

**THE TOTAL SYNTHESIS
OF NATURAL PRODUCTS**

The Total Synthesis of Natural Products

VOLUME 7

Edited by

John ApSimon

Ottawa—Carleton Chemistry Institute

and

*Department of Chemistry
Carleton University, Ottawa*

A WILEY-INTERSCIENCE PUBLICATION

JOHN WILEY & SONS

NEW YORK • CHICHESTER • BRISBANE • TORONTO • SINGAPORE

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Library of Congress Cataloging in Publication Data:

The Total synthesis of natural products.

“A Wiley-Interscience publication.”

Original imprint, v. 1: New York: Wiley-Interscience, 1973.

Includes bibliographical references and indexes.

1. Chemistry, Organic—Synthesis. I. ApSimon, John.

QD262.T655 1973 547'.2 72-4075

ISBN 0-471-03251-4 (v. 1)

ISBN 0-471-88076-0 (v. 7)

ERRATA
for
THE TOTAL SYNTHESIS OF
NATURAL PRODUCTS, VOLUME 7

Edited by John ApSimon

The names of the authors of Chapter 1 should be as follows in both the contributor list and the table of contents:

R. K. Boeckman, Jr.
S. W. Goldstein

Contributors to Volume 7

J. Adams, Merck Frosst Canada Inc., Kirkland, Quebec, Canada

J. G. Atkinson, Merck Frosst Canada Inc., Kirkland, Quebec, Canada

Yvonne Bessière, Borex, Switzerland

R. H. Boeckman, Department of Chemistry, University of Rochester, Rochester,
New York

M. Goldstein, Department of Chemistry, University of Rochester, Rochester,
New York

Y. Guindon, Merck Frosst Canada, Inc., Kirkland, Quebec, Canada

J. Rokach, Merck Frosst Canada, Inc., Kirkland, Quebec, Canada

Alan F. Thomas, Research Laboratory, Firmenich SA, Geneva, Switzerland

R. N. Young, Merck Frosst Canada, Inc., Kirkland, Quebec, Canada

Preface

It is always a great pleasure to introduce another volume in this series, signalling among other things the health of the art and science of organic synthesis.

This volume contains a chapter updating monoterpene synthesis and reviews the newer areas of leukotrienes and macrocyclic lactones. My grateful thanks are due to the authors of these contributions for their efforts in producing definitive work on their specialty areas.

Future volumes in this series are in the pipeline and I am always prepared to receive suggestions for areas to cover, and offers to help!!

JOHN APSIMON

*Ottawa, Canada
January 1988*

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The Total Synthesis of Macrocyclic Lactones

R. K. BOECKMAN Jr. and S.W. GOLDSTEIN

Department of Chemistry, University of Rochester, Rochester, New York

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INTRODUCTION

This chapter in Volume 7 of *The Total Synthesis of Natural Products* deals almost exclusively with the total synthesis of naturally occurring macrocyclic lactones (macrolides), polylactones (diolides, tetrolides, etc.), and their aglycones. Our use of the term macrolide transcends the original usage where it was restricted to the C₁₂–C₁₆ macrocyclic lactone antibiotics. Although several reviews on the synthesis of macrolides have been published,^{1–4} these have dealt mainly with the ring-forming lactonization step. We have attempted to chronicle the development of total synthesis in this field from the early efforts directed toward relatively simple targets to the current day assaults on the extremely complex, highly functionalized members of this class.

The chapter is divided into sections that deal with the various target compounds in approximate order of increasing complexity. Section 1 deals with simple monolactones which lack complex substituents such as sugars, esters, and the like attached to the lactone ring. This section includes primarily compounds that exhibit little or no biological activity, such as recifeioidide and diplodialide A. The syntheses in this area are generally quite straightforward and for expedience we have omitted some of the simplest compounds. The omission of some of these early studies is not intended to in any way diminish their value, for these efforts laid the foundations for later advances.

Section 2 deals with the synthesis of the more familiar biologically active macrolides, including the erythronolides, tylosin, and the leucomycin–carbomycin group. These compounds, many of which have important medicinal

uses, possess more highly oxygenated ring systems and are linked, via glycosidic linkages, to one or more sugar units.

Section 3 deals with the polycyclic macrolides such as cytochalasin B and hybridalactone. These compounds also exhibit profound biological activity. Since they are substantially more complicated than the other monolactones, we felt a separate section was warranted.

Section 4 deals with the total synthesis of macrolides having more than one lactone linkage in the macrocyclic ring. Compounds included in this group range from the dimeric lactone pyrenophorin and the trichothecanes to the tetrameric lactone nonactin.

Throughout this chapter we have attempted to be as comprehensive as possible in our coverage of the literature through 1984, with selected coverage of early parts of 1985 in the broad area of macrolide total synthesis. However, we have very possibly overlooked some work in the area. We regret the oversight, and we wish to apologize in advance to any workers in the area whose efforts have been inadvertently omitted.

1. SIMPLE MONOCYCLIC MACROLIDES

A. Recifeiolide

Recifeiolide (1), one of the simplest naturally occurring macrocyclic lactones, is isolated from the fungus *Cephalosporium recifie*.⁵ Since only one chiral center is present in this molecule, recifeiolide is the common benchmark for macrolide methodology. The first synthesis of this compound, by Corey's group at Harvard, began with 4-hydroxy-1-pentyne (2) (Scheme 1.1).⁶ Protection of the alcohol as the THP ether followed by hydrostannation afforded a 85:15 mixture of vinyl stannanes 3 with the (*E*)-isomer predominating. The stereospecific conversion of the stannanes 3 to the corresponding vinyl cuprates 4 was achieved by metalation with *n*-butyl lithium followed by quenching into pentynyl copper. The cuprates 4 were then coupled with either 7-iodo-heptanitrile or ethyl 7-iodohepanoate and the alcohol protecting group was removed to afford a 54–56% yield of alkylated products 5a or 5b. At this stage, chromatographic separation

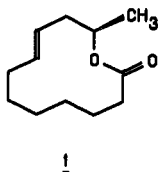
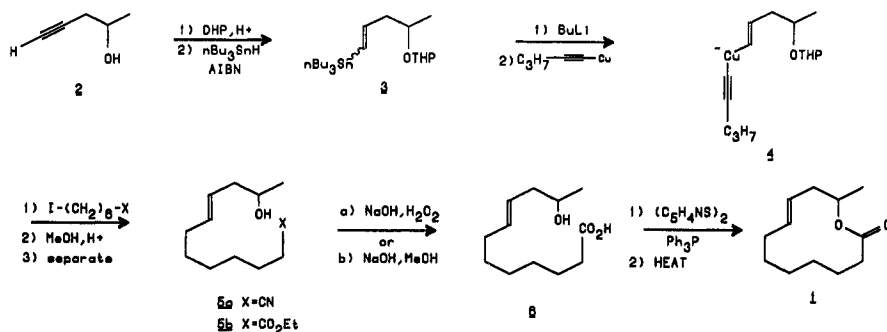


Figure 1.1. Recifeiolide (1).

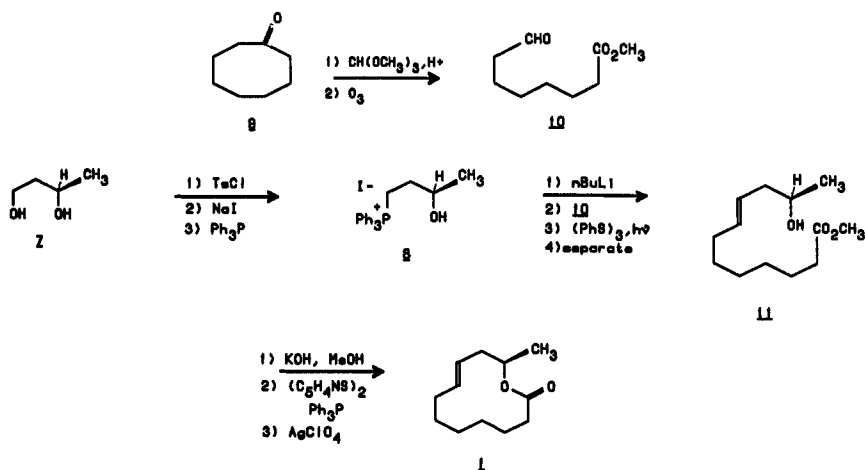
of the olefin isomers yielded (*E*)-**5a** or (*E*)-**5b**, which encompass all the required carbons for conversion to **1**. Alkaline hydrolysis gave the key intermediate seco acid **6** (98%). The final cyclization was accomplished by conversion to the 2-thiopyridyl ester and subsequent thermolysis in dilute xylene to afford recifeiolid (1) in 52% overall yield from **6**.



Scheme 1.1. Corey's recifeiolid synthesis.

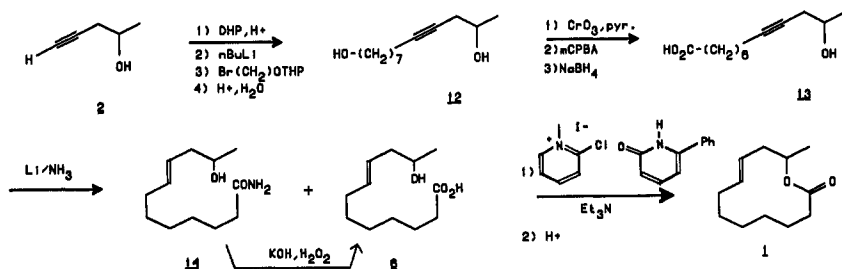
The same year, Gerlach described a synthesis of optically active **1** from (*R*)-1,3-butanediol (**7**) (Scheme 1.2).⁷ The diastereomeric esters produced from (–) camphorsulfonyl chloride and racemic 1,3-butanediol were fractionally recrystallized and then hydrolyzed to afford enantiomerically pure **7**. Tosylation of the primary alcohol, displacement with sodium iodide, and conversion to the phosphonium salt **8** proceeded in 58% yield. Methyl-8-oxo-octanoate (**10**), the ozonolysis product of the enol ether of cyclooctanone (**9**), was subjected to Wittig condensation with the dilithio anion of **8** to give **11** as a mixture of olefin isomers in 32% yield. The ratio, initially 68:32 (*E*:*Z*), was easily enriched further to 83:17 (*E*:*Z*) by photolysis in the presence of diphenyl disulfide. The synthesis was then completed by hydrolysis of the ester to the seco acid, conversion to the 2-thiopyridyl ester, and silver-mediated ring closure to afford **1** (70%). Gerlach's synthesis, while producing the optically active natural product, still did not address the problem posed by the olefin geometry.

A third approach employing lactonization as the final step was published by Mukaiyama in 1977 (Scheme 1.3).⁸ Alcohol **2** was protected as the THP acetal and alkylated with a protected 7-bromoheptanol to give diol **12** in 52% yield following acidic deprotection. As **12** contains all of the required carbon atoms for conversion to the target **1**, the remaining steps involve only the manipulation of the oxidation states of the various functional groups and the final lactonization. Accordingly, a series of straightforward oxidations and a reduction then allowed the isolation of hydroxy acid **13** in 50% yield. Lithium metal reduction of the



Scheme 1.2. Gerlach's recifeiolid synthesis.

alkyne then furnished the seco acid **6** in 53% along with a small amount of the corresponding amide **14**, which was readily hydrolyzed back to **6**. Lactonization involving a double activation sequence furnished an 87% yield of **1**.



Scheme 1.3. Mukaiyama's recifeiolid synthesis.

The aforementioned method for carboxyl group activation proceeds via intermediate **6a**, which is then subjected to an intramolecular attack by the secondary alcohol. Among the noteworthy aspects of this synthesis were the rapid entry into the system and the specific formation of the (*E*)-olefin geometry.

Utimoto and co-workers have successfully achieved a concise synthesis of the optically active seco acid **6** beginning with 1-nonen-8-yne (**15**) (see Scheme 1.4).⁹ Hydroalumination of enyne **15** with Dibal and conversion to the alanate with *n*-butyl lithium, followed by treatment with (*R*)-propylene oxide afforded

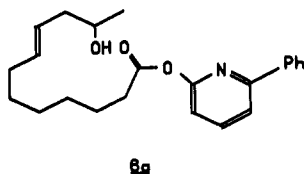
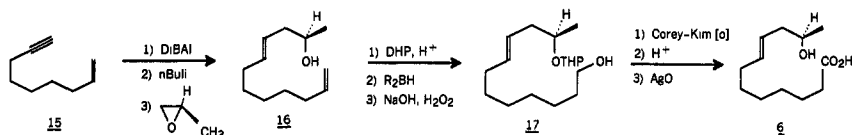


Figure 1.2.

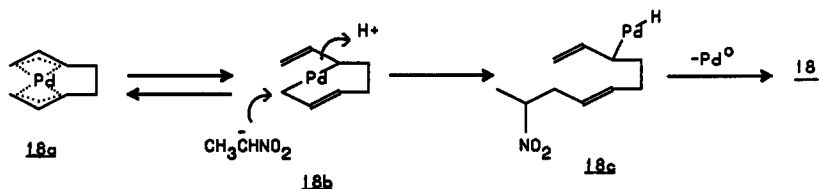
alcohol **16** in 55% yield. Not surprisingly, the syn hydroalumination step produced >99% of the (*E*)-internal olefin. Protection of the alcohol as the THP ether followed by hydroboration and oxidation gave the monoprotected diol **17** (74%). Seco acid **6** was obtained following a Corey–Kim oxidation, acidic hydrolysis of the THP ether (75%), and subsequent silver oxide oxidation (98%). The conversion of **6** to recifeiolide (**1**) then followed the Gerlach procedure.⁷



Scheme 1.4. Utimoto's recifeiolide synthesis.

A novel method of stereospecific olefin formation was used by Tsuji for the elaboration of intermediate **18** (Scheme 1.5).¹⁰ Palladium(II)-mediated telomerization of butadiene in nitroethane gave a 56% isolated yield of the (*E*)-nitro olefin **18**. One rationale for the high stereospecificity in the bond-forming steps of this reaction arises from an examination of the mechanism. The addition of Pd^{+2} to butadiene causes initial formation of a dimeric bis π -allyl palladium species. The bis π -allyl species **18a** and the σ -allyl species **18b** (Eq. 1.1) are in rapid equilibrium and the latter intermediate may be intercepted by a nucleophile. Thus the addition of nitroethane to **18b** results in the formation of **18c** with retention of the (*E*)-olefin geometry. Reductive elimination of palladium then produces **18** with retention of the (*E*)-olefin geometry.

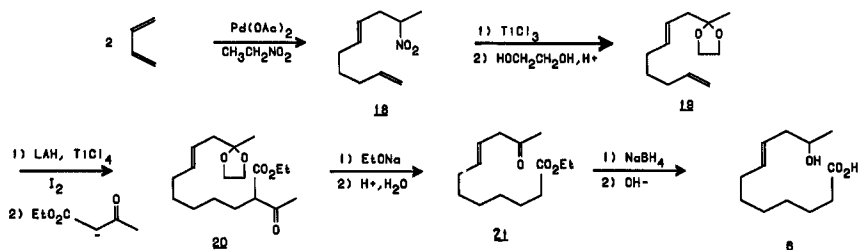
After conversion to **19** (70% yield) via Nef reaction and ketalization, selective modification of the terminal olefin by reaction with LAH-TiCl_4 , quenching with I_2 , and displacement of the resulting terminal halogen with ethyl acetoacetate anion afforded **20** in 48% overall yield. Deacetylation with sodium ethoxide followed by deketalization under acidic conditions produced an 88% yield of keto ester **21**. Seco acid **6** was then obtained (in 29% yield from **18**) after reduction of the ketone and ester hydrolysis. Clearly, the significance of this



Telecyclization of butadiene

(1.1)

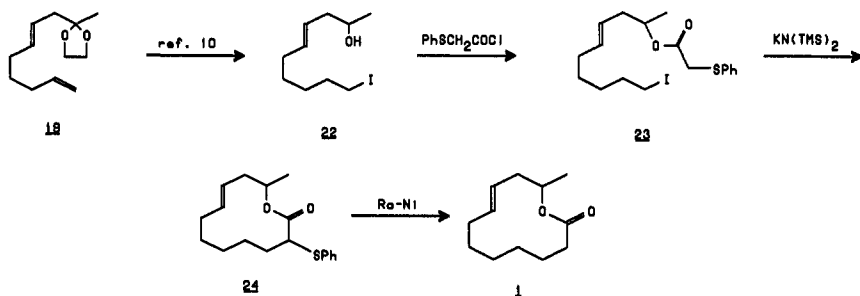
synthesis was the utilization of inexpensive starting materials and the excellent specificity of the olefin-forming reaction. Tsuji has employed this methodology for the synthesis of several other natural products.



Scheme 1.5. Tsuji's first recifeiolide synthesis.

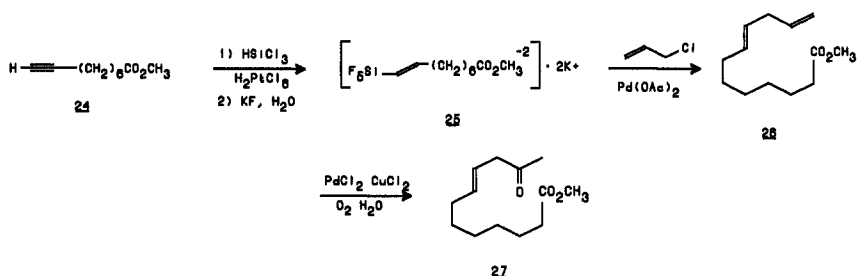
The second Tsuji synthesis, which appeared (see Scheme 1.6) in the latter part of 1978, employed a strategy similar to his earlier work for construction of the basic carbon framework.¹¹ Ketal diene **19** was transformed to halo alcohol **22** by the use of chemistry established in his previous synthesis.¹⁰ Acylation with phenylthioacetyl chloride readily afforded ester **23**. Intramolecular alkylation resulting in ring closure was brought about by deprotonation with sodium hexamethyldisilazane to give lactone **24** in 71% yield. Synthetic **1** was then obtained in 90% yield following Raney nickel reduction.

Kumada's group at Kyoto installed the (*E*)-olefin required for recifeiolide (**1**) via syn addition to a terminal acetylene (Scheme 1.7).¹² Beginning with methyl 8-nonynoate, chloroplatinic-acid-catalyzed addition of trichlorosilane gave the corresponding (*E*)-silyl olefin. Halogen exchange and formation of the silicate with aqueous KF afforded **25** in 62% yield. Alkylation with allyl chloride mediated by $\text{Pd}(\text{OAc})_2$ gave diene **26**, which was transformed by Wacker oxidation to ketone **27** (37%). This completed a formal total synthesis of **1**, as the conversion of **27** to the natural product had previously been achieved by Tsuji.¹⁰ Although somewhat suggestive of Utimoto's approach, the Kumada



Scheme 1.6. Tsuji's second recifeiolide synthesis.

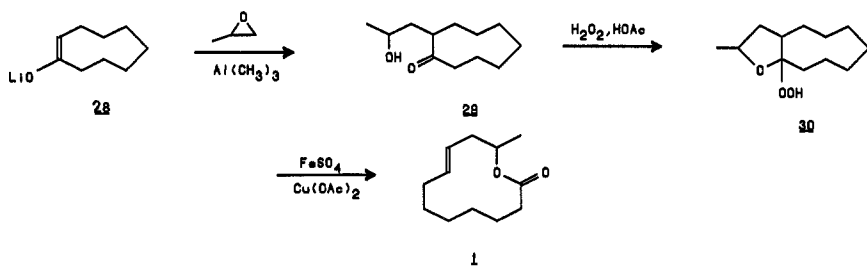
synthesis was less complicated, since fewer oxidation state changes and protecting group manipulations were required.



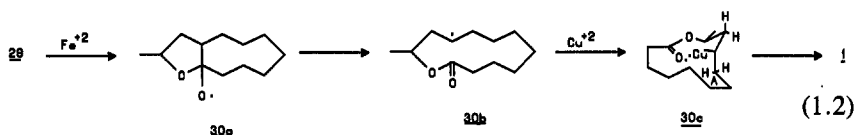
Scheme 1.7. Kumada's recifeiolide synthesis.

By far the most concise synthesis of **1** has arisen from the work of Schreiber in 1980 (see Scheme 1.8).¹³ The lithium enolate **28** was monoalkylated with propylene oxide in the presence of trimethyl aluminum to give keto alcohol **29** in 96% yield (based on recovered **28**). The addition of hydrogen peroxide under acidic conditions then made available the hydroperoxide **30** in 99% yield. A ferrous-ion-induced fragmentation then gave the natural product **1** in 96% yield as a single olefin isomer.

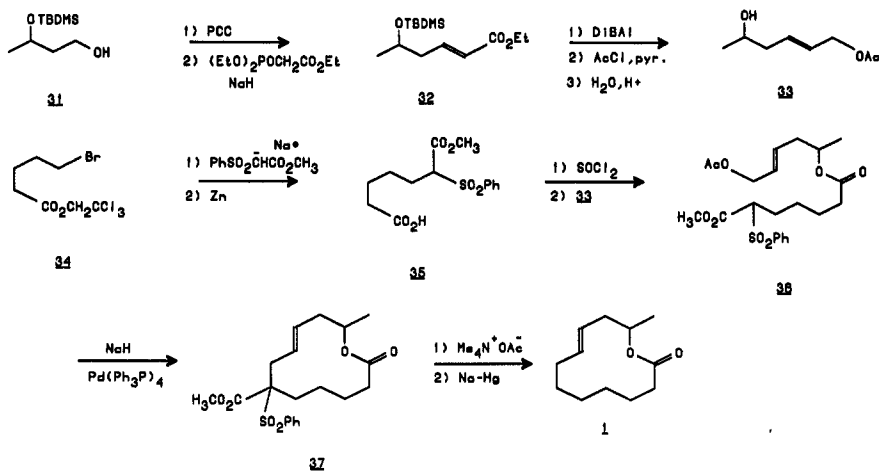
The mechanism of the key fragmentation involves initial transfer of an electron to hydroperoxide **30** (Eq. 1.2) from Fe^{+2} , forming intermediate **30a**, which then cleaves homolytically to the carbon radical **30b**. Oxidative coupling with Cu(OAc)_2 then forms **30c** in which the ester moiety is in the stable *Z*-configuration, stabilized by internal coordination via a pseudo six-membered ring. From this intermediate, only one hydrogen atom (H_A) is available for syn elimination and, accordingly, only the (*E*)-olefin is produced.



Scheme 1.8. Schreiber's recifeiolide synthesis.



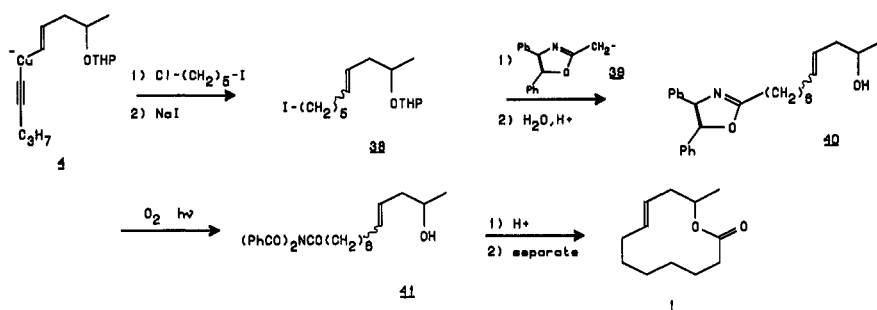
Trost chose to exemplify the utility of organopalladium coupling reactions for carbon-carbon bond formation by use of this process for the ring closure step in a synthesis of **1** (Scheme 1.9).¹⁴ To this end, monoprotected diol **31** was oxidized and chain extended to form the α,β -unsaturated ester **32**. Reduction to the allylic alcohol followed by acetylation and desilylation gave **33** in 53% overall yield from **31**. Carboxylic acid **35** was then obtained via a two-step sequence from bromo ester **34** (84%) by alkylation with methyl



Scheme 1.9. Trost's recifeiolide synthesis.

phenylsulfonylacetate followed by reductive cleavage of the ester. Formation of the analogous acid chloride permitted coupling of **35** and **33** to afford ester **36** in 79% yield. Formation of the 12-membered ring lactone was then achieved by palladium-catalyzed cyclization to afford **37** (78%), with no apparent formation of either any (*Z*)-olefin or 10-membered ring lactone. The stereospecificity of this reaction is quite dramatic when compared with the loss of olefin geometry observed in acyclic cases.¹⁵ The synthesis of **1** was efficiently completed by decarboalkoxylation and reductive desulfonylation to give synthetic **1** in 81% yield. Although this synthesis is somewhat complex for a molecule as structurally simple as **1**, clearly Trost selected recifeiolid as a vehicle to explore methodology useful for the construction of more complex macrolides.

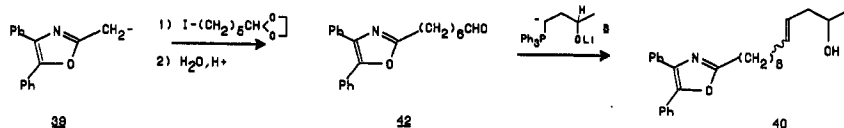
Wasserman has completed two syntheses of recifeiolid, both employing the use of oxazoles as acetic acid dianion equivalents.¹⁶ The first (Scheme 1.10) utilized a route previously developed by Corey⁶ for his synthesis of **1**. Cuprate **4** was alkylated and then converted to iodide **38** in a straightforward manner. Alkylation with oxazole anion **39** and removal of the THP with acid then led directly to alcohol **40**. Liberation of the carboximide moiety was achieved by treatment with singlet oxygen to afford **41**, which led to the isolation of synthetic **1** after an acid-mediated lactonization step, and separation of the olefin isomers.



Scheme 1.10. Wasserman's first recifeiolid synthesis.

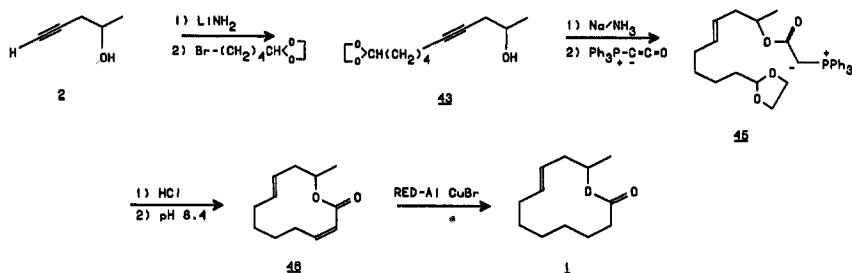
Wasserman's second synthesis,¹⁶ shown in Scheme 1.11, was similar to a strategy utilized by Gerlach.⁷ Anion **39** was alkylated with the acetal of 6-iodohexanal and deprotected to produce aldehyde **42**. A Wittig condensation with the dilithio dianion of racemic **8** afforded the known intermediate **40** as an 8:2 mixture of (*E*)- and (*Z*)-olefin isomers, respectively.

The most recent synthesis of **1** is that of Bestmann.¹⁷ Acetylenic alcohol **2** was converted to the dianion and alkylated with the acetal of 4-bromopentanal to give alkyne **53**. Subsequent reduction of the triple bond with sodium in ammonia generated exclusively the required (*E*)-olefin geometry. *O*-Alkylation



Scheme 1.11. Wasserman's second recifeiolide synthesis.

of the intermediate alcohol with ketylenetriphenylphosphorane (**44**) then afforded the stabilized Wittig reagent **45**. Cleavage of the acetal with acid followed by base treatment to regenerate the stabilized ylide induced an intramolecular Wittig condensation which provided the α,β -unsaturated lactone **46**. Finally, selective reduction of the conjugated double bond was achieved with Redal and CuBr to afford **1**.



Scheme 1.12. Bestmann's recifeiolide synthesis.

B. Diplodialides

The diplodialides are a family of ten-membered ring macrocyclic lactones isolated from the pathogenic fungus *Diplodia pinea*. Structural studies by Wada in 1976 had shown these compounds to be quite similar to recifeiolide (**1**), with an additional oxygen functionality included β to the lactone carbonyl.¹⁸ Diplodialides A, B, C, and D (**47–50**) are the four most common members of this group.

The first synthesis of these compounds was also that of Wada in 1977 (Scheme 1.13).¹⁹ Ethyl 5-oxohexanoate (**51**) was reduced with NaBH₄ and the resulting alcohol protected with dihydropyran to give **52**. Reduction of the ester moiety to a primary alcohol followed by conversion to the bromide **53** was achieved by conventional means. Alkylation of the dianion of ethyl acetoacetate with **53** afforded a 78% yield the β -keto ester **54**, which possesses all the carbons required for the construction of the diplodialides. Protection of the ketone as the dithiane

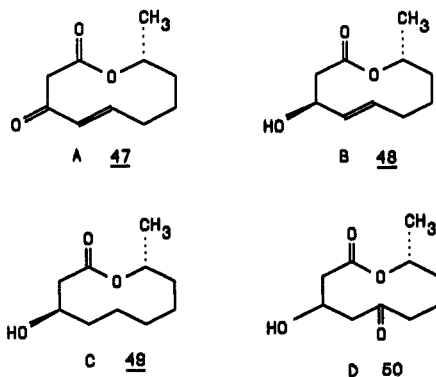
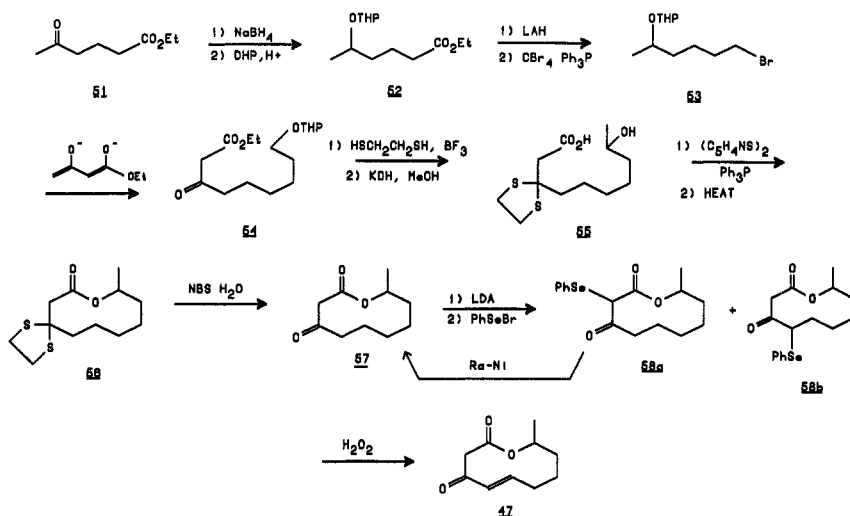


Figure 1.3. Diplodialide A (47); B (48); C (49); D (50).

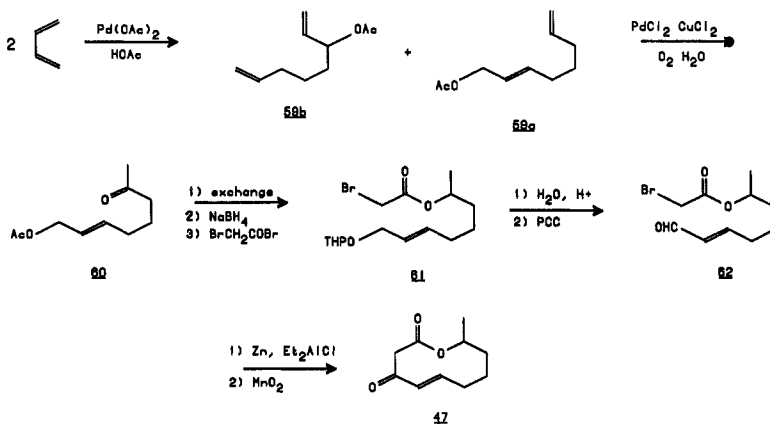
using $\text{BF}_3\text{-Et}_2\text{O}$ and ethanedithiol, which caused concomitant cleavage of the THP ether, followed by basic hydrolysis of the ethyl ester, furnished acid **55** (72%). Lactonization using the Corey procedure afforded macrocycle **56** in 30% yield. Removal of the dithioketal with NBS in water gave an 82% yield of the keto lactone **57**. The double bond was then introduced by a selenylation–oxidation sequence. Accordingly, treatment of **57** with excess LDA followed phenylselenenyl bromide afforded selenyl lactone **58a** (17%), the desired **58b** (23%), and



Scheme 1.13. Wada's diplodialide A synthesis.

recovered starting material **57** (41%). Undesired **58a** was readily reconverted to **57** in 71% yield with Raney nickel. Synthetic diploidalide-A (**47**) was then obtained from **58b** in 59% yield after oxidation and selenoxide elimination.

The following year, Tsuji published a synthesis of **47** utilizing the now familiar butadiene telomerization technique (Scheme 1.14).²⁰ When butadiene was reacted in the presence of $\text{Pd}(\text{OAc})_2$ and acetic acid, diene acetates **59a** and **59b** were formed. The desired terminal acetate **59a** was easily separated from a small amount of the isomeric **59b** by fractional distillation. Conversion of the terminal olefin into what will subsequently become the secondary alcohol was achieved by Wacker oxidation which produced ketone **60** (77%). After substitution of a THP ether for the acetate, the ketone was reduced and the resulting alcohol was acylated with bromoacetyl bromide to afford **61**. Acidic cleavage of the THP ether followed by oxidation then provided ester aldehyde **62**. Final ring closure was achieved using a modified version of the Reformatsky reaction. Thus treatment of **62** with zinc and diethylaluminum chloride gave **48** as a mixture of alcohol diastereomers in 45% yield. Oxidation of the allylic alcohol with MnO_2 then afforded synthetic **47**.

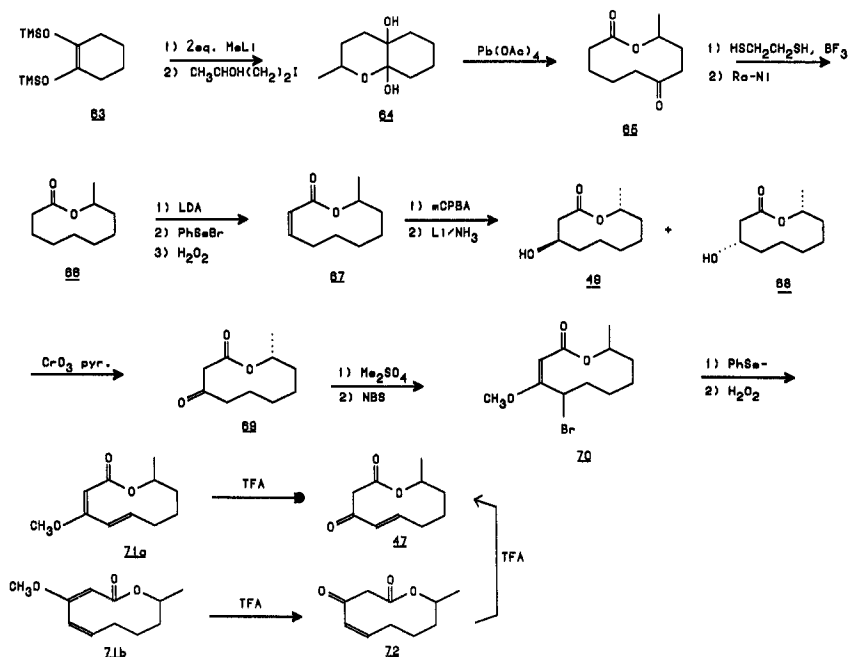


Scheme 1.14. Tsuji's diploidalide A synthesis.

The studies of Ban and Wakamatsu culminated in the preparation of three natural compounds from a single synthetic route (Scheme 1.15).²¹ The enediol bis silyl ether **63** was converted to the dianion and immediately alkylated with 1-iodo-3-butanol to give glycol **64** as a mixture of diastereomers in 87% yield. Diol fragmentation with lead tetraacetate afforded keto lactone **65** in quantitative yield. Formation of the dithioacetal and subsequent Raney nickel desulfurization then gave **66** (81%). Macrocyclic lactone **66** is the simple natural product

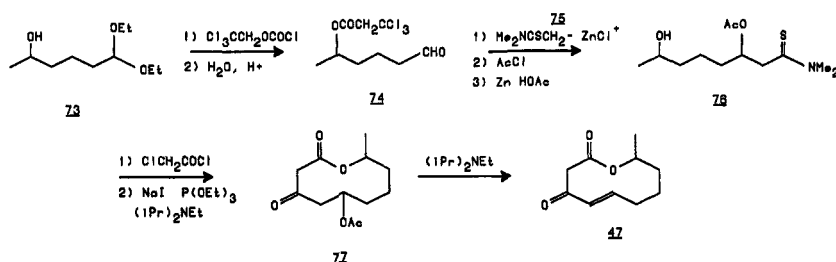
Phorcantholide I, isolated from the metasternal gland secretion of *Phoracantha synonyma*.

Oxidation β to the lactone carbonyl, which is required to obtain the diplodialide system, was then effected via the following two reaction sequences. Selenylation–elimination furnished the unsaturated lactone **67** (82%). Epoxidation of **67** followed by lithium–ammonia reduction gave diplodialide-C (**49**) and the diastereomeric alcohol **68** in 40–45% yield from the mixture of β - and α -epoxides, respectively. For the preparation of **47**, the intermediates **68** and **49** were not isolated, but rather directly oxidized to provide β -keto lactone **69** (63% from **67**). Formation of the vinylogous ester, followed by allylic bromination, led to the diastereomeric halides **70** in 81% yield. Displacement of bromide by the phenylselenenyl anion produced the intermediate selenolactones which were subjected to oxidation and selenoxide elimination to dienes **71a** and **71b**. At this point in the synthesis, the assignment of olefin geometry in **71a** and **71b** was not possible; however, the sequence was stereospecific since each diastereomer of bromide **70** produced a single olefin isomer. Treatment of **71a** with trifluoroacetic acid at -20°C produced synthetic **47** in 72% yield, thus confirming the γ,δ -double bond in this isomer was of the (*E*)-geometry, as required. Similar treatment of **71b** gave a 7:5 ratio of **47** and **72** (44%), the former presumably from isomerization of the kinetic (*Z*)-olefin, along with unchanged **71b** (56%).



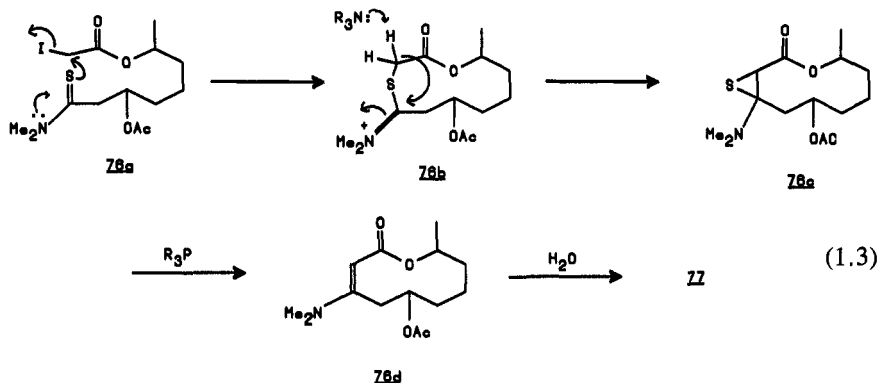
Scheme 1.15. Ban's diplodialide A and C synthesis.

Ireland utilized a sulfide ring contraction process for the ring-forming step of his synthesis of **47** (see Scheme 1.16).²² The diethyl acetal of 5-hydroxyhexanal (**73**) was converted to the trichloroethyl carbonate and the acetal hydrolyzed to produce aldehyde **74** in 86% yield. Addition of the zinc enolate of *N,N*-dimethylethanethioamide (**75**) to **74** then afforded an intermediate hydroxy thioamide which was subjected to acylation and reductive carbonate cleavage to yield **76** (53%). Acylation with chloroacetyl chloride was followed by ring closure to give the macrocycle **77** (24%).

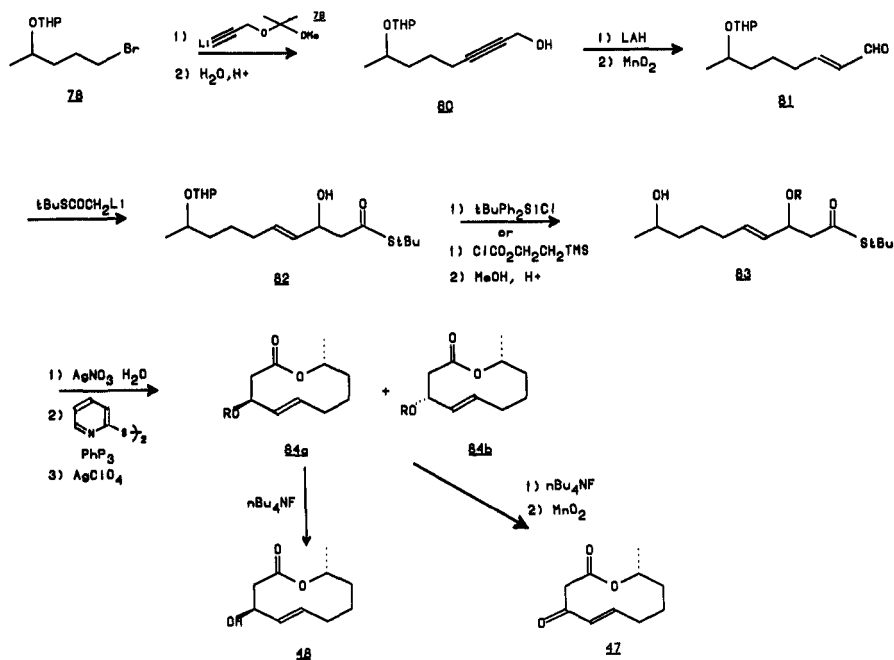


Scheme 1.16. Ireland's diplodialide A synthesis.

The multistep ring-closure process, for which a plausible mechanism is outlined in Eq. 1.3, involves initial alkylation on sulfur in the thioamide **76a** to give the thioimmonium ion intermediate **76b**. Deprotonation forms the episulfide **76c**, from which sulfur is extruded by the phosphine leading to enamine **76d**. Hydrolysis of the enamine then produces the β -dicarbonyl compound **77**. Elimination of acetic acid from **77** then afforded diplodialide-A (**47**) in 80% yield. Although requiring very few steps, the crucial ring-closure reaction proceeded in disappointingly low yield.



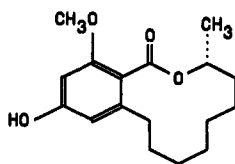
Gerlach has successfully prepared both diplodialides A and B (**47–48**) from a common macrocyclic intermediate, as shown in Scheme 1.17.²³ The THP ether of 4-bromo-2-pentanol (**78**) was alkylated with the lithium anion derived from the protected propargyl alcohol **79** to give, following mild acid hydrolysis, **80** in 76% yield. The LAH reduction of the acetylenic bond in **80** followed by oxidation to the enal **81** proceeded in ~75% yield. Homologation of **81** using the lithium enolate of *t*-butyl thioacetate then furnished an 81% yield of allylic alcohol **82**. Protection of the free alcohol in **82** either as the *t*-butyldiphenylsilyl ether or the trimethylsilylethyl carbonate, and acidic cleavage of the THP group gave **83** in 81–83% overall yield. Cyclization was achieved by initial conversion to the acid followed by silver-mediated ring closure via the 2-thiopyridyl ester to afford a mixture of diastereomeric lactones **84a** and **84b** in 56% (R = *t*-butyldiphenylsilyl) or 11% (R = trimethylsilylethoxycarbonyl) yields, respectively. Diastereomer **84a** (with either protecting group) was readily converted to synthetic diplodialide-B (**48**) in excellent yield. Diplodialide-A (**47**) was isolated in good overall yield following the deprotection of either **84a** or **84b** and subsequent allylic oxidation.



Scheme 1.17. Gerlach's diplodialide A and B synthesis.

C. Lasiodiplodin

The culture filtrates of the organism *Lasiodiplodia theobromae* afforded a plant growth inhibitor which was identified as lasiodiplodin (**90**) after structural studies.²⁴ From a retrosynthetic viewpoint, construction of the aromatic residue of **90** (a resorcinol ester) lends itself quite nicely to methodology involving addition of an acetoacetate moiety to a functionalized olefin. Different variants of this strategy are employed in the following syntheses of **90**.



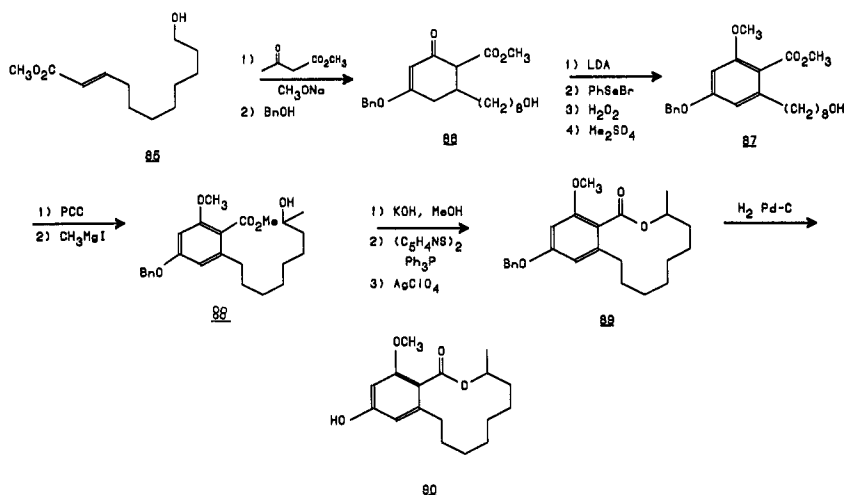
90

Figure 1.3A. Lasiodiplodin (**90**).

Gerlach initiated his synthetic route (Scheme 1.18) by condensation of 11-hydroxy-2-undecenoic acid methyl ester (**85**) with methyl acetoacetate under basic conditions to give the vinylogous methyl ester.²⁵ Further treatment with benzyl alcohol then gave the corresponding benzyl compound **86** in 48% yield. This readily available dialkyl cyclohexenone contains the basic framework required for the construction of the lasiodiplodin system. Oxidation of **86** to the related phenol via a selenylation–oxidation–elimination sequence and protection as the methyl ether afforded **87** in 60% overall yield. A point well worth noting is the differentiation of the two phenolic hydroxy groups in **87**, a requirement that is an impediment in some of the syntheses which will be discussed subsequently. Oxidation of **87** to the corresponding aldehyde and addition of methyl Grignard reagent provided **88** (66%). Lactonization was effected via the methodology previously employed by Gerlach to give macrocycle **89** in good yield. Hydrogenolysis of the benzyl ether then gave lasiodiplodin (**90**) in 83% yield.

Tsuji has completed a synthesis of *O*-methyl lasiodiplodin (**97**), a simple analog of the natural product **90**.²⁶ While **97** itself is not found in nature, the strategy is closely related to those employed for **90** and thus the preparation of **97** is also discussed in detail (see Scheme 1.19).

Methyl acetoacetate was condensed with diketene under basic conditions to give the resorcinyl ester **92** in 45% yield. Formation of the monomethyl ether followed by benzylic bromination afforded a 51% yield of **93**. The remaining



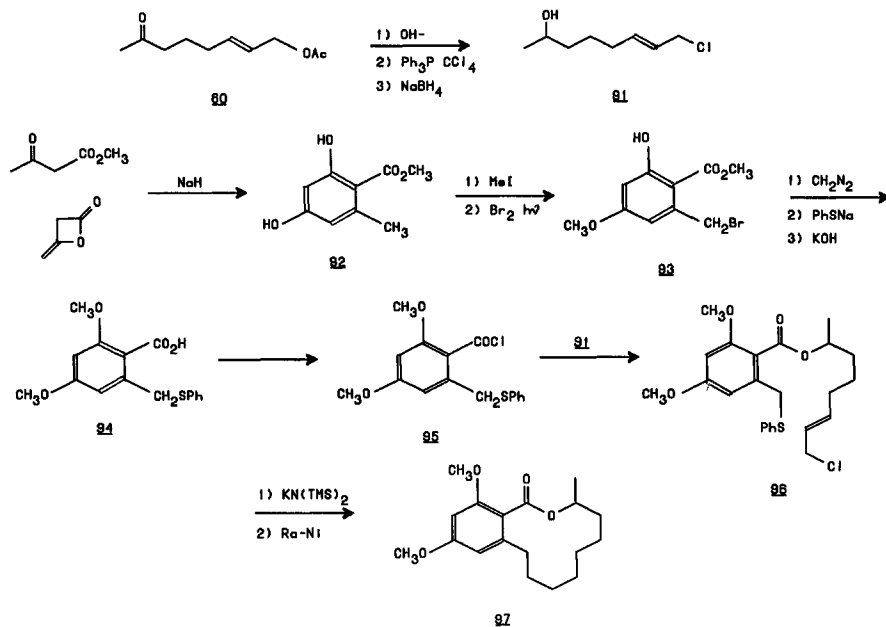
Scheme 1.18. Gerlach's first lasiodiplodin synthesis.

functionalization of the aromatic ring was achieved by methylation of the residual phenolic hydroxyl group, substitution at the benzylic position with thiophenoxide, and basic hydrolysis of the ester to furnish acid **94**.

The acyclic carbon framework was derived from Tsuji's previous work on the telomerization of butadiene. Thus allylic acetate **60** was converted to the related allylic chloride and the carbonyl was reduced to give **91** in good yield.

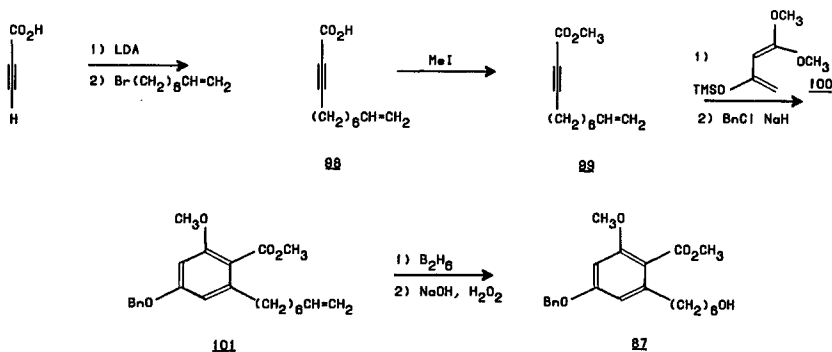
Conversion to benzoate ester **96**, obtained by conversion of **94** into the corresponding acid chloride **95** followed by addition of alcohol **91**, then set the stage for macrolide formation. This cyclization was effected by deprotonation and intramolecular alkylation at the benzylic position in 41% yield. Desulfurization and concomitant reduction of the olefin then provided *O*-methyl lasiodiplodin (**97**) in 68% yield. Although Tsuji was readily able to construct the six-membered ring at the proper oxidation level, the symmetry implicit in this strategy precluded the required differentiation of the phenolic hydroxyl groups.

Danishefsky has exploited his widely utilized silyloxydiene chemistry to complete a formal total synthesis of **90** (Scheme 1.20).²⁷ By employing the appropriate oxidation levels for both the diene and dienophile, a resorcinyll ester possessing the required differentiation of the phenolic groups was obtained without further oxidative manipulation. To this end, the dianion of propiolic acid was alkylated with 1-bromo-7-octene to give acid **98** in 68% yield. Further alkylation with methyl iodide then gave the ester **99**. A Diels–Alder reaction with diene **100**, a derivative of methyl acetoacetate, and alkyne **99** then furnished an initial phenolic intermediate which was protected as the benzyl ether to afford

Scheme 1.19. Tsuji's *O*-methyl lasiodiplodin synthesis.

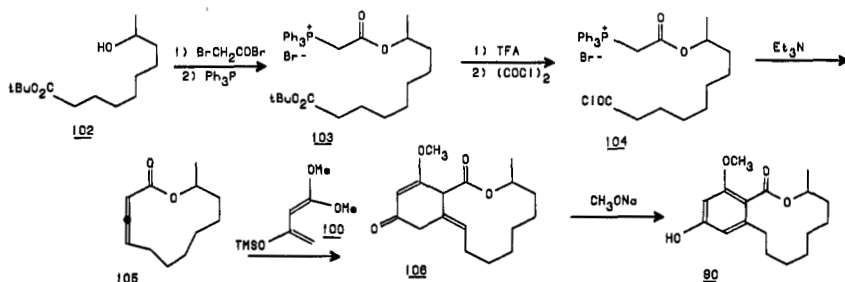
overall a 35% yield of **101**. This substance was subsequently intersected with Gerlach's earlier synthesis of lasiodiplodin by a hydroboration-oxidation sequence to give **87** (80%).

The second Gerlach synthesis of **90** involves an interesting permutation of the synthesis just described.²⁸ *t*-Butyl 9-hydroxydecanoate (**102**) was acylated with bromoacetyl bromide and then converted to the stabilized Wittig reagent



Scheme 1.20. Danishefsky's lasiodiplodin synthesis.

103 (Scheme 1.21). Transformation of ester **103** into acid chloride **104** then set the stage for the novel macrocyclization step. Deprotonation of **104** induced an intramolecular Wittig condensation followed by immediate loss of HCl to produce allenic lactone **105** in 42% yield. Subsequent [4 + 2] cycloaddition of diene **100** with **105** gave cyclohexene **106** in 55% yield. Aromatization of **106** under basic conditions then afforded a 50% yield of lasiodiplodin (**90**).



Scheme 1.21. Gerlach's second lasiodiplodin synthesis.

D. Curvularin

Curvularin (**107**) is a 12-membered ring keto lactone containing a fused 1,3 dihydroxybenzene ring. This mold metabolite, isolated from the extracts of the *Curvularia* species and *Penicillium steckii*, has some rather unexpected chemistry associated with it.²⁹

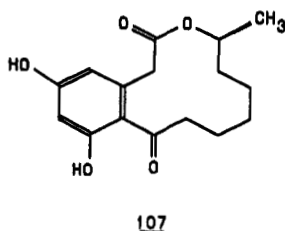


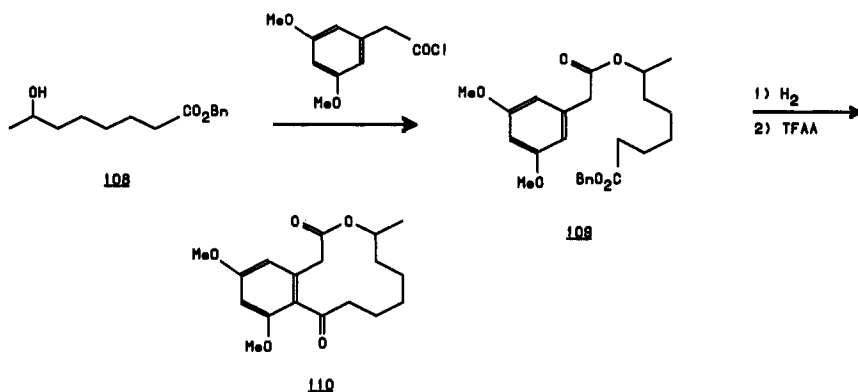
Figure 1.4. Curvularin (**107**).

Not surprisingly, Bycroft reported failure to effect formation of the macrocycle from the seco acid via an intramolecular lactonization.³⁰ All attempts at the use of either DCC or trifluoroacetic anhydride under a variety of conditions failed

to give any of the macrocyclic lactone. These studies, however, predated the development of the macrolactonization technology of Corey involving the thiopyridyl esters by several years.

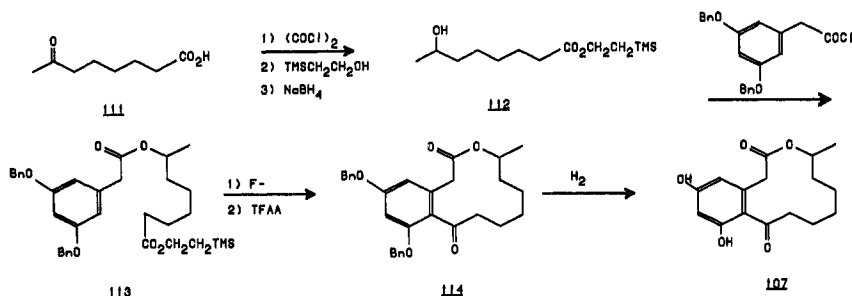
Several of the synthetic studies in this area deal with the preparation of the closely related di-*O*-methylcurvularin **110**. Because much of the existing chemistry in this area has employed **110** as the target molecule, syntheses of **110** are discussed in detail.

Bycroft was able to achieve the synthesis of **110** via a slightly modified route (Scheme 1.22).³⁰ Condensation of benzyl 7-hydroxyoctanoate (**108**) with 3,5-dimethoxyphenylacetyl chloride provided the expected diester **109**. Hydrogenolysis of the benzyl ester gave the desired acid, which was induced to close to the lactone via intramolecular Friedel–Crafts acylation to afford **110**.

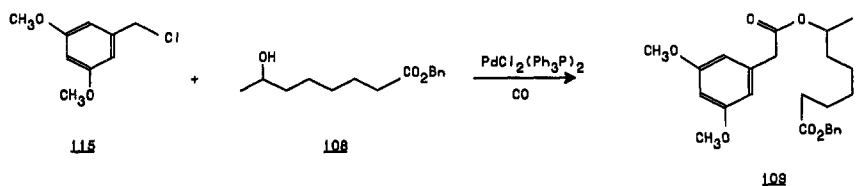


Scheme 1.22. Bycroft's di-*O*-methyl curvularin synthesis.

The Gerlach synthesis of **107** some 10 years later is indeed very similar to the Bycroft route with the notable exception of the protecting group manipulations.³¹ Conversion of 7-oxooctanoic acid (**111**) to the acid chloride, esterification with 2-trimethylsilylethanol, and reduction of the ketone led to the isolation of **112** in 45% yield (Scheme 1.23). Esterification of 3,5-dibenzoyloxyphenylacetyl chloride with **112** then produced ester **113** cleanly. Cleavage of the trimethylsilylethyl group with fluoride gave the related acid, which then underwent Friedel–Crafts acylation to afford a 33% yield di-*O*-benzylcurvularin (**114**). Hydrogenolysis of the benzyl ethers subsequently afforded the natural product **107**. Gerlach also reported a synthesis of **107** in optically active form beginning with (*S*) γ -valerolactone, although that route is somewhat lengthier.



Scheme 1.23. Gerlach's curvularin synthesis.



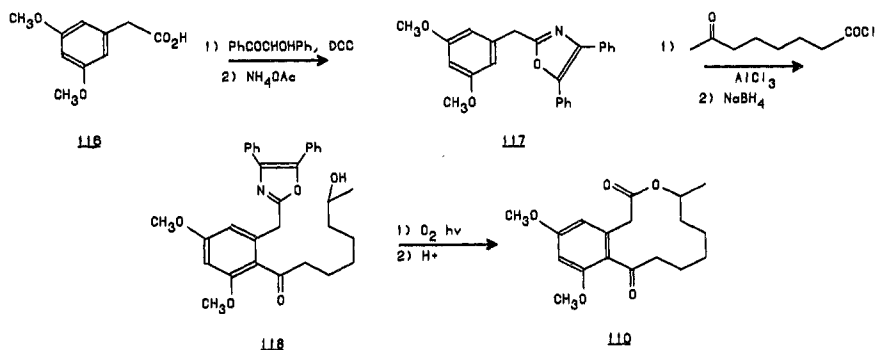
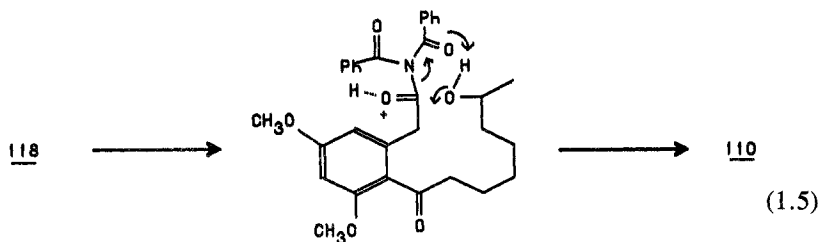
Tsuiji's carbonylation approach

(1.4)

Tsuiji has employed a palladium-catalyzed carbonylation reaction in a formal synthesis of **110** (Eq. 1.4).³² Thus reaction of 3,5-dimethoxybenzyl chloride (**115**) with hydroxy ester **108** in the presence of 10 mole % of $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ under a CO atmosphere produced diester **109** in 70% yield. Bycroft had previously converted **109** to the unnatural product **110**.

Wasserman was able to obtain the curvularin skeleton via an intramolecular lactonization as the key step (Scheme 1.24).³³ In this sequence, the oxazole technology previously developed by this group was first employed to protect a carboxylic acid and later, after conversion to the carboximide, served to provide a good activating group for the lactonization. Accordingly, 3,5-dimethoxyphenylacetic acid (**116**) was condensed with benzoin and after treatment of the intermediate with ammonium acetate, oxazole **117** was obtained in 68% yield. Friedel-Crafts acylation of **117** with 7-oxooctanoyl chloride followed by reduction of the aliphatic carbonyl afforded **118** in 47% yield. Photooxygenation of the oxazole moiety of **118** then gave a triamide which cyclized under acidic conditions to give **110**.

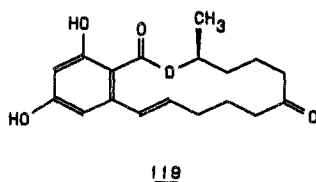
The apparent advantage of the latter method of lactonization over those studied by Bycroft is the ability of the benzoyl groups to assist proton removal via a six-membered ring transition state (Eq. 1.5).

Scheme 1.24. Wasserman's di-*O*-methyl curvularin synthesis.

E. Zearalenone

Zearalenone (**119**) is a 14-membered resorcylic keto lactone isolated from the fungus *Gibberella zeae*.^{34a-c} Anabolic and uterotrophic activity have been exhibited by this compound.^{34d}

The first synthesis of **119** was that described by a Merck group as outlined in Scheme 1.25.³⁵ Construction of the aliphatic segment began with the reduction of 5-oxo-hexanoic acid (**120**) to form the intermediate δ -lactone. The addition

Figure 1.4A. Zearalenone (**119**).

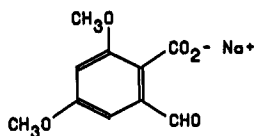
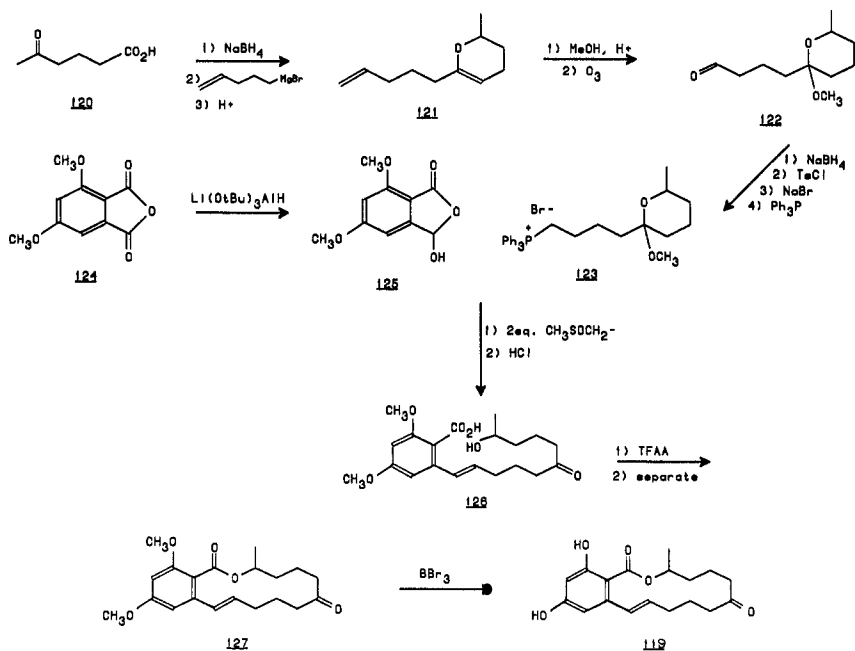
**125a**

Figure 1.5.

of 5-pentenyl magnesium bromide followed by acid treatment and distillation afforded a 50% yield of the cyclic enol ether **121**. Protection of the enolic double bond as the dimethyl ketal and ozonolysis of the terminal double bond then gave aldehyde **122** (82%). Straightforward conversion to the phosphonium salt **123** was effected in 55% overall yield via reduction to the alcohol, conversion to the bromide via the tosylate, and finally displacement with triphenylphosphine.

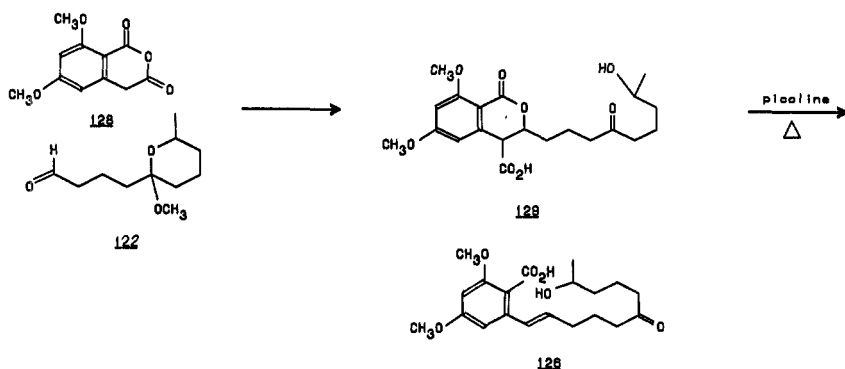
The aromatic synthon was obtained by reduction of 3,5-dimethoxyphthalic anhydride (**124**) to hydroxyphthalide **125**. Wittig coupling of the two fragments (**125** was first converted to the sodium carboxylate **125a** with dimethyl anion) and acid treatment afforded the seco acid **126** as a 1:1 mixture of olefin isomers.



Scheme 1.25. Merck's first zearealenone synthesis.

Lactonization of this mixture with trifluoroacetic anhydride and chromatographic separation of the olefin isomers gave dimethylzearalenone (**127**) in 15% yield. Finally, conversion to **119** was effected via a demethylation with boron tribromide in 22% yield. Clearly the least attractive aspect of this synthesis was the lack of stereoselectivity in the Wittig reaction.

The Merck group later published a concise synthesis of **126**, a compound they had previously utilized (Scheme 1.26).³⁶ Knoevenagel condensation of 3,5-dimethoxyhomophthalic anhydride **128** (an aromatic analog of a malonic ester) and aldehyde **122** formed a mixture of lactonic acids **129**. Conversion of **129** in hot γ -picoline to the seco acid **126** then constituted a formal total synthesis of zearalenone (**119**).



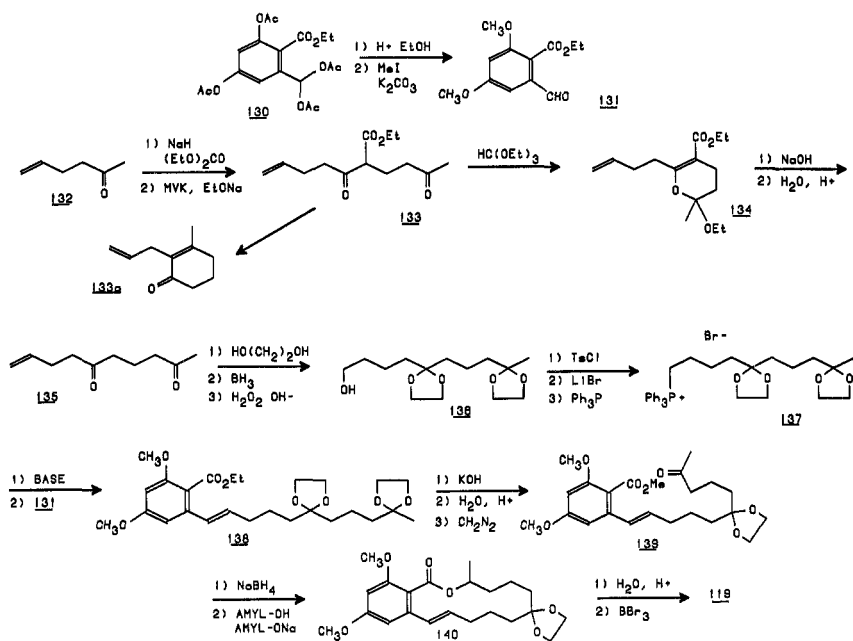
Scheme 1.26. Merck's second zearalenone synthesis.

Fried's group at Syntex has described a similar synthesis of zearalenone employing a Wittig condensation and ring closure by intramolecular lactonization (Scheme 1.27).³⁷ The aromatic residue **131** was constructed from the known ethyl *o*-orsellinate diacetate (**130**) by acid hydrolysis and methylation of the phenolic hydroxy groups.

The aliphatic portion of the molecule was constructed beginning with the carboethoxylation of 1-hexene-5-one (**132**) in 88% yield. Chain extension by means of Michael addition of the resulting β -keto ester to methyl vinyl ketone then gave a 57% yield of diketo ester **133**. Direct methods of decarboxylation to give **135** afforded only cyclohexenone **133a**, so a rather roundabout procedure was employed. Treatment with triethyl orthoformate and catalytic acid afforded vinylogous ester **134**. Basic hydrolysis of the ester followed by acid workup caused the overall decarboalkoxylation to give the 1,5-diketone **135**. Protection of both carbonyls as ethylene glycol ketals, followed by hydroboration-oxidation

led directly to primary alcohol **136**. Conversion to the phosphonium salt **137** was then achieved via tosylation, displacement with bromide, and reaction with triphenylphosphine.

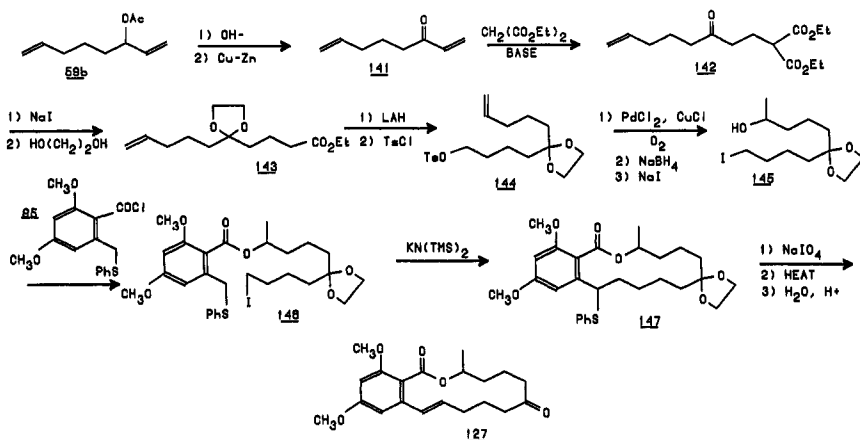
Wittig reaction of **137** and benzaldehyde **131** led to the isolation of olefin **138**, whose geometry was undetermined. Monodeprotection of the methyl ketone ketal was fortuitously achieved by hydrolysis of the ester to the corresponding acid with concomitant hydrolysis of the ketal and esterification to give **139**. The reason for the observed selectivity is unknown; however, it is clear that none of the corresponding diketone or the regioisomeric monoketone was formed. Reduction to the alcohol followed by base-catalyzed intramolecular ester exchange gave the protected natural product **140**. Although lactonization proceeded in only 8% yield, the synthesis was completed by removal of the ketal with acid and demethylation with BBr_3 to provide synthetic **119**. It is interesting to note that the Wittig condensation produced a 1:1 mixture of olefin isomers in the first Merck synthesis, yet Fried reports isolation of only the (*E*)-isomer. This could have arisen by undetected removal or loss of the (*Z*)-isomer at an intermediate stage.



Scheme 1.27. Fried's zearelenone synthesis.

Tsuji has completed three syntheses of zearalenone (**119**), all by quite similar routes. The first, shown in Scheme 1.28, began with acetate **59b**, the minor product from the telomerization of butadiene in acetic acid.³⁸ Cleavage to the alcohol and gas-phase dehydrogenation led to enone **141**. Chain extension to **142** was accomplished in 70% yield by way of Michael addition of diethyl malonate to enone **141**. Decarboalkoxylation and protection of the ketone then gave **143** (63%). Conversion of the ester to the primary tosylate **144** was achieved by conventional methods in 62% yield. A Wacker oxidation of the terminal olefin followed by reduction and exchange of the tosylate for an iodide then provided the aliphatic segment **145** in 64% yield.

Acylation of **145** with acid chloride **95** afforded ester **146** in 90% yield. Ester **146**, containing all the necessary carbons at easily adjustable oxidation states, required only cyclization and minor functional group manipulations to afford the zearalenone system. As in Tsuji's previous synthesis of di-*O*-methyl lasiodiploidin,²⁶ macrocyclization was effected via deprotonation at the benzylic position and intramolecular alkylation to give **147** in 85% yield. Oxidative elimination of the thiophenyl group and removal of the ketal with acid afforded **127** (67%). the Merck group had previously demonstrated the ready conversion of **127** to zearalenone (**119**).

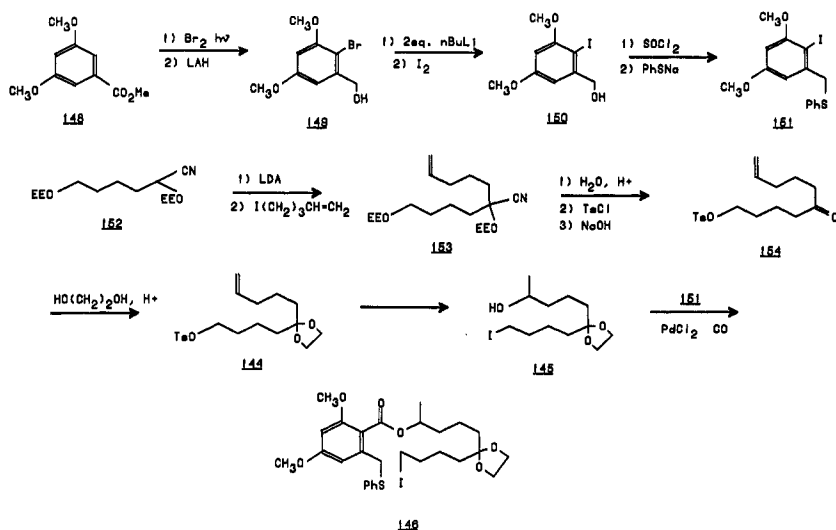


Scheme 1.28. Tsuji's first zearalenone synthesis.

The second formal total synthesis by Tsuji employed the carbonylation technique previously explored in several other of his syntheses.³⁹ As shown in Scheme 1.29, construction of the aromatic residue began with bromination and

reduction of methyl 3,5-dimethoxybenzoate (**148**) to afford aryl bromide **149** in 52% yield. Formation of the dianion with two equivalents of *n*-butyllithium and quenching with I_2 gave a 63% yield of the iodide **150**. The thiophenyl ether **151** required for the final ring closure was then obtained by conversion of the alcohol to the intermediate chloride and displacement with sodium phenylthiolate in 88% overall yield.

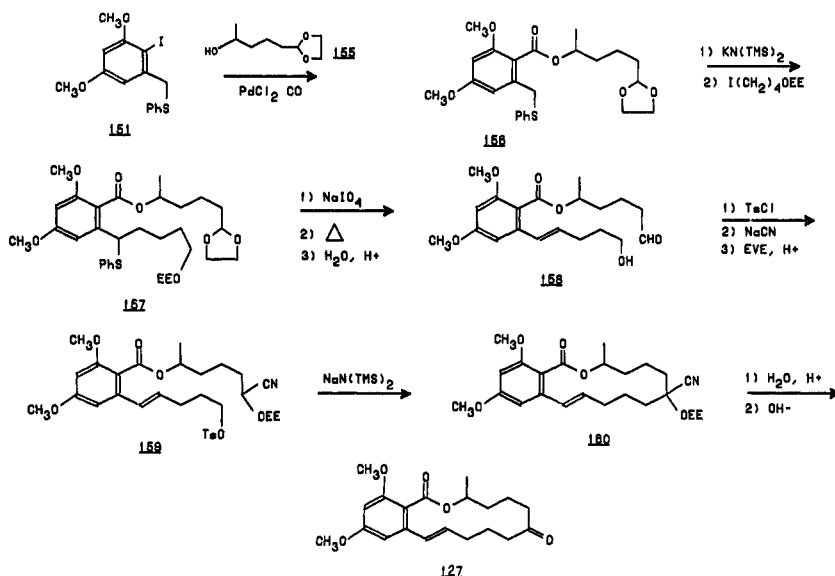
Preparation of the aliphatic segment began with alkylation of the protected cyanohydrin **152** with 5-iodo-1-pentene to give **153** (90%). Removal of the protecting groups with acid, tosylation of the primary alcohol, and regeneration of the ketone afforded **154**. Protection of the ketone as the ketal then provided **144**, a compound previously converted to iodo alcohol **145**. Conversion of **145** and **151** to intermediate **146**, which had previously been converted to zearalenone (**119**), was readily accomplished in 70% isolated yield by the usual carbonylation procedure.³⁸ Although somewhat lengthy sequences were employed for construction of the two subunits, formation of the ester linkage proceeded smoothly.



Scheme 1.29. Tsuji's second zearalenone synthesis.

The third formal total synthesis (Scheme 1.30) to arise from Tsuji's laboratories appears to be a combination of the previous two.⁴⁰ The carbonylation reaction between iodide **151** and alcohol **155** gave the expected ester **156** (70%). Intermolecular benzylic alkylation with protected 4-iodobutanol then gave **157** in 90% yield. Hydroxy aldehyde **158** was then obtained in 75% yield following

the oxidative elimination of the thiophenyl group and acidic hydrolysis. Tosylation of the primary alcohol, followed by conversion of aldehyde **158** to the protected cyanohydrin, gave cyclization precursor **159** (90%). Intramolecular alkylation afforded an 85% yield of macrocycle **160**. Lactone **160** was then converted via cleavage of the cyanohydrin to ketone **127** in 90% yield, constituting a formal total synthesis of zearelenone (**119**).



Scheme 1.30. Tsuji's third zearelenone synthesis.

F. Brefeldin A

Brefeldin A (**161**) is a 13-membered ring lactone isolated from a number of natural sources including various species of *Penicillium* as well as *Asochyta imperfecta*.⁴¹ This substance exhibits a wide variety of biological activity ranging from antiviral and antifungal to antimitotic and antitumor activity.^{41c,42}

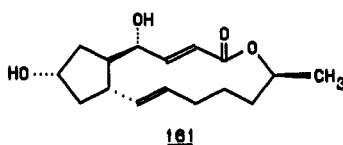


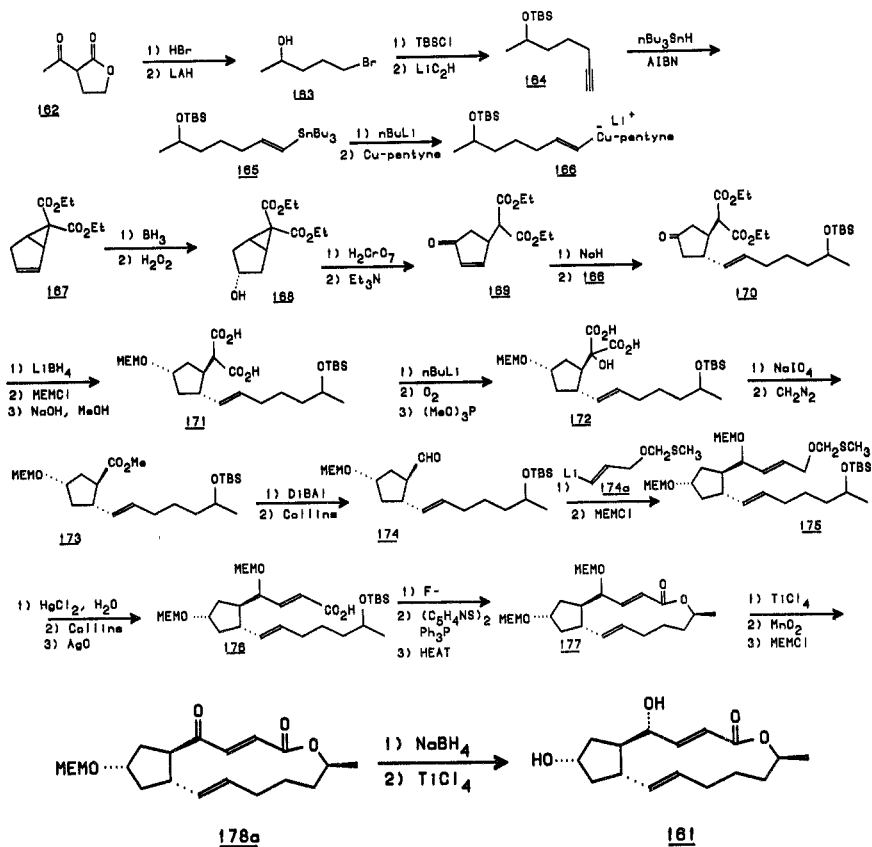
Figure 1.6. Brefeldin A (**161**).

The initial synthesis of brefeldin A was reported by Corey and is outlined in Scheme 1.31.⁴³ Development of the acyclic residue (C_{10} – C_{16}) began with the HBr cleavage of α -acetyl- γ -butyrolactone (**162**) and reduction of the intermediate ketone to bromoalcohol **163** in 85% yield. Protection of the alcohol and displacement of the halogen with acetylide ion then gave a 98% yield of **164**. Syn addition of tributyltin hydride proceeded in 94% yield via a radical chain mechanism to give olefin **165**, whose Z-geometry is to become the $\Delta^{10,11}$ double bond. Metalation and formation of the cuprate **166** then set the stage for construction of the cyclopentane ring.

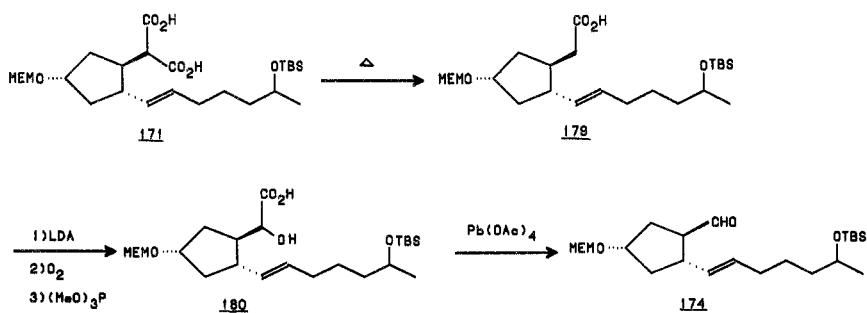
The known bicyclo[3.1.0]hexene **167** was hydroborated and oxidized to afford anti alcohol **168** in up to 80% yield. Chromic acid oxidation of **168** was followed by β elimination of malonate anion with Et_3N to produce enone **169** (86%). Initial deprotonation of **169** followed by the addition of cuprate **166** afforded an 82% yield of **170**. As expected, Michael addition to the enone occurred *anti* to the malonate unit. Reduction of ketone **170** with $LiBH_4$ gave a 4:1 mixture of C_7 alcohols, the major product being the desired α -hydroxy isomer. Chromatographic separation of the alcohols, followed by protection and ester cleavage, then gave the diacid **171**.

Finally, the C_4 sidechain must be converted into the required 4-oxo-crotonate. To this end, α -hydroxylation of **171** gave alcohol **172**, which was immediately subjected to oxidative decarboxylation and esterification to provide **173** in 60% yield. Aldehyde **174** was then isolated in 95% yield after a reduction–oxidation sequence. The remaining carbon atoms required for brefeldin A were added in the form of anion **174a**. The resulting mixture of alcohols was converted to the related MEM ethers **175** in 82% yield (the stereochemistry of the addition is unimportant as this center will later become a carbonyl group). Elaboration to the acid **176** then proceeded in a straightforward manner via oxidation of the related alcohol. Removal of the silyl ether and lactonization via the 2-thiopyridyl ester cleanly gave the macrocycle **177**. Quite surprisingly, only the compound with the natural configuration at C-15 cyclized to the lactone, the epimeric hydroxy acid being recovered after an aqueous workup. Deprotection of the residual hydroxyl groups, oxidation of the allylic alcohol, and reprotection of the cyclopentanol provided **178a**. Stereospecific reduction of the C-4 carbonyl to the desired α -hydroxy group and removal of the final protecting group led to synthetic brefeldin A (**161**). This first total synthesis of **161** was clearly the basis, in part, for every subsequent approach. Although the reproducibility of the diastereoselective lactonization step has been challenged by some workers, overall this concise solution for the stereochemical problems is considered a benchmark for work in the area.

Corey later described a modification of several steps of his earlier synthesis (see Scheme 1.32).⁴⁴ Diacid **171** was smoothly decarboxylated in quantitative yield to give the mono acid **179**, which was α -oxygenated as in the previous route. The resulting hydroxy acid **180** was then subjected to oxidative



Scheme 1.31. Corey's first brefeldin A synthesis.

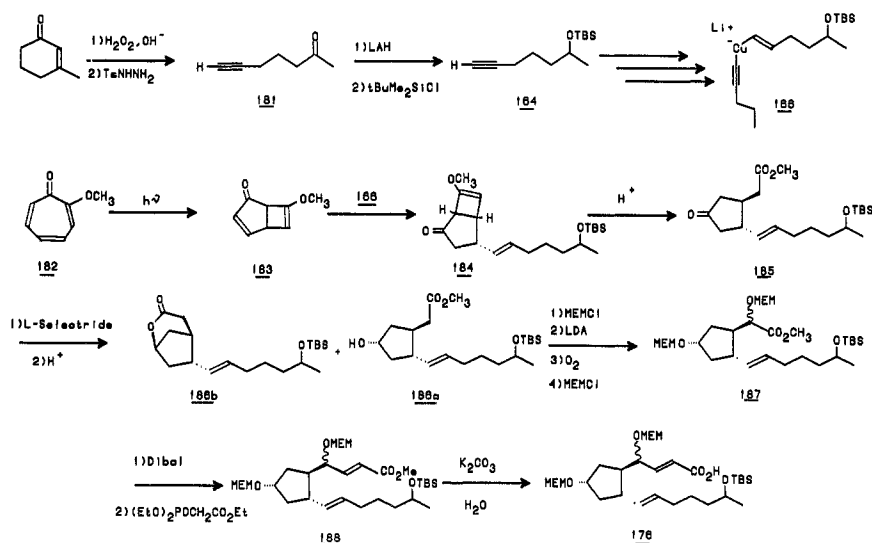


Scheme 1.32. Corey's second brefeldin A synthesis.

decarboxylation with lead tetraacetate to afford **174** in 78% overall yield from **171**. The synthesis was then completed as outlined in Scheme 1.31, with the exception of some minor protecting-group modifications.

Crabbe and Greene employed a similar approach in their synthesis of a Corey intermediate.⁴⁵ The synthesis, depicted in Scheme 1.33, began by construction of cuprate **166** via a slightly different route. 3-Methyl cyclohexenone (**180**) was epoxidized and subjected to Eschenmoser–Tanabe fragmentation to give the acetylenic ketone **181**. Reduction of ketone **181** to the alcohol and protection afforded **164**, which had been previously converted to cuprate **166** by Corey.

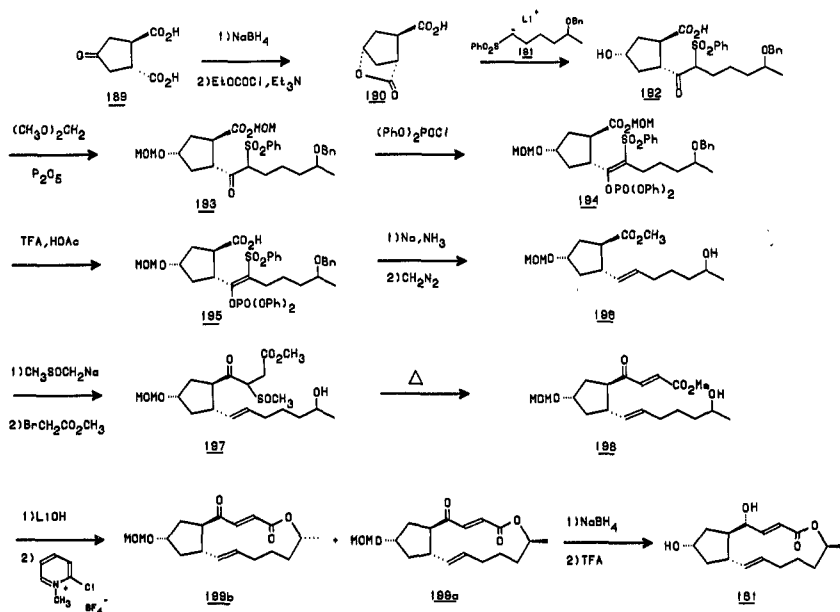
Construction of the cyclopentane unit began with bicyclic ketone **183** obtained by photolysis of α -tropolone methyl ether (**182**). Stereoselective addition of cuprate **166** occurred on the face opposite the fused cyclobutene ring to give **184** in 82% yield. Acid treatment then led to ester **185**, a compound containing the desired *trans* stereochemistry at C-3 to C-4 of the cyclopentane ring. Ketone reduction gave a 3.5:1 mixture of alcohols, with the desired α -alcohol predominating. Further treatment with acid then led to a readily separable mixture of lactone **186b** and the desired brefeldin A precursor **186a**. Hydroxy ester **186a** was then protected as the MEM ether, and the ester group converted to the corresponding α -hydroxy ester and similarly protected to afford **187** (67%). Reduction of the ester to the aldehyde and a subsequent phosphonate condensation gave a 60% yield of **188**. Hydrolysis to the carboxylic acid **176** thus intersected Corey's initial route,⁴³ and constituted a formal total synthesis of **161**. The



Scheme 1.33. Crabbe and Greene's first brefeldin A synthesis.

