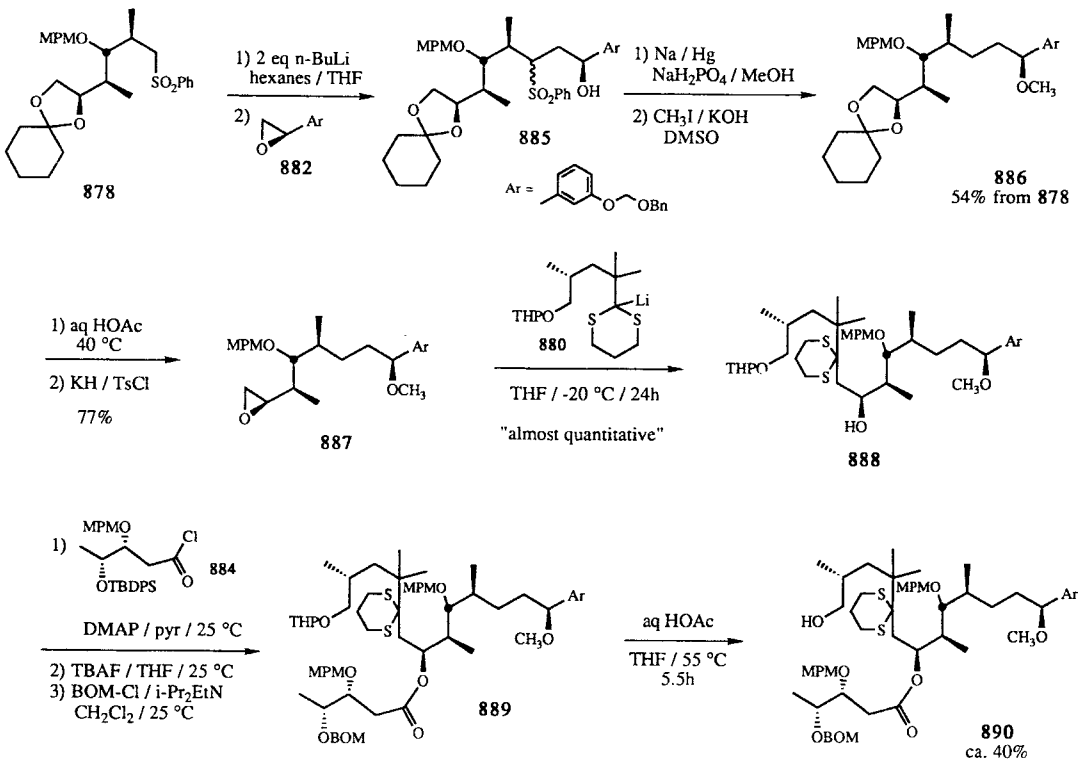
Although not culminating in a completed metabolite synthesis, the work of Ireland in this area is worthy of note.[125] Utilizing extensive studies on the hetero Diels–Alder reaction performed by this group, the C-3 nor-hydroxy compound **915** was assembled (Scheme 139). The key step involved the [4 + 2] cycloaddition of optically active partners **901** and **904**. The vinyl ether **901** was prepared from the lactone **900** by reaction with the Tebbe



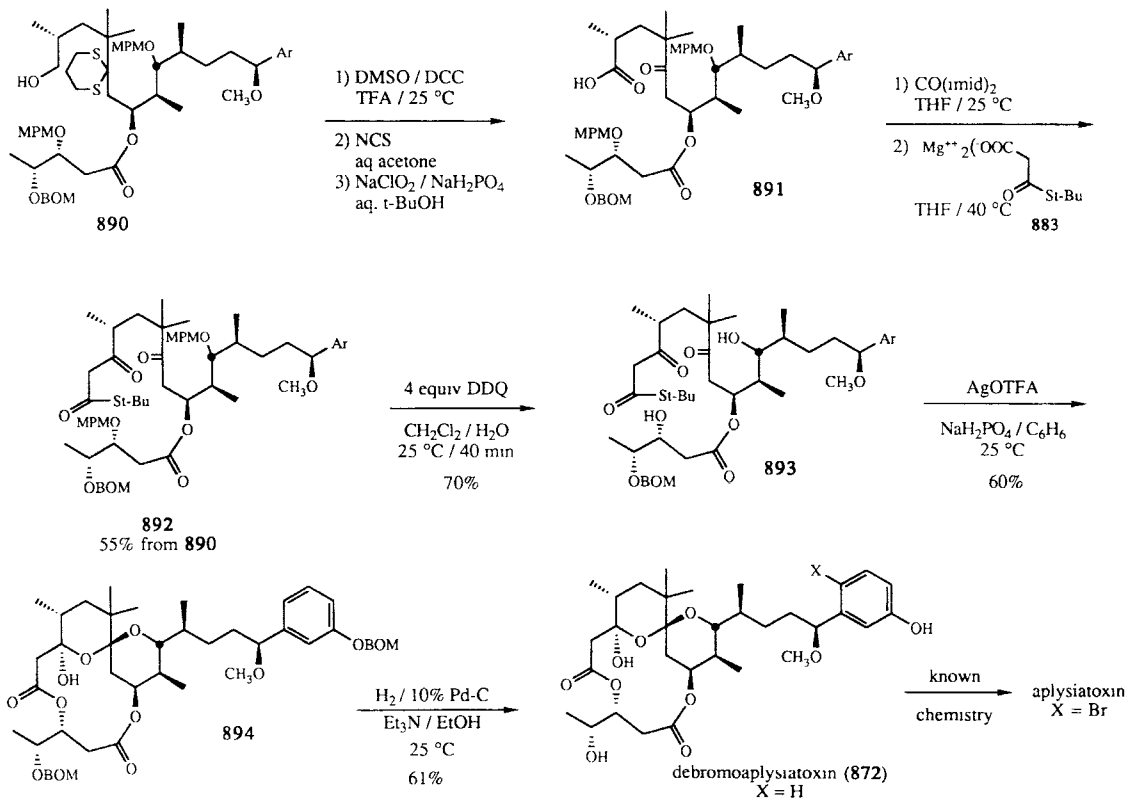
SCHEME 134. Fragments used in the Kishi debromoaplysiatoxin synthesis.