Greene–Crabbe synthesis differs from the Corey route only in the Michael addition substrate and the method for formation of the γ -oxo-crotonate.

The Bartlett synthesis of brefeldin A, outlined in Scheme 1.34, began with the *trans*-disubstituted cyclopentane ring intact.⁴⁶ Thus the known keto diacid **189** was reduced to the alcohol and lactonized to **190** via the mixed anhydride in 72% overall yield. Sulfone anion **191**, in the presence of two additional equivalents of LDA to deprotonate the initial carboxylic acid and the resulting α -keto sulfone, was added to the lactone to give a 91% yield of sulfone **192**. Protection of both the alcohol and carboxyl group as the MOM derivative and conversion of the α -keto sulfone to the enol phosphate produced **194** in 79% yield via **193**. Selective deprotection of the MOM ester was achieved with TFA in acetic acid to afford a 95% yield of carboxylic acid **194**. Reduction of **194** with sodium in ammonia transformed the enol phosphate to the intermediate alkyne, which suffered further reduction to the (*E*)-olefin as well as cleavage of the benzyl ether. Subsequent esterification with diazomethane then provided methyl ester **196** in 53% overall yield. Addition of dimsyl anion to ester **196** and alkylation of the resulting α -sulfinyl ketone afforded ester **197**. Thermal elimination of the sulfoxide then provided a 62% yield of γ -oxo-crotonate **198**. Hydrolysis of the ester and subsequent lactonization using the Mukaiyama procedure provided a 1:1 mixture of macrocycles **199a** and **199b** in 37% yield.



Scheme 1.34. Bartlett's brefeldin A synthesis.

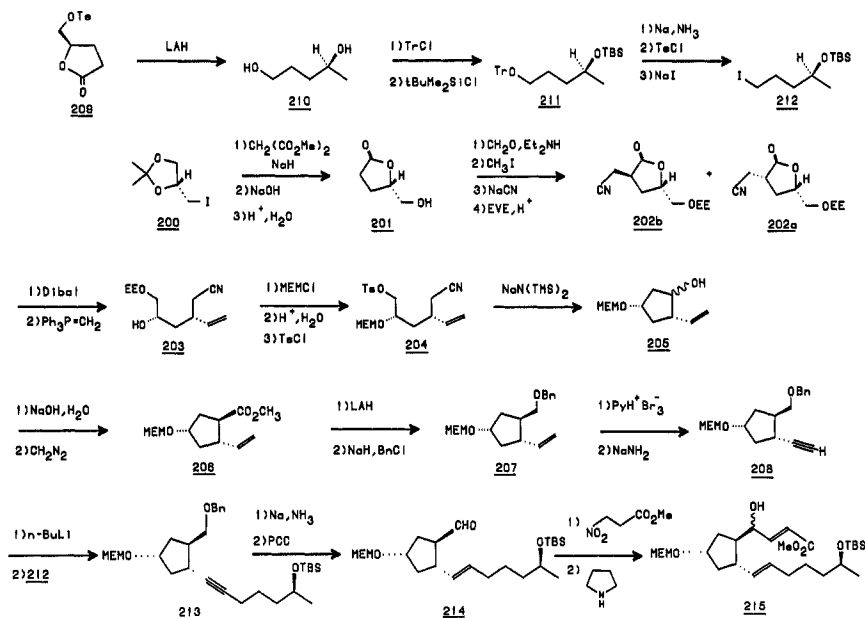
Contrary to the report by Corey,⁴³ no diastereoselectivity was seen in the ring-forming reaction. After separation of the desired **199a**, the C-4 carbonyl was selectively reduced to the α -hydroxyl and the MOM ether cleaved to afford a 48% yield of synthetic **161**. The most interesting features of this synthesis are the novel methods for formation of the oxo-crotonate and conversion of the α -keto sulfone into the (*E*)-olefin.

A rather lengthy synthesis of enantiomerically pure **161** is described in Scheme 1.35.⁴⁷ The construction of the cyclopentane unit began with the initial conversion of D-mannitol to the protected iodo diol **200** via established procedures. Displacement of the primary iodide with dimethylmalonate, hydrolysis, and lactonization with loss of CO then gave **201**. A Mannich condensation followed by cyanide addition and alcohol protection gave a 64:36 ratio of **202a:202b** in good overall yield. The desired **202a** possessed the required *cis* stereochemistry between C-2 and C-4 of the γ -lactone, which will lead to the *cis* disposition of the substituents at C-7 and C-9 in the target.

Reduction of **202a** to the lactol and a subsequent Wittig reaction led to **203** in 52% yield. Protecting-group exchange and tosylation of the resulting primary alcohol provided the cyclization precursor **204** (76%). Base treatment then afforded an 87% yield of cyclopentanes **205** epimeric at the nitrile (an epimerizable position). Hydrolysis and esterification of either isomer led to the *trans* geminally substituted cyclopentane **206** in 82% yield. Reduction of **206** and protection of the ester produced benzyl ether **207**, which was converted to alkyne **208** via a bromination–dehydrobromination sequence in 78% yield.

The acyclic segment required for this approach was derived from L-glutamic acid, which was readily converted to lactone **209** along conventional lines. Reduction of **209** gave **210**, which was sequentially protected first at the primary alcohol to afford **211** (66%). Reductive removal of the trityl group and conversion of the resulting alcohol to the halide gave a 63% yield of acyclic iodide **212**. Deprotonation of acetylene **208** and alkylation with **212** afforded alkyne **213** (82%). Sodium in ammonia reduction of the triple bond with concurrent deprotection of the primary alcohol followed by oxidation afforded a 75% yield of aldehyde **214**. Condensation of **214** with methyl β -nitropropionate gave the intermediate α -nitro alcohol, which was converted to the unsaturated ester **215** in 54% yield by elimination. Conversion to synthetic (+)-**161** then proceeded along a route similar to the Corey synthesis.⁴⁴

Winterfeldt's synthesis of brefeldin A (Scheme 1.36) also entailed use of a Michael addition in an *anti* fashion to a 4-substituted cyclopentenone.⁴⁸ Dithiane anion **217** was added in a 1,4 sense to enone **216** to give, after elimination of acetic acid, cyclopentenone **218**. Addition of cuprate **219** to **218** in the expected *anti* manner cleanly afforded the *trans* cyclopentane **220**. Hydride reduction gave the unnatural β -alcohol, which was inverted by a Mitsunobu reaction and the resulting ester cleaved to the desired α -alcohol **221**. Protection of the alcohol

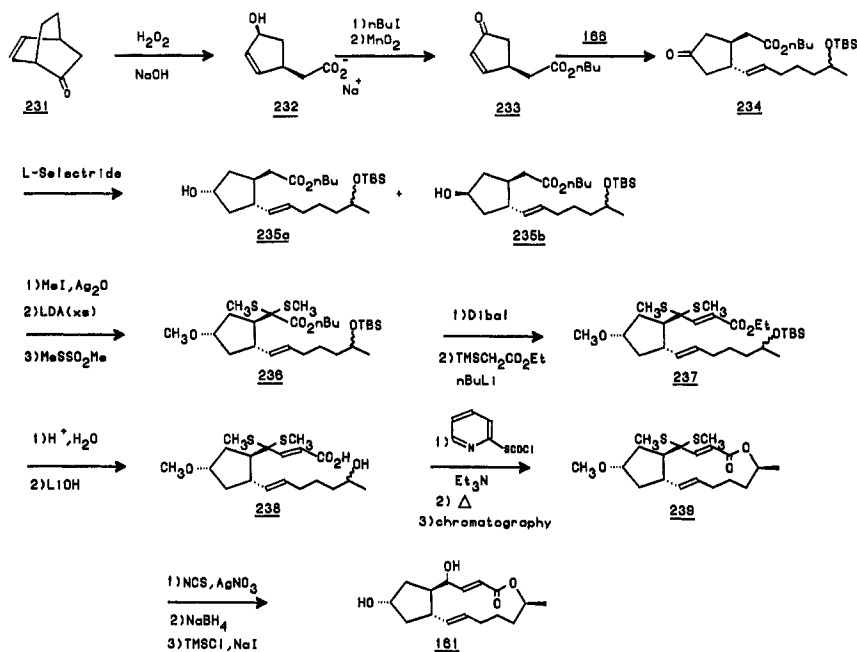


Scheme 1.35. Kitahara's brefeldin A synthesis.

and ketal hydrolysis led to ketone **222**, which was reduced in a stereorandom manner and protected to give **223**. Chain extension to the unsaturated ester **225** via aldehyde **224** then proceeded along conventional lines. Silyl ether cleavage and ester hydrolysis cleanly afforded the seco acid **226**. Pyridinium-salt-mediated lactonization (the Mukaiyama procedure) gave a stereorandom mixture of epimers at C-15, which was deprotected to provide the macrocyclic lactones **178a** and **178b**. Selective reduction of the ketone followed by removal of the MEM protecting group gave a 1:1 mixture of brefeldin A (**161**) and its C-15 epimer **227**. Among the clever elements of the Winterfeldt approach is the sequence of 1,4 additions *anti* to existing substitution on the cyclopentanone. The use of acyl anion equivalent **217** also avoided excessive manipulation of the oxidation state at the C-4 center.

The general problem of lack of selectivity in the lactonization step was dealt with in subsequent studies by Winterfeldt, as outlined in Scheme 1.37.⁴⁹ Compound **224** was desilylated to afford a mixture of diastereomeric secondary alcohols **228a** and **228b**. Esterification of these alcohols with dimethylphosphorylacetic acid then gave the cyclization precursors **229a** and **229b**. Deprotonation and subsequent phosphonate condensation unfortunately led to a stereoselective cyclization of the undesired diastereomer. Thus isolation

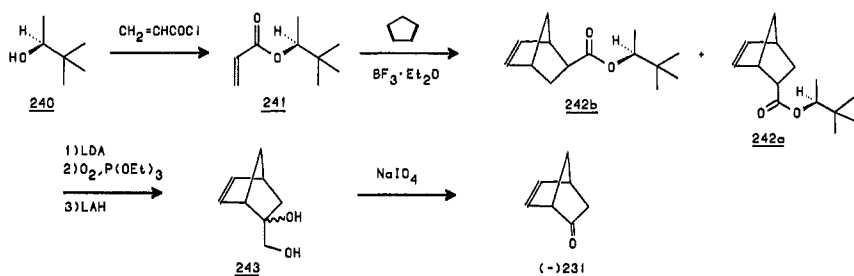
Alcohol **235b** could be converted to **235a** in 40% overall yield via ester cleavage, inversion by an intramolecular Mitsunobu reaction, hydrolysis, and reesterification. Cyclopentanol **235a** was then protected as the methyl ether and the position adjacent to the butyl ester was oxidized by bis-sulfonylation to give **236** (89%). Chain extension to **237** was effected in 73% yield via conversion to the related aldehyde and Peterson olefination with ethyl trimethylsilylacetate anion. A series of hydrolyses then led to the hydroxy acid **238** in 80% yield. Nonselective lactonization under modified Corey conditions gave a 70% yield of a mixture of C-15 epimers from which **239** could be isolated. Synthetic **161** was finally obtained following hydrolysis, reduction of the dithio ketal, and cleavage of the methyl ether.



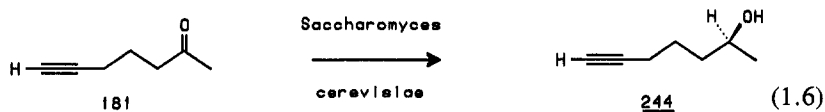
Scheme 1.38. Greene's second brefeldin A synthesis.

A third approach to brefeldin A by Greene dealt with a version of the second synthesis designed to provide optically active **161**, as shown in Scheme 1.39.⁵¹ Enantiomerically pure alcohol (*S*)-(+)-**240**, obtained via resolution of the derived phthalate mono ester with brucine, was acylated with acryloyl chloride to afford **241**. Lewis acid promoted Diels–Alder reaction of **241** and cyclopentadiene then led to a 75% yield of diastereomers **242a** (endo) and **242b** (exo) in a 97:3 ratio.

Earlier work had shown these compounds to have the (1*S*) and (1*R*)-configuration, respectively. Isolation of the major endo addition product followed by the introduction of oxygen adjacent to the ester and subsequent reduction gave diol **243**. Periodate cleavage then led to a 50% overall yield of (1*S*)-(–)-norbornenone **231**.



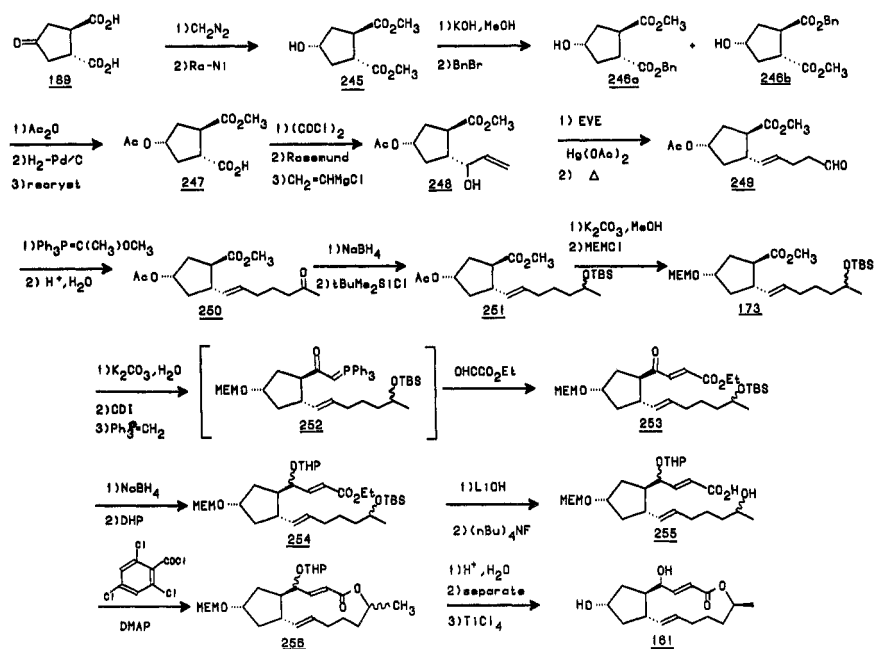
The acyclic portion of brefeldin A was elaborated by means of a microbial reduction (Eq. 1.6). Thus acetylenic ketone **181** was reduced with baker's yeast (*Saccharomyces cerevisiae*) to afford the (*S*)-(+)-alcohol **244** in 56% yield and >99% ee. Completion of the synthesis of **161** from intermediates **231** and **244** was then achieved as previously outlined.⁵⁰



Yamaguchi employed a strategy not unlike the Bartlett approach to brefeldin A, as depicted in Scheme 1.40.⁵² Keto diacid **189** was esterified and reduced with $\text{Ra}(\text{Ni})$ to afford a 92% yield of **245**. Alcohol participation in a *syn*-selective hydrolysis followed by reesterification with benzyl alcohol led to the formation of **246a** and **246b** in a 19:1 ratio. Protection of the alcohol as the acetate and hydrogenolysis of the benzyl ester followed by fractional recrystallization gave a 87% overall yield of **247**. Acid **247** was converted to allylic alcohol **248** in 65% yield via Rosemund reduction of the derived acid chloride to the aldehyde and addition of vinylmagnesium bromide.

The aliphatic chain was extended first by three carbon atoms via a Claisen rearrangement to aldehyde **249**, which was further lengthened by two carbon atoms to the methyl ketone **250** by a Wittig reaction followed by hydrolysis

(44%). Reduction of the ketone and subsequent protection to afford **251** proved uneventful. Acetate hydrolysis followed by re-protection of the alcohol as the MEM ether gave **173** in 84% overall yield. Chain extension of the ester to the required 4-oxo-crotonate was achieved by conversion of **173** via the acid and corresponding acyl imidazolide to the stabilized ylid **252**, which was not isolated. Addition of ethyl glyoxylate to **252** then gave a 68% yield of **253**. Reduction of ketone **253** afforded a 4:1 mixture of C-4 alcohol epimers, in which the desired α -hydroxy compound was the minor component. The mixture of alcohols was then converted to the THP ethers **254** in 71% yield. Conversion to the hydroxy-acid cyclization precursor **255** employed a conventional sequence. Lactonization via the mixed anhydride of 2,4,6-trichlorobenzoic acid gave the macrocycle **256** in 94% yield as a mixture of four diastereomers about the ring. Hydrolysis of the THP group, chromatographic separation of the diastereomers, and finally cleavage of the MEM ether led to the isolation of synthetic **161**.

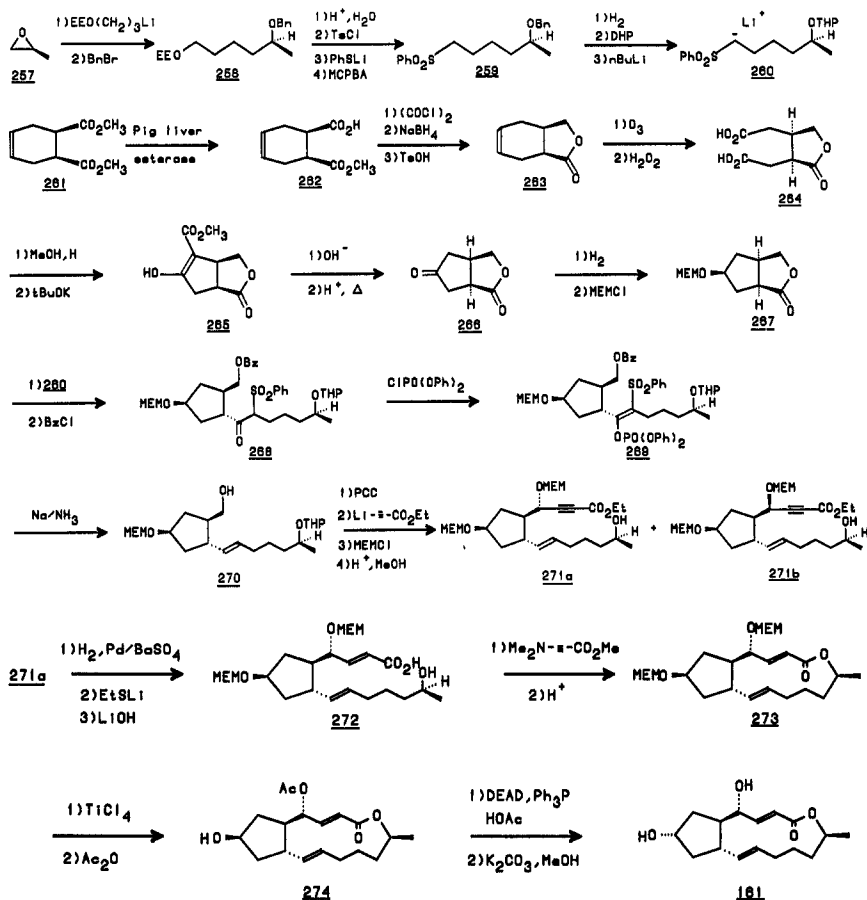


Scheme 1.40. Yamaguchi's brefeldin A synthesis.

Enzymatic degradation was the cornerstone of a synthesis of optically active **161** developed by Gais (Scheme 1.41).⁵³ Construction of the acyclic portion of brefeldin A began with the addition of ethoxyethyl protected 1-lithio-3-propanol

to (*S*)-propylene oxide (**257**) and *in situ* benzylation to afford **258**. Conversion to the sulfone **259** was effected in 50% overall yield (97% ee) via the corresponding alcohol, tosylate, and sulfide, respectively. Exchange of the benzyl ether for a THP ether and metalation adjacent to the sulfone afforded the anion **260**.

Construction of the enantiomerically pure cyclopentane unit for **161** hinged on the ability of an enzyme to react preferentially with one of two enantiotopically related functional groups. To this end, the reaction of the meso diester **261** with commercially available pig liver esterase resulted in almost exclusive hydrolysis at the 1*R* ester group to afford the mono ester **262** in 92% yield and >99% ee. Reduction to the alcohol was accomplished via the intermediate acid chloride, which was then cyclized to the lactone **263**. Oxidative ring opening followed

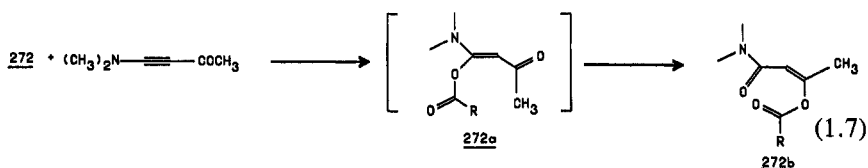


Scheme 1.41. Gais's brefeldin A synthesis.

by peroxide treatment gave the diacid **264** in 87% yield. Esterification and Dieckmann condensation afforded a 79% yield of cyclopentane **265**, which was subsequently hydrolyzed and decarboxylated to give **266** (96%). Reduction of the ketone from the least-hindered side of the rigid bicyclo[3.3.0] system provided the unnatural β -alcohol, which was protected as the MEM ether to give **267** in 91% yield.

Anion **260** was then condensed with **267** and the resulting alkoxide benzoylated *in situ*, to afford **268** in 90% yield. Clearly the initial *cis* 1,2-substituted product had isomerized to the more stable *trans* 1,2 isomer. As in the Bartlett approach,⁴⁶ the α -keto sulfone was converted to the enol phosphate **269** and sodium-ammonia reduction afforded the (*E*)-olefin **270** via the intermediate alkyne. Oxidation of **270** to the aldehyde and addition of ethyl 3-lithio propynoate afforded a 4:1 ratio of addition products, the major being the desired α -alcohol. Protection of this alcohol as a MEM ether and cleavage of the THP group gave a 4:1 ratio of **271a** and **271b** (epimers at C-4) in 90% overall yield. *Syn* reduction of the alkyne **271a** followed by isomerization and ester hydrolysis afforded an 89% yield of hydroxy acid **272**. Lactonization with methyl 3-dimethylaminopropynoate then gave the macrocycle **273** (71%).

As outlined in Eq. 1.7, the carboxyl group in **268a** rapidly undergoes a 1,5 acyl transfer to give **268b**, resulting in a highly activated carboxyl group which undergoes acid promoted lactonization to afford the corresponding macrolactone in good yield.



Removal of the MEM ethers and selective reprotection of the allylic hydroxyl group as the acetate afforded **274**. Mitsunobu inversion of the cyclopentanol and acetate cleavage then provided synthetic brefeldin A (**161**).

2. ANTIBIOTIC MACROLIDES

A. A26771B

Antibiotic A26771B (**1**) is a 16-membered ring macrocyclic lactone isolated from the fermentation broth of *Penicillium turbatum*.⁵⁴ As the name implies, this compound possesses antibiotic activity and is the simplest macrocyclic compound

covered in this chapter which has additional carbon units (in this case a succinyl group) attached to an oxygen on the ring.

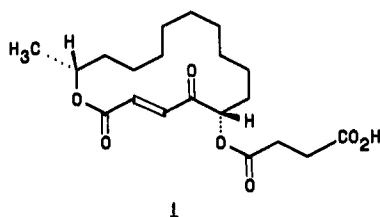
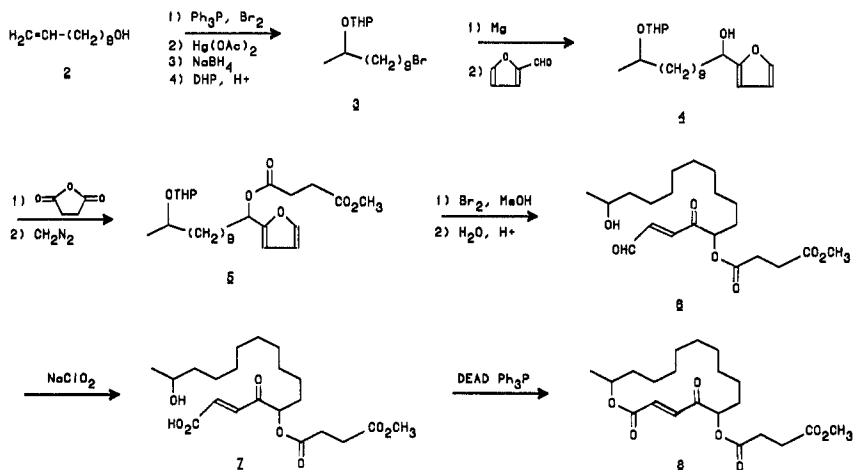


Figure 2.1. A26771B (1)

The first synthesis in this area is that of Hase in Helsinki in 1979 (Scheme 2.1).⁵⁵ While a total synthesis of the natural product **1** was not complete, a rather straightforward synthesis of **8**, the methyl ester of **1**, was achieved. Thus, 10-undecen-1-ol (**2**) was converted to the bromide and the olefin transformed into a secondary alcohol via an oxymercuration–reduction sequence. This secondary alcohol was then protected as the THP ether to give **3** in 57% yield. Conversion of **3** to the corresponding Grignard reagent and addition to furfural afforded **4** (63%). Addition of the succinyl sidechain and esterification led to **5** (containing all of the required carbons for construction of the natural product) in 95% yield. Unmasking of the furan ring to a 1,4 dicarbonyl group was now achieved via oxidation and acid-catalyzed ring opening to afford keto aldehyde **6** (23%).



Scheme 2.1. Hase's A26771B synthesis.

Selective oxidation of the enal to the unsaturated acid with sodium chlorite gave the seco acid **7** in 69% yield. Lactonization under Mitsunobu conditions afforded an 8% yield of diastereomeric macrocycles from which **8** could be isolated. Clearly the utilization of a furfural moiety as a hydroxy 1,4 dicarbonyl equivalent was the linchpin of this as well as several other syntheses in this area.

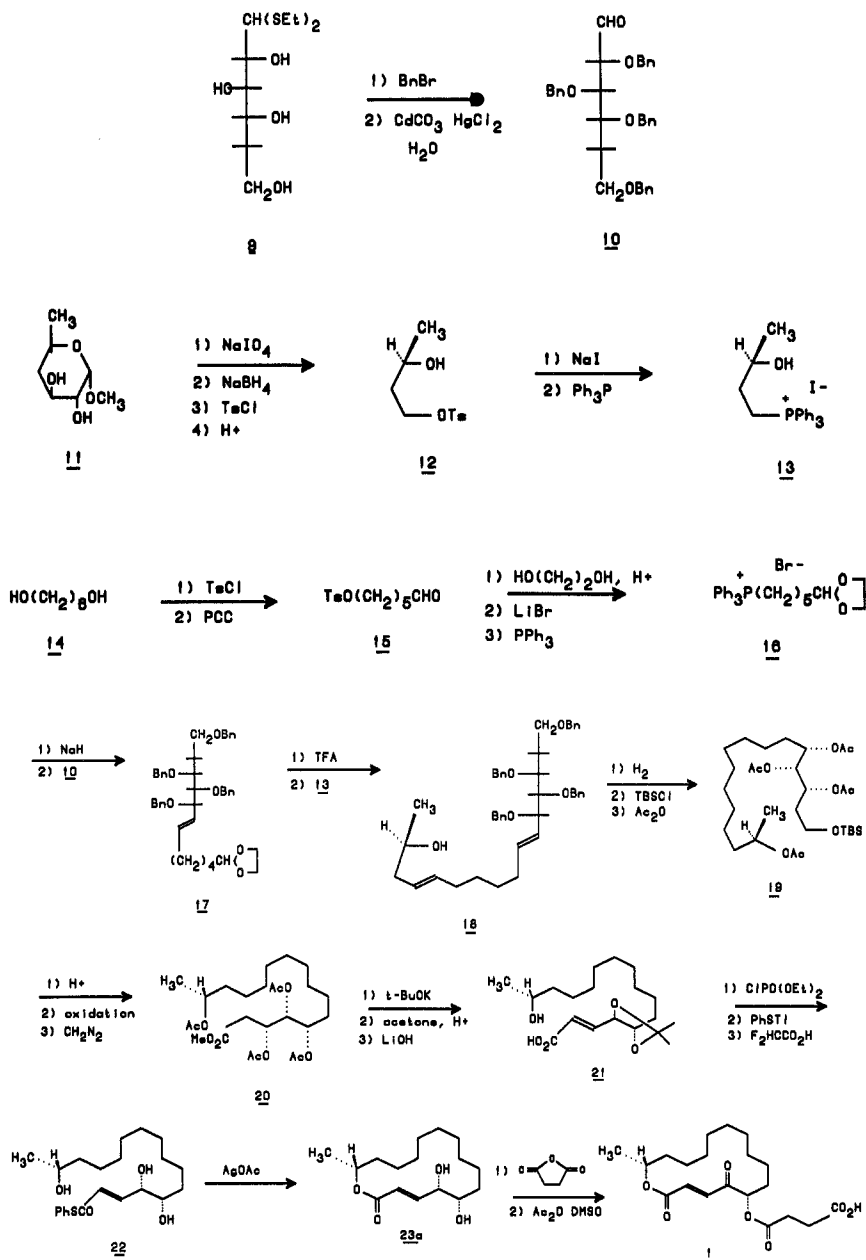
The first synthesis of enantiomerically pure **1** was completed in 1980 by Tatsuta (Scheme 2.2).^{56a} D-Glucose was converted via previously published procedures to the protected hexose **9**. Benzylation of the hydroxy groups and cleavage of the thioacetal then gave intermediate **10** in 80% yield. This fragment will later be annealed onto a carbon chain and become C-1 to C-6 of the natural product.

A second fragment, also derived from D-glucose, which will correspond to C-13 to C-16, was constructed as follows. Deoxyxylose **11** (prepared from D-glucose by literature procedures) was oxidatively cleaved, reduced, and tosylated to give compound **12**. Displacement with NaI and conversion to the phosphonium salt gave **13** in good overall yield.

The remaining carbons in the framework of A26771B are derived from 1,6-hexanediol (**14**). Selective tosylation and oxidation gave **15**, which was then converted to the acetal phosphonium salt **16** by conventional means. A Wittig condensation with aldehyde **10** gave the (*E*)-olefin **17** (although the geometry of the double bond is of no consequence). Cleavage of the acetal with acid gave the corresponding aldehyde, which was allowed to undergo a second Wittig condensation with **13**, which provided the 16-carbon intermediate **18** in 54% overall yield. Exhaustive hydrogenation gave the saturated tetraol, whose primary alcohol was then protected as the silyl ether and the remaining hydroxyl groups protected as acetates to obtain **19** (71%). Desilylation and oxidation to the acid was followed by esterification to give **20** in 84% yield. β -Elimination of acetic acid led to the unsaturated ester, which was converted to the acetonide, followed by ester hydrolysis to give a 76% yield of the protected seco acid **21**. Masamune's method of carboxyl activation and conversion to the thioester gave **22** (74% following acetal cleavage). Cyclization was then induced by the addition of silver acetate, which gave rise to lactone **23a** in 10% yield. Selective esterification with succinic anhydride and oxidation of the allylic alcohol then gave the natural product **1** in 51% yield.

A subsequent publication by Tatsuta^{56b} contains the experimental details and optimization of several steps in the synthesis, including the lactonization, as well as the construction of all the other stereoisomers of the natural product. The number of chemical manipulations required for the synthesis of A26771B, a compound containing only two chiral centers, makes this approach a bit cumbersome.

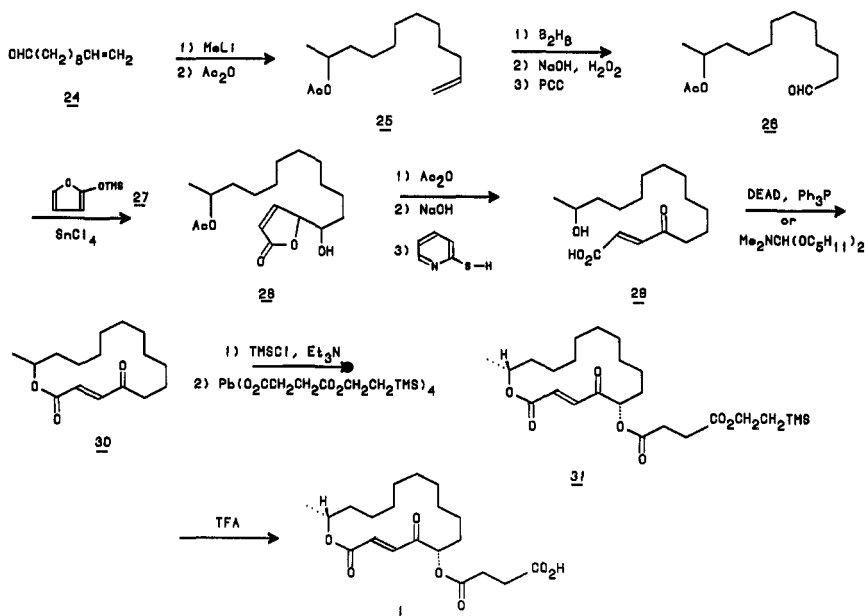
Takei has completed a synthesis of A26771B in a manner reminiscent of Hase's work (Scheme 2.3).⁵⁷ The synthesis begins with the addition of methyl lithium to 10-undecenal (**24**) and acetylation of the resulting alcohol to give **25**



Scheme 2.2. Tatsuta's A26771B synthesis.

in 98% yield. A hydroboration–oxidation sequence gave the primary alcohol, which was further oxidized to aldehyde **26** (70%). Lewis-acid-mediated addition of 2-trimethylsilyloxyfuran (**27**) afforded a 94% yield of γ -hydroxy butenolide **28**. It should be noted that dehydration of the γ -hydroxy group would lead to a 2-hydroxy furan oxidation level, the chemical equivalent of the 4-oxo-crotonate synthon required for the synthesis.

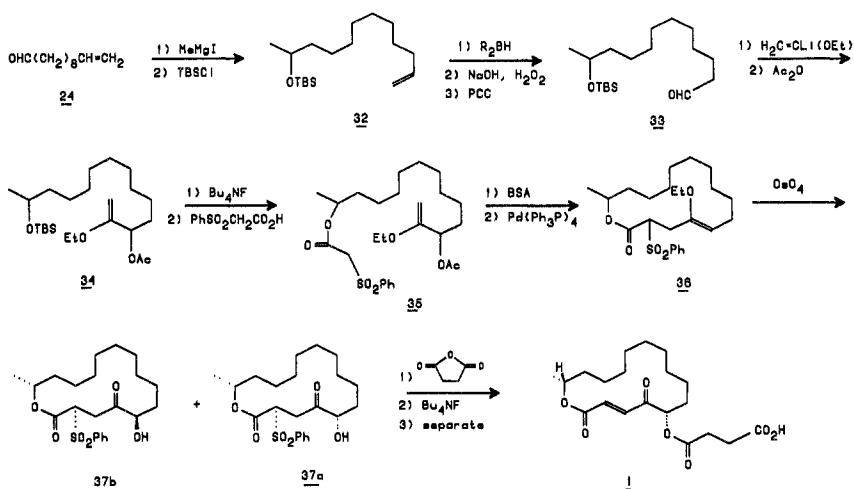
To this end, dehydration with acetic anhydride, hydrolytic ring opening and isomerization to the (*E*)-olefin with 2-thiopyridine gave the desired seco acid **29** (74%). Lactonization utilizing either Mitsunobu conditions or DMF acetal gave a comparable yield (37–39%) of the macrocycle **30**. Conversion to the silyl enol ether and oxidative coupling with lead(IV) tetrakis (β -trimethylsilylethyl succinate) gave **31** in 40% yield. The use of this complex oxidizing reagent permitted for the facile deprotection to the natural product, a step that eluded Hase. There was no report of the formation of the *anti* diastereomer; however, the low isolated yield and information provided by Trost⁵⁸ about a similar oxidation (*vide infra*) suggests that the *anti* isomer was probably formed. Acidic desilylation then provided synthetic **1**.



Scheme 2.3. Takei's A26771B synthesis.

Trost began the synthesis of A26771B with the same starting material as Takei; however, his novel palladium-coupling chemistry was employed for the cyclization step.⁵⁸ The transformation of aldehyde **24** to silyloxy aldehyde **33** via **32** proceeded along conventional lines (Scheme 2.4). The addition of α -lithio ethyl vinyl ether and acylation of the resulting alcohol gave allylic acetate **34**. Desilylation and esterification with benzenesulfonylacetic acid gave the cyclization afforded macrocycle **36** (~60%). In what is overall an S_N2' displacement, Trost not only formed the macrocyclic ring, but also effected migration of the double bond such that it was possible to oxidize adjacent to the masked carbonyl.

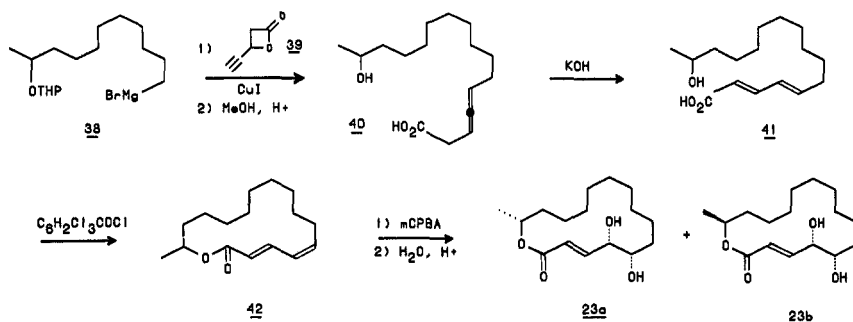
Accordingly, bishydroxylation of the enol ether then gave an 80% yield of hydroxy ketones **37a** and **37b**. The ratio of these two compounds varied depending upon the reaction conditions, but the desired *syn* compound **37a** always was major product in at least a 3:1 ratio. Succinylation of the mixture of **37a** and **37b** followed by β -elimination of phenylsulfonic acid gave a mixture of diastereomeric lactones from which synthetic **1** could be isolated.



Scheme 2.4. Trost's A26771B synthesis.

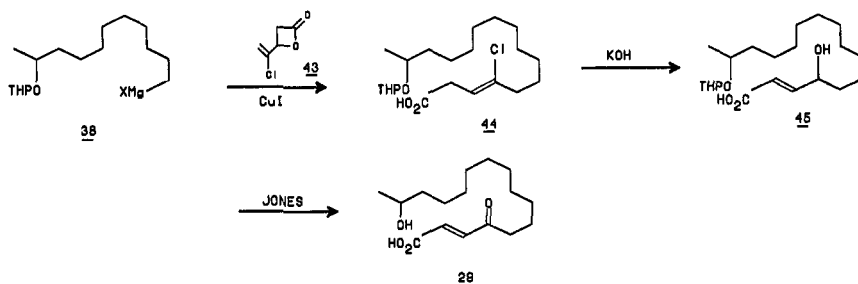
Two short formal total syntheses were reported by Fujisawa, both employing diketene derivatives for C-1 to C-4 of the carbon framework.^{59,60} In the first sequence, Grignard reagent **38** was treated with β -lactone **39** and a catalytic amount of CuI to afford allene **40** after acidic workup (Scheme 2.5). Base isomerization to a mixture of (*E,E*)- and (*E,Z*)-diene isomers **41** occurred in 85% overall yield. Lactonization using the Yamaguchi procedure (trichlorobenzoyl

chloride) provided macrocycle **42** (as a mixture of dienes) in 91% yield. Epoxidation and acidic hydrolysis of the epoxide gave 63% yield of **23a** and its C-15 epimer **23b**. The former had been converted by Tatsuta to A26771B (**1**).^{56a}



Scheme 2.5. Fujisawa's first A26771B synthesis.

In Fujisawa's second approach, as shown in Scheme 2.6, Grignard reagent **38** was added to β-lactone **43** with CuI catalysis to give vinyl chloride **44** in 90% yield. Conjugation of the olefin concomitant with hydrolysis of the chloride gave allylic alcohol **45**, which was oxidized to hydroxy acid **29** in 56% overall yield. The conversion of **29** into **1** had previously been accomplished by Takei.⁵⁷



Scheme 2.6. Fujisawa's second A26771B synthesis.

B. Methymycin

Methymycin (**48**) is a 12-membered ring macrocyclic lactone isolated from the fermentation broth of *Streptomyces M-2140*.⁶¹ Methymycin (**48**) (sugar = desosamine) and its aglycone methynolide (**47**) are the first compounds to be discussed in this section which can be degraded to Prelog–Djerassi lactone (**52**).

Although a number of syntheses of this important degradation product have been described, coverage of this aspect of macrolide synthesis is beyond the scope of this chapter. For details, the reader is directed to existing reviews and the citations therein.⁶² Although **52** is a common starting material for many of the synthetic studies in this area, its synthesis is not described. However, where an analog of **52** was used as a synthetic intermediate, as in the case of **80** (Scheme 2.9), the synthesis of that compound is discussed.

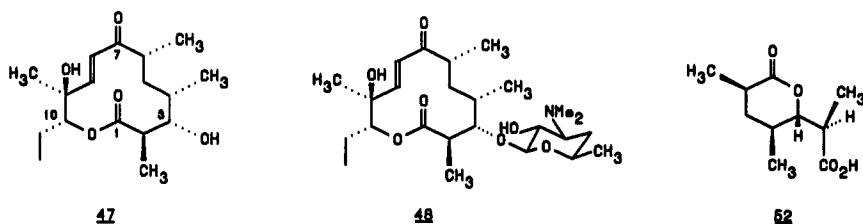


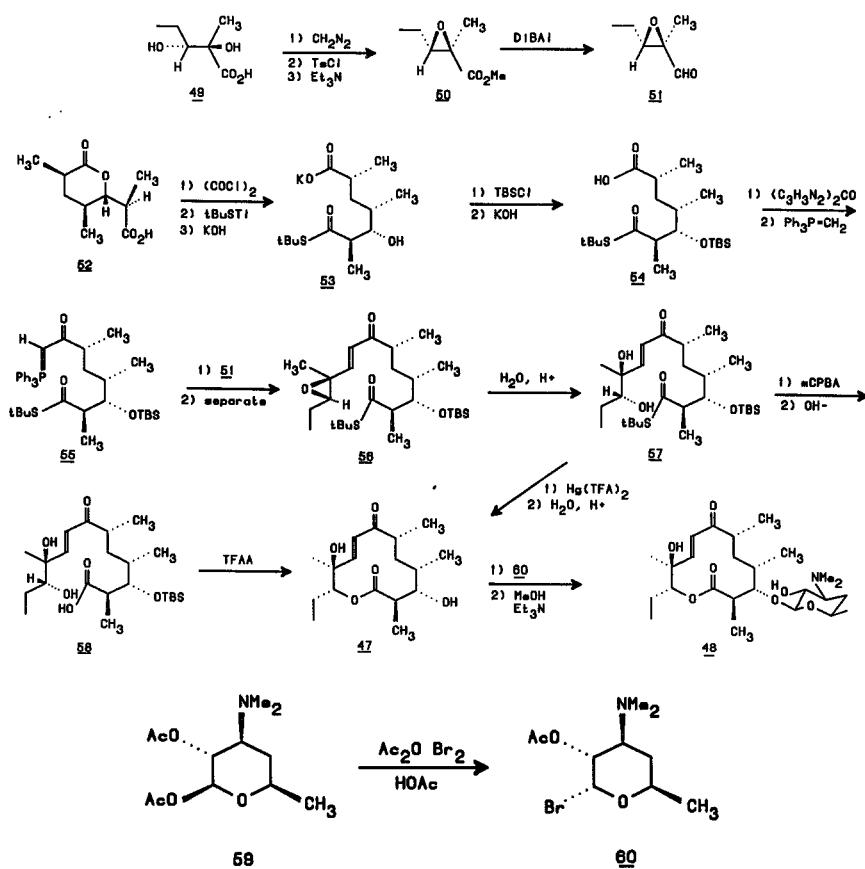
Figure 2.2. Methynolide (**47**), methymycin (**48**), and Prelog–Djerassi lactone (**52**).

The first syntheses of both the natural product **48** and its aglycone **47** were described by Masamune in 1975 (Scheme 2.7).⁶³ As have most of the subsequent synthetic studies in this area, Masamune constructed **47** and **48** from two fragments, C-8 to C-11 and the segment corresponding to Prelog–Djerassi lactone, C-1 to C-7. Preparation of the former fragment began with the optical resolution of erythro 2,3-dihydroxy-2-methylvaleric acid to afford the (+)-enantiomer **49**. Esterification and formation of the epoxide **50** via the corresponding tosylate, followed by reduction, gave the aldehyde **51** in 75% overall yield.

The second fragment began with the conversion of synthetic racemic **52** into the corresponding *t*-butyl thioester and hydrolysis to the acyclic carboxylate salt **53**. Silylation of both the acid and the hydroxy group followed by silyl ester cleavage gave acid **54** in 90% overall yield. Stabilized Wittig reagent **55** was constructed in 95% yield via carboxyl activation and addition of methylenetriphenylphosphorane. Condensation of **55** with enantiomerically pure aldehyde **51** gave a 1:1 mixture of diastereomers **56**, which was hydrolyzed to the corresponding diol **57** in about 24% overall yield. Oxidative ester cleavage gave the seco acid **58**, which was lactonized to methynolide (**47**) in up to 25% yield with trifluoroacetic anhydride. A second more reproducible route to **47** was developed using Hg^{+2} -mediated cyclization of the thioester **57** and acidic desilylation to afford **47** in 30% yield.

Conversion of the aglycone **47** to the natural product **48** involved appending an amino sugar onto the carbon framework. The protected sugar diacetylidesosamine (**59**) was transformed into the activated α -bromo compound **60**. The addition of aglycone **47** followed by acetate cleavage gave a 1:5 mixture

of α - and β -anomers. Chromatographic separation of the β -isomer then provided **48**.

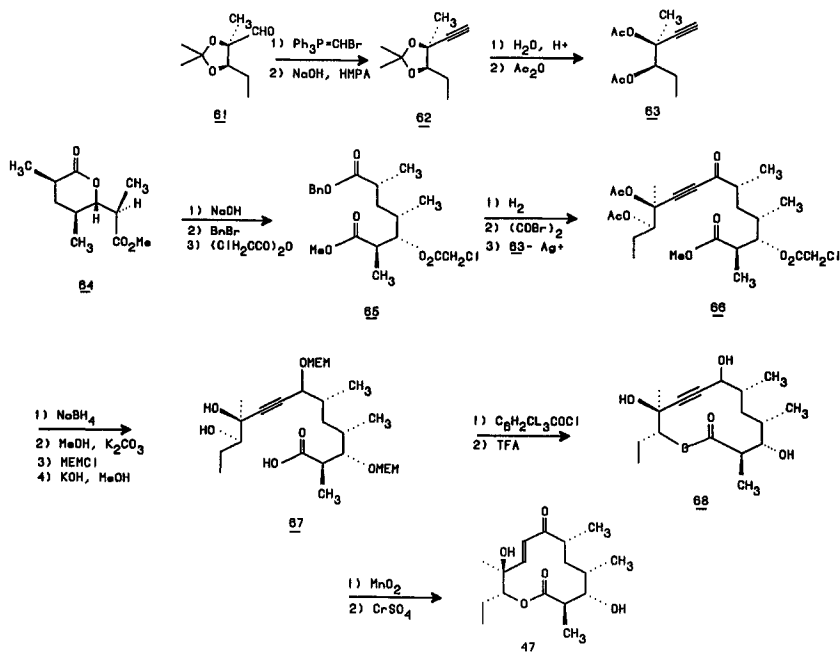


Scheme 2.7. Masamune's methymycin synthesis.

Several years later Yamaguchi constructed the aglycone **47** via a slightly different route, as shown in Scheme 2.8.⁶⁴ Acid **49** (Scheme 2.7) was converted in a straightforward manner to the aldehyde **81**. Olefination to the terminal bromide and base treatment gave a 77% yield of the acetylene **62**. Ketal cleavage and acetylation then gave the C-8 to C-11 nucleophilic fragment **63** (96%).

As in the Masamune synthesis, construction of the C-7 fragment began with a Prelog–Djerassi lactone analog. Accordingly, compound **64**, the methyl ester of **52**, was selectively hydrolyzed and reesterified to the methyl benzyl diester. The remaining hydroxyl group was protected as the chloroacetate to give **65** in

87% yield. Union of the two fragments was then effected by formation of the acyl bromide, followed by addition of the silver salt of **63** to give the propargyl ketone **66** (81%). Ketone **66** possesses all the required carbons and the proper stereochemistry required for construction of methynolide. Reduction of **66**, protecting-group exchange, and cleavage of the ester proceeded smoothly to seco acid **67** in 74% yield. Lactonization using trichlorobenzoyl chloride, followed by removal of the MEM groups with acid, afforded macrocycle **68** (28%). Selective oxidation of the propargyl alcohol to the corresponding ketone and reduction with chromous sulfate gave the synthetic aglycone **47** in 46% yield. The rapid construction of the macrocyclic framework as well as the stereospecific reduction to a single olefin isomer are features of this synthesis well worth noting.



Scheme 2.8. Yamaguchi's methynolide synthesis.

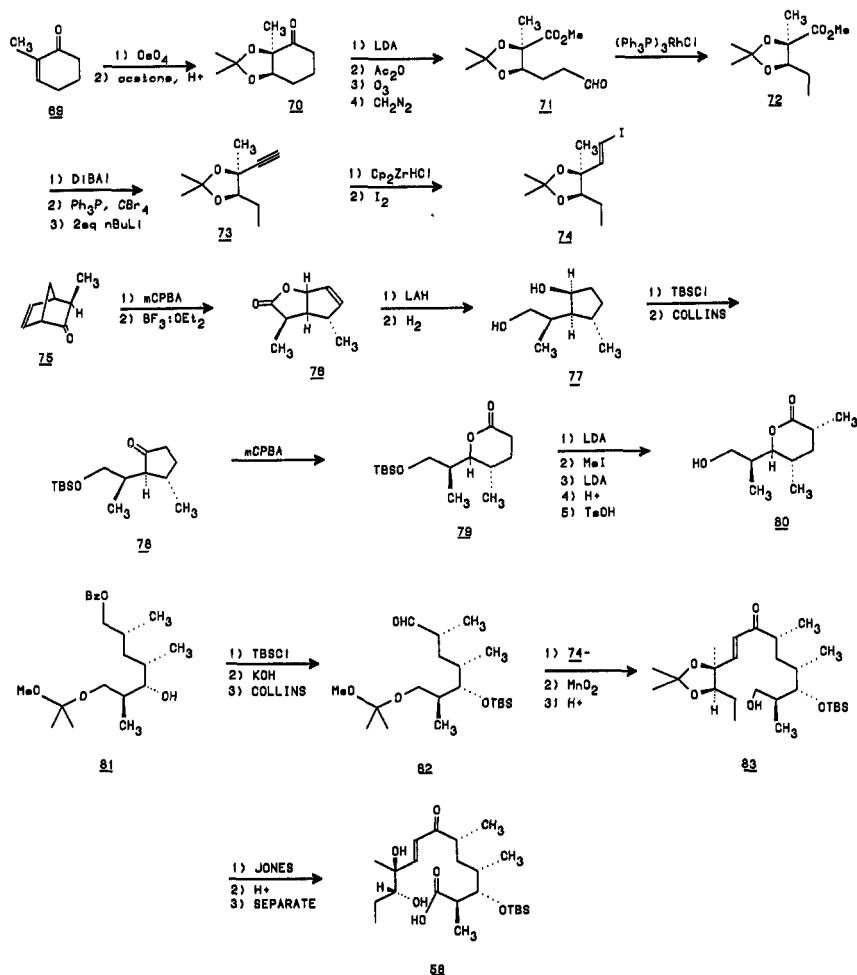
The same year Grieco's group published a synthesis of seco acid **58** by a route reminiscent of the Masamune and Yamaguchi approaches.⁶⁵ The C-8 to C-11 fragment was constructed from 2-methylcyclohexenone (**69**) as shown in Scheme 2.9. Osmylation and protection as the acetone afforded a 65% yield of **70**. This intermediate was then converted into ester aldehyde **71** (66%) via enol acetate formation, ozonolysis, and esterification with diazomethane.

Reductive deformylation of **71** then gave a 50% yield of pentanoate **72**, which still required an additional carbon atom to obtain the required fragment. This homologation was then accomplished via reduction of ester **72** to the aldehyde, chain extension to the terminal dibromide, and conversion to the acetylene **73** (55%). Hydrozirconation followed by quenching with iodine afforded the desired fragment **74** in 67% yield.

Construction of the second fragment corresponding to a Prelog–Djerassi lactone derivative began with the transformation of the known bicycloheptanone **75** into lactone **76** in 84% yield by way of a Baeyer–Villiger oxidation and treatment with $\text{BF}_3\text{--Et}_2\text{O}$. Reduction and hydrogenolysis then gave the diol **77** in 80% yield. Selective tosylation of the primary alcohol followed by oxidation of the secondary alcohol produced cyclopentanone **78** (93%), which was followed by ring expansion to the δ -lactone via a Baeyer–Villiger oxidation to afford a 95% yield of **79**. Methylation (1:1; α : β isomers) followed by epimerization (3.5:1; α : β) and acidic desilylation gave the Prelog–Djerassi lactone derivative **80** in 63% yield. Protection of the primary alcohol in **80**, reductive ring opening, and selective protection of the resulting primary alcohol provided a 63% yield of **81**. Silylation, benzoate cleavage, and oxidation then produced the electrophilic C-1 to C-7 fragment **82** (90%).

Metalation of the vinyl iodide **74** and addition to aldehyde **82** followed by oxidation of the resultant allylic alcohol and mild acid treatment afforded a 63% yield of **83** as a 1:1 mixture of diastereomers. Jones oxidation, ketal cleavage, and chromatographic separation gave the seco acid **58**, which had previously been converted to methynolide (**47**) by Masamune.⁶³ Although construction of the C-8 to C-11 fragment is a bit more tedious and proceeds in lower yield than the Yamaguchi route, the high stereospecificity of the steps make this sequence quite appealing.

Ireland has completed a rather novel synthesis of seco acid **58** by a series of stereoselective additions to a rigid bicyclic ketal as shown in Scheme 2.10.⁶⁶ The known glycal **84** was converted to its propionate ester, which was subjected to Ireland–Claisen rearrangement to give ester **85** in 87% yield as 9:1 mixture of diastereomers. Hydrolysis of the benzyl acetal, protection of the resulting primary alcohol, and oxidation of the remaining secondary alcohol afforded the unsaturated ketone **86** in 93% yield. Addition of lithium dimethyl cuprate then gave the expected β -methyl compound **87** (78%) contaminated with about 5% of the α -epimer. Conversion to the key cyclic acetal **88** occurred in 56% yield via transformation of the silyl group to an acetate and the slow addition of this exocyclic enone precursor to a mixture of triethylamine and ethyl vinyl ketone. The resulting heteroatom Diels–Alder reaction gave a mixture of epimers (74:26) at the ketal carbon, from which the desired **88** was isolated as the major component. Methylenation of ketone **88** and reduction gave the diequatorially disposed dimethyl ketal **89**. A sequence involving hydroboration–oxidation gave alcohol **90**, which was then oxidized under Swern conditions to afford ketone



Scheme 2.9. Grieco's methynolide synthesis.

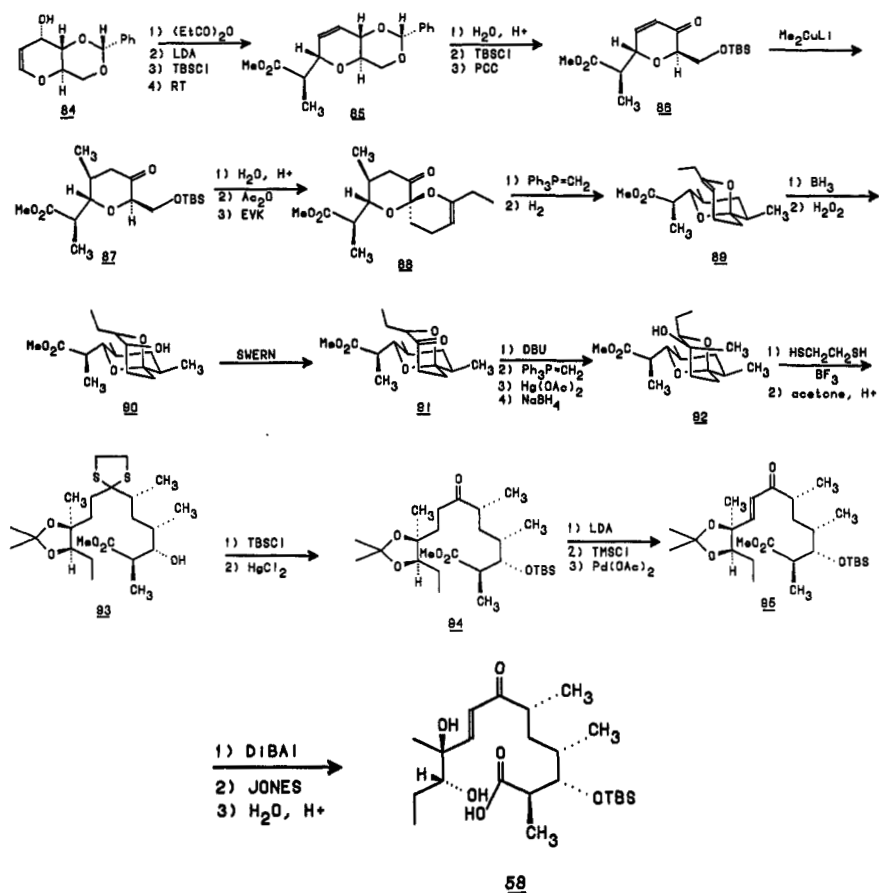
91 in 84% overall yield. The axial ethyl group of **91** was epimerized to the equatorial position followed by olefination and an oxymercuration–reduction sequence to give the desired tertiary alcohol **92**. This compound, which contains all of the stereochemistry required for the construction of methynolide, was contaminated with about 14% of the corresponding primary alcohol from the oxymercuration sequence.

Opening of the spiroketal **92** with ethanedithiol and protection of the resulting 1,2 diol as the acetonide produced **93** (40%). Silylation followed by hydrolysis of the thioketal gave **94** (90%). Saegusa oxidation of the derived silyl enol ether

afforded enone **95** in 96% yield. Conversion to the seco acid **58** was then effected in 26% yield via a reduction–oxidation sequence and acetonide cleavage. Direct hydrolysis of **95** apparently caused some epimerization of the C-6 methyl group. Seco acid **58** had been previously converted to **48** by Masamune.⁶³ Clearly the most attractive feature of the Ireland synthesis is the highly stereoselective manner in which the ring substituents are introduced via the spirocyclic ring template.

C. Neomethynolide

Neomethymycin (**96a**) is a 12-membered ring macrocyclic lactone similar in structure to methymycin (**48**) save that the β -hydroxy group at C-10 has been



Scheme 2.10. Ireland's methynolide synthesis.

transposed to C-12. Originally coisolated with methymycin from *Streptomyces M-2140*,^{67a} the aglycone neomethynolide (**96**) was later isolated^{67b} from the culture filtrate of a mutant strain *S. venezuelae* MCRL-0376. The sole synthetic effort in this area is that of Yamaguchi (Scheme 2.11) and the strategy follows that previously employed in his methynolide synthesis.⁶⁸

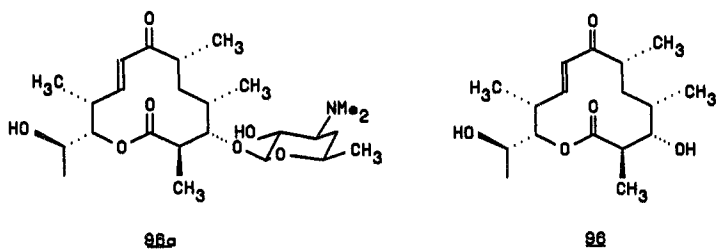
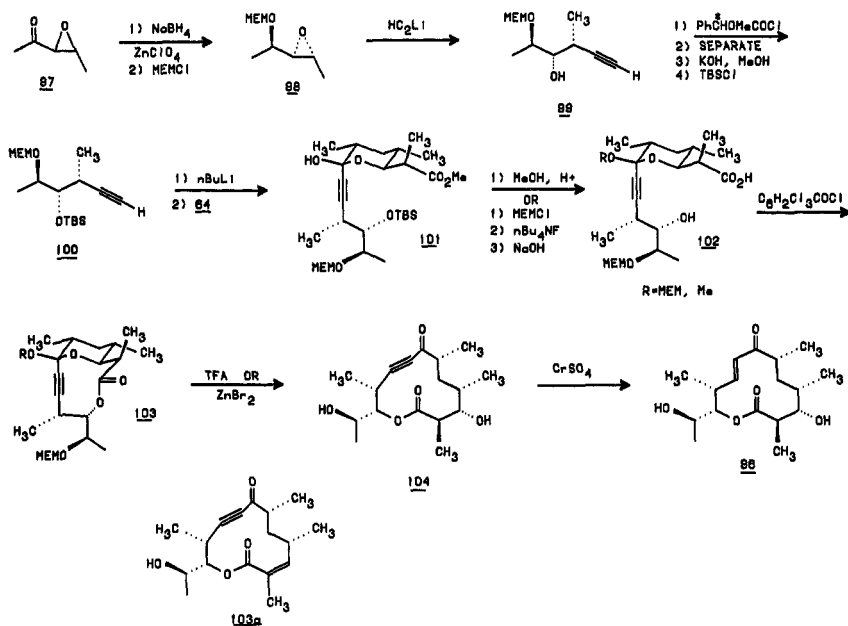


Figure 2.3. Neomethymycin (**96a**) and neomethynolide (**96**)

Epoxy ketone **97** was stereoselectively reduced with ZnBH_4 (prepared *in situ* from NaBH_4 and ZnClO_4), and the resulting alcohol was protected to give **98** in 80% yield. Opening epoxide **98** with lithium acetylide then provided **99** (65%). Following an optical resolution employing the corresponding (*S*)-(+)-*O*-methylmandeloyl esters and subsequent hydrolysis, (–)-**99** was silylated to give **100**. Metalation of the terminal alkyne and addition to Prelog–Djerassi lactonic ester derivative **64** afforded a mixture of hemiketals **101** (90%). Conversion of the hemiketals **101** to the methyl ketals resulted in a 3.5:1 mixture of axial and equatorial anomers. However, the analogous protection with MEMC1 afforded a much more favorable 1:4 ratio of anomers. Desilylation and ester hydrolysis of either equatorial anomer then gave the corresponding hydroxy acid **102**. Lactonization to the highly strained, bridged bicyclic lactone **103** was achieved, albeit in low overall yield, providing material contaminated by the analogous elimination product **103a**. Cleavage of the ketals and MEM group hydrolysis then gave the related macrocyclic propargyl ketone **104** in good overall yield. Reduction of **104** with chromous sulfate afforded neomethynolide (**96**) in high yield (65%).

D. 6-Deoxyerythronolide B

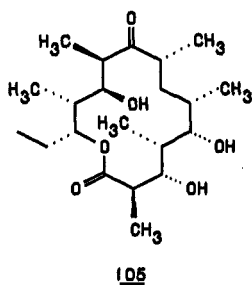
6-Deoxyerythronolide B (**105**) is a 14-membered lactone with 10 asymmetric centers arrayed on the framework of the macrocyclic ring. This compound, produced by the mutant strain *Streptomyces erythreus*,⁶⁹ is the common biosynthetic precursor of erythronolide A and B. A rather novel approach to this compound



Scheme 2.11. Yamaguchi's neomethynolide synthesis.

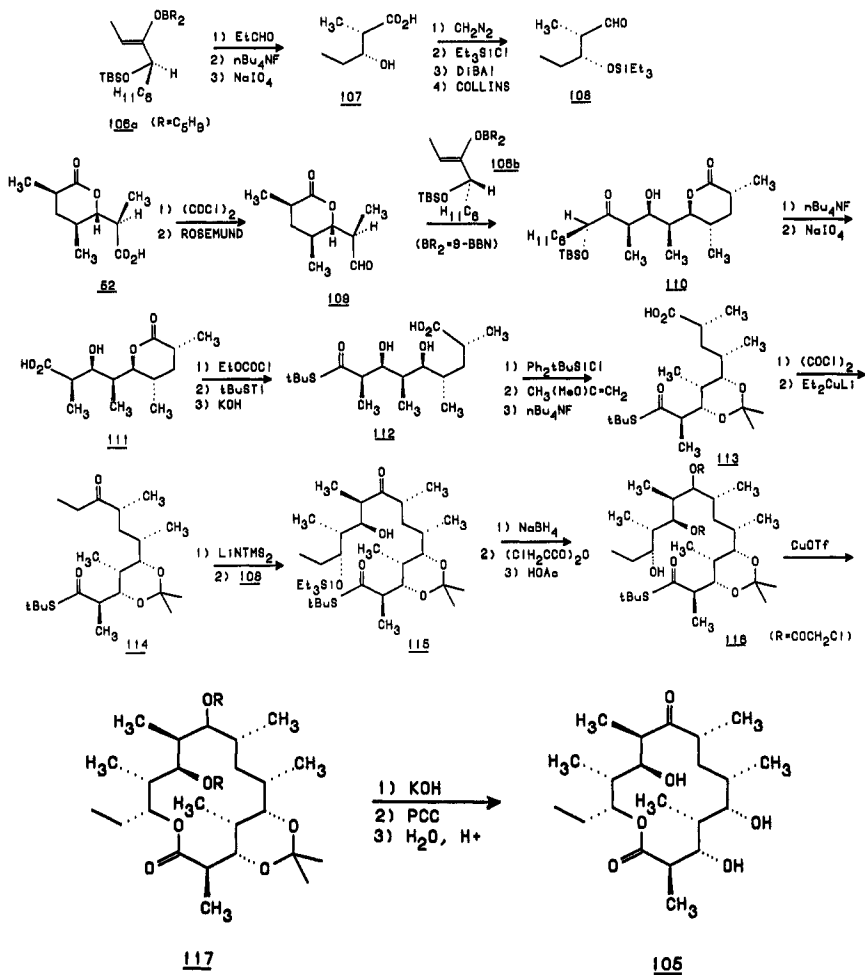
developed by Masamune, shown in Scheme 2.12, makes use of a series of highly stereoselective aldol condensations.⁷⁰

An aldol condensation (selectivity 100:1) between the reagent **106a** (produced from optically active mandelic acid), known to induce (*R*) chirality, and propionaldehyde, followed by desilylation and oxidative cleavage of the resulting α -hydroxy ketone gave the β -hydroxy acid **107** in 85% yield. Esterification, silylation, and a reduction–oxidation sequence then afforded a 75% overall yield

Figure 2.4. 6-Deoxyerythronolide B (**105**)

of aldehyde **108**, the fragment corresponding to C-11 to C-13 of the macrocyclic ring.

Construction of the remaining fragment began with Prelog–Djerassi lactone (**52**). Accordingly, conversion to the acid chloride and Rosemund reduction gave aldehyde **109**, which underwent a subsequent aldol condensation with reagent **106a**, which induces (*S*)-chirality, to afford **110** (14:1) in 71% yield. Desilylation and oxidative cleavage afforded a quantitative yield of acid **111**, which was readily converted to thioester **112**. Silylation of the carboxyl group followed by acetone formation and liberation of the acid gave **113** in 46% overall yield



Scheme 2.12. Masamune's 6-deoxyerythronolide B synthesis.

from **111**. Transformation of the acid to the ethyl ketone **114** via the acid chloride then gave the C-1 to C-10 fragment (84%). The required aldol condensation between segments **108** and **114** proceeded in chelation-controlled fashion (stereoselectivity 17:1) to give an 88% yield of hydroxy ketone **115**. The ketone was reduced (to prevent hemiketal formation), the two secondary alcohols were protected, and the silyl group was removed to provide **116**. Copper (I) triflate mediated cyclization, presumably proceeding through the triflic ester, gave the lactones **117** in 23–41% yield. The observed difference in cyclization yield between the two diastereomers of **116** was presumably attributable to differing rates of lactonization of the two diastereomers, which apparently adopt rather different conformations. Acetate cleavage, selective oxidation, and ketal hydrolysis then gave synthetic 6-deoxyerythronolide B (**105**).

E. Narbonolide

Narbomycin (**118b**) and its aglycone narbonolide (**118a**) are both isolated⁷¹ from the fermentation broth of *Streptomyces venezuelae* MCRL-0376. Masamune has also reported the only synthesis of a member of this class of compounds, employing a route nearly identical to his synthesis of 6-deoxyerythronolide B.⁷²

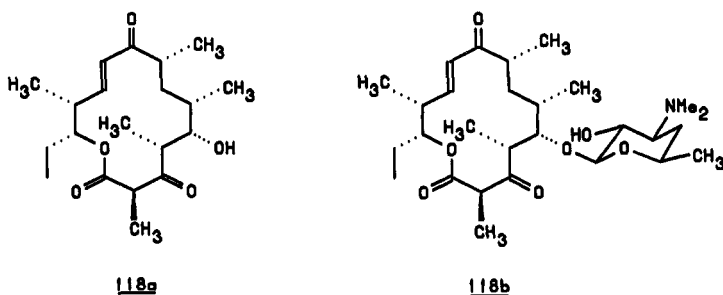
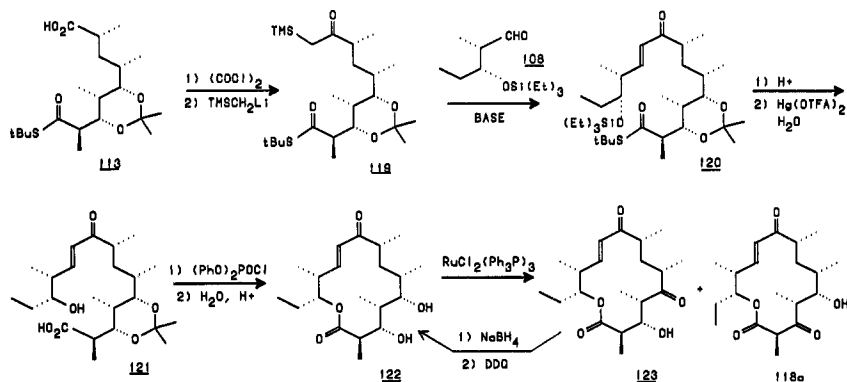


Figure 2.5. Narbonolide (**118a**) and narbomycin (**118b**)

Intermediate **113** was transformed into the trimethylsilyl methyl ketone **119** in quantitative yield via the acid chloride, followed by the addition of trimethylsilylmethyl lithium (Scheme 2.13). Subsequent Peterson olefination of aldehyde **108** with **119** resulted in the required unsaturated ketone **120** in 95% yield. Subsequent desilylation and thioester hydrolysis afforded a 97% of the seco acid **121**. Lactonization was achieved in 32% yield via the phosphoric acid-mixed anhydride, however this procedure also formed about 25% of the dimeric bis lactone. Following removal of the acetonide under the action of acid, a nonselective oxidation with $\text{RuCl}_2(\text{Ph}_3\text{P})_3$ produced a 1:1 mixture of the natural

118a and the corresponding C-5-oxidized ketone **123** in 92% yield. Fortunately, ketone **123** can be recycled to the diol **122** with NaBH_4 followed by allylic oxidation with DDQ in 70% overall yield.



Scheme 2.13. Masamunes's narbonolide synthesis.

F. Erythromycins

Among the most biologically important mold metabolites are the 14-membered ring macrocyclic lactones, the erythromycins. Indeed, their application as powerful broad-spectrum antibiotics is well documented in the medical literature. The two most common members of this group, erythromycin A (**147**) and B (**124b**), and their respective aglycones erythronolide A (**146**) and B (**124a**), differ only in the oxidation state at C-12. Isolated from the fermentation broth of *Streptomyces erythreus*,^{73a} these complex macrolides contain 10 asymmetric centers and 2 unusual sugars, L-cladinose and D-desosamine, attached to the lactone ring. Furthermore, erythronolide B (**124a**) has been implicated as the biosynthetic precursor of all the erythromycins.^{73b}

Owing to the complexity of the erythronolides, the problems involved in a synthetic approach seemed at one time insurmountable. The late R. B. Woodward once wrote, "Erythromycin, with all of our advantages, looks at present hopelessly complex, particularly in view of its plethora of asymmetric centers."⁷⁴ Yet Woodward's group completed a remarkable synthesis of erythromycin B after his death.

The first reported synthesis of a member of this class, that of erythronolide B, was completed by Corey and is depicted in Scheme 2.14.⁷⁵ The retrosynthetic strategy involved the use of two segments, C-10 to C-13 and C-1 to C-9, the former arising from selective ring opening of an epoxide and the latter from a series of manipulations on a rigid cyclohexane derivative.

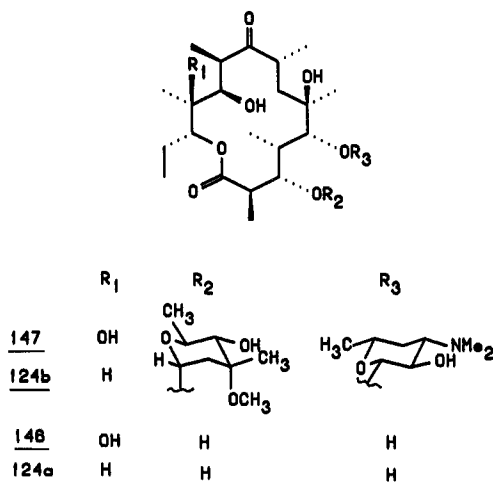


Figure 2.6. Erythromycin A (**147**), B (**124b**); erythronolide A (**146**), B (**124a**)

Construction of the C-1 to C-9, fragment began with dienone **125**, obtained from 2,4,6-trimethyl phenol and allyl bromide. Hydroboration of **125** followed by oxidation then gave a 72% yield of carboxylic acid **126**. Bromolactonization of **126**, which provided **127** (96%), set up the stereochemistry at what will later become the C-5 hydroxyl group. Epoxy keto acid **128** was subsequently obtained in 98% yield following alkaline hydrolysis. Corey reported that the resolution of **128** by recrystallization of the diastereomeric 1- α -naphthylethylamine salts was possible however, for the purposes of completion of the synthesis, racemic **128** was utilized.

A second bromolactonization afforded **129** in 91% yield. The formation of this bicyclic lactone achieved not only the introduction of the oxygen at what will become the C-1 position, but also the formation of a rigid oxodecalin ring system which allows the stereoselective introduction of the C-2 center. Tin hydride reduction of the halogen followed by reduction of the epoxide to the epimeric β -hydroxy ketones **130** proceeded in 71% overall yield. The mixture of epimers was the result of equilibration of the intermediate radical during the tin hydride reduction (**130a**:**130b** = 13:87); however, the desired epimer **130b** was the predominant product. Reduction with Ra-Ni followed by protection and recrystallization then afforded pure **131** in 75% yield from the mixture of ketones **130**. Methylation of the lactone and hydrolysis afforded the hydroxy acid **132** (76%). The minor epimer **132a** could readily be converted to the more stable lactone and hydrolyzed to the major acid **132b**, possibly via a ketene intermediate. Subsequent Jones oxidation then led to keto acid **133** (80%). Baeyer–Villiger ring expansion and conversion of the derived acid to the thioester gave **134**, thus completing the C-1 to C-9 segment.

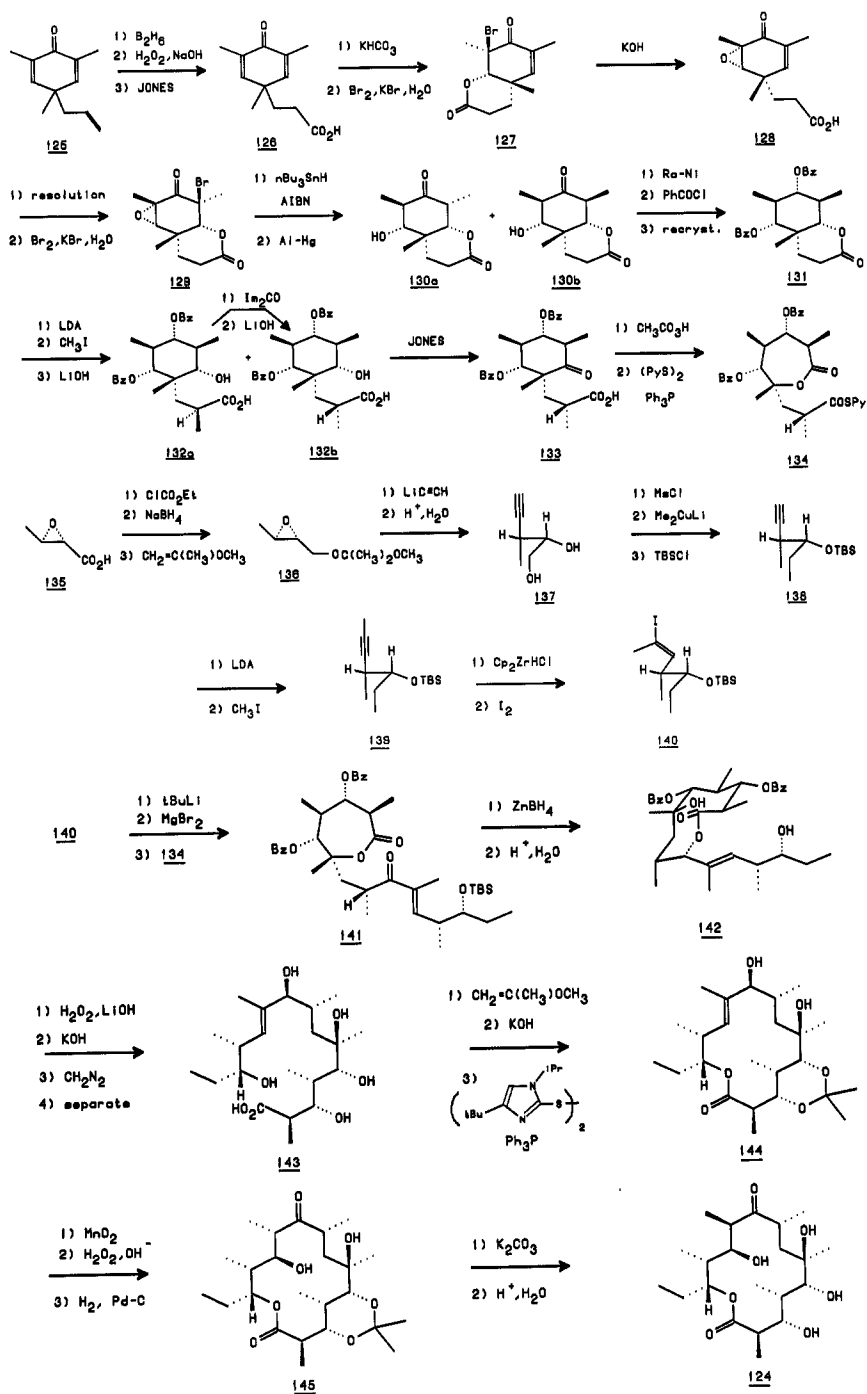
Racemic *trans*-2,3-epoxybutyric acid was resolved with (-)-1- α -naphthylethylamine to give the (2*S*,3*R*)-enantiomer **135**. Reduction to the alcohol via the mixed anhydride and protection gave **136** (76%). Lithium acetylide opening of the epoxide and acidic hydrolysis gave a 90% yield of diol **137** contaminated with about 10% of the product corresponding to regioisomeric epoxide opening. Mesylation and displacement of the primary alcohol gave the analogous ethyl compound, which was protected as the silyl ether **138**. Metalation and alkylation then converted the terminal acetylene into **139** in 66% overall yield from **137**. Hydrozirconation followed by quenching with I₂ gave the C-10 to C-13 fragment **140** in 84% yield as a single olefin isomer in optically pure form.

Metalation of the vinyl iodide **140** provided the required nucleophilic organometallic reagent, which added smoothly to the electrophilic thioester **134** to give keto lactone **141** in 90% yield. Stereoselective reduction of the enone in a 1,2 fashion induced a translactonization which, after desilylation, afforded the 10-membered ring lactone **142** as a single diastereomer (64%). Benzoate hydrolysis, lactone ring cleavage, esterification, and diastereomer separation (due to the coupling of optically active **140** and racemic **134**) gave pentaol **143**. Formation of the acetonide between hydroxy groups at C-3 and C-5 followed by ester cleavage gave a seco acid that was subsequently lactonized in 36% overall yield via the 2-thioimidazolyl ester to give macrolactone **144**.

Completion of erythronolide B then required the introduction of a β -hydroxy group at C-11 (erythronolide numbering). Accordingly, **144** was oxidized to the enone and epoxidized to give the desired β -epoxide. Hydrogenolysis then gave the C-10 α , C-11 β compound **145**. Final conversion to erythronolide B (**124**) was accomplished via base-catalyzed epimerization of the C-10 methyl group followed by cleavage of the acetonide with acid.

A second synthetic study in this area by Corey culminated in the synthesis of erythronolide A (**146**) as outlined in Scheme 2.15.⁷⁶ The strategy employed in this synthesis was quite similar to that utilized for erythronolide B save two important points. Quite obviously, the additional hydroxyl group at C-12 requires a somewhat different route to the C-10 to C-13 fragment. Second, the presence of the C-12 hydroxyl group resulted in significantly more protecting-group manipulations relative to the sequence employed in the previous synthesis.

Construction of C-10 to C-13 fragment began with the addition of 1-lithiopropyne to 2-pentanone followed by dehydration with acid, affording a mixture of **148a,b** and **c** from which the desired **148a** was isolated as the major isomer. Osmylation followed by recrystallization then gave pure diol **149** in 65% yield. Optical resolution via the *O*-methylmandeloyl esters, protection of the tertiary alcohol as the MTM ether, and hydrolysis of the esters gave enantiomerically pure **150**. Conversion to the vinyl iodide **151** then proceeded by analogy to the previous synthesis. Thus silylation of the remaining alcohol, hydroboration-oxidation of the alkyne to the boronic ester, followed by a mercuriation-iodination



Scheme 2.14. Corey's erythronolide B synthesis.

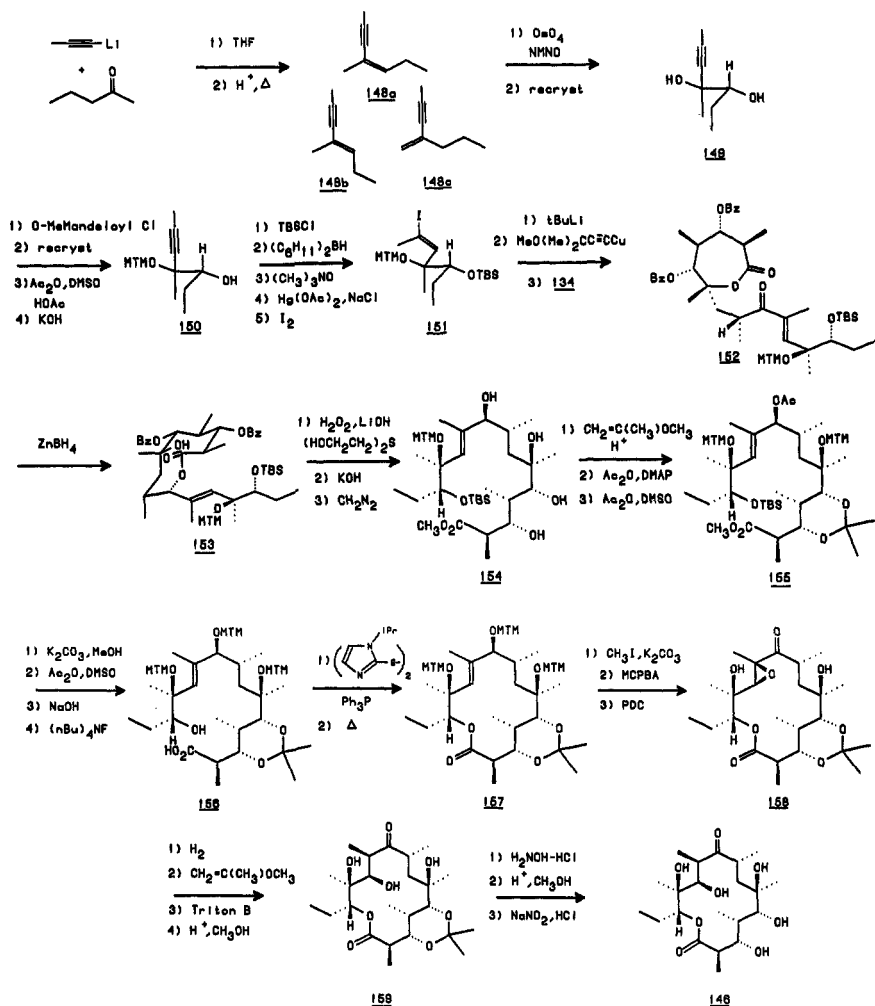
sequence afforded a 75% yield of vinyl iodide **151**. Metalation of **151** and transformation to the mixed cuprate followed by addition of **134** produced the enone **152** in 78% yield. As before, reduction of the enone gave the ring-expanded 10-membered ring lactone **153** (57%). Successful hydrolysis of the lactone in this sequence required the addition of 2,2'-dihydroxydiethyl sulfide to the alkaline medium in order to avoid cleavage of the MTM group. Benzoate hydrolysis and esterification then produced **154** in 82% yield. After the C-3,C-5 diol was protected as the acetonide, the C-9 hydroxyl group was selectively acylated, and the remaining hydroxyl group protected as the MTM ether to give a 76% yield of the protected hexaol **155**. Exchange of the acetate for an MTM ether at C-9, followed by a series of hydrolyses, led to the seco acid **156** in 56% yield. Lactonization, as in the previous case, occurred via an intermediate thioester to give the macrocycle **157** in 30% yield.

Completion of the synthesis was then achieved along the lines previously developed for erythronolide B. Thus cleavage of the MTM groups followed by epoxidation and oxidation gave the keto epoxide **158** in 74% yield. After epoxide hydrogenolysis to give the β -hydroxy ketone and protection of this hydroxyl group, the C-10 methyl group was then epimerized. This was followed by selective deprotection of the C-11 hydroxyl group to afford **159** in 22% overall yield. Direct acid hydrolysis of **159** led to substantial amounts of decomposition, so an alternate approach was developed. Accordingly, reaction with hydroxylamine led directly to the oxime that was stable to the acidic conditions required for acetonide cleavage. Nitrous-acid cleavage of the pentaol oxime then provided erythronolide A (**146**) in 41% yield.

Among the more beautiful and truly imaginative syntheses accomplished in the 1970s and 1980s was Woodward's synthesis of erythromycin A.⁷⁷ In typical Woodwardian fashion, he recognized and indeed utilized the marked similarities in stereochemistry between fragments C-3 to C-8 and C-9 to C-13, each being constructed from the common intermediate **166**.

The synthesis began, as shown in Scheme 2.16, with the alkylation and subsequent hydrolysis of compounds **160** and **161** to afford aldol precursor **162**. An enantioselective aldol condensation, using D-proline as a catalyst, gave a 70% yield of **163** and **164** in a 1:1 ratio, both diastereomers being formed in 36% ee. Isolation of the desired **164** followed by dehydration and recrystallization then gave optically pure (+) **165** in 10–12% yield from the racemates **160** and **161**. A stereospecific sequence involving ketone reduction and protection as the MOM ether followed by bishydroxylation of the olefin and subsequent acetonide formation gave the key intermediate **166** (74%).