reagent (Scheme 137). The lactone, in turn, was derived via standard manipulations from the alcohol **895**, using the Sharpless kinetic resolution of **896** to enter the desired enantiomeric series. Enone **904** was produced from (*S*)-**902** and was used as a mixture of epimers at C-15 (Scheme 138). It was shown, however, that the absolute stereochemistry at C-15 could be induced by reduction of the corresponding ketone using the Noyori chiral binaphthol reagent producing **905**.

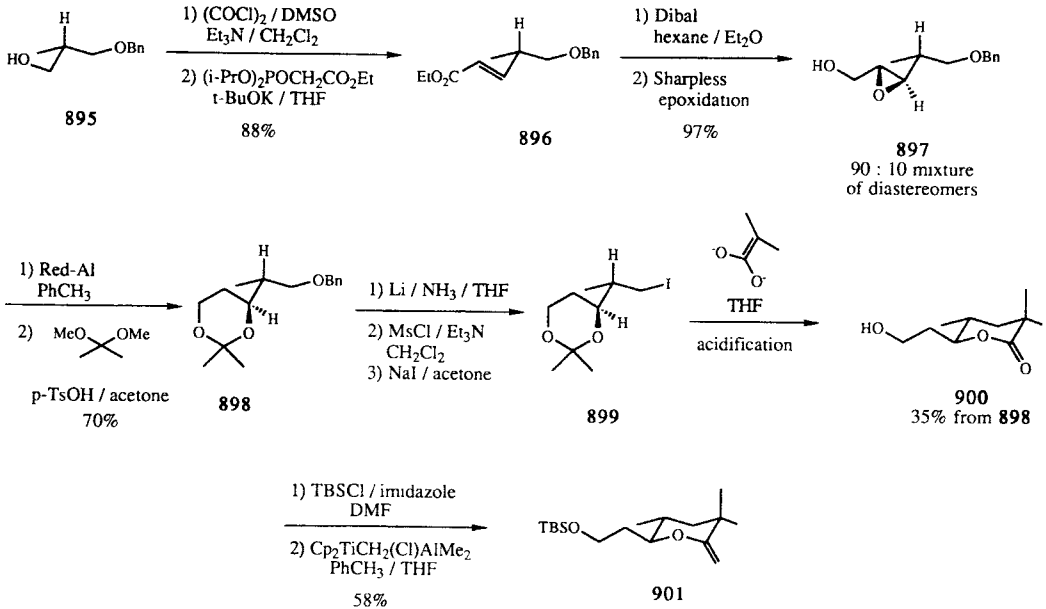
The cycloaddition between **901** and **904** proceeded to give **906**, which was manipulated to **907** (Scheme 139). Spiroepimerization of **907** was induced by HCl in $CHCl_3$ leading to **908**, which possessed the maximum number of equatorial substituents. Apparently, steric considerations outweighed the stereoelectronic preference of the anomeric effect. After a series of standard transformations to give **911**, the diastereomers were separated, providing **912**. Unfortunately, the key remote oxidation of **912** → **916** could not be realized



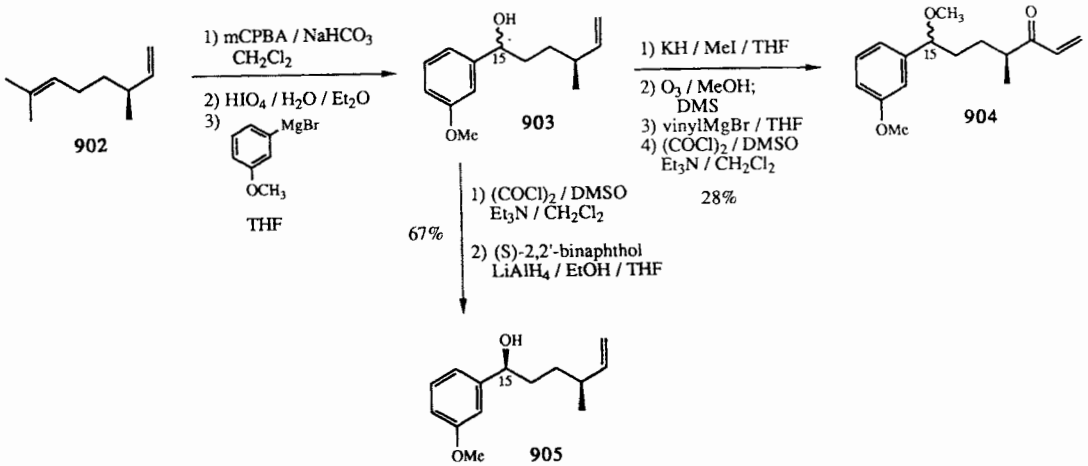
SCHEME 135. Initial assembly of debromoaplysiatoxin fragments.