The fragment corresponding to C-9 to C-13 was then constructed by a Raney-nickel desulfurization and debenzylolation to afford an intermediate alcohol, which was dehydrated and oxidatively cleaved to afford **167** in an overall yield of 80%. Ketone **168**, the C-3 to C-8 segment, was produced in 85% yield from **166** via acid deprotection of the MOM group followed by oxidation. Annulation of the



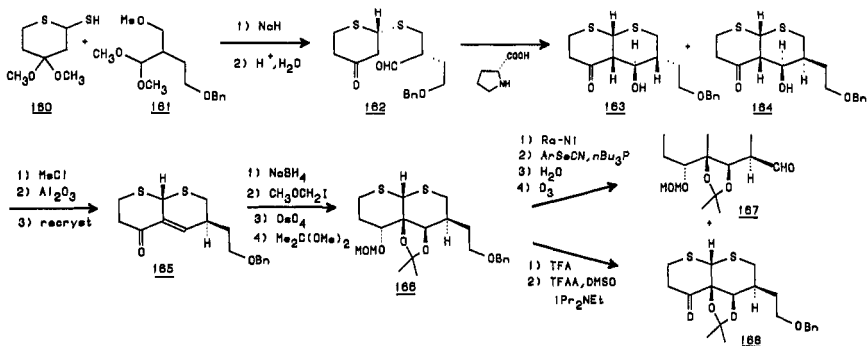
Scheme 2.15. Corey's erythronolide A synthesis.

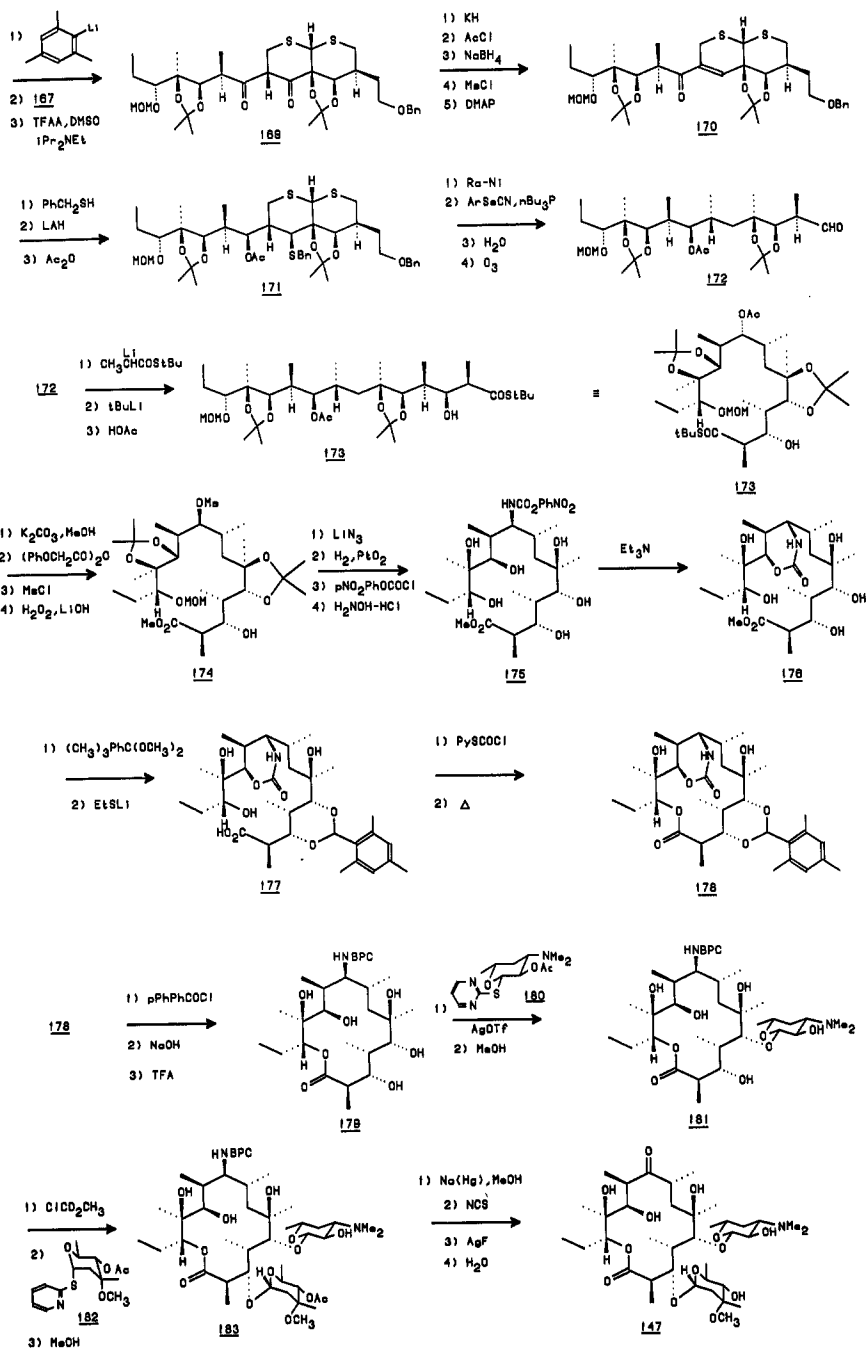
two fragments occurred via an aldol condensation and oxidation to give the carbon skeleton **169**, corresponding to C-3 through C-13, (76%). This 1,3 dione was regiospecifically reduced to give the acyl dithiadecalin **170**. Control of the stereochemistry at C-8 was now achieved via the 1,4 addition of a readily removable moiety, in this case benzyl thiol, and protonation of the resulting enol from the least hindered side of the *cis*-fused ring system. Reduction and protection of the C-9 ketone gave **171** in 76% yield. Intermediate **171** was then elaborated into aldehyde **172** in 66% yield, as previously described for the conversion of

166 to 167. Coupling of **172** with the C-1 to C-2 fragment, derived from the enolate of *t*-butyl thiopropionate, proceeded in a "Cram" stereoselective manner, thus producing a compound with the wrong stereochemistry at C-2. A deprotonation-kinetic reprotonation sequence permitted epimerization of this center to give the desired **173** in 90%. If this extended carbon chain is now aligned properly, the resemblance to erythronolide A is apparent.

Earlier studies with derivatives of the natural product had shown that the lactonization step proceeded with greater efficacy if a cyclic bridge was formed between the C-11 hydroxyl group and a C-9 appendage with an (*S*) configuration. The C-9 hydroxyl group was therefore converted to a more appropriate functional group, for in this case the stereochemistry of this group destined to become ultimately the carbonyl was inconsequential. Thus acetate hydrolysis, selective protection of the C-3 hydroxyl group, and mesylation at C-9 followed by C-3 deprotection afforded **174** in 75%. Azide displacement and reduction produced a primary amine, which was protected, followed by cleavage of the acetonide groups to afford carbamate **175**. Base treatment then formed the cyclic carbamate **176** in 53% yield, which contained the required C-9 to C-11 bridge. Formation of the C-3,C-5 cyclic acetal and ester dealkylation gave seco acid **177**, which was followed by lactonization using Corey's thiopyridine method to give macrolactone **178** in 60% overall yield.

With construction of the macrocycle now completed, conversion to the target required the addition of the two sugar moieties and manipulation of the protecting groups. To this end, acylation and deprotection of **178** gave the pentaol **179** in 70% yield. Glycosidation with D-desosamine derivative **180** and subsequent methanolysis gave the C-5 β -glycoside **181** (36%). Reformation of the desosamine carbonate and reaction with L-cladinose derivative **182** gave the expected α -glycoside **183** in 55% yield following methanolysis. Conversion to the natural product **147** was achieved by amide deprotection, oxidation of the amine to the imine, and hydrolysis in 30% overall yield.





Scheme 2.16. Continued.

Because of the intricacies associated with construction of the erythronolide framework, this group of macrolides served as the yardstick for accomplishment in this area, and as such has attracted considerable attention. Consequently, we would like to develop, for the benefit of the reader, several other synthetic approaches that have been described (some of which are still under investigation). Although not total syntheses in the strictest sense, all of the efforts presented here have made substantial progress toward the elaboration of the stereochemistry of this complex system. We have by necessity exercised editorial judgment as to which among a number of ongoing efforts have been included in this chapter. Additionally, several other unpublished routes have recently been reviewed.⁴

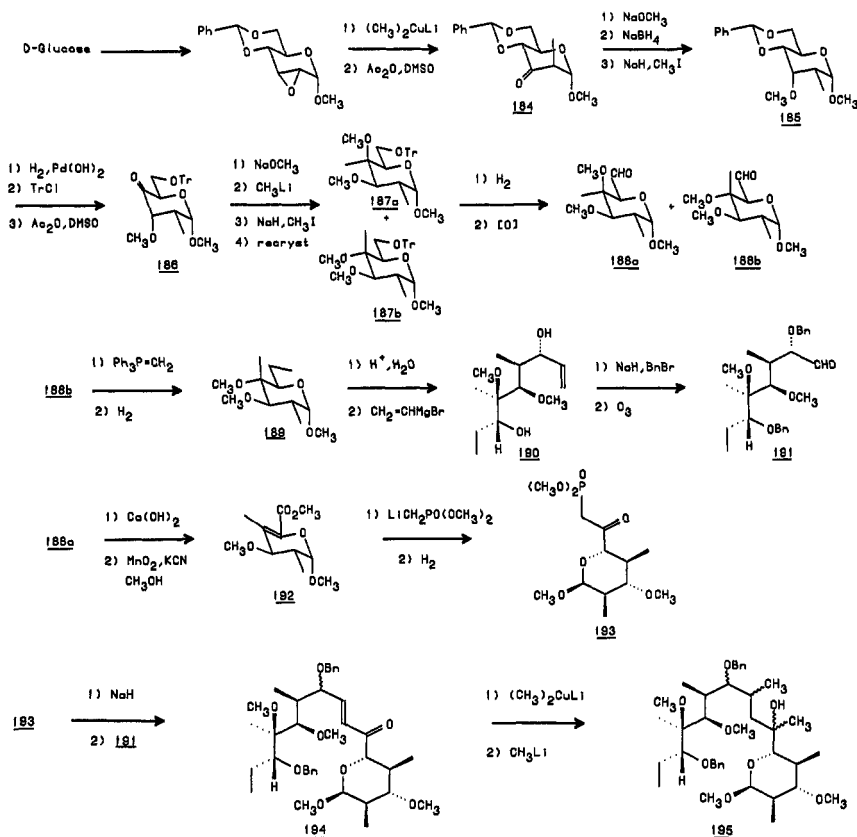
The first approach to the erythronolide system examined in this section was described by Hanessian and is depicted in Scheme 2.17.⁷⁸ Hanessian also recognized the similarities between the C-1 to C-6 and C-9 to C-15 fragments, and thus constructed a common precursor of the two segments from the appropriate sugar. To this end, D-glucose was transformed along established protocols into the epoxy acetal **183**. Diaxial opening of the epoxide with dimethyl cuprate followed by oxidation afforded a 62% yield of ketone **184**. Epimerization of the axial methyl group to the more stable equatorial conformation and a reduction–etherification sequence then gave **185** (68%). Hydrogenolysis of the benzyl acetal of **185**, selective reprotection of the primary alcohol as the trityl ether, and subsequent oxidation of the secondary alcohol afforded ketone **186** in 83% yield. A second epimerization of methoxy group to the equatorial position, followed by the addition of methyl lithium and methylation of the resulting tertiary alcohol gave a mixture of compounds **187a** and **187b**. Fractional recrystallization then allowed the isolation of the major diastereomer **187b**, and a mixture of **187a** and **187b** from the mother liquors.

Elaboration of the C-8 to C-15 fragment continued with detritylation and oxidation of **187b** to give **188b** in 90–95% yield. Olefination and reduction then gave **189** (85%), which had the desired stereochemistry at C-1 to C-15, but lacked one carbon required for completion of the segment. This homologation was accomplished by hydrolysis to the free sugar subsequent to the addition of vinyl Grignard reagent to give **190** as a mixture of alcohol diastereomers in 72% yield. The fact that **190** was isolated as a mixture was inconsequential as this position corresponds ultimately to the C-9 ketone in the natural product. Protection and oxidation then afforded a 56% yield of **191**.

Construction of the C-1 to C-7 fragment proceeded from the mixture of **187a** and **187b** remaining as the mother liquors after isolation of **187b**. Similar to the sequence employed previously, reductive detritylation and oxidation of this mixture afforded a mixture of the β -methoxy aldehydes **188a** and **188b** in excellent yield. Base treatment followed by a Corey–Ganem oxidation then gave the unsaturated ester **192**. Phosphate reagent **193** was isolated in 76% yield by addition of lithium dimethylphosphonoacetate to **192** and subsequent reduction.

Coupling of the two fragments **191** and **193** occurred under typical Wadsworth–Emmons conditions to give **194**, the carbon backbone of erythronolide A in 59%

yield. Hanessian then completed the synthesis by 1,4 addition of dimethyl cuprate and conversion of the ketone at C-6 into a mixture of tertiary alcohols affording **195** (51%). The resulting complex mixture of four diastereomers is greatly simplified once it is recognized that the C-8 methyl group may be epimerized to the correct configuration after the oxidation of C-9 to the ketone. Thus only the stereochemistry at the remaining center C-6 was not controlled.

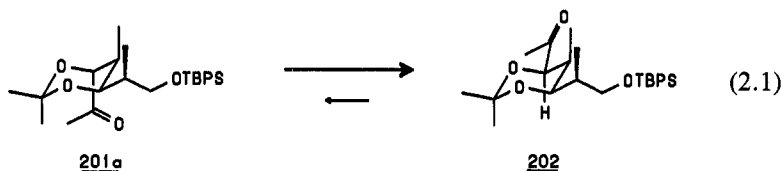


Scheme 2.17. Hanessian's erythronolide approach.

Stork had also recognized the symmetry element present in the erythronolide A skeleton. The Stork approach is outlined in Scheme 2.18.⁷⁹ Cyclopentadiene was converted into the optically pure (1*S*,2*S*)-(+)-2-methyl-3-cyclopenten-1-ol (**196**) utilizing literature procedures. Stereoselective syn epoxidation followed by oxidation and base treatment afforded an alcohol which was silylated to give **197** in 71% overall yield. As expected, the γ -silyloxy group induced the addition

of dimethyl cuprate in an anti fashion, and the resulting enolate was then trapped as the silyl enol ether **198** in 88% yield. Ozonolysis followed by aldehyde reduction and acid treatment provided lactone **199** (70%). Reduction to the lactol and the addition of 2-propenyl lithium gave **200** (88%) as a mixture of isomers at the allylic alcohol center. Protecting-group exchange then afforded the acetonides **201** in 91% yield. Ozonolysis and acetyl-group epimerization provided **202** as the only isomer in 92% yield, thus completing the C-1 to C-6 fragment.

The choice of the acetonide protecting group for the 1,3 diol was instrumental in the epimerization of what is destined to become the C-5 center. As Eq. 2.1 shows, a destabilizing 1,3 diaxial interaction occurs between the acetyl group and a methyl group of the acetonide. Epimerization of the acetyl group from the axial to the equatorial position thus eliminates this unfavorable interaction.

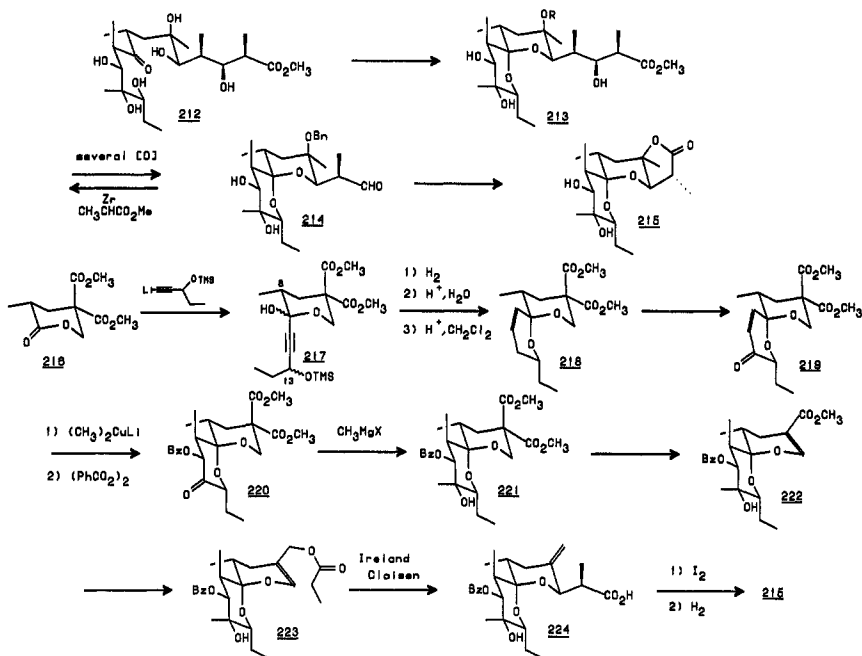


Stork then took advantage of the symmetry element by converting **198** into the C-7 to C-15 segment. Accordingly, **198** was oxidized to the corresponding enone under Saegusa conditions. Hydrogenation (predominantly anti to the silyloxy group) followed by deprotonation and trapping as the silyl enol ether allowed isolation of **203**, the major product, contaminated with a small amount of **198** in 87% overall yield. Conversion to the triol **205** via the intermediate lactone **204** was effected as previously described for the synthesis of intermediate **200**. Tosylation of the primary alcohol of **205**, formation of the cyclic cyclopentyl ketal between what will become C-9 and C-11, displacement with thiophenoxide, and oxidation gave sulfoxide **206** in 76% yield. A repeat of the ozonolysis-epimerization sequence afforded methyl ketone **207**, which was then treated with the Grignard reagent from 2-bromopropene. The addition, which occurred in a chelation-controlled fashion, gave tertiary alcohol **208** in 69% overall yield.

Union of the two segments was now effected via formation of the dianion of **208** and subsequent addition to ketone **202** to afford **209** in 80% yield. Although contaminated with a small amount of the C-6 epimer (ratio 5:1), the major component **209** contained all the necessary carbon atoms and possessed the required stereochemistry (except the C-13 alcohol) for the completion of erythronolide A. To this end, the methylene group was ozonolyzed, and the sulfoxide reductively cleaved, providing ketone **210** (84%). Stereoselective reduction of the ketone concomitant with cleavage of the silyl ether gave an 85% yield of **211** as a 20:1 mixture of C-13 isomers. Intermediate **211** contains all the stereochemical centers present in erythronolide A.

an equatorial environment. Allylic oxidation then gave enone **219**, which was converted to **220** via stereoselective addition of dimethyl cuprate and subsequent trapping of the enolate with dibenzoyl peroxide. Addition of the cuprate reagent occurred from the equatorial face of **219**, since the axial face is hindered by a 1,3 diaxial interaction due to the C-8 methyl group in the second ring. Axial addition of methyl Grignard reagent to the C-12 ketone then gave **221** in good yield.

With the stereochemistry at C-8 to C-13 established, attention was now turned to the C-4 to C-6 fragment (the centers at C-2 and C-3 having already been introduced during the conversion of **214** to **213**). Oxidative decarboxylation of **221** gave the vinylogous ester **222**. Reduction and acylation provided **223**, which was subjected to an Ireland enolate-Claisen rearrangement that afforded a 4:1 mixture of diastereomers in which the desired **224** predominated. Iodolactonization of **224** and reductive removal of the halogen gave **215**, identical with the compound obtained by degradation of erythronolide A.



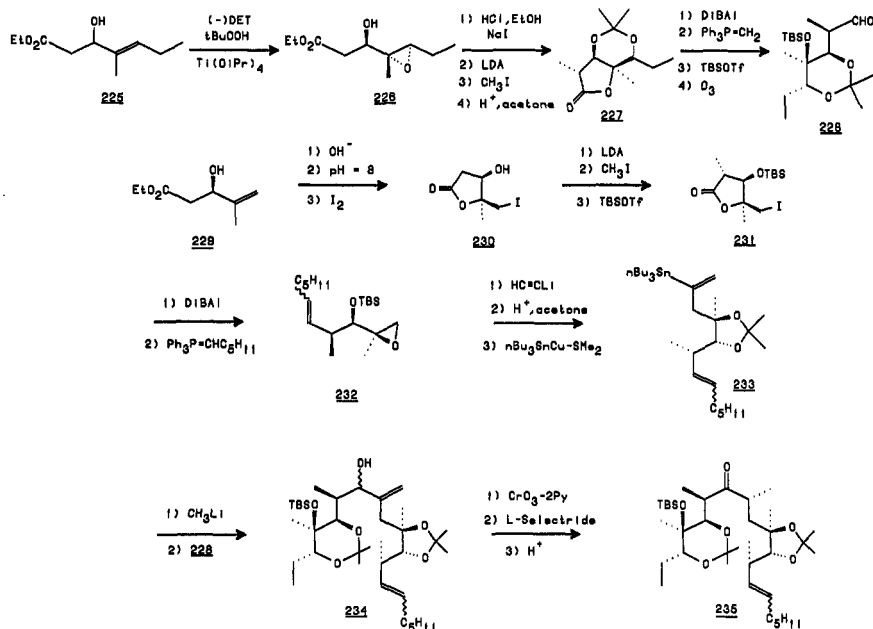
Scheme 2.19. Deslongchamp's erythronolide approach.

Another concise approach to the erythronolide ring system was developed by Chamberlin and co-workers, as described in Scheme 2.20.⁸¹ Like Woodward

and Stork, the strategy employed here utilized the similarity of the two erythronolide fragments C-3 to C-8 and C-9 to C-15.

Racemic hydroxy ester **225** was converted, via a Sharpless kinetic resolution, to the enantiomerically pure epoxide **226**. This epoxide was then converted to the diol γ -lactone by intramolecular attack of the ester, assisted by nucleophilic dealkylation with iodide ion. Deprotonation and methylation anti to the alkoxide followed by acetone formation afforded **227** in 56% yield. Dibal reduction, protection of the resulting aldehyde as the terminal olefin, silylation of the tertiary alcohol, and liberation of the aldehyde via ozonolysis provided a 45% yield of the C-9 to C-15 fragment **228**.

The remaining segment, C-3 to C-8, was constructed by a similar route. Optically active allylic alcohol **229**, produced from lithio ethylacetate and methacrolein followed by a second Sharpless kinetic resolution, was hydrolyzed to the corresponding hydroxy acid. Neutralization followed by iodolactonization then gave **230** in 85% yield. This highly stereoselective cyclization produced a *cis-trans* ratio of 20:1 via a one-pot procedure. Deprotonation and methylation afforded the expected *anti* α -methyl compound, contaminated with about 10% of the *syn* compound but none of the methyl ether. Formation of the silyl ether then produced **231** in 66% yield. Dibal reduction to the aldehyde concomitant



Scheme 2.20. Chamberlin's erythronolide approach.

G. Leucomycin A₃ and Carbomycin B

280a $R_1 = R_2 = O$

280b $R_1 = H$ $R_2 = OH$

Figure 2.7. Leucomycin A₃ (260b) and carbomycin B (260a)

The first synthesis was developed in Tatsuta's laboratories and is outlined in Scheme 2.21.⁸³ The C-11 to C-15 fragment, containing one chiral center, was constructed from the 2-deoxy-D-arabino-pyranoside **236**. Thus treatment of **236** with sulfonyl chloride followed by NaI in methanol gave the dichloropyranoside **237** (41%). Conversion to the pyranose **238** was accomplished in 78% overall yield by acylation, reductive dehalogenation, and hydrolysis. Tosylation then gave the unstable glycal **239**, which was immediately oxymercurated and hydrolyzed to give enal **240** in 51% yield.

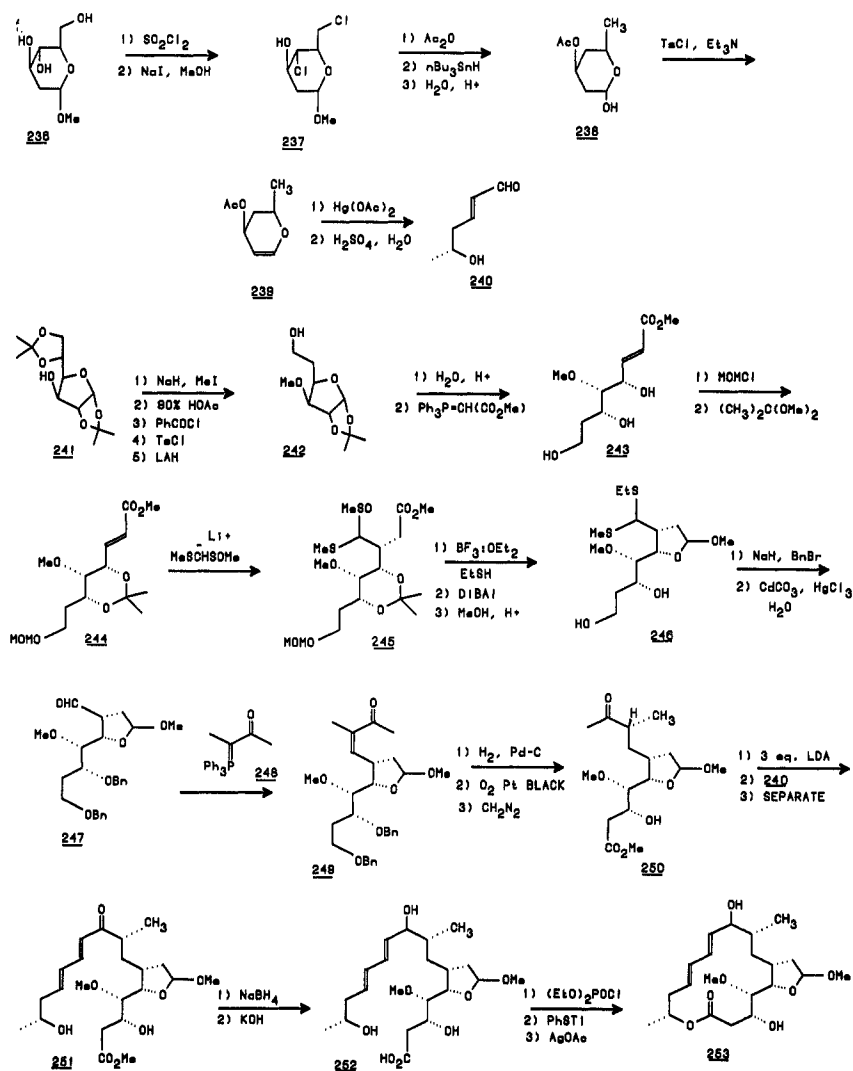
The sequence for construction of the second chiral fragment, C-1 to C-6, also utilized a carbohydrate, in this case D-glucose. Glucose diacetone (241) was protected and reduced in five steps to give **242** in 75% overall yield. Hydrolysis to the furanose and Wittig condensation with carbomethoxymethylenetriphenylphosphorane produced the unsaturated ester **243** (75%). A series of alcohol protections then afforded acetone **244** in 61% overall yield. The stereochemical center at C-6 was now introduced by the stereospecific addition of an acyl anion equivalent in the form of the lithium anion of methyl methylthiomethyl sulfoxide. Surprisingly, only one C-6 isomer, **245**, was obtained (79%). This material was then converted to **246**, which was isolated as a single anomer by sulfide exchange, reduction, and internal acetal formation (56%). Protection of the hydroxyl groups and subsequent liberation of the formyl group gave **247** in 85% yield. Chain extension with stabilized Wittig reagent **248** afforded the C-1 to C-10 segment **249** as a single olefin isomer (91%). As expected, reduction of the sp^2 center at C-8 in **249** occurred stereorandomly concomitant with cleavage of the benzyl ethers providing the corresponding diol. Selective oxidation of the primary alcohol and esterification gave the (8*R*) keto ester **250** in 44% yield accompanied by the analogous (8*S*) compound (27%). Recycling the undesired (8*S*) epimer by equilibration improved the overall efficiency of the route.

The pure (8*R*) ketone **250** was then subjected to an aldol condensation with the optically active aldehyde **240**, followed by dehydration and separation, which led to the dienone **251** (67%). Reduction and ester hydrolysis then gave a 39% yield of seco acid **252** contaminated with 22% of the 2,3 unsaturated acid resulting from dehydration. Lactonization to the macrolide using the Masamune procedure gave lactone **253** in 17% overall yield.

With construction of the macrocyclic ring completed, attention was now focused on the disaccharide unit. Selective oxidation of the allylic alcohol, acylation of the C-3 hydroxyl group, and formation of the ethylene glycol acetal gave the protected aglycone **254** in 15% yield. The final acetal formation step also produced the hydroxyethylated furanoside as a by-product, which could be recycled back into the protection sequence. Glycosidation of **254** with the mycaminose derivative **255** led to isolation of the monoglycoside **256** (16%) following selective deacylation in methanol. The 4' position of the monoglycoside was then successfully condensed with the mycarosyl glycal **257** in the presence of **258**. Dibromohydantoin **258** apparently produces a bromonium ion upon reaction with the glycal, which is in turn intercepted by the free 4' hydroxy

group to afford the bromo disaccharide **259** (11%) and recovered **256** (65%). Acidic cleavage of the acetal and reductive dehalogenation then afforded the synthetic natural product **260b** in 90% yield.

Nicolaou and co-workers have also completed a synthesis of carbomycin B employing a strategy similar to Tatsuta's, as depicted in Scheme 2.22.⁸⁴ Assembly of the C-11 to C-15 fragment began with the known optically active (*R*)-3-



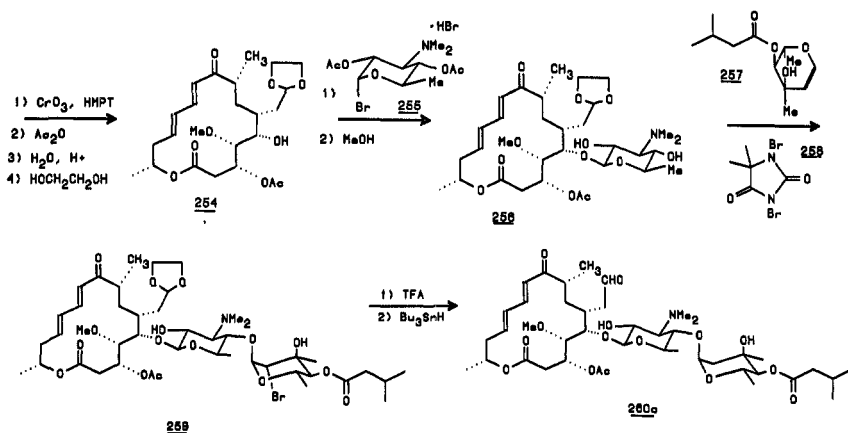
Scheme 2.21. Tatsuta's carbomycin B synthesis.

hydroxybutyric acid (**261**). Esterification and alcohol protection followed by reduction and oxidation gave aldehyde **262** in 49% overall yield. Chain extension via a Wittig condensation followed by a second reduction-oxidation sequence and deprotection yielded **240** (47%).

Construction of the remaining fragment began with the pyranoside **242**. Thus protection of the primary alcohol followed by hydrolysis to the pyranose afforded **263** in 81% yield. Compound **264** was then isolated in 70% yield after chain extension and protection of the 1,3 diol as the acetonide. The stage was now set for the introduction of C-8 and C-9 via a conjugate addition to the unsaturated ester. Although **264** was obtained as a 4:1 ratio (*E:Z*) of olefin isomers, subsequent Michael addition afforded similar results with either isolated isomer. Accordingly, the mixture of olefins was used for preparative purposes. Thus CuI-mediated addition of methallyl lithium gave a mixture of addition products (93:7) in 81% yield, in which the desired **265** predominated.

A series of deprotection, reduction, and reprotection steps provided a 69% yield of silyl ether **226**, which was subjected to a hydroboration-oxidation sequence to afford aldehyde **267** (87%) as a mixture of isomer at C-8. Aldehyde **267** was then converted to the Emmons reagent **268** via a sequence involving addition of lithium dimethyl methylphosphonate, oxidation to the keto phosphonate, deprotection, and oxidation in 65% overall yield.

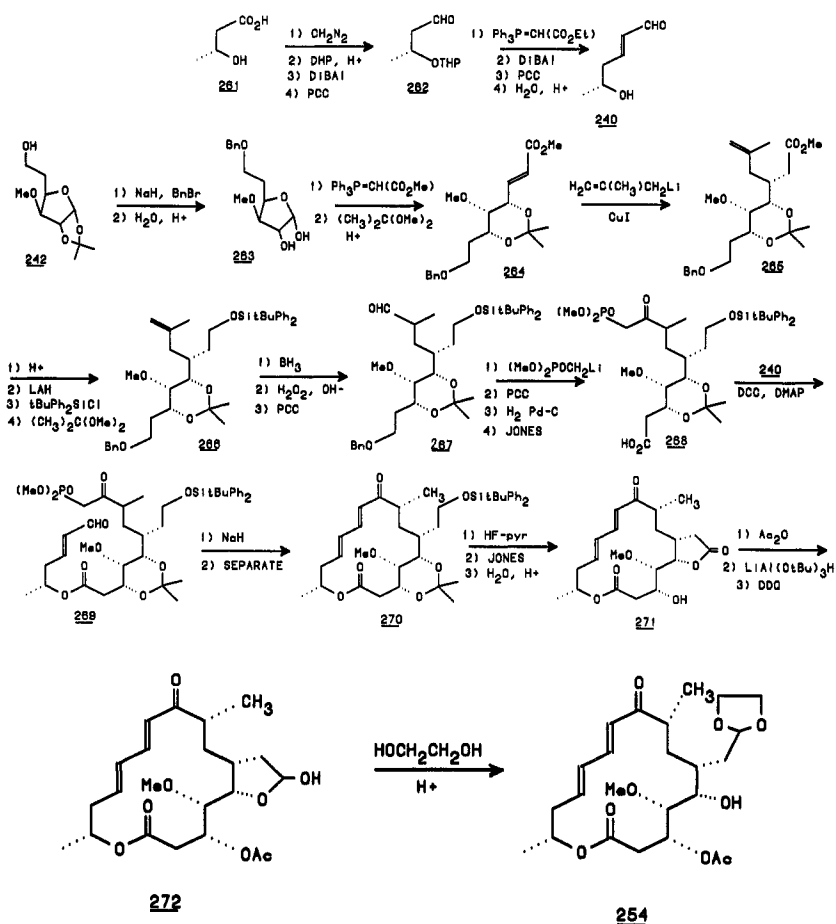
DCC-mediated condensation of hydroxy aldehyde **240** and acid **268** gave the aldehyde ester **269** (70%). An intramolecular olefination followed by chromatographic separation of the desired C-8 diastereomer led to the isolation of the 16-membered ring macrocycle **270** in 20% yield. Desilylation, oxidation, and cyclization then afforded a 47% yield of γ -lactone **271**. Acylation of the C-3 hydroxyl group was followed by reduction of the γ -lactone and C-9 carbonyl.



Scheme 2.21. Continued.

Selective reoxidation of the allylic C-9 alcohol functionality with DDQ then gave lactol **272**. Treatment with ethylene glycol under acidic conditions produced intermediate **254**, which had previously been converted to carbomycin B by Tatsuta.⁸³

The conversion of carbomycin B (**260a**) into leucomycin A₃ (**260b**) had been previously achieved by Tatsuta^{83b} and by Freiberg during prior structural studies on these compounds.⁸⁵ This conversion involved a simple protection–reduction–deprotection sequence.



Scheme 2.22. Nicolaou's carbomycin B synthesis.

H. Protomycinolide IV

Protomycinolide IV (**273**), a 16-membered macrolide, is isolated from the fermentation broth of the microorganism *Micromonospora griseorubida* *sp. nov.*⁸⁶ Unique among the medium-sized macrocyclic lactones, it contains three (*E*)-substituted olefins in addition to six asymmetric centers. The sole synthetic study in this area comes from Yamaguchi's laboratories, as outlined in Scheme 2.23.⁸⁷

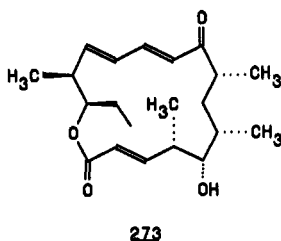
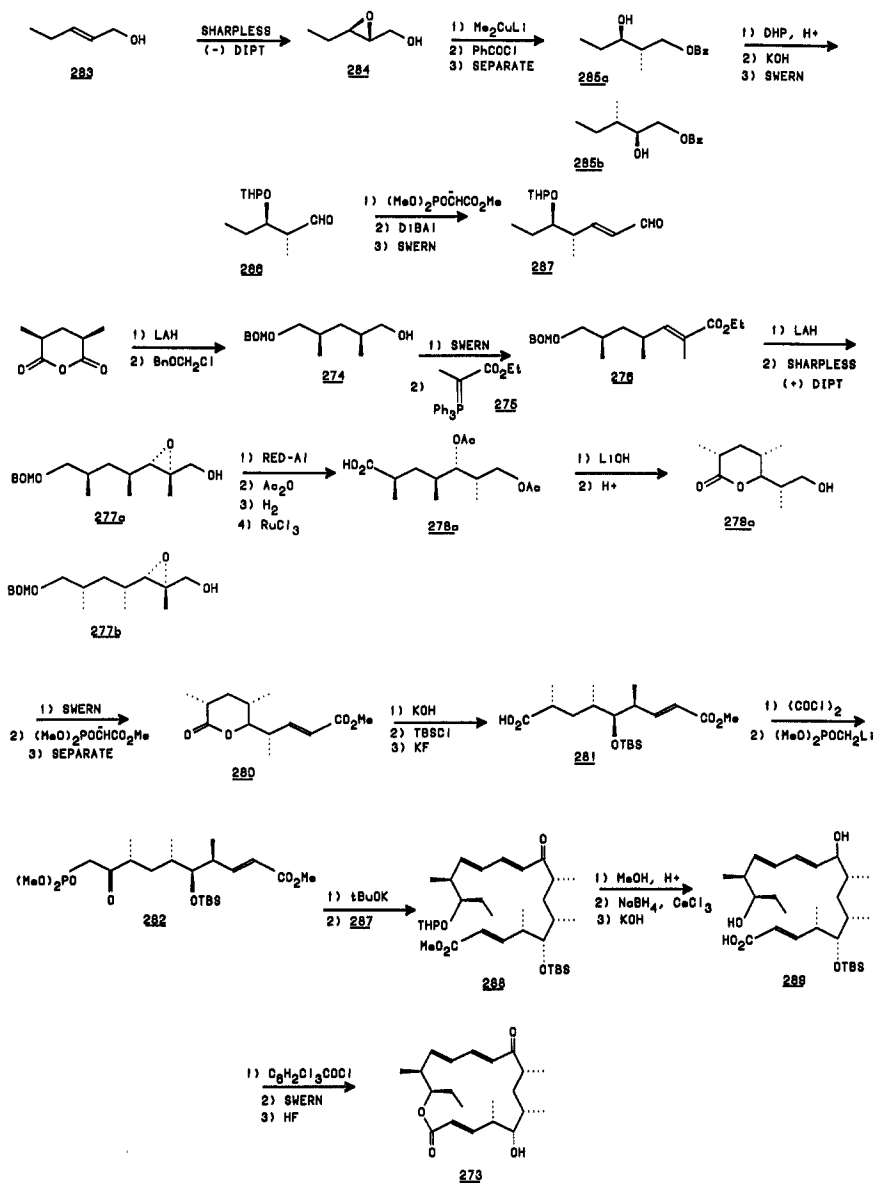


Figure 2.8. Protomycinolide IV (**273**)

Reduction of meso 2,4-dimethylglutaric anhydride and selective monoprotection as the benzyloxymethyl (BOM) ether afforded a 56% yield of **274**. Swern oxidation and condensation with the stabilized Wittig reagent **275** effected conversion to the chain-extended (*E*)-unsaturated ester **276** (90%). Chromatography then removed the small amount (5%) of the undesired (*Z*)-isomer produced. Reduction to the allylic alcohol was followed by an enantioselective epoxidation using (+)-diisopropyl tartrate to give a 1:1 ratio of **277a** and its diastereomer **277b** in 92% overall yield. Although it was possible to separate the diastereomers at this stage, for convenience, purification was performed later in the sequence. Accordingly, the subsequent steps were performed on both **277a** and **277b**; however, for simplification only the products arising from **277a** are shown.

Redal reduction was regioselective in affording a preponderance of 1,3 diols over 1,2 diols (9:1). Acylation and chromatographic purification produced pure 1,3 diacetates. After hydrogenolysis of the BOM group and oxidation, carboxylic acid **278a** was obtained in 86% overall yield. Acetate cleavage and acid-mediated lactonization gave δ -lactone **279a**. Extension of the side chain was accomplished by Swern oxidation followed by condensation with sodium trimethyl phosphonoacetate. Chromatographic purification now permitted separation of the isomer arising from **277b**, to afford pure **280** (41%). Lactone hydrolysis,



Scheme 2.23. Yamaguchi's protomycinolide IV synthesis.

disilylation, and silyl ester cleavage gave a 98% yield of **281**. This intermediate was readily converted in 56% yield to the keto phosphonate **282**, thus completing the C-1 to C-10 segment.

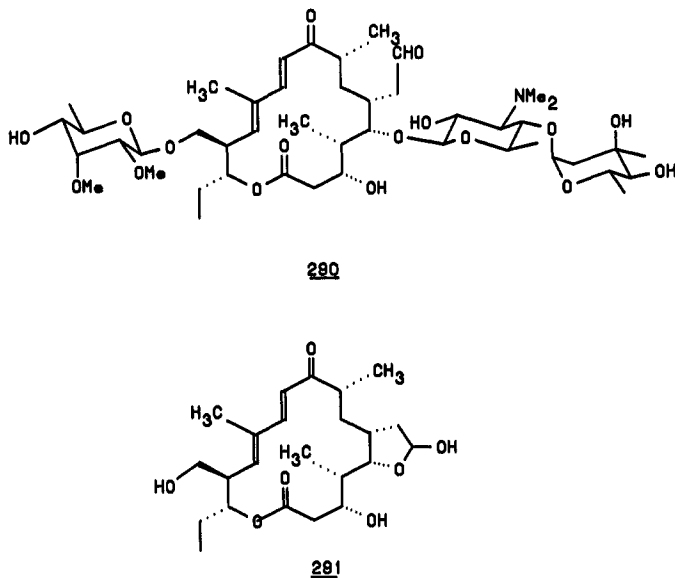
Construction of the C-11 to C-15 fragment began with the Sharpless epoxidation of (*E*)-2-penten-1-ol (**283**). When (–)-diisopropyl tartrate was employed, the resulting epoxide **284** was produced in >95% ee (80%). Opening of this epoxide with lithium dimethyl cuprate was nonregioselective; however, after benzylation of the primary alcohols, the desired **285a** could be obtained after chromatography in 39% yield from **284**. Protection of the secondary alcohol in **285a** as the THP ether followed by benzoate hydrolysis and oxidation then smoothly provided **286** (95%). Finally, chain extension then afforded the required unsaturated aldehyde **287** in 74% yield.

The two segments **282** and **287** were now joined by a Wadsworth–Emmons olefination producing trienone **288**. This intermediate contains all of the required carbons and the proper stereochemical array for the completion of protomycinolide IV (**273**). Hydrolysis of the THP group followed by nonstereoselective C-9 carbonyl reduction and ester cleavage gave the seco acid **289** in 70% yield from **282**. Separately, the C-9 diastereomeric alcohols were subjected to lactonization mediated by trichlorobenzoyl chloride followed by Swern oxidation and desilylation, each producing synthetic **273** in 19% overall yield.

I. Tylosin

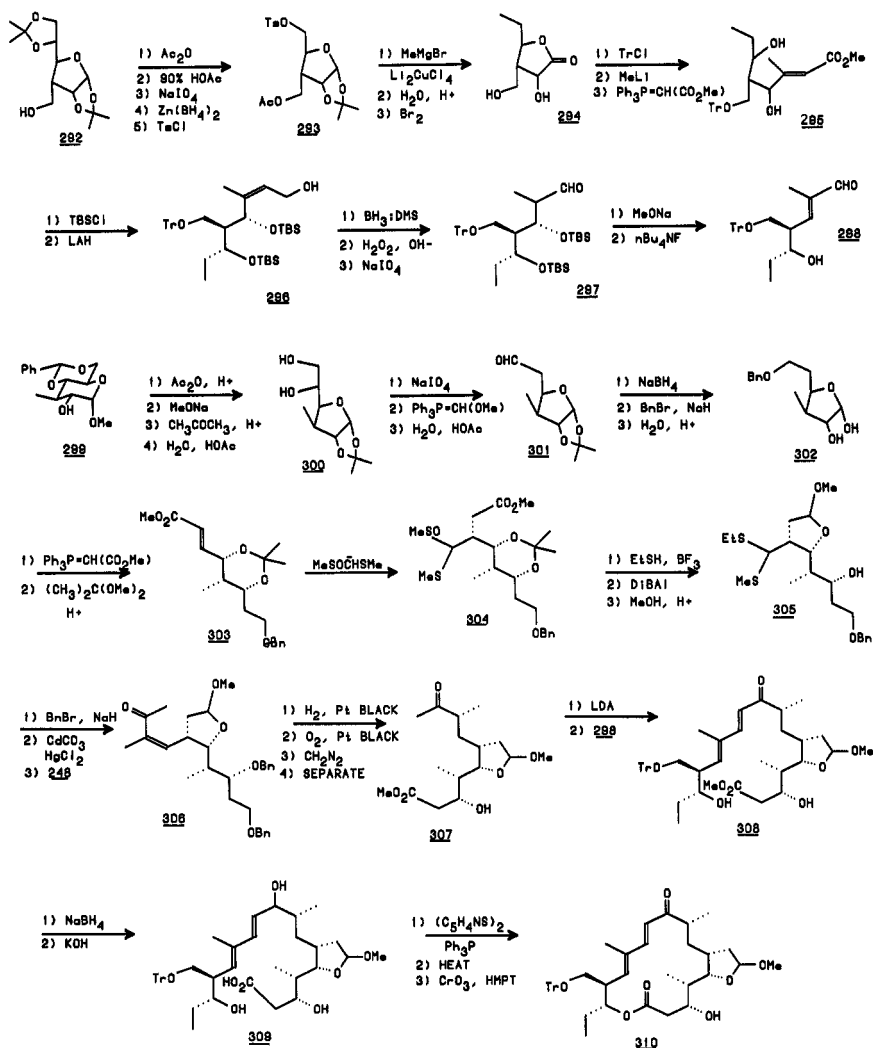
Among the more medicinally important 16-membered ring macrocyclic lactones is tylosin (**290**). This compound enjoys widespread use as a therapeutic agent and is marketed for the treatment of chronic respiratory ailments in chickens. Natural **290** was isolated from the fermentation broth of the microorganism *Streptomyces fradiae* and has several interesting structural features which must be considered in any synthetic approach.⁸⁸ Much like its chemically similar relative leucomycin A₃ (**260a**), tylosin contains the 4'-*O*-(α -L-mycarosyl)-D-mycaminose disaccharide moiety which is attached to the C-5 hydroxyl group. Additionally, tylosin has a mycinose residue attached to the C-14 hydroxymethyl group. Owing to the extraordinary complexity of this natural product, most synthetic efforts have been targeted to the hydrolysis product of tylosin, tylonide hemiacetal (**291**), or a simple derivative thereof.

The initial synthetic study in this area is that of Tatsuta and closely mimics his earlier synthesis of leucomycin A₃,⁸³ as can be seen from Scheme 2.24.⁸⁹ D-Glucose was transformed via literature procedures into the allofuranose **292**. Acetylation of **292** followed by selective hydrolysis of the 5,6 acetonide, oxidative

Figure 2.9. Tylosin (**290**) and Tylonide Hemiacetal (**291**)

cleavage of the resulting diol, reduction, and tosylation produced **293** in 80% overall yield. Chain elongation and oxidation to **294** was achieved (69%) via addition of methyl Grignard reagent mediated by Kochi's salt, hydrolysis, and oxidation by bromine. After protection of the primary alcohol as the trityl ether, addition of methyl lithium gave the related hemiketal, which was homologated by means of a Wittig condensation to give a 49% yield of **295**. Bissilylation followed by LAH reduction then afforded a mixture of allylic alcohols **296** (93%). Removal of one carbon was now effected by hydroboration–oxidation followed by glycol cleavage to afford aldehyde **297**. The completed C-11 to C-15 segment **298** was then isolated in 57% overall yield from **296** after β -elimination and desilylation.

Construction of the C-1 to C-10 segment began with the 3-C-methyl-D-glucoside **299** which was available from D-glucose. Following transformation of **299** in 42% overall yield to furanoside **300**, oxidative cleavage to the aldehyde and chain extension provided the homologous aldehyde **301** (92%). This segment was now further elaborated in a fashion analogous to the leucomycin A_3 synthesis.⁸³ Conversion via **302** to the unsaturated ester **303** (73%) was followed by stereospecific Michael addition to afford **304** (79%). Thiol exchange and acetal formation gave **305** (58%), which was then converted to the unsaturated ketone **306** (77%). Transformation to **307** (52%) and its (8*S*)-epimer (27%) set the stage for the coupling of the two fragments.



Scheme 2.24. Tatsuda's tylonide synthesis.

Aldol condensation between ketone **307** and aldehyde **298** afforded the (*E,E*)-dienone **308** in 41% yield. Nonselective reduction of the C-9 ketone and base hydrolysis then produced a 77% yield of the seco acids **309**. Lactonization utilizing the Corey thiopyridyl ester method and selective oxidation of the C-9 allylic hydroxyl group afforded the protected aglycone **310** in 59% yield.

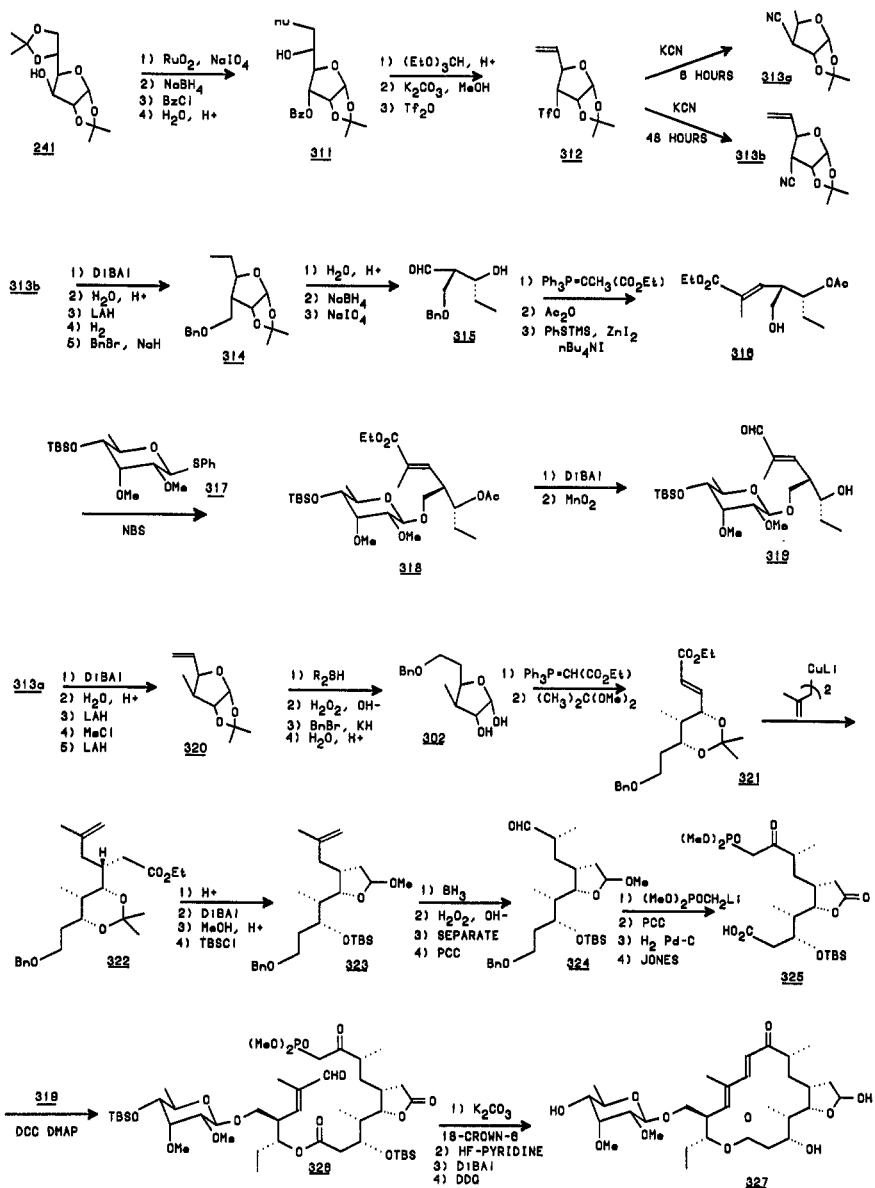
Nicolaou and co-workers successfully prepared a tylonide derivative with the mycinose sugar attached to the proper position on the lactone ring (Scheme

2.25).⁹⁰ The strategy utilized was similar to Tatsuta's in that two major fragments corresponding to C-1 to C-10 and C-11 to C-15 were prepared and joined. Construction of the segments was similar to the Nicolaou synthesis of leucomycin A₃.⁸⁴

Thus glucose diacetone (241) was oxidized and reduced, thereby inverting the C₃ hydroxyl group. Protection of the C-3 hydroxyl group followed by selective acetone cleavage produced 311. Transformation of diol 311 to the olefin followed by benzoate hydrolysis and conversion to the triflate gave 312 in 35% overall yield from 241. Cyanide displacement of the triflate led to the isolation of the kinetic product 313a (80%). If, however, the reaction was allowed to continue for a longer period of time, it was possible to isolate, after a chromatographic separation, the thermodynamic α -cyanide 313b in 60% yield. The latter isomer was then converted into the C-11 to C-15 segment as follows.

The cyanide group was transformed into the analogous hydroxymethyl group, which was then protected following hydrogenation of the olefin to afford a 66% yield of 314. Hydrolysis of the acetone and reduction gave the corresponding triol which was oxidatively cleaved in 92% to the hydroxy aldehyde 315. Chain extension to the (*E*)-unsaturated ester and protecting-group exchange gave the desired carbon fragment 316 in 63% yield. Mycinose derivative 317, prepared from L-(+)-rhamnose, was then condensed with 316 in the presence of NBS to give pyranoside 318. Although isolated as 3:2 mixture of β : α anomers, the desired β compound could be secured after a separation in 50% yield. Conversion to the unsaturated aldehyde 319 then completed the synthesis of the C-11 to C-15 fragment with the carbohydrate unit in place.

Kinetic cyanide addition product 313a was now employed in the construction of the remaining segment for the tylosin synthesis. Accordingly, 313a was subjected to successive reduction, mesylation, and reduction to provide the C-3 methyl compound 320 in 55% overall yield. Hydroboration of the olefin followed by protection of the resulting alcohol and acetone hydrolysis gave 302 (an intermediate also employed by Tatsuta) in 90% yield. From this point on, the route employed follows the Nicolaou leucomycin A₃ synthesis.⁸⁴ Formation of the (*E*)-unsaturated ester 321 (82%) and subsequent Michael addition gave a 5:1 mixture of C-6 stereoisomers 322 (84%). Formation of the acetal 323 (51%) and hydroboration followed by chromatography led to the isolation of pure 324 (70%), possessing the required (*R*)-configuration at C-8. This intermediate was smoothly transformed to keto phosphonate 325 in 92% yield. Esterification of 325 with the hydroxy aldehyde 319 gave the cyclization precursor 326 in 88% yield. Intramolecular Wadsworth-Emmons condensation using anhydrous K₂CO₃ and 18-crown-6 in toluene afforded an 80% yield of the macrocycle without epimerization at C-8. The final conversion to *O*-mycinoyl-tylosin (327) was accomplished by Dibal reduction followed by selective oxidation at C-9 with DDQ (76%).



Scheme 2.25. Nicolaou's tylonide synthesis.

Masamune has also completed a synthesis of tylonide hemiacetal (**291**) based on the creative use of enantioselective aldol condensations, as shown in Scheme 2.26.⁹¹ The aldol condensation of **328**, derived from (*R*)-hexahydromandelic acid and propanal, was found to be >100:1 diastereoselective, affording the 2,3 *syn* compound **329** in 97% yield. Transformation to the β,γ -unsaturated ester **330** occurred via selenoxide elimination and periodate cleavage followed by esterification. Formation of the silyl ether, reduction, and protection of the ester followed by ozonolysis of the terminal olefin gave the diol-protected aldehyde **331**. The C-11 to C-15 segment **332** was then completed via chain elongation and a subsequent reduction–oxidation sequence in 34% overall yield from **330**.

Construction of the remaining fragment began with 4-benzyloxybutyric acid **333**, derived from γ -butyrolactone. Alkylation of the dianion with methallyl chloride followed by reduction and oxidation gave the aldehyde **334** (70%). Condensation with the (*S*)-boron enolate reagent **106b** produced solely **335** and its epimer at the benzyloxyethyl sidechain in 80% combined yield. Chromatographic separation then allowed isolation of pure **335**. Silylation of the free hydroxyl group followed by hydroboration with the chiral hydroborating reagent (–)-bis(isopinocampheyl)borane and oxidation gave exclusively the primary alcohol **336** in 90% yield. It should be mentioned that if the same hydroboration–oxidation sequence was repeated employing 9-BBN, a mixture of epimers was produced. Fortunately, the “chiral environment” present in **335** exerts little if any negative effect at the hydroboration site. Additionally, this high degree of selectivity (>50:1) with a methallyl type substrate is rare, indeed this selectivity may be the result of a superposition of the effects of both the “environment” and the chiral reducing reagent. Selective removal of the triethylsilyl group with acid, followed by oxidation with Fetizon’s reagent, gave the desired lactone **337** (70%). Desilylation, ketone reduction, and glycol cleavage then effected degradation of the side chain and removal of the superfluous chiral auxiliary, affording **338** in 73% yield.

A second aldol condensation was now required to set the stereochemistry at the pro C-3 hydroxyl group. Thus condensation of chiral boron enolate **339** with aldehyde **338** led to the isolation of **340** and its epimer (at what will become C-3) in a 4:1 ratio in 80% yield. Intermediate **340** was carried forward by oxidative removal of the chiral auxiliary, benzyl group hydrogenolysis, exhaustive silylation, and cleavage of the silyl ester to **341** in 80% yield. Protection of the carboxylic acid as the *t*-butyl thioester and selective cleavage of the primary silyl ether gave **342** (68%). Collins oxidation followed by acid treatment produced the corresponding lactol involving the C-5 alcohol and the acetaldehyde sidechain. Methanolysis then gave acetal **343** in 84% overall yield. Activation of the C-9 carboxyl group and addition of trimethylsilylmethyl lithium gave the required C-1 to C-10 fragment **344** in 60% yield.

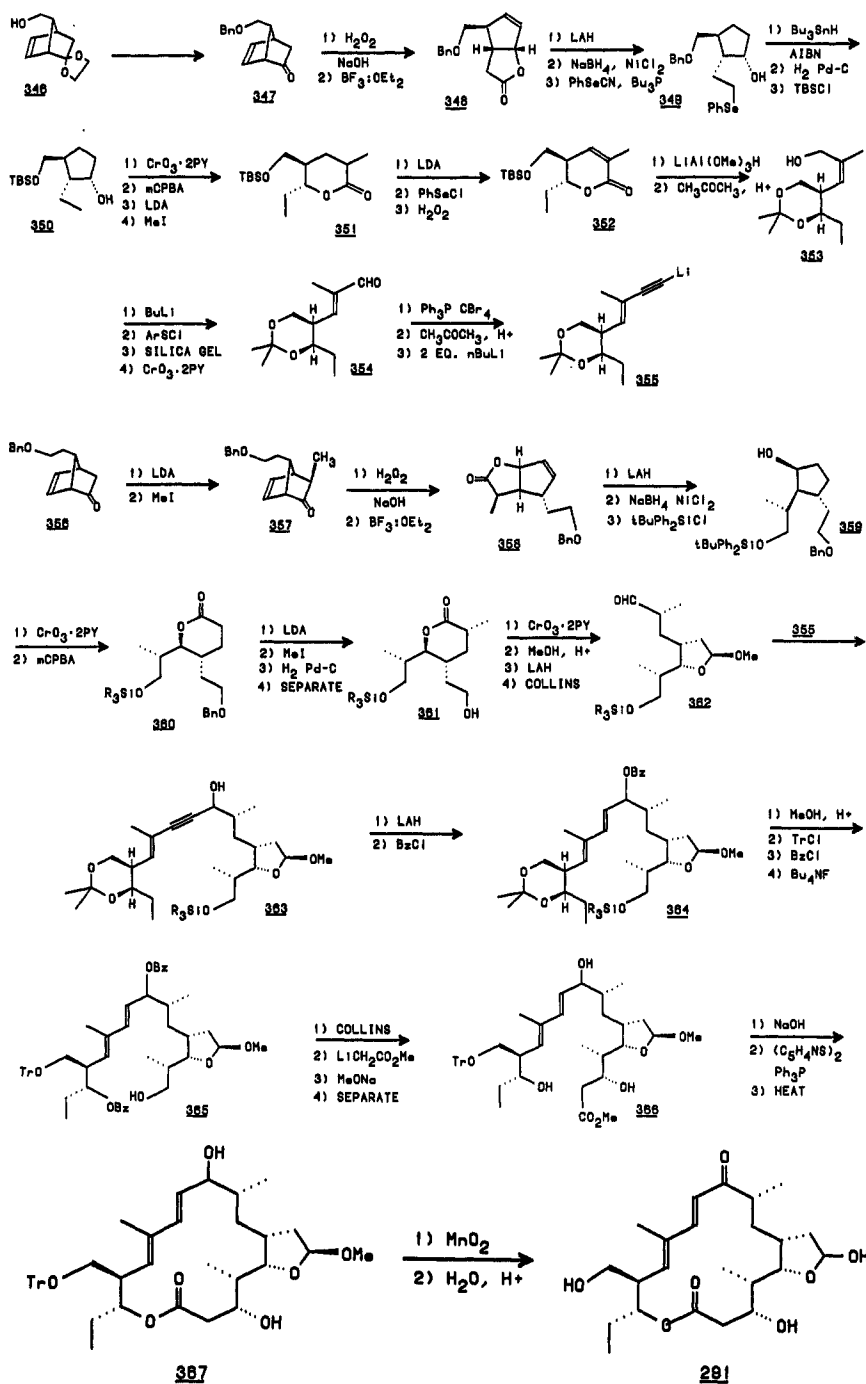
The two segments were then connected via a Peterson olefination involving the lithium anion of **344** and aldehyde **332** to give the required (*E,E*)-dienone. Thioester cleavage followed by desilylation gave seco acid **345** in 50% overall

yield from **344**. Lactonization was then effected via the mixed phosphoric anhydride followed by desilylation to give tylonide hemiacetal (**291**) in 32% yield.

The final endeavor in this area was reported by Grieco.⁹² By employing a series of chemical manipulations beginning with the common intermediate, bicyclo[2.2.1]heptane **346**, Grieco was able to construct both the C-1 to C-9 and C-10 to C-15 segments as shown in Scheme 2.27. Thus enantiomerically pure **346** was protected and hydrolyzed to give **347** (87%). A Baeyer–Villiger oxidation followed by $\text{BF}_3\text{--Et}_2\text{O}$ mediated lactonization gave an 89% yield of **348**. Lactone **348** was then subjected to hydride reduction, *in situ* hydrogenation, and replacement of the primary alcohol with phenylselenide to afford **349** (70%). Reductive deselenation and exchange of the benzyl ether for a silyl ether gave **350**. Introduction of the pro C-15 hydroxyl was then accomplished via oxidation of the secondary alcohol to the corresponding ketone and Baeyer–Villiger oxidation. Alkylation with methyl iodide then gave **351** in 74% overall yield. This substance was readily converted to the olefin **352** by means of alkylation with phenylselenenyl chloride and oxidative elimination. Subsequent reduction of the lactone concomitant with silyl ether cleavage and acetone formation from the 1,3 diol gave **353**, which possesses the wrong olefin geometry. This problem was remedied by equilibration via a sulfenate ester–sulfoxide interconversion and subsequent oxidation to give **354**. Homologation of aldehyde **354** was then accomplished via the intermediate terminal dibromide providing the nucleophilic C-10 to C-15 subunit **355**.

The remaining fragment encompassing C-1 to C-9 was constructed from **356** available from **346** by a one-carbon homologation. Alkylation of **356** with methyl iodide occurred exclusively from the *exo* face to give a 74% yield of **357**. Following the sequence previously documented for **347**, Baeyer–Villiger oxidation and rearrangement gave **358**, which was then subjected to successive reductions and protection to afford **359**. Oxidation of alcohol **359** to the corresponding ketone and a second Baeyer–Villiger reaction then provided the δ -lactone **360**. Alkylation of **360** with methyl iodide then gave a 1:1 mixture of two epimeric lactones which were debenzylated and separated to afford a 47% yield of **361**, which has the required (*R*)-configuration at the pro C-5 center. As had been observed by Masamune,⁹¹ oxidation of the hydroxy ethyl sidechain in **361** to the corresponding aldehyde resulted in cleavage of the lactone and formation of the cyclic hemiacetal with the C-5 hydroxyl. Formation of the related mixed methyl acetal followed by conversion of the acid to the aldehyde **382** (82% from **361**) then completed the C-1 to C-9 segment.

Addition of lithium reagent derived from **355** to **382** produced a 1:1 mixture of adducts **363** in 75% yield. As this pro C-9 center will later be oxidized to the ketone, this mixture is of no consequence. LAH reduction of the propargyl alcohol followed by protection of the C-9 hydroxyl as the benzoate gave a 73% yield of the (*E,E*)-diene **364**. The primary and secondary alcohols, freed by cleavage of the acetone, were protected as the trityl ether and benzoate, respectively, followed by desilylation to afford **365**. The required two-carbon unit



Scheme 2.27. Grieco's tyloside hemiacetal synthesis.

corresponding to C-1 to C-2 was introduced via Collins oxidation to the aldehyde and addition of lithio methyl acetate. Unfortunately, this condensation was completely stereorandom, affording a 1:1 mixture of C-3 stereoisomers. Cleavage of the benzoates in the resulting β -hydroxy esters, and a chromatographic separation, gave the triols **366** (mixture at C-9) in 30% yield from **365**. Hydrolysis to the seco acid followed by lactonization via the Corey procedure gave the macrocyclic diols **367** in 19% yield. Conversion to tytonide hemiacetal (**291**) was then accomplished (80%) by selective oxidation of the allylic alcohol and acetal hydrolysis.

J. Milbemycin β_3

Milbemycin β_3 (**383**) is a 16-membered macrocyclic lactone isolated from the fermentation broth of *Streptomyces B-41-146* and is the simplest member of a family of compounds structurally related to the avermectins.⁹³ Milbemycin β_3 has been demonstrated to have marked insecticidal as well as limited antibiotic activity. Structurally, **383** is a 16-membered lactone fused to an aromatic ring. Although nearly devoid of asymmetric centers on the cyclic framework, it does contain the rather unusual spiroketal moiety.

The first synthesis of this compound to be completed was the result of studies by Smith and co-workers in 1982.⁹⁴ The readily available flavor constituent cycлотene (**368**) (Scheme 2.28) was reduced and isomerized to 2-methyl-2-cyclopenten-1-one (**369**) in 64% yield. Addition of dimethyl cuprate followed by isomerization and Baeyer–Villiger oxidation gave the racemic δ -lactone **370** (86%). Addition of allyl Grignard reagent followed by formation of the methyl ketal provided a 71% yield of **371**, which possesses the expected axial methoxy group. Conversion of the terminal olefin into the functionalized isoxazoline **373** was accomplished in 68% by the 1,3 dipolar cycloaddition of nitrile oxide **372**.

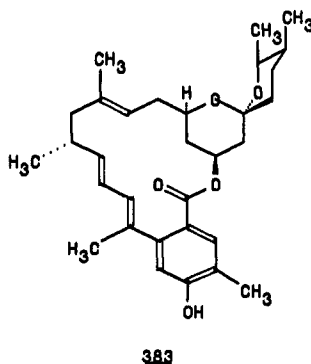
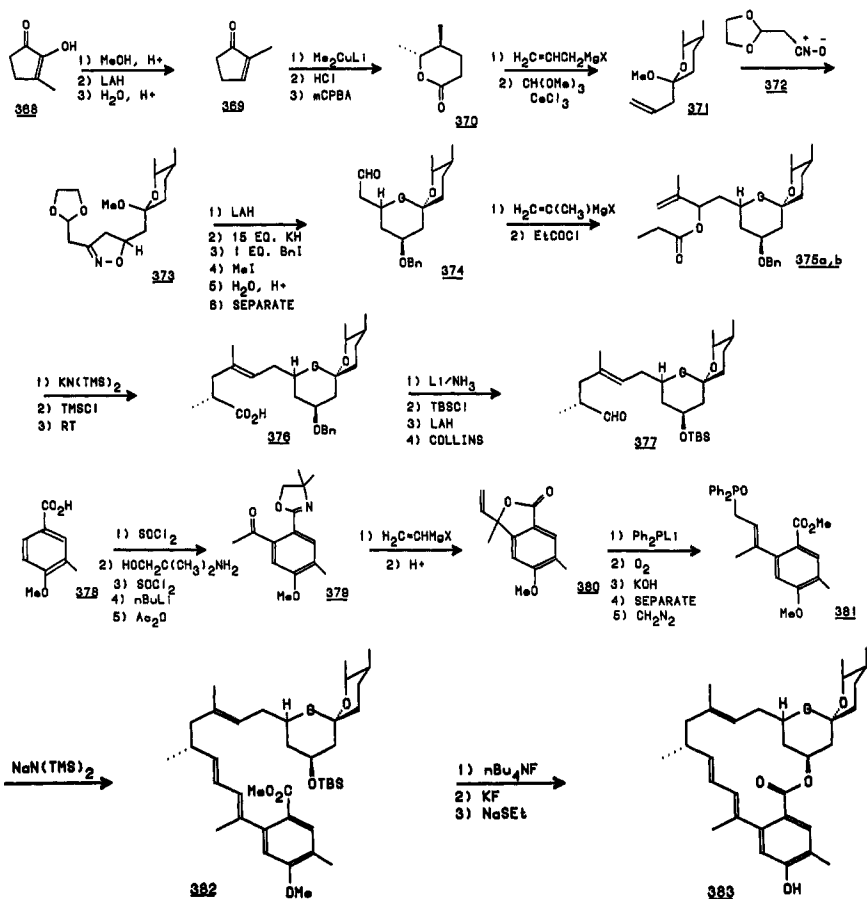


Figure 2.10. Milbemycin β_3 (**383**)

Lithium aluminum hydride reduction then gave a mixture of four diastereomeric aminols, which were selectively alkylated on oxygen with benzyl iodide. Quaternization of the nitrogen with methyl iodide, hydrolysis, and chromatography then gave the spiroketal **374** in 20–23% yield from **373**. Treatment of spiroketal **374** with isopropenyl Grignard reagent followed by quenching with propionyl chloride gave a 2:1 mixture of diastereomeric propionates **375** in 71% yield. Chromatographic separation of the minor isomer **375a** and subsequent Ireland enolate–Claisen rearrangement furnished the desired α -methyl acid **376** in 54–57% yield. Conversion to the C-7 to C-15 spiroketal fragment **377** was then accomplished by exchange of the benzyl ether for a silyl ether and conversion of the carboxylic acid to the corresponding aldehyde in 59% overall yield.



Scheme 2.28. Smith's milbemycin β_3 synthesis.

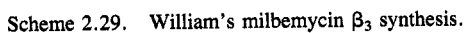
The C-1 to C-6 fragment containing the aromatic ring was constructed from 3-methyl-*p*-anisic acid (**378**). Thus transformation to the oxazoline permitted metalation at the *ortho* position and acylation gave the functionalized acetophenone **379** (50%). Addition of vinyl Grignard reagent and subsequent acid treatment furnished the lactone **380** (84%). A sidechain must now be elaborated that will permit introduction of the aldehyde segment **377**. This transformation was accomplished via S_N2 displacement at the terminal position with lithium diphenylphosphide and subsequent oxidation to the phosphine oxide with oxygen. Although the configuration of the newly created olefin was predominately (*Z*), the (*Z*)-isomer could be converted to a 1:1 (*E*:*Z*) mixture by heating with strong base. Methyl ester formation after isolation of the (*E*)-isomer then provided the C-1 to C-6 fragment **371**.

Fusion of the two pieces was accomplished by deprotonation of the phosphine oxide and condensation with **377** to give an 85–95% yield of a mixture of dienes **382**, with the (*E,E*)-diene predominating (7:1). The synthesis of milbemycin β_3 was then completed by desilylation and lactonization followed by cleavage of the methyl ether to furnish racemic **383** in 65% yield.

The second published synthesis to date in this area is from Williams's group at Indiana, as shown in Scheme 2.29.⁹⁵ Starting with (–)-citronellol (**384**), dehydration of the alcohol and oxidation of the trisubstituted olefin produced the carboxylic acid **385**. Iodolactonization followed by reductive dehalogenation then gave (+)-**370** in 40% overall yield (cis:trans 1:15). (*R*)-Sulfoxide **386**, available from (+)-glyceraldehyde acetonide, was deprotonated and condensed with lactone **370** to afford **387** as a mixture of diastereomers at the C—S bond. Internal ketalization provided the spiroketal **388**, which led to **389** after protection of the primary alcohol as the benzoate and thermal elimination of the sulfoxide. Functionalization of the relatively unreactive olefin in **389** was then accomplished by conversion to the halohydrin with aqueous *t*BuOCl and reductive dehalogenation providing the epimeric alcohols **390a** and **390b** (5:1). The undesired **390a** could readily be converted to **390b** in 70% yield via an oxidation–reduction sequence. Protection of the secondary alcohol of **390b** as the silyl ether followed by benzoate cleavage and oxidation gave the C-12 to C-15 spiroketal fragment **391**.

Construction of the acyclic segment **395** was initiated by conversion of (–)-citronellal (**392**) into bromo aldehyde **393**. Formation of the unsaturated aldehyde via the intermediate enamine was followed by reduction to the allylic alcohol **394**. Elimination of the vinyl bromide in **394** to the acetylene was followed by the addition of trimethylaluminum to give the terminal vinyl alane. The intermediate alane was then quenched with iodine to furnish the corresponding iodo-vinyl alcohol, which was protected as the THP ether to afford **395**.

The two segments were joined by addition of the lithium reagent derived from halogen–metal exchange of iodide **395** to aldehyde **391** to produce a mixture of diastereomeric alcohols **396**. As simple reductive deoxygenation proved



troublesome, the alcohols **396** were transformed into the corresponding xanthates which, via an *in situ* [3,3] sigmatropic rearrangement, gave solely the (*E*)-olefinic thiocarbonates **397**. Reductive cleavage of the mixture of thiocarbonates, followed by deprotection and oxidation of the primary alcohol gave enal **398**. Introduction of the aromatic residue was accomplished by the addition of the dianion **399** and subsequent lactonization to give the δ -lactone **400**. Desilylation and elimination then provided seco acid **401**, which was then converted to optically pure synthetic milbemycin β_3 (**383**) by cyclization and cleavage of the MOM ether.

3. POLYCYCLIC MACROLIDES

A. Cytochalasins

The cytochalasins are an extraordinarily interesting class of compounds from both a chemical and biological point of view.⁹⁶ Produced by a number of organisms, these substances have profound biological activity ranging from the inhibition of cytoplasmic cleavage in mammalian cells to the mediation of platelet aggregation and release of growth hormones.

The only syntheses of members of the cytochalasin class that contain a macrocyclic lactone come from the Stork group at Columbia. The first of these studies resulted in the synthesis of cytochalasin B (**20**) by clever elaboration of the stereochemical centers at the two bridgehead positions as well as at C-5 and C-8 by means of a Diels–Alder cycloaddition (Scheme 3.1).⁹⁷

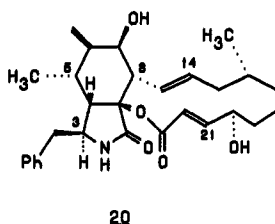
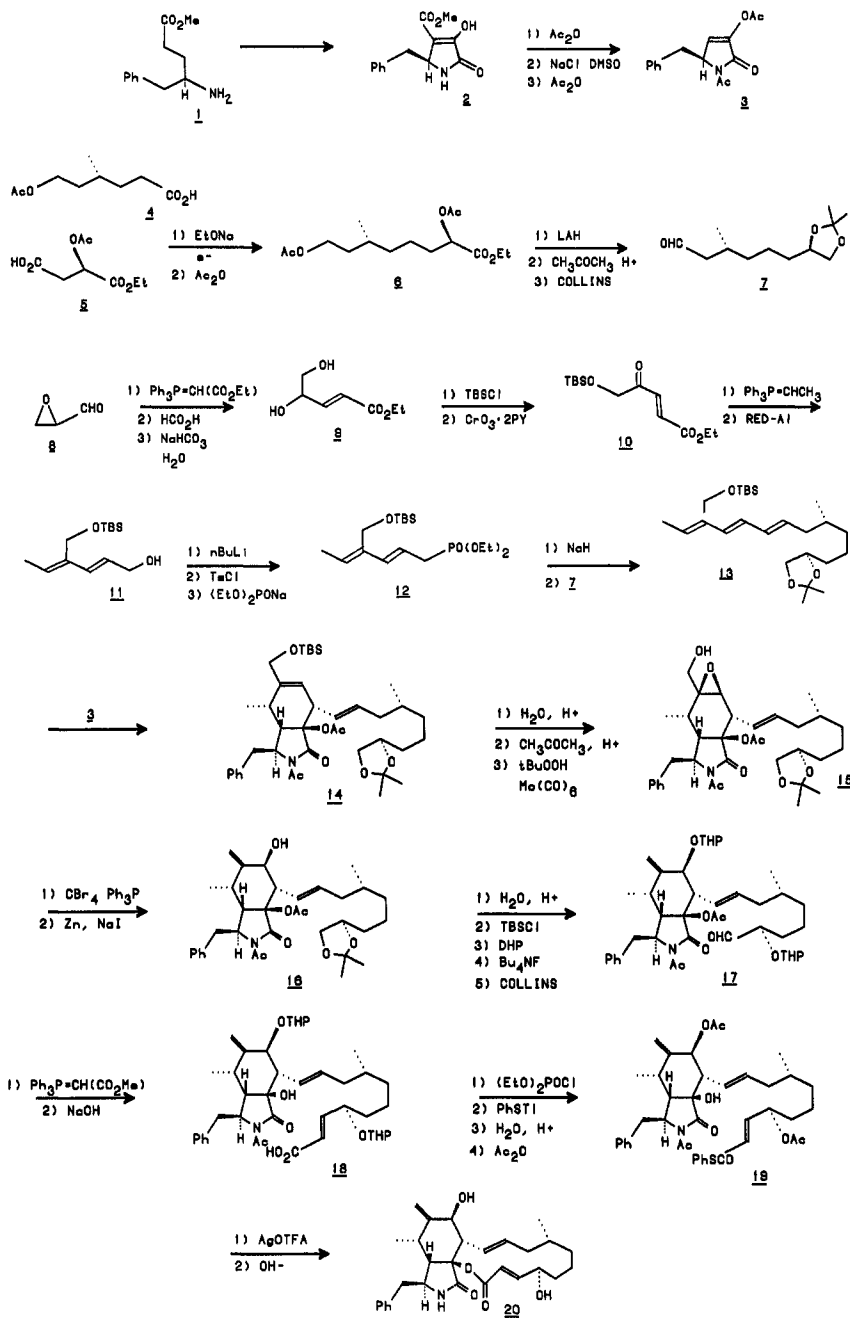


Figure 3.1. Cytochalasin B (**20**)

The tetrahydropyrrole moiety was constructed from amino ester **1**, available by an Arndt–Eistert homologation of a protected L-phenylalanine. Conversion by previously described chemistry then provided **2**, which was transformed to **3** by acylation, decarboalkoxylation, and reprotection.

The macrocyclic framework was constructed beginning with **4**, available from (+)-citronellol, and **5** obtained from (+)-malic acid. Kolbe reductive coupling and reacylation then gave the coupled ester **6** in 42% yield. Reduction of this material to the triol followed by protection of the 1,2 diol as the acetone and Collins oxidation gave the desired aldehyde **7**.



Scheme 3.1. Stork's first cytochalasin B Synthesis.

Construction of the triene required for the Diels–Alder cycloaddition began with the chain extension of glycinaldehyde (**8**) to the α,β -unsaturated ester and hydrolysis to the diol **9** in 66% overall yield. Selective protection of the primary alcohol as the silyl ether and oxidation of the free secondary hydroxyl group gave the unsaturated keto ester **10** (78%). Ester **10** was condensed with ethylidene triphenylphosphorane and reduced to afford a 66% yield of a mixture of dienes **11**. Upon NMR analysis, this material was established to be a mixture of the desired (*E,E*)- and (*Z,Z*)-isomers (5.7:1). Chromatographic separation led to isolation of the pure (*E,E*)-isomer, which was readily converted to the corresponding phosphonate **12** (73%).

The required chain extension of **12** was accomplished via deprotonation with NaH and condensation with aldehyde **7** to afford the Diels–Alder precursor **13** in 50% yield. Thermolysis of triene **13** and lactam **3** in xylene at 170°C for four days resulted in the desired cycloaddition to **14**. Chromatographic purification permitted isolation of pure **14** in addition to a small amount of an *exo* isomer (>4:1 ratio). Acid treatment induced cleavage of both the silyl ether and acetonide. Reprotection of the diol and selective epoxidation of the $\Delta^{6,7}$ olefin produced **15** in 64% yield from **12**. Epoxide **12** was then transformed to the isomeric allylic alcohol **16** by conversion of the alcohol to the bromide followed by reductive elimination. Protecting-group manipulation and subsequent oxidation gave aldehyde **17**, which was homologated and hydrolyzed to give seco acid **18** in 32% overall yield from **16**.

Masamune, in his studies of lactonization methodology, had previously converted **18** into cytochalasin B (**20**) as follows.⁹⁸ The carboxylic acid moiety was converted to the thioester via the intermediate phosphoric anhydride. Exchange of the THP ethers for acetate groups then led to lactonization precursor **19**. Silver-mediated cyclization (36%) followed by hydrolysis of the acetates afforded synthetic **20**.

The second Stork synthesis employed the same Diels–Alder strategy; however, an intramolecular variant of the cycloaddition was utilized, as shown in Scheme 3.2.⁹⁹

Construction of the pyrrolidine ring began with condensation of α -formyl amine **21**, derived from L-phenylalanine, with the phosphonate reagent **22**. Isolation of the unsaturated lactam **23** followed by protecting-group exchange gave the hydroxypyrrolone **24** in 70% overall yield from **21**.

Synthesis of the acyclic portion began, as in the previous synthesis, with enantiomerically pure citronellol (**25**). Protection of the alcohol as the benzyl ether and oxidative cleavage of the olefin to the aldehyde gave **26** (85%). Chain extension via the masked acyl anion equivalent **27**, alcohol protection, and concomitant β -elimination and isomerization of the allene to the alkyne with butyl lithium gave **28**. The resulting protected ketone must now be converted to the β -alcohol required for the completion of the synthesis. Thus hydrolysis to the ketone followed by enantioselective reduction with (–)-*N*-methylephedrine–



LAH complex provided the desired (*R*)-alcohol in 90% ee. Silylation of the alcohol afforded the desired propargyl ether **29** (59% from **26**). Carboalkoxylation of the terminal alkyne of **26** was then effected in 92% yield to give **30**. Hydrogenation of the triple bond followed by cleavage of the benzyl group and oxidation of the primary alcohol gave the aldehyde **31** (80%). Finally, triene **33** required for the Diels–Alder reaction was obtained in 69% yield by the condensation of aldehyde **31** and phosphonate **32**, derived from tiglic aldehyde, as described in the previous synthesis. Ester hydrolysis and condensation with hydroxypyrrolone **24** using the Mukaiyama method gave the cyclization precursor **34** in 69% yield.

Thermolysis of **24** at 180–190°C for 6 days gave a 35% yield of the desired *endo* product **35a** contaminated with the *exo* isomer **35b**. The ratio of these adducts was quite acceptable (4:1 *endo:exo*). With the basic cytochalasin ring system in hand, what remained was the introduction of the required unsaturation adjacent to the lactone and oxidation of the cyclohexene ring. The former was achieved in 70–76% yield by selenylation followed by oxidative elimination to afford solely the (*E*)-olefin **36**. Hydroxylation was initiated by nitrogen acylation followed by stereo- and regioselective epoxidation of the $\Delta^{6,7}$ olefin. Deacylation and desilylation then afforded cytochalasin F (**37**) in 51% yield. Cytochalasin B (**20**) was obtained in a similar way by isomerization of the intermediate epoxide to the allylic alcohol with aluminum isopropoxide, followed by deacylation and desilylation.

At this point, we diverge slightly from the main focus of this chapter and include two syntheses of large-ring carbocyclic cytochalasins. Although not lactones, these compounds are sufficiently similar to their oxygenated counterparts that their detailed discussion is warranted.

The first of these synthetic efforts arises from work of the Vedejs group at Wisconsin and is depicted in Scheme 3.3.¹⁰⁰ The overall strategy employs the well-documented Diels–Alder sequence for stereocontrol in the cyclohexane ring and a [2,3] sigmatropic rearrangement for construction of the 11-membered carbocyclic rings of cytochalasin D (**51**) and zygosporin G (**52**).

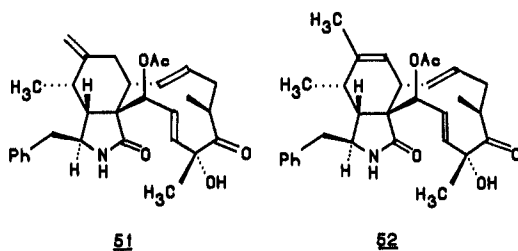
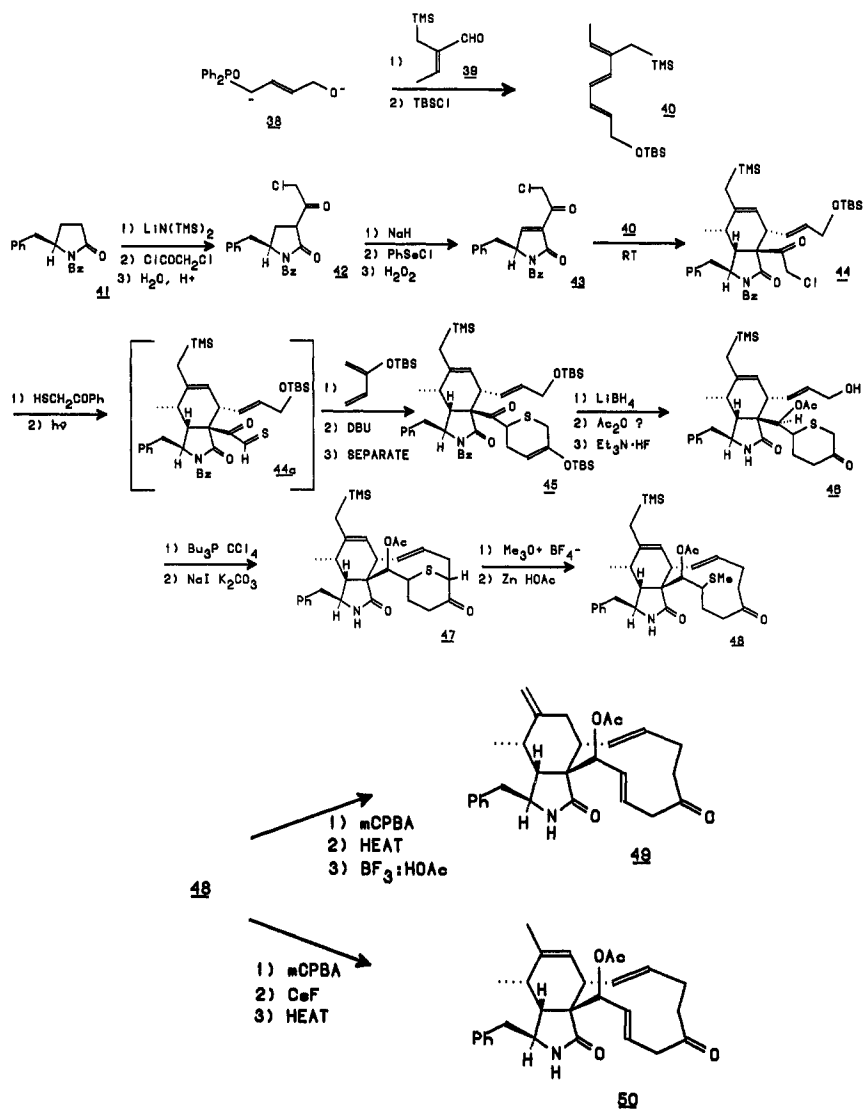


Figure 3.2. Cytochalasin D (**51**) and Zygosporin G (**52**)

Construction of the diene required for the cycloaddition began with the condensation of aldehyde **39**, derived from acrolein and ethyl 3-trimethylsilyl propionate anion, with the phosphine oxide **38**. Silylation then gave the protected trienol **40** in good overall yield.