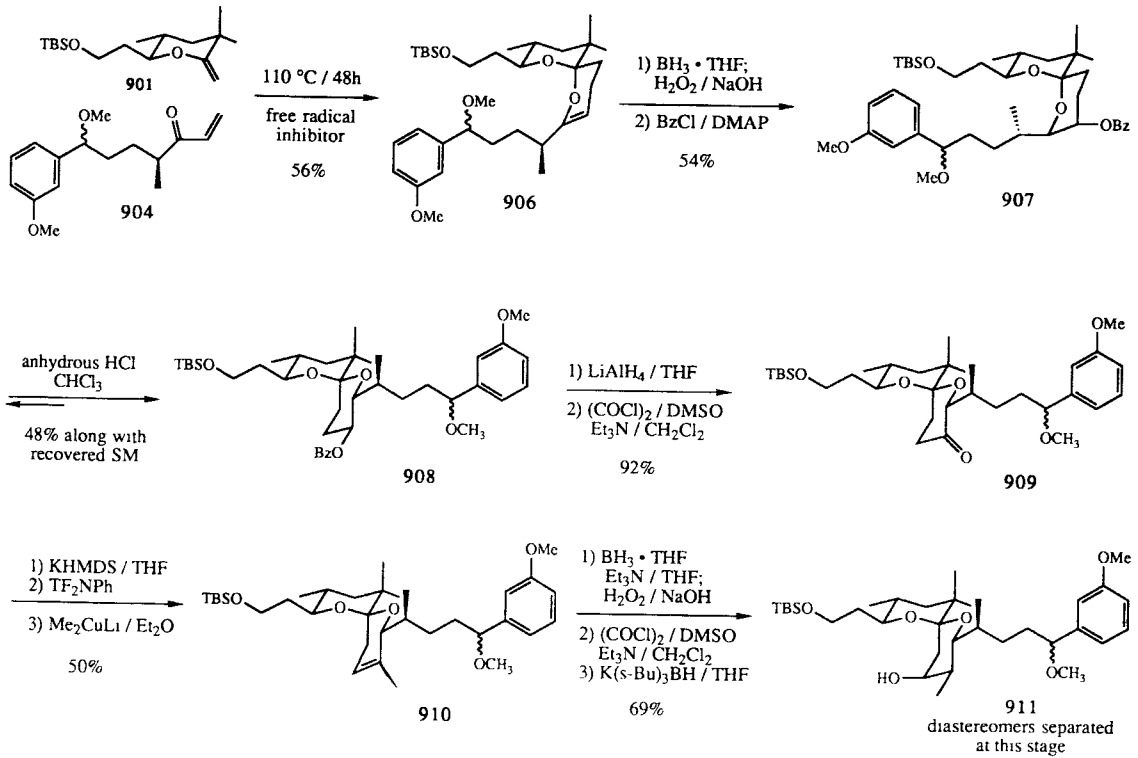
SCHEME 136. Final assembly of debromoaplysiatoxin (Kishi).



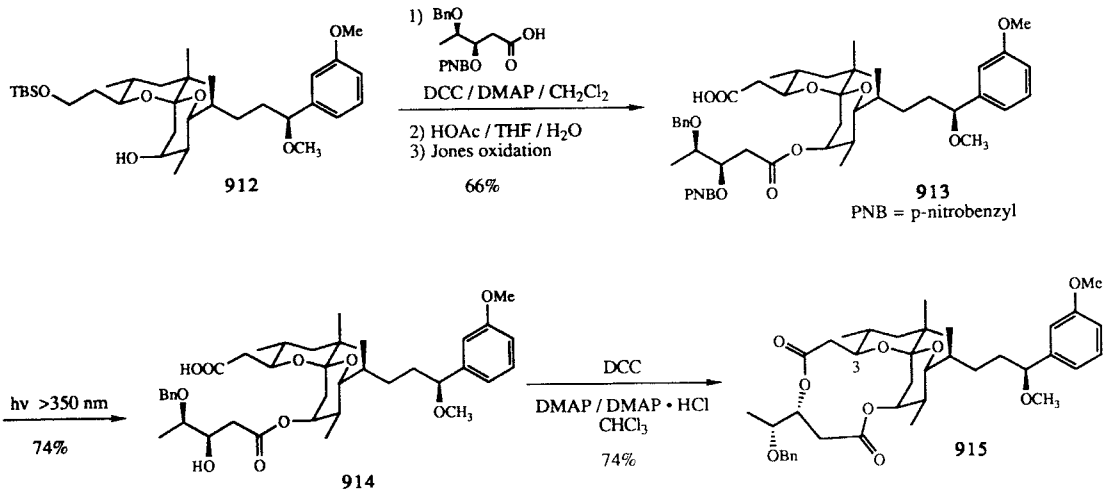
SCHEME 137. Synthesis of vinyl ether **901** (Ireland).



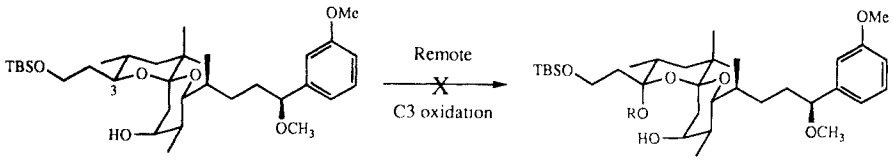
SCHEME 138. Synthesis of enone **904**.



SCHEME 139. Cycloaddition of **901** with **904** and subsequent transformations (Ireland).



SCHEME 139. Cycloaddition of **901** and **904** and subsequent transformations (Ireland) (*continued*).



912 916

SCHEME 141. Attempted remote oxidation of **912** → **916** (Ireland).

under a variety of conditions (Scheme 141). Anticipating eventual success, compound **912** was converted to **915**, featuring a DCC/DMAP-mediated macrocyclization.