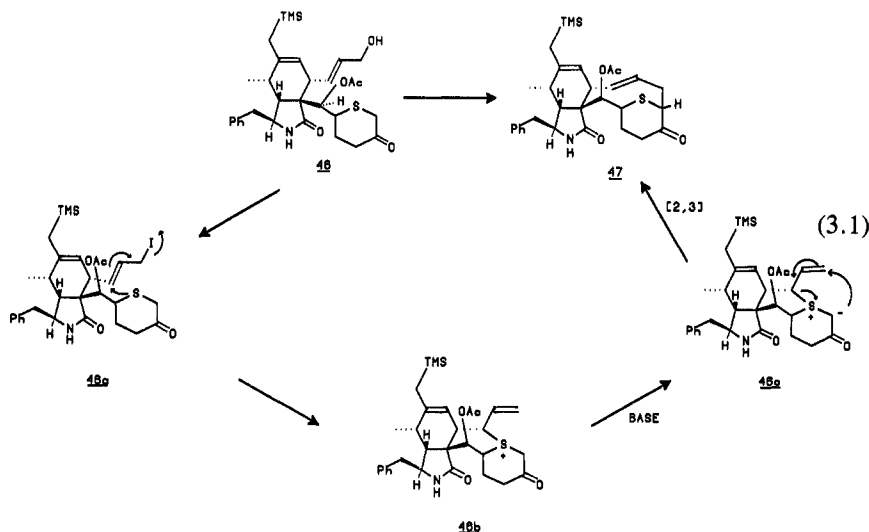


Scheme 3.3. Vedej's cytochalasin D and zygosporin G approach.

Pyrrolidone **41**, obtained by literature procedures from phenylalanine, was acylated adjacent to the amide carbonyl to give **42**, followed by oxidation to the dienophile **43**. The ensuing cycloaddition with diene **40** afforded the functionalized octahydroisindole **44** in 77% yield from **41**. The reaction mixture from the room-temperature Diels–Alder reaction was contaminated with small amounts of an undetermined isomeric by-product (**44**:by-product >15:1). The additional carbons required for the macrocyclic ring were now appended via a cleverly conceived sulfur-ylide ring expansion.

Substitution at the chloromethyl group with phenacyl thiol followed by photolysis gave the highly unstable acyl thioaldehyde **44a**. When this photolysis was done in the presence of the highly reactive diene 2-*t*-butyldimethylsilyloxy-butadiene, the thioaldehyde could be trapped by [4 + 2] cycloaddition to provide, after equilibration and chromatography, a 53% yield of **45**. Reduction of ketone **45** with LiBH_4 resulted in concomitant cleavage of benzamide. Subsequent removal of the silyl groups with fluoride afforded a 50–60% yield of **46**. Ring expansion then provided a 60% yield of the tetracyclic ketone **47**, as a diastereomeric mixture (at the newly created bridgehead center) of (*E*)-olefins, thus establishing the crucial (*E*)-geometry of the large-ring olefin.

The latter, a key step in the Vedejs synthesis, does not occur by the obvious pathway involving intramolecular alkylation, but rather through a [2,3] sigmatropic rearrangement, as shown in Eq. 3.1. Conversion of **46** to the allylic iodide **46a** via the intermediate chloride sets the stage for $\text{S}_{\text{N}}2'$ alkylation at sulfur, producing the allylic sulfonium salt **46b**. Deprotonation follows to ylide **46c**, which undergoes rapid [2,3] sigmatropic rearrangement to produce **47**.

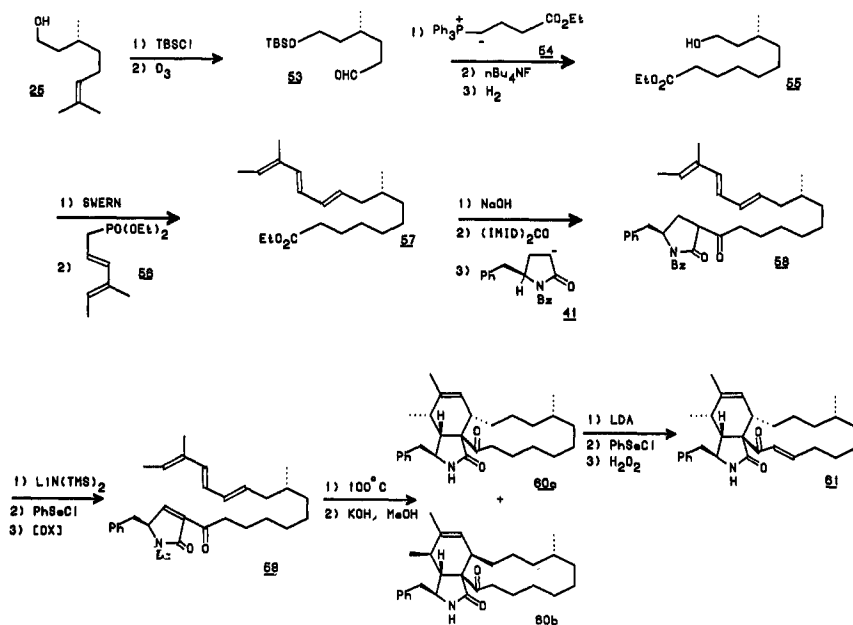


Methylation of the sulfur produced a second sulfonium salt which was reduced with zinc to afford a 92% yield of the 11-membered carbocycle **48**. Oxidation of the sulfide to the sulfoxide and pyrolytic elimination gave solely the (*E*)-olefin geometry. Finally, treatment with $\text{BF}_3\cdot\text{HOAc}$ induced desilylation with double-bond migration to give **49** (72%), possessing the cytochalasin D ring system.

Alternatively, oxidation of the sulfide to the sulfoxide followed by desilylation without allylic migration using CsF and sulfoxide pyrolysis gave **50**, having the zygosporin G ring system in 63% yield.

The second synthesis, that of the carbocyclic cytochalasin proxiphomin (**61**) by Thomas, is described in Scheme 3.4.¹⁰¹ The strategy is rather similar to the second synthesis of cytochalasin B by Stork with the necessary modifications.

The route began with (+)-citronellol (**25**), which was protected as the silyl ether and ozonolyzed to afford aldehyde **53** (83%). Chain extension using the Wittig reagent **54** was followed by silyl ether cleavage and hydrogenation of the olefin to give a 60–80% yield of **55**. Swern oxidation and subsequent olefination with phosphonate anion **56** then gave the diene portion of the Diels–Alder precursor **57** (52%), contaminated with less than 5% of the *cis* olefin at the newly created double bond. Cleavage of ester to the acid was followed by activation of the carboxyl group as the acyl imidazolide. Treatment of this acylating agent with the lithium anion of pyrrolidone **41** then gave the β -decarbonyl compound **58** in 54–72% yield. Introduction of the double bond was



Scheme 3.4. Thomas's proxiphomin synthesis.

then effected via a selenylation–oxidation sequence to give the Diels–Alder precursor **59** (60–70%).

Thermolysis at 100°C produced a nearly 1:1 mixture of *endo* and *exo* cyclization products in 50–55% yield. Hydrolysis of the benzoyl group then gave the chromatographically separable *endo*-**60a** and *exo*-**60b** isomers in 75% yield. Completion of the synthesis of proxiphomin (**61**) was achieved by a selenylation–oxidation sequence on the *endo* diastereomer **60a**.

B. Hybridalactone

The marine alga *Laurencia hybrida* produces a compound that has been isolated and characterized as hybridalactone (**73**).¹⁰² Structurally, this compound contains a 13-membered lactone ring fused to a cyclopentane ring. The macrocyclic ring, in addition to containing two (*Z*)-olefins, has a substituted cyclopropane ring appended α to the lactone oxygen.

The sole synthesis of hybridalactone (**73**) is due to Corey at Harvard.¹⁰³ The synthesis involved the use of the novel bicyclo[2.2.2]octyl ortho esters beginning with **62** (Scheme 3.5). This material, obtained from 5-hexynoic acid, was converted via the homologous trimethylsilylmethyl acetylene into allenic iodide **63** in 75% overall yield.

Enantiomerically pure (+)-**64**, available from the racemate by recrystallization of the diastereomeric bisulfite complexes with (–)- α -phenylethylamine, was converted to the (*Z*)-enol tosylate **65** (49%). This material was separated from the corresponding (*E*)-olefin (3%) and starting material **64** (19%) by chromatography. Condensation of **65** with optically active *cis*-2-ethylcyclopropyl lithium (**66**) afforded a single cyclobutanol **67** in 76% yield. Fragmentation to the desired *trans*-disubstituted cyclopropane ring was induced by addition of tetrabutylammonium fluoride, which also served to equilibrate the initially formed *cis* compound to a mixture of **68b** to **68a** (9:1) in a combined yield of 86%. The less stable **68a** could readily be equilibrated to the mixture (9:1) of **68a,b** by treatment with carbonate in methanol.

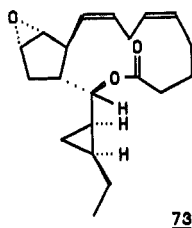
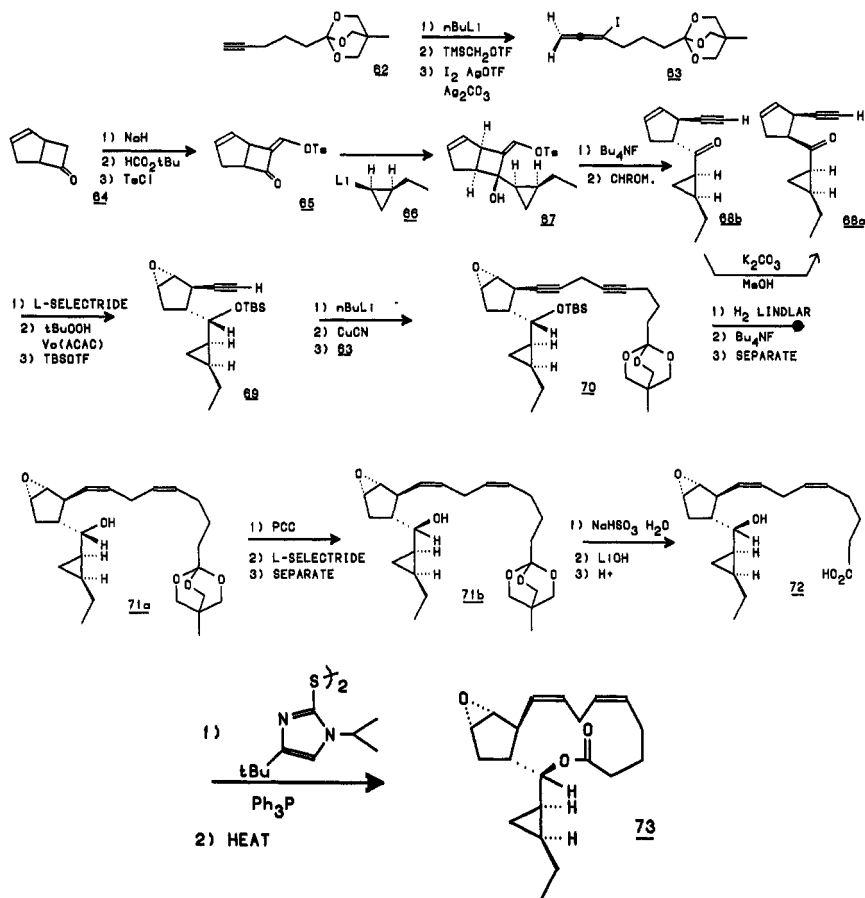


Figure 3.3. Hybridalactone (**73**)



Scheme 3.5. Corey's hybridalactone synthesis.

Reduction of **68a** with L-selectride gave a 6:1 mixture of cyclopropyl carbinols in 92% with the (*R*)-alcohol predominating. Highly stereoselective hydroxyl-directed epoxidation from the α -face of the cyclopentane ring followed by silylation of the alcohol gave **69** (contaminated with a small amount of the product derived from the *S*-alcohol) in 84% yield. This intermediate was then coupled with the allenyl iodide **63** via the cuprate of **69** to afford an 86% yield of the diyne **70**. Partial reduction of the alkynes followed by desilylation and chromatography afforded **71a** and **71b** in 79% and 13% yields, respectively. Conversion of the undesired major (*R*)-isomer **71a** into the minor (*S*)-compound was accomplished via an oxidation-reduction sequence to provide **71b** in 75% yield contaminated with 16% of the (*R*)-**71a**. Orthoester **71b** was then cleaved

to the seco acid **72** (96%), which upon lactonization via the intermediate 2-thioimidazole thioester produced synthetic **73** in 83% yield.

4. MACROCYCLIC POLYOLIDES

A. Diolides

(1) *Pyrenophorin*

Pyrenophorin (**9**) is a bis lactone antibiotic produced by the microorganism *Pyrenophora avenae*.¹⁰⁴ Diolide **9** is a head-to-tail dimer of a 7-hydroxy-2-ene-4-one carboxylic acid with methyl groups appended to the diolide ring. Retrosynthetically, the central strategy employed in almost all approaches is lactonization of the appropriate monomeric hydroxy acid to the diolide.

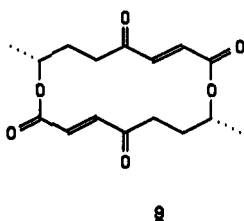
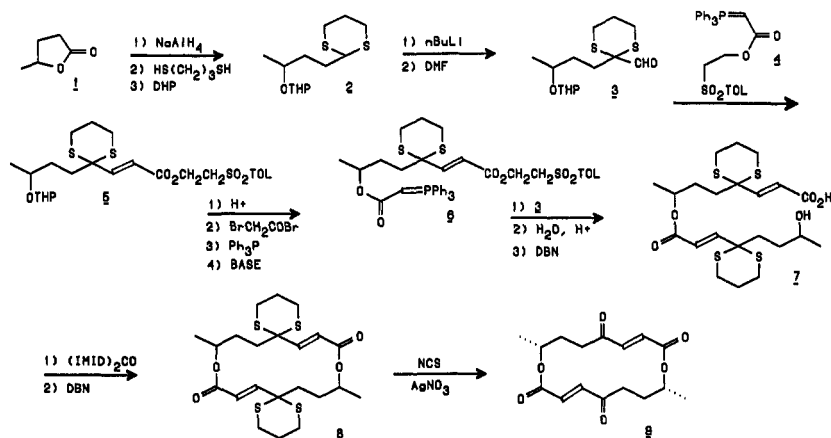


Figure 4.1. Pyrenophorin (**9**)

The first synthesis in this area is the work of Raphael and Colvin in 1976, who employed the novel 2-ethyl sulfonyl ester-protecting group as outlined in Scheme 4.1.¹⁰⁵ Reduction of γ -butyrolactone (**1**) with NaAlH_4 , followed by conversion of the resulting lactol to the thioacetal THP ether, led to **2** in 25% overall yield. Chain extension to the homologous aldehyde **3** was effected in 68% yield via metalation of the dithiane and formylation with DMF. Wittig reagent **4**, prepared from 2-tosyl ethanol, bromoacetyl bromide, and triphenylphosphine, was condensed with aldehyde **3** to give the protected 1,4 dicarbonyl compound **5** (35%).

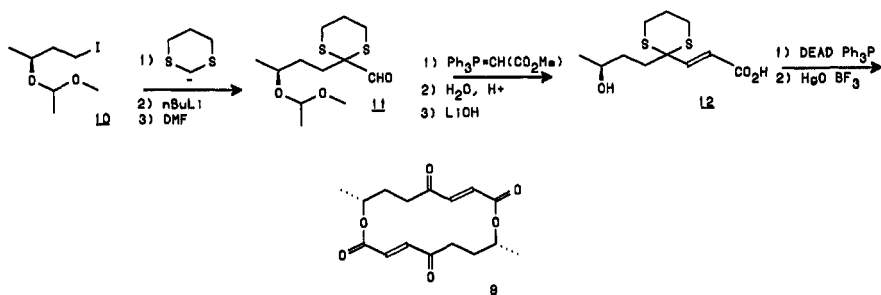
Having completed the monomeric unit of **9**, attention was now focused on the dimerization protocol. This transformation was achieved by essentially repeating the procedures utilized for the construction of the monomeric unit **5**. To this end, cleavage of the THP ether with acid, acylation with bromoacetyl bromide, and treatment with triphenylphosphine converted **5** to the stabilized Wittig reagent **6** in 79% yield. Ylide **6** was then condensed with aldehyde **3**, followed by sequential cleavage of the THP ether and ethylsulfonyl ester to

provide a 37% overall yield of seco acid **7**. Carboxyl activation via conversion to the intermediate imidazolide was followed by a base-induced cyclization to afford the protected pyrenophorin derivative **8** in 61% yield. Thioacetal cleavage then gave a mixture of synthetic **9** and its meso diastereomer **18**.



Scheme 4.1. Raphael and Colvin's pyrenophorin synthesis.

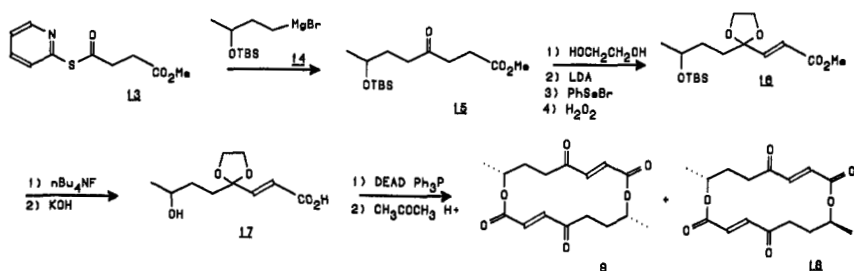
Seebach completed the first synthesis of optically active **9** as depicted in Scheme 4.2.¹⁰⁶ Protected alcohol **10**, available from an optically active β -hydroxy butyric ester, was alkylated with 2-lithio-1,3-dithiane. Deprotonation of this material followed by formylation with DMF then afforded **11**. Chain extension to the unsaturated ester was accomplished via a Wittig condensation and deprotection to produce the monomeric unit **12** in 57% overall yield from **10**. Double lactonization under Mitsunobu conditions (DEAD- Ph_3P) afforded a 60%



Scheme 4.2. Seebach's pyrenophorin synthesis.

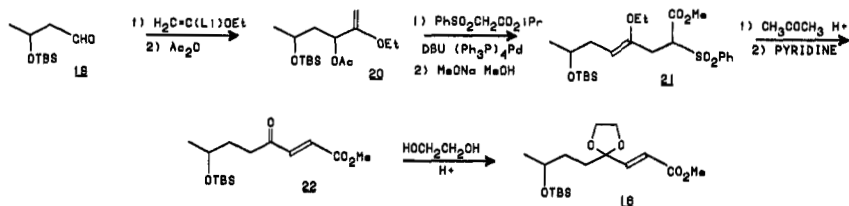
yield of the protected diolide, which was converted into the optically active **9** in 60% via thioacetal cleavage.

Gerlach has also prepared pyrenophorin (**9**) and its meso diastereomer, as shown in Scheme 4.3.¹⁰⁷ The activated thioester **13** was condensed with Grignard reagent **14**, affording a 65% yield of ketone **15**. After protection of the ketone carbonyl, introduction of the double bond via a selenylation–oxidation sequence produced **16** (36%). Seco acid **17** was obtained in 79% yield by desilylation followed by basic hydrolysis of the ester. Cyclization to the dimer, again under Mitsunobu conditions, afforded a 24% yield of a 1:1 mixture of the protected precursor of **9** and the corresponding meso diastereomer, which were then converted to **9** and **18** by hydrolysis.



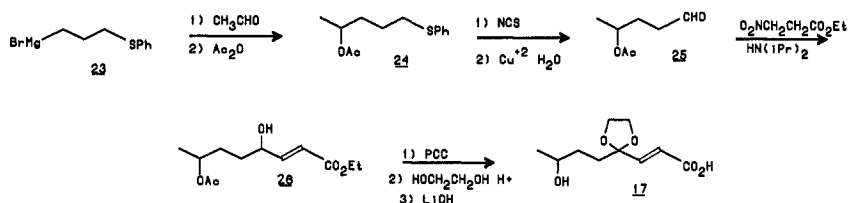
Scheme 4.3. Gerlach's pyrenophorin synthesis.

Scheme 4.4 details a short synthesis by Trost of an intermediate employed in the Gerlach synthesis of **9**.¹⁰⁸ Protected aldol **19** was reacted with α -lithio ethyl vinyl ether and the resulting alkoxide intermediate acylated to provide the protected diol **20** in 75% yield. Chain extension by way of a palladium-mediated allylic displacement with isopropyl phenylsulfonylacetate followed by ester exchange afforded a 62% yield of **21**. Hydrolysis of the enol ether and β -elimination of the sulfonyl group produced **22** in 66% yield. Ketalization of **22** then gave **16**, which had been previously converted to the natural product in 50% yield.¹⁰⁷



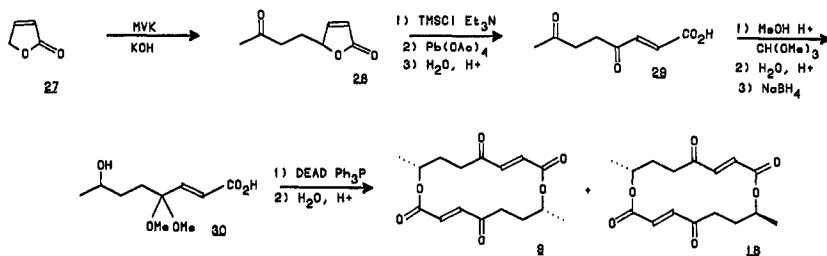
Scheme 4.4. Trost's pyrenophorin synthesis.

Bakuzis has explored the use of an interesting β -acrylate anion equivalent in his synthesis of **9** (Scheme 4.5).¹⁰⁹ The Grignard reagent from 3-bromopropyl phenyl sulfide was condensed with acetaldehyde and the resulting alkoxide was acylated to procure **24** (70%). Oxidation of the sulfide to aldehyde **25** proceeded in 74% yield. Reaction of **25** with ethyl 3-nitropropionate followed by elimination of HNO_2 from the intermediate afforded **26**. The latter step, equivalent to the addition of the β -carbanion of ethyl acrylate, occurred in 38% yield. Oxidation of alcohol **26**, protection of the resulting ketone, and saponification gave **17**. This intermediate was then dimerized as previously described to a mixture of **9** and its meso diastereomer.



Scheme 4.5. Bakuzis's pyrenophorin synthesis.

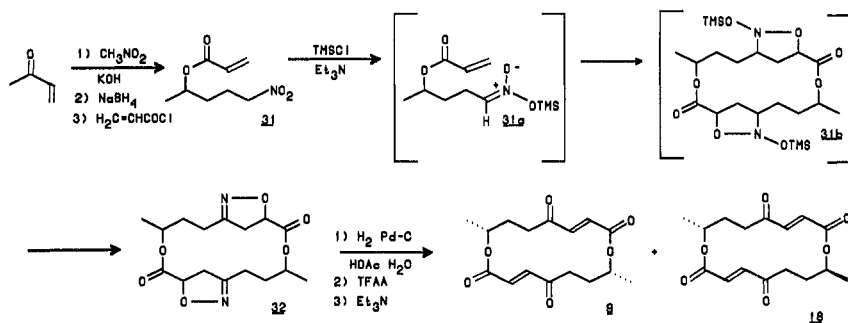
Takei utilized a furan as the synthetic equivalent of a 1,4 dicarbonyl compound in his synthesis of pyrenophorin as described in Scheme 4.6.¹¹⁰ Thus butenolide **27**, obtained by Michael addition of butenolide **27** to methyl vinyl ketone, was silylated to provide the silyloxyfuran. Treatment with lead tetraacetate followed by aqueous hydrolysis gave **29** in 55% yield. Protection of the ketones as dimethyl ketals followed by selective removal of the C-7 ketal and reduction gave seco acid **30**. Dimerization and hydrolysis gave a mixture of **9** and **18** (17% from **29**).



Scheme 4.6. Takei's first pyrenophorin synthesis.

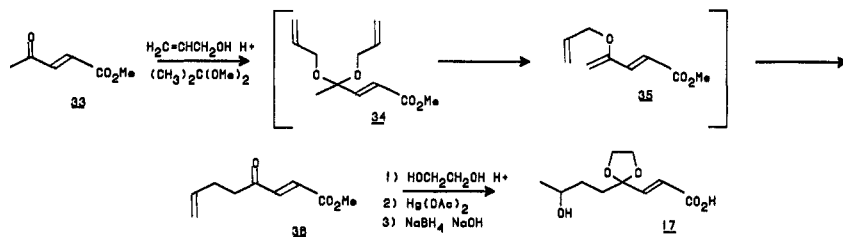
A very clever 1,3 dipolar cycloaddition sequence was employed by Takei in his second synthesis of **9** (Scheme 4.7).¹¹¹ Key intermediate **31** was obtained

by Michael addition of nitromethane to methyl vinyl ketone followed by reduction and acylation with acryloyl chloride. Addition of TMSCl and triethylamine produced dipole **31a** (containing an internal dipolarophile) which then underwent dimerization (to **31b**) and elimination of trimethylsilanol to afford a diastereomeric mixture of diolides **32** in 85% yield. Hydrogenolysis of this mixture in the presence of aqueous acid converted the isoxazolines to a mixture of β -hydroxy ketones. Dehydration then afforded a 1:1 mixture of **9** and **18** in 67% yield from **32**.



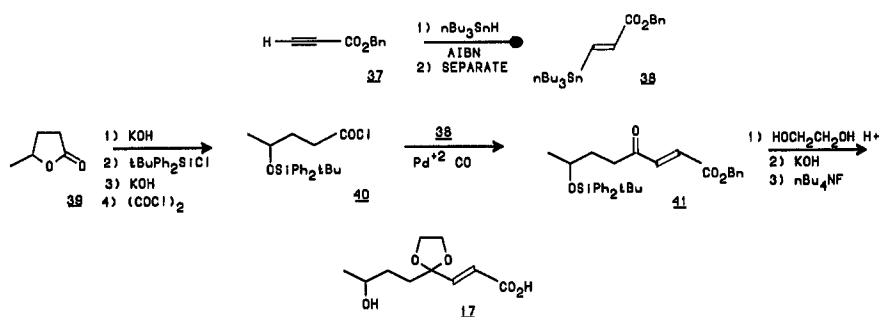
Scheme 4.7. Takei's second pyrenophorin synthesis.

An approach to the monomeric unit of pyrenophorin employing a Claisen rearrangement was described by Hase as depicted in Scheme 4.7.¹¹² The known methyl 4-oxo-2-pentenoate (**33**) was effectively α -allylated by the addition of allyl alcohol and a dehydrating agent. The initially formed diallyl acetal **34** was thermolyzed to give **35** with the loss of allyl alcohol (both **34** and **35** could be isolated under mild conditions). Subsequent Claisen rearrangement of **35** under the reaction conditions then gave **36** in 89% isolated yield from the keto ester **33**. Ketalization of **33** with ethylene glycol, oxymercuration of the terminal olefin, and reduction produced monomeric hydroxy acid **17** in 42% overall yield.



Scheme 4.8. Hase's pyrenophorin synthesis.

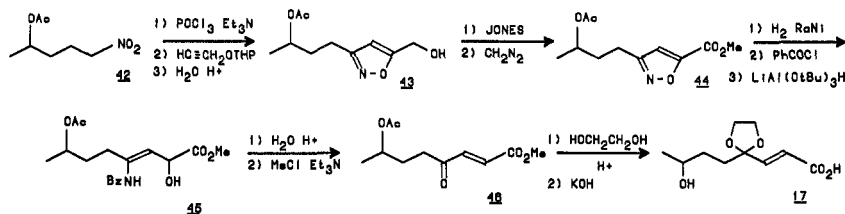
Stille utilized a palladium catalyzed carbonylation sequence developed in his laboratories to prepare the protected monomeric intermediate **17** as delineated in Scheme 4.9.¹¹³ Benzyl propiolate (**37**) was subjected to hydrostannylation to give a 1:1 mixture of (*E*)- and (*Z*)-vinyl stannanes in 90% yield, from which the pure (*E*)-isomer **38** was obtained by chromatography. The remaining segment of **17** was constructed from γ -valerolactone **39** via hydrolytic ring opening and exhaustive silylation followed by conversion of the silyl ester to the acid chloride **40** (71% overall yield). Coupling of **38** and **40** mediated by benzylchlorobis(tri-phenylphosphine)palladium(II) in the presence of CO then afforded a 71% yield of keto acrylate **41**. After ketalization, saponification of **41** and cleavage of the silyl ether afforded **17** in 53% yield.



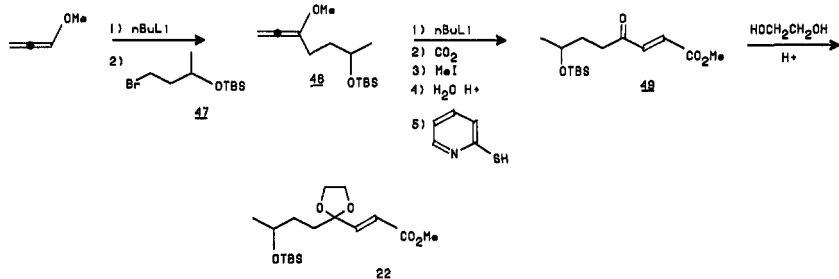
Scheme 4.9. Stille's pyrenophorin synthesis.

A second approach involving a 1,3 dipolar cycloaddition is shown in Scheme 4.10.¹¹⁴ Nitroacetate **42**, presumably obtained in a fashion similar to **31**, was converted to the corresponding nitrile oxide and trapped with the THP ether of propargyl alcohol in 59% yield. Acid hydrolysis of the adduct then produced isoxazole **43**, which was further oxidized and esterified to afford **44** in 80% yield. Hydrogenolysis of the N—O bond gave the vinylogous amide, which was benzoylated on nitrogen and reduced to provide the β -hydroxy enamide **45**. Aqueous hydrolysis of the enamide to the β -hydroxy ketone and dehydration gave **46** in 58% overall yield. Ketalization followed by acetate hydrolysis then afforded monomeric intermediate **17** (88%).

The use of lithiated methoxyallene as both an acyl and β -acrylyl anion equivalent was examined by Linstumelle in the studies depicted in Scheme 4.11.¹¹⁵ After α -metalation, methoxyallene was alkylated with bromo silyl ether **47** to afford **48**. A second metalation at the terminus of the allene was quenched sequentially with carbon dioxide and methyl iodide to give the corresponding allenic ester. Hydrolysis of the enol ether and equilibration gave solely the (*E*)- γ -keto acrylate **49** in 30% overall yield. Ketalization then provided **16**, which had previously been converted to pyrenophorin (**9**).¹⁰⁷

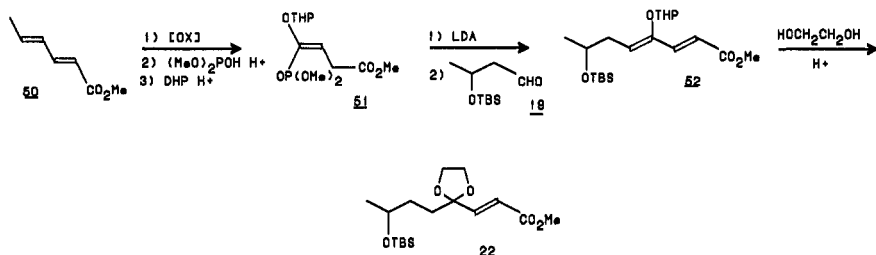


Scheme 4.10. Pollini's pyrenophorin synthesis.



Scheme 4.11. Linstrumelle's pyrenophorin synthesis.

Use of a γ -keto acrylate anion equivalent to prepare **16** is described in Scheme 4.12.¹¹⁶ Methyl sorbate (**50**) was degraded to the corresponding β -formyl acrylate. Acid-mediated addition of dimethylphosphite to the formyl group followed by concomitant protection of the resulting alcohol as the THP ether and olefin migration gave **51**. Wadsworth–Emmons condensation of the anion obtained from **51** upon deprotonation with LDA with aldehyde **19** gave dienoate **52**. Ester **52** afforded the previously characterized ester **16** via transketalization.



Scheme 4.12. Krief's pyrenophorin synthesis.

(2) Vermiculine

The second member of the diolide group whose structure became known is vermiculine (**56**), an antimicrobial metabolite of *Penicillium vermiculatum*.¹¹⁷ The structure of **56** is extremely similar to pyrenophorin, differing only in the replacement of the methyl side chains by acetone units. Thus the dimerization strategy, previously outlined for pyrenophorin, was embraced in most of the existing synthetic approaches.

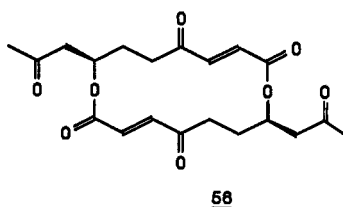
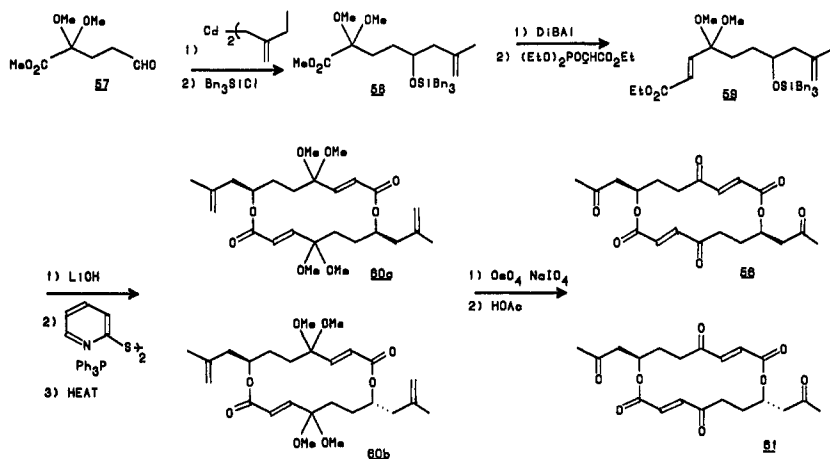


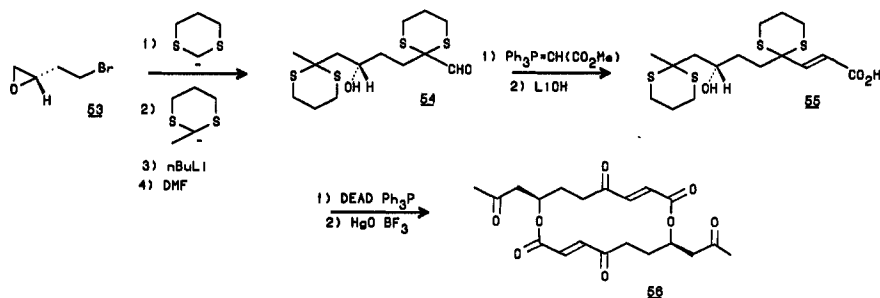
Figure 4.2. Vermiculine (**56**)

The first synthesis of vermiculine by Corey, outlined in Scheme 4.14, employed an isopropenyl group as a protected version of the acetone sidechain.¹¹⁸ Aldehyde **57**, the Dibal reduction product of readily available dimethyl 2,2-dimethoxyglutarate, was condensed with dimethylallyl cadmium and the resulting alcohol silylated to produce **58** (70%). Reduction of ester **58** to the aldehyde followed by two-carbon homologation afforded a 94% yield of α,β unsaturated ester **59**. Hydrolysis of **59** to the acid and conversion to the 2-thiopyridyl ester (77%) set the stage for double lactonization. This transformation was accomplished by thermolysis of a diluted solution of the thioester, affording a 30% yield of the diastomeric diolides **60a** and **60b** (1:1). The former was then converted by oxidation into the synthetic **56** and the latter into the meso isomer **61**, both in 70% yield.

The second recorded synthesis of vermiculine (**56**) (see Scheme 4.14) arises from the work of Seebach and co-workers and is quite similar to their pyrenophorin synthesis.¹⁰⁶ The sequence began with the conversion of malic acid into the optically pure bromo epoxide **53** by literature procedures. Sequential addition of the acyl anion equivalents 2-lithio-1,3-dithiane and 2-lithio-2-methyl-1,3-dithiane created a precursor containing the two carbonyl groups in masked form. Metalation of the monosubstituted dithiane followed by formylation gave **54**. This substance was found to exist primarily in cyclic hemiacetal form; however, the acyclic aldehyde could be intercepted by a stabilized Wittig reagent effecting



Scheme 4.13. Corey's vermiculine synthesis.

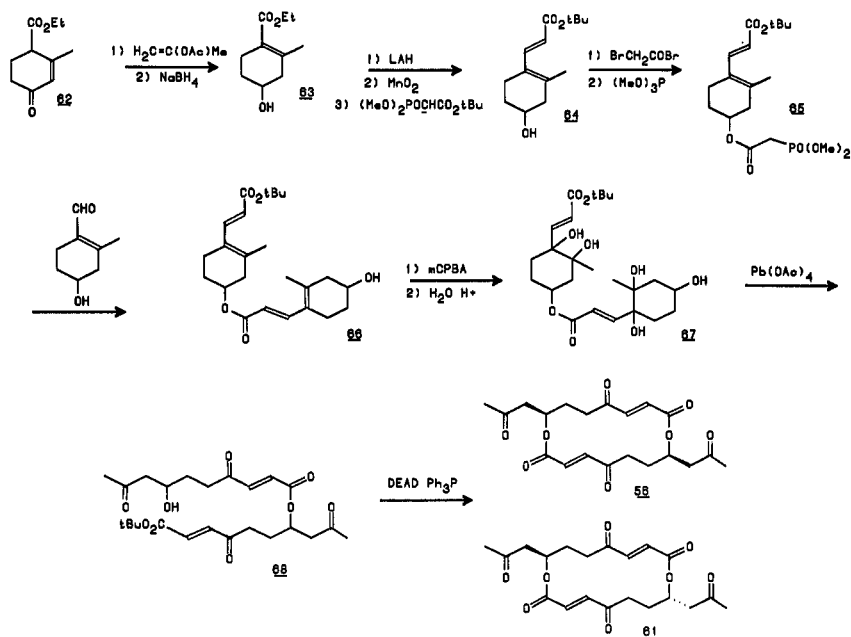


Scheme 4.14. Seebach's vermiculine synthesis.

the required two-carbon homologation. The resulting α,β -unsaturated ester was then hydrolyzed to the corresponding carboxylic acid to afford a 30% overall yield of **55**. As in the pyrenophorin synthesis, diolide formation employed a double Mitsunobu reaction (25%). Cleavage of the thioketals in the resulting diolide afforded optically active vermiculine (**56**) in 70% yield.

White undertook a rather different approach to the construction of **56**, as shown in Scheme 4.15.¹¹⁹ Hagemann's ester (**62**) was converted to the related dienol acetate and reduced to give a 68% yield of the hydroxy ester **63**, contaminated with a small amount of the isomeric allylic alcohol. A reduction-oxidation sequence produced the intermediate aldehyde, which was subjected to chain extension by Wadsworth-Emmons reaction to produce the diene ester **64** in 56% yield.

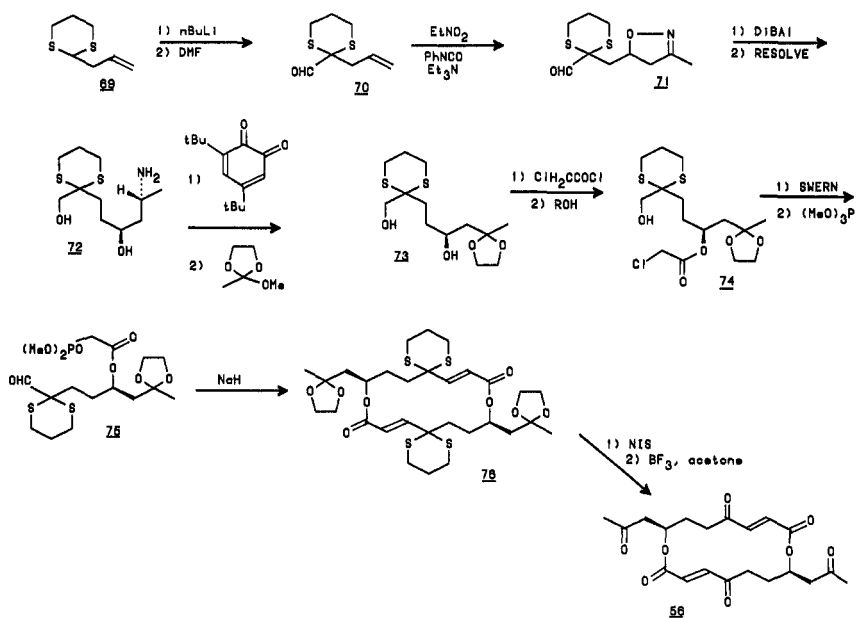
The White strategy did not involve the usual construction of the monomeric hydroxy acid followed by dimerization, but rather, formation of one ester linkage between two protected monomeric units followed by liberation of the other hydroxy acid moiety and lactonization. Accordingly, **64** was esterified and elaborated to the related phosphonate **65** in 78% yield. Condensation with the unsaturated aldehyde derived from **63** then provided a 95% yield of **66**. Selective oxidation of both γ,δ double bonds with *m*CPBA followed by hydration of the epoxides gave the tetraol **67** as a mixture of diastereomers in good yield. Oxidative cleavage of the glycols with lead tetraacetate then produced hydroxy ester **68** in 49% yield from **66**. An intramolecular Mitsunobu reaction generated a 15% yield of the natural product **56** accompanied by the meso isomer **61**.



Scheme 4.15. White's vermiculine synthesis.

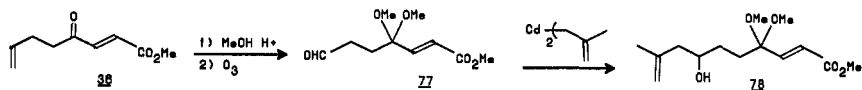
Burri at Hoffmann-La Roche chose to couple the two monomeric units via an intramolecular Wadsworth–Emmons reaction rather than lactonization (see Scheme 4.16).¹²⁰ Thus dithiane **70**, obtained by formylation of the anion derived from **69**, underwent a regiospecific 1,3 dipolar cycloaddition with acetonitrile oxide to afford isoxazoline **71**. Dibal reduction to the related amino alcohol followed by optical resolution with D-camphorsulfonic acid led to the isolation

of the pure (5'*R*,3'*S*)-enantiomer **72**. Selective oxidation of the primary amine of **72** to the corresponding ketone was followed by *trans*-ketalization with ethylene glycol orthoacetate providing ketal **73**. Bisacylation with chloroacetyl chloride followed by selective cleavage of the primary acetate then afforded chloro ester **74**. Completion of the monomeric unit was achieved via Swern oxidation and Arbuzov reaction with trimethylphosphite to give the phosphonate **75** in 31% overall yield from the resolved amino alcohol. Dimeric olefination was effected upon deprotonation to yield the macrocycle **76**, which could be converted in 81% yield to optically active vermiculine (**56**) via sequential cleavage of the thioketal and ketal protecting groups.



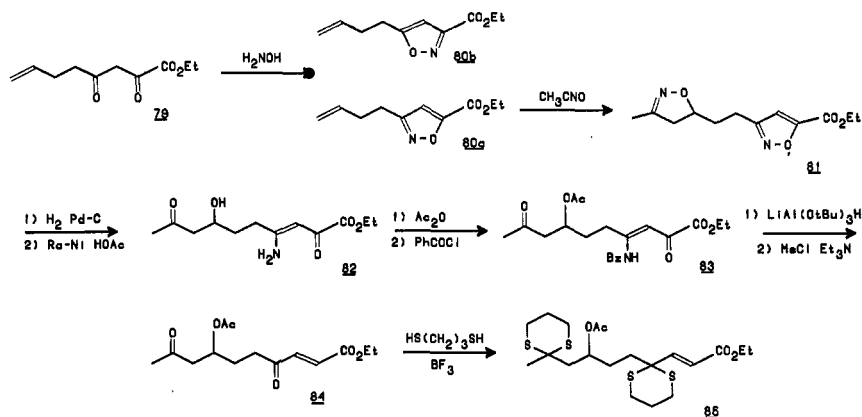
Scheme 4.16. Burri's vermiculine synthesis.

Hase modified his synthesis of pyrenophorin in such a manner that a vermiculine intermediate was readily accessible, as shown in Scheme 4.17.¹¹² Ketone **36** was protected as the dimethyl ketal and the terminal olefin oxidatively cleaved to give aldehyde **77** in 40% yield. The addition of diisobutenyl cadmium afforded a 78% yield of **78**, a compound very similar to Corey's intermediate **59**.¹¹⁸



Scheme 4.17. Hase's vermiculine synthesis.

The Italian group led by Pollini also modified their synthesis of pyrenophorin to permit an easy entry into the vermiculine system (Scheme 4.18).¹¹⁴ Accordingly, the known oxalate derivative **79** was reacted with hydroxylamine to give a 7:3 mixture of **80a** and **80b**, the former being separable by spinning-band distillation. The olefinic moiety of **80a** then underwent a regiospecific 1,3 dipolar cycloaddition with acetonitrile oxide to give the bis-heterocycle **81** in 88% yield. Hydrogenation of **81** over Pd-C followed by a second hydrogenation with Raney-nickel in acid gave **82** (79%). The chemistry used to convert **82** to vermiculine is quite similar to the pyrenophorin synthesis. Acylation of **82** gave **83** (90%), which was elaborated via **84** (62%) to **85** (60%), a compound very similar to the Seebach intermediate **55**.¹⁰⁶



Scheme 4.18. Pollini's vermiculine synthesis.

(3). *Aplasmomycin*

The marine strain of *Streptomyces griseus* produces the boron-containing macrocyclic dilactone aplasmomycin (**106**).¹²¹ Belonging to a family of borate-bridged macrocycles (which includes boromycin), **106** exhibits activity against gram-positive bacteria and the microorganisms of *Plasmodia*. Structurally, **106**

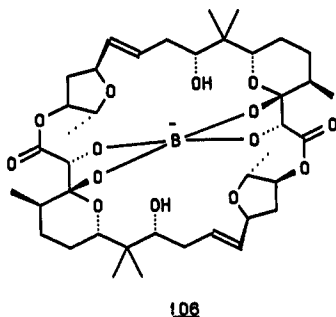


Figure 4.3. Aplasmomycin (106)

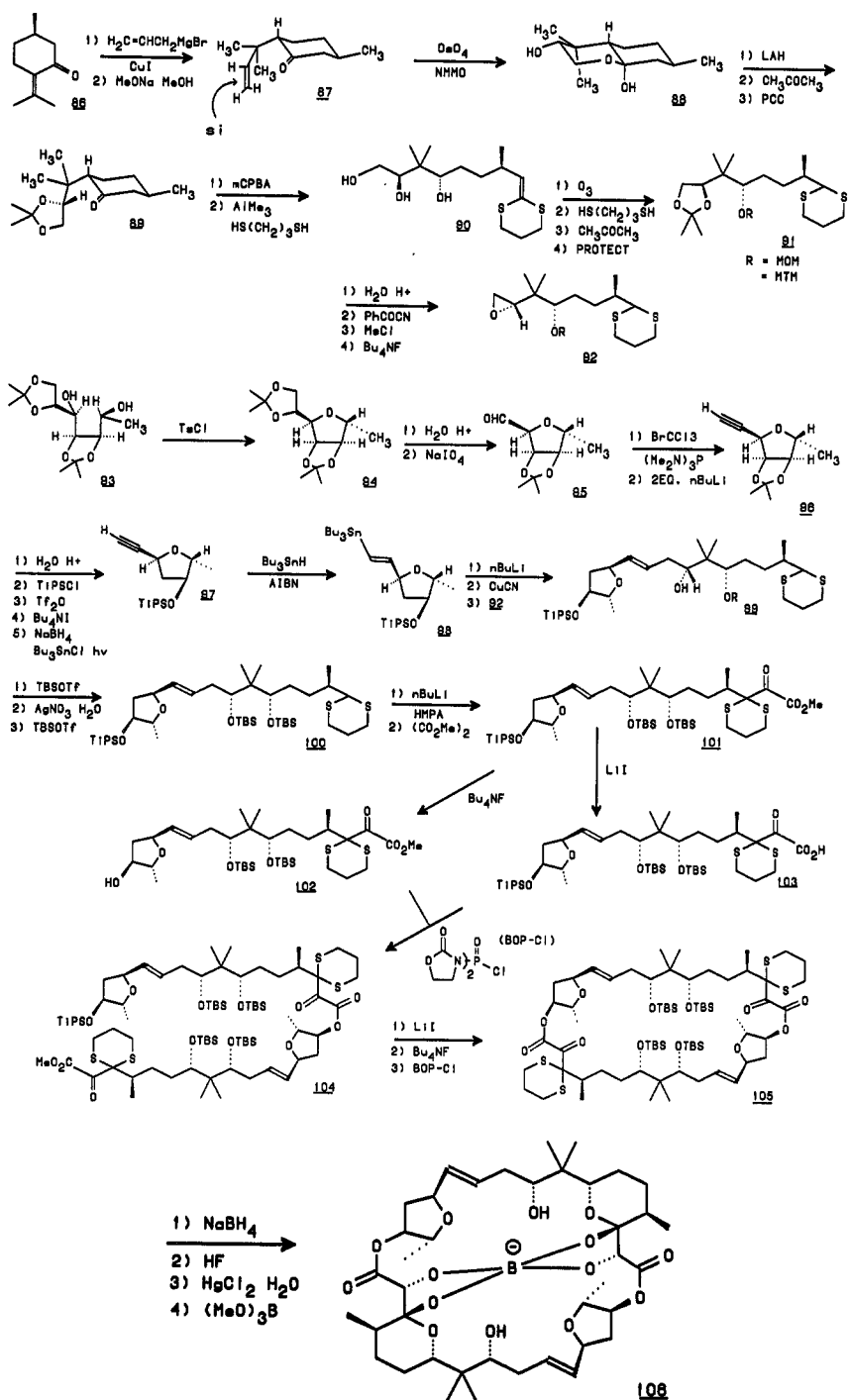
is a dimeric diolide containing two hemiketal centers and a borate bridge across the macrocyclic ring.

The sole completed synthetic effort in this area is that of Corey.¹²² From a strategic point of view, **106** may be dissected at the two lactone linkages. The monomer unit was then constructed from (+)-pulegone (C-3 to C-10) and D-mannose (C-11 to C-17), thus insuring the correct absolute configuration in the final product.

The synthesis was begun, as shown in Scheme 4.19, by the Cu^{+1} -catalyzed conjugate addition of allyl Grignard reagent to (+)-pulegone (**86**) (88%). Base-catalyzed equilibration afforded a mixture of diastereomers (85:15 *trans:cis*) from which the major isomer **87** could be separated chromatographically. Stereo-specific bishydroxylation from the *si* face of the allyl group then led to a 76% yield of hemiketal **88**.

The stereochemical outcome of this crucial transformation is explicable if steric factors within the cyclohexane ring are considered. If a chair cyclohexanone is assumed, the lowest energy conformation will be one in which the geminal methyl groups of the sidechain are furthest away from the carbonyl. Additionally, it is expected that an *s-trans* orientation would be favored between the vicinal vinyl C-H and the methyl C-C bonds. Bases on this conformation, approach of the osmium tetroxide to the lessencumbered face of the double bond anti to the carbonyl results in the formation of the observed products **88**.

Hemiketal **88** was further transformed by standard methods to the keto acetone **89** in 70% yield. Baeyer-Villiger oxidation of **89** followed by treatment with bisdimethylaluminum-1,3-propanedithiolate gave the ketenethioacetal **90** in 87% yield. Degradation of the chain in **90** by one carbon (ozonolysis and thioacetalization) was followed by conversion of the 1,2 diol to the acetone. The remaining hydroxyl group was then protected as either the MOM or the MTM ether to give **91** (R = MTM:42% or R = MOM:46% from **90**). The required C-3 to C-10 synthon **92** was completed by the conversion of the acetone to the corresponding epoxide with inversion at the secondary center in 80% yield.



Scheme 4.19. Corey's aplasmomycin synthesis.

Construction of the second fragment of the monomeric unit began with the chelation-controlled addition of methyl lithium to the open-chain form of D-mannose diacetone to give **93** in 99% yield. Inversion of the methyl carbinol center concomitant with formation of the furan derivative produced **94** (91%). Hydrolysis of the side-chain acetone of **94** and oxidation cleavage of the resulting glycol to aldehyde **95** (86%) was followed by conversion to the terminal acetylene **96** (74%). Hydrolysis of the remaining acetone was followed by the selective (12.5:1) silylation of the hydroxyl group remote from the *syn* acetylene sidechain. Removal of the free alcohol was accomplished (via the intermediate triflate and iodide) by tin hydride reduction to afford **97** in 56% overall yield. Hydrostannylation of the alkyne gave a 75% yield of an 85:15 mixture of (*E*)- and (*Z*)-vinyl stannanes. Following chromatographic separation of the desired (*E*)-isomer **98**, the minor (*Z*)-isomer could be thermally equilibrated to the same 85:15 mixture.

Coupling of the two fragments **92** and **98** took place via lithiation of the vinyl stannane and conversion to the cuprate, followed by addition to epoxide **92** to give **99** in 89% yield. Conversion of **99** (R = MTM) to bis-silyl ether **100** was accomplished in 85% yield utilizing conventional methods. Homologation by a two-carbon unit was achieved by metalation of the dithiane group followed by the addition of dimethyloxalate to give the α -keto ester **101** in 96% yield.

Manipulation of the various protecting groups was now required in order to couple the two segments together prior to final lactonization. To this end, treatment **101** with one equivalent of fluoride resulted in specific desilylation of the secondary TIPS ether to give **102** (97%). Cleavage of the methyl ester of **101** was accomplished by treatment with LiI to afford a quantitative yield of carboxylic acid **103**. The key coupling was then effected by the addition of *N,N*-bis[2-oxo-3-oxazolidinyl]phosphordiamidic chloride (BOP-Cl) to the subunits **102** and **103** to give ester **104** in 98% yield. The deprotection and coupling sequence was then repeated to afford a 71% yield of diolide **105**. Reduction of the α -carbonyl groups followed by desilylation and thioacetal cleavage gave a 79% yield of deboro aplasmomycin and a diastereomer in a 1:1 ratio. Silica gel chromatography and subsequent treatment with trimethyl borate then afforded aplasmomycin (**106**) in 75% yield.

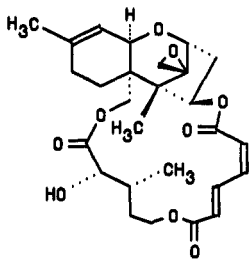
The MOM ether of **91** was also converted to **106** via a slightly shorter albeit similar route.

B. Macrocyclic Trichothecin Triolides

(1) *Verrucaric A*

The macrocyclic trichothecane lactonic esters are a biologically important class of compounds produced by various species of the *Myrothecium* group of micro-organisms. This family of substances has exhibited marked biological activity

in the antifungal, antiviral, antibiotic, and antitumor areas.¹²³ Indeed, one of these compounds, verrucarín A (**116**), has been shown to cause a 50% inhibition of the growth of P-815 tumor cells in mice at a concentration of 6×10^{-4} $\mu\text{g/mL}$.^{123b}



116

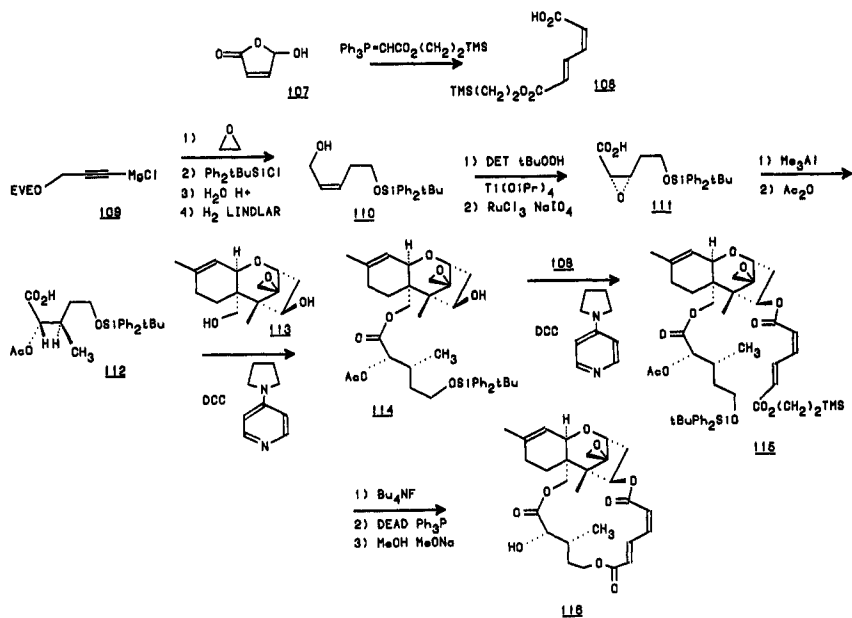
Figure 4.4. Verrucarín A (**116**)

From a structural standpoint, these compounds consist of a trichothecane sesquiterpene diol linked through ester bonds to a diacid derived from esterification of the (*E*)-acid of a (*Z,E*)-muconic acid with a 5-hydroxypentanoic acid segment (containing various substitution patterns). As the synthesis of the sesquiterpene diol unit is beyond the scope of this chapter, we have limited discussion to the methods employed for formation of the macrocyclic ring of these substances. Papers concerning the construction of the various trichothecane diol systems may be found by consulting the references cited in this section.

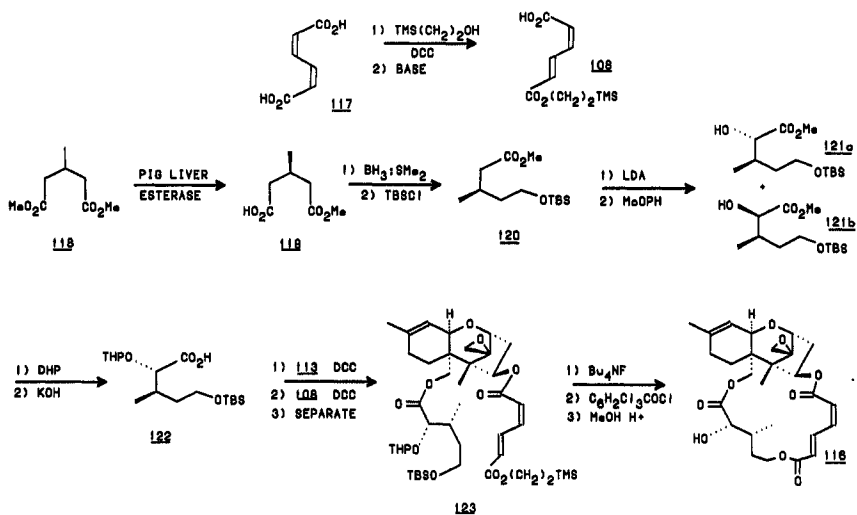
The first synthesis of a member of this class, verrucarín A (**116**) is a result of the efforts of Still and is outlined in Scheme 4.20.¹²⁴ Construction of the muconic acid fragment began with pseudoacid **107**, available from the electrochemical oxidation of furfural. A one-carbon homologation with a stabilized ylide afforded solely the (*E,Z*)-isomer of β -trimethylsilylethyl ester **108** in 72% yield.

Preparation of the hydroxypentanoic acid fragment was initiated by addition of the protected propargyl alcohol anion **109** to ethylene oxide. After silylation of the resulting alcohol, the ethoxy ethyl group was removed and the alkyne partially reduced to afford the (*Z*)-alcohol **110** in 52% overall yield. Enantio-specific epoxidation of **110** under Sharpless's conditions and subsequent oxidation provided a 69% yield of diastereomerically pure epoxy acid **111**. Treatment with trimethylaluminum gave almost exclusively the β -methyl acid, which was acylated to afford **112** (78%).

Selective esterification of the primary alcohol of natural verrucarol (**113**) with **112** cleanly provided **114** in 95% yield. Although **114** is apparently resistant to a second esterification with **112**, the more reactive muconic acid derivative **108**



Scheme 4.20. Still's Verrucaric A Synthesis.



Scheme 4.21. Tamm's verrucaric A synthesis.

will couple with the secondary alcohol in **114** under the same conditions to give **115** (86%). Conversion of **115** to verrucarín A (**116**) was then accomplished by desilylation, lactonization under Mitsunobu conditions (52%), and acetate cleavage (70%) to afford the natural product (**116**).

Tamm has also completed a synthesis of verrucarín A (**116**), as described in Scheme 4.21.¹²⁵ The muconic acid unit was obtained via peroxide oxidation of catechol to produce diacid **117**, which was esterified to provide the (*E,Z*)-half-ester **108**.

The hydroxy pentanoic acid was elaborated from dimethyl 3-methylglutarate (**118**) by enantioselective hydrolysis with pig-liver esterase to give the half-ester **119** in 95% yield. Reduction to the hydroxy ester followed by silylation then gave **120**. Oxidation of the enolate derived from **120** with MoOPH gave a mixture of α -hydroxy esters **121a** and **121b**, from which **121a** was isolated by chromatography and elaborated into **122**. Sequential esterification of verrucarol (**113**) with **122** (55%) and muconic acid **108** (95%) gave **123**. The latter esterification resulted in partial isomerization of the diene to the (*E,E*)-isomer (2:1, *E,Z:E,E*), thus chromatographic purification of **123** was required. Desilylation of **123** followed by lactonization via the Mukaiyama method gave the macrocycle in 50% yield. Cleavage of the THP ether with acid then afforded verrucarín A (**116**).

(2) Verrucarín J

Rousch at MIT has completed a synthesis of verrucarín J (**124**), as shown in Scheme 4.22.¹²⁶ The pentanoic acid moiety was elaborated from 3-butyn-1-ol **125** by use of the Negishi carbometalation procedure, followed by quenching with chloroformate, which afforded **126** in 20–25% yield. Silylation of the primary alcohol followed by reductive cleavage of the ester group gave the required acid **127** (59%). Coupling of **127** with verrucarol (**113**) using DCC gave a 82–85% yield of the expected C-15 ester. Apparently some olefin

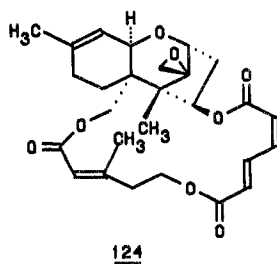
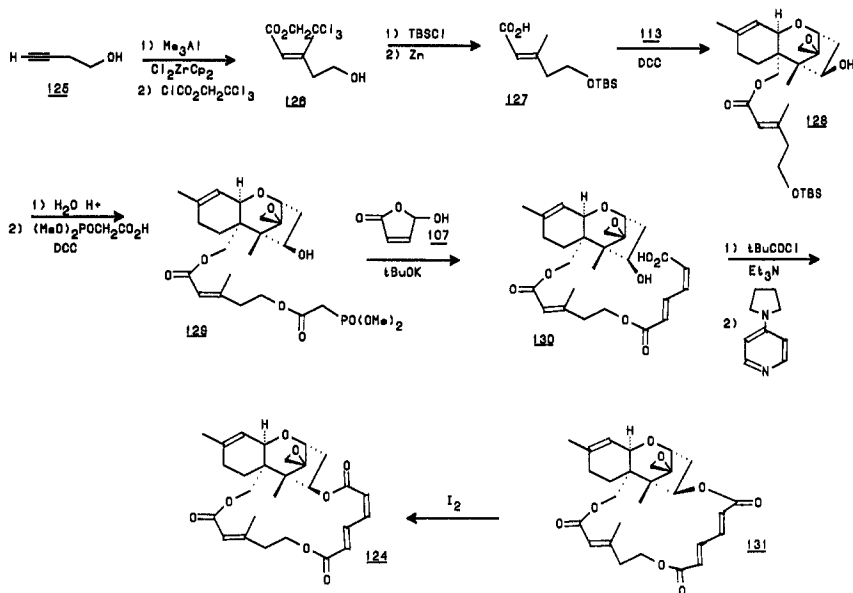


Figure 4.5. Verrucarín J (**124**)

isomerization occurred during esterification (4:1, *E:Z*), although chromatographic separation permitted isolation of **128** in 60% yield accompanied by 16% of the (*Z*)-isomer. Cleavage of the silyl group of **128** with acid followed by esterification with dimethyl phosphonoacetic acid gave a 51% yield of **129**, a precursor suitable for introduction of the muconic acid fragment.



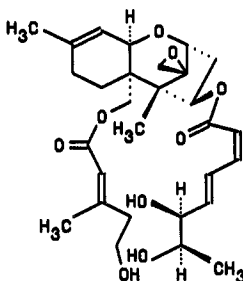
Scheme 4.22. Rousch's Verrucarín J Synthesis.

Accordingly, treatment of **129** with potassium *t*-butoxide and pseudoacid **107** gave a 58% yield of the required (*E,Z*)-muconic ester **130**. Macrolactonization was then achieved via the mixed pivaloyl anhydride in the presence of 4-pyrrolidinopyridine to afford verrucarín (**124**) in 60% yield along with its (*E,E*)-muconate isomer **131** (30%). The latter could be isomerized with I_2 in benzene to provide additional **124** (61%) contaminated with another muconic ester isomer.

(3) *Trichoverrin B*

The work of Fraser-Reid and Jarvis, shown in Scheme 4.23 culminated in the total synthesis of trichoverrin B (**132**) and its conversion into verrucarín J (**124**).¹²⁷ Construction of the pentanoic acid segment began with the protection of keto alcohol **133**. Two-carbon homologation of the resulting ketone by a Wadsworth–

Emmons reaction, followed by deprotection of the alcohol, afforded a 62% yield of a mixture of (*E*)- and (*Z*)-isomers (1:5) of **134**. The (*E*)-ester **134** was then converted into the acyl imidazolidine **135** in 54% overall yield.



132

Figure 4.6. Trichoverrin B (**132**)

The required muconic acid fragment was constructed from α,β -unsaturated aldehyde **136**, readily available from triacetyl-D-galactal. Chain extension using the anion of ethyl trimethylsilylacetate gave a mixture of diene esters (2:1, *Z,E:E,E*), from which (*Z,E*)-acid **137** was isolated in 45% yield following deacylation, bis-silylation, chromatography, and ester saponification. Coupling to 15-acetylverrucarol via the acyl imidazolidine derived from **137** produced **138** as a 1:1 mixture of (*Z,E*)- and (*Z,Z*)-dienes. A chromatographic separation followed by acetate cleavage afforded (*Z,E*)-**138** in acceptable overall yield. Deprotonation of **138** and acylation with **135** gave after desilylation, a 36% yield of trichoverrin B (**132**).

Treatment of **132** with PDC resulted in oxidative cleavage of the diol to the corresponding aldehyde. Further oxidation of the presumed cyclic hemiacetal intermediate then gave verrucarol J (**124**) in 50% yield.

(4) *Roridin E*

The roridin family constitutes another subclass of the trichothecane macrolides. Two examples of this group are roridin E (**148**) and baccharin B₅ (**150**). The latter is isolated from the plant *Baccharis megapotamica* and is a potent antileukemic agent.¹²⁸ Structurally, this class of compounds is quite similar to the verrucarins discussed above, with the exception of the replacement of the hydroxypentanoic acid–muconic ester linkage by an ether bond and some additional carbon substitution.

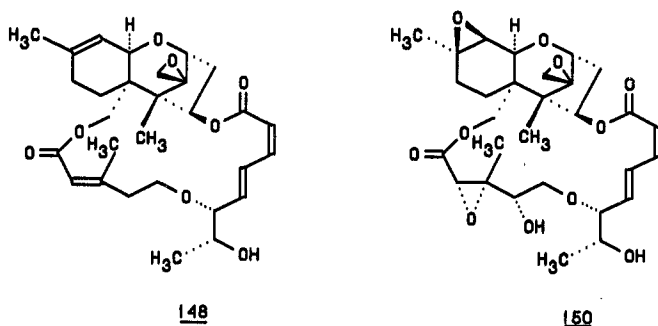
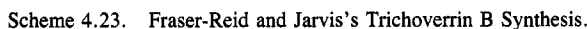
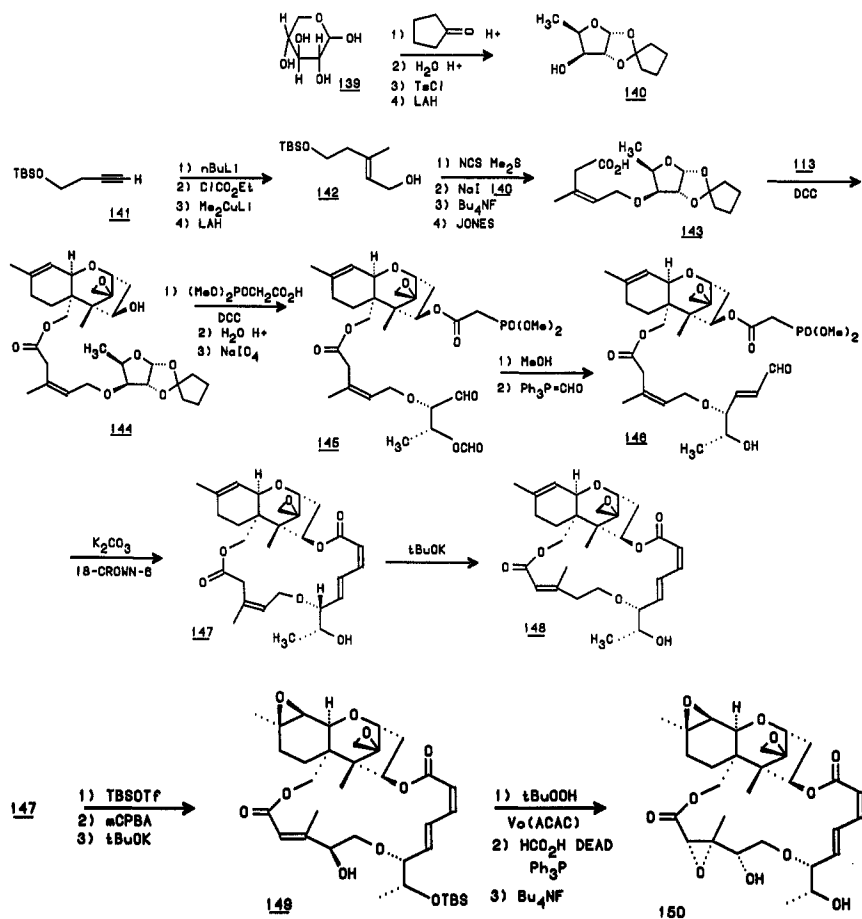


Figure 4.7. Roridin E (148) and Baccharin B₅ (150).

The Still synthesis, depicted in Scheme 4.24, began with the construction of the fragment that will link the diene ester and the hydroxypentanoic acid.¹²⁹ To this end, D-xylose (**139**) was converted to the dicyclopentyl ketal, which was selectively hydrolyzed, tosylated, and reduced to give the C-6, C-13 synthon **140** (65%).

The hydroxypentanoic acid segment was obtained via metalation and carbonylation of 1-silyloxy-3-butyne (**141**). Conjugate addition of lithium dimethylcuprate followed by reduction provided a 45% yield of allylic alcohol **142**. Coupling with alcohol **140** was effected via conversion of **142** to the



Scheme 4.24. Still's Roridin E Synthesis.

analogous allylic chloride and *O*-alkylation of **140** under Finkelstein conditions. Desilylation of the resulting silyl ether and Jones oxidation then provided **143** in 75% overall yield. Selective esterification of **143** at the verrucarol (**113**) C-15 position was then achieved in good yield utilizing DCC affording **144**.

The remaining transformations require the elaboration of the dienoic ester and cyclization with the hydroxypentanoic side chain. Accordingly, esterification of the C-4 hydroxyl of **144** with dimethyl phosphonoacetic acid followed by ketal hydrolysis to the furanose and periodate cleavage gave the β -formyloxy aldehyde **145**. Deformylation of the hydroxyl group in methanol and two-carbon homologation of the aldehyde with formylmethylenetriphenylphosphorane produced **146**. The stage was now set for macrocyclic ring closure. Thus treatment of **146** with

K_2CO_3 and 18-crown-6 initiated an intramolecular Wadsworth–Emmons reaction that provided a mixture of (*E,Z*)- and (*E,E*)-dienoic esters. Chromatographic purification then afforded the desired (*E,Z*)-dienoate **147** (45%). Finally, base treatment of **147** induced olefin migration into conjugation with the ester carbonyl providing 70% yield of roridin E (**148**).

(5) Baccharin B₅

The more highly oxygenated baccharin B₅ (**150**) may be obtained by stereoselective epoxidation of **147** with *m*CPBA following silylation of the free hydroxyl group providing the intermediate epoxide (see Scheme 4.24).¹²⁹ The conformation of the macrocyclic ring coupled with the sterically hindered nature of the α face of the tricyclic ring resulted in >15:1 selectivity in the epoxidation. Treatment of this epoxide with base induced β -elimination to produce the (*E*)- γ -hydroxy- α,β -unsaturated ester **149** in 60% overall yield from **147**. Hydroxyl-directed epoxidation then gave a single α -epoxide in 90% yield. Inversion of the free alcohol in this intermediate under Mitsunobu conditions and desilylation then afforded semisynthetic baccharin B₅ (**150**).

C. Tetralides

(1) Nonactin

The polyether nonactin (**174**) is an antibiotic tetralide produced by the *Streptomyces* family of microorganisms.¹³⁰ From a biological point of view, nonactin and the other compounds in this family of tetrameric lactones have the ability to strongly complex potassium ion and to facilitate the transport of potassium across membranes by providing a lipophilic shell. Ion transport has been shown to have a strong influence on important biological functions such as oxidative phosphorylation and mitochondrial respiration.^{130c-e}

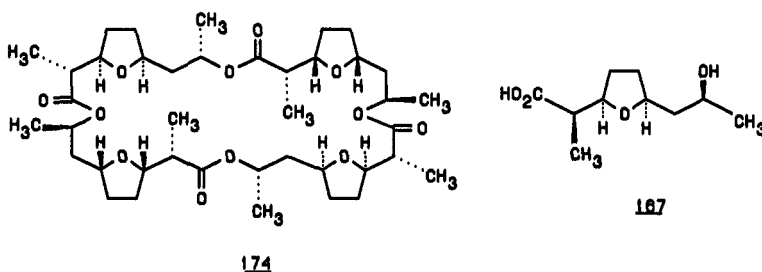
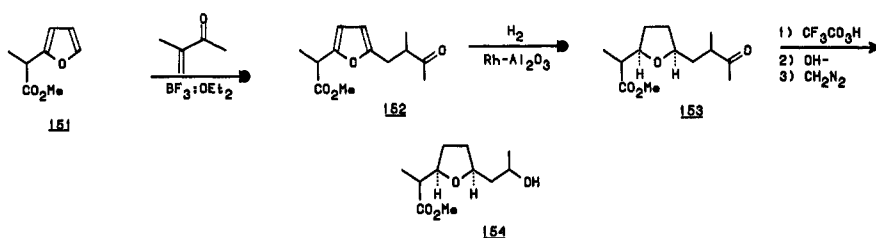


Figure 4.8. Nonactin (**174**) and Nonactic acid (**167**)

With respect to structure, nonactin (**174**) is a 32-membered ring with four ester linkages. The large ring consists of alternating enantiomers of the monomeric unit nonactic acid (**167**). Although the individual monomers are optically active, the cyclic tetramer possesses meso symmetry and displays no optical activity. Several reviews on the chemistry of nonactin have appeared.¹³¹

The early synthetic endeavors in this area focused mainly on the synthesis of various nonactic acid derivatives. The scenario utilized in almost all of these early studies involved the hydrogenation of a 2,5-disubstituted furan ring to give a *cis*-disubstituted tetrahydrofuran.

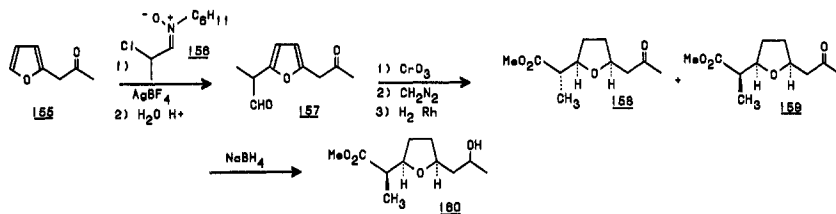
The first synthetic studies in this area were reported by Beck and Henseleit and are depicted in Scheme 4.25.¹³² Furan **151**, available via monomethylation of the corresponding methyl furanylacetate, was reacted with 2-methyl-1-buten-3-one to give the 2,5-disubstituted furan **152** (64%). Following hydrogenation to give the *cis*-substituted compound **153**, the ketone was subjected to Baeyer–Villiger oxidation, the resulting acetate was cleaved, and the acid was esterified. The final mixture of compounds contained all four diastereomers from which racemic methyl nonactate (**154**) could be separated by chromatography.



Scheme 4.25. Beck's and Henseleit's methyl nonactate synthesis.

Two syntheses of nonactic acid were recorded by Gerlach and later the monomer was converted to nonactin (**174**).¹³³ The first synthesis (Scheme 4.26) began with the 2-(2-oxo-1-propyl)furan (**155**), which provided keto aldehyde **157** after "alkylation" with chloronitrone **156** and hydrolysis. Oxidation of **157** to the keto acid and subsequent esterification, while successful, was complicated by the presence of by-products resulting from electrophilic substitution. Subsequent hydrogenation of the keto ester gave the two *cis*-tetrahydrofurans **158** and **159** in a 1:4 ratio. Equilibration of the center α to the ester apparently occurs without inducing β -elimination of the furan ring oxygen. Hydride reduction of ketone **159** then gave a 1:1 mixture of C-8 alcohols **160** from which racemic methyl nonactate (**154**) could be isolated.

The second Gerlach synthesis of nonactic acid, detailed in Scheme 4.27, controlled the stereochemistry of the C-8 alcohol center early on, and formed



Scheme 4.26. Gerlach's first methyl nonactate syntheses.

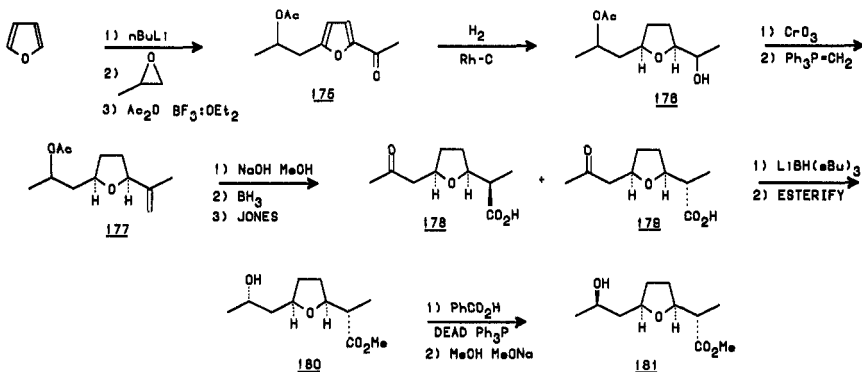
the tetralactone in stepwise fashion.¹³⁰ Acetylacetone (**161**) was converted to the dianion and treated with allyl bromide, and the two carbonyl groups were reduced. Chromatographic separation of the diol mixture resulted in isolation of the erythro and threo diols **162** and **163**, respectively, in 70% total yield. The latter compound was acetylated and ozonolyzed to provide an 88% yield of aldehyde **164**. Chain extension via the phosphonate reagent **165** afforded a good yield of unsaturated ester **166** as a mixture of olefin isomers (3:7, *Z:E*). Deacylation-induced addition of the proximate hydroxyl in a 1,4 fashion to afford predominantly the *cis*-2,5-dihydrofuran **167**. As before, base equilibration during this transformation resulted in a mixture enriched in acid **167**, which possesses the natural configuration at C-2. Chromatography was employed to obtain pure nonactic acid **167**.

Conversion of **167** to nonactin (**174**) requires the proper manipulation of protecting groups and choice of esterification partners. Accordingly, **167** was converted to the benzyl ether **168** (80%) and the *t*-butyl ester **169** (70%) via known procedures. Coupling of these differentiated monomers to give the protected dimer **170** was accomplished in 70% yield via activation of the carboxyl group with 2,4,6-trimethylbenzenesulfonyl chloride. Cleavage of the benzyl ether gave the alcohol **171**, while a parallel reaction involving ester saponification provided **172**. Conversion of the two dimeric units **171** and **172** to the acyclic tetramer **173** was effected via the sulfonyl mixed anhydride of **172**. Following removal of the protecting groups on the termini of **173**, macrolactonization was accomplished via silver-mediated cyclization of the analogous 2-thiopyridyl thioester to give a statistical mixture of all possible diastereomers. Chromatography followed by recrystallization then afforded the meso isomer nonactin (**174**).

White has also completed two syntheses of racemic methyl nonactate (**154**).¹³⁴ The first approach controlled the C-8 alcohol stereochemistry, and the second provided a rapid entry into the ring system. The first sequence, outlined in Scheme 4.28, began with the opening of propylene oxide by 2-lithiofuran. The Friedel-Crafts acylation that followed also resulted in protection of the alcohol as the acetate to give **175** in 81% overall yield. Hydrogenation of the furan ring over rhodium on charcoal gave a 96% yield of tetrahydrofuran diastereomers

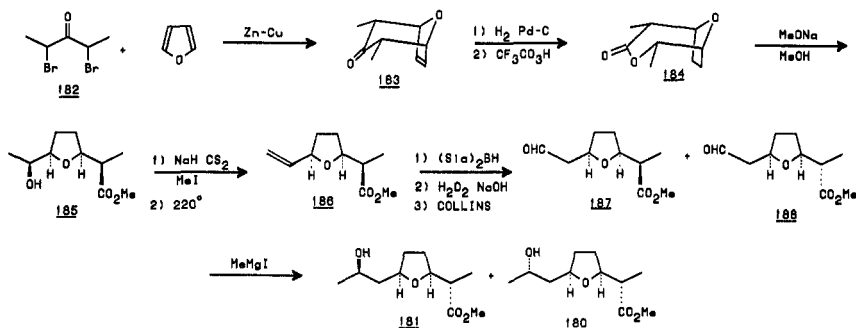


The second White synthesis of **154** (depicted in Scheme 4.29) began with the treatment of dibromoketone **181** with zinc–copper couple to give a 2-oxo-1,3-dipole, which upon condensation with furan gave the oxabicyclo[3.2.1] system **182**. Hydrogenation of the double bond followed by Baeyer–Villiger reaction afforded lactone **183** in 92% yield. The prior three steps have created the stereochemistry (albeit undesired but manipulable) not only at the C-3 and C-6



Scheme 4.28. White's first methyl nonactate synthesis.

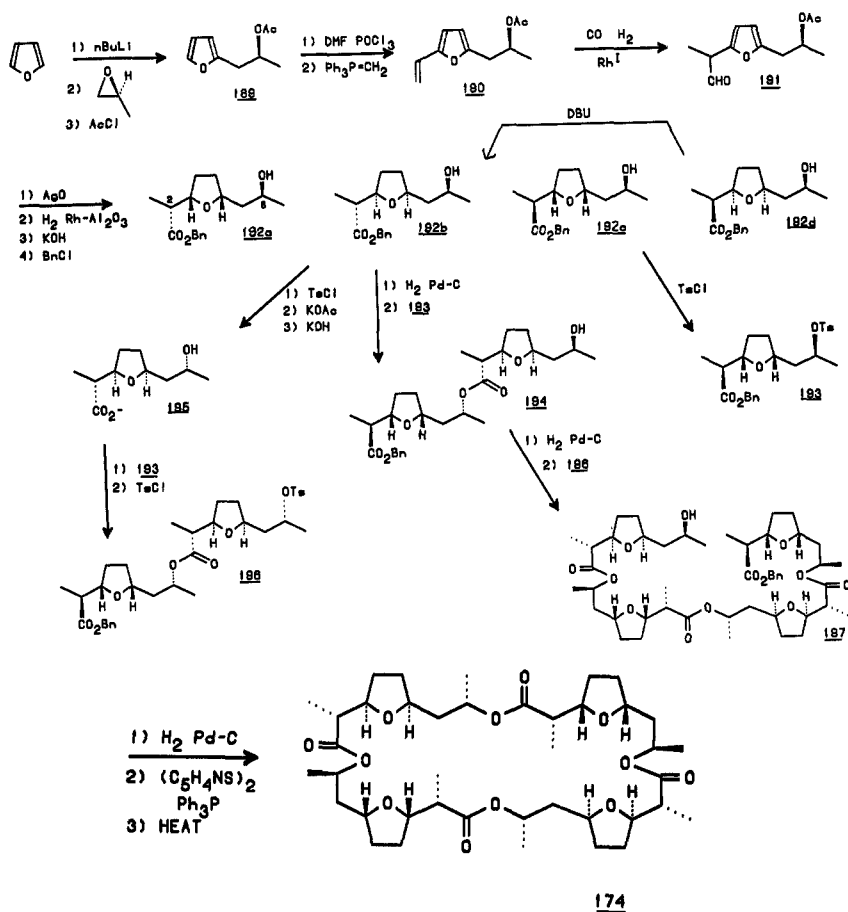
positions of the tetrahydrofuran but also at the C-2 and C-8 centers in the sidechains (nonactic acid numbering). Methanolysis of the lactone then afforded the expected tetrahydrofuran derivative **184**. Elimination of the secondary alcohol in **184** to vinyl ester **185** proceeded via the corresponding xanthate (42%). Hydroboration-oxidation of **185** gave a stereorandom mixture (1:1) of ester aldehydes **186** and **187**, the equilibration presumably resulting from exposure to base. Aldehyde **187**, which has the desired natural configuration at the ester side chain, was converted in a nonstereoselective manner to racemic methyl nonactate (**154**) and methyl 8-epi-nonactate (**180**).



Scheme 4.29. White's second methyl nonactate synthesis.

Schmidt and co-workers reported the first stereoselective synthesis of both enantiomers of a nonactic acid derivative, as well as nonactin itself.¹³⁵ As depicted in Scheme 4.30, 2-lithiofuran was reacted with (*S*)-propylene oxide to

give, following acylation of the oxygen, furan **188** in 51% yield. A Vilsmeier reaction on **188** followed by olefination gave vinyl furan **189** in 46% yield. Rhodium-catalyzed carbonylation of **189** provided **190** as a mixture of diastereomers (40%). Aldehyde **190** was then subjected to sequential oxidation to the acid, reduction of the furan to the *cis*-substituted tetrahydrofuran, and esterification with benzyl alcohol to obtain a stereoisomeric mixture of hydroxy ester (68%). Chromatographic purification of this mixture led to isolation of the four expected diastereomers: **191a** (2*R*,3*S*,6*R*,8*S*); **191b** (2*R*,3*R*,6*S*,8*S*); **191c** (2*S*,3*S*,6*R*,8*S*); **191d** (2*S*,3*R*,6*S*,8*S*). As shown by Gerlach¹³³ and by Schmidt in a previous synthesis of racemic materials, the C-2 position in **191d** is readily epimerizable to predominately the natural configuration under basic conditions.



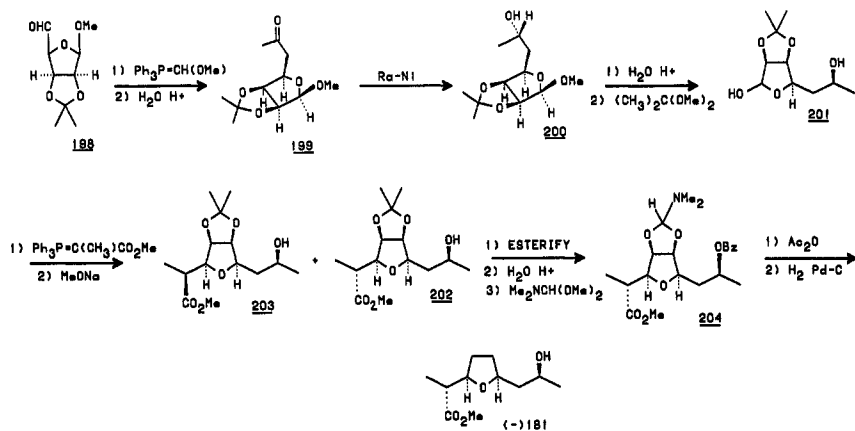
Scheme 4.30. Schmidt's nonactin synthesis.

To this end, equilibration with DBU converted pure **191d** to a 2:1 mixture of **191b** and **191d**. Tosylation of **191c** gave **192** (85%), in which the C-8 center can now be inverted. Coupling of the enantiomerically related intermediates **191b** and **192** was now achieved by cleavage of the benzyl ester in **191b**, followed by esterification with **192** to give **193** in 75% yield. Inversion of the C-8 center of **191b** was accomplished via tosylation, displacement with potassium acetate, and ester cleavage to give **194** in 48% overall yield. Construction of the second alternating enantiomeric sequence was accomplished via the alkylation of **194** with **192**, followed by tosylation to give **195** in 62% overall yield. Deprotection of the benzyl ether of **193** followed by alkylation with **195** then gave solely the acyclic tetramer **196**, which possessed the required alternating sequence of enantiomers. Closure to the tetralide was then effected by hydrogenolysis of the benzyl ester and lactonization to afford nonactin (**174**) in 20% yield.

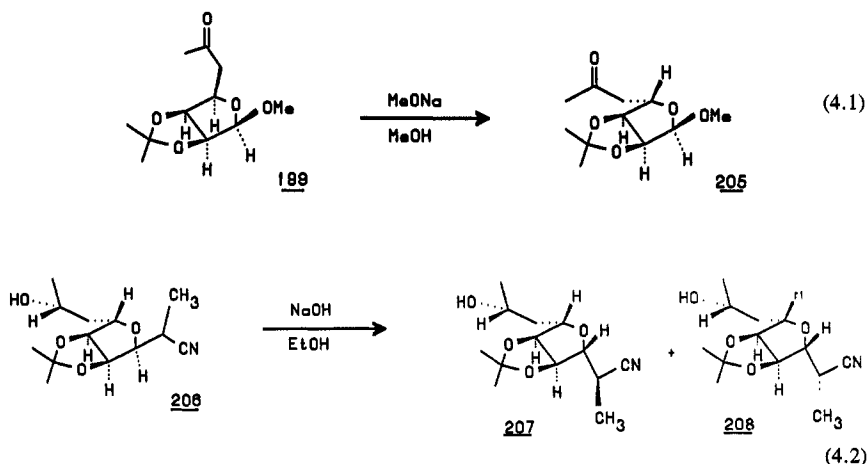
Fraser-Reid, in a beautiful display of carbohydrate manipulation, converted D-ribose into an intermediate from which both enantiomers of optically pure methyl nonactate (**204**) were constructed (Scheme 4.31).¹³⁶ Furanoside **197**, obtained by known methods from D-ribose, was further elaborated by olefination and hydrolysis, affording methyl ketone **198**. Reduction of ketone **198** with Raney nickel through a chelated intermediate afforded the (*S*)-alcohol **199**, contaminated with a small amount of the (*R*)-epimer (9:1, *S*:*R*). Hydrolysis of the methyl acetal and reprotection gave **200**, which was then condensed with a stabilized ylide to afford **201** and **202** (initial ratio 1:3). Equilibration under basic conditions altered this mixture to 3:2 favoring **202**. Upon separation of this mixture and recycling of the undesired epimer, nearly complete conversion to **202**, possessing the required (2*R*,8*S*)-configuration, was achieved. The remaining steps essentially result in reductive deoxygenation of the protected diol in the furan ring. To this end, the C-8 hydroxyl was protected as the benzoate, the acetone was removed, and the resulting diol was transformed into the DMF acetal **203**. Refluxing in acetic anhydride provided the $\Delta^{3,4}$ dihydrofuran, which was directly reduced to (–)-methyl nonactate [(–)-**204**].

The antipode [(+)-**204**] was obtained along similar lines with two minor modifications. Since the stereochemistry of the ring hydroxyl groups is of no consequence, they could be utilized for the inversion of the remaining centers. Accordingly, as described in Eq. 4.1, compound **198** was transformed (90% conversion) to the thermodynamically more stable **205**. Presumably this inversion occurs via β -elimination and readdition of the ring oxygen resulting in the sidechain occupying the face opposite the bulky dioxolane group.

The remainder of the sequence proceeds in similar fashion to the route to (–)-**204**, with the exception of the formation of β -oxy-nitrile **206** from **200** (Eq. 4.2). Fraser-Reid found that in this series, the esters analogous to **202** and **203** but epimeric at C-6 could not be converted to the corresponding *cis*-2,5-tetrahydrofurans; however, nitrile **206** did undergo β -elimination and readdition to give both sidechains anti to the dioxolane. The products from this inversion

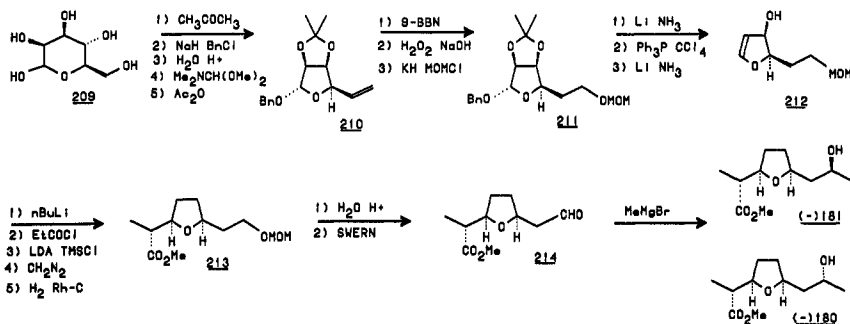


Scheme 4.31. Fraser-Reid's methyl nonactate synthesis.



207 and **208**, formed in a 1:1 ratio, could be converted via recycling and analogous chemical manipulations to (+)-methyl nonactate [(+)-**204**].

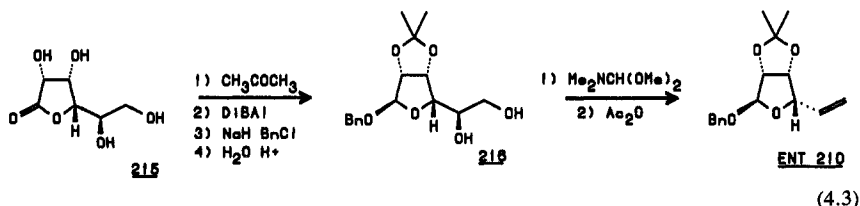
The Ireland contribution to nonactic acid synthesis, outlined in Scheme 4.32, involves a silyl ketene acetal formation and Claisen rearrangement in the key step.¹³⁷ D-Mannose (**209**) was readily converted in a straightforward manner to dihydrofuran **212** via **210** and **211** in 36% overall yield. Esterification of the free alcohol with propionyl chloride followed by the an enolate Claisen rearrangement afforded a mixture (89:11) of tetrahydrofuryl propionates **213** after catalytic reduction.



Scheme 4.32. Ireland's methyl nonactate synthesis.

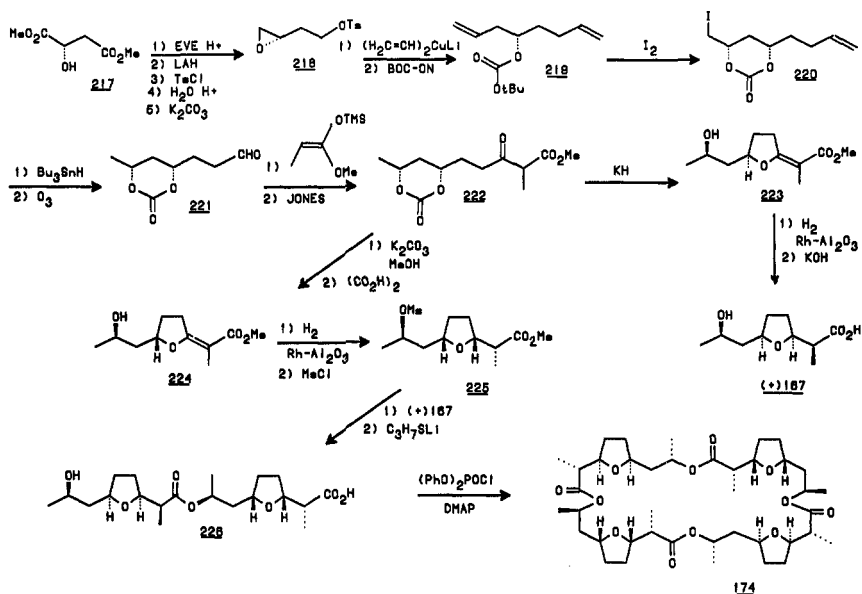
The intermediate enolate in this key rearrangement is presumably the (*Z*)-enolate isomer, which rearranges through a boat-like transition state, resulting in the observed 89:11 ratio of **213** to 2-*epi*-**213** after reduction. Ester **213**, after purification, was converted to **214** by removal of the MOM ether and oxidation. Addition of methyl Grignard reagent to aldehyde **214** then afforded a 1:1 mixture of (–)-methyl nonactate [(–)-**204**] and (–)-8-*epi* methyl nonactate [(–)-**180**] in 33 and 36% overall yield, respectively, from **213**.

A similar set of transformations was also done in an antipodal series which led to (+)-**204**. Thus D-gluconic acid γ -lactone (**215**) was converted via a straightforward protection and reduction sequence to furanoside **216**. Reductive deoxygenation via the intermediate DMF acetal gave *ent*-**210** in 11% overall yield from **215**. Conversion of *ent*-**210** to a mixture of (+)-methyl nonactate [(+)-**204**] and (+)-8-*epi* methyl nonactate [(+)-**180**] was then accomplished in a manner identical to that described for the (–)-enantiomer.



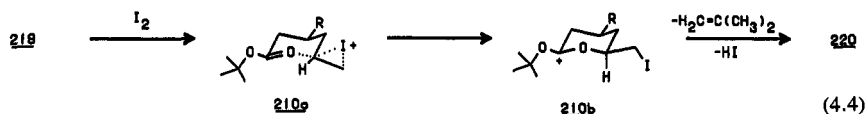
The Bartlett nonactic acid synthesis, outlined in Scheme 4.33, arose from this group's work in the area of acyclic stereocontrol.¹³⁸ From a common intermediate constructed using the carbonate cyclization methodology, Bartlett was able to obtain either antipode of nonactic acid and thus nonactin. To this end, dimethyl-(*S*)-(–)-malic acid **217** was converted by a series of routine chemical transformations to epoxy tosylate **218** in 75% overall yield. Cleavage

of epoxide **218** and tosylate displacement with two equivalents of lithium divinylcuprate followed by protection of the resulting alcohol as the *t*-butyl carbonate provided **219** (90%). Iodine-induced cyclization produced a mixture (6.5:1 *cis:trans*) of iodocarbonates from which **226** could be isolated in 55% yield.



Scheme 4.33. Bartlett's nonactive synthesis.

As Eq. 4.4 describes, the initial intermediate is most plausibly the pseudoequatorial iodonium ion **219a** having the equatorial sidechain. Displacement by the carbonate oxygen via a six-membered ring transition state results in formation of the oxo-stabilized cation **210b**. Loss of isobutylene then produces the *cis*-substituted iodocarbonate **220**.

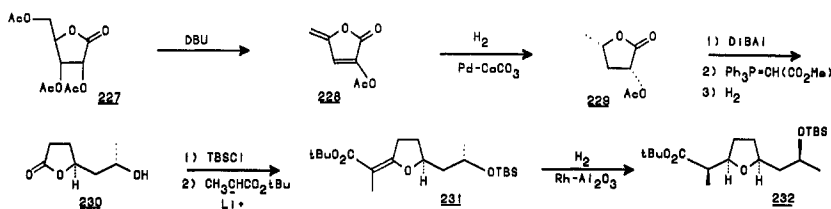


Reductive removal of the halogen was achieved with tributyltin hydride and subsequent ozonolysis gave aldehyde **221**. An aldol condensation of **221** with the trimethylsilyl enol ether of methyl propionate, followed by Jones oxidation

provided the key intermediate **222** in 73% overall yield from **220**. Bartlett reasoned that displacement at the C-6 alcohol center with the β -keto-ester unit would lead to the (+)-enantiomeric series, while allowing C-6 to act as the nucleophile should result in the (-)-series. To this end, treatment of **222** with KH resulted in O-alkylation of the keto ester at C-6 of the carbonate to yield **223**, which possessed the required (6*R*,8*R*)-stereochemistry. As expected, the (*E*)-geometry was preferred in the vinylogous carbonate. Reduction of this olefin predominately from the least-hindered face followed by ester hydrolysis gave (+)-nonactic acid [(+)-**167**] in 81% isolated yield. The final product was contaminated with small amounts of products resulting from reduction syn to the propyl side chain and from reduction of the (*Z*)-vinylogous carbonate.

The enantiomeric series was obtained by hydrolysis of carbonate **222** followed by dehydration to give **224** (76%). An analogous hydrogenation of the vinylogous carbonate gave the 2,5-*cis*-dialkyltetrahydrofuran, which was converted to mesylate **225** in 80% yield. Displacement with inversion at C-8 of **225** was achieved by the addition of the potassium salt of (+)-**167**, and the resulting ester was demethylated to give dimer **226** in 69% yield. Formation of the tetralide utilizing the Masamune method then afforded a 15–20% yield of nonactin (**174**).

Perhaps the shortest entry to a stereocontrolled synthesis of a nonactic acid derivative is outlined in Scheme 4.34.¹³⁹ Tri-*O*-acetyl-D-ribonolactone (**227**) was treated with DBU to give the double elimination product **228** (94%). Hydrogenation then gave a 90% yield of the *cis*-3,5-disubstituted γ -lactone **229**. Reduction to the lactol, two-carbon homologation, hydrogenation, and lactonization then afforded **230** in 43% yield. After the secondary alcohol was protected as the silyl ether, an aldol condensation followed by dehydration led to the vinylogous carbonate **231** (75%). Hydrogenation then proceeded predominately from the face anti to the propyl sidechain to give the nonactic acid derivative **232**.



Scheme 4.34. Barrett's nonactate synthesis.

REFERENCES

- (a) Nicolaou, K.C. *Tetrahedron* **1977**, *33*, 683. (b) Masamune, S.; Bates, G.S.; Corcoran, W. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 585. (c) Back, T.G. *Tetrahedron* **1977**, *33*, 3041.

2. (a) Masamune, S. *Aldrichimica Acta* **1978**, *11*, 23. (b) Masamune, S.; Choy, W. *Ibid.*, **1982**, *15*, 47.
3. Masamune, S.; McCarthy, P.A., In *Macrolides*; Omura, S., Ed.; Academic: New York, 1984; Chapter 4.
4. Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569.
5. Vesonder, R. F.; Stodola, F. H.; Wickerham, L. J.; Ellis, J. J.; Rothwedder, W. K. *Can. J. Chem.* **1971**, *49*, 2029.
6. Corey, E. J.; Ulrich, P.; Fitzpatrick, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 222.
7. Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta.* **1976**, *59*, 755.
8. Narasaka, K.; Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1977**, 959.
9. Utimoto, K.; Uchida, K.; Yamaya, M.; Nozaki, H. *Tetrahedron Lett.* **1977**, 3641.
10. Tsuji, J.; Yamakawa, T.; Mandai, T. *Tetrahedron Lett.* **1978**, 565.
11. Takahashi, T.; Hashiguchi, S.; Kasuga, K.; Tsuji, J. *J. Am. Chem. Soc.* **1978**, *100*, 7424.
12. Yoshida, J.; Tamao, K.; Takahashi, M.; Kumada, M. *Tetrahedron Lett.* **1978**, 2161.
13. Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6163.
14. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743.
15. Trost, B. M.; Verhoeven, T. R. *J. Org. Chem.* **1976**, *41*, 3216.
16. Wasserman, H. H.; Gambale, R. J.; Pulwer, M. J. *Tetrahedron* **1981**, *37*, 4059.
17. Bestmann, H. J.; Schobert, R. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 780.
18. (a) Ishida, T.; Wada, K. *J. Chem. Soc. Chem. Comm.* **1975**, 209. (b) Wada, K.; Ishida, T. *Ibid.* **1976**, 340.
19. (a) Ishida, T.; Wada, K. *J. Chem. Soc. Chem. Comm.* **1977**, 337. (b) Ishida, T.; Wada, K. *J. Chem. Soc. Perkins I* **1979**, 323.
20. Tsuji, J.; Mandai, T. *Tetrahedron Lett.* **1978**, 1817.
21. Wakamatsu, T.; Akasaka, K.; Ban, Y. *J. Org. Chem.* **1979**, *44*, 2008.
22. Ireland, R. E.; Brown, Jr., F. R. *J. Org. Chem.* **1980**, *45*, 1868.
23. Shenvi, A. B.; Gerlach, H. *Helv. Chim. Acta* **1980**, *63*, 2426.
24. Aldridge, D. C.; Galt, S.; Giles, D.; Turner, W. B. *J. Chem. Soc. C* **1971**, 1623.
25. Gerlach, H.; Thalmann, A. *Helv. Chim. Acta.* **1977**, *60*, 2866.
26. Takahashi, T.; Kasuga, K.; Tsuji, J. *Tetrahedron Lett.* **1977**, 4917.
27. Danishefsky, S.; Etheredge, S. J. *J. Org. Chem.* **1979**, *44*, 4716.
28. Fink, M.; Gaier, H.; Gerlach, H. *Helv. Chim. Acta* **1982**, *65*, 2563.
29. (a) Birch, A. J.; Musgrave, O. C.; Rickards, R. W.; Smith, H. *J. Chem. Soc.* **1959**, 3146. (b) Musgrave, O. C. *Ibid.* **1957**, 1104.
30. Baker, P. M.; Bycroft, B. W.; Roberts, J. C. *J. Chem. Soc. Chem. Comm.* **1967**, 1913.
31. Gerlach, H. *Helv. Chim. Acta* **1977**, *60*, 3039.
32. Takahashi, T.; Ikeda, H.; Tsuji, J. *Tetrahedron Lett.* **1980**, 3885.
33. Wasserman, H. H.; Gambale, R.J.; Pulwer, M. J. *Tetrahedron* **1981**, *37*, 4059.
34. (a) Urry, W. H.; Wehrmeister, H. L.; Hodge, E. B.; Hiddy, P.H. *Tetrahedron Lett.* **1966**, 3109. (b) Kuo, C. H.; Taub, D.; Hoffsommer, R. D.; Wendler, N. L. *J. Chem. Soc. Chem. Comm.* **1967**, 761. (c) Mirocha, C. J.; Christensen, C. M.; Nelson, G. H. *Appl. Microbiol.* **1967**, *15*, 497. (d) Stob, M.; Baldwin, R. S.; Tuite, J.; Andrews, F. N.; Gillette, K. G. *Nature* **1962**, *196*, 1318.
35. Taub, B.; Girotra, N. N.; Hoffsommer, R. D.; Kuo, C. H.; Slates, H. L.; Weber, S.; Wendler, N. L. *Tetrahedron* **1968**, 2443.
36. Girotra, N. N.; Wendler, N. L. *J. Org. Chem.* **1969**, *34*, 3192.

37. Vlattas, I.; Harrison, I. T.; Tökes, L.; Fried, J. H.; Cross, A. D. *J. Org. Chem.* **1968**, *33*, 4176.
38. Takahashi, T.; Kasuga, K.; Takahashi, M.; Tsuji, J. *J. Am. Chem. Soc.* **1979**, *101*, 4072.
39. Takahashi, T.; Nagashima, T.; Tsuji, J. *Chem. Lett.* **1980**, 369.
40. Takahashi, T.; Ikeda, H.; Tsuji, J. *Tetrahedron Lett.* **1981**, *22*, 1363.
41. (a) Harri, E.; Loeffler, W.; Sigg, H. P.; Stähelin, H.; Tamm, C. *Helv. Chim. Acta* **1963**, *46*, 1235. (b) Weber, H. P.; Hauser, D.; Sigg, H. P. *Ibid.* **1971**, *54*, 2763. (c) See also Reference 46 and references therein.
42. (a) Tamura, G.; Ando, K.; Suzuki, S.; Takatsuki, A.; Arima, K. *J. Antibiot. Ser. A.* **1968**, *21*, 160. (b) Betina, V. *Neoplasma* **1969**, *16*, 23.
43. Corey, E. J.; Wollenberg, R. H. *Tetrahedron Lett.* **1976**, 4705.
44. Corey, E. J.; Wollenberg, R. H.; Williams, D. R. *Tetrahedron Lett.* **1977**, 2243.
45. Baudouy, R.; Crabbe, P.; Greene, A. E.; LeDrian, C.; Orr, A. F. *Tetrahedron Lett.* **1977**, 2973.
46. Bartlett, P. A.; Green, III, F. R. *J. Am. Chem. Soc.* **1978**, *100*, 4858.
47. Kitahara, T.; Mori, K.; Matsui, M. *Tetrahedron Lett.* **1979**, 3021.
48. Köksal, Y.; Raddatz, P.; Winterfeldt, E. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 472.
49. Raddatz, P.; Winterfeldt, E. *Ibid.* **1981**, *20*, 286.
50. Greene, A. E.; LeDrian, C.; Crabbe, P. *J. Am. Chem. Soc.* **1980**, *102*, 7583.
51. LeDrian, C.; Greene, A. E. *Ibid.* **1982**, *104*, 5473.
52. Hondo, M.; Hirata, K.; Sueoka, H.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1981**, 2679.
53. (a) Gais, H.-J.; Lukas, K. L. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 142. (b) Gais, H.-J. *Ibid.* **1984**, *23*, 143. (c) Gais, H.-J.; Lied, T. *Ibid.* **1984**, *23*, 145.
54. Michel, K. H.; Demarco, P. V.; Nagarajan, R. *J. Antibiot.* **1977**, *30*, 571.
55. Hase, T. A.; Nylund, E.-L. *Tetrahedron Lett.* **1979**, 2633.
56. (a) Tasuta, K.; Nakagawa, A.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, 1479. (b) Tasuta, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3248.
57. Asaoka, M.; Yanagida, N.; Takei, H. *Tetrahedron Lett.* **1980**, 4611.
58. Trost, B. M.; Brickner, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 568.
59. Fujisawa, T.; Okada, N.; Takeuchi, M.; Sato, T. *Chem. Lett.* **1983**, 1271.
60. Kawashima, M.; Fujisawa, T. *Chem. Lett.* **1984**, 1851.
61. (a) Keller-Schierlein, W. *Fortschr. Chem. Org. Naturst.* **1973**, *30*, 313. (b) Celmer, W. D. *Pure Appl. Chem.* **1971**, *28*, 413. (c) Djerassi, C.; Zderic, J. A. *J. Am. Chem. Soc.* **1956**, *78*, 2907, 6390. (d) Manwaring, D. G.; Rickards, R. W.; Smith, R. M. *Tetrahedron Lett.* **1970**, 1025.
62. For an extensive list of many recent syntheses of Prelog-Djerassi lactone, the reader is directed to Reference 4 and the citations therein.
63. (a) Masamune, S.; Kim, C. V.; Wilson, K. E.; Spessard, G. O.; Georgiou, P. E.; Bates, G. S. *J. Am. Chem. Soc.* **1975**, *97*, 3512. (b) Masamune, S.; Yamamoto, H.; Kamata, S.; Fukuzawa, A. *Ibid.* **1975**, *97*, 3513.
64. Inanaga, J.; Katsuki, T.; Takimoto, S.; Ouchida, S.; Inoue, K.; Nakano, A.; Okukado, N.; Yamaguchi, M. *Chem. Lett.* **1979**, 1021.
65. Grieco, P. A.; Ohfuné, Y.; Yokoyama, Y.; Owens, Y. *J. Am. Chem. Soc.* **1979**, *101*, 4749.
66. (a) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479. (b) Ireland, R. E.; Daub, J. P.; Mandel, G. S.; Mandel, N. S. *J. Org. Chem.* **1983**, *48*, 1312.
67. (a) Djerassi, C.; Halpern, O. *Tetrahedron* **1958**, *3*, 255. (b) Maezawa, I.; Kinumaki, A.; Suzuki, M. *J. Antibiot.* **1974**, *27*, 84.
68. Inanaga, J.; Kawanami, Y.; Yanaguchi, M. *Chem. Lett.* **1981**, 1415.

69. (a) Martin, J. R.; Rosenbrook, W. *Biochemistry* **1967**, *6*, 435. (b) Perun, T. L.; Egan, R. S. *Tetrahedron Lett.* **1969**, 387. (c) Egan, R. S.; Perun, T. L.; Martin, J. R.; Mitscher, L. A. *Tetrahedron* **1973**, *29*, 2525.
70. Masamune, S.; Hirama, M.; Mori, S.; Ali, A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568.
71. (a) Hori, T.; Meazawa, I.; Naghama, N.; Susuki, M. *J. Chem. Soc. Chem. Comm.* **1971**, 304. (b) Maezawa, I.; Hori, T.; Suzuki, M. *Agric. Biol. Chem.* **1974**, *38*, 539. (c) Corbaz, R.; Ettlinger, L.; Gäumann, E.; Keller-Schierlein, W.; Neipp, L.; Prelog, V.; Reusser, P.; Zähler, H. *Helv. Chim. Acta* **1955**, *38*, 1202.
72. Kaiho, T.; Masamune, S.; Toyoda, T. *J. Org. Chem.* **1982**, *47*, 1612.
73. (a) Keller-Schierlein, W. *Prog. Chem. Org. Nat. Prod.* **1973**, *30*, 314. (b) Oleinick, N. L. In *Antibiotics*, Corcoran, J. W.; Hahn, F. E., Eds.; Springer-Verlag: New York, **1975**; Vol. III, pp. 396-419.
74. *Perspectives in Organic Chemistry*; Todd, A., Ed.; Interscience: New York, **1956**; p. 160.
75. (a) Corey, E. J.; Trybulski, E. J.; Melvin, L. S.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falck, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, E.; Yoo, S. *J. Am. Chem. Soc.* **1978**, *100*, 4618. (b) Corey, E. J.; Kim, S.; Yoo, S.; Nicolaou, K. C.; Melvin, L. S.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *Ibid.* **1978**, *100*, 4620.
76. Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. P.; Falck, J. R. *Ibid.* **1979**, *101*, 7131.
77. Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chênevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, A.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B.S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tasuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, R. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3210, 3213, 3215.
78. (a) Hanessian, S.; Rancourt, G. *Can. J. Chem.* **1977**, *55*, 1111. (b) Hanessian, S.; Rancourt, G.; Guidon, Y. *Ibid.* **1978**, *56*, 1943.
79. Stork, G.; Paterson, I.; Lee, F. K. C. *J. Am. Chem. Soc.* **1982**, *104*, 4686.
80. Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, **1983**; pp. 330-335. We thank Professor Deslongchamps for a preprint of this work.
81. Chamberlin, A. R. private communication.
82. (a) Hochstein, F. A.; Murai, K. *J. Am. Chem. Soc.* **1954**, *76*, 5080. (b) Hata, T.; Sano, Y.; Ohno, N.; Yokoyama, Y.; Matsumae, A.; Ito, S. *J. Antibiot.* **1953**, *A6*, B7.
83. (a) Tatsuta, K.; Amemiya, Y.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, 2837. (b) Tasuta, K.; Tanaka, A.; Fujimoto, K.; Kinoshita, M.; Umezawa, S. *J. Am. Chem. Soc.* **1977**, *99*, 5826.
84. Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 1222, 1224.
85. Freiberg, L. A.; Egan, R. S.; Washburn, W. H. *J. Org. Chem.* **1974**, *39*, 2474.
86. Hayashi, M.; Ohara, H.; Ohno, M.; Sakakibara, H.; Sato, S.; Harada, K.; Suzuki, M. *J. Antibiot.* **1981**, *34*, 1075.
87. Hondo, M.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, 3857.
88. (a) Hamill, R. L.; Haney, M. E.; Stamper, M.; Wiley, P. F. *Antibiot. Chemother. (Washington, D.C.)* **1961**, *11*, 328. (b) Omura, S.; Matsubara, H.; Nakagawa, A.; Furusaki, A.; Matsumoto, T. *J. Ibid.* **1980**, *33*, 915.

89. Tatsuta, K.; Ameniya, Y.; Kanemura, Y.; Kinoshita, M. *Tetrahedron Lett.* **1981**, 3997.
90. Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 2027, 2030.
91. (a) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521. (b) Masamune, S.; Lu, L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *Ibid.* **1982**, *104*, 5523.
92. Grieco, P. A.; Inanaga, J.; Lin, N.-L.; Yanami, T. *J. Am. Chem. Soc.* **1982**, *104*, 5781.
93. (a) Springer, J. P.; Arison, B. H.; Hirschfield, J. M.; Hoogsteen, K. *J. Am. Chem. Soc.* **1981**, *103*, 4221. (b) Mishima, H.; Kurbayashi, M.; Tamura, L. *Tetrahedron Lett.* **1985**, 711.
94. Smith, III, A. B.; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4015.
95. Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. *J. Am. Chem. Soc.* **1982**, *104*, 4708.
96. Binder, M.; Tamm, C. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 370.
97. Stork, G.; Nakahara, Y.; Greenlee, W. G. *J. Am. Chem. Soc.* **1978**, *100*, 7775.
98. Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756.
99. Stork, G.; Nakamura, E. *Ibid.* **1983**, *105*, 5510.
100. Vedejs, E.; Reid, J. G. *Ibid.* **1984**, *106*, 4617.
101. Taploczay, D. J.; Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc. Chem. Comm.* **1985**, 143.
102. Higgs, M. D.; Mulheirn, L. J. *Tetrahedron* **1981**, *37*, 4259.
103. Corey, E. J.; De, B. *J. Am. Chem. Soc.* **1984**, *106*, 2735.
104. Nozoe, S.; Hirai, K.; Tsuda, L.; Ishibashi, K.; Shirasaka, M.; Grove, J. F. *Tetrahedron Lett.* **1965**, 4675.
105. Colvin, E. W.; Purcell, T. A.; Raphael, R. A. *J. Chem. Soc. Perkin I* **1976**, 1718.
106. Seebach, D.; Seuring, B.; Kalinowski, H.-O.; Lubosch, W.; Renger, B. *Angew. Chem.* **1977**, *89*, 270.
107. Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1977**, *60*, 2860.
108. Trost, B. M.; Gowland, F. W. *J. Org. Chem.* **1979**, *44*, 3448.
109. Bakuzis, P.; Bakuzis, M. L. F.; Weingartner, T. F. *Tetrahedron Lett.* **1978**, 2317.
110. Asaoka, M.; Yanagida, N.; Sugimura, N.; Takei, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1061.
111. Asaoka, M.; Mukuta, T.; Takei, H. *Tetrahedron Lett.* **1981**, 735.
112. Hase, T. A.; Ourila, A.; Holmberg, C. *J. Org. Chem.* **1981**, *46*, 3137.
113. Labadie, J. W.; Stille, J. K. *Tetrahedron Lett.* **1983**, 4283.
114. Baraldi, P. G.; Barco, A.; Benetti, S.; Moroder, F.; Pollini, G. P.; Simoni, D. *J. Org. Chem.* **1978**, *43*, 1297.
115. Derguini, F.; Linstrumelle, G. *Tetrahedron Lett.* **1984**, 5763.
116. Dumont, W.; Vermeyen, C.; Krief, A. *Ibid.* **1984**, 2883.
117. (a) Fuska, J.; Nemec, P.; Kuhr, I. *J. Antibiot.* **1972**, *25*, 208. (b) Boeckman, Jr., R. K.; Fayos, J.; Clardy, J. *J. Am. Chem. Soc.* **1974**, *96*, 5954.
118. Corey, E. J.; Nicolaou, K. C.; Toru, T. *Ibid.* **1975**, *97*, 2287.
119. Fukuyama, Y.; Kirkemo, C. L.; White, J. D. *Ibid.* **1977**, *99*, 646.
120. Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, R. *Ibid.* **1978**, *100*, 7069.
121. (a) Okazaki, T.; Kitahara, T.; Okami, Y. *J. Antibiot.* **1975**, *28*, 176. (b) Nakamuara, H.; Sitaka, Y.; Kitahara, T.; Okazaki, T.; Okami, Y. *Ibid.* **1977**, *30*, 714.
122. Corey, E. J.; Pan, B.-C.; Hua, D. H.; Deardorf, D. R. *J. Am. Chem. Soc.* **1982**, *104*, 6816, 6818.

123. (a) Tamm, C. *Fortschr. Chem. Org. Naturst.* **1974**, 31, 63. (b) Härrä, E.; Loeffler, W.; Sigg, H. P.; Stählin, H.; Tamm, C.; Wiesinger, D. *Helv. Chim. Acta* **1962**, 45, 839.
124. Still, W. C.; Ohmizu, H. *J. Org. Chem.* **1981**, 46, 5242.
125. Mohr, P.; Tori, M.; Grossen, P.; Herold, P.; Tamm, C. *Helv. Chim. Acta* **1982**, 65, 1412.
126. (a) Roush, W. R.; Blizzard, J. A. *J. Org. Chem.* **1983**, 48, 759. (b) Roush, W. R.; Blizzard, T. A. *Ibid* **1984**, 49, 1772.
127. Esmond R.; Fraser-Reid, B.; Jarvis, B. B. *Ibid.* **1982**, 47, 3358.
128. (a) Kupchan, S. M.; Jarvis, B. B.; Dailey, R. G.; Bright, W.; Bryan, R. F.; Shieuri, Y. *J. Am. Chem. Soc.* **1976**, 98, 7092. (b) Jarvis, B. B.; Stahly, G. P.; Pavanadasivam, G.; Mazzola, E. P. *J. Med. Chem.* **1980**, 23, 1054.
129. Still, W. C.; Gennari, C.; Noguez, J. A.; Pearson, D. A. *J. Am. Chem. Soc.* **1984**, 106, 260.
130. (a) Keller-Schierlein, W.; Gerlach, H. *Fortschr. Chem. Org. Naturst.* **1968**, 2, 161. (b) Dominguez, J.; Dunitz, J. D.; Gerlach, H.; Prelog, V. *Helv. Chim. Acta* **1962**, 45, 129. (c) Prestegard, J. H.; Chan, S. I. *J. Am. Chem. Soc.* **1970**, 92, 4440. (d) Graven, S.; Hardy, H.; Estrada, S. *Biochemistry* **1967**, 6, 365. (e) Graven, S.; Hardy, H.; Johnson, D.; Rutter, A. *Ibid.* **1966**, 5, 1729.
131. Bartlett, P. A. *Tetrahedron* **1980**, 36, 3.
132. Beck, G.; Henseleit, E. *Chem. Ber.* **1971**, 104, 21.
133. (a) Gerlach, H.; Wetter, H. *Helv. Chim. Acta* **1974**, 57, 2306. (b) Gerlach, H.; Oertle, K.; Thalmann, A.; Saervi, S. *Ibid.* **1975**, 58, 2036.
134. Arco, M. J.; Trammell, M. H.; White, J. D. *J. Org. Chem.* **1976**, 41, 2075.
135. Schmidt, U.; Gambos, J.; Haslinger, E.; Zak, H. *Chem. Ber.* **1976**, 109, 2628.
136. Sun, K. M.; Fraser-Reid, B. *Can. J. Chem.* **1980**, 58, 2732.
137. (a) Ireland, R. E.; Vevert, J.-P. *J. Org. Chem.* **1980**, 45, 4260. (b) Ireland, R. E.; Vevert, J.-P. *Can. J. Chem.* **1981**, 59, 572.
138. Bartlett, P. A.; Meadows, J. D.; Ottow, E. *J. Am. Chem. Soc.* **1984**, 106, 5304.
139. Barrett, A. G. M.; Sheth, H. G. *J. Org. Chem.* **1983**, 48, 5017.

Synthesis of the Leukotrienes

J. ROKACH, Y. GUINDON, R.N. YOUNG, J. ADAMS,
and J.G. ATKINSON

Merck Frosst Canada Inc.

Kirkland, Quebec, Canada

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- (2) Synthesis of the 11-, 12-, and 15-HETEs and HPETEs

B. Synthesis of Isomeric LTA₄'s

- (1) Synthesis of (±)-11, 12-LTA₄
- (2) Enantiospecific Synthesis of 11,12-LTA₄
- (3) Biomimetic Synthesis of (14*S*, 15*S*)-LTA₄
- (4) Total Synthesis of (14*S*, 15*S*)-LTA₄

C. Synthesis of diHETEs

- (1) Synthesis of 8,15-diHETEs
- (2) Synthesis of (5*S*, 15*S*)-diHETE and (8*S*, 15*S*)-diHETE

References**5. Leukotriene Analogs****A. Analogs of LTA₄, LTC₄, LTD₄, LTE₄, and LTF₄**

- (1) Olefin Isomers
- (2) Hydro-Analogs of LTA₄, LTC₄, LTD₄, and LTE₄
- (3) Dehydro-Analogs of LTA₄, LTC₄, LTD₄, and LTE₄
- (4) Positional Isomers of LTA₄, LTC₄, LTD₄, and LTE₄
- (5) Homo- and Nor-Leukotriene Analogs
- (6) Other Analogs of Leukotriene A₄
- (7) Analogs of LTC₄, D₄, and E₄ Where the 5-Hydroxy or 6-Peptide Portion Has Been Modified

B. Analogs of LTB₄

- (1) Stereoisomers of LTB₄
- (2) LTB₅ and LTB₃

(3) LTB₄ Amides

References

6. Conclusion

1. THE LEUKOTRIENES

Introduction

The leukotrienes, a family of compounds derived from the oxidative metabolism of arachidonic acid, have attracted the attention of a large portion of the scientific community in recent years. This present chapter deals primarily with the different chemical aspects associated with this field of research, in particular, their discovery their biogenesis, the strategic considerations envisaged in their synthesis, and the syntheses of the products associated with the 5-, 8-, 9-, 11-, 12-, and 15-lipoxygenase cascades. The literature to mid-1985 is covered.¹

A. Aspects of Nomenclature

The leukotrienes, a new class of acyclic eicosanoids, are normally named using either a systematic or an abbreviated nomenclature. A note is in order on this latter system, which was introduced by Samuelsson.²

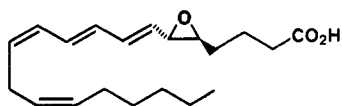
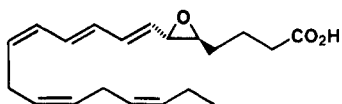
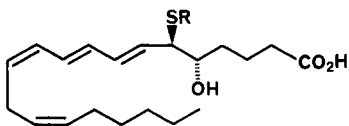
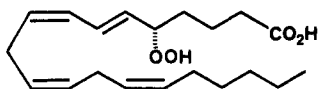
The term 'leukotriene' is derived from the fact that the compounds were first discovered in leukocytes and are characterized by a conjugated triene unit.

Leukotrienes are normally referred to as LTX_n, where LT stands for leukotriene, X denotes a specific class of leukotriene of a given nature, and *n* is a numerical subscript, used after the generic name, which denotes the total number of double bonds in the C-20 chain. For instance, LTA₄ is (5*S*)-*trans*-5,6-oxido-7,9-*trans*-11,14-*cis*-eicosatetraenoic acid; LTB₄ is (5*S*,12*R*)-dihydroxy-6,14-*cis*-8,10-*trans*-eicosatetraenoic acid; and LTC₄ is (5*S*)-hydroxy-(6*R*-*S*-glutathionyl-7,9-*trans*-11,14-*cis*-eicosatetraenoic acid.

The acronym HPETE describes a hydroperoxy-eicosatetraenoic acid and a HETE is a monohydroxy-eicosanoid. Some examples are illustrated in Scheme 1.1.

B. Historical Background

In recent years, work on the biochemistry and chemistry of the leukotrienes¹ has culminated in the characterization and chemical identification in 1979 of the constituents³ of SRS-A (slow reacting substance of anaphylaxis):⁴⁻⁶ LTC₄, LTD₄,

LTA₄LTA₅LTC₄: SR=glutathioneLTD₄: SR=cysteinyl glycineLTE₄: SR=cysteineLTF₄: SR=γ-glutamyl cysteine

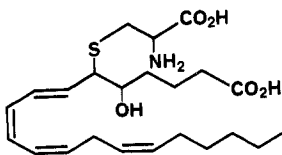
5-HPETE

Scheme 1.1

and LTE₄. This had a major impact on biomedical science since, for the last 40 years, SRS-A had been postulated to be a major mediator of inflammation and allergy.

As with any major discovery, a number of prerequisite conditions had to be met. The formidable biological profile associated with SRS-A, and its putative implication in diseases such as asthma, served as a source of motivation. However, the minute amount of products isolated from natural sources and their chemical instability prevented their purification and structural elucidation using the classical approaches (including X-ray). This made it obvious to researchers that the characterization of the SRS-A constituents, from a chemical and biological point of view, would be dependent on their total synthesis; thus the importance of organic chemistry in this field. Another critical requirement was the improvement of nondegradative technology for the separation of chemically sensitive products. The development of HPLC techniques in the 1970s was therefore pivotal to the success of these efforts.

The advancement of knowledge in the field of leukotrienes then permitted Samuelsson in 1979⁷ to formulate the hypothesis that SRS was, indeed, a peptido-leukotriene (Scheme 1.2) derived from arachidonic acid.



Scheme 1.2

Samuelsson had arrived at this hypothesis based on a series of important findings from his group and others, some of which are summarized below.

- 1972 Samuelsson⁸ et al. showed that a lipoxygenase-derived product is present in mamalian tissues (12-HETE in platelets).
- 1975 Austen⁹ et al. noted that a calcium ionophore induced basophil leukemia cells to produce SRS-A-like material.
- 1976 Borgeat et al.¹⁰ demonstrated the production of 5-HETE from arachidonic acid in rabbit neutrophils.
- 1977 Jakschick et al.¹¹ and Bach et al.¹² demonstrated the incorporation of arachidonic acid into SRS-A.
- 1978 Morris, Piper, and their collaborators¹³ succeeded in preparing highly purified SRS-A.
- 1979 Borgeat and Samuelsson¹⁴ reported a new class of lipid products, dihydroxyeicosatetraenoic acids, including LTB₄. They also noted certain similarities between the UV spectra of these products and that of SRS-A. They postulated that LTB₄ could be derived from an unstable intermediate, which was later identified as LTA₄.¹⁵

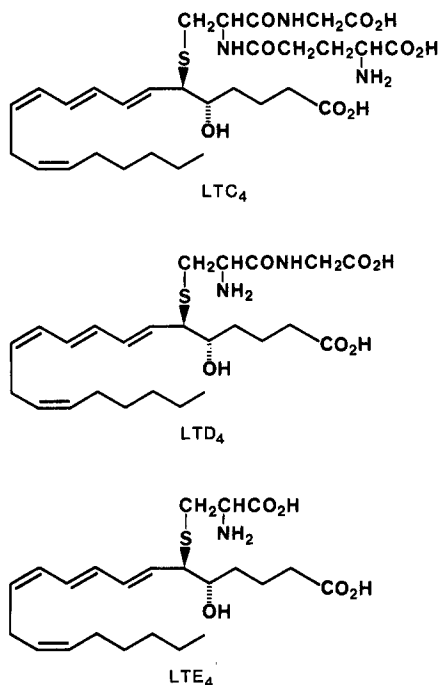
The Samuelsson proposal for the chemical nature of SRS acted as a powerful catalyst and resulted in the mobilization of a large part of the research community, which led, in 1979/1980, to the synthesis (Corey et al.^{16,19} and the Merck Frosst group^{17,18}) and characterization²⁰⁻²³ of the elusive SRS-A as a mixture of LTC₄, LTD₄, and LTE₄ (Scheme 1.3).

C. Biogenesis of Leukotrienes—The 5-HPETE Cascade

The 5-lipoxygenase pathway from which the potent leukotrienes LTB₄, LTC₄, LTD₄, and LTE₄ are derived is, to date, the most important known lipoxygenase pathway available to arachidonic acid.

As detailed in Scheme 1.4 the primary biosynthetic step in this cascade is the introduction of a hydroperoxy group at the 5-position by a “5-lipoxygenase” enzyme^{10,24} to give the hydroperoxy-eicosanoid 5-HPETE.

Isotopic ¹⁸O labeling experiments suggested that the formation of 5-HPETE occurs via radical trapping of oxygen. The 5-HPETE is then transformed into the (5S, 6S)-epoxide LTA₄ by a loss of water, involving stereospecific elimination of a C-10 hydrogen from 5-HPETE.²⁵



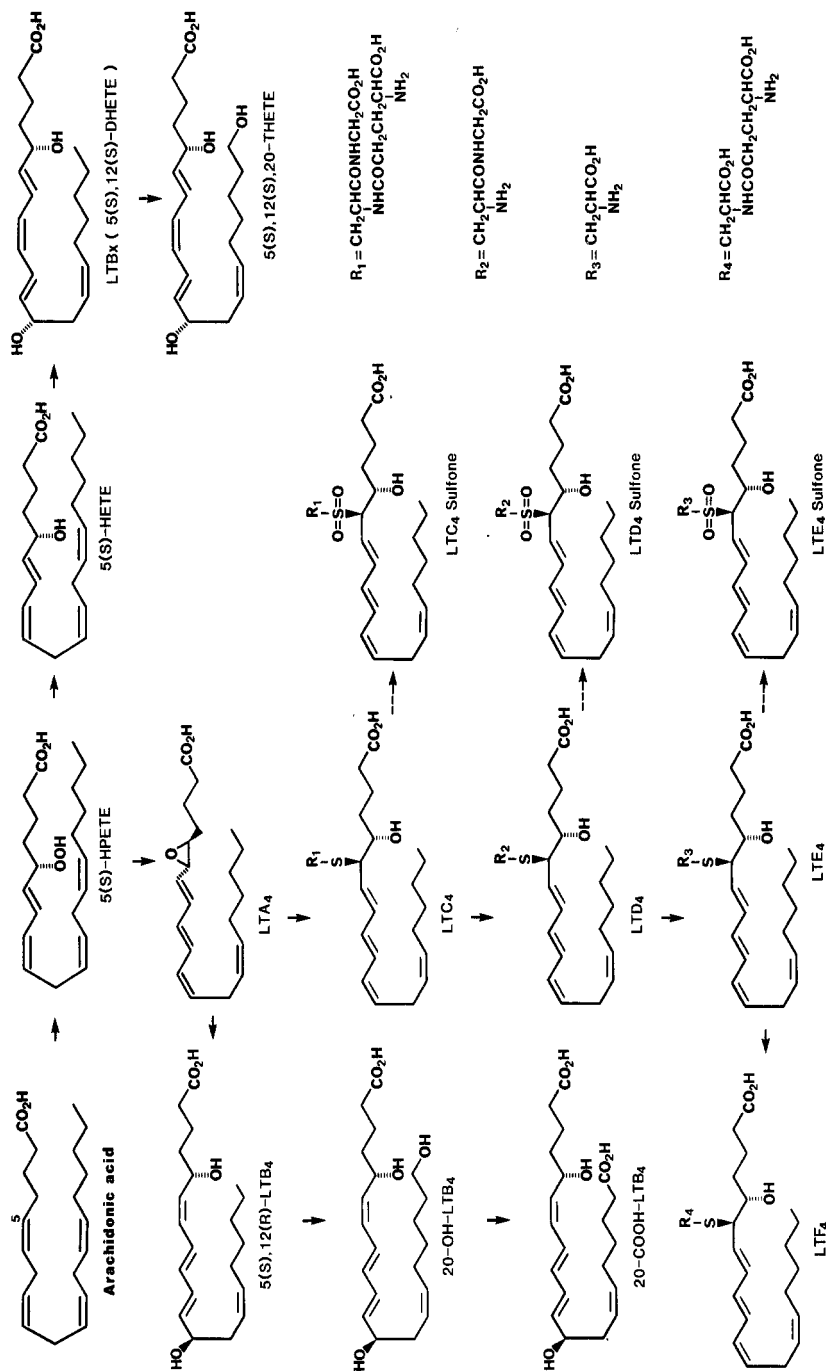
Scheme 1.3. Components of SRS-A

Evidence for the formation of LTA₄ as a direct intermediate in LTB₄ and LTC₄ biosynthesis has been reported.^{15b} Thus LTB₄ may be converted by a specific epoxide hydrolase^{26,27} to the (5*S*,12*R*)-dihydroxytriene LTB₄. The ¹⁸O labeling experiments have shown that the hydroxyl group at C-12 originates from water.²⁸ Alternatively, LTA₄ may be converted to LTC₄ by a microsomal enzyme, leukotriene-C₄ synthetase.²⁹ Leukotriene C₄ can then be cleaved by successive peptidases to yield leukotrienes D₄ and E₄.

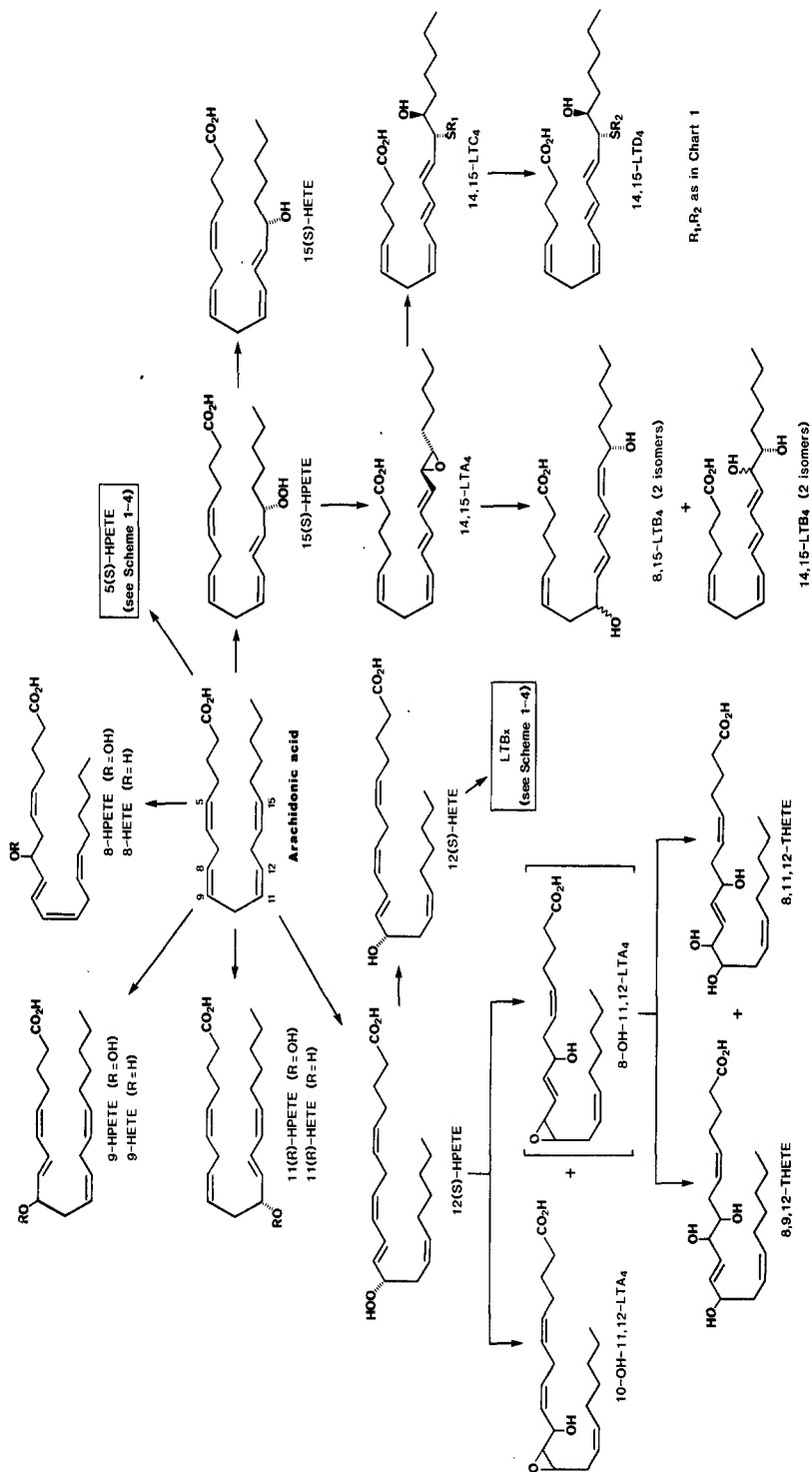
As shown in Scheme 1.4, LTB₄ can also be metabolized by terminal oxidation, first to the primary alcohol 20-OH-LTB₄, then to the dicarboxylic acid 20-COOH-LTB₄. Sulfone analogs of LTC₄, LTD₄, and LTE₄ have been postulated³¹ (see Scheme 1.4), although there is some question about whether the sulfones actually occur as natural products.³²

Similar biosynthetic steps, when permitted, are possible at other sites of the arachidonic acid chain, as illustrated in Scheme 1.5

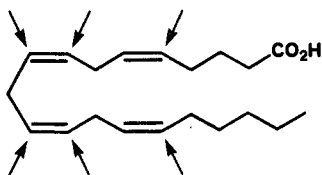
Some of the products that have been identified following such transformations are exemplified in Scheme 1.6



Scheme 1.4. Arachidonic acid metabolism: Principal products of the 5-lipoxygenase pathway.



Scheme 1.5. Possible oxidation sites of arachidonic acid.



Scheme 1.6. Arachidonic acid metabolism: Principal products of the lipoxygenase pathway.

D. Biological Activities of Leukotrienes

Leukotrienes C_4 and D_4 , and to some extent the others, account for the biological activity that has been associated with the slow-reacting substance of anaphylaxis (SRS-A).^{30,33} They are, for instance, potent myotropic agents on a variety of types of smooth muscle. Both LTC_4 and LTD_4 are potent contractile agents on the human bronchus,³⁴ human parenchymal strips, and human trachea³⁵ *in vitro*. When given to normal volunteers *in vivo* they induce prolonged bronchoconstriction³⁶ at low doses.

Leukotrienes C_4 and D_4 also have very pronounced effects on the cardiovascular system. They are, for example, very effective coronary artery vasoconstrictors.³⁷ A number of "indirect effects" have also been attributed to LTC_4 and LTD_4 . For example, these agents effect the secretion of mucous³⁸ in the respiratory tract and cause negative inotropic effects³⁹ in mammalian heart preparations. Many other biological activities have been associated with the peptido-leukotrienes.

The most important aspect of the biological profile of LTB_4 seems to be its capacity to stimulate leukotriene and lymphocyte functions *in vitro*. At very low concentrations leukotriene B_4 stimulates, the chemotaxis, chemokinesis, and aggregation of polymorphonuclear (PMN) leukocytes.⁴⁰ In addition to its effects on PMN, LTB_4 has been shown to be a potent chemotactic and chemokinetic agent for eosinophils, to stimulate the chemokinesis of macrophages and monocytes⁴¹ and the chemotaxis of fibroblasts.⁴² Some of these *in vitro* effects of LTB_4 have also been observed *in vivo*.³³

Leukotriene B_4 also has important effects on lymphocyte function. For example, it significantly enhances the proliferation of mitogen-stimulated suppressor-cytotoxic T-lymphocytes and significantly inhibits the proliferation of mitogen-stimulated helper-induced T-lymphocytes.⁴³ The net effect of LTB_4 on blood T-lymphocytes was an immunosuppression.

The potent constricting effects of LTC_4 and LTD_4 in both peripheral and large-airway smooth-muscle preparations from human lung, combined with the observation that antigen challenge of human asthmatic lung leads to the release of SRS-A,⁴⁴ suggests a critical role of the leukotrienes in diseases such as asthma.

The chemotactic activities of LTB₄ could suggest a role for this mediator in clinical conditions in which accumulation of leukocytes, for example, is recognized as one of the main features. (e.g., ulcerative colitis, rheumatoid arthritis, gout, and psoriasis).⁴⁰

Rarely has a group of low-molecular-weight molecules been associated with such a number of pathological or regulatory conditions, hence the continued high level of interest and research into a more detailed understanding of their place in both normal and abnormal physiological conditions.

References

1. (a) For reviews see, for example; Samuelsson, B. *Angew. Chem.* **1983**, 22, 805. (b) See various authors in *SRS-A and Leukotrienes*; Piper, P. J. Ed.; Research Studies Press: Chichester, 1981. (c) See various authors in *Advances in Prostaglandin, Thromboxane and Leukotriene Research*, Samuelsson B.; Paoletti, R. Eds.; Raven: New York, 1982; Vol. 9. (d) Marx, J. L. *Science* **1982**, 215, 1380. (e) See various authors in *The Leukotrienes: Chemistry and Biology*, Chakrin, L.W.; Bailey, D.M. Eds.; Academic: Orlando, 1984. (f) Rokach, J.; Adams, J. *Acc. Chem. Res.* **1985**, 18, 87. (g) Corey, E.J. *Experientia* **1982**, 38, 1259. (h) Green, R.H.; Lambeth, P.F. *Tetrahedron* **1983**, 39, 1687.
2. (a) Samuelsson, B.; Borgeat, P.; Hammarstroem, S.; Murphy, R.C. *Prostaglandins* **1979**, 17, 785. (b) Samuelsson, B.; Hammarstroem, S. *Prostaglandins* **1980**, 19, 645.
3. Hammarstroem, S.; Murphy, R.C.; Samuelsson, B.; Clark, D.A.; Mioskowski, C.; Corey, E.J. *Biochem. Biophys. Res. Comm.* **1979**, 91, 1266.
4. Kellaway, C.H.; Trethewie, W.R. *J. Exp. Physiol.* **1940**, 30, 121.
5. Brocklehurst, W. E. *J. Physiol. (Lond.)* **1953**, 120, 16P.
6. Orange, R.P.; Austen, K. F. *Adv. Immunol.* **1969**, 10, 105.
7. (a) First disclosed at the Fourth International Prostaglandin Conference; Washington, D.C., May 27-31, 1979 (b) Murphy, R.C.; Hammarstroem, S.; Samuelsson, B. *Proc. Natl. Acad. Sci. USA* **1979**, 76, 4275.
8. Hamberg, M.; Samuelsson, B. *Proc. Natl. Acad. Sci. USA* **1972**, 71, 3400.
9. Lewis, R.A.; Goetzl, E.J.; Wasserman, S.I.; Valone, F.H.; Rubin, R. H.; Austen, K.F. *J. Immunol.* **1975**, 114, 87.
10. Borgeat, P.; Hamberg, M.; Samuelsson, B. *J. Biol. Chem.* **1976**, 251, 7816; **1976**, 252, 8772.
11. Jakschik, B.A.; Falkenhein, S.; Parker, C.W. *Proc. Natl. Acad. Sci. USA* **1977**, 74, 4577.
12. Bach, M.K.; Brashler, J.R.; Gorman, R.R. *Prostaglandins* **1977**, 14, 21.
13. Morris, H. R.; Taylor, G.W.; Piper, P.J.; Sirois, P.; Tippins, J.R. *FEBS Lett.* **1978**, 87, 203.
14. Borgeat, P.; Samuelsson, B. *J. Biol. Chem.* **1979**, 254, 2643.
15. (a) Borgeat, P.; Samuelsson, B. *Proc. Natl. Acad. Sci. USA* **1979**, 76, 3213. (b) Raadmark, O.; Malmsten, C.; Samuelsson, B.; Clark, D.A.; Goto, G.; Marfat, A.; Corey, E.J. *Biochem. Biophys. Res. Commun.* **1980**, 92, 954.
16. Corey, E.J.; Clark, D.A.; Goto, G.; Marfat, A.; Mioskowski, C.; Samuelsson, B.; Hammarstroem, S. *J. Am. Chem. Soc.* **1980**, 102, 1436.
17. Rokach, J.; Girard, Y.; Guindon, Y.; Atkinson, J.G.; Larue, M.; Young, R.N.; Masson, P.; Holme, G. *Tetrahedron Lett.* **1980**, 21, 1485.

18. Rokach, J.; Girard, Y.; Guindon, Y.; Atkinson, J.G.; Larue, M.; Young, R.N.; Masson, P.; Hamel, R.; Piechuta, H.; Holme, G. In *SRS-A and Leukotrienes*, Piper, P., Ed.; Research Study Press: New York, 1981; p. 65.
19. Corey, E.J.; Clark, D.A.; Marfat, A.; Goto, G. *Tetrahedron Lett.* **1980**, *21*, 3143.
20. Hammarstroem, S.; Samuelsson, B.; Clark, D.A.; Goto, G.; Marfat, A.; Mioskowski, C.; Corey, E.J. *Biochem. Biophys. Res. Commun.* **1980**, *92*, 946.
21. Morris, H.R.; Taylor, G.W.; Piper P.J.; Tippins, J.R. *Nature* **1980**, *285*, 104.
22. Lewis, R.A.; Austen, K.F.; Drazen, J.M.; Clark, D.A.; Marfat, A.; Corey, E.J. *Proc. natl. Acad. Sci. USA* **1980**, *77*, 3710.
23. Morris, H.R.; Taylor, G.W.; Rokach, J.; Girard, Y.; Piper, P.J.; Tippins, J.R.; Samhoun, M.N.; *Prostaglandins* **1980**, *20*, 601.
24. (a) Goetze, A.M.; Fayer, L.F.; Bouska, J.; Barnemeier, D.; Carter, G.W. *Prostaglandins* **1985**, *29*, 689. (b) Rouzer, C.A.; Samuelsson, B. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 6040.
25. Raadmark, O.; Malmsten, C.; Samuelsson, B.; Goto, G.; Marfat, A.; Corey, E.J. *J. Biol. Chem.* **1980**, *255*, 11828.
26. Evans, J.F.; Dupuis, P.; Ford-Hutchinson, A.W. *Biochim. Biophys. Acta* **1985**, *840*, 43.
27. Raadmark, O.; Shimizu, T.; Jornvall, H.; Samuelsson, B. *J. Biol. Chem* **1984**, *259*, 12339.
28. Samuelsson, B.; In *SRS-A and Leukotrienes*, Piper, P.; Ed.; Research Studies Press: Chichester, 1981; p. 45.
29. Bach, M.K.; Brashler, J.R. Morton, D.R. Jr.; *Arch. Biochem. Biophys.* **1984**, *230*, 455.
30. Samuelsson, B. *Science* **1983**, *220*, 568.
31. Ohnishi, H.; Kosuzume, H.; Kitamura, Y.; Yamaguchi, K.; Nobuhara, M.; Suzuki, Y.; *Prostaglandins* **1980**, *20*, 655.
32. Girard, Y.; Larue, M.; Jones, T.R.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 1023.
33. (a) Samuelsson, B.; In *Advances in Prostaglandin Thromboxane and Leukotriene Research*, Samuelsson, B.; Paoletti, R.; Ramwell, P.W.; Eds.; Raven:New York, 1983; Vol. 11, p. 1. (b) Piper, P.J. *Physiol. Rev.* **1984**, *64*, 744. (c) Ford-Hutchinson, A.W.; In *Biochemistry of Arachidonic Acid Metabolism*, Lands, W.E.M., Ed.; Martinus Nijhoff: Boston, 1985; p. 269.
34. Dahlen, S.E.; Hedqvist, P.; Hammarstroem, S.; Samuelsson, B. *Nature* **1980**, *288*, 484.
35. Jones, T.R.; Davis, C.; Daniel, E.E. *Can. J. Physiol. Pharmacol.* **1982**, *60*, 638.
36. Weiss, J.W.; Drazen, J.M.; Coles, N.; McFadden, E.R.; Weller, P.W.; Corey, E.J.; Lewis, R.A.; Austen, K.F. *Science* **1982**, *216*, 196.
37. Letts, L.G.; Piper, P.J.; Newman, D.L.; In *Leukotrienes and Other Lipoxygenase Products*, Piper, P.J. Ed.; Research Studies Press: Chichester, 1983; p. 94.
38. Richardson, P.S.; Peatfield, A.C.; Jackson, D.M.; Piper, P.J.; In *Leukotrienes and Other Lipoxygenase Products*, Piper, P.J. Ed.; Research Studies Press: Chichester, 1983; p. 178.
39. Letts, L.G.; Piper, P.J. *J. Physiol.* **1981**, *317*, 94P.
40. (a) Ford-Hutchinson, A.W.; Bray, M.A.; Doig, M.V.; Shipley, M.E.; Smith, M.J.H. *Nature* **1980**, *286*, 264. (b) Goetzl, E.J.; Pickett, W.C.; *J. Immunol.* **1980**, *125*, 1789.
41. Smith, M.J.H.; Ford-Hutchinson, A.W.; Bray, M.A. *J. Pharm. Pharmacol.* **1980**, *32*, 517.
42. Mensing, H.; Czarnetzki, B.M. *J. Invest. Dermatol.* **1984**, *82*, 9.
43. (a) Ford-Hutchinson, A.W. *J. Allergy Clin. Immunol.* **1984**, *74*, 437. (b) Payan, D.G.; Missirlian-Bastian, A.; Goetzl, E.J. *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 3501.
44. Dahlen, S.; Hansson, G.; Hedqvist, P.; Bjorck, T.; Granstroem, E.; Dahlen, B. *Proc. Natl. Acad. Sci. USA* **1983**, *80*, 1712.

2. SYNTHESIS OF LEUKOTRIENES—STRATEGIC CONSIDERATIONS

Introduction

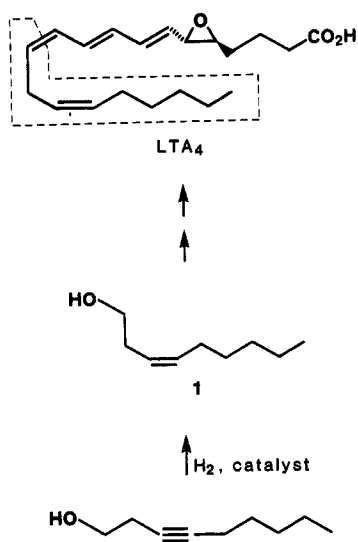
Inspection of the eicosanoid structures forces the synthetic chemist to focus on several features with regard to the construction of the twenty-carbon alicyclic skeleton. First, one is concerned with the appropriate placement and geometry of olefins. Depending upon which arachidonic acid metabolite is of interest, conjugated dienes and trienes as well as isolated double bonds must be of precisely defined geometries. Owing to the chemical instability of many of the leukotrienes, synthetic efforts must take into consideration the danger of *cis-trans* isomerization in a given sequence and synthetic designs must be adjusted accordingly. A second structural feature that demands careful planning when designing a synthesis is that of stereochemistry of the hydroxyl groups and/or the thiopeptide appendage at various points on the C₂₀ chain. With the exception of the HETEs (which bear only one asymmetric center) all of the other arachidonic acid metabolites have at least two chiral centers and any efficient synthetic plan should attempt to avoid the formation of unwanted diastereomers. The alcohols are generally carried through a synthetic sequence in a protected form which can be unmasked at later stages in the synthesis. Finally, the ubiquitous carboxylic acid in all of the eicosanoid metabolites can be suitably protected as its corresponding ester.

A. Formation and Geometric Control of Olefins

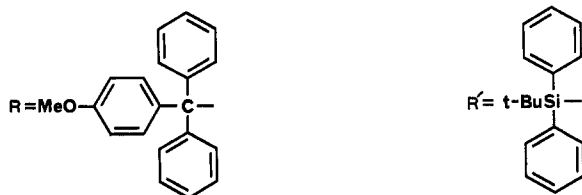
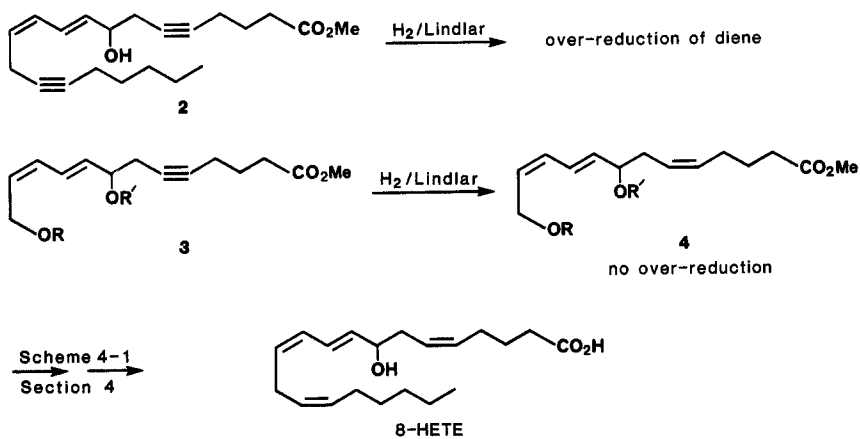
The formation of conjugated and isolated unsaturated hydrocarbons has long been a challenging problem for the organic chemist. Much of the methodology for the synthesis of leukotrienes derives from the vast repertoire of chemical reactions developed by the synthetic chemist. This section discusses the use of acetylenes as useful precursors for isolated *cis* double bonds, as well as their utility in carbon—carbon bond-forming reactions. Second, the well-known Wittig reaction is examined with regard to the formation of dienes and trienes. Finally, methodology involving masked dienes is presented to demonstrate their versatility in the synthesis of HETEs as well as diHETEs.

(1) Acetylenes

The simplest and most straightforward use of acetylenes in leukotriene synthesis is as a protected *cis* double bond. Scheme 2.1 shows the use of 3-nonyne-1-ol as a starting material which will eventually become the C-12 to C-20 chain of LTA₄ (Scheme 3.20). Semihydrogenation over a Lindlar¹ or nickel boride² catalyst ensures a high yield of the *cis* olefin **1**. Scheme 2.2 shows a limitation



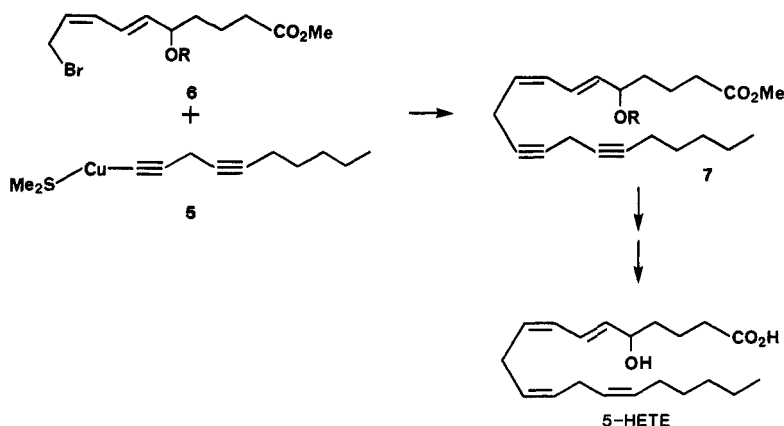
Scheme 2.1. Semihydrogenation of acetylenes.



Scheme 2.2. Semihydrogenation of acetylenes.

in the semihydrogenation method, namely that dienes and trienes are often competitively reduced along with the acetylene. A solution to this problem involves protection of the diene from the catalyst by using a bulky protecting group (i.e., **3** $\rightarrow$ **4**) on alcohols adjacent to the diene and poisoning the catalyst to ensure a controlled rate of reduction.³

Another powerful use of the acetylene function is in carbon-carbon bond formation. In the final stages of the Merck Frosst ($\pm$)-5-HETE synthesis⁴ (Scheme 2.3), the copper acetylide **5** is coupled to bromide **6** to produce the C₂₀ compound **7**, which is then semihydrogenated, and after removing the protecting groups, ($\pm$)-5-HETE was obtained.

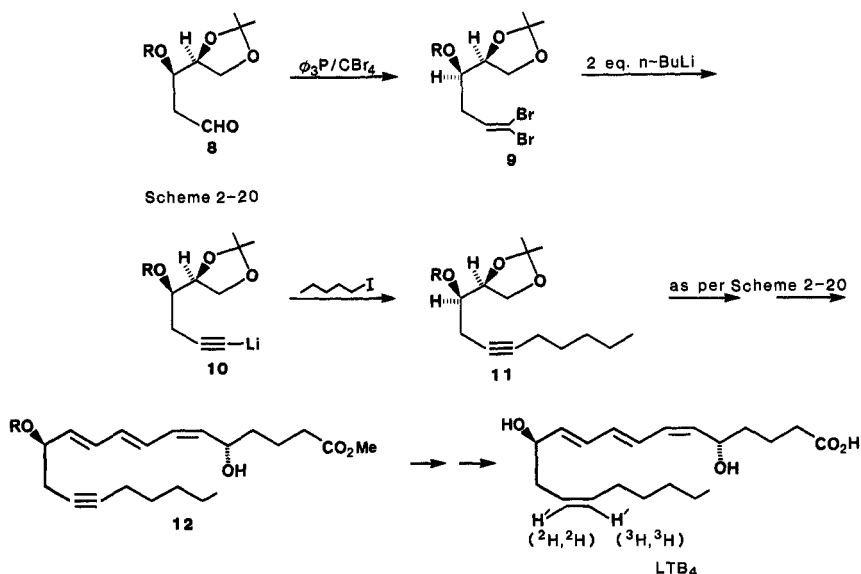


Scheme 2.3. Acetylenes in C-C bond formation.

In a final example using acetylenes,⁵ Scheme 2.4 depicts the formation of an acetylene within the chain at what will be C-14 to C-15 for 14,15-dehydro-LTB₄. Aldehyde **8** (Scheme 2.20) undergoes a Wittig type reaction to form the vinyl dibromide **9**, which upon treatment with 2 equivalents of *n*-BuLi provides the acetylide **10** which, condensed with iodopentane to give **12**, could be semihydrogenated using ¹H₂, ²H₂, or ³H₂, providing useful chemical tracers of LTB₄ for biological studies (See Section 5).

(2) The Wittig Reaction

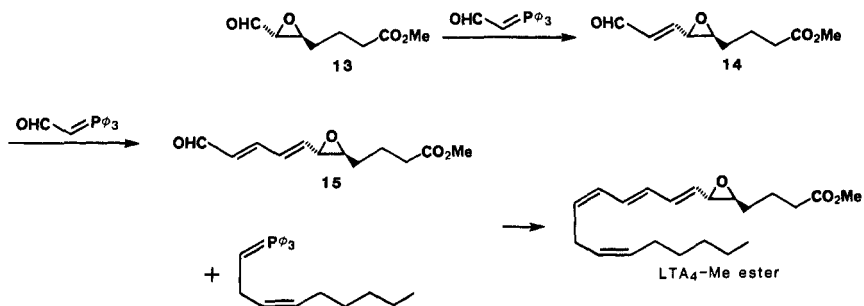
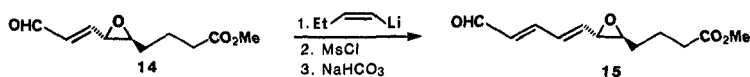
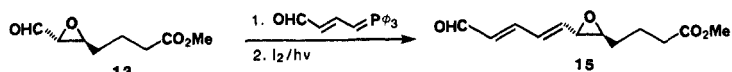
The Wittig reaction in organic chemistry remains the most widely used method of constructing *cis* or *trans* double bonds. The conventional wisdom surrounding



this much-studied reaction dictates that unstabilized phosphoranes react with aldehydes to give *cis* double bonds and stabilized phosphoranes react with aldehydes to give *trans* double bonds. Relying on this empirical rule, an efficient synthesis of LTA₄ by the Merck Frosst group is shown in Scheme 2.5. Aldehyde **13** (Scheme 3.25) is homologated in stepwise fashion to the *trans-trans* diene aldehyde **15** by successive stabilized Wittig reactions using formylmethylenetriphenylphosphorane. The last step involves a nonstabilized Wittig reaction to place the isolated *cis* double bond at C-11, to form the requisite *trans-trans-cis* triene. Toda and co-workers⁷ at Ono pharmaceuticals have reported a variation on this sequence using ethoxyvinyl lithium, derived from the corresponding tri-*n*-butyl (ethoxyvinyl) tin compound, which is condensed with aldehyde **14** and the resulting alcohol is trapped with MsCl. Hydrolysis and elimination of the unstable mesylate intermediate provides diene aldehyde **15**.

An even shorter sequence was used by Ernest,⁸ in which the diene aldehyde is generated in one step (Scheme 2.5). However, a mixture of *cis* and *trans* compounds is obtained. Isomerization using catalytic amounts of iodine corrects the olefin geometry to the desired *trans-trans* compound **15**.

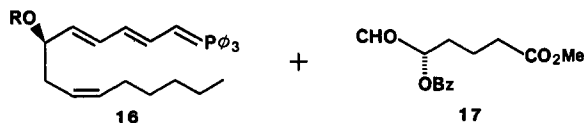
In more complex systems the nonstabilized Wittig reaction tends to be less reliable in obtaining exclusively *cis* double bonds. This may be seen in the Merck Frosst LTB₄ synthesis (Scheme 2.6), where as much as 20% *trans* compound is obtained, which must be separated by HPLC.

Merck Frosst⁶Toda⁷Ernest⁸Scheme 2.5. Wittig reaction: Approaches to LTA₄.

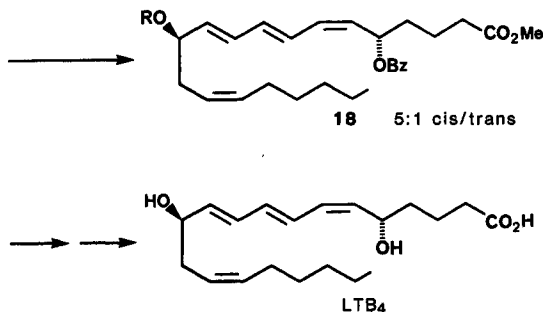
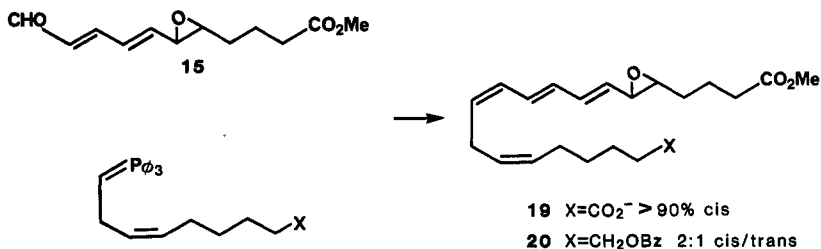
One can observe pronounced differences even with very subtle changes in the reacting substrates. Scheme 2.7 shows how the change of moieties at C-20, nine carbons removed from the newly forming double bond, can affect the resulting olefin geometry.

Finally, a most dramatic example of the subtle requirements of the Wittig reaction is seen in the Merck Frosst (5*S*,12*S*)-diHETE (LTB_x) synthesis (Scheme 2.8).¹⁰ Not only does a nonstabilized Wittig *not* give a predominance of *cis* olefin, but the (5*R*)-substrate **21** produces a 3:2 *trans/cis* ratio, while (5*S*)-**22** affords a 19:1 *trans/cis* selectivity. This remote change in stereochemistry is sufficient to completely alter the course of the reaction.

In summary, the Wittig reaction appears to offer great versatility for the formation of conjugated systems. Stabilized Wittig reactions almost always give the expected *trans* olefin. However, the limiting factor resides in the questionable reliability of the unstabilized Wittig reaction to give *cis* olefins. In reactions with complex substrates, the predictability of the olefin geometry is diminished.



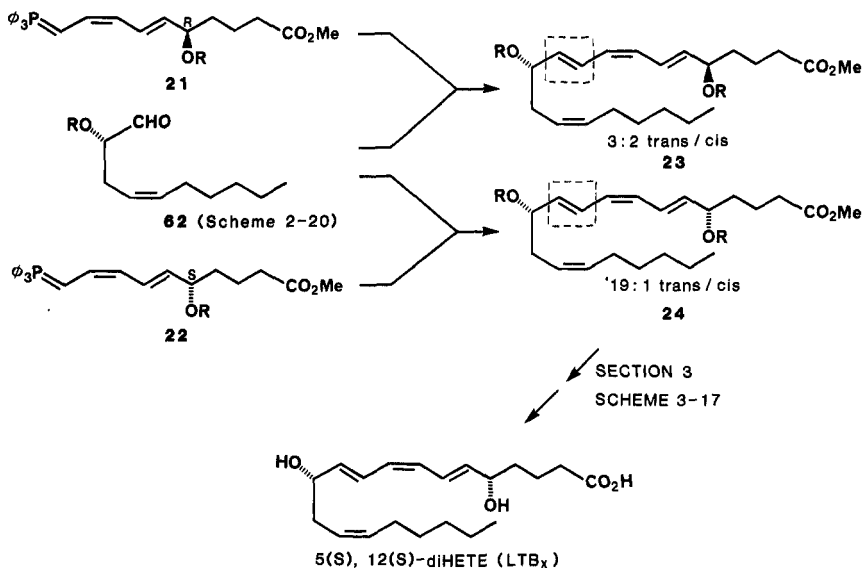
(Scheme 2-20)


 Scheme 2.6. Wittig reaction for LTB₄.


Scheme 2.7. Wittig reaction for ω-oxidized leukotrienes (Section 3).

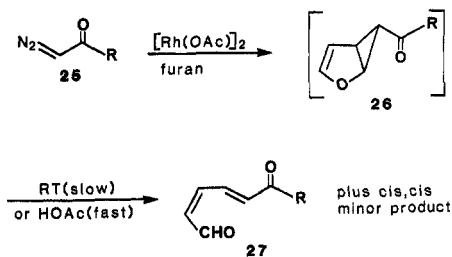
(3) Masked Dienes and Trienes

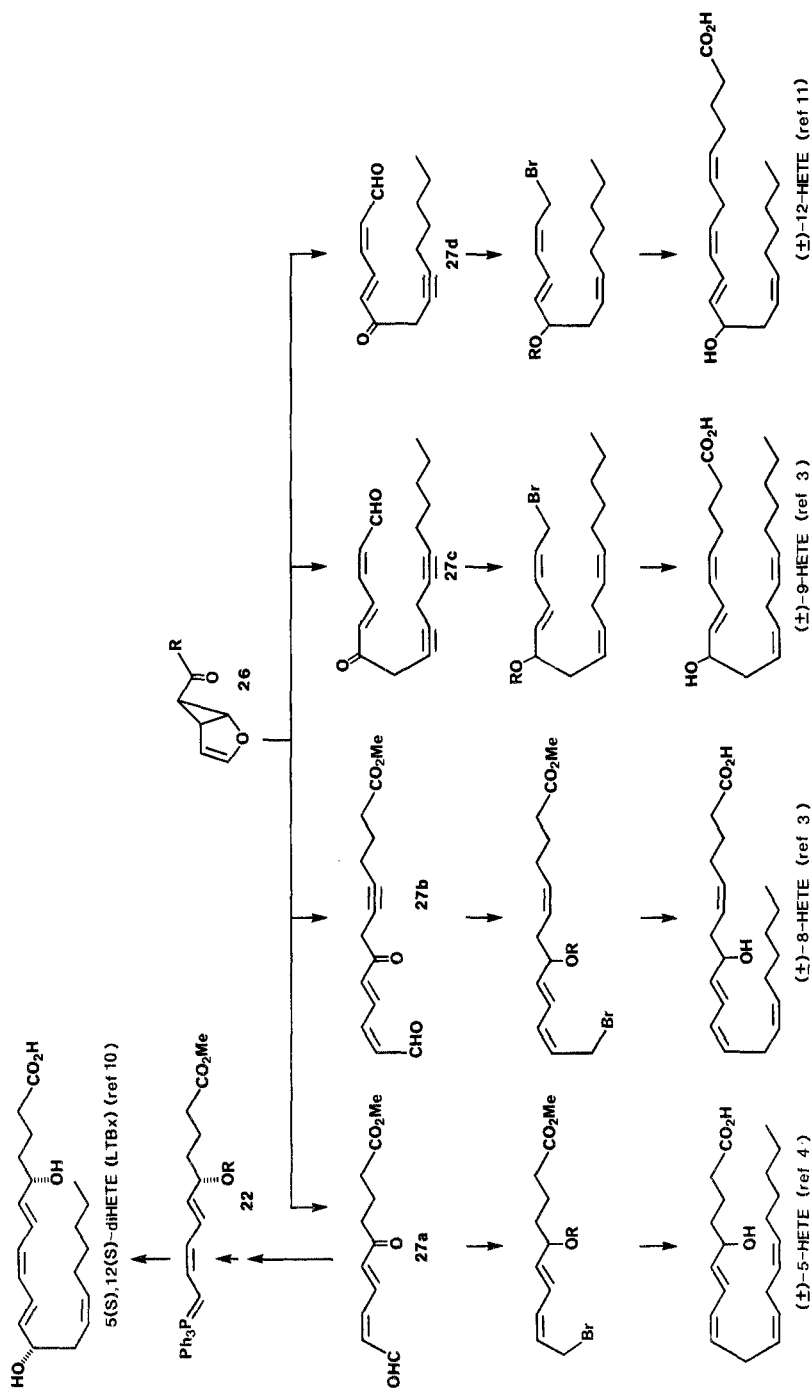
Analysis of triene structures in leukotrienes or the dienes in the HETEs reveals in all cases that a *cis,trans* dienes (partial structure) is commonly shared. The Merck Frosst group has recently described a methodology for the delivery of *cis,trans* dienes in the synthesis of various HETEs. Scheme 2.9 depicts the basic route whereby α-diazo ketones **25** react, via a carbenoid species, with furan to produce an unstable cyclopropyl furan intermediate **26**. This reaction is efficiently

Scheme 2.8. The Wittig reaction for (5*S*,12*S*)-diHETE (LTB_x).

catalyzed by $[\text{Rh}(\text{OAc})_2]_2$. Cyclopropyl furans have been shown to slowly convert to the *cis*, *trans* dicarbonyl compounds **27** via thermal processes. The electrocyclic ring-opening reaction can be accelerated using mild acid. Some *cis*,*cis* diene is also observed as a minor product. Nevertheless, the process is high yielding and efficient.

Appropriate selection of the chain denoted by R (Schemes 2.9 and 2.10) leads to precursors **27** of different members of the HETE family. To date (±)-5-HETE,⁴ (±)-8-HETE,³ (±)-9-HETE,³ and (±)-12-HETE,¹¹ have all been synthesized using this generalized procedure.

Scheme 2.9. Cyclopropylfuran route to *cis*-*trans* dienes.

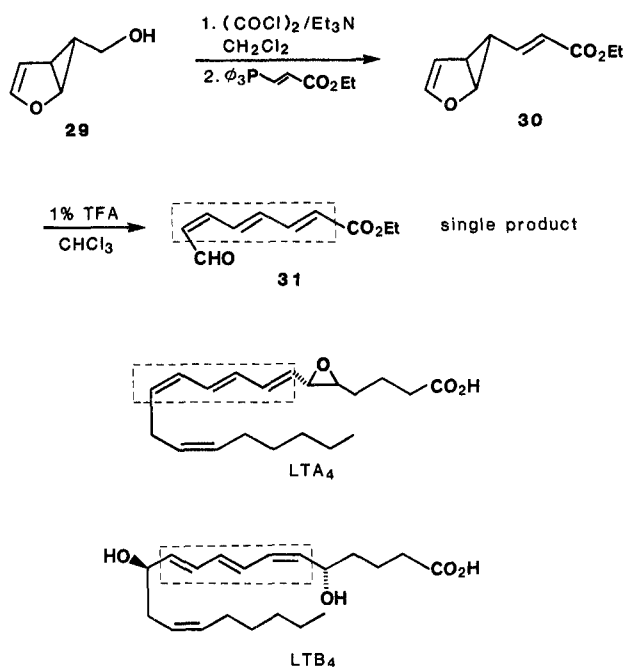


Scheme 2.10. Cyclopropylfuran route to HETEs and diHETE (LTB_x).

This approach was also extended to include a synthesis of the triene (5*S*, 12*S*)-diHETE,¹⁰ whereby the cyclopropylfuran route was employed and diene dicarbonyl compound **27a** was converted to a suitable phosphonium salt **22**.

Wittig technology was used to form the *trans*-*cis*-*trans* triene unit in the final stages of the synthesis (see Scheme 2.10).

Recently a simple and efficient route leading directly to trienes of a single geometry (*cis*-*trans*-*trans*) was achieved.¹² Scheme 2.11 outlines how cyclopropylfuran alcohol **29** can be oxidized and homologated using a two-step low-temperature Swern oxidation-Wittig sequence to form ester homolog **30**. Treatment of this material with 1% trifluoroacetic acid produced the *cis*-*trans*-*trans* triene functionalized at both ends at different oxidation levels. Comparing this synthon with LTA₄ or LTB₄, one can appreciate the synthetic utility of such an approach.



Scheme 2.11. Formation of trienes via cyclopropylfurans.

(4) Conclusion

In summary, the synthetic techniques described to control the olefin formation and geometry can be exploited separately or in most cases in combination to effect short and efficient syntheses of the C₂₀ eicosanoid chain. The subject of stereochemistry of hydroxyl groups has been deliberately avoided to highlight the skeletal features of leukotrienes. The next section focuses solely on stereochemistry, although one must realize that any good synthetic design requires that both geometry and stereochemistry be taken into account.