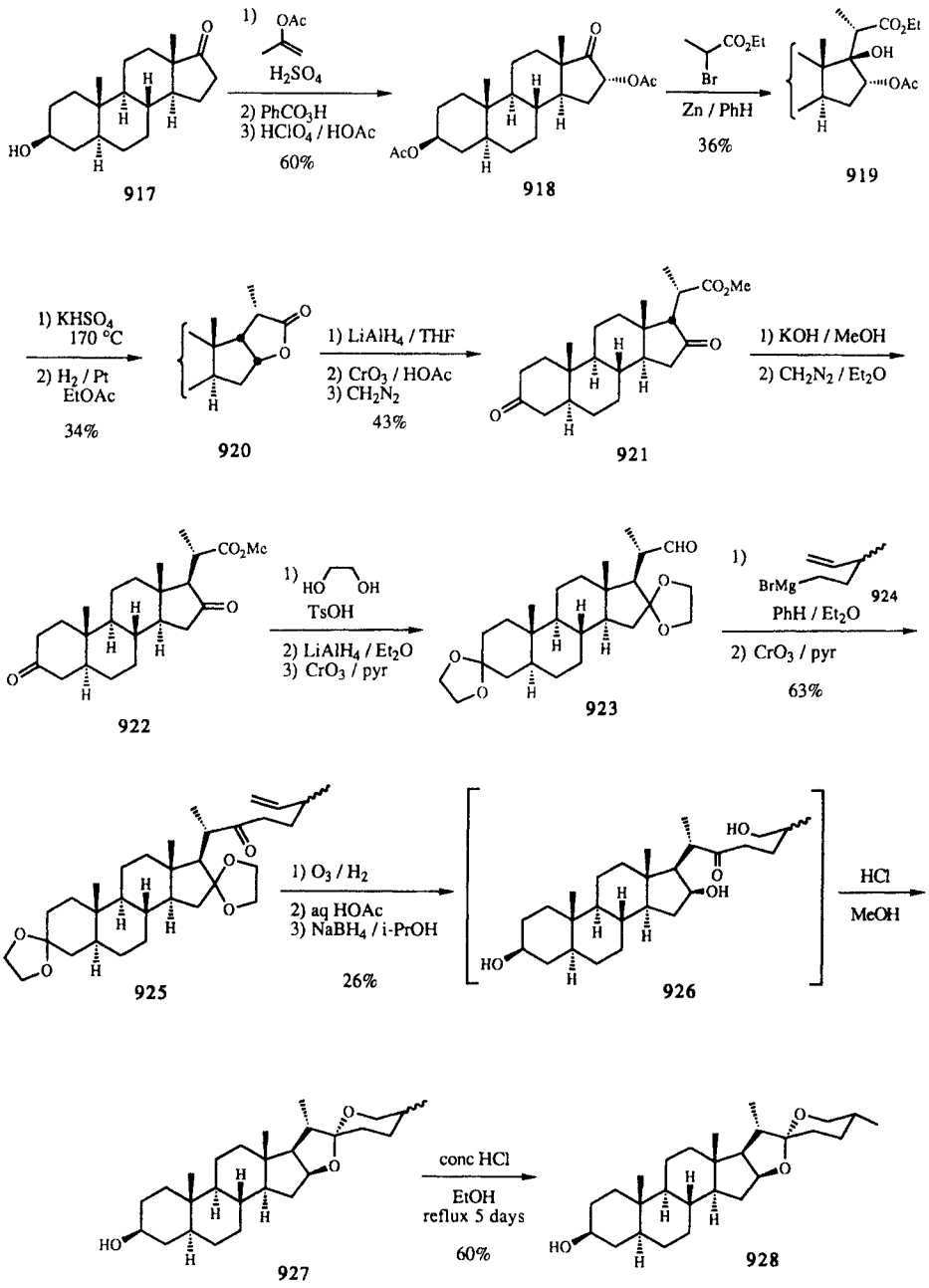
10. MISCELLANEOUS NATURAL PRODUCTS

A. Sapogenins

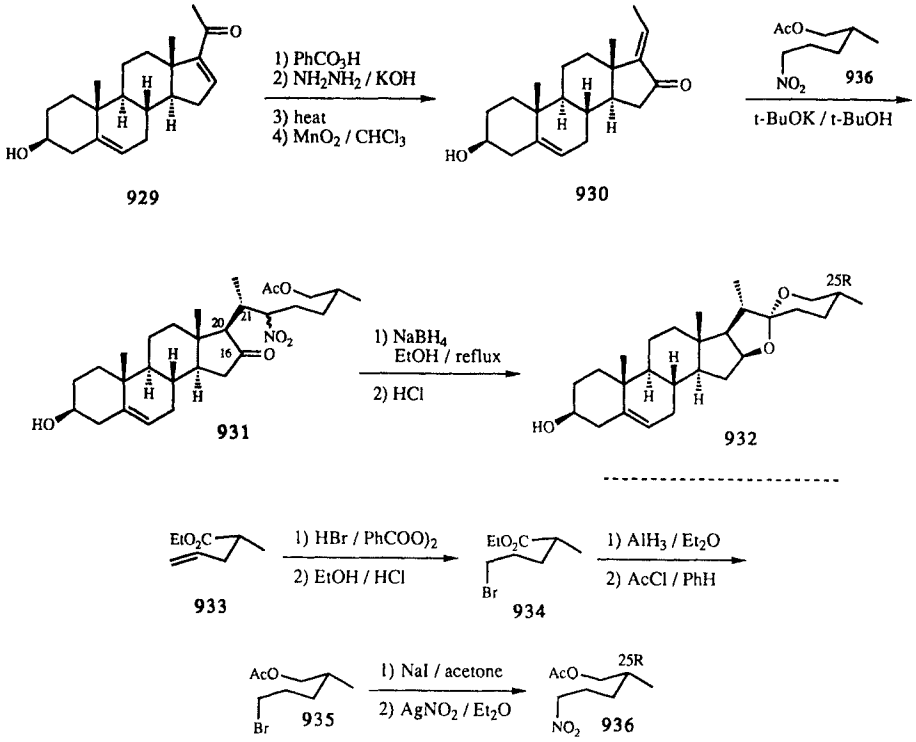
Steroidal sapogenins, the aglycones of plant saponins, were the first large class of spiroketals derived from nature. Largely through the work of Marker and Djerassi, the structures of many members of this family were elucidated in the 1930s and 1940s, primarily by chemical techniques.[126] Early interest in synthesis in this series was fueled by the potential uses of readily available sapogenins as starting materials for syntheses of other steroids. Interest has since waned considerably.