B. Stereochemical Strategies

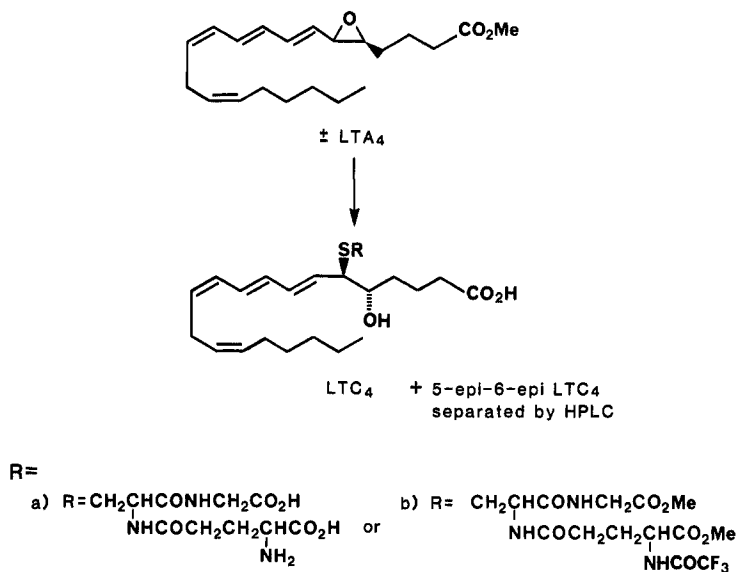
The stereochemical features of the leukotrienes include usually one or two hydroxyl groups on the C₂₀ chain in the form of HETEs or diHETEs, or a thiopeptide for the contractile slow-reacting substances (SRS-A). Three synthetic strategic approaches are presented here, highlighting some of the key steps in the syntheses of LTA₄ and LTB₄. In many cases the importance of obtaining optically pure material is paramount, particularly when the samples are used in a biological test. Nevertheless, racemic materials have also found utility as HPLC standards and are historically the first syntheses in most cases.

(1) Optical Resolution

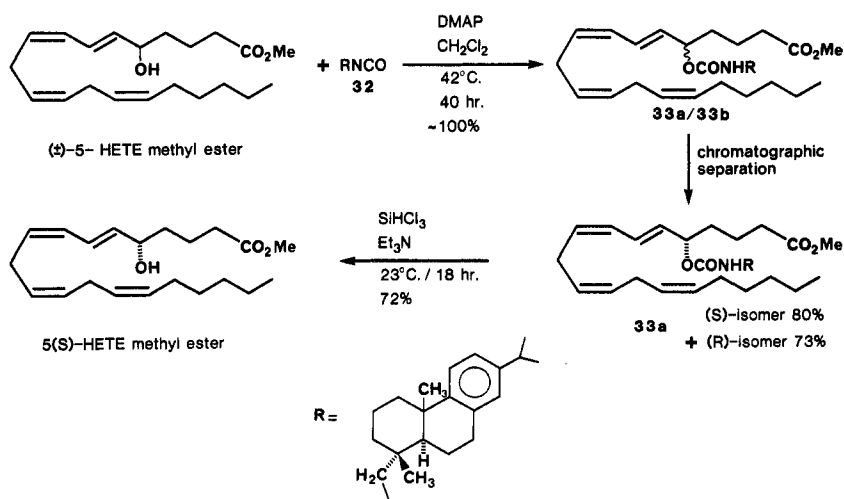
One of the oldest techniques to obtain optically pure material is via classical resolution. This can be accomplished in two ways, by using either an external or an internal resolving agent. In the earlier work to obtain LTC₄, racemic LTA₄ was subjected to the nucleophilic addition of glutathione (Scheme 2.12) to give a mixture of diastereomeric products.¹⁶ The separation of these diastereomers via HPLC provided LTC₄ and 5-epi,6-epi-LTC₄.

Corey has developed a method to resolve the (±)-5-HETE methyl ester enantiomers using the isocyanate of dehydroabietylamine **32** to form diastereomeric carbamates **33a–33b**¹³ (Scheme 2.13). Separation of the diastereomers was achieved by column chromatography and the free alcohol was regenerated using trichlorosilane. The two examples given above constitute chemical resolution using external agents.

The Merck Frosst group used the acetonide of L-glyceraldehyde **34** readily obtained from L-arabinose as a starting material for the olefin **35**¹⁴ (Scheme 2.14). Epoxidation produced a 1:2 mixture of epoxy esters **36a** and **37b**.

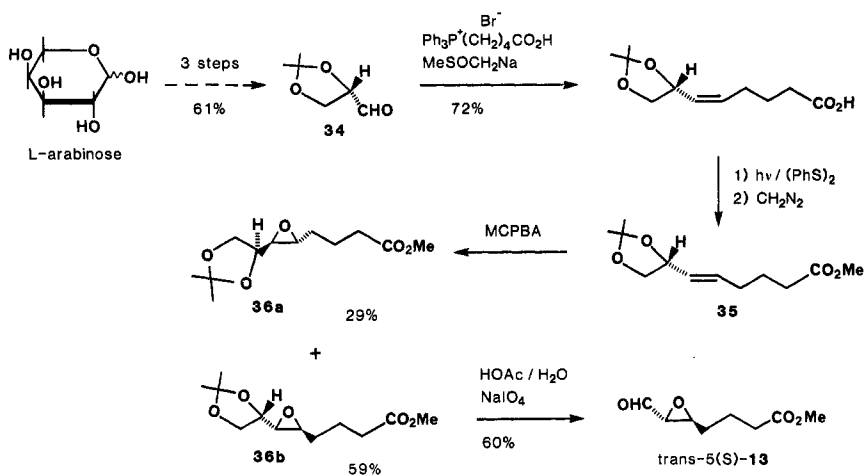


Scheme 2.12. Resolution of racemic LTA_4 by conversion to LTC_4 diastereomers.



Scheme 2.13. Resolution of 5-HETE methyl ester.

Separation of diastereomers by chromatography and hydrolysis of the acetonide and periodate cleavage of **36b** produced epoxy aldehyde **13**, a precursor for LTA₄ synthesis (see Section 3, Scheme 3.30). Thus the chiral center of the acetonide serves as an internal resolving agent of the epoxides.



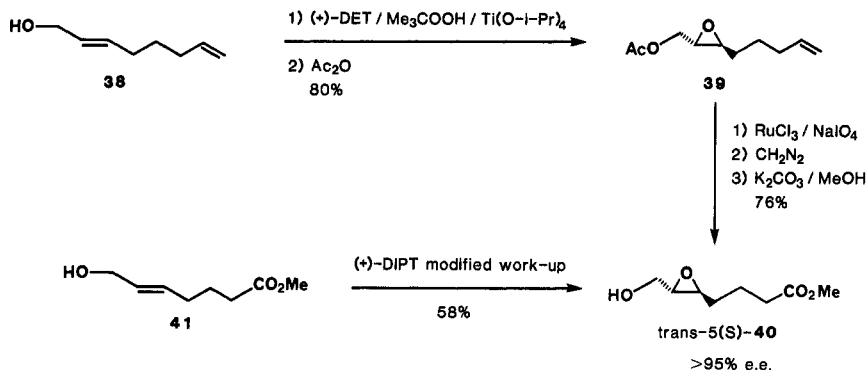
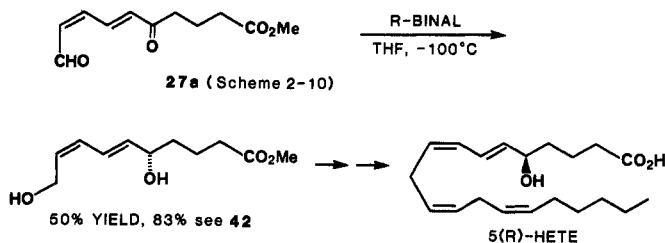
Scheme 2.14. Synthesis of LTA₄ from L-arabinose via L-glyceraldehyde.

(2) Chiral Induction

Induction of chirality in a molecule represents a more sophisticated solution to the obtention of optically active material and is a very active and popular area of research in organic chemistry. It is inherently less wasteful in approach since only the “correct” isomer is formed in the reaction.

A very utilitarian sequence was developed by Sharpless, using his chiral epoxidation method,¹⁵ to prepare epoxy alcohol **40**. Scheme 2.15 depicts the sequence, starting with the inexpensive diene alcohol **38**. As pointed out by Sharpless, the original procedure gave poor yields of relatively water-soluble epoxides such as **40**, but a modified work-up procedure largely circumvents this difficulty, allowing for direct oxidation of **41** in excellent optical purity.

In a synthesis of (5R)-HETE the Merck Frosst group used the Noyori chiral reduction¹⁶ on an intermediate to give the desired (5S)-diol **42** in 83% ee¹⁷ (Scheme 2.16). While this approach works in theory, both optical purity and yield are not high enough to be synthetically useful.

Scheme 2.15. Synthesis of LTA₄ intermediates by asymmetric epoxidation.

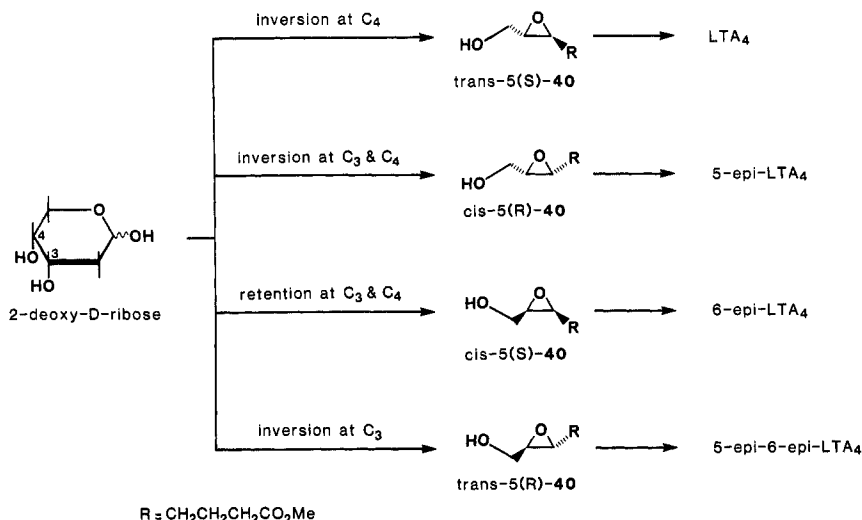
Scheme 2.16. Chiral reduction for (5R)-HETE.

(3) Optically Pure Precursors

The most effective strategic approach to obtain optically pure leukotrienes (100% ee) has been to use natural products as starting materials, where the desired chirality is contained within the starting molecule. This type of thinking has also become standard fare for the organic chemist in the planning of syntheses. Inspection of the "chiral pool" often leads, as it has done in the leukotriene field, to search amongst carbohydrate sugars as suitable starting materials.

One such approach may be witnessed in the Merck Frosst route to LTA₄ and its three unnatural epoxide isomers.⁶ Scheme 2.17 demonstrates conceptually how the chiral centers of optically pure 2-deoxy-D-ribose can be appropriately manipulated to obtain all four optical isomer intermediates for LTA₄.

Scheme 2.18 outlines the stereospecific total syntheses of all four of the optical isomers of LTA₄ from 2-deoxy-D-ribose.⁶ The readily available triol ester 43 was regioselectively functionalized on the primary hydroxyl group using the sterically hindered mesitylene sulfonyl chloride (Met-Cl). Treatment with sodium

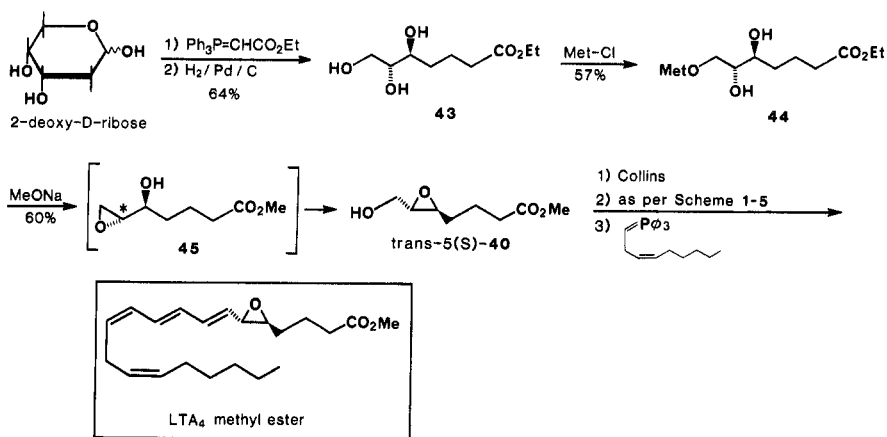


Scheme 2.17. Stereochemical relationship between 2-Deoxy-D-Ribose and LTA_4 optical isomers.

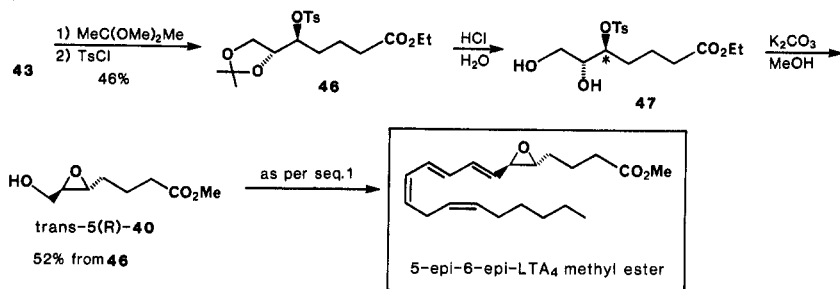
methoxide in methanol then yielded the desired epoxy alcohol *trans*-(5*S*)-**40**. The terminal epoxide **45** is an intermediate in the reaction and undergoes epoxide transposition under the basic reaction conditions. The asterisk in **45** and subsequent structures indicates the point of inversion, which is effected to achieve the desired stereochemistry as schematically indicated in Scheme 2.17. The epoxy alcohol was then oxidized to the epoxy aldehyde *trans*-(5*S*)-**13**, which was converted to LTA_4 (see Scheme 2.5). In Sequence 2, in order to obtain the enantiomer of LTA_4 methyl ester, inversion was effected at the former C_3 hydroxyl group of 2-deoxy-D-ribose by selectively blocking the terminal diol unit of **43**, followed by tosylation of the remaining secondary alcohol to obtain **45**. Removal of the acetonide blocking group and treatment with base then gave the epoxyl alcohol *trans*-(5*R*)-**40**, which was converted to 5-epi-6-epi- LTA_4 methyl ester by the same sequence of reactions as for LTA_4 methyl ester.

To obtain 6-epi- LTA_4 methyl ester (6-epi- LTA_4 Me ester) it was necessary to retain the original stereochemistry at C-3 and C-4 of 2-deoxy-D-ribose. Operationally, this was carried out by effecting a double inversion at one center, as illustrated in Sequence 3, on compounds **46** and **49**. In contrast, to obtain 5-epi- LTA_4 methyl ester, inversion at both centers was required. This was achieved as illustrated in Sequence 4, in which the mono-inverted compound **48** was converted to the tosyl lactone **50**. Treatment of the lactone with methoxide opened the ring to the methyl ester, and the alkoxide intermediate displaced the tosylate group, with inversion at the second center, to give the desired *cis*-(5*R*)-**40** which was converted to 5-epi- LTA_4 methyl ester.

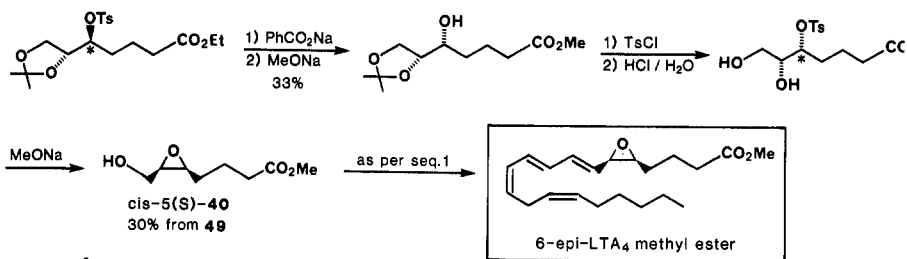
Sequence 1



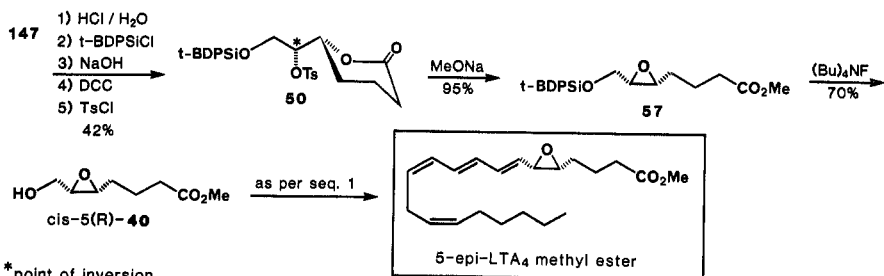
Sequence 2



Sequence 3



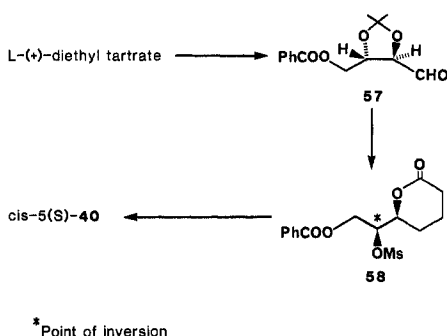
Sequence 4



*point of inversion

Scheme 2.18. Synthesis of LTA₄ and its optical isomers from 2-deoxy-D-ribose.

Another approach, adopted by the Hoffman LaRoche group, employed different carbohydrate precursors in their synthesis of LTA₄.¹⁸ The synthesis of *trans*-(5*S*)-**40**, starting from erythrose acetonide **52**, is outlined in Scheme 2.19. Acid treatment of **54** brought about deprotection of the diol unit followed by intramolecular lactonization to yield the crystalline lactone **55**, with the desired hydroxyl group free to be converted into a suitable leaving group **56**, which was smoothly transformed to the target structure. Aldehyde intermediate **57** epimeric at C-3 with respect to **52** was obtained in a straightforward sequence from L-(+)-diethyl tartrate, and was carried through the same reactions as **52** to obtain the *cis* epoxy alcohol *cis*-(5*S*)-**40**.

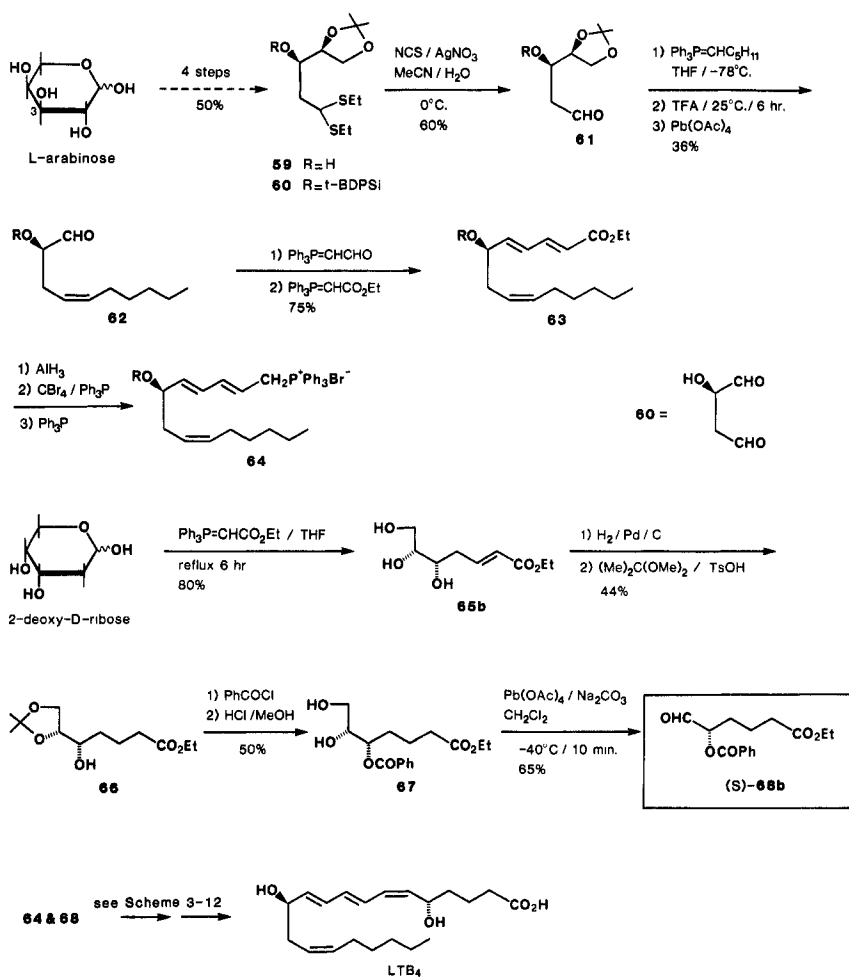


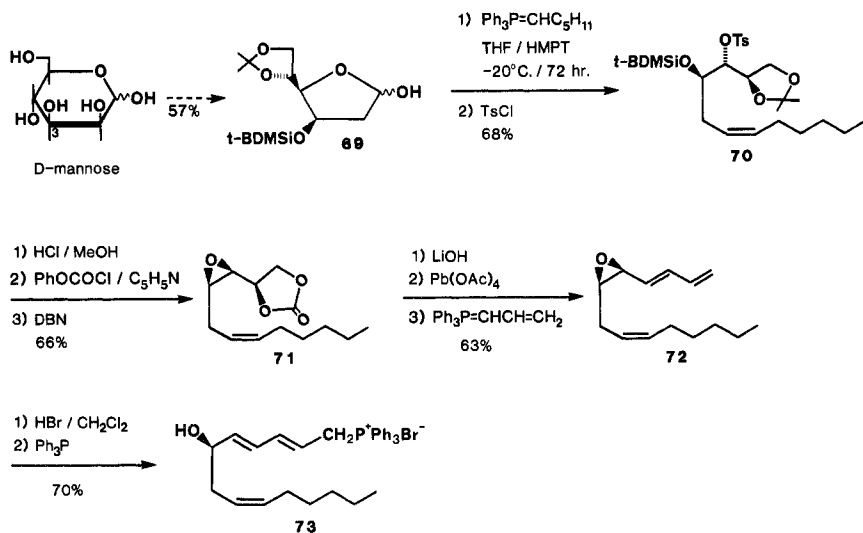
Scheme 2.19. Synthesis of LTA₄ intermediates from D-erythrose and L-(+)-tartrate.

The synthesis of LTB₄ poses a more complex challenge from the point of view of stereochemical control. The chiral centers at C-5 and C-12 are rather remote and most synthetic endeavors require a convergent approach whereby a substrate containing the (5*S*)-protected alcohol is joined to a substrate bearing a (12*R*)-protected alcohol.

The Merck Frosst solution employed L-arabinose as a starting material, which was converted to the protected differentiated dialdehyde synthon **60** which functionally serves as a masked (*R*)-2-OH-succinaldehyde.¹⁹ The protected hydroxyl is the future 12(*R*)-hydroxyl in LTB₄. Scheme 2.20 describes the synthesis of **63**, the “left” part of LTB₄. This intermediate is elaborated in several steps to phosphonium salt **64**, which is then coupled to chiral aldehyde **68b**, which comes from 2-deoxy-D-ribose following the route shown in the same scheme. Aldehyde synthon **68** contains the (5*S*)-protected hydroxyl necessary for LTB₄. The asterisks indicated in the scheme for L-arabinose and 2-deoxy-D-ribose correspond to the stereocenters retained in intermediates **63** and **68**, respectively.

In a final example, the synthesis of the “left” side of LTB₄ by Corey, outlined in Scheme 2.21, starts from the derivative **69** obtained from D-mannose.²⁰ The triol tosylate resulting from deblocking of **70** underwent regioselective reaction with phenylchloroformate to give a 1,2-diol carbonate, allowing the remaining free alcohol to form epoxide **71** by internal displacement of the tosylate group. Reaction of the conjugated epoxydiene unit in **72** with 1 equivalent of HBr very cleanly gave a terminal bromo alcohol, which was quaternized with triphenylphosphine to yield the Wittig salt **73**.

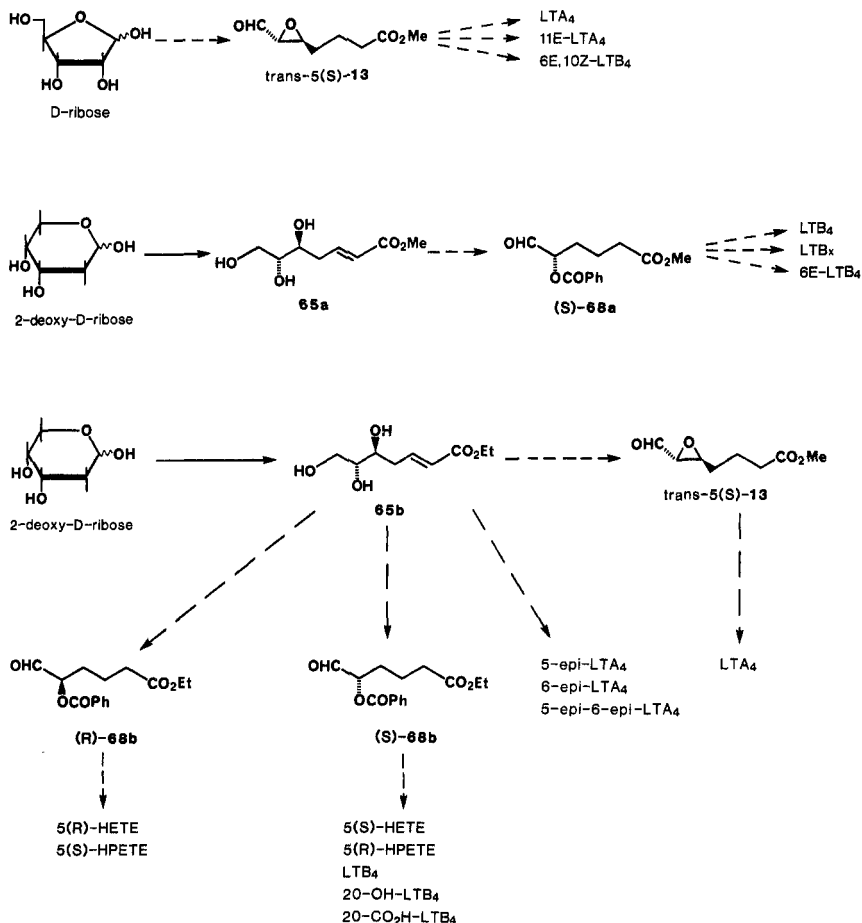
Scheme 2.20. Synthesis of LTB₅.


 Scheme 2.21. Synthesis of LTB₄.

In a broad synthetic program it is very desirable to be able to take advantage of intermediates developed for a specific synthesis in as many other syntheses as possible. Thus Corey's group, which established the utility of epoxyaldehyde *trans*-5(*S*)-**13** for the synthesis of LTA₄ (Scheme 3.26), also utilized it for the synthesis of (11*E*)-LTA₄ (Scheme 3.26) and (6*E*, 10*Z*)-LTB₄ (not shown).²¹

In the synthesis of LTB₄-like compounds, Corey's group used the aldehyde benzoate (*S*)-**68a** in syntheses of LTB₄ (Schemes 3.10 and 3.11), LTB_x (Scheme 3.16), and (6*E*)-LTB₄ (not shown).²²

The most general approach to the synthesis of the lipxygenase-derived products has been developed by the Merck Frosst group using the triol **65b**, derived in one step from 2-deoxy-D-ribose, as a key intermediate to a wide variety of compounds. Thus the epoxyaldehyde *trans*-5(*S*)-**13**, as well as its three unnatural epimers, were prepared from **65b**, en route to synthesis of LTA₄ and the three epimers of LTA₄ (Schemes 2.17 and 2.18). From **65b** were also prepared the (*R*)- and (*S*)-isomers of aldehyde benzoate **68b** (Scheme 3.8), from which were obtained (5*S*)-HETE (Scheme 3.3), (5*R*)-HETE (Scheme 3.4), LTB₄ (Schemes 3.10 and 3.12), 20-OH-LTB₄ (Scheme 3.14), and 20-CO₂H-LTB₄ (Scheme 3.15). The breadth of applicability of this approach has made it possible to supply the scientific community at large with the key leukotrienes, thus facilitating investigations of their biological properties in many laboratories.



C. Conclusion

The aim of this section has been to identify the general synthetic challenges toward the synthesis of leukotrienes and arachidonic acid metabolites. Several examples of varying synthetic achievements were presented to illustrate common strategies which are part of the modern-day organic chemist's repertoire. Irrespective of the application of these strategies to leukotrienes, much of the work described can be related to synthetic strategy in general.

It is hoped that the lessons learned from these examples will benefit chemists planning future syntheses.

While it is true that this chapter has left out many of the notable syntheses in the field, the omission was deliberate, so as to highlight certain aspects of generalized synthetic strategies, rather than to focus on singularly unique (albeit elegant) reactions. The following sections systematically document in full the synthetic achievements in the leukotriene field.

References

1. Lindlar catalyst purchased from Strem Chemicals Co.
2. Brown, C.A.; Ahuja, V.K. *J. Chem. Soc. Chem. Comm.* **1973**, 553.
3. Adams, J.; Rokach, J. *Tetrahedron Lett.* **1984**, 25, 35.
4. Rokach, J.; Adams, J.; Perry, R. *Tetrahedron Lett.* **1983**, 24, 5185.
5. Adams, J.; Zamboni, R.; Rokach, J.; unpublished results.
6. Rokach, J.; Zamboni, R.; Lau, C.-K.; Guindon, Y. *Tetrahedron Lett.* **1981**, 22, 2759.
7. Okuyama, S.; Miyamoto, S.; Shimoji, K.; Konishi, Y.; Fukushima D.; Niwa, H.; Arai, Y.; Toda, M.; Hayashi, M. *Chem. Pharm. Bull.* **1982**, 30, 2453.
8. Ernest, I.; Main, A.J.; Menasse, R. *Tetrahedron Lett.* **1982**, 23, 167.
9. Guindon, Y.; Zamboni R.; Lau, C.-K.; Rokach, J. *Tetrahedron Lett.* **1982**, 23, 739.
10. Adams, J.; Leblanc, Y.; Rokach, J.; *Tetrahedron Lett.* **1984**, 25, 1227.
11. Leblanc, Y.; Fitzsimmons, B.; Adams, J.; Perez, F.; Rokach, J. *J. Org. Chem.*, **1986**, 51, 789.
12. Fitzsimmons, B.; Adams, J.; Leblanc, Y.; Rokach, J.; unpublished results.
13. Corey, E.J.; Hashimoto, S.; *Tetrahedron Lett.* **1981**, 22, 299.
14. Rokach, J.; Young, R.N.; Kakushima, M.; Lau, C.-K. Seguin, S.; Frenette, R.; Guindon, Y.; *Tetrahedron Lett.* **1981**, 22, 979.
15. Rossiter, B.E.; Katsuki, T.; Sharpless, K.B.; *J. Am. Chem. Soc.* **1981**, 103, 464.
16. Noyori, R.; Tomino, I.; Tanimoto, Y.; *J. Am. Chem. Soc.* **1979**, 101, 3129.
17. Adams, J.; Rokach, J.; unpublished results.
18. Gohen, N.; Bunner, B.L.; Lopresti, R.J.; *Tetrahedron Lett.* **1980**, 21, 4163.
19. Zamboni, R.; Rokach, J.; *Tetrahedron Lett.* **1982**, 23, 2631.
20. Corey, E.J.; Marfat, A.; Goto, G.; Brion, F.; *J. Am. Chem. Soc.* **1980**, 102, 7984.
21. Corey, E.J.; Niwa, H.; Knolle, J.; *J. Am. Chem. Soc.* **1978**, 100, 1942.
22. Corey, E.J.; Marfat, A.; Hoover, D.J.; *Tetrahedron Lett.* **1981**, 22, 1587.

3. THE 5-LIPOXYGENASE CASCADE

A. Synthesis of the 5-HETEs and 5-HPETEs

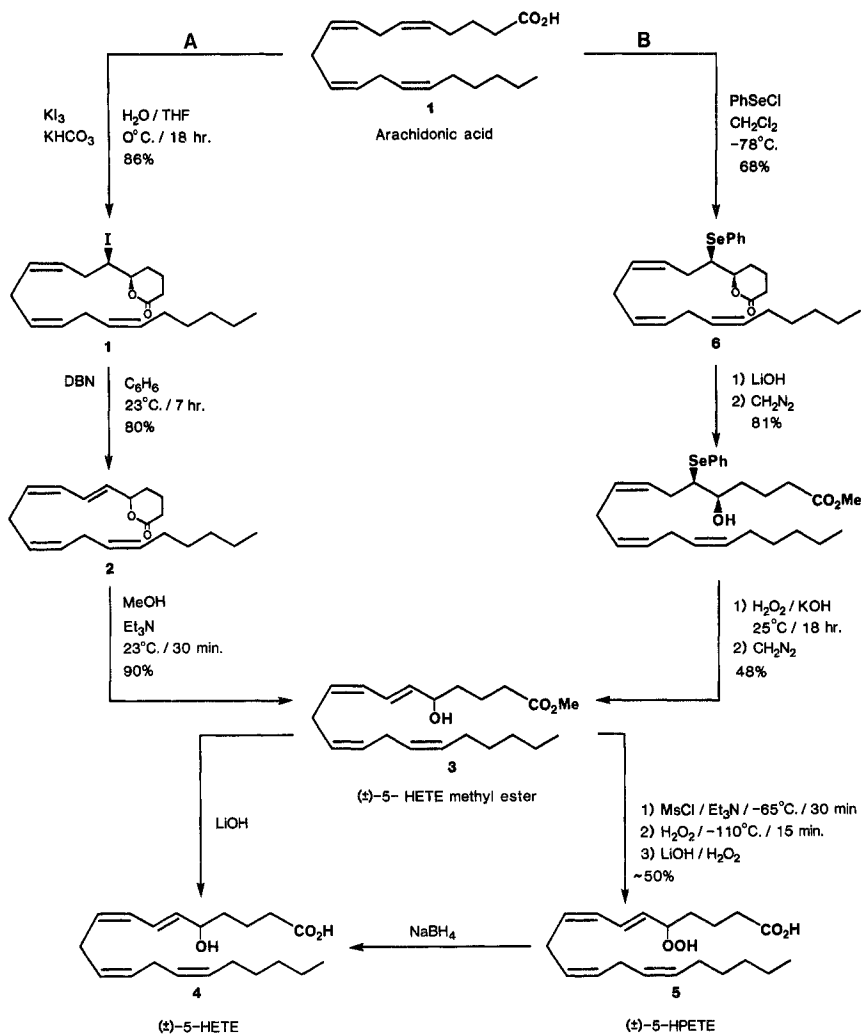
The HPETEs and HETEs are the primary products of the action of lipoxygenase on arachidonic acid, and from them, by further biochemical transformations, are derived all the remaining transmitters with which this review is concerned. In particular, (5*S*)-HPETE is the starting point from which are derived all of the most important leukotrienes studied to date.

(1) *Synthesis of Racemic 5-HETE and Its Hydroperoxide 5-HPETE*

Two syntheses of ($\pm$)-5-HETE methyl ester have been reported starting from arachidonic acid (Scheme 3.1), using electrophilic reagents to form δ -lactones, thus introducing the desired oxygen function directly into the 5-position. In the first synthesis¹ (path A), iodolactonization gave the lactone **1** which, after elimination of HI, gave the lactone **2** of ($\pm$)-5-HETE. Methanolysis then produced the methyl ester **3**, which was hydrolyzed to **4**, ($\pm$)-5-HETE. Mesylation of **3** followed by solvolysis with H₂O₂ and hydrolysis gave **5**, ($\pm$)-5-HPETE, which was reduced to **4** with NaBH₄. The second synthesis² (path B) employed selenolactonization to give the desired lactone **6**. After conversion to the methyl ester, the latter was oxidized to its selenoxide, which underwent elimination at room temperature to yield **3**, the methyl ester of ($\pm$)-5-HETE, in 48% yield along with 12% of the (8,9 *E*)-isomer of **3**. The selenoxide elimination was studied extensively and it was found that strongly basic conditions were necessary to avoid extensive isomerization of the (8,9 *Z*)-double bond to the (*E*)-isomer.

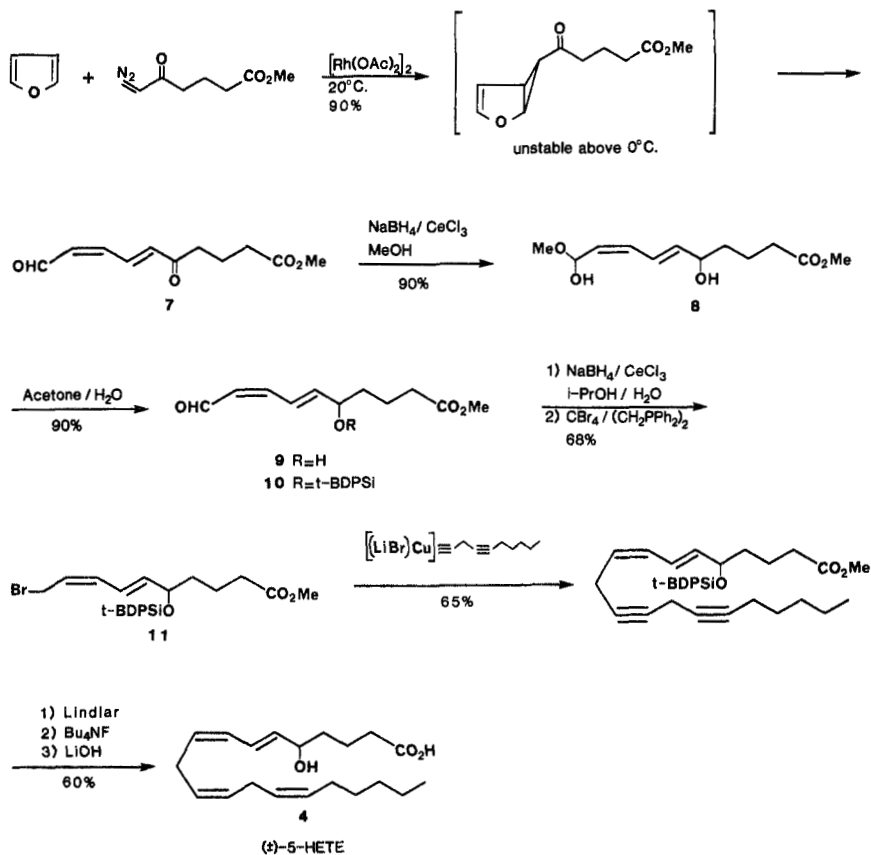
A third synthesis of racemic 5-HETE has been reported by Rokach and co-workers,³ as outlined in Scheme 3.2. Its basis stems from several observations made during the course of their original synthesis of LTC₄ (to be discussed later). Central to this synthesis was the important development of cyclopropafurans as the source of conjugated *cis-trans* dienes. This strategy is discussed in detail in Section 2, Schemes 2.9 and 2.10.

One key aspect of the sequence of Scheme 3.2 was the use of CeCl₃ to effect selective carbonyl reductions, as pioneered by Luche and co-workers.⁴ The CeCl₃ serves two purposes in the reduction of **7** to **8**, most importantly, that of allowing selective reduction of the ketone group over the aldehyde. It also exerts a buffering action so that the ester group in **8** and in the alcohol precursor of **11** is not hydrolyzed by water in the solvent. Furthermore, it probably also serves to suppress 1,4-reduction in these conjugated systems. Another point of some interest was the surprising stability of the hemiacetal **8**. Evaporation with benzene, benzene-acetic acid, chloroform, acetone, or water only slowly removed the methanol. But, fortunately, two or three evaporations with water—acetic acid—



Scheme 3.1. Synthesis of (±)-5-HETE and (±)-5-HPETE.

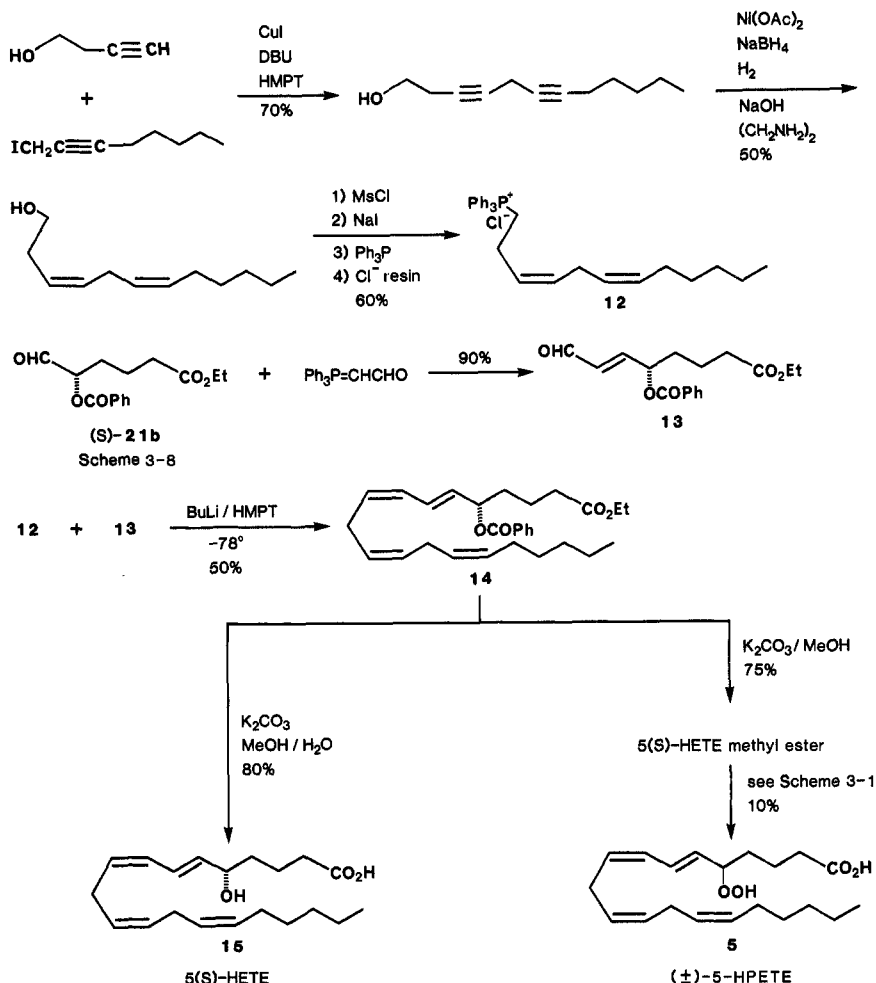
acetone (10:1:100) yielded the free aldehyde **9** in good yield. The preparation of the bromide **11** was first carried out using CBr_4 -triphenylphosphine, but the yield was rather low (30-40%). It was then found that the use of diphos in place of triphenylphosphine resulted in a much cleaner and higher yielding (75%) reaction. Whether the use of diphos in such reactions is of some general utility awaits further study. The utility of the copper diacetylide was discussed in Section 2, Scheme 2.3.



(2) Synthesis of (5*S*) and (5*R*)-HETE

The naturally occurring isomer of 5-HETE has the (*S*)-configuration at C-5. Corey and Hashimoto⁵ have reported the chemical resolution of ($\pm$)-5-HETE methyl ester as discussed in Section 2, Scheme 2.13

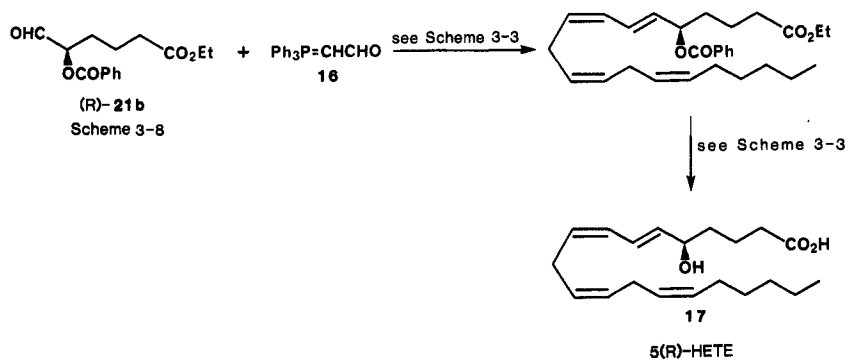
More recently, Rokach and Zamboni^{6,7} have reported the first stereospecific total synthesis of both the natural (5*S*)- and unnatural (5*R*)-isomers of the 5-HETEs. The key to these syntheses, outlined in Schemes 3.3 and 3.4 was the use of the two enantiomeric aldehydes, (*S*)-**21b** and (*R*)-**21b**, containing the asymmetric center which becomes C-5 in the final products. The detailed synthesis of these key intermediates, both obtained from 2-deoxy-D-ribose, will be presented fully in Section 3.B

Scheme 3.3. Synthesis of (5*S*)-HETE and (±)-5-HPETE.

Unfortunately, attempts to synthesize the optically active 5-HPETEs by displacement of the mesylates of (5*S*)- or (5*R*)-HETE methyl ester with hydrogen peroxide resulted in racemization and formation of (±)-5-HPETE.

(3) Random Chemical Oxygenation of Arachidonic Acid

When it became clear that the lipoxygenase pathway in mammalian systems was the source of previously unknown, but very important, biochemical transmitters,



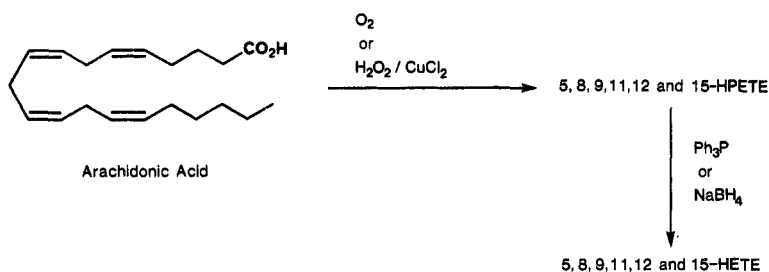
Scheme 3.4. Synthesis of (5R)-HETE.

the need to have the mono-HETEs and HPETEs readily available for comparison purposes was immediately felt. Consequently, the direct oxidation of arachidonic acid under free radical conditions and with singlet oxygen was investigated as a possible direct route to these compounds. Both processes are of course nonstereospecific and the compounds are all obtained in their racemic form.

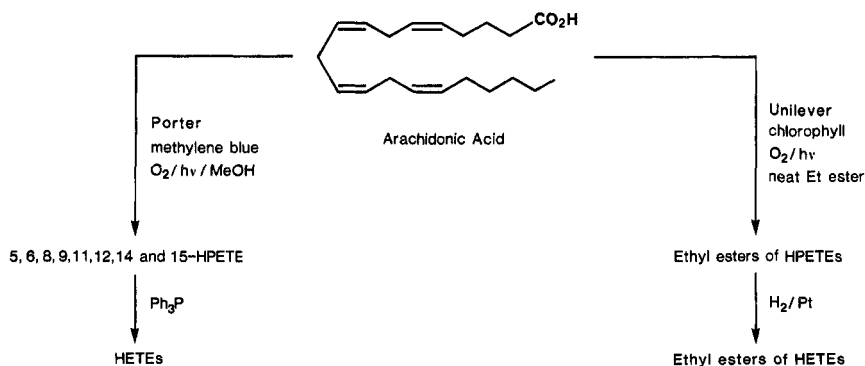
Two laboratories have independently reported details of the free radical oxygenation of arachidonic acid. Under free radical conditions the doubly allylic methylene groups at C-7, C-10, and C-13 are much more susceptible to hydrogen abstraction than the monoallylic methylenes at C-4 and C-16. As a result, only the six naturally occurring HPETEs are formed under these conditions. Porter et al.⁸ exposed neat arachidonic (Scheme 3.5) or its methyl ester to O_2 at room temperature for 48 hours and subsequently isolated the HPETEs produced by HPLC. The HETEs were obtained by reduction of the peroxides with triphenylphosphine. Boeynants et al.⁹ generated the mixture of HPETEs using $\text{H}_2\text{O}_2/\text{CuCl}_2$ in methanol and directly reduced them to the mixture of HETEs for HPLC analysis. Both groups proved the structure of the individual HETEs by mass spectral analysis of the trimethylsilylated methyl esters. These methods are limited in that only milligram quantities can be prepared easily, but they do provide a facile one-step preparation of all the naturally occurring HETEs and HPETEs that are useful for comparison purposes.

Porter's group also studied the products of singlet oxygen oxygenation of arachidonic acid (Scheme 3.6).¹⁰ Singlet oxygen is nonselective in its site of attack on double bonds and as a result eight mono-HPETEs were obtained from arachidonic acid. Both the HPETEs and the HETEs, obtained by reduction, were analyzed as their methyl esters. It is worth noting that a virtually identical study was carried out on the ethyl ester of arachidonic acid 13 years earlier by workers in the Unilever Laboratories¹¹ (Scheme 3.6). These workers did not attempt to isolate the individual HPETEs or HETEs, but in a monu-

mental piece of degradative work combined with gas chromatography and mass spectrometry, came to conclusions identical to those of Porter et al.¹⁰ with regard to the position of oxygenation in the eight HPETE ethyl esters obtained.



Scheme 3.5. Free radical oxygenation of arachidonic acid.



Scheme 3.6. Singlet oxygen oxygenation of arachidonic acid.

B. Synthesis of LTB₄ and Related Compounds

Of the more highly oxygenated products from arachidonic acid, the compound which has attracted the greatest attention both biologically and synthetically is leukotriene B₄ (LTB₄, Scheme 1.4). A number of other polyoxygenated derivatives are known in addition to those in Schemes 1.4 and 1.6, but less is known about their biological roles and they have been the object of little synthetic effort.

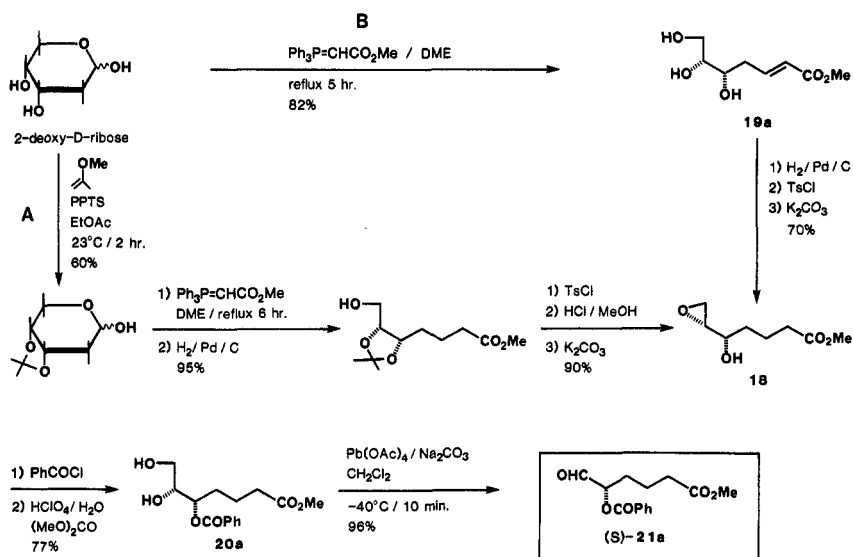
The strategic considerations regarding the synthesis of LTB₄ and related compounds are discussed in Section 2, Schemes 2.4, 2.6, 2.8, 2.10, 2.11, 2.20, and 2.21.

(1) A Key Synthon: (*S*)-, (*R*)-, and Racemic 5-Benzoyloxy-6-Oxohexanoic Acid Esters

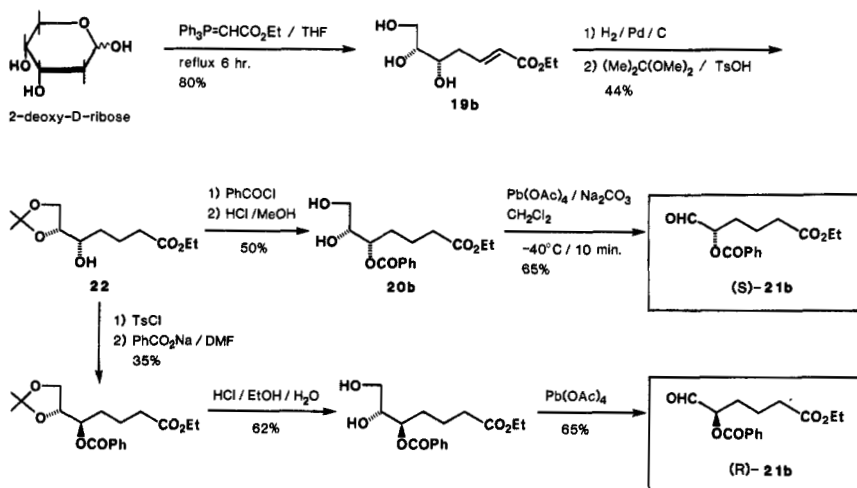
The (*S*)-isomer of the title compound has been used as a synthon in all but one of the reported syntheses of LTB₄ as well as the synthesis of LTB_x and a synthesis of (*5R*)- and (*5S*)-HETE, as discussed above in Section 3.A.2. Corey's group has described two syntheses of the methyl ester (*S*)-**21a**, both starting from 2-deoxy-D-ribose. In path A¹² (Scheme 3.7), 2-deoxy-D-ribose was first protected as the acetonide, which was transformed to the epoxide **18**. The latter was also obtained in a second synthesis (path B),¹³ which bypassed the initial protection of 2-deoxy-D-ribose as an acetonide.

Drawing on experience from their work on the synthesis of LTA₄ (to be described in Section 3.C) the Merck Frosst group also developed a synthesis of the ethyl ester (*S*)-**21b** from 2-deoxy-D-ribose (Scheme 3.8).¹⁴ The intermediate acetonide **22** served to protect the terminal diol unit and allow benzylation to be effected on the desired hydroxyl group, thus serving the same protective purpose as the terminal epoxide in **18** (Scheme 3.7). But in addition, the acetonide **22** also served as a common intermediate to obtain the (*R*)-isomer of **21b** used in the synthesis of (*5R*)-HETE, as shown previously in Scheme 3.4.

Spur et al.¹⁵ also recently described a synthesis of (*S*)-**21a**, starting from the relatively inexpensive D-arabinose.

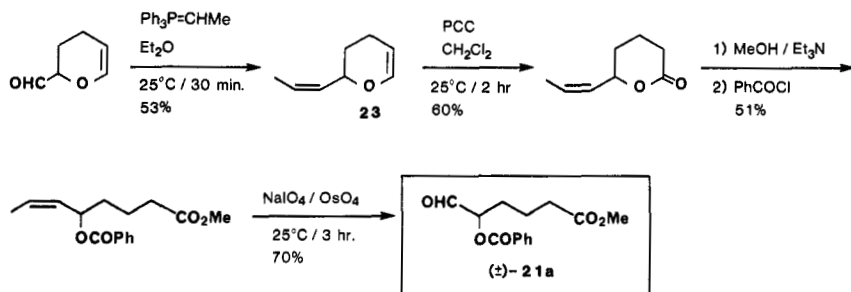


Scheme 3.7. Synthesis of methyl (*S*)-5-benzoyloxy-6-oxohexanoate.

Scheme 3.8. Synthesis of ethyl (*S*)- and (*R*)-5-benzoyloxy-6-oxohexanoate.

In addition to the chemical syntheses described above, Sih and co-workers¹⁶ have developed microbiological methodology to prepare both (*S*)- and (*R*)-**21a**, and Fuganti et al.¹⁷ have described a somewhat lengthy preparation of (*S*)-**21a** based upon yeast fermentation technology.

In addition to this synthesis of the resolved isomers of **21**, an Italian group¹⁸ has devised a novel synthesis of the racemic form of **21a** from the dimer of acrolein (Scheme 3.9). Worthy of note is the key conversion of the dihydropyran **23** to a δ -lactone with pyridinium chlorochromate (PCC). These workers have subsequently published an improved version of this basic route.¹⁹

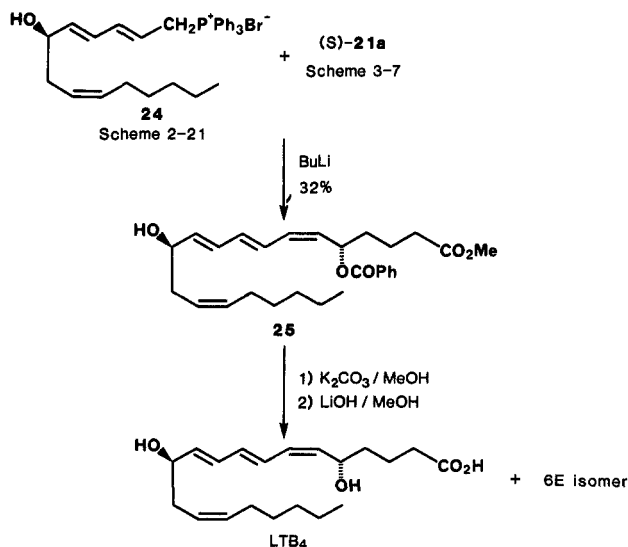
Scheme 3.9. Synthesis of methyl ($\pm$)-5-benzoyloxy-6-oxohexanoate.

(2) *Synthesis of LTB₄*

As mentioned earlier, all but one of the syntheses of LTB₄ reported to date have employed aldehyde esters **21a** (methyl ester) or **21b** (ethyl ester), derived from 2-deoxy-D-ribose, as the source of chirality at carbon 5. Two syntheses of LTB₄ have been reported from the Merck Frosst laboratories, two from the laboratory of Professor Corey, and one by Nicolau.

The first synthesis of LTB₄, from Corey's laboratory, outlined in Section 2, Scheme 2.21, and in Scheme 3.10, starts from D-mannose.¹² In this synthesis, carbon 3 of D-mannose becomes carbon 12 in LTB₄. Hydrolysis of **25** then yielded LTB₄, which was separated from an accompanying 15% of the (6*E*)-isomer by HPLC.

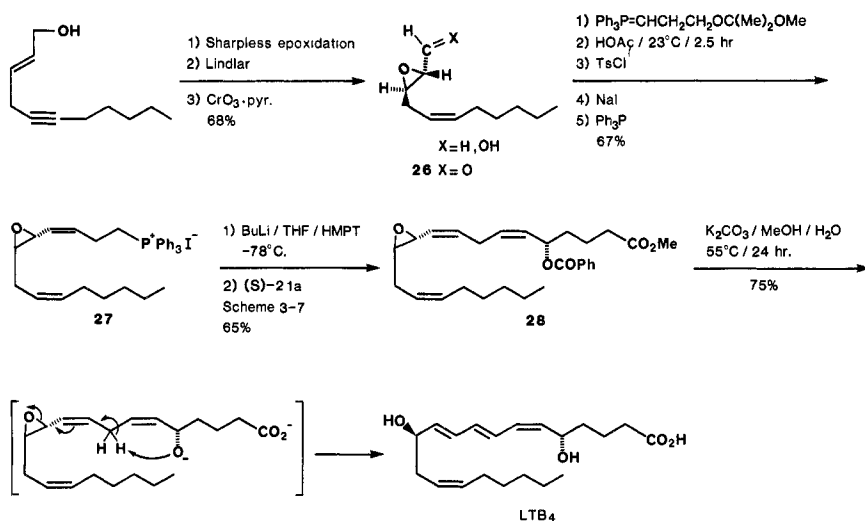
A significantly shorter synthesis of the phosphonium salt **24** (= **73**, Scheme 2.21) has since been published by workers in the Glaxo laboratories.²⁰



Scheme 3.10. Synthesis of LTB₄.

In a second synthesis of LTB₄,¹³ Corey's group made use of the excellent method of asymmetric epoxidation developed by Sharpless and co-workers²¹ to obtain an optically active epoxy alcohol (Scheme 3.11). In this sequence, the Wittig reagent **27** seems to condense much more cleanly with (S)-**21a** than did **24** (Scheme 3.10). The key and very elegant step in the synthesis was the hydrolysis and rearrangement of the intermediate **28**, which undergoes a very

facile intramolecular eliminative opening of the epoxide ring, as depicted, to yield LTB₄ directly. In simple terms, phosphonium salts **24** and **27** are equivalent, except that in the latter, the opening of the epoxide ring has been deferred to a more propitious moment.



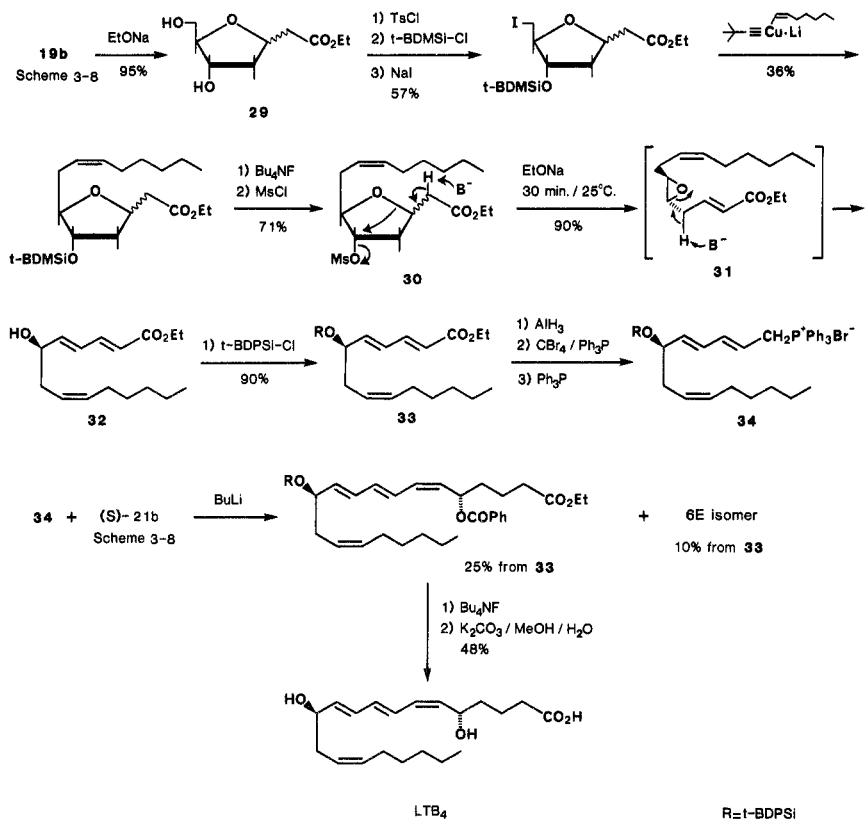
Scheme 3.11. Synthesis of LTB₄.

The first synthesis of LTB₄ from the Merck Frosst laboratories¹⁴ is outlined in Scheme 3.12. One key aspect of this synthesis is that 2-deoxy-D-ribose serves as the source of chirality for both asymmetric centers of LTB₄, with C-3 becoming C-5 in LTB₄ [(S)-**21b**, Scheme 3.8] and C-4 becoming C-12 (**32**, Scheme 3.12). The critical chemical step which made this synthesis possible was the novel finding that certain C-glycosides, containing a suitable leaving group in the tetrahydrofuran ring, unravel completely upon base treatment, giving rise to a conjugated diene unit in high yield, as depicted in the sequence **30** → **31** → **32**. The epoxide **31** is considered to be a true intermediate, since in other cases it could be isolated.

The second Merck Frosst synthesis (from L-arabinose) is discussed in detail in Section 2, Scheme 2.20.

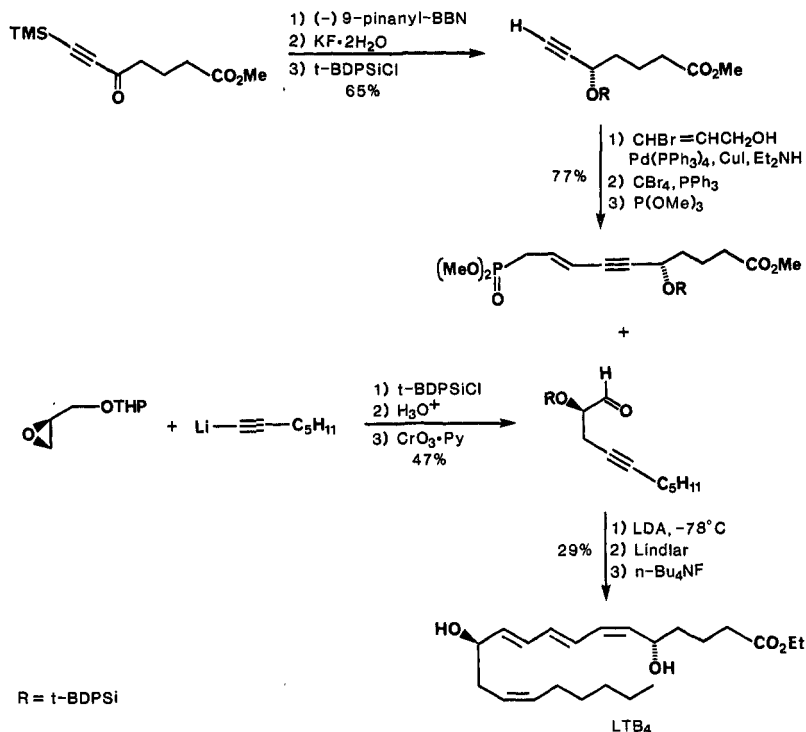
An alternative synthesis of synthon **62**, Scheme 2.20, based on a yeast fermentation, has been described by Fuganti et al.¹⁷ and a versatile approach to α-benzoyloxyaldehydes from D-mannitol has given **62**, R = benzoyl.²³

A clean biochemical preparation of LTB₄ from LTA₄ has also been developed by Maycock et al.²²



Scheme 3.12. Synthesis of LTB₄.

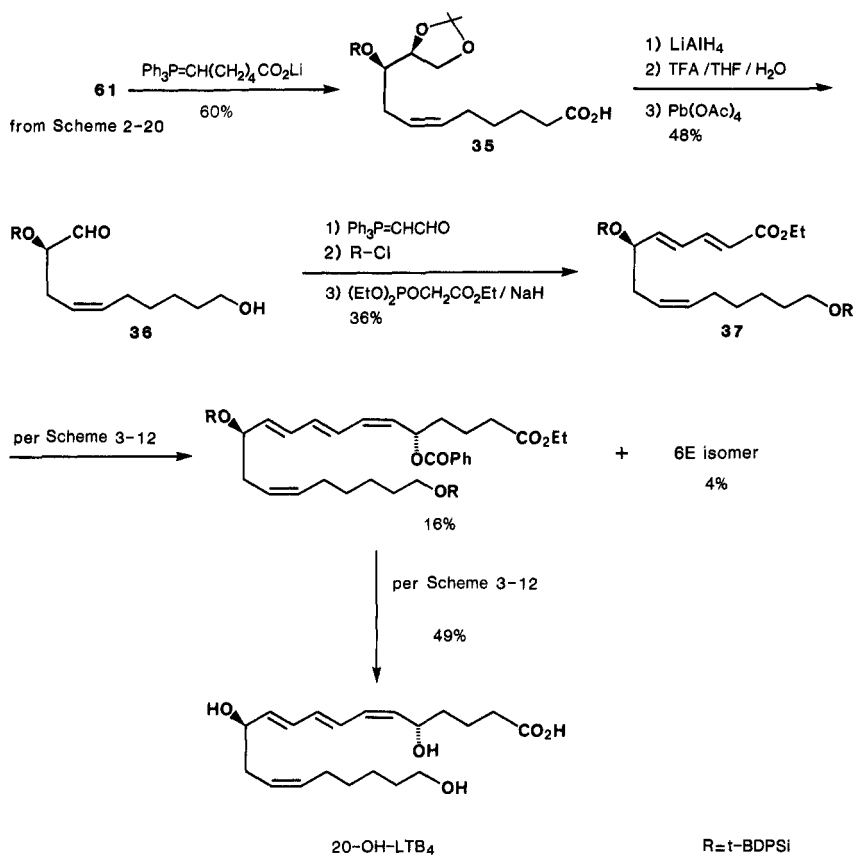
A quite different approach to the synthesis of LTB₄ from Nicolau's²⁴ group is outlined in Scheme 3.13. Extensive use is made of acetylene chemistry to build up the 20-carbon chain, and semihydrogenation is used to introduce the desired *cis* double bonds. (See Section 2, Schemes 2.1–2.3 for a discussion of the strategic use of acetylenes.) The introduction of the C-5 hydroxyl group in over 97% optical purity constitutes a real-life example of the usefulness of asymmetric reducing agents such as 9-pinanyl-BBN. Semihydrogenation of similar acetylenic intermediates with deuterium or tritium can be used to obtain labeled LTB₄ (Scheme 2.4).

Scheme 3.13. Synthesis of LTB_4 .

(3) Synthesis of 20-Hydroxy LTB_4

As seen in Scheme 1.4, LTB_4 is further metabolized by terminal oxidation, first to the primary alcohol 20-OH- LTB_4 , then to the dicarboxylic acid 20- CO_2H - LTB_4 . The terminal aldehyde is presumably an intermediate in the formation of the latter, but it has not yet been found in biological systems.

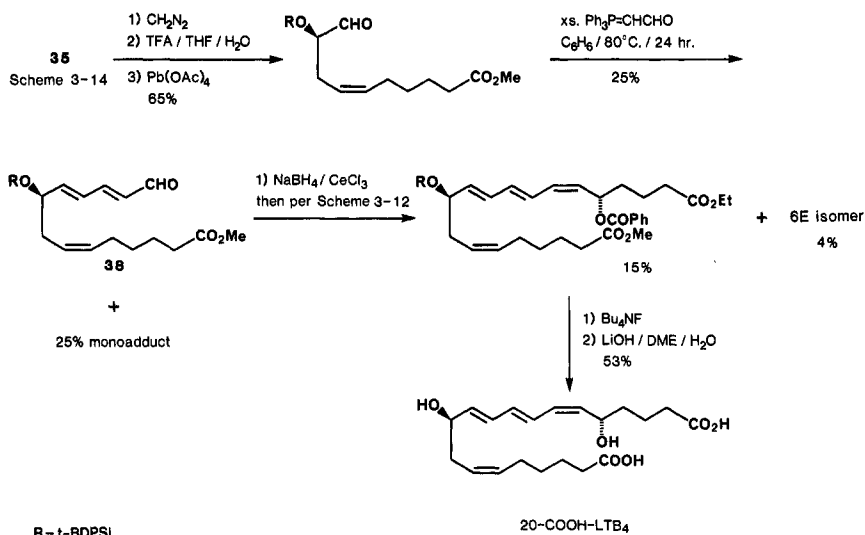
A synthesis of 20-OH- LTB_4 has now been carried out in the Merck Frosst laboratories,²⁵ using as a key intermediate the aldehyde **61** (Scheme 2.20) previously employed in one of the syntheses of LTB_4 . The use of this aldehyde permits the ready introduction of various functionalities into the terminal six carbons of eicosatetraenoic acid structures, and as outlined in Scheme 3.14, provided the basis for the synthesis of 20-OH- LTB_4 . For the conversion of **36** to **37**, a two-step sequence for adding the four-carbon unit was again found

Scheme 3.14. Synthesis of 20-hydroxy-LTB₄.

advantageous, as in the case of homologation of the analogous aldehyde **62** (Scheme 2.20). The remainder of the synthesis was completed using methodology very similar to that shown in Scheme 3.12 for the synthesis of LTB₄.

(4) Synthesis of 20-Carboxy LTB₄

Utilizing the acid **35** (Scheme 3.14) as the starting material, the Merck Frosst group has also realized a synthesis of the C-20 terminal acid 20-CO₂H-LTB₄ (Scheme 3.15).²⁵ In this case the four-carbon homologation was carried out in one step, using formylmethylene triphenylphosphine, in spite of the modest yield obtained (25%) of **38**. This was done to differentiate the carbonyl groups in **38**

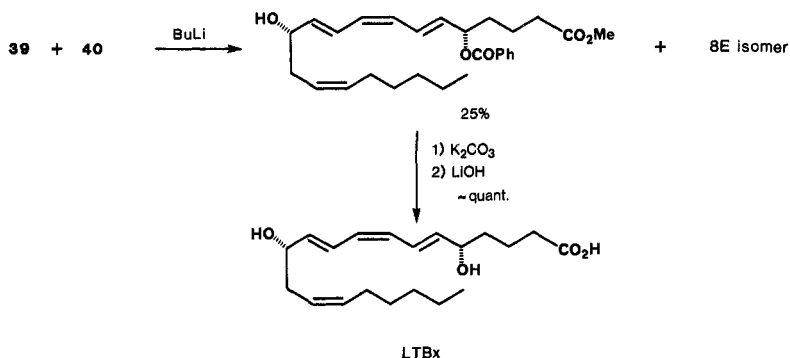
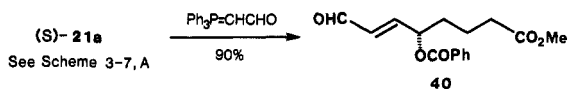
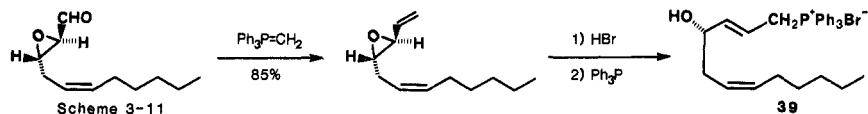
Scheme 3.15. Synthesis of 20-carboxy-LTB₄.

and so preserve the desired terminal ester functionality. As described earlier (Scheme 3.2), advantage was again taken of the work of Luche⁴ to cleanly reduce the aldehyde group in **38** to the primary allylic alcohol. In a slight variation from related hydrolyses, it was found necessary to use LiOH instead of K₂CO₃ in the final hydrolysis to 20-CO₂H-LTB₄.

(5) Synthesis of LTB_x[(5S, 12S)-DiHETE]

A dihydroxyeicosatetraenoic acid, isomeric with LTB₄, was reported simultaneously by two groups^{26,27} as being formed from arachidonic acid in leukocytes. In contrast to LTB₄, it is formed by two successive lipoxygenase reactions, and the trivial names LTB_x or (5S,12S)-DiHETE (from dihydroxyeicostetraenoic acid) have been used as practical designations (Scheme 1.4).

A total synthesis of LTB_x has been reported by Corey et al.²⁸ as outlined in Scheme 3.16. By using the Sharpless asymmetric oxidation,²¹ the enantiomer of the epoxy alcohol in Scheme 3.11 was obtained, from which the corresponding aldehyde was then prepared. The epoxy olefin was transformed to the desired Wittig salt **39**, which was condensed with the homologated aldehyde **40**, giving a modest yield of the desired (8Z)-isomer. Again, the benzoyloxy aldehyde

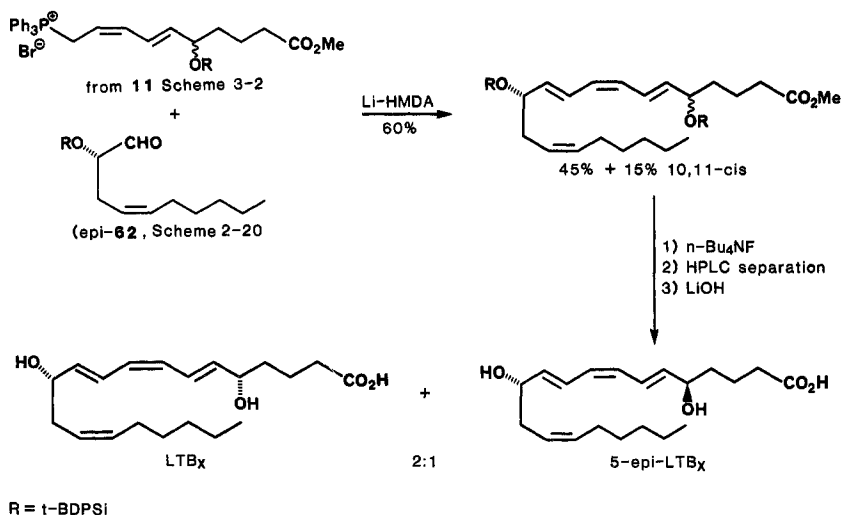
Scheme 3.16. Synthesis of LTB_x.

(S)-21a was the source of chirality for C-5, as in the syntheses of LTB₄ and its more highly oxygenated derivatives.

A quite different synthesis of LTB_x from the Merck Frosst group²⁹ is outlined in Scheme 3.17. The starting synthons were available from previously described chemistry, and in particular the phosphonium salt was a further example of the use of cyclopropafurans to obtain conjugated *cis-trans* diene units (Section 2, Scheme 2.10). The fascinating results of the Wittig reaction in this synthesis are discussed in detail in Section 2, Scheme 2.8. The present synthesis also yielded the unnatural 5-*epi*-LTB_x, along with the 10,11-*cis*-double bond isomers, thus making them available for biological studies.

C. Synthesis of LTA₄ and Its 5,6-Epoxy Epimers

As can be seen from Scheme 1.4, LTA₄ occupies a pivotal biochemical position, being the precursor of both the important chemotactic agent LTB₄ and the potent contractile components of SRS-A, LTC₄, LTD₄, and LTE₄. Because LTA₄ (as

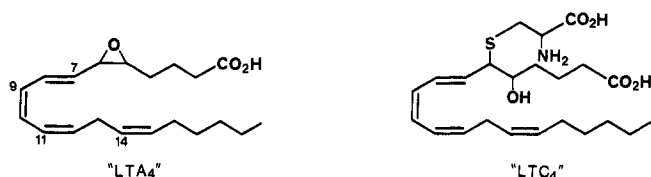
Scheme 3.17. Synthesis of LTB_x and 5-epi-LTB_x.

its methyl ester) has also been the widely used precursor of synthetic LTC₄, LTD₄, and LTE₄, a number of syntheses of it have been developed, including the racemic and optically active forms, *cis*- and *trans*-epoxy isomers, and a variety of double-bond geometrical isomers.

(1) *The Double-Bond Stereochemical Problem in the Leukotrienes: 1,7-Hydrogen Migration*

The history of the structure assignments for the leukotrienes is somewhat unique in modern natural products chemistry as the complete structures were only assigned after comparison with totally synthetic material of known relative and absolute stereochemistry. In his original proposal of structures for LTA₄ and LTC₄, Samuelsson pointed out that several areas of uncertainty remained.³⁰ The structures he suggested were as shown in Chart 3.1, and the areas of uncertainty were (a) the relative and absolute stereochemistry at C-5 and C-6, (b) whether or not the cysteine unit was further derivatized, and (c) the geometry of the double bonds at C-7 and C-9.

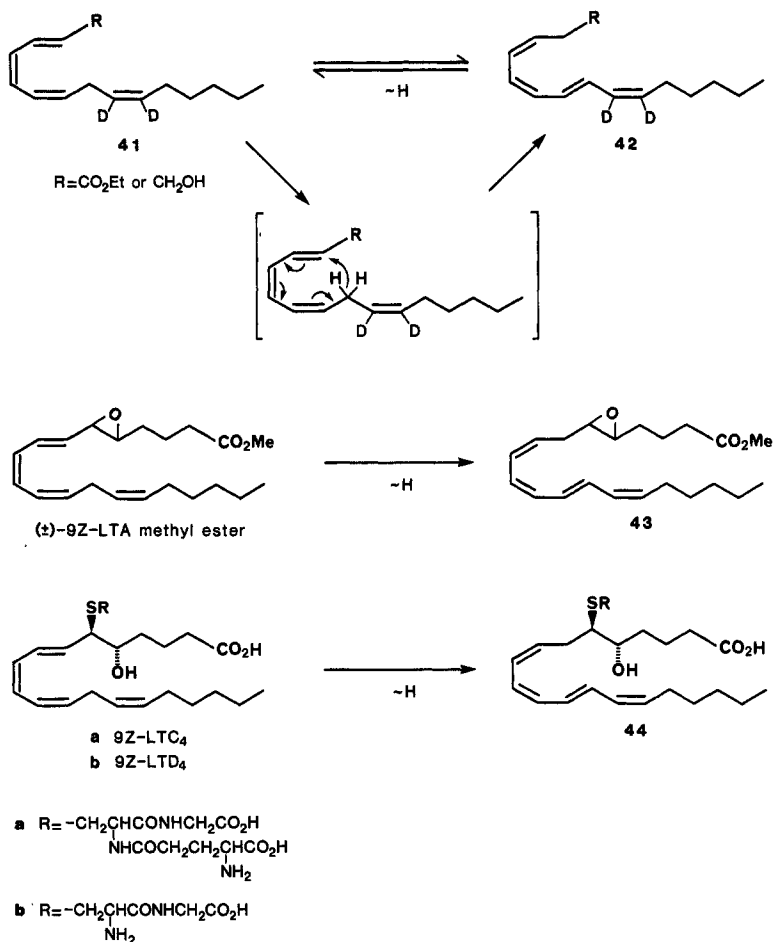
Despite these uncertainties, several groups set out to prepare the proposed leukotriene structures, and during these syntheses some interesting observations were made with respect to the double-bond stereochemistry which eventually lead to modification of the proposed structures for LTA₄ and LTC₄. These observations are outlined here in a historical context to indicate their contribution to the final structure proof of the leukotrienes.

Chart 3.1. Originally proposed structures for LTA₄ and LTC₄.

The Merck Frosst group first noted something unexpected in the behavior of compounds in which the conjugated triene unit in the leukotrienes possessed the (*E-Z-Z*)-stereochemistry, as originally suggested by Samuelsson (Chart 3.1). In the early stages of their first synthesis of the leukotrienes,³¹ compound **41** (R = CO₂Et, Scheme 3.18) was prepared as the intended precursor for the C-6 to C-20 portion of the target structures. However, it was unexpectedly found that **41** (R = CO₂Et or CH₂OH) rearranged spontaneously at room temperature over a 24-hour period to a 1:2 mixture of **41** and **42**. This rearrangement appears to be a relatively facile example of an allowed sigmatropic antarafacial [1,7]-hydrogen migration as depicted.³² The Merck Frosst workers concluded that, as there was no obvious reason why the structures of LTA₄ and LTC₄ as depicted in Chart 3.1 should not undergo a similar rearrangement, Samuelsson's tentatively proposed stereochemistry required revision. Samuelsson's evidence for the (*Z*)-geometry of the C-11 and C-14 double bonds being based on solid grounds,³⁰ it was most reasonable to suppose that the C-9 double bond must have (*E*)- rather than (*Z*)- stereochemistry. With (*E*)-geometry at C-9 and C-10, it becomes sterically impossible for the molecule to assume the cyclic transition state necessary for the [1,7]-hydrogen migration to occur. This still left open the question of the correct geometry at the C-7 double bond, but it was assumed that the thermodynamically more favorable (*E*)-configuration was most probable. Subsequent synthesis and comparison with the natural products then confirmed the proposed revision of the stereochemistry of the C-9 double bond.

Subsequently, a group at the Lilly Research Centre³³ and Sih and co-workers³⁴ prepared (±)-LTA₄ methyl ester (Scheme 3.18) with the originally proposed (9*Z*)-geometry (Chart 3.1) and both groups found that it did indeed rearrange readily at room temperature to the conjugated tetraene **43**, as predicted by Rokach and co-workers.³¹ Both groups also prepared the (9*Z*)-isomers of LTC₄^{34,35} and LTD₄³⁶ and found that these fully functionalized leukotrienes also readily undergo the same [1,7]-hydrogen migration to produce the conjugated tetraene isomers **44**. The Lilly group also concluded that an earlier report³⁷ of the synthesis of (9*Z*)-LTC₄ was in error and that the (9*Z*,11*E*)-isomer had actually been obtained.

It is important to note that all of these [1,7]-hydrogen migrations proceed in



Scheme 3.18. [1,7]-Hydrogen migrations in leukotriene-like structures.

a matter of hours at or below room temperature, which, as was pointed out,^{31,35} eliminated the (9Z)-structures for the natural products.

(2) Linear Synthesis of Racemic LTA₄

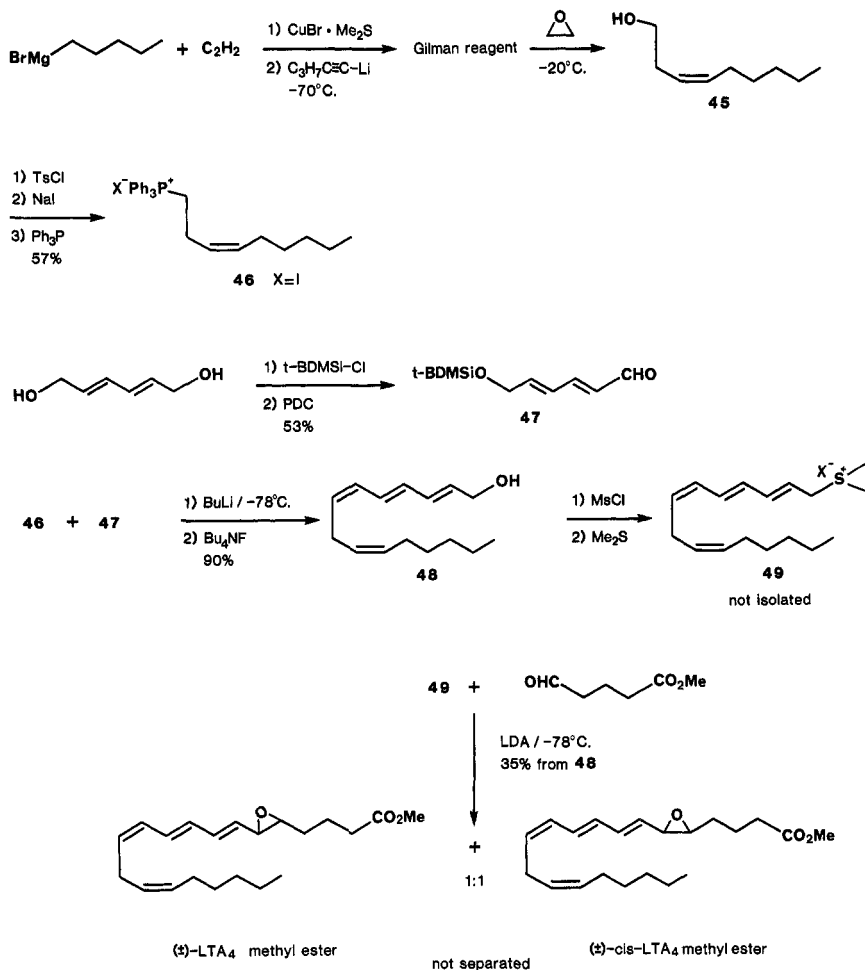
There have been several linear (as opposed to convergent) syntheses of racemic LTA₄ methyl ester. All employ a sulfonium ylid at or near the last step to generate the epoxide by condensation with an aldehyde. It is conceivable that an optically active ylid would induce optical activity in the epoxide-forming

step, but to date only optically inactive sulfonium salts have been used for this reaction.

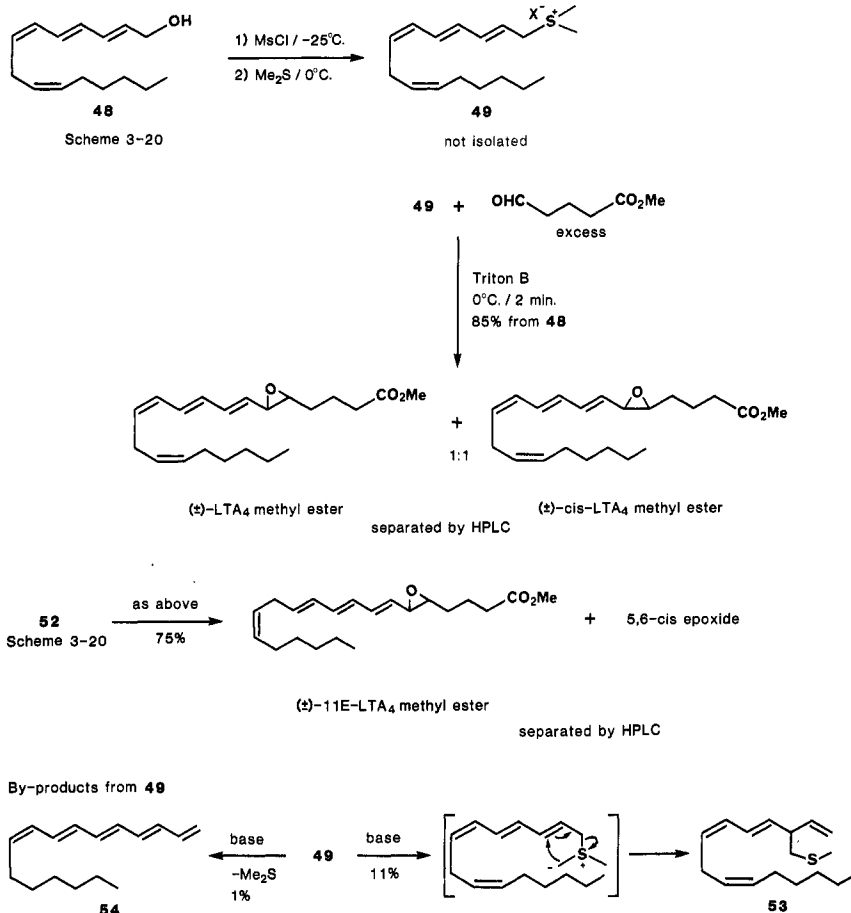
The first synthesis of racemic LTA₄ methyl ester, as a mixture with its *cis* isomer, was reported by Corey et al.³⁸ as outlined in Scheme 3.19. Alcohol **45** was used as the synthon for the C-12 portion of the target structure and (*E,E*)-2,4-hexadien-1,6-diol became C-6 to C-11. The functionality in the diol was differentiated by its transformation to **47**, which then underwent a Wittig reaction with **46** to yield the 15-carbon alcohol **48**. The formation of the mesylate of **48** and the reaction of sulfonium salt **49** with methyl 4-formylbutyrate using LDA as a base is also a difficult step and only modest yields of the target compounds are obtained.^{31,38}

A synthesis of racemic LTA₄ methyl ester was also carried out by Rokach and co-workers during their first synthesis of LTC₄.³¹ During the course of this work, they also synthesized ($\pm$)-*cis*-LTA₄ methyl ester and ($\pm$)-(11*E*)-LTA₄ methyl ester. The preparation of the key intermediates for these syntheses is shown in Scheme 3.20, where the required alcohol was prepared by the simple procedure of hydrogenation of the commercially available 3-nonyn-1-ol (see also Scheme 2.1), thus making the widely used phosphonium salt **46** cheaply and readily available. Synthons **50** and **51**, for C-6 to C-11, were readily available by the photochemical addition of ethyl diazoacetate (EDA) to furan,³⁹ but a major practical improvement on this reaction was made with the finding that the addition was catalyzed efficiently and rapidly by rhodium (II) acetate.^{40,41} These muconic acid semialdehyde derivatives (**50** and **51**) have readily differentiated functionality on either end of the diene unit and the broader potential utility of such 1,4-dicarbonyl-1,3-butadienes is discussed in Section 2, (Schemes 2.9–2.11). The synthesis of the alcohols **48** and **52** was straightforward, except to note that in the Wittig reaction the chloride salt of **46** gave only 10–15% of the undesired (*E*)-isomer as compared with 25 and 35% from the bromide and iodide, respectively.⁴¹ Compound **41** (Scheme 3.18) was prepared by a Wittig reaction between **46** and aldehyde **50**.

The syntheses of the three racemic isomers of LTA₄ methyl ester were then completed as indicated in Scheme 3.21. In the original report,³¹ the use of LDA to form the sulfonium ylid from **49** gave a yield of only 10–20% of the epoxide mixture. A major improvement in this step was subsequently realized with the finding that it could be reliably effected with Triton B in 85% yield,^{42,43} and an indication of the usefulness of the overall synthesis (Scheme 3.20 and 3.21) is that as much as 35 g of the mixture of ($\pm$)-LTA₄ methyl ester and ($\pm$)-*cis*-LTA₄ methyl ester has been prepared in a single reaction from 28 g of **48**.⁴¹ Finally, two minor by-products resulting from alternative base-catalyzed reactions of **49** have been identified as the tetraene sulfide **53**, arising from a sigmatropic rearrangement of the ylid, and the conjugated pentaene **54**.

Scheme 3.19. Synthesis of (±)-LTA₄ methyl ester.

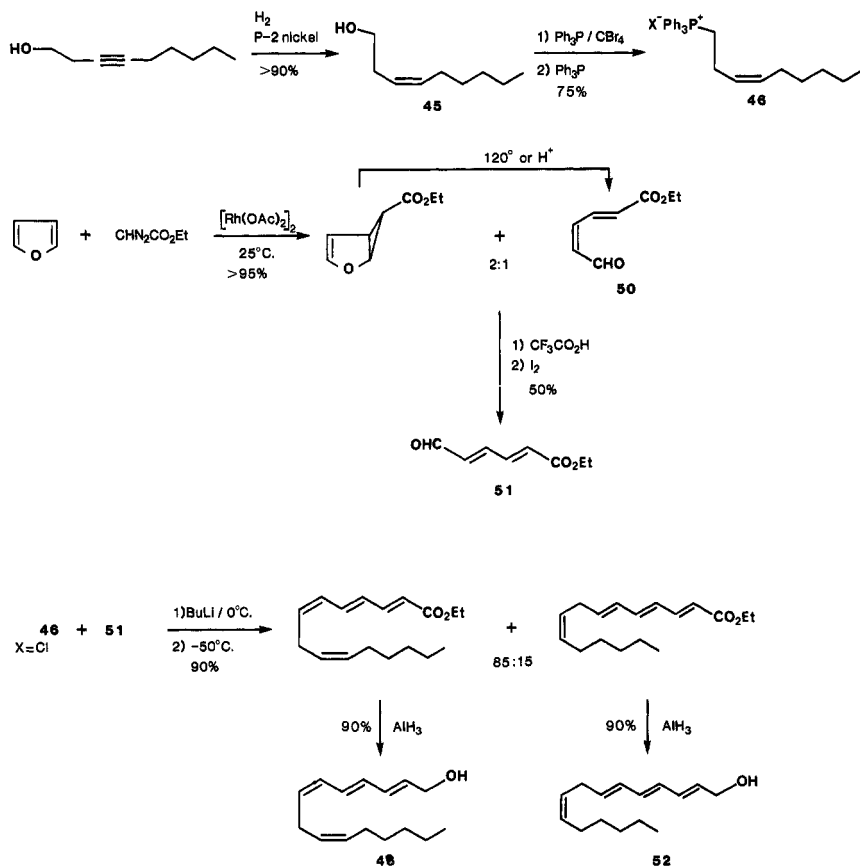
Workers from Hoffmann-La Roche have also devised a linear synthesis of racemic LTA₄ methyl ester during the course of a synthesis of LTE₄.^{44,45} They too employed a sulfonium salt (Scheme 3.22) in the epoxide-forming step to obtain a dienediylne epoxide. This step was made reasonably efficient by the use of a two-phase reaction system with a phase-transfer catalyst. Their sequence is also amenable to reasonable scale-up as they describe the preparation of 18 g of the epoxide mixture in a single reaction. A unique aspect of this synthesis is

Scheme 3.20. Preparation of intermediates for $(\pm)\text{-LTA}_4$ synthesis.

that it is the only one reported that does not employ a Wittig reaction to obtain any of the four double bonds in the molecule.

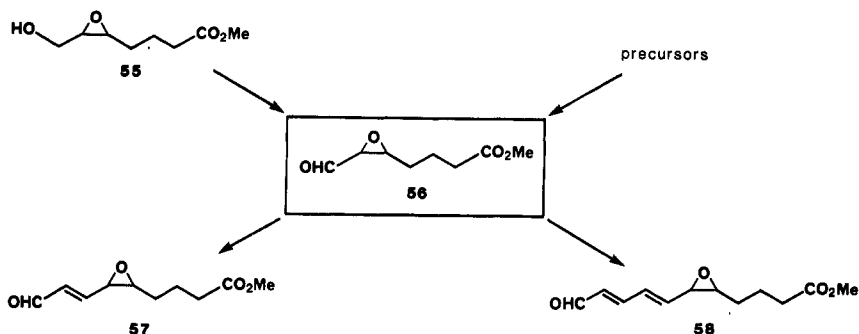
(3) Convergent Synthesis of Racemic LTA_4 and Double-Bond Isomers

In all the reported convergent syntheses of LTA_4 , including the racemic form, the natural and three possible unnatural chiral forms, and various double-bond geometrical isomers, the epoxy aldehydo ester **56** has been found to be a key intermediate. Consequently a number of ingenious syntheses of the various stereo

Scheme 3.21. Synthesis of (±)-LTA₄ methyl ester and isomers.

and optical isomers of **56** have been devised. As outlined schematically in Chart 3.2, **56** has often been obtained from the corresponding alcohol **55**, although several other syntheses from various precursors have also been developed. Compound **56** has then often been extended by various methodologies to the advanced synthons **57** and **58**.

Several convergent syntheses of racemic LTA₄ methyl ester have been reported. The first of these was by Gleason and co-workers,⁴⁶ who developed a very short, efficient synthesis of the key intermediate (±)-*trans*-**56** (Scheme 3.23). Corey and co-workers⁴⁷ also prepared the same racemic intermediate, albeit by a slightly longer route. Scheme 3.23 summarizes the synthesis of the various intermediates and Scheme 3.24 indicates the various isomers of (±)-LTA₄ methyl ester obtained. The group at the Lilly Research Centre has examined

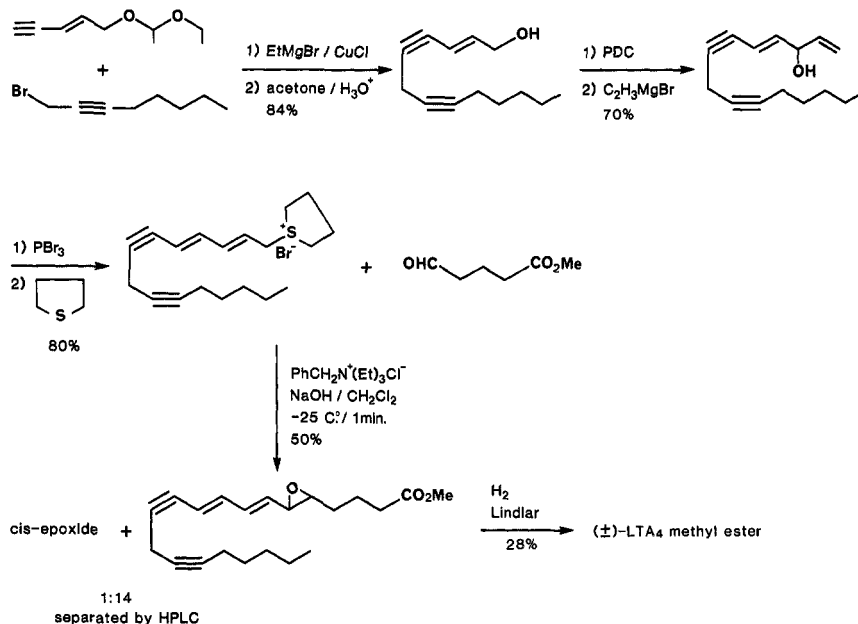
Chart 3.2. Key intermediates in convergent synthesis of LTA₄.

these syntheses in detail^{33,35,48} in order to characterize the four principal products indicated in Scheme 3.24. Gleason et al.⁴⁶ reported the obtention of the mixture of two geometric isomers from the Wittig reaction between ($\pm$)-*trans*-**57** and **59**, but did not separate them. Based on the results of the Lilly group,³³ it seems most probable that they had obtained ($\pm$)-LTA₄ methyl ester and its (9*Z*, 11*E*)-isomer. The Lilly workers also isolated four minor isomers of LTA₄ methyl ester,⁴⁸ but did not obtain sufficient material to assign their double-bond stereochemistry, although they report the UV and mass spectra, as well as HPLC behavior.

A Glaxo group⁴⁹ has subsequently reported a synthesis of racemic LTA₄ methyl ester, free of double-bond geometric isomers, by coupling of the phosphonate **60** with ($\pm$)-*trans*-**56**, in 34% yield. The phosphonate was clearly advantageous, since the triphenylphosphonium salt corresponding to **49** gave a 1:1 mixture of the (7*E*)- and (7*Z*)-isomers of LTA₄ methyl ester.⁴⁹ Takeda and co-workers describe an alternative synthesis of **60** based on a novel rearrangement of β,γ -allenic esters to ($\alpha E,\gamma Z$)-unsaturated esters, but the overall procedure is relatively low yielding.⁵⁰

(4) Convergent Synthesis of Chiral LTA₄ and Its 5,6-Epoxy Epimers

As expected, considerable effort has been put into developing syntheses for the naturally occurring, chirally pure form of LTA₄ both to prepare LTC₄, LTD₄, and LTE₄ and to study its enzymatic conversion to these compounds and to LTB₄ (Scheme 1.4). To study the effect of the stereochemistry at C-5 and C-6 on biological activity, there has also been a need to obtain the three unnatural stereoisomers (5-*epi*, 6-*epi*, and 5,6-*diepi*) of LTC₄, LTD₄, and LTE₄. As a result, considerable effort has gone into developing syntheses for the three unnatural

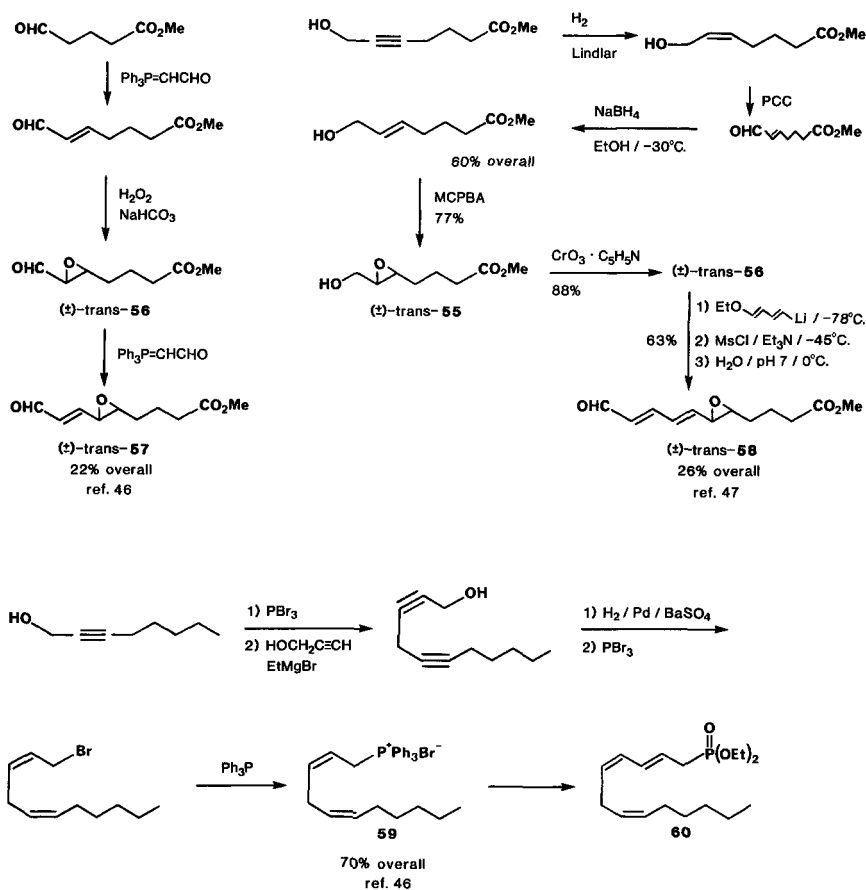
Scheme 3.22. Synthesis of (±)- LTA_4 methyl ester.

stereoisomers of LTA_4 , which are the immediate precursors of the desired leukotriene stereoisomers.

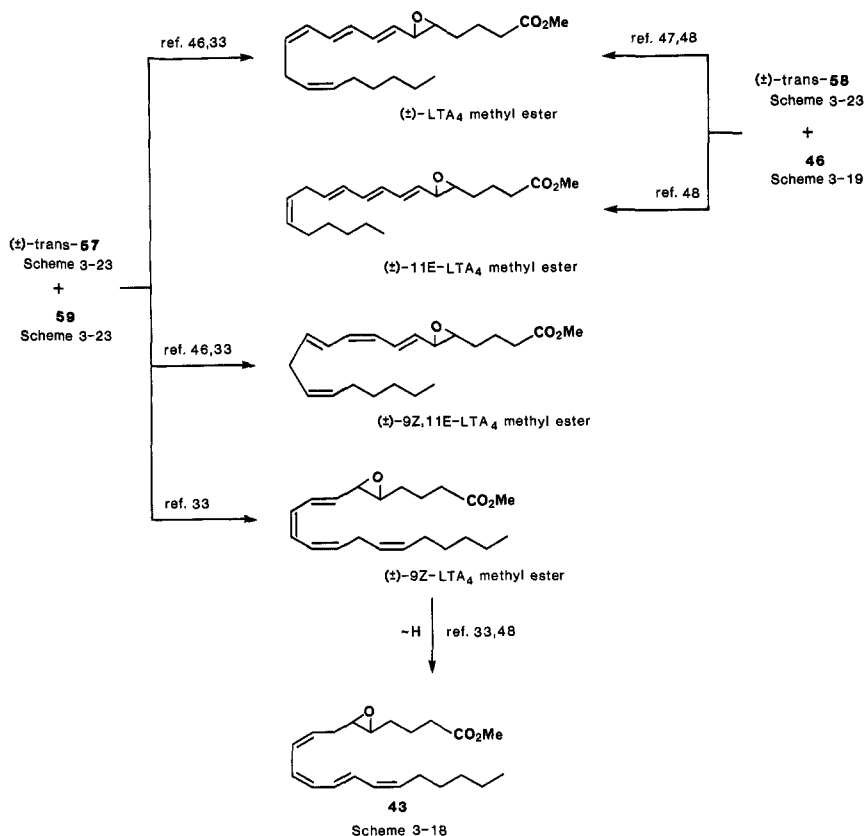
*Synthesis of LTA_4 , 5-*epi*- LTA_4 , 6-*epi*- LTA_4 , and 5-*epi*-6-*epi*- LTA_4 from 2-deoxy-D-ribose*

The only complete study of the synthesis of LTA_4 and its three optical isomers (as their methyl esters) has been carried out by the group at Merck Frosst, which has resulted in two syntheses of this series of key compounds.^{51,52} The particularly successful and satisfying aspect of these syntheses is that from a single chiral starting material, 2-deoxy-D-ribose, by appropriate manipulation of its chiral centers, all four of the optically active isomers of LTA_4 were obtained. This strategy is discussed further in Section 2, Scheme 2.17, and its application to a synthesis of the four optical isomers of LTA_4 is detailed in Scheme 2.18.

In the second synthesis from the Merck Frosst group,⁵² 2-deoxy-D-ribose was used to obtain the C-glycoside **29** as described previously in Scheme 3.12. The key to the C-glycoside synthesis was the finding that with a suitable located leaving group, these structures open upon base treatment, as illustrated in

Scheme 3.23. Intermediates for racemic LTA₄ methyl ester.

Sequences 1, 2, and 3 of Scheme 3.25, to yield unsaturated epoxy alcohols. In Sequence 1, the terminal epoxide was isolated prior to conversion to *trans*(5*S*)-**55**. Sequence 2 of Scheme 3.25 illustrates the complete unraveling of the *C*-glycoside to yield a conjugated diene diol as a reaction competing with the formation of the desired epoxy alcohol. The formation of compounds such as the diene diol formed the basis for one of the syntheses of LTB₄ described earlier in Scheme 3.12.¹⁴ In Sequence 3, one of the necessary inversions was effected by a highly stereoselective reduction of ketone **62** with the hindered reagent lithium perhydro-9*B*-boraphenylhydride to obtain alcohol **63**. Conversion of the terminal epoxide **64a** to the desired *cis*-(5*R*)-**55** was unexpectedly difficult, as compared with the corresponding reaction in Sequence 1. The difficulty was ascribed to steric



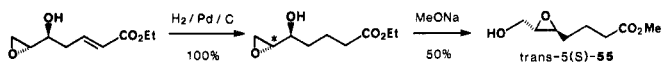
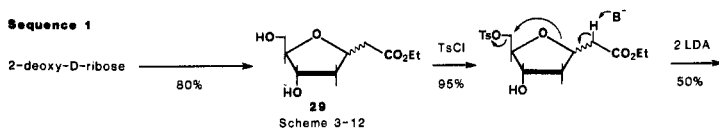
Scheme 3.24. Convergent syntheses of racemic LTA₄ methyl ester and double-bond isomers.

interference between the epoxide ring and the ester side chain in the transition state necessary for the formation of the *cis*-epoxide. Among the attempts to improve the reaction, **64b** was treated with lithium iodide in hot methanol (Sequence 4), with the rather amusing result that a reasonable yield of the *trans*-epoxy alcohol was obtained. The proposed mechanism for this unexpected result implicates the formation of a small amount of **65**, which can either revert to starting material or be drained off to the more stable *trans*-(5*R*)-**55**.

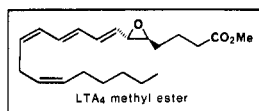
Synthesis of LTA₄ and Double-Bond Isomers from D-Ribose

The first stereospecific total synthesis of LTA₄ was carried out by Corey and co-workers,³⁷ and they established the general utility of the key intermediates of the general structures shown in Chart 3.2. In Scheme 3.26 is outlined Corey's

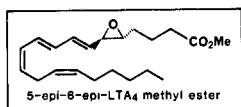
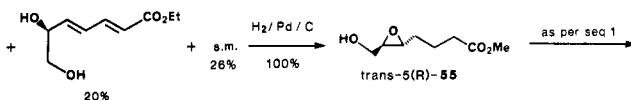
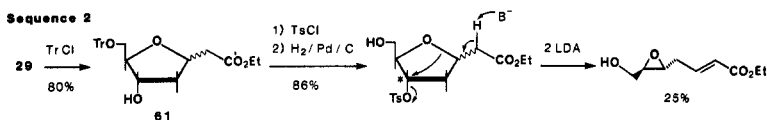
Sequence 1



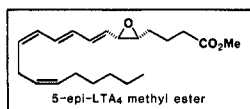
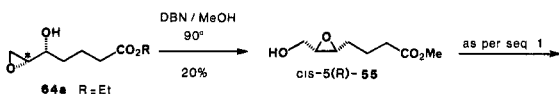
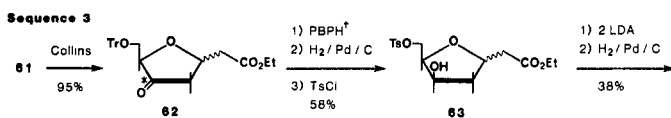
- 1) Collins
 - 2) $2 \text{ Ph}_3\text{P}=\text{CHCHO}$
 - 3) **46** X = Cl, Scheme 3-20
- 13%



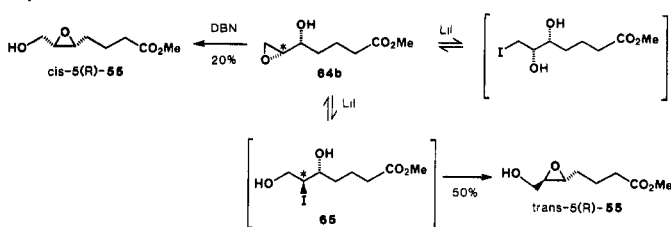
Sequence 2



Sequence 3



Sequence 4



[†]PBPH = perhydro-9B-boraphenyl hydride

*Point of inversion

Scheme 3.25. c-Glycoside route to LTA₄, 5-epi-LTA₄, and 5-epi-6-epi-LTA₄.

synthesis of LTA₄ methyl ester, starting from the 2,3,5-tribenzoyl derivative of D-ribose. A clean reductive removal of the allylic benzoate proved to be a particularly effective method to remove what had been the C₂ oxygen function of ribose. The selective removal of the acetate group from the saturated derivative of **66** using 0.005% HCl in methanol to uncover only the central oxygen as a hydroxyl group was a striking example of chemoselectivity. Tosylation then yielded **67**, which upon mild base treatment in methanol was debenzoylated and transformed directly to the desired *trans*-(5*S*)-**55**.

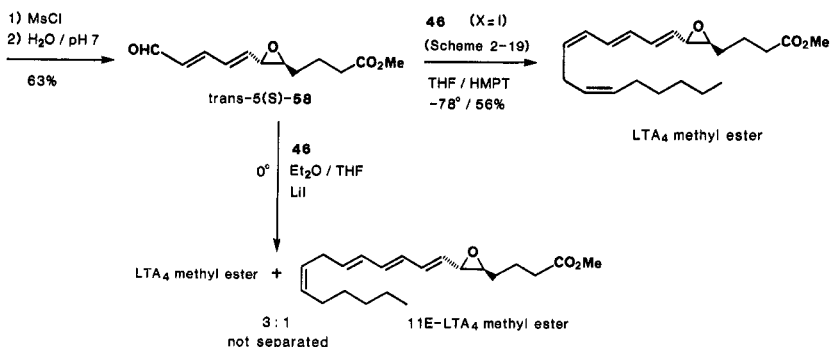
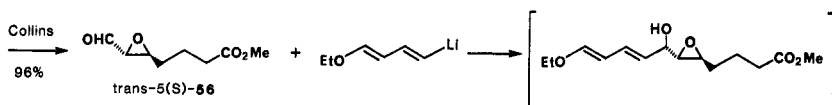
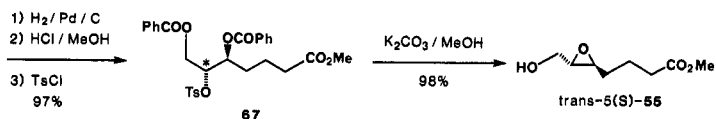
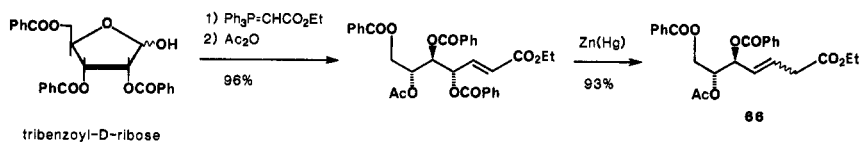
This conversion of **67** to *trans*-(5*S*)-**55** is a somewhat surprising result. The primary benzoate in **67** would be expected to hydrolyze first and form the terminal epoxide. Hydrolysis of the secondary benzoate, followed by epoxide rearrangement, should then give the internal epoxide, but it would be a *cis*-epoxide as a result of two inversions at the starred carbon. Since there seems to be no reason to doubt the *trans* nature of the epoxide, one must postulate a migration of one of the benzoate groups in **67** during hydrolysis, during the initial Wittig reaction, or during the acid methanolysis of the acetate group in the preparation of **67**. The last two possibilities could yield an isomer of **67** with a primary tosylate and two secondary benzoates, base hydrolysis of which would lead to the observed *trans*-epoxide.

After oxidation to the aldehyde *trans*-(5*S*)-**56**, the latter was reacted with the Wollenberg reagent, 4-lithio-1-methoxybutadiene, to effect a four-carbon chain extension to *trans*-(5*S*)-**58**. Corey subsequently reported that the use of the Wollenberg reagent was difficult to reproduce, and described an improved procedure using 4-lithio-1-methoxybut-1-en-3-yne.⁵³ A Wittig reaction with **46** (Scheme 3.19) then yielded LTA₄ methyl ester.

The last Wittig reaction also yielded a certain amount of the (11*E*)-isomer of LTA₄ methyl ester, and conditions were varied to increase the yield of the latter,⁵⁴ as shown in Scheme 3.26. Although the (11*E*)-isomer was not separated from LTA₄, the mixture was used to prepare the (11*E*)-isomer of LTC₄.⁵⁴

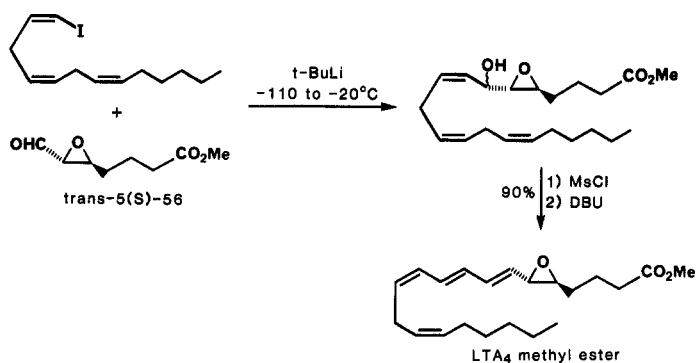
In a quite different approach to LTA₄ methyl ester (Scheme 3.27), Corey⁵⁵ utilized the condensation of a 13-carbon vinyl lithium reagent with the epoxy-aldehyde to generate a mixture of diastereomeric carbinols. Mesylation and elimination with base led directly to LTA₄ methyl ester, apparently free of double-bond isomers.

Ernest and co-workers,⁵⁶ using Corey's methodology³⁷ to prepare the key aldehyde intermediate *trans*-(5*S*)-**56**, developed a synthesis of the (7*Z*)-isomer of LTA₄ methyl ester (Scheme 3.28). These workers used the ylid **68** containing the crotonaldehyde unit as an alternative to the Wollenberg reagent to add four carbons to *trans*-(5*S*)-**56**. However, they found that the major product possessed the (*Z,E*)-diene structure **69**. Using a fraction enriched in **69**, they prepared (7*Z*)-LTA₄ methyl ester, which still contained about 10% of LTA₄. They also converted **69** to the (*E,E*)-diene, *trans*-(5*S*)-**58**, from which they also prepared

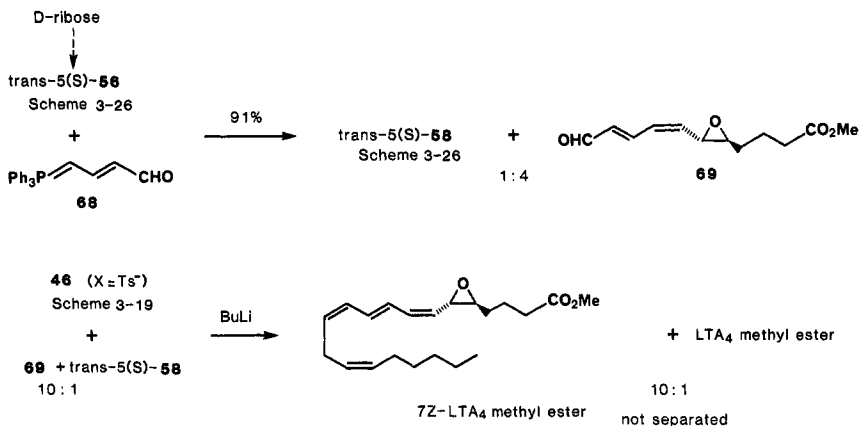


* Point of inversion

Scheme 3.26. Synthesis of LTA₄ and (11E)-LTA₄ from D-ribose.



Scheme 3.27. Synthesis of LTA₄ from D-ribose.

Scheme 3.28. Synthesis of (7Z)-LTA₄ from D-ribose.

LTA₄ methyl ester, and obtained it as a crystalline compound for the first time (m.p. 28–32°C).

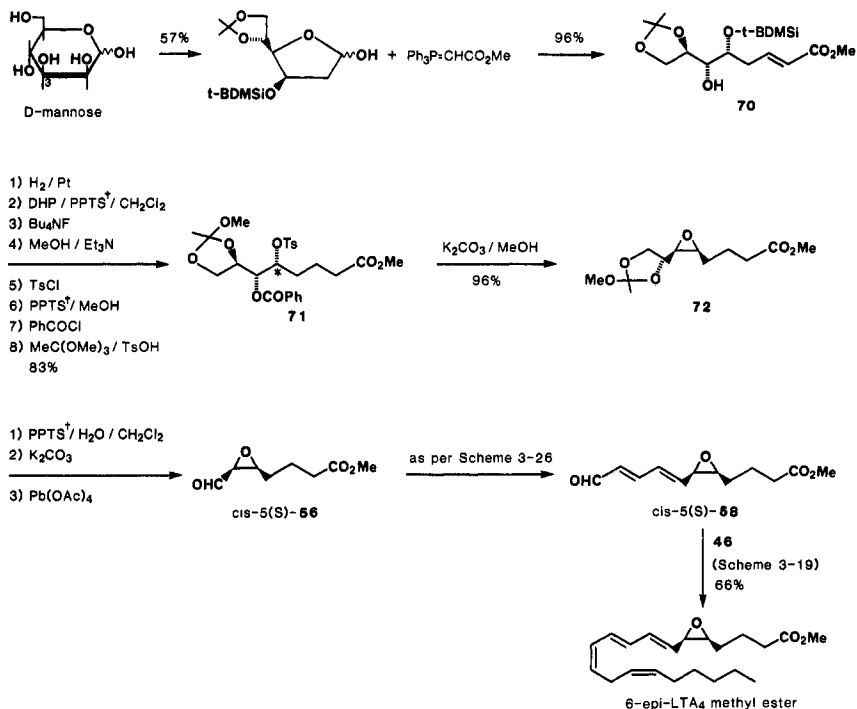
Synthesis of 6-*epi*-LTA₄ from D-Mannose

As indicated earlier, the variation of stereochemistry at C-5 and C-6 of the leukotrienes has been of considerable interest to researchers seeking to ascertain the effects of such changes on biological activity. Corey's group reported the first synthesis of 6-*epi*-LTA₄ as part of their efforts in this field,⁵⁷ and their synthesis is outlined in Scheme 3.29. They started with the indicated hemiacetal readily derived from D-mannose (and which they subsequently also used in the first synthesis of LTB₄,¹² Section 2), to obtain **70** by a Wittig reaction. Hydrogenation and extensive manipulation of functionality converted **70** to **71**. Although no explanation was given for changing the terminal diol protecting group from the acetonide in **70** to the orthoester in **71**, it was presumably done because of the acid sensitivity of the epoxide and because much milder acid conditions are required to remove the orthoester group than the acetonide in **72**.

Synthesis of LTA₄ from L-Arabinose

Starting with the acetonide of L-glyceraldehyde, readily obtained from L-arabinose, Rokach and co-workers have reported another type of synthesis of LTA₄ methyl ester, as outlined in Section 2, Scheme 2.14, and Scheme 3.30.⁵⁸

Chain extension of *trans*-(5S)-**56** by four carbons was carried out with formylmethylene triphenylphosphorane in which *trans*-(5S)-**57** was first obtained in 84% yield. The second Wittig reaction to obtain *trans*-(5S)-**58** was much



[†]PPTS=pyridinium p-toluenesulfonate

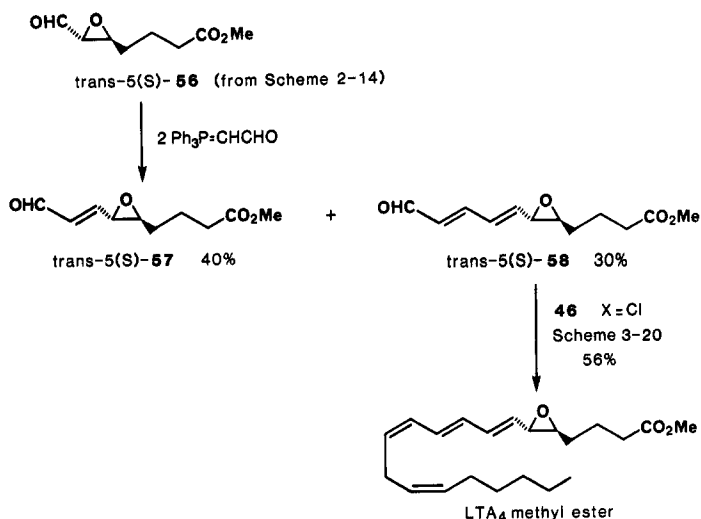
*Point of inversion

Scheme 3.29. Synthesis of 6-epi-LTA₄ from D-mannose.

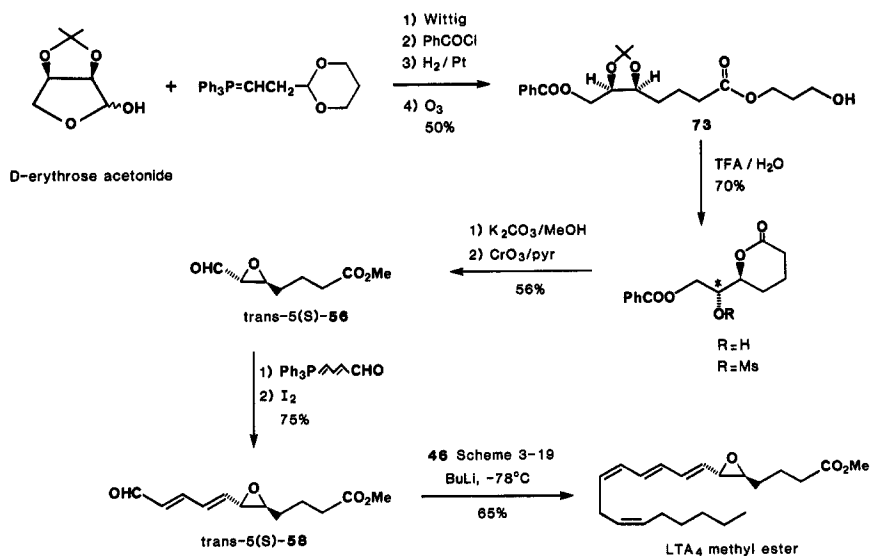
slower, and it was found more practical to carry out a one-pot double Wittig reaction with two equivalents of reagent, as shown in the scheme.

Synthesis of LTA₄ from D-Erythrose

The Hoffmann–La Roche group has described a detailed study of the preparation of LTA₄ methyl ester from both an erythrose and a glucose derivative.^{59,60} The first proved to be quite effective, and is outlined in Scheme 3.31. Acid treatment of **73** liberated the diol unit and triggered lactonization to yield the crystalline lactone in 70% yield. The desired hydroxyl group was thus free to be converted into a suitable leaving group, which was smoothly transformed by base in methanol into the desired epoxy alcohol methyl ester. They reported difficulty using the Wollenberg reagent to add four carbons to the epoxy aldehyde, and found the method of Ernest (Scheme 3.28) to be the most satisfactory.



Scheme 3.30. Synthesis of LTA_4 from L-arabinose via D-mannitol via D-Glyceraldehyde.



Scheme 3.31. Synthesis of LTA_4 from D-erythrose.

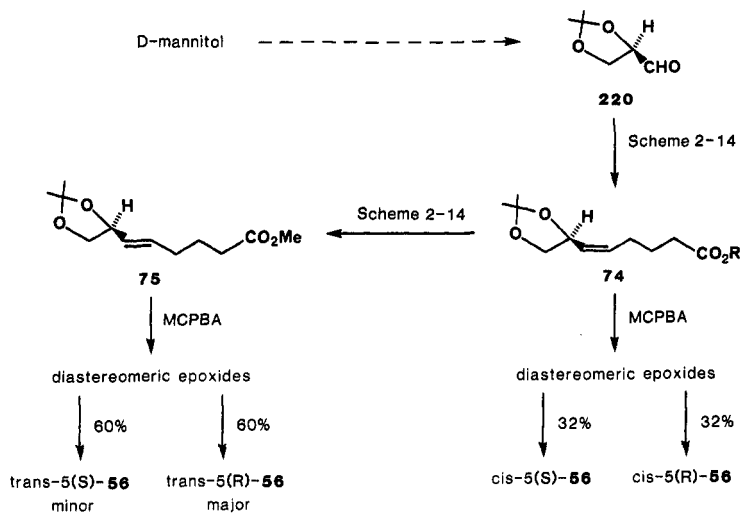
In the same publications, the authors describe a synthesis of an intermediate epoxy alcohol, epimeric at C-6 which could be used to prepare 6-*epi*-LTA₄ methyl ester.

(5) Preparation of LTA₄ Synthons

Several other interesting syntheses of the key intermediates **55** and **56** (the elaboration of which to LTA₄ has just been detailed) have been reported and are summarized in this section.

Concurrently with the previously described synthesis of LTA₄ from L-glyceraldehyde acetonide, Rokach and co-workers prepared the three unnatural isomers of aldehyde **56**.⁵⁸ The syntheses were based on the same reaction as outlined in Scheme 2.14, and are illustrated briefly in Scheme 3.32. From D-glyceraldehyde acetonide, epoxidation of the derived **75** gave a diastereomeric mixture of separable epoxides in which the unnatural enantiomer *trans*-(5*R*)-**56** was now the major component. Epoxidation of (*Z*)-ester **74** (R = Me) gave a diastereomeric mixture of *cis*-epoxides, which after separation and oxidative cleavage gave the enantiomeric *cis*-aldehydoepoxides **56**.

Sharpless's successful use of his chiral epoxidation technology has been discussed in Section 2, Scheme 2.15. Using the Sharpless procedure, Corey, Hashimoto, and Barton also described an analogous, though somewhat longer,



Scheme 3.32. Synthesis of LTA₄ intermediates from D-mannitol via D-glyceraldehyde.

synthesis of *trans*-(5*S*)-**40** (Scheme 2.15) from (*E*)-8-methyl-2,7-nonadien-1-ol.⁶¹ The difficulty with water-soluble molecules mentioned by Sharpless was circumvented by Pridgen et al.⁶² by masking the ester moiety of **41** (Scheme 2.15) in the form of a 4,5-diphenyloxazole unit, but the procedure is much longer (6 steps, 16% overall yield), and either of the approaches described by Sharpless⁶³ appears to be preferable.

Starting with 3,5-dibenzoyl-2-deoxy-D-ribose, Marriott and Bantick⁶⁴ developed an abbreviated synthesis of Corey's tosylate intermediate, **67** (Scheme 3.26). Their sequence is similar to that shown in Scheme 3.25, but by starting with the deoxy sugar there is of course no need to remove the oxygen function, nor was it necessary to acetylate the hydroxyl group as in **66**, thus eliminating a protection/deprotection sequence.

(6) Biomimetic Synthesis of LTA₄

As indicated in Scheme 1.4, (5*S*)-HPETE is generally considered to be the biochemical precursor of LTA₄, although solid biochemical evidence on this point has not yet been obtained. A reasonable biochemical mechanism for this conversion would be the formation of a phosphate or sulfate ester of the hydroperoxide which would undergo elimination of the anion by nucleophilic attack of the adjacent π -electrons of the double bond on the peroxide oxygen, with concomitant loss of a proton from the methylene group at C-10.

Two groups, those of Corey and Sih, have reported studies on chemical analogs of the proposed biochemical mechanism, in which they activated the hydroperoxide function by forming the corresponding mesylate or trifluoromethanesulfonate (triflate). In no case were the peroxy esters isolated as they underwent elimination under the conditions of formation, even at -110°C .

Corey's group was the first to report the successful conversion of (5*S*)-HPETE methyl ester (Scheme 3.33) into LTA₄ methyl ester in 25% yield via the biomimetic mechanism, using the triflate ester of the hydroperoxide.⁶⁵ Shortly thereafter, Sih and co-workers reported the same transformation in 15% yield using the mesylate ester.⁶⁶ Corey emphasized the sensitivity of the reaction conditions in order to obtain a reasonably successful conversion of the HPETE into LTA₄, and he found that a significant amount of ketone **76** was also formed by a 1,2-elimination of the peroxy triflate. Sih subsequently confirmed this sensitivity to conditions, and in a detailed study of the reaction, found that a third product, (9*Z*)-LTA₄ methyl ester, was also formed in significant amount.³⁴ This compound was found to undergo a facile [1,7]-hydrogen migration as discussed earlier in Section 3.C (1). In a subsequent report, Corey and Barton provided an improved procedure for the reaction and confirmed the formation of (9*Z*)-LTA₄ methyl ester.⁶⁷

Two points with regard to the stereochemistry of the epoxide-forming reaction are to be emphasized. Using optically active (5*S*)-HPETE methyl ester, Corey

et al. obtained optically pure LTA₄ methyl ester, indicating that the stereochemistry of the C-5-oxygen bond in the transformation is unaffected. And both groups of workers found that the *trans*-epoxide is formed exclusively, with no *cis*-epoxide being observed.

It should be pointed out that Scheme 3.33 depicts the reaction of optically active compounds,⁶⁵ but the data of references 34 and 67 were obtained using racemic 5-HPETE as starting material.

This biomimetic route represents a convenient synthesis of small amounts of LTA₄ and hence of LTC₄, LTD₄, and LTE₄,^{65,66} but the reactivity of the peroxide intermediates would probably make scale-up difficult.

Corey's group subsequently developed a novel and more efficient conversion of racemic 5-HPETE to racemic LTA₄ methyl ester.⁶⁸ It was found that allylic hydroperoxides undergo a remarkable intramolecular rearrangement upon treatment with trifluoroacetic anhydride to produce epoxy alcohols in high yields. Standard transformations then effected the conversion of this intermediate to racemic LTA₄ methyl ester.

D. Synthesis of LTC₄, LTD₄, LTE₄, LTF₄ and Their Epimers

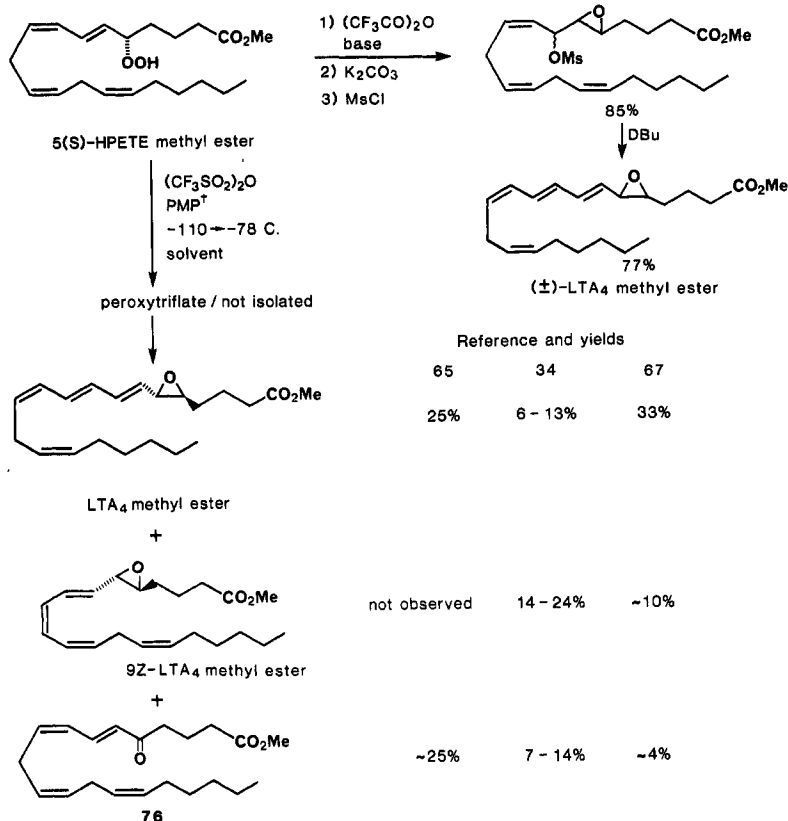
Of all the products derived from the lipoxygenase metabolism of arachidonic acid, the group attracting the greatest attention biologically and chemically are those compounds that make up the material known as "slow-reacting substance of anaphylaxis" (SRS-A).^{69c,70} SRS-A is now known to be made up of varying amounts of the cysteine containing eicosanoids LTC₄, LTD₄, and LTE₄ (Scheme 1.4), and the synthesis of these and related compounds is detailed in this section.

(1) Synthesis of Naturally Occurring Leukotrienes

As mentioned above, the title compounds are now known to constitute the active components of SRS-A, and as such have been the subject of intense biological and synthetic research. All the syntheses of these thioether structures have converged on LTA₄ methyl ester, the various syntheses of which were outlined in Section 3.C. Three groups, that of Corey at Harvard University, the Merck Frosst Canada group, and workers at Hoffmann-La Roche, independently developed synthetic routes to LTA₄ methyl ester and hence to various components of the SRS-A complex.

Harvard Synthesis of LTC₄ and LTD₄

The first synthesis of LTC₄ was achieved by Corey's group, and as chiral intermediates were employed, it also established the full stereochemistry of the

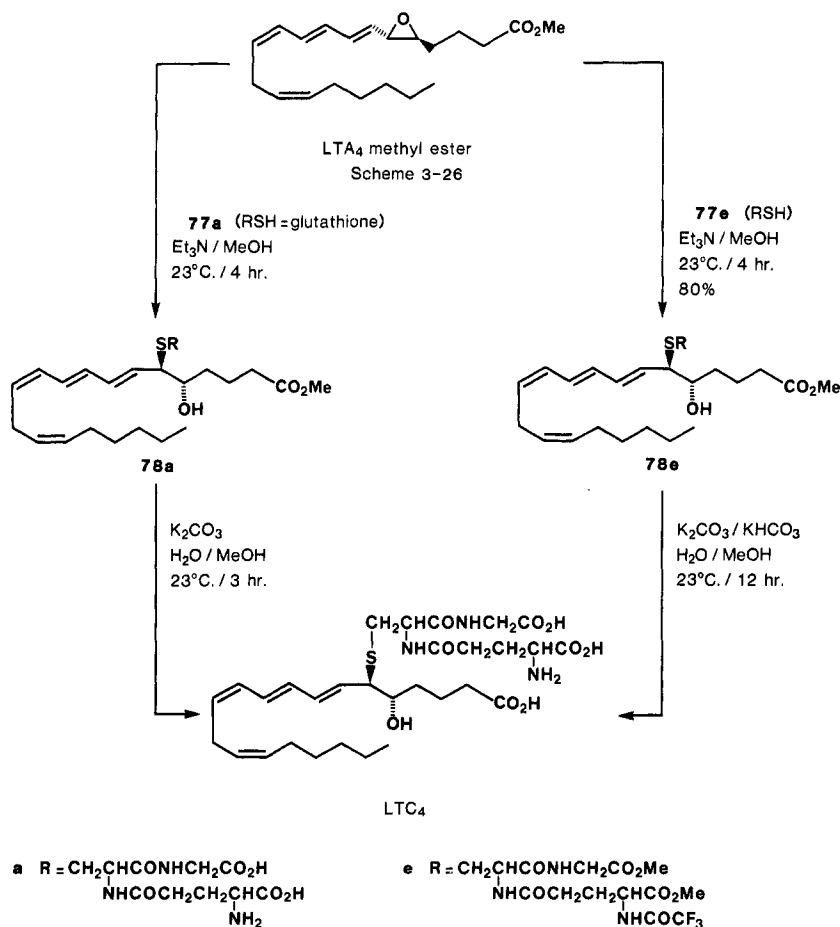


† PMP = 1,2,2,6,6-pentamethylpiperidine

Scheme 3.33. Biomimetic synthesis of LTA₄ methyl ester.

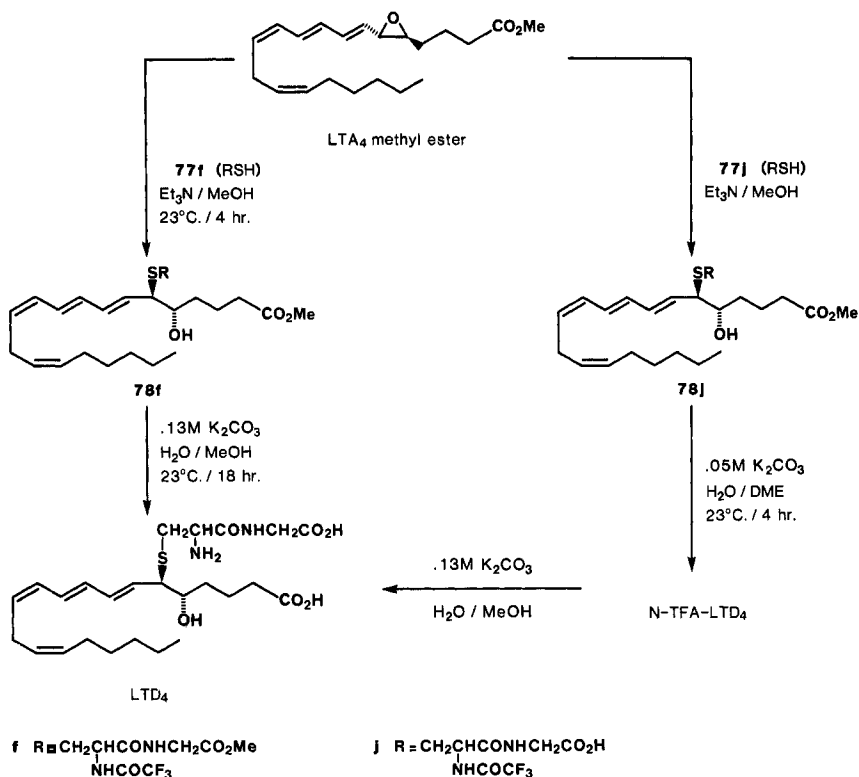
compound.³⁷ As outlined in Scheme 3.34, the epoxide group in LTA₄ methyl ester was found to undergo a clean S_N2 reaction at C-6 under basic conditions with the thiol of **77a** (glutathione) or **77e** (*N*-trifluoroacetylglutathione dimethyl ester, *N*-TFA-GSH-Me₂) to yield the adducts **78a** and **78e**, respectively. Mild basic hydrolysis of these adducts yielded LTC₄. The synthetic material was found to be identical with natural LTC₄ by comparison of their UV spectra, HPLC properties, biological activity, and reaction with soybean lipoxygenase to produce a conjugated tetraene.^{37,71}

It should be noted that when the coupling reaction between a model epoxide and thiols was carried out under solvolytic conditions (LiClO₄ in MeOH), attack

Scheme 3.34. Synthesis of LTC₄ from optically active LTA₄.

of the thiol occurred at the terminal double bond of the conjugated system rather than at the allylic position.

In a similar sequence of reactions, Corey and co-workers subsequently synthesized LTD₄ by first coupling **77f** (NTFA-cys-gly-Me) with LTA₄ methyl ester (Scheme 3.35).⁵⁴ Hydrolysis of **78f** under the same conditions as used for the hydrolysis of **78e** (Scheme 3.34) was incomplete and gave a mixture of LTD₄ and the *N*-trifluoroacetyl derivative of LTD₄, which was prepared separately for comparison by mild hydrolysis of **78j**. Under somewhat more basic conditions, for a longer period of time, the hydrolysis of **78f** was completed to yield LTD₄.

Scheme 3.35. Synthesis of LTD₄ from optically active LTA₄.

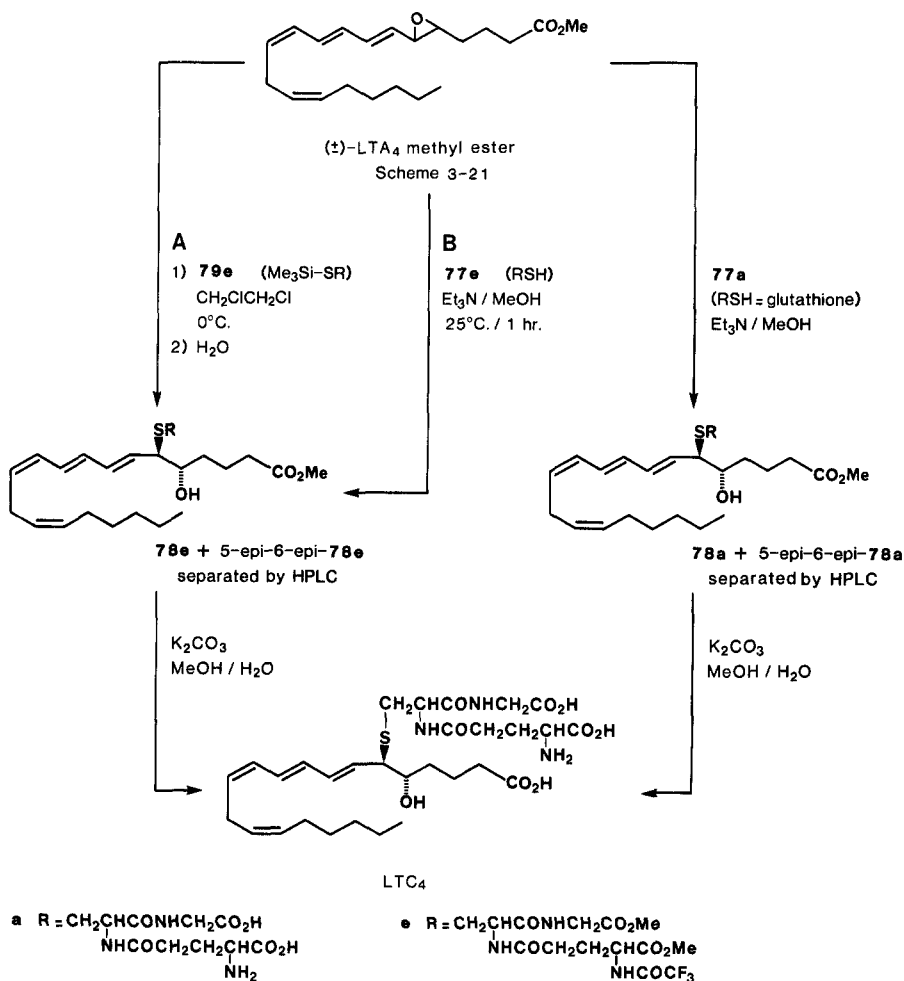
Identity of the synthetic material with naturally occurring LTD₄ was secured by the same criteria as in the case of LTC₄.⁷²

Merck Frosst Group Synthesis of LTC₄, LTD₄, and LTE₄

In a second independent synthesis, the Merck Frosst group disclosed the preparation of LTC₄ from racemic LTA₄ methyl ester as outlined in Scheme 3.36.³¹ The initial synthesis (path A) utilized the novel reagent **79e**, the *S*-trimethylsilyl derivative of *N*-TFA-GSH-Me₂, to react with the epoxide to generate the diastereomers **78e** and 5-*epi*-6-*epi*-**78e**, which were separated by HPLC. Hydrolysis of these separated derivatives led to two isomers of LTC₄, one of which showed the potent biological activity characteristic of natural LTC₄. The material was further characterized by its UV spectrum and conversion by lipoxygenase to a conjugated tetraene, a reaction also characteristic of natural

LTC₄. The same pair of isomers of LTC₄ was also obtained by reacting free glutathione **77a** with (±)-LTA₄ methyl ester followed by hydrolysis of the separated diastereomers **78a** and 5-*epi*-6-*epi*-**78a**. With the more recent availability of fast atom bombardment mass spectrometry, a comparison of the natural and synthetic LTC₄ served to further establish their identity.⁷³

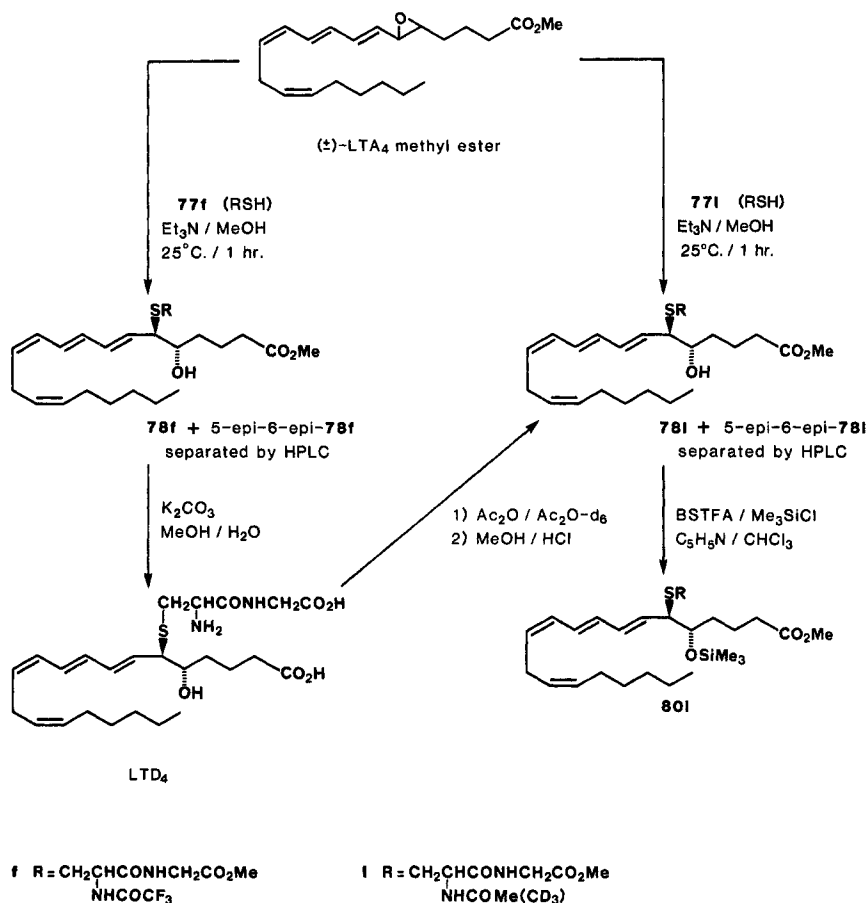
It was subsequently found that the trimethylsilyl reagents of structure **79** provided a general and mild synthesis of β-hydroxythioethers from a variety of epoxides,⁷⁴ but in the reaction of amino-acid type thiols with LTA₄, the best



Scheme 3.36. Synthesis of LTC₄ from racemic LTA₄.

conditions turned out to be the base-catalyzed reaction of the free thiol with the epoxide (path B).^{41,42}

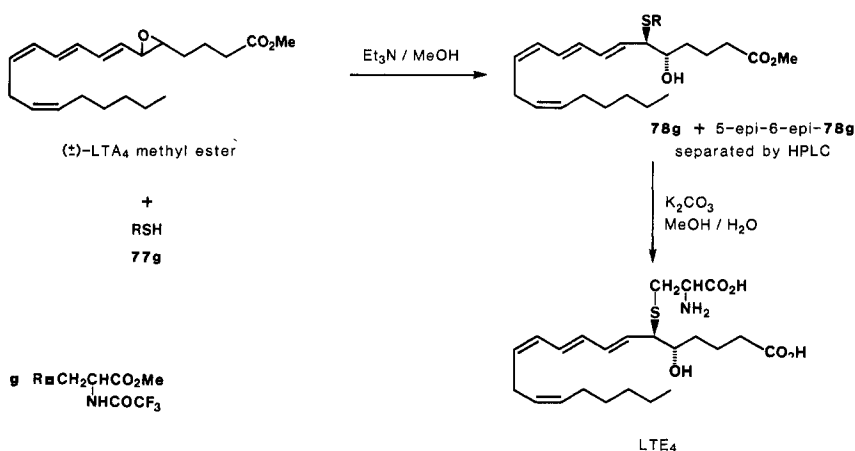
A synthesis of LTD₄ from the reaction of racemic LTA₄ methyl ester with *N*-TFA-cys-gly-Me, **77f**, was carried out by the Merck Frosst group as shown in Scheme 3.37. A detailed comparison of the active diastereomer thus obtained with naturally derived LTD₄ was carried out in collaboration with Morris, Piper, and their colleagues.⁷⁵ They were found to be identical in their UV spectra, HPLC behavior, biological activity, and reaction with soybean lipoxygenase. Furthermore, the mass spectra of the deuterium-labeled derivative **80l** prepared from both synthetic and natural LTD₄ were found to be identical. It should be noted that this work constituted the first positive structure identification of LTD₄.



Scheme 3.37. Synthesis of LTD₄ from racemic LTA₄.

The synthesis of LTE_4 was carried out as indicated in Scheme 3.38 by the condensation of racemic LTA_4 methyl ester with *N*-TFA-cys-Me **77g** followed by separation of the diastereomers and hydrolysis.⁴³

The Merck Frosst group also carried out the synthesis of the pure natural isomers of LTC_4 , LTD_4 , and LTE_4 from optically active LTA_4 methyl ester. As illustrated in Scheme 3.39, these preparations involve the same chemistry as that previously described.⁵⁸ Comparison of the biologically active leukotriene diastereomers obtained from racemic LTA_4 methyl ester (Schemes 3.36–3.38) with the pure compounds prepared as in Scheme 3.39 established the identity of the compounds from the different syntheses.

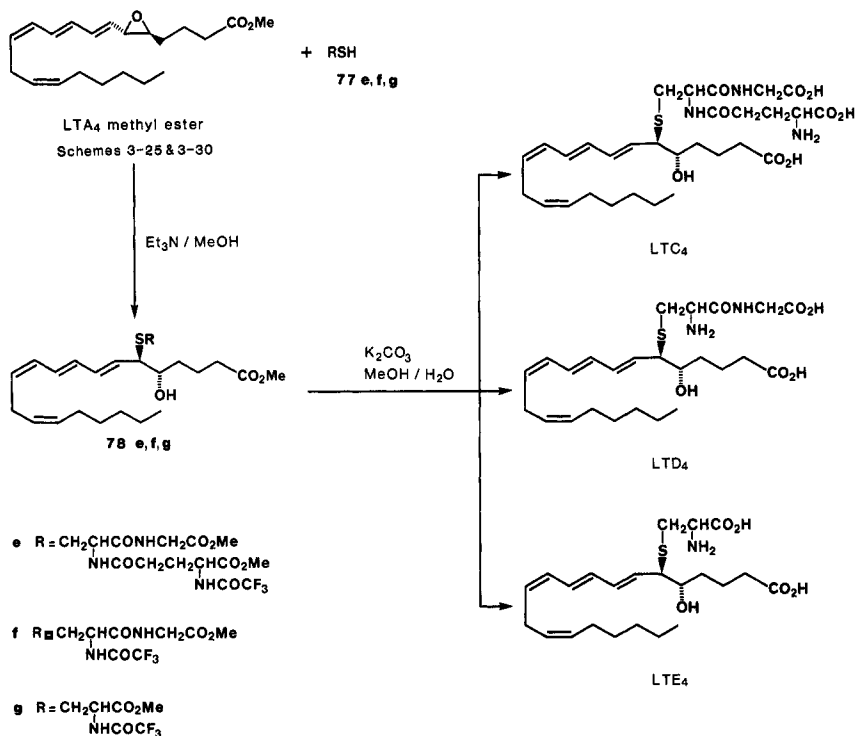


Scheme 3.38. Synthesis of LTE_4 from racemic LTA_4 .

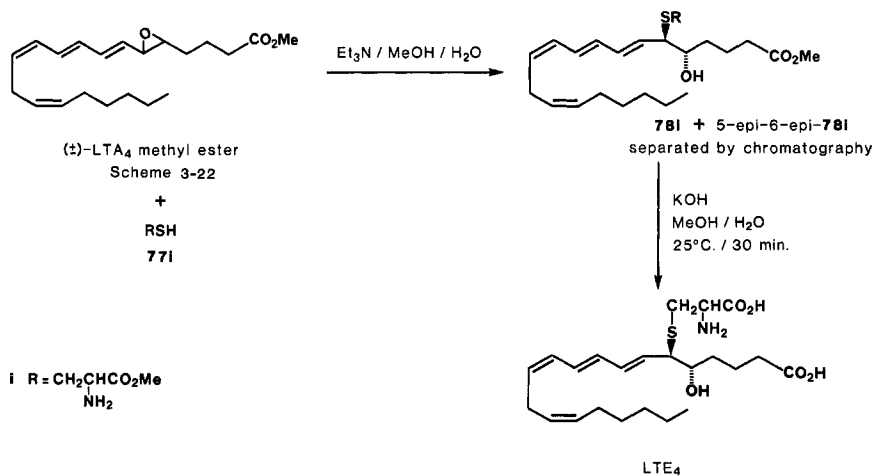
Hoffmann-La Roche Synthesis of LTC_4 , LTD_4 , and LTE_4

The third independent synthesis of a leukotriene, LTE_4 , was achieved by Rosenberger and co-workers as outlined in Scheme 3.40.^{44,45} They coupled cysteine methyl ester **77i** with racemic LTA_4 methyl ester and separated the resulting diastereomers of **78i**. By a nice piece of degradative chemistry they were able to assign the absolute stereochemistry to the two diastereomers obtained. Hydrolysis led to the two diastereomers of LTE_4 , the more active of which was found to possess the (5*S*,6*R*)-configuration, as in LTC_4 and LTD_4 .

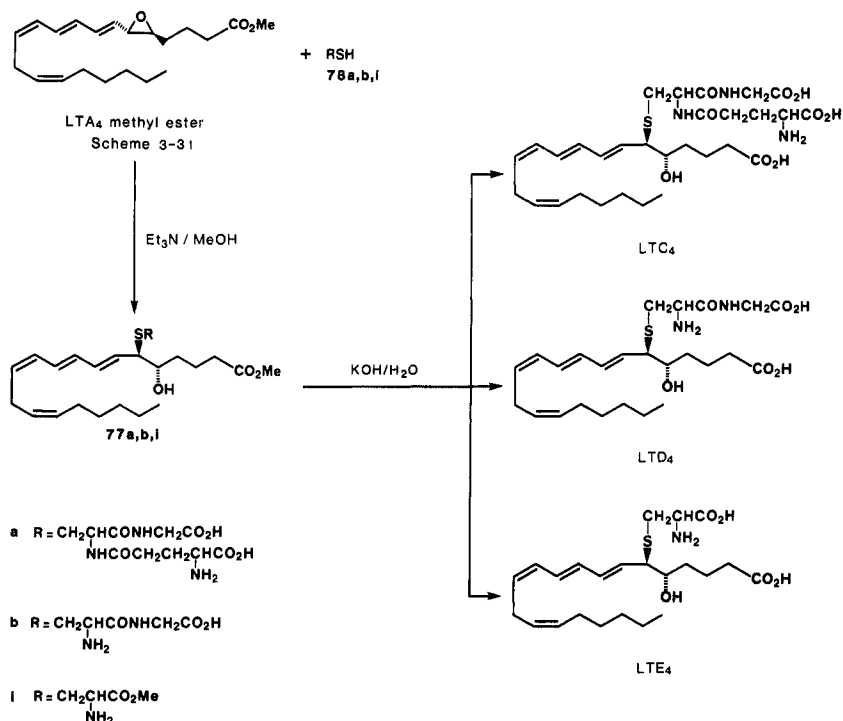
The Hoffmann–La Roche group later followed up on their original synthesis of optically active LTA_4 (Scheme 3.31, Ref. 59), using it in a total synthesis of LTC_4 , LTD_4 , and LTE_4 ,⁶⁰ as outlined in Scheme 3.41.



Scheme 3.39. Synthesis of LTC₄, LTD₄, and LTE₄ from optically active LTA₄.

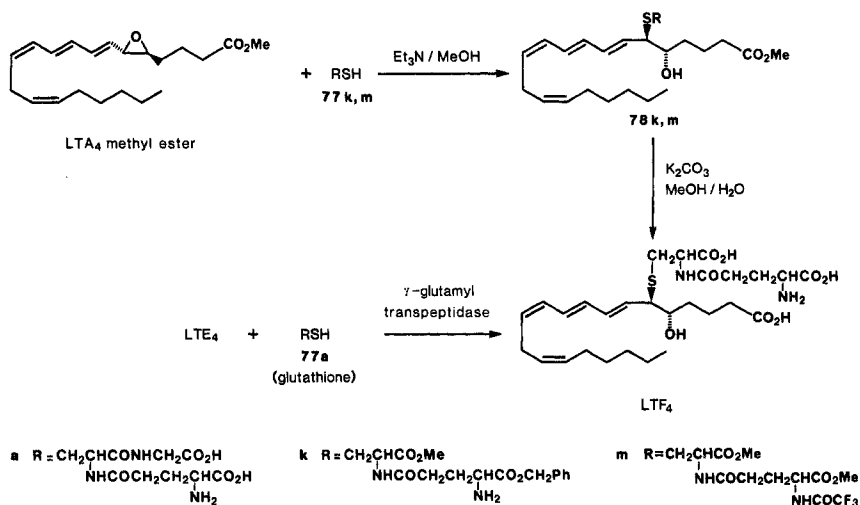


Scheme 3.40. Synthesis of LTE₄ from racemic LTA₄.

Scheme 3.41. Synthesis of LTC₄, LTD₄, and LTE₄ from optically active LTA₄.

Synthesis of LTF₄

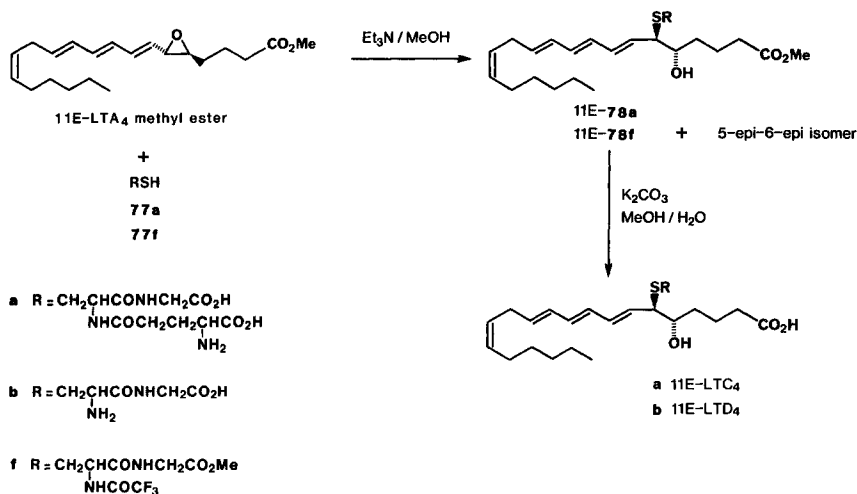
This more recent member of cysteine-containing eicosanoids contains the γ -glutamylcysteinyl dipeptide unit (see Scheme 1.4), that is, glutathione with glycine removed. Although it has not, at this writing, been isolated as a natural product, two groups have generated it biochemically from LTE₄,^{76,77} indicating that it probably will be found in whole-cell systems. Three independent syntheses of LTF₄ were published in 1982, and all employed the condensation of an appropriate derivative of cys- γ -glu with LTA₄ methyl ester, followed by hydrolysis (Scheme 3.42). The Ono group⁷⁸ coupled the dimethyl ester of *N*-trifluoroacetyl cys- γ -glu with LTA₄ methyl ester, followed by hydrolysis. They prepared the compound as one of many synthetic analogs of the leukotrienes, and it was actually made before it was identified as a possible natural product. The Merck Frosst group coupled the methyl benzyl diester of cys- γ -glu with LTA₄, followed by hydrolysis.⁷⁹ Glaxo chemists reacted the dimethyl ester of *N*-trifluoroacetyl cys- γ -glu with racemic LTA₄ methyl ester, and separated the hydrolyzed diastereoisomers by HPLC.⁸⁰

Scheme 3.42. Synthesis of LTF₄ from optically active LTA₄.

(2) The (11*E*)-Isomer of the Leukotrienes and Its Mechanism of Formation

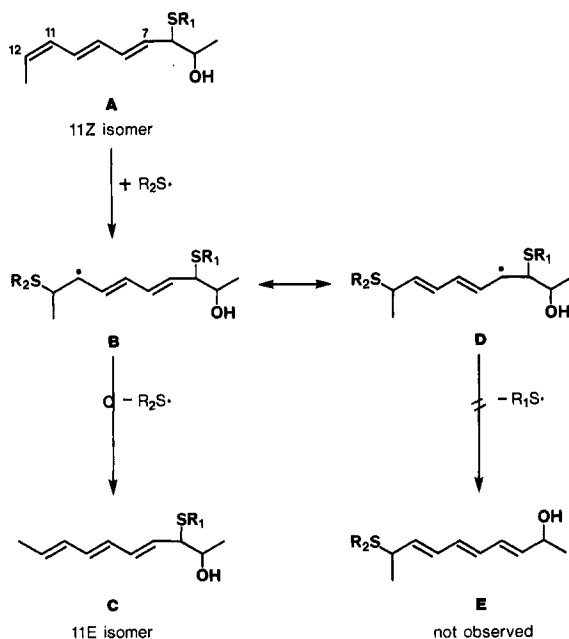
The (11*E*)-double bond isomer of the leukotrienes has been the object of several studies because it has been isolated as a minor component from several biological systems. Corey's group was the first to prepare an (11*E*)-isomer in this series with their synthesis of (11*E*)-LTC₄,⁵⁴ as shown in Scheme 3.43. The Lilly³⁶ and Merck Frosst⁴¹ groups subsequently prepared (11*E*)-LTD₄ from racemic (11*E*)-LTA₄ methyl ester and separated the 5,6-epimers of (11*E*)-78f prior to hydrolysis. The biological activities for contraction of the guinea pig ileum by the (11*E*)-isomers of the LTC₄, LTD₄, and LTE₄ were found by Sih and co-workers to be 1/3, 1/5, and 1/8 that of the natural compounds, respectively.⁸¹

As mentioned earlier, the (11*E*)-isomers of LTC₄, LTD₄, and LTE₄ have been obtained during the course of their isolation from various biological sources. Sih and his co-workers⁸¹ carried out a very careful study of the formation of the (11*E*)-isomers of LTC₄ and LTE₄ under both biological and chemical conditions of preparation. Working in the absence and presence of free thiols and using the free radical inhibitor 4-hydroxy-2,2,6,6-tetramethylpiperidinoxyl (HTMP), they demonstrated quite conclusively that the formation of the (11*E*)-isomers is a free-radical-catalyzed reaction requiring the presence of free thiol groups in the medium. They further conclude that their formation in biological systems is probably not an enzymatic process, but rather a chemical one catalyzed by endogenously formed thiol radicals. Thus, at present, it would seem to be a matter of semantics whether the (11*E*)-isomers should be called natural products,

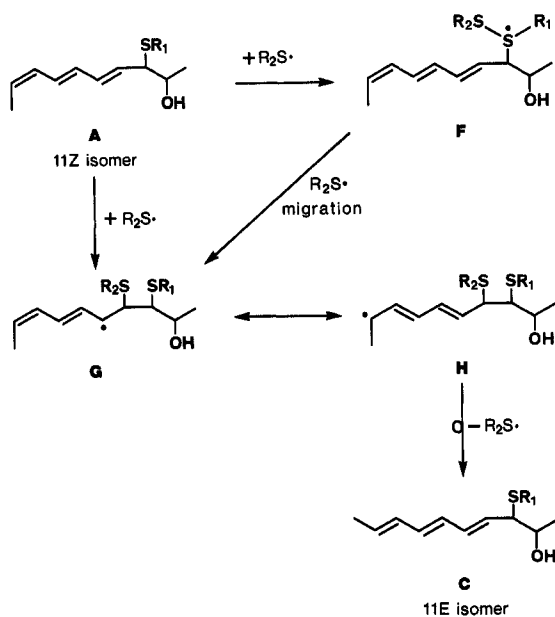
Scheme 3.43. Synthesis of (11*E*)-LTC₄ and (11*E*)-LTD₄.

since they are probably formed in biological systems, but by a nonenzymatic process.

With regard to the mechanism of the (11*Z*) → (11*E*) isomerization, both Corey⁵⁴ and Sih⁸¹ suggest a reversible addition of a thiol radical to C-12 of the triene unit, as a result of which the more stable (*E*)-isomer **C** is formed (Scheme 3.44, part structures **A**, **B**, **C**). Sih has quite conclusively shown that there is no incorporation of label in recovered (11*E*)-LTE₄ when radioactive free cysteine is present as the thiol source, thus ruling out the sequence **A** → **B** → **D** → **E**, which would have yielded an isomeric LTE₄ containing radioactive cysteine, now attached to C-12. It is rather striking that an intermediate such as **B**, which should be in facile resonance equilibrium with **D**, should eliminate R₂S (**B** → **C**) to the complete exclusion of the known⁸² alternate possibility (**D** → **E**) with loss of R₁S•. This has led Atkinson and Rokach⁸⁶ to suggest an alternative mechanistic possibility (Scheme 3.45) in which the external thiol radical (R₂S•) adds to C-7 rather than to C-12, generating the resonance stabilized pair **G** ↔ **H**. Such a radical intermediate can then eliminate *only* R₂S•, generating **C** exclusively, as is observed. Regioselective addition to C-7 to give rise to **G** may be explained by the formation of a σ-sulfuranyl radical similar to structures investigated by Perkins et al.,⁸³ which could then rearrange to **G**, or by a more conventional type of hydrogen-bonding association between the polar groups of R₁ and R₂.



Scheme 3.44. Proposed mechanism for formation of (11*E*)-leukotrienes.



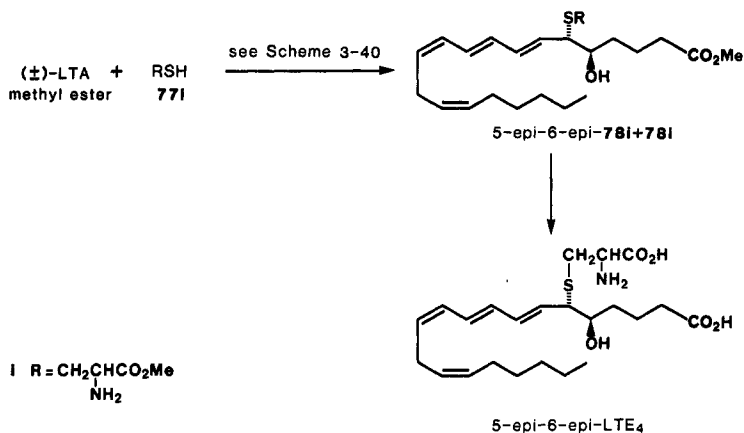
Scheme 3.45. New mechanism for formation of (11*E*)-leukotrienes.

(3) Synthesis of the 5,6-Epipimers of the Leukotrienes

During the course of synthesis and structure proof of the leukotrienes, it was important to synthesize the four optical isomers derivable from the two asymmetric centers at C-5 and C-6 of the eicosatetraenoic acid chain in order to fully confirm that the natural compounds had the (5*S*,6*R*) configuration. It was also of considerable scientific interest to find out what effect changes in configuration on these centers would have upon the biological activity of the compounds.

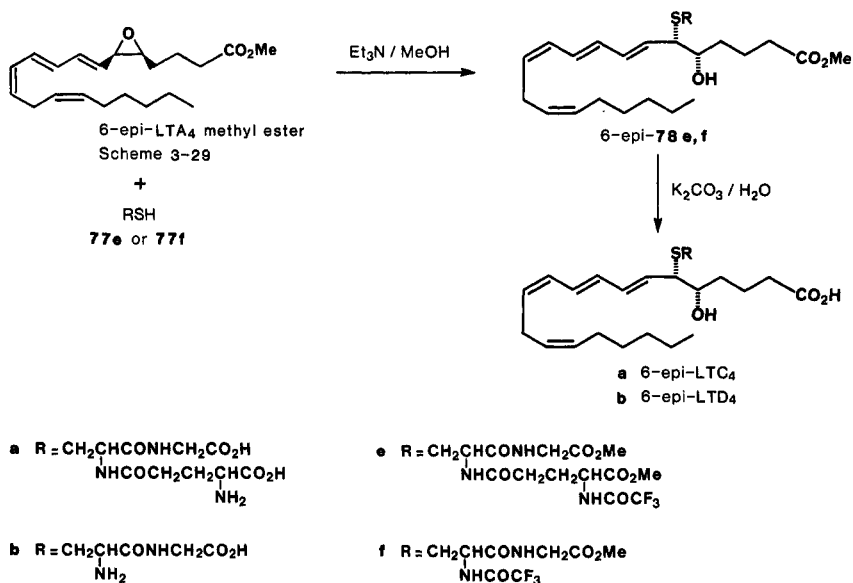
Hoffman-La Roche Synthesis of 5-epi-6-epi-LTE₄

Since they started with racemic LTA₄ methyl ester, Rosenberger and co-workers obtained a mixture of **78i** and 5-epi-6-epi-**78i**, which were separated by chromatography.^{44,45} Hydrolysis of the latter then yielded 5-epi-6-epi-LTE₄ (Scheme 3.46), which showed one-half the biological activity of the natural isomer. Interestingly, the LTE₄ isomer incorporating D-cysteine (instead of L-cysteine) was as active as the natural product.

Scheme 3.46. Synthesis of 5-epi-6-epi-LTE₄.*Harvard Synthesis of 6-epi-LTC₄ and 6-epi-LTD₄*

As part of their work in the structure proof of the natural leukotrienes, Corey's group carried out a stereospecific synthesis of 6-epi-LTA₄ methyl ester as discussed earlier (Scheme 3.29). Coupling of the epoxide with the appropriately

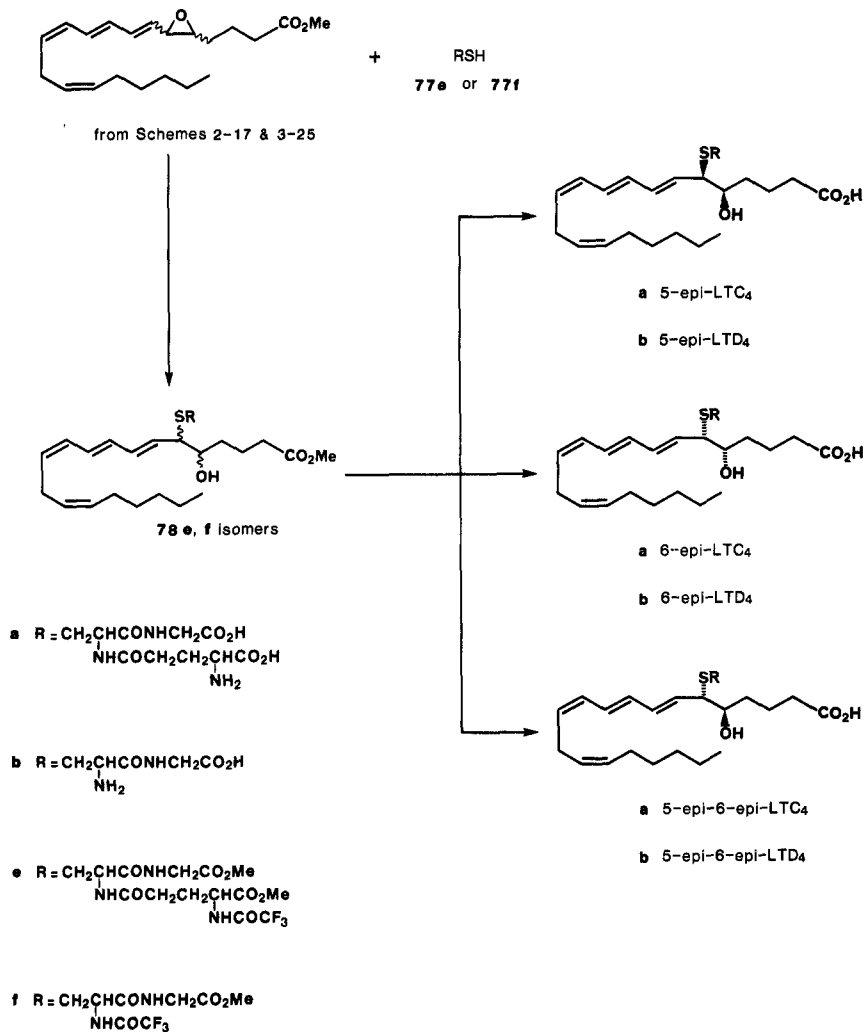
blocked derivative of glutathione **77e** or cysteinylglycine **77f**, followed by hydrolysis of the 6-epi-**78** derivatives yielded the desired 6-epi-LTC₄ and 6-epi-LTD₄ (Scheme 3.47).⁵⁷ On guinea pig parenchymal strips, 6-epi-LTC₄ had 1/10 the activity of natural LTC₄ and 6-epi-LTD₄ had 1/500 the activity of LTD₄.



Scheme 3.47. Synthesis of 6-epi-LTC₄ and 6-epi-LTD₄.

Merck Frosst Synthesis of 5-epi, 6-epi, and 5-epi-6-epi-LTC₄ and LTD₄

Following up on their stereospecific total syntheses of the four optical isomers of LTA₄ methyl ester, described above in Section 3.D., the Merck Frosst group has prepared the three possible unnatural 5,6-isomers of LTC₄ and LTD₄.⁸⁴ Scheme 3.48 summarizes the preparation of the six compounds thus obtained. The same compounds were also obtained starting from racemic LTA₄ methyl ester and racemic *cis*-LTA₄ methyl ester, and the structure of each pair of diastereomers so obtained was assigned by comparison with the individual isomers obtained from the optically pure epoxides.⁴¹ In the LTC₄ series, on the guinea pig ileum (in Tyrode's solution containing 1 μg/mL of timolol), 5-epi-LTC₄, 6-epi-LTC₄, and 5-epi-6-epi-LTC₄ showed 1/20, 1/70, and 1/60 the potency of LTC₄, respectively; in the LTD₄ series, 5-epi-LTD₄ had 1/20 the activity of natural LTD₄ and 5-epi-6-epi-LTD₄ had 1/30 the activity.⁸⁵ Rather surprisingly, 6-epi-LTD₄ showed weak antagonist rather than agonist activity.

Scheme 3.48. Synthesis of the 5-epi, 6-epi, and 5-epi-6-epi-isomers of LTC₄ and LTD₄.