The classic synthesis in this area is that of tigogenin (**928**) by Sondheimer and co-workers,[127] which was described in the late 1950s. Beginning with isoandrosterone (**917**, Scheme 142), a C-16 acetoxy group was introduced and the ketone treated with the Reformatsky reagent from ethyl bromopropionate, leading to **919** in moderate yield, which possessed the incorrect configuration at both C-16 and C-17. A series of transformations led to **921**, where the configuration at C-17 was inverted thermodynamically, giving **922**. Addition of the racemic Grignard reagent **924** to aldehyde **923** and oxidation furnished ketone **925**. Ozonolysis of the vinyl group and aqueous hydrolysis led to a triketone–aldehyde (not shown), which was reduced at C-3, C-16, and C-26, but not at C-22, providing intermediate **926** which was cyclized to a mixture of tigogenin (25*R*) and neotigogenin (25*S*) which could be equilibrated to tigogenin upon prolonged reaction with HCl in ethanol.[128]

A decade later, Kessar and co-workers described a general approach to both the 25*S* and 25*R* sapogenins.[129] By combining an optically active C-22–C-25 fragment with a tetracyclic nucleus, the stereochemistry at C-25



SCHEME 142. Sondheimer synthesis of tigogenin.

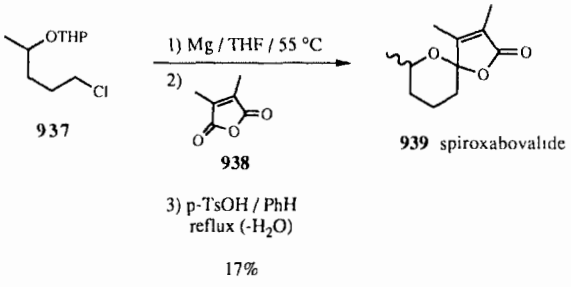


SCHEME 143. Kessar synthesis of diosgenin.

could be controlled. Dehydropregnenolone (**929**, Scheme 143) was converted in four steps to the unsaturated ketone **930**. Michael addition of a nitro compound resulted in the correct configuration at C-20 and C-21.[130] Treatment of the nitro compound sequentially with $NaBH_4$ and acid results in C-16 ketone reduction, deacetylation, Nef reaction, and spirocyclization in one vessel to give sapogenins. Use of a 25*R*-nitro compound (made from **933**) results in diosgenin (**932**). Use of a 25*S*-nitro compound (made by an analogous route) results in yamogenin, the C-25 epimer of **932**. A further synthesis of isonarthogenin was also described by this group.[131, 132]

B. Spiroxabovalide

A correlation of the gross structure of spiroxabovalide **939** was provided by Demole,[133] who synthesized the metabolite by adding the Grignard reagent from chloride **937** to dimethyl maleic anhydride (Scheme 144). Acid treatment



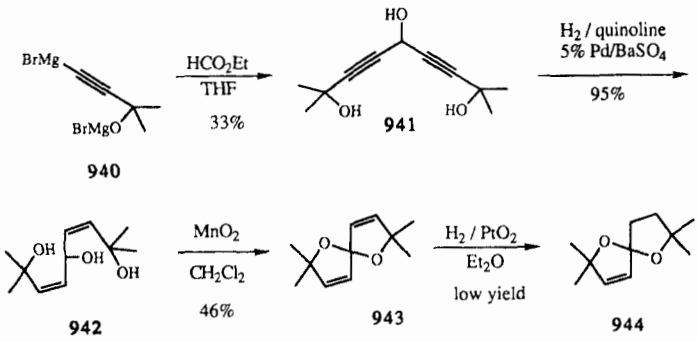
SCHEME 144. Demole spiroxabovalide synthesis.

led to deprotection and ring closure providing **939** as a mixture of diastereomers.

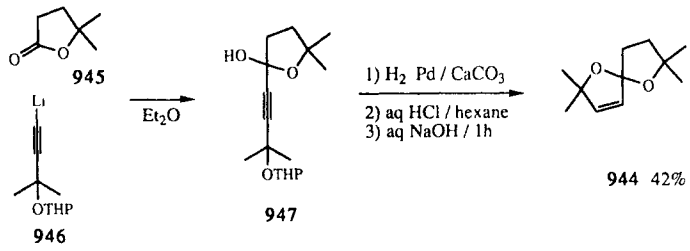
C. Hop Oil Metabolites

Burgstahler reported some of the earliest examples of syntheses of naturally occurring spiroketals of low complexity.[134] Their approach in 1973 foreshadowed many similar approaches to spiroketals developed in the early 1980s. The unsaturated spiroketals **943** and **944** (Scheme 145), which were isolated from a variety of Japanese hops,[135] were produced by coupling of the alkyne salt **940** with ethyl formate to give **941**. Partial hydrogenation led to triol **942**, which was oxidized and cyclized to **943**. Metabolite **944** was produced in low yield from **943** by hydrogenation.

Smith[29b] also prepared the metabolite **944** by a lactone–alkyne approach which did not rely on partial hydrogenation of the diene **943** (Scheme 146).



SCHEME 145. Burgstahler synthesis of hop oil metabolites.

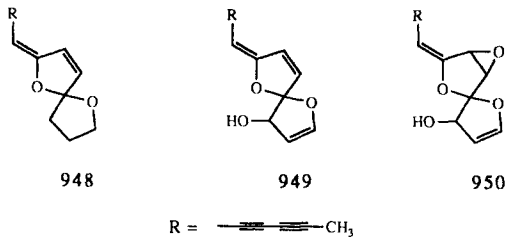


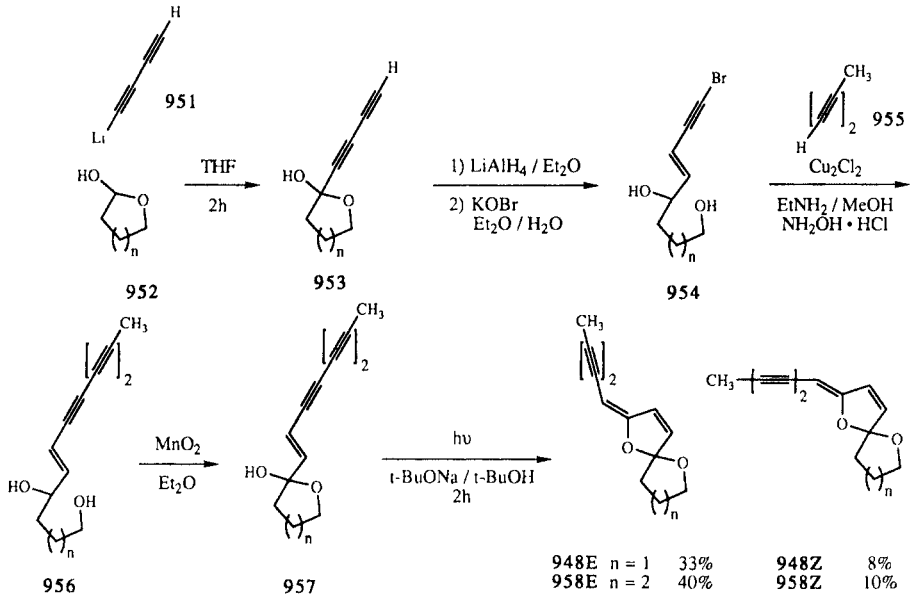
SCHEME 146. Smith hop oil metabolite synthesis.

Addition of the acetylide **946** to 4,4-dimethyl γ-butyrolactone afforded the addition product **947**. Hydrogenation and cyclization yielded **944** in 42% yield.

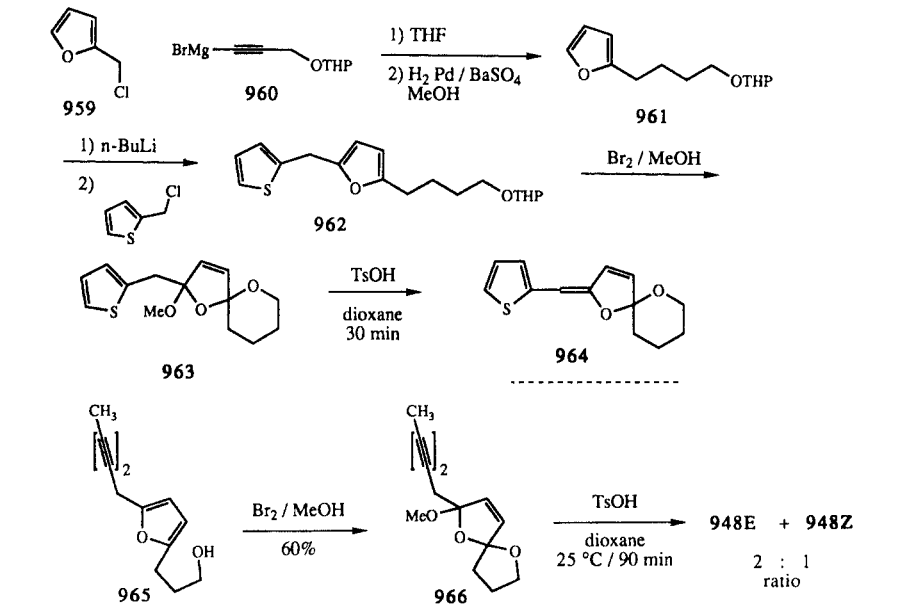
D. Spiroketal Enol Ethers of the Asteraceae

Bohlmann and co-workers described a large number of spiroketals originating from plants in the family Asteraceae. Some typical members of this class are exemplified by **948–950**. Generally, the metabolites possess one or more acetylene units in the side chain and are found as both enol ether olefinic isomers. This topic has been reviewed.[136] As part of the structure elucidation process, several of the metabolites have been synthesized via general methods. Scheme 147 shows a method based on a photochemically promoted base-induced cyclization.[137] To prepare the three consecutive acetylene units of the penultimate precursor **956**, methyl diacetylene **955** was coupled to an acetylenic bromide (**954**), producing **956**. Base-induced cyclization of the hemiacetal **957** provided the *E* enol ethers **948** and **958** as the major products along with a small amount of the corresponding *Z* isomers. An alternative furan-based general synthesis is shown in Scheme 148.[138] For example, the thiophene-furan **962** was pieced together by simple alkylation chemistry. Treatment of **962** with bromine in methanol resulted in cyclization to





SCHEME 147. Bohlmann synthesis of Asteraceae metabolites.

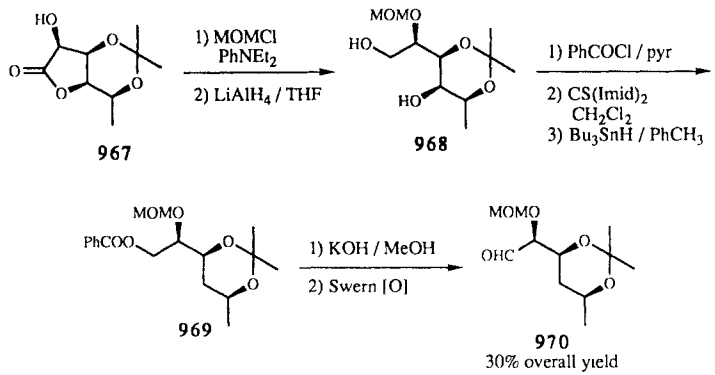


SCHEME 148. Bohlmann furan-based synthesis of Asteraceae metabolites.

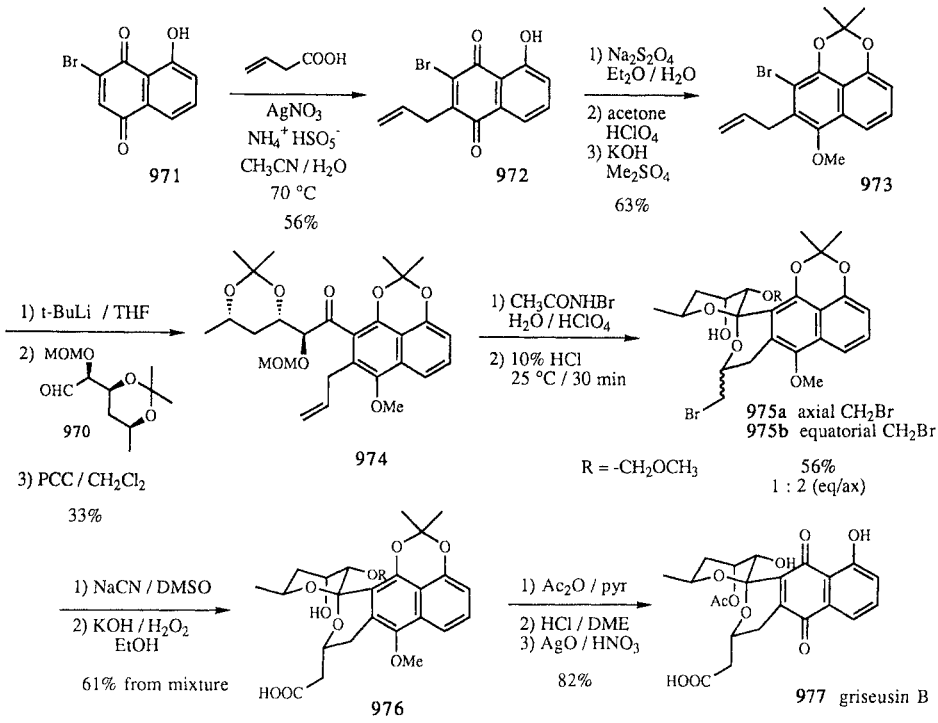
spiroketal **963**, which underwent loss of methanol with formation of the exocyclic enol ether **964** under acidic conditions. A similar sequence of reactions was used to convert furan **965** into spiroketal **966** and thence to the previously encountered isomers **948E** and **948Z**.

E. Griseusins A and B

Griseusins A and B (**980** and **977**) were isolated from *Streptomyces griseus* by Tsuji[139] and are reported to exhibit activity versus gram-positive bacteria. Yoshii[140] has described the synthesis of both metabolites in optically pure form with griseusin A arising via a biomimetic oxidation of griseusin B. The precursor to the tetrahydropyran with three asymmetric centers was the aldehyde **970** (Scheme 149). This substance was made via standard technology from the known sugar derivative **967**. The aromatic portion arose from 3-bromojuglone **971**, as shown in Scheme 150. Allylation via a modified Hunsdiecker process led to introduction of a carbon segment to the quinone nucleus (**972**). Reduction of the quinone to the hydroquinone and *in situ* acetonide formation and methylation led to bromide **973**. Halogen–metal exchange resulted in the aryllithium which was added to the aldehyde **970**, giving a mixture of carbinols which was oxidized to the ketone **974**. Addition of HOBr across the olefin and *in situ* spirocyclization led to the isomeric spiroketals **975**, in which the undesired isomer **975a** predominated. This was corrected in the next sequence, wherein the bromide mixture was converted to a cyanide mixture and hydrolyzed by aqueous base to provide a single spiroketal **976** possessing the desired configurations at all stereocenters. It was found in earlier studies[141] that the undesired C-3 epimer could be

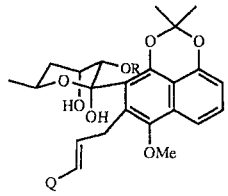


SCHEME 149. Synthesis of griseusin intermediate **970** (Yoshii).



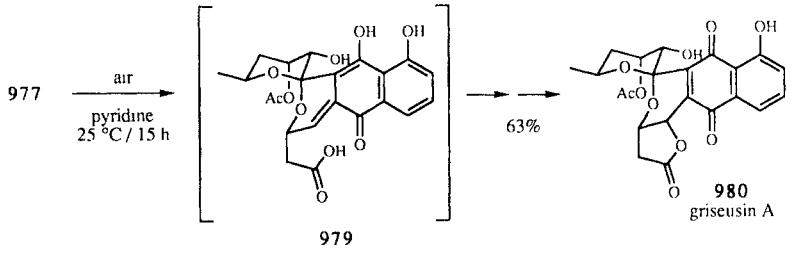
SCHEME 150. Yoshi synthesis of griseusin A and B.

isomerized to the desired configuration by base, presumably involving a retro Michael–Michael process involving **978** as an intermediate. Adjustment of functionality and oxidation to the quinone led from **976** to (+)-griseusin B (**977**). In the isolation of the metabolites from the natural source, it was found that griseusin B could be converted to griseusin A (**980**) when a solution of **977** in pyridine was allowed to stand overnight. This was presumed to occur via conjugate addition to the transient quinone methide **979**, generating a



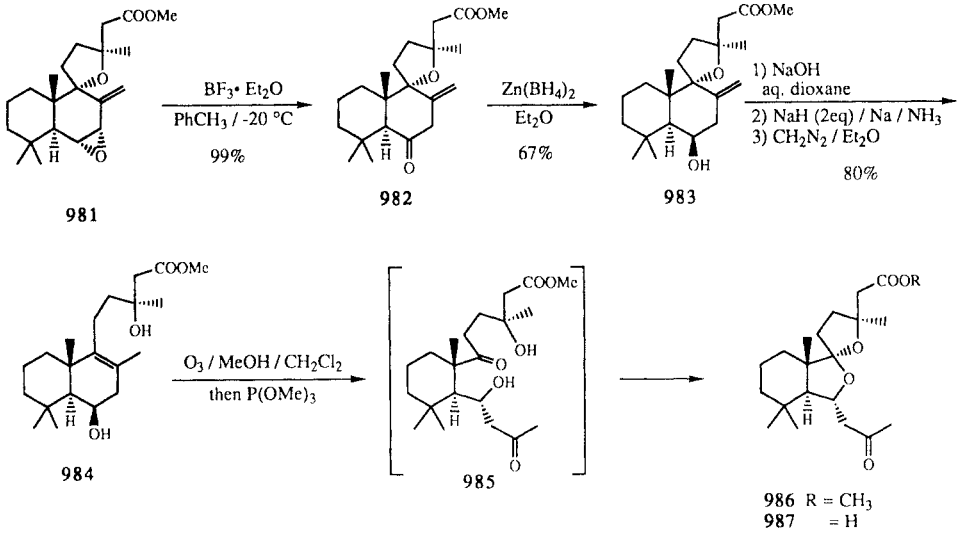
978 Q = -CN, -COOH

hydroquinone (not shown) which is air-oxidized to griseusin A. This transformation[142] was confirmed by the Yoshii group, producing **980** from **977** in good yield. Thus, the absolute configurations of the metabolites were firmly established.

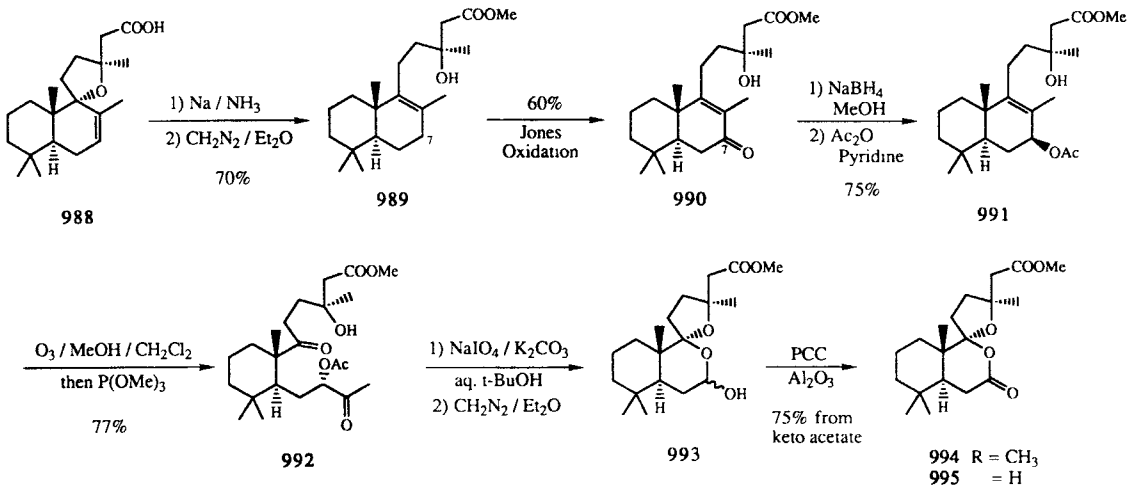


F. Metabolites of *Grindelia* Species

Ruveda and co-workers have synthesized two plant metabolites from *Grindelia* species starting from co-ocurring metabolites. In synthesizing the spiro[4.4] system of methyl strictanonate, the B ring of the naturally derived **981** was oxidatively cleaved (Scheme 151).[143] NIH shift of epoxide **981** resulted in the β,γ-unsaturated ketone **982**, which was reduced to give the



SCHEME 151. Sierra-Ruveda synthesis of methyl strictanonate (**986**).



SCHEME 152. Sierra-Ruveda synthesis of methyl grindelistrictate (**994**).

β-alcohol **983**. Allylic reduction of **983** occurred with olefin migration to **984**. Ozonolysis of **984** led to the acylic dihydroxyketone **985**, which cyclized *in situ* to **986** providing the correct relative stereochemistry at the spiro carbon. A similar strategy was used to convert grindelic acid (**988**) to methyl grindelistrictate (**994**, Scheme 152).[144] Allylic reduction of **988** led to **989**. Allylic oxidation installed a ketone at C-7. Stereoselective reduction and acetylation gave the β-alcohol **991**. Ozonolysis opened the B ring to **992**, which was oxidatively cleaved and recyclized to the hemispiroketal **993**. PCC oxidation completed the interconversion.

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