References

1. Corey, E.J.; Albright, J.D.; Barton, A.E.; Hashimoto, S. *J. Am. Chem. Soc.* **1980**, *102*, 1435.
2. Baldwin, J.E.; Reed, N.V.; Thomas, E.J. *Tetrahedron* **1981**, *37*, supplement No. 9, 263.
3. Rokach, J.; Adams, J.; Perry, R. *Tetrahedron Lett.* **1983**, *24*, 5185.
4. Gemal, A.L.; Luche, J.L., *Tetrahedron Lett.* **1981**, *22*, 4077.
5. Corey, E.J.; Hashimoto, S. *Tetrahedron Lett.* **1981**, *22*, 299.

6. Rokach, J.; Zamboni, R.; in *Leukotrienes and Other Lipoxygenase Products*, Piper, P.J. Ed.; Research Studies Press: Chichester, 1983; p.15.
7. Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1983**, *24*, 999.
8. Porter, N.A.; Wolf, R.A.; Yarbrow, E.M.; Weenen, H. *Biochem. Biophys. Res. Commun.* **1979**, *89*, 1058.
9. Boeynaems, J.M.; Brash, A.R.; Oates, J.A.; Hubbard, W.C. *Anal. Biochem.* **1980**, *104*, 259.
10. Porter, N.A.; Logan, J.; Kontoyiannidou, V.; *J. Org. Chem.* **1979**, *44*, 3177.
11. Cobern, D.; Hobbs, J.S.; Lucas, R.A.; MacKenzie, D.J. *J. Chem. Soc. (C)* **1966**, 1897.
12. Corey, E.J.; Marfat, A.; Goto, G.; Brion, F. *J. Am. Chem. Soc.* **1980**, *102*, 7984.
13. Corey, E.J.; Marfat, A.; Munroe, J.; Kim, K.S.; Hopkins, P.B.; Brion, F. *Tetrahedron Lett.* **1981**, *22*, 1077.
14. Guindon, Y.; Zamboni, R.; Lau, C.-K.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 739.
15. Spur, B.; Crea, A.; Peters, W.; Konig, W.; *Arch. Pharm. (Weinheim)* **1985**, *318*, 225.
16. Takaishi, T.; Yang, Y.-L.; DiTullio, D.; Sih, C.J. *Tetrahedron Lett.* **1982**, *23*, 5489.
17. Fuganti, C.; Servi, S.; and Zirotti, C. *Tetrahedron Lett.* **1983**, *24*, 5285.
18. Traverso, G.; Pirillo, D. *Farmaco. Ed. Sci.* **1981**, *36*, 888.
19. Pirillo, D.; Gazzaniga, A.; Traverso, G.; *J. Chem. Res. Synop.* **1983**, 1.
20. Mills, L.S.; North, P.C. *Tetrahedron Lett.*, **1983**, 24,409.
21. Sharpless, K.B.; Katsuki, T. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
22. Maycock, A.; Anderson, M.S.; DeSousa, D.M.; Kuehl, F.A. Jr. *J. Biol. Chem.* **1982**, *257*, 13911.
23. Le Merrer, Y.; Duréault, A.; Gravier, C.; Languin, D.; Depeyaz, J.C. *Tetrahedron Lett.* **1985**, *26*, 319.
24. Nicolaou, K.C.; Zipkin, R.E.; Dolle, R.E.; Harris, B.D. *J. Am. Chem. Soc.* **1984**, *106*, 3548.
25. Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 4751.
26. Borgeat, P.; Picard, S.; Vallerand, P.; Sirois, P. *Prostaglandins Med.* **1981**, *6*, 557.
27. Lindgren, J.A.; Hansson, G.; Samuelsson, B. *FEBS Lett.* **1981**, *128*, 329.
28. Corey, E.J.; Marfat, A.; Laguzza, B.C. *Tetrahedron Lett.* **1981**, *22*, 3339.
29. Adams, J.; Leblanc, Y.; Rokach, J. *Tetrahedron Lett.* **1984**, *25*, 1227.
30. Murphy, R.C.; Hammarstroem, S.; Samuelsson, B. *Proc. Natl. Acad. Sci. USA* **1979**, *76*, 4275.
31. Rokach, J.; Girard, Y.; Guindon, Y.; Atkinson, J.G.; Larue, M.; Young, R.N.; Masson, P.; Holme, G. *Tetrahedron Lett.* **1980**, *21*, 1485.
32. Spangler, C.W. *Chem. Rev.* **1976**, *76*, 187.
33. Baker, S.R.; Jamieson, W.B.; McKay, S.W.; Morgan, S.E.; Rackham, D.M.; Ross, W.J.; Shrubbsall, P.R. *Tetrahedron Lett.* **1980**, *21*, 4123.
34. Atrache, V.; Pai, J.-K.; Sok, D.-E.; Sih, C.J. *Tetrahedron Lett.* **1981**, *22*, 3443.
35. Baker, S.R.; Jamieson, W.B.; Osborne, D.J.; Ross, W.J. *Tetrahedron Lett.* **1981**, *22*, 2505.
36. Baker, S.R.; Boot, J.R.; Jamieson, W.B.; Osborne, D.J.; Sweatman, W.J.F. *Biochem. Biophys. Res. Commun.* **1981**, *103*, 1258.
37. Corey, E.J.; Clark, D.A.; Goto, G.; Marfat, A.; Mioskowski, C.; Samuelsson, B.; Hammarstroem, S. *J. Am. Chem. Soc.* **1980**, *102*, 1436, 3663.
38. Corey, E.J.; Arai, Y.; Mioskowski, C. *J. Am. Chem. Soc.* **1979**, *101*, 6748.
39. von Schenck, G.O.; Steinmetz, R. *Justus Liebigs Ann. Chem.* **1963**, *668*, 19.

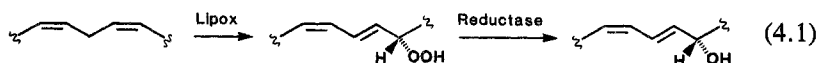
40. Rokach, J.; Guindon, Y.; Zamboni, R.; Lau, C.K.; Girard, Y.; Larue, M.; Perry, R.A.; Atkinson, J.G. *Abstract Bulletin, 16th Middle Atlantic Regional Meeting* No. 276, April 21–23, 1982.
41. Rokach J.; Girard, Y.; Guindon, Y.; Atkinson, J.G.; Larue, M.; Young, R.N.; unpublished results.
42. Holme, G.; Brunet, G.; Piechuta, H.; Masson, P.; Girard, Y.; Rokach, J. *Prostaglandins* **1980**, 20, 717.
43. Rokach J.; Girard, Y.; Guindon, Y.; Atkinson, J.G.; Larue, M.; Young, R.N.; Masson, P.; Hamel, R.; Piechuta, H.; Holme, G. In *SRS-A and Leukotrienes*, Piper, P.J. Ed.; Research Studies Press: Chichester, 1981; p.65.
44. Rosenberger, M.; Newkom, C. *J. Am. Chem. Soc.* **1980**, 102, 5425.
45. Rosenberger, M.; Newkom, C.; Aig, E.R. *J. Am. Chem. Soc.* **1983**, 105, 3656.
46. Gleason, J.G.; Bryan, D.B.; Kinzig, C.M. *Tetrahedron Lett.* **1980**, 21, 1129.
47. Corey, E.J.; Park, H.; Barton, A.; Nii, Y.; *Tetrahedron Lett.* **1980**, 21, 4243.
48. McKay, S.W.; Mallen, D.N.B.; Shrubsall, P.R.; Smith, J.M.; Baker, S.R.; Jamieson, W.B.; Ross, W.J.; Morgan, S.E.; Rackham, D.M. *J. Chromatogr.* **1981**, 214, 249.
49. Buck, J.C.; Ellis, F.; North, P.C. *Tetrahedron Lett.* **1982**, 23, 4161.
50. Tsuboi, S.; Masuda, T.; Takeda, A. *Chem. Lett.* **1983**, 1829.
51. Rokach, J.; Zamboni, R.; Lau, C.-K.; Guindon, Y. *Tetrahedron Lett.* **1981**, 22, 2759.
52. Rokach, J.; Lau, C.-K.; Zamboni, R.; Guindon, Y. *Tetrahedron Lett.* **1981**, 22, 2763.
53. Corey, E.J.; Albright, J.O. *J. Org. Chem.* **1983**, 48, 2114.
54. Corey, E.J.; Clarke, D.A.; Marfat, A.; Goto, G. *Tetrahedron Lett.* **1980**, 21, 3143.
55. Corey, E.J.; Mehrotra, M. M.; Cashman, J.R.; *Tetrahedron Lett.* **1983**, 24, 4917.
56. Ernest, I.; Main, A.J.; Menassé, R. *Tetrahedron Lett.* **1982**, 23, 167.
57. Corey, E.J.; Goto, G. *Tetrahedron Lett.* **1980**, 21, 3463.
58. Rokach, J.; Young, R.N.; Kakushima, M.; Lau, C.-K.; Séguin, R.; Frenette, R.; Guindon, Y.; *Tetrahedron Lett.* **1981**, 22, 979.
59. Cohen, N.; Banner, B.L.; Lopresti, R.J. *Tetrahedron Lett.* **1980**, 21, 4163.
60. Cohen, N.; Banner, B.L.; Lopresti, R.J.; Wong, F.; Rosenberger, M.; Liu, Y.Y.; Thom, E.; Liebman, A.A. *J. Am. Chem. Soc.* **1983**, 105, 3661.
61. Corey, E.J.; Hashimoto, S.; Barton, A.E.; *J. Am. Chem. Soc.* **1981**, 103, 721.
62. Pridgen, L.N.; Shilcrat, S.C.; Lantos, I.; *Tetrahedron Lett.* **1984**, 25, 2835.
63. Rossiter, B.E.; Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.* **1981**, 103, 464.
64. Marriott, D.P.; Bantick, J.R. *Tetrahedron Lett.* **1981**, 22, 3657.
65. Corey, E.J.; Barton, A.E.; Clark, D.A. *J. Am. Chem. Soc.* **1980**, 102, 4278.
66. Hougum, J.; Pai, J.-K.; Atrache, V.; Sok, D.-E.; Sih, C.J. *Proc. Natl. Acad. Sci. USA* **1980**, 77, 5688.
67. Corey, E.J.; Barton, A.E. *Tetrahedron Lett.* **1982**, 23, 2351.
68. Corey, E.J.; Su, W.; Mehrotra, M.M.; *Tetrahedron Lett.* **1984**, 25, 5123.
69. For reviews see: (a) Samuelsson, B. *Pure Appl. Chem.* **1981**, 53, 1203. (b) Marx, J.L.; *Science* **1982**, 215, 1380. (c) Various authors in *Advances in Prostaglandin, Thromboxane and Leukotriene Research* Samuelsson, B.; Paoletti, R. Eds.; Raven: New York, 1982; Vol. 9; (d) Bailey, D.M.; Casey, F.B. *Annu. Rep. Med. Chem.* Hess, H.J., Ed.; Academic: New York, 1982; Vol. 17, Chap. 21.
70. Orange, R.P.; Austen, K.F.; *Adv. Immunol.* **1969**, 10, 105.

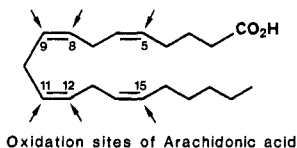
71. Hammerström, S.; Samuelsson, B.; Clark, D.A.; Goto, G.; Marfat, A.; Mioskowski, C.; Corey, E.J.; *Biochem. Biophys. Res. Commun.* **1980**, *92*, 946.
72. Lewis, R.A.; Austen, K.F.; Drazen, J.M.; Clark, D.A.; Marfat, A.; Corey, E.J.; *Proc. Natl. Acad. Sci. USA* **1980**, *77*, 3710.
73. Murphy, R.C.; Mathews, W.R.; Rokach, J.; Fenselau, C.; *Prostaglandins* **1982**, *23*, 201.
74. Guindon, Y.; Young, R.N.; and Frenette, R.; *Synth. Commun.* **1981**, *11*, 391.
75. Morris, H.R.; Taylor, G.W.; Rokach, J.; Girard, Y.; Piper, P.J.; Tippins, J.R.; Samhoun, M.N.; *Prostaglandins* **1980**, *20*, 601.
76. Anderson, M.E.; Allison, R.D.; Meister, A.; *Proc. Natl. Acad. Sci. USA* **1982**, *79*, 1088.
77. Bernström, K.; Hammarström, S.; *Biochem. Biophys. Res. Commun.* **1982**, *109*, 800.
78. Okuyama, S.; Miyamoto, S.; Shimoji, K.; Konishi, Y.; Fukushima, D.; Niwa, H.; Arai, Y.; Toda, M.; Hayashi, M.; *Chem. Pharm. Bull.* **1982**, *30*, 2453.
79. Denis, D.; Charleson, S.; Rackham, A.; Jones, T.R.; Ford-Hutchinson, A.W.; Lord, A.; Cirino, M.; Girard, Y.; Larue, M.; Rokach, J.; *Prostaglandins* **1982**, *24*, 801.
80. Ellis, F.; Mills, L.S.; North, P.C.; *Tetrahedron Lett.* **1982**, *23*, 3735.
81. Atrache, V.; Sok, D-E; Pai, J-K; Sih, C.J.; *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 1523.
82. (a) Huyser, E.S.; Kellogg, R.M.; *J. Org. Chem.* **1965**, *30*, 2867. (b) Hall, D.N.; Oswald, A.A.; Griesbaum, K.; *J. Org. Chem.* **1965**, *30*, 3829.
83. Perkins, C.W.; Martin, J.C.; Arduengo, A.J.; Lau, W.; Alegria, A.; Kochi, J.K.; *J. Am. Chem. Soc.* **1980**, *102*, 7753.
84. Rokach, J.; Guindon, Y.; Girard, Y.; Lau, C.K.; unpublished results.
85. Holme, G.; Masson, P.; Girard, Y.; Rokach, J.; unpublished results.
86. Atkinson, J.G.; Rokach, J.; unpublished results.

4. NON-5-LIPOXYGENASE PATHWAYS

Introduction

Lipoxygenase enzymes are known to oxidize arachidonic acid at six possible positions. The chemical requirement for this oxidation (Eq. 4.1) appears simply to be a skipped *cis* diene which can produce (via the enzyme) a stabilized allylic radical, which then traps molecular oxygen to form a conjugated *cis-trans* diene hydroperoxide. Chart 4.1 shows the six possible mono-oxidation products as members of the HETE family. All of these compounds have been shown to be natural products. Only in the cases of 8 and 9 HETEs is the absolute stereochemistry not definitively known. Nevertheless, it is speculated that 8-HETE has the alcohol in the (*S*)-configuration and 9-HETE is of the (*R*) absolute





Hydroxy elcosatetraenoic acids (HETEs)

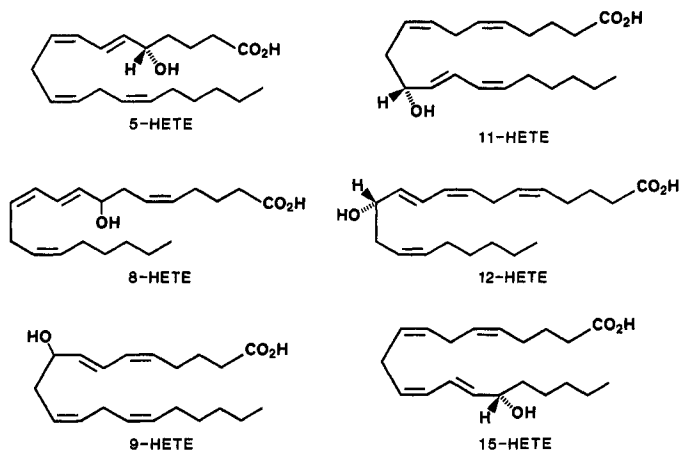


Chart 4.1

stereochemistry paralleling their symmetrical congeners (12*S*)-HETE and (11*R*)-HETE, respectively.

As has been shown for the 5-lipoxygenase cascade, the unstable intermediate HPETE can give rise to various epoxides through an enzymatic dehydration step. Thus other lipoxygenase pathways may produce oxido compounds 8,9-LTA₄, 11,12-LTA₄, and 14,15-LTA₄. Each of these epoxides can undergo further metabolic changes paralleling the 5-lipoxygenase route with one important distinction. To date no peptido-leukotrienes have been found to occur naturally for the 8-, 11-, or 15-lipoxygenase pathways.

Not all of the compounds shown have been identified as natural products. However, the logical extension of the 5-lipoxygenase pathway predicts the formation of many of these products, given that the necessary enzymes are present.

In general, less is known about the biological roles of the non-5-lipoxygenase pathways. This is largely because of the focus on the SRS-A leukotrienes, which are believed to be important mediators in various diseases. Nevertheless, more attention is being given to the alternate pathways of late since it appears that many of the eicosanoid metabolites may have regulatory or modulating roles in normal physiology as well as disease states. For example, it has been proposed that the presence of 15-HETE diminishes the amount of 5-lipoxygenase products produced in leukocytes. It has been demonstrated that 15-HETE can be converted to 5,15-diHETE and thus is functionally an inhibitor of 5-HETE production. 15-HETE, long known to be produced in plants, has recently been shown to occur in mammalian leukocytes as well. 12-HETE is produced by blood platelets and has been isolated from the psoriatic scales of humans. Surprisingly, however, this latter source apparently produces the (12*R*)-isomer, not the well-known (12*S*)-isomer.¹⁹ The 11-HETE metabolite is the reductive product of 11-HPETE, which via the cyclooxygenase system yields PGG₂, the precursor to all prostaglandins. Both 8- and 9-HETEs do not have defined biological activity, although together with the other HETEs have been shown to possess weak chemotactic activity.

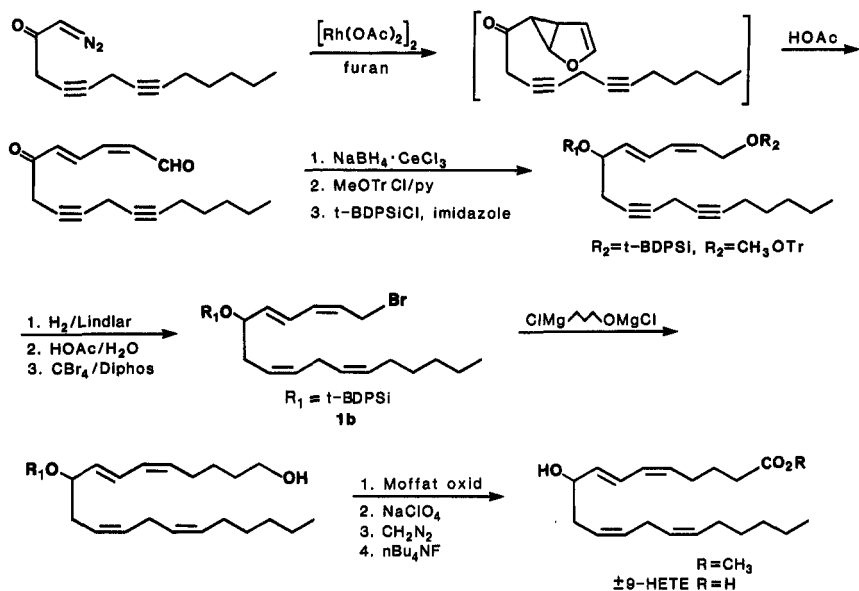
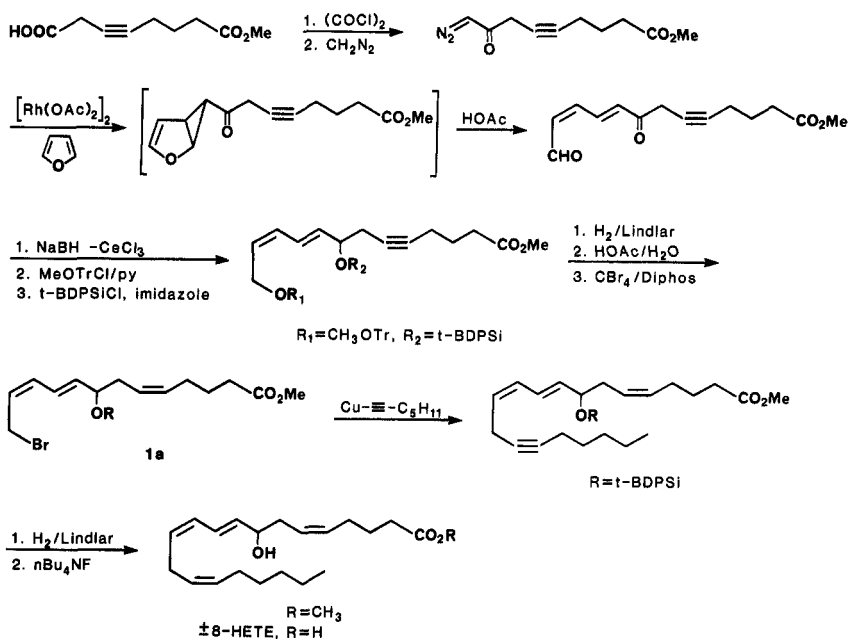
The 8,15-diHETEs may be formed by hydrolysis of 14,15-LTA₄ or alternatively by sequential oxidations via 15- and 8-lipoxygenases. Originally, the (8*S*,15*S*)-diHETE was thought to be as potent a chemotaxin as LTB₄, but this was recently shown not to be the case. Interestingly, (14*R*,15*S*)-diHETE inhibits superoxide release from cells (*in vitro*).

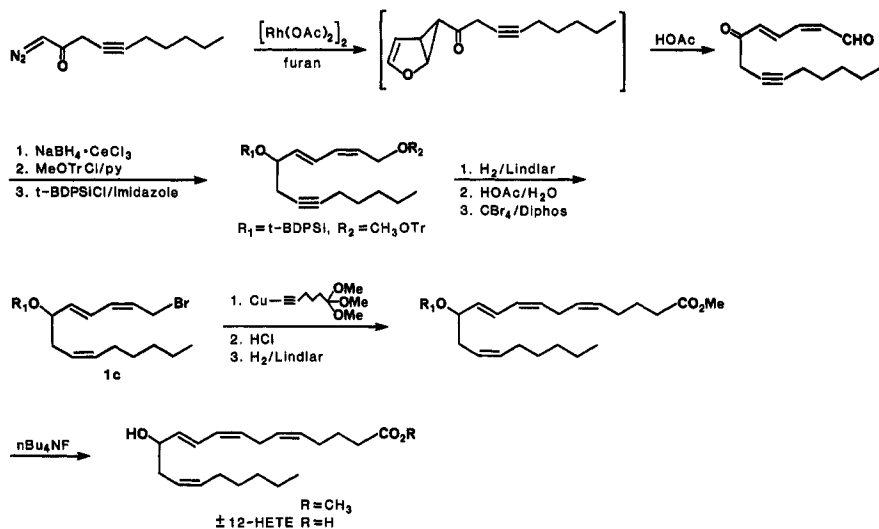
In summary, while isolated experiments have demonstrated certain biological properties of non-5-lipoxygenase metabolites, it is too early to ascribe any physiological significance to most of these products. Nevertheless, to further the scientific efforts relating to non-5-lipoxygenase cascades, many of these products have been synthesized and are presently under intensive biological investigation.

A. Synthesis of the HETEs

(1) Synthesis of (±)-8-, (±)-9-, and (±)-12-HETE

The Merck Frosst synthetic methodology using cyclopropylfurans to generate *cis-trans* dienes, initially developed for (±5)-HETE, was applied to three additional members of the HETE family. Schemes 4.1–4.3 outline the approach to (±)-8-, (±)-9-,¹ and (±)-12-HETE.² In each case a *cis-trans* diene allylic bromide **1a**, **b**, or **c** was alkylated by a chain-extending reaction to form the necessary C₂₀ eicosanoid skeleton. The syntheses further demonstrate the generality and efficiency of the cyclopropylfuran approach.



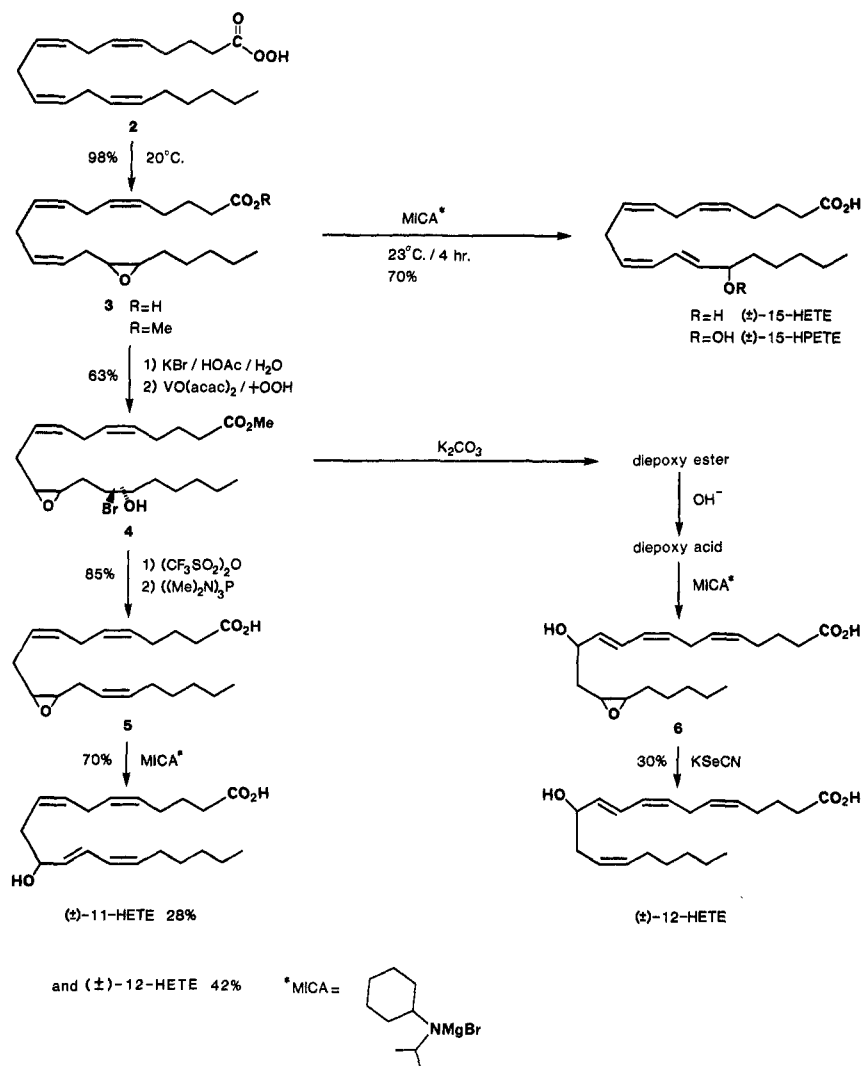


Scheme 4.3. Synthesis of (±)-12-HETE.

(2) Synthesis of the 11-, 12-, and 15-HETEs and HPETEs

Synthesis of (±)-11-, (±)-12-, and (±)-15-HETE and (±)-15-HPETE

The syntheses of racemic 11-, 12-, and 15-HETE and 15-HPETE have been reported by Corey et al.³, and are all based on the earlier remarkable finding⁴ that the peroxide of arachidonic acid **2** (Scheme 4.4) undergoes spontaneous intramolecular epoxidation to give exclusively 14,15-epoxyarachidonic acid, **3**. As shown in Scheme 4.4, all four title compounds were then obtained from epoxide **3** by appropriate manipulations. The conversion of an allylic or a homoallylic epoxide to a diene alcohol by the magnesium amide of isopropylcyclohexylamine (MICA) was of considerable utility and was used to obtain (±)-15-HETE directly from **3** and to obtain a mixture of (±)-11-HETE and (±)-12-HETE from epoxide **5**, and was used in an alternative synthesis of (±)-12-HETE to obtain the precursor **6**. The stereospecific removal of the elements of hypobromous acid from **4** “presented formidable obstacles” and was finally effected by reductive elimination of the bromo triflate with hexamethylphosphorous triamide, which generated the (14,15-*Z*) double bond in **5** with ~95% stereospecificity. The conversion of (±)-15-HETE to (±)-15-HPETE was carried out by a sequence analogous to that used to prepare (±)-5-HPETE (Scheme 3.1).

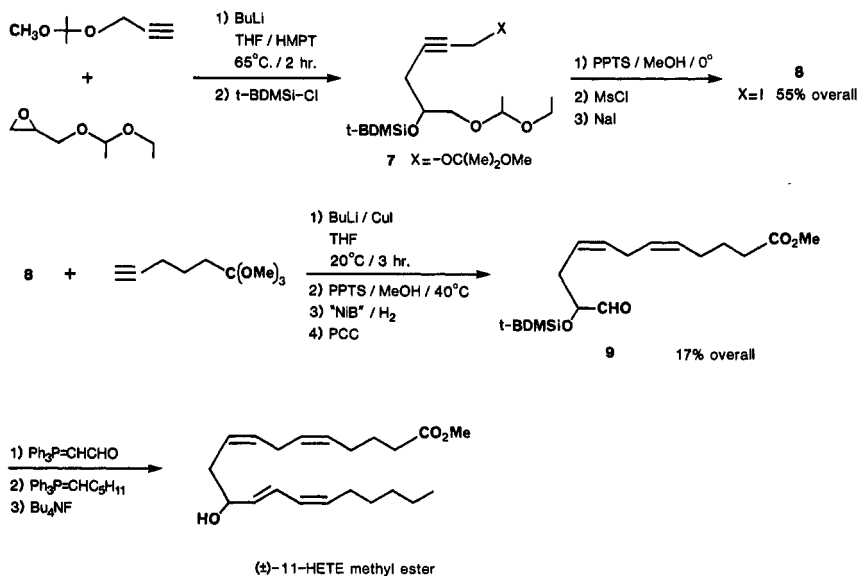


Scheme 4.4. Synthesis of (±)-11,12 and 15-HETE and 15-HETE.

Synthesis of (±)-11-HETE

Just and Luthe⁵ have recently reported the synthesis of the racemic methyl ester of 11-HETE, starting from a derivative of glycidol (Scheme 4.5). Since optically active glycidol is available, they point out that their synthesis could also be applied to obtain the natural (*R*)-isomer. They found that the ketal blocking

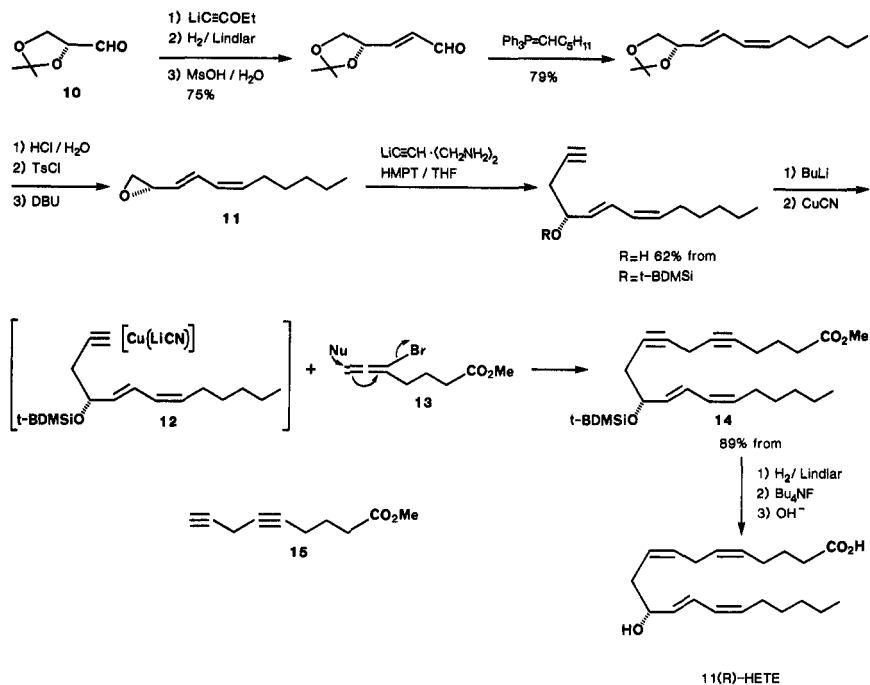
group in **7** could be removed with pyridinium *p*-toluenesulfonate (PPTS) at 0°C without removing the acetal blocking group. Then in order to obtain **9**, the acetal group was removed by treatment with the same reagent at 40°C, thus demonstrating a delicate but useful differentiation between these two types of alcohol-protecting groups.



Scheme 4.5. Synthesis of (±)-11-HETE.

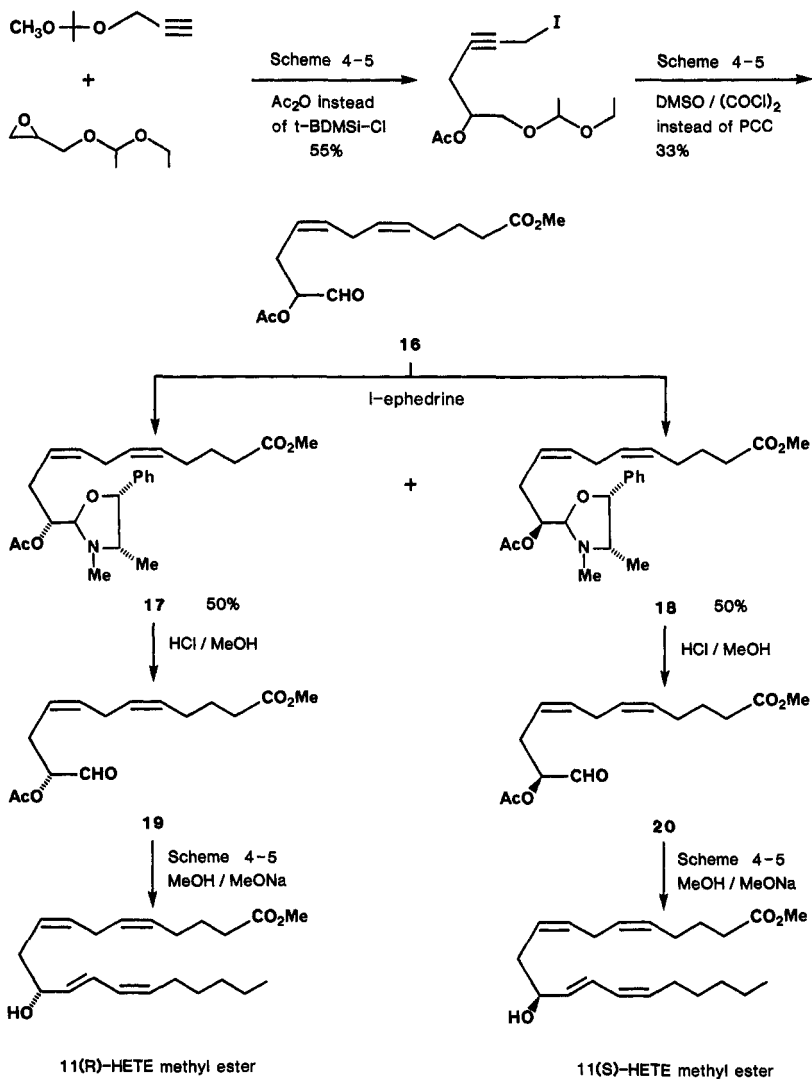
Synthesis of (11*R*)- and (11*S*)-HETE

A stereospecific total synthesis of (11*R*)-HETE, carried out by Corey and Kang,⁶ is outlined in Scheme 4.6. The optically active starting material is the acetonide **10** of D-glyceraldehyde. Of note is the condensation of lithium acetylide with epoxide **11**, which takes place predominantly at the nonallylic position, a phenomenon that depends on the presence of HMPT as a cosolvent. Another reaction of considerable potential interest is the nucleophilic displacement of the allenic bromide **13** by the reagent **12** (see **13**, arrows). Although allenic bromides are not a widely used species, the reaction, if general, would provide a novel synthesis of skipped dienes. The shorter and more obvious synthesis of **14** by coupling the acetylenic anion of **15** with **11** was frustrated by the finding that the CH₂ group between the two acetylenic bonds was of comparable acidity to the terminal acetylenic hydrogen.



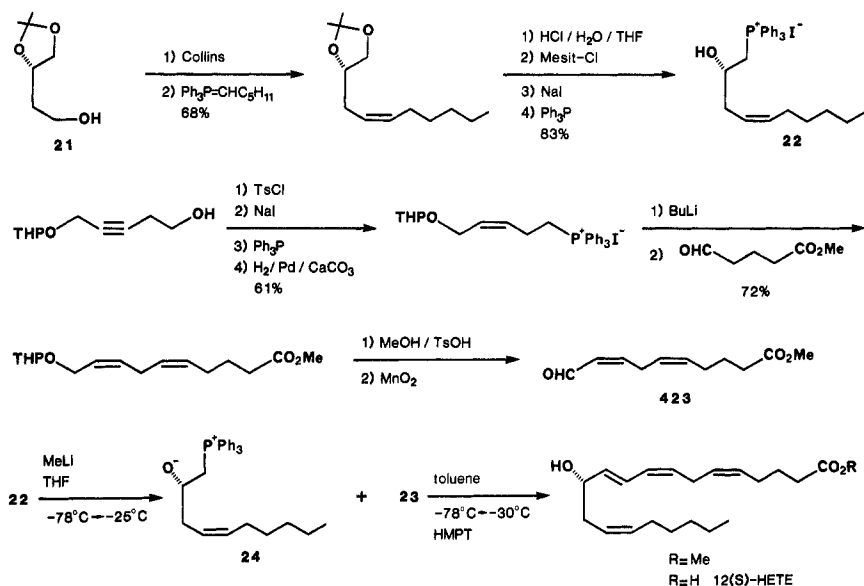
Scheme 4.6. Synthesis of (11*R*)-HETE.

Just and his co-workers,⁷ making good use of their experience with the diastereomeric oxazolidines obtained by the condensation of 1-ephedrine with α -acetoxyaldehydes, have accomplished a synthesis of both (11*R*)- and (11*S*)-HETE (Scheme 4.7). The overall synthetic approach was the same as that used in their synthesis of ($\pm$)-11-HETE⁵ (Scheme 4.5) with two significant improvements on their published chemistry. By using acetic anhydride instead of *t*-butyldimethylsilyl chloride for alcohol protection, they were able to obtain the α -acetoxyaldehyde **16** directly instead of converting the silylated analog **7** (Scheme 4.5) to **16**.⁸ This was important because the silylated oxazolidines corresponding to **17** and **18** were not easily separable. A second improvement was the oxidation of the primary alcohol precursor to **16** using dimethylsulfoxide-oxalyl chloride at low temperature in place of PCC, which raised the yield from 45 to 85%.⁸ The diastereomeric oxazolidines **17** and **18** were then separable by flash chromatography and were easily hydrolyzed to the desired resolved aldehydes **19** and **20**. The synthesis of the methyl esters of (11*R*)-HETE and (11*S*)-HETE was then completed essentially as outlined in Scheme 4.5.

Scheme 4.7. Synthesis of (11*R*) and (11*S*)-HETE.*Synthesis of (12*S*)- and (12*R*)-HETE*

(12*S*)-HETE was the first product shown to arise from a lipoxygenase reaction of arachidonic acid in mammalian systems.⁹ Chronologically it was also the first lipoxygenase product to be synthesized. As outlined in Scheme 4.8, Corey et al.¹⁰ carried out a stereospecific total synthesis from acetone alcohol **21** which

was readily prepared from diethyl (*S*)-malate. The unsaturated aldehyde **23** was found to be stereochemically very unstable and had to be used immediately in the Wittig reaction with **22**. The Wittig reaction was a particularly critical step and the desired (*E*)-stereochemistry was obtained by taking advantage of earlier work from Corey's laboratory which had demonstrated that β -oxido ylides such as **24** gave predominantly (*E*)- rather than (*Z*)-olefins, as is usually observed with unstabilized phosphonium ylides.

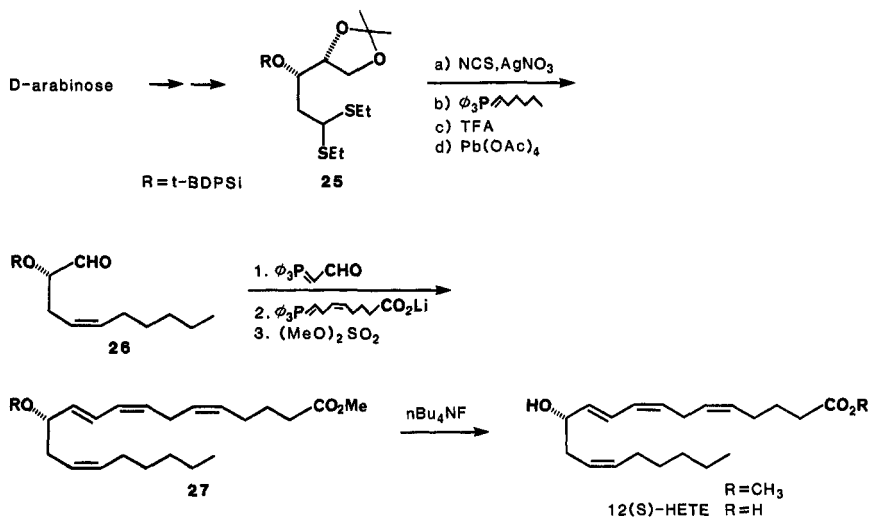


Scheme 4.8. Synthesis of (12*S*)-HETE.

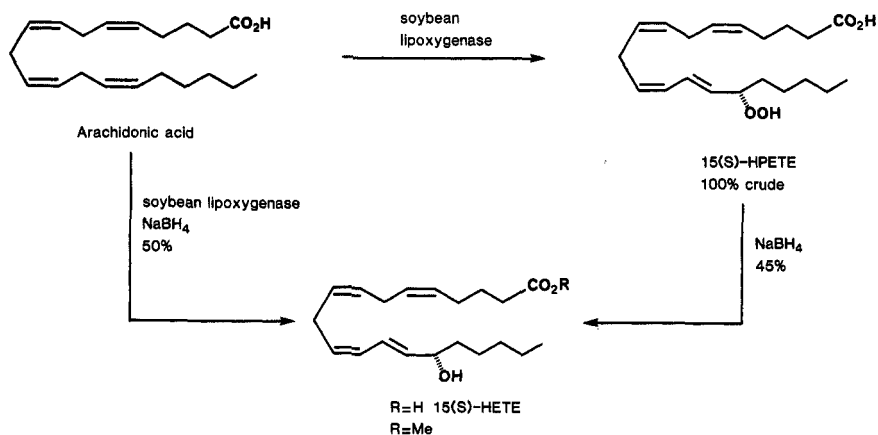
The Merck Frosst synthesis (Scheme 4.9) is quite efficient and straightforward, starting from the masked dialdehyde synthon **25**, which is derived from D-arabinose (see Scheme 2.20).¹¹ Homologation of aldehyde **26** with formylmethylenetriphenylphosphorane followed by a second Wittig reaction led to protected (12*S*)-HETE, **27**. The same sequence, starting from L-arabinose, provided the recently¹⁹ discovered (12*R*)-HETE.¹¹

Biochemical Synthesis of (15*S*)-HETE and (15*S*)-HPETE

No stereospecific synthesis of 15-HETE has yet been reported, because good biochemical syntheses make this last of the HETEs readily available. Although not strictly within the scope of the present review, it is worthwhile pointing out

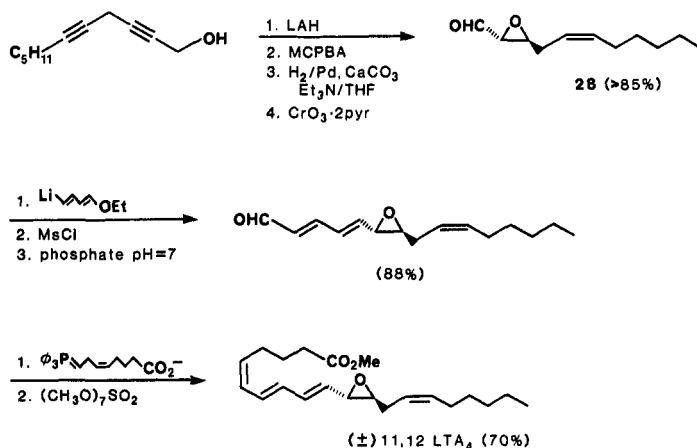
Scheme 4.9. Synthesis of (12*S*)-HETE.

the excellent preparation optimized by Baldwin, Davies, and their co-workers.¹² Using a commercially available soybean lipoxygenase, they describe conditions for preparing 500 mg of pure (15*S*)-HETE (Scheme 4.10) in about one working day. Somewhat surprisingly, they found that by adding NaBH_4 directly to the reaction mixture, the yield was improved and the reaction was somewhat faster. Conditions are described for isolating either (15*S*)-HETE itself or its methyl ester.

Scheme 4.10. Biochemical Synthesis of (15*S*)-HETE and (15*S*)-HPETE.

B. Synthesis of Isomeric LTA₄'s(1) Synthesis of (±)-11,12-LTA₄

Corey reported a racemic synthesis of 11,12-LTA₄ beginning with undeca-2,5-diyn-1-ol and forming the racemic epoxy aldehyde **28** (Scheme 4.11).¹³ The remainder of the synthesis parallels his approach to LTA₄.



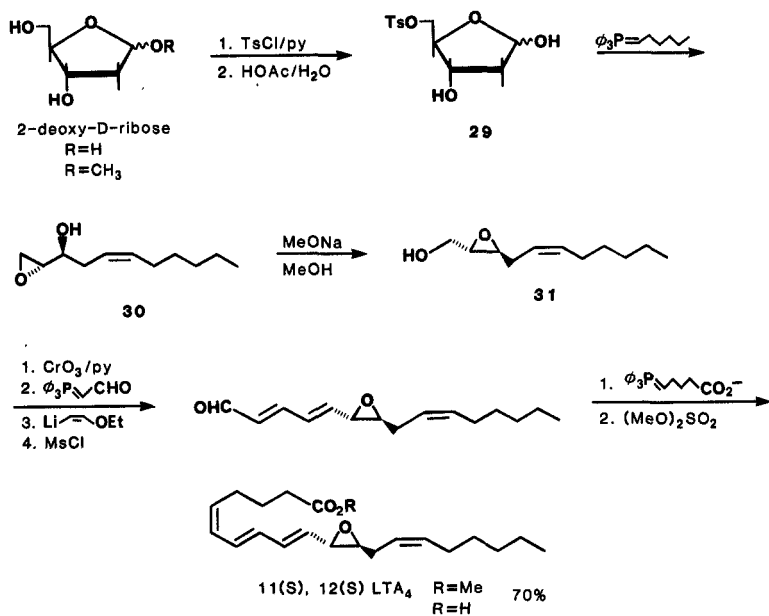
Scheme 4.11. Synthesis of (±)-11,12-LTA₄.

(2) Enantiospecific Synthesis of 11,12-LTA₄

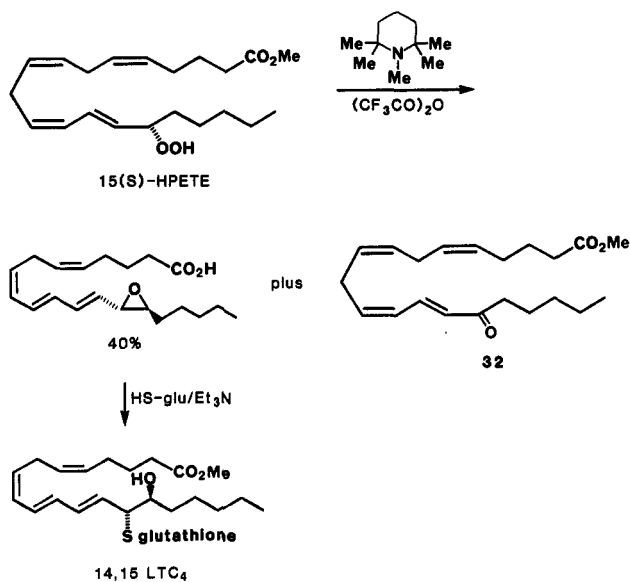
The Merck Frosst approach to optically pure 11,12-LTA₄ employs the versatile route from 2-deoxy-D-ribose (Scheme 4.12).⁴ The tosylate **29** was prepared from the methyl furanoside, and Wittig reaction with hexylidene triphenylphosphorane resulted in the *in situ* formation of epoxy alcohol **30**, which does not rearrange under the reaction conditions. The Paine rearrangement occurs upon treatment of **30** with MeONa/MeOH to epoxy alcohol **31**, which is then carried on in a similar fashion to the LTA₄ route to optically pure 11,12-LTA₄.

(3) Biomimetic Synthesis of (14*S*,15*S*)-LTA₄

While 14,15-LTA₄ itself has not been isolated from natural sources, Samuelsson has obtained strong evidence that it is formed and is the intermediate in further biochemical transformations. Scheme 4.13 indicates the sequence used by Corey



Scheme 4.12. Synthesis of optically pure 11,12-LTA₄.

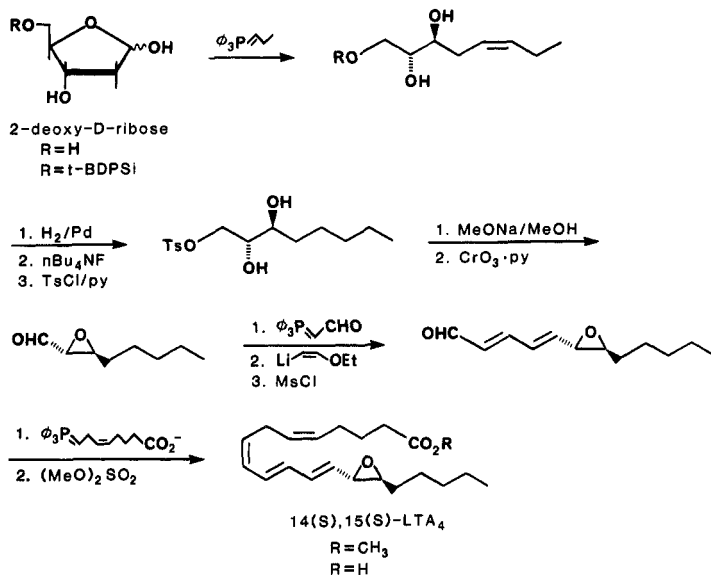


Scheme 4.13. Biomimetic synthesis of (14S,15S)-LTA₄.

in a biomimetic approach to (14*S*,15*S*)-LTA₄ from 15-HPETE.¹³ Forming the hydroperoxytrifluoroacetyl ester under basic conditions afforded a modest yield of the desired epoxide as well as the corresponding 15-keto product **32**. The epoxy triene was opened with glutathione to make analog 14,15-LTC₄ (Scheme 5.16b).

(4) Total Synthesis of (14*S*,15*S*)-LTA₄

The Merck Frosst group synthesized (14*S*,15*S*)-LTA₄ in a very similar approach to LTA₄, using 2-deoxy-D-ribose in a totally stereocontrolled manner.¹⁵ Scheme 4.14 highlights the synthesis.

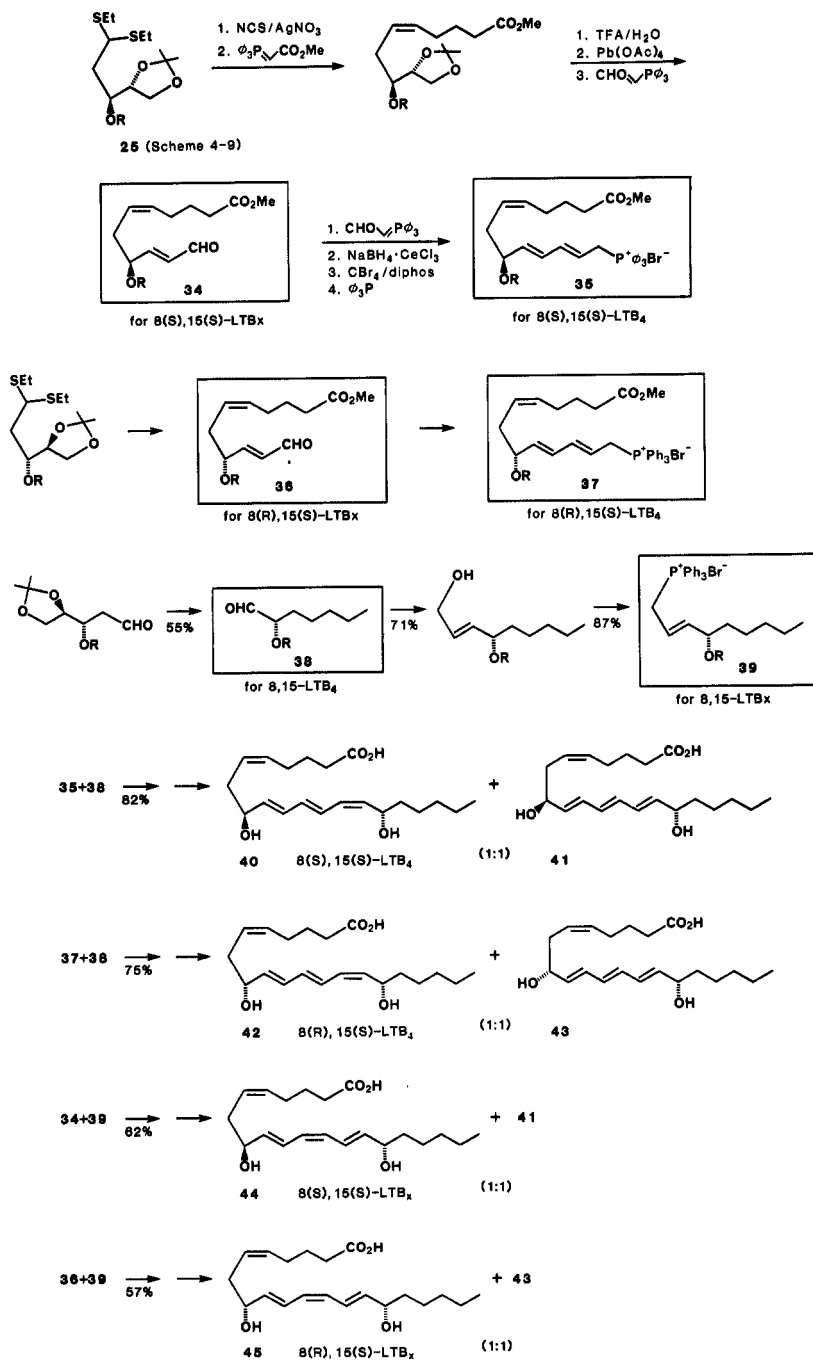


Scheme 4.14. Total synthesis of (14*S*,15*S*)-LTA₄.

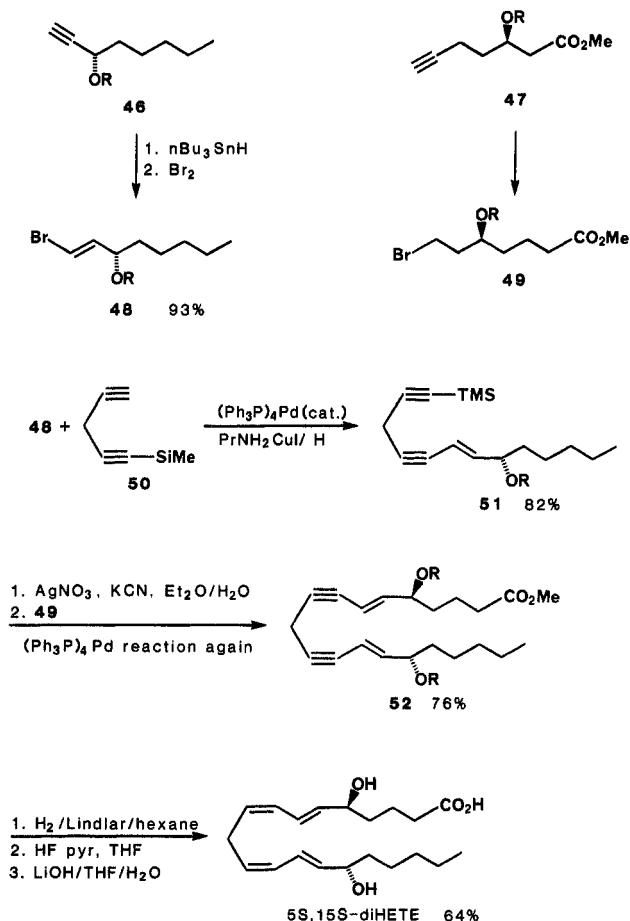
C. Synthesis of diHETEs

(1) Synthesis of 8,15-diHETEs

By analogy to the 5,12-diHETEs derived either from LTA₄ (LTA₄ → LTB₄) or by double lipoxygenation (arachidonic acid → (5*S*,12*S*)-diHETE), the 8,15-diHETEs (see Scheme 1.6) have been found to be produced by eosinophils.¹⁶



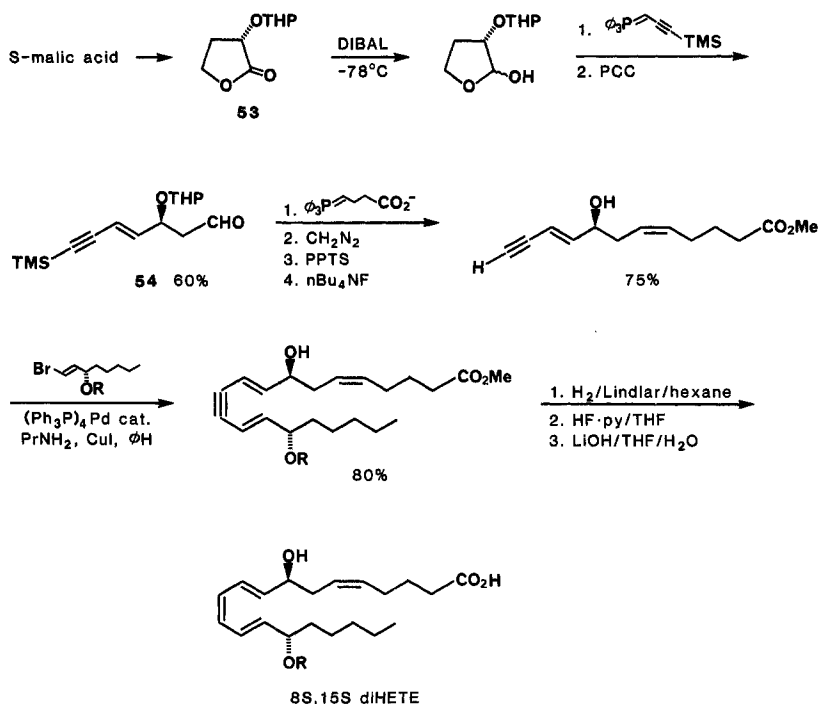
Scheme 4.15. Total synthesis of 6-isomeric 8,15-dihETES.



Scheme 4.16. Total synthesis of (5S,15S)-diHETE.

The Merck Frosst group was the first to produce these compounds synthetically.¹⁷ Scheme 4.15 indicates how masked dialdehyde synthon **25** (Scheme 4.9) and its epimer **33** were converted to all of the necessary synthetic intermediates **34–39** required for the 8,15-diHETEs.

The stereochemistry of the hydroxyls and olefin geometries are carefully controlled and six isomeric 8,15-diHETEs (**40–45**) were realized. In each case a Wittig reaction was used to assemble the C₂₀ skeleton and the stereoselectivity was 1:1. Initial biological findings have shown these compounds to be virtually inactive compared to LTB₄, and their physiological roles remain unknown.



Scheme 4.17

(2) Synthesis of (5S,15S)-diHETE and (8S,15S)-diHETE

Recently Nicolaou¹⁸ reported the synthesis of (5S,15S)-diHETEs and a positional isomer (8S,15S)-diHETE. Both of these compounds may be formed using commercially available soybean lipoxygenase, and are formed by sequential lipoxygenase catalysed oxidations at specific points on arachidonic acid.

The synthesis of (5S,15S)-diHETE is shown in Scheme 4.16 and makes use of Pd-Cu coupling of a terminal acetylene to *trans* vinyl bromides (**48** + **50** $\rightarrow$ **51** and **51** + **49** $\rightarrow$ **52**) to obtain enynes. The acetylenes are reduced by catalytic hydrogenation to give the requisite *cis-trans* dienes. Acetylenes **46** and **47** bear the suitable optically active secondary alcohols for the (5S) and (15S)-alcohol functions in the natural product and are derived from chiral reductions of the corresponding ketones.¹⁸

The synthesis of (8S,15S)-diHETE (Scheme 4.17) is similar and differs only in the use of *S*-malic acid as a starting material to obtain lactone **53**, which is converted to the acyclic enyne **54** by a Wittig reaction.

REFERENCES

1. Adams, J.; Rokach, J. *Tetrahedron Lett.* **1984**, 25, 35.
2. Leblanc, Y.; Fitzsimmons, B. J.; Adams, J.; Perez, F.; Rokach, J. *J. Org. Chem.* **1986**, 51, 789.
3. Corey, E. J.; Marfat, A.; Falck, J. R.; Albright, J. O. *J. Am. Chem. Soc.* **1980**, 102, 1433.
4. Corey, E. J.; Niwa, H.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, 101, 1586.
5. Just, G.; Luthe, C. *Tetrahedron Lett.* **1982**, 23, 1331.
6. Corey, E. J.; Kang, J. *J. Am. Chem. Soc.* **1981**, 103, 4618.
7. Just, G.; Luthe, C.; Potvin, P. *Tetrahedron Lett.* **1982**, 23, 2285.
8. Just, G.; Luthe, C.; Phan Viet, M. T.; *Can. J. Chem.*, **1983**, 61, 712.
9. Hamberg, M.; Samuelsson, B. *Proc. Natl. Acad. Sci. USA* **1978**, 71, 3400.
10. Corey, E. J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, 100, 1942.
11. Leblanc, Y.; Fitzsimmons, B. J.; Adams, J.; Perez, F.; Rokach, J. *J. Org. Chem.*, **1986**, 51, 789.
12. Baldwin, J. E.; Davies, D. I.; Hughes, L.; Gutteridge, N. J. A. *J. Chem. Soc. Perkin 1*, **1979**, 115.
13. Corey, E. J.; Goto, G.; Marfat, A. *J. Am. Chem. Soc.* **1980**, 102, 6607.
14. Zamboni, R.; Milette, S.; Rokach, J. *Tetrahedron Lett.* **1984**, 25, 5835.
15. Zamboni, R.; Milette, S.; Rokach, J. *Tetrahedron Lett.* **1983**, 24, 4899.
16. Turk, J.; Maas, R. L.; Brash, A. R.; Roberts II, L. J.; Oates, J. A. *J. Biol. Chem.* **1983**, 257, 7068.
17. Fitzsimmons, B. J.; Rokach, J. *Tetrahedron Lett.* **1984**, 25, 3043.
18. Nicolaou, K. C.; Webber, S. E. *J. Am. Chem. Soc.* **1984**, 106, 5734.
19. Woollard, P. M. *J. Invest. Dermatol.* **1985**, 84, 455.

5. LEUKOTRIENE ANALOGS

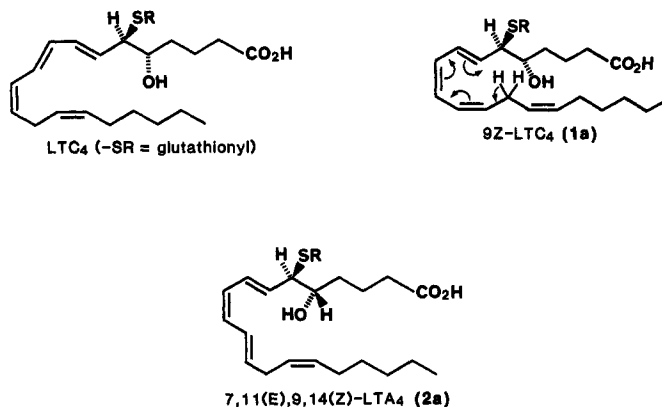
A. Analogs of LTA₄, LTC₄, LTD₄, LTE₄, and LTF₄

(1) Olefin Isomers

(7E,9,11,14Z)-LTC₄ and-LTD₄ and (7,11E,9,14Z)-LTC₄ and-LTD₄

Although a number of isomeric analogs of LTA₄ and the peptidolipids LTC₄, D₄, and E₄ were prepared during the synthesis and structure elucidation of SRS-A, researchers have subsequently gone on to prepare many stereoisomers of the leukotrienes for chemical and biochemical study. Baker and co-workers¹ prepared a number of LTC₄ analogs to correct confusion about the identity of the (9Z)-LTC₄ isomer (7E,9,11,14Z)-LTC₄ (**1a**). Corey and Samuelsson reported² the synthesis of (9Z)-LTC₄ (**1a**) in one of their earliest papers. However, the compound was considered to be an unstable structure by Rokach et al.³ and by Sih.⁴ They felt that the (7E,9,11,14Z)-LTC₄ (**1a**) should undergo a facile 1,7-hydride shift to give a conjugated tetraene as had been observed for several similar analogs and synthetic intermediates (Scheme 5.1). Baker et al. postulated

that Corey had in fact prepared the (7,11*E*,9,14*Z*)-analog (**2a**). As final proof they prepared natural stereochemistry LTA₄, (7*E*,9,11,14*Z*)-LTA₄ (**3**), and (7,11*E*,9,14*Z*)-LTA₄ (**4**) and converted them all to the corresponding LTC₄ analogs (Schemes 5.2a,b). They were able to demonstrate the expected thermal instability of the (7*E*,9,11,14*Z*)-isomer **1a** and they further demonstrated that the (7,11*E*,9,14*Z*)-isomer **2a** had UV characteristics and stability consistent with that reported by Corey et al. for (9*Z*)-LTC₄².



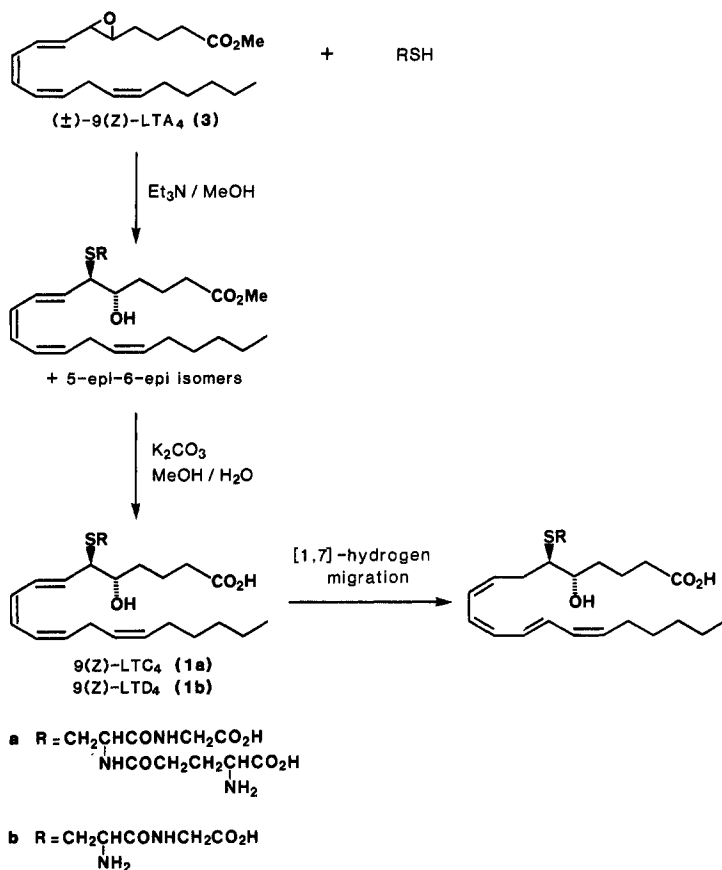
Scheme 5.1

(7,11,14*Z*,9*E*)-LTA₄ and -LTD₄

In a study of methods of leukotriene synthesis, Ernest and co-workers⁵ discovered that triphenylphosphoranylidene-crotonaldehyde **5** reacts with the epoxyaldehyde **6** to give a 1:4 mixture of the key leukotriene A₄ intermediate (*E,E*)-epoxydiene aldehyde **7** together with the novel (*Z,E*)-epoxydiene aldehyde **8** (Scheme 5.3). The availability of **8** made possible the preparation of (7,11,14*Z*,9*E*)-LTA₄ (**9**) and (7,11,14*Z*,9*E*)-LTD₄ (**10**) (about 1/10 as active as LTD₄ as a contractile agonist on guinea pig ileum tissue).

(7,14*Z*,9,11*E*)-LTA₄, -LTC₄, -LTD₄, and -LTE₄

Spur et al.⁶ prepared LTA₄, C₄, D₄, and E₄ analogs having the (7,14*Z*,9,11*E*)-stereochemistry, as is found in LTB₄, using the (*Z,E*)-dienealdehyde **8** of Ernest,⁵ which when reacted in THF (−78°C) with the ylid derived from (*Z*)-3-nonen-1-yltriphenylphosphonium bromide (**11**) gave (7,14*Z*,9,11*E*)-LTA₄ methyl ester (**12**) with 85% geometrical purity (Scheme 5.4).

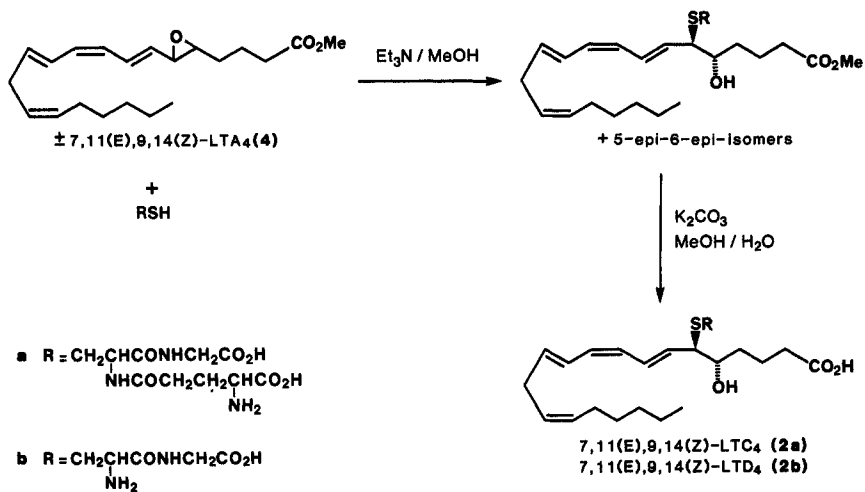
Scheme 5.2a. Synthesis of (7*E*,9,11,14*Z*)-LTC₄ and -LTD₄.

Interestingly, the derived LTC₄ analog **13a** was found to be only weakly active on the guinea pig ileum, while the LTD₄ (**13b**) and LTE₄ (**13c**) analogs were essentially inactive.

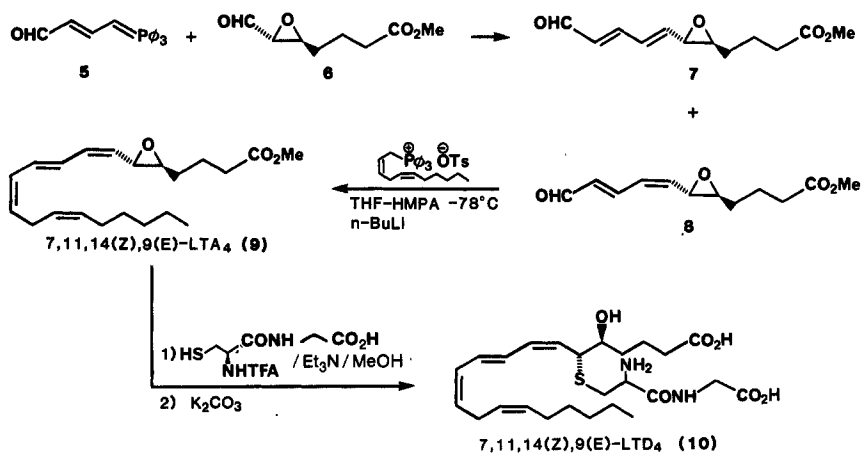
(2) Hydro-Analogs of LTA₄, LTC₄, LTD₄, and LTE₄

To study the effect of the double bonds on the biological activity of leukotrienes, to facilitate enzymic studies, and in some cases to prepare more stable analogs of leukotrienes, a number of research groups have prepared partially or fully saturated analogs of the SRS-A leukotrienes.

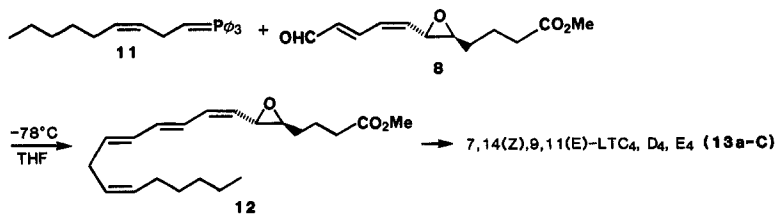
Drazen et al.⁷ reported the preparation and biological activities of 14,15-dihydro-LTC₄ (**14a**) and LTD₄ (**14b**) (almost equiactive with the parent



Scheme 5.2b. Synthesis of (7,11*E*,9,14*Z*)-LTC₄ and -LTD₄.

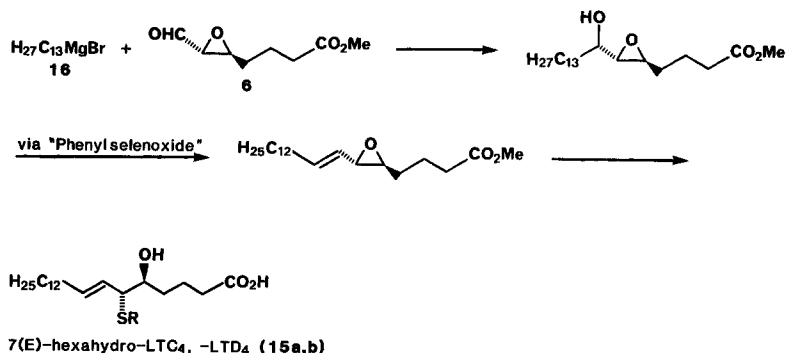


Scheme 5.3. Synthesis of (7,11,14*Z*,9*E*)-LTD₄.



Scheme 5.4. Synthesis of (7,14*Z*,9,11*E*)-LTC₄, -LTD₄, and LTE₄.

compounds), as well as the (7*Z*)- and (7*E*)-hexahydro-analogs of LTC₄ and LTD₄ (0.5–35% of the activity of LTC₄, LTD₄). The latter (**15a,b**) were prepared from the epoxy aldehyde (**6**) and tridecylmagnesium bromide (**16**) followed by phenylselenoxide elimination (Scheme 5.5).



Scheme 5.5. Synthesis of (7*E*)-hexahydro-LTC₄ and -LTD₄.

Spur et al. prepared 14,15-dihydro-LTE₄ (LTE₃) (**14c**)⁸ and (7*E*,9*Z*)-11,12,14,15-tetrahydro-LTA₄ (**17**), -LTC₄ and -LTD₄ (**18a,b**) analogs by standard methodology.

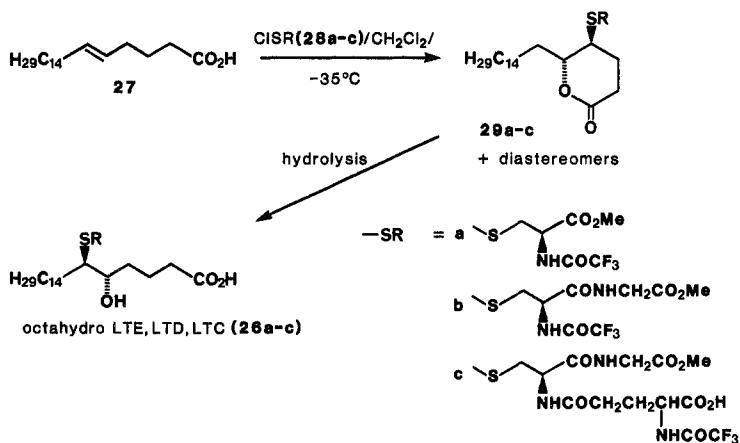
In an extensive study on leukotriene analogs, the group of Okuyama et al.⁹ from Ono Pharmaceuticals reported syntheses of (7*Z*)-9,10-dihydro-LTA₄ (**19**), (9*Z*)-11,12-dihydro-LTA₄ (**20**), and 14,15-dihydro-LTA₄ (**21**) (Scheme 5.6) which were converted, via conjugation with the appropriate peptide and subsequent hydrolysis, to their corresponding dihydro-LTC₄ and -LTD₄ analogs. These products possess 5–10% of the activity of the parent structures.

Young et al.¹⁰ were able to prepare (7,9*E*)-11,12,14,15-tetrahydro-LTA₄ (**22**) and (7,9*E*,14*Z*)-11,12-dihydro-LTA₄ (**23**) analogs by reacting the appropriate epoxyaldehydes with the corresponding phosphonate Wittig–Horner reagents under carefully controlled conditions to provide almost exclusively (>90%) the desired (*E*)-stereochemistry of the formed double bonds (Scheme 5.7). The compounds were converted to the corresponding LTD₄ analogs (**24,25**) which retained about 1% of the activity of LTD₄.

Hammarstroem et al.^{11,12} prepared 14,15-dihydro-LTC₄ (**14a**) and -LTD₄ (**14b**) analogs enzymatically in mouse mastocytoma cells provided with 5,8,11-eicosatrienoic acid as substrate.

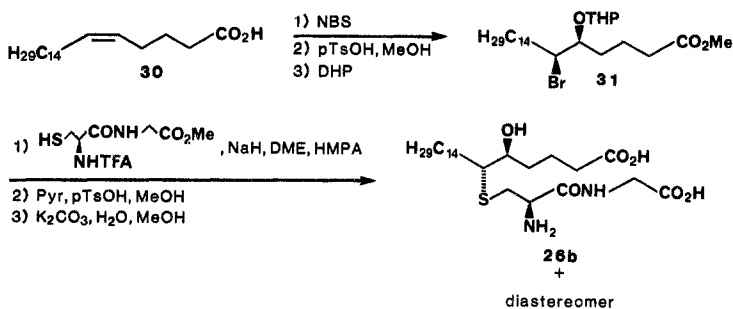
Young et al.¹³ prepared the fully saturated analogs of LTC₄, D₄, and E₄ (**26a–c**) via reaction of (5*E*)-eicosenoic acid (**27**) in a sulfenyllactonization

reaction with sulfenylchlorides **28a–c**, derived from reaction of chlorine with suitably protected cystinyl, cystinylbisglycine, or oxidized glutathione derivatives. The reactions were stereo- and regioselective and provided the derivatives via the lactones **29a–c** in two steps after separation of the formed diastereomers (Scheme 5.8). The derived LTC₄, D₄, and E₄ analogs were 100–1000 times less active than LTD₄ as contractile agonists on guinea pig trachea.



Scheme 5.8. Synthesis of Perhydro-LTC₄, -LTD₄, and -LTE₄.

The Ono group⁹ prepared the same LTD₄ analog (**26b**) as a diastereomeric mixture from (5*Z*)-eicosenoic acid (**30**) via bromolactonization, methanolysis, protection of the 5-hydroxy group (**31**), and subsequent displacement of the bromide with protected cysteinylglycine and final hydrolysis (Scheme 5.9).



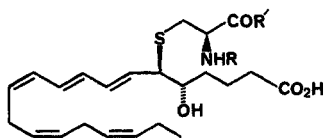
Scheme 5.9. Ono synthesis of Perhydro-LTD₄.

(3) Dehydro-Analogs of LTA_4 , LTC_4 , LTD_4 , and LTE_4

Many workers have prepared leukotriene analogs with either extra double bonds or, where certain double bonds have been replaced with triple bonds.

The LT_5 's

Hammarstroem^{11,14} prepared 5-hydroxy-6-S-glutathionyl-(7,9*E*,11,14,17*Z*)-eicosapentaenoic acid (LTC_5) (**32a**) and LTD_5 (**32b**) (Scheme 5.10) by incubating mouse mastocytoma cells with eicosapentaenoic acid (EPA). The LTC_5 and LTD_5 along with LTE_5 (**32a-c**) were prepared by Spur et al.,¹⁵ and by Lee and co-workers,¹⁶ and were found to be generally less active than the parent tetraeneic compounds. These findings have led to the proposal that dietary substitution of EPA for arachidonic acid could attenuate leukotriene-based biological responses *in vivo*.



LTC_5 $R = CONHCH_2CH_2CH(NH_2)CO_2H$; $R' = NHCH_2CO_2H$ (**32a**)

LTD_5 $R = H$; $R' = NHCH_2CO_2H$ (**32b**)

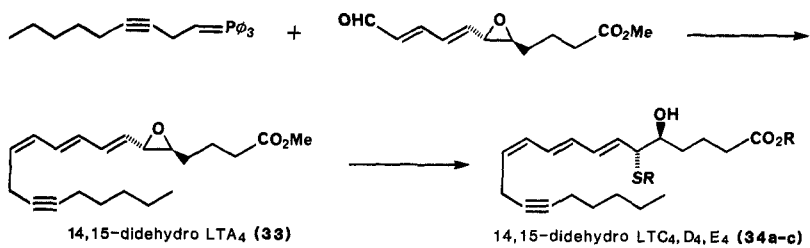
LTE_5 $R = H$; $R' = OH$ (**32c**)

Scheme 5.10. LTC_5 , LTD_5 , and LTE_5 .

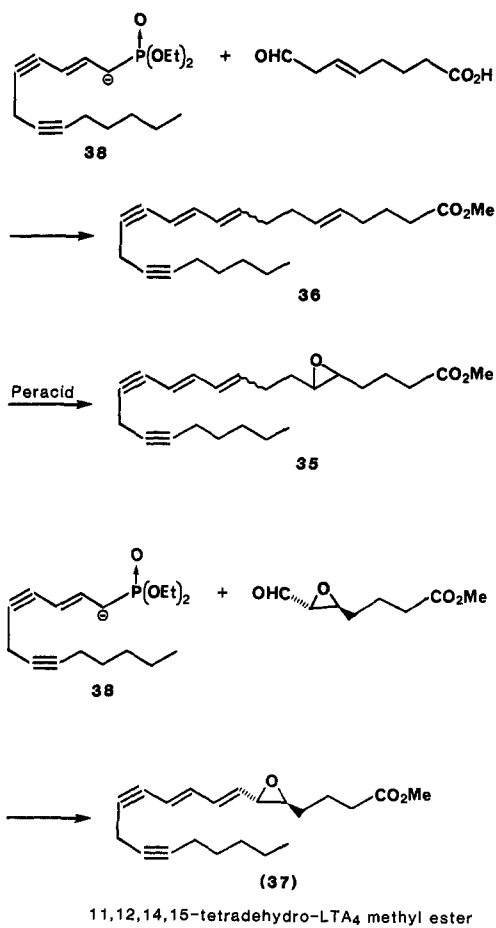
Acetyleno-Leukotrienes A_4 , C_4 , D_4 , and E_4

Acetyleno-analogs of leukotrienes have been prepared as intermediates in many leukotriene syntheses previously discussed and are not discussed here. A number of workers have, however, prepared unusual acetyleno-leukotrienes for the purpose of studying their biological activities.

Spur et al.¹⁷ prepared 14,15-didehydro-leukotriene A_4 (**33**) and the corresponding LTC_4 , LTD_4 , and LTE_4 analogs (**34a-c**) (Scheme 5.11), while Russian workers¹⁸ have reported the preparation of an unusual (C-22) bis-dehydro- LTA_4 analog (**35**). The isolated olefin in the intermediate triene/diyne **36** was selectively epoxidized to give the racemic LTA_4 analog **35** (Scheme 5.12). They also reported the synthesis of the ($\pm$)-11,12,14,15-bis-dehydro- LTA_4 (**37**) from reacting the same phosphonate Wittig-Horner reagent (**38**) with ($\pm$)-6-formyl-5,6-epoxyhexanoate (Scheme 5.12).

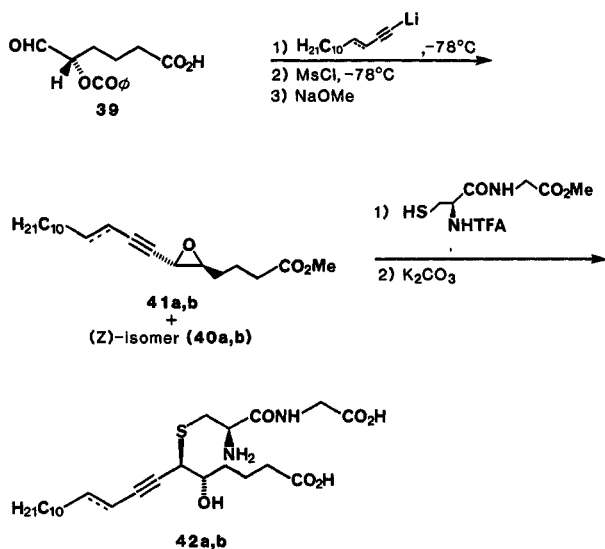


Scheme 5.11. Synthesis of 14,15-didehydro-LTC₄, -LTD₄, and -LTE₄.



Scheme 5.12. Synthesis of bis-acetyleno-analogs of LTA₄ and LTA₄.

Young and co-workers¹⁹ have prepared partially saturated acetyleno-analogs of LTA₄ and LTD₄ via novel methodology. Desiring to place an acetylene function at C-7, the often-used chiral synthon 6-formyl-5,6-epoxyhexanoate (**6**) could not be used. Instead ethyl (5*S*)-5-formyl-5-benzoyloxy-pentanoate (**39**) (an LTB₄ synthon)²⁰ was reacted in a one-pot sequence with appropriate lithium acetylides followed by *in situ* mesylation of the formed alkoxide and subsequent hydrolysis of the benzoate with concomitant elimination of the mesylate to provide the chiral *cis*- (**40a,b**) and *trans*-epoxides (**41a,b**) (Scheme 5.13). Conjugation with cysteinylglycine gave the LTD analogs **42a,b**. They also prepared the *trans*-racemic-7-yne-epoxide ($\pm$)**41a** via selective epoxidation of methyl (5*E*)-eicosa-5-en-7-ynoate **43**. Subsequent conjugation with cysteinylglycine gave the LTD₄ analog **42a** together with its (5*R*,6*S*)-diastereomer (Scheme 5.14). These compounds were very much less active ($>1/1000$) than LTD₄.

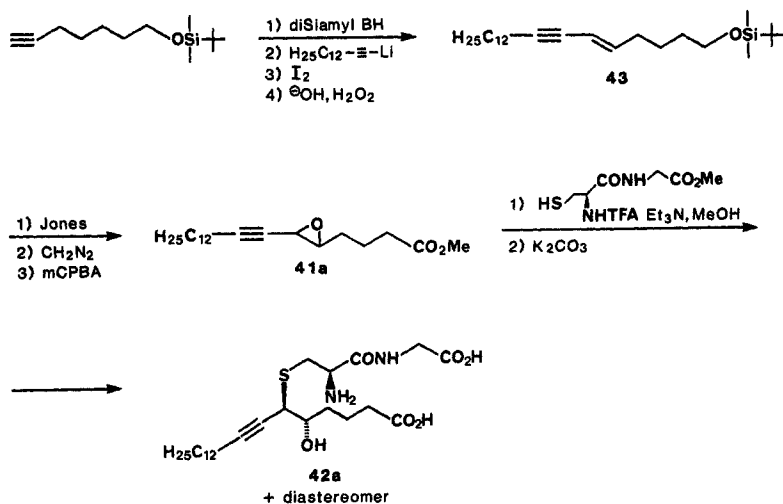


Scheme 5.13. Chiral synthesis of 7,8-dehydro analogs of LTA₄ and LTD₄.

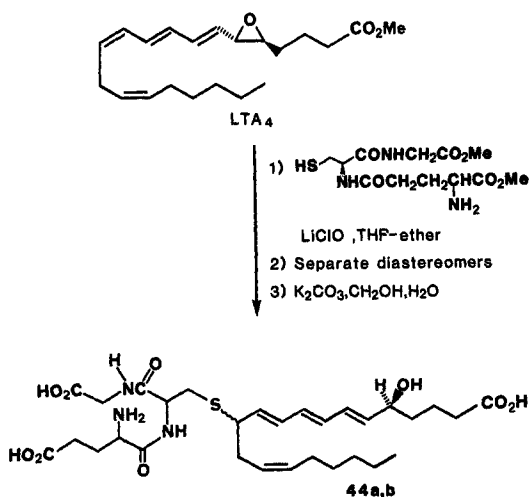
(4) Positional Isomers of LTA₄, LTC₄, LTD₄, and LTE₄

In general, moving the 5-hydroxy-6-thioether functionality of LTC₄, D₄, and E₄ to other positions in the molecules has been accompanied by dramatic losses in biological activity. However, several of these analogs are produced by cells.

Corey and Clark²¹ prepared the two diastereomeric analogs of LTC₄ having the glutathionyl residue at C-12 and with the (6,8,10*E*,14*Z*)-stereochemistry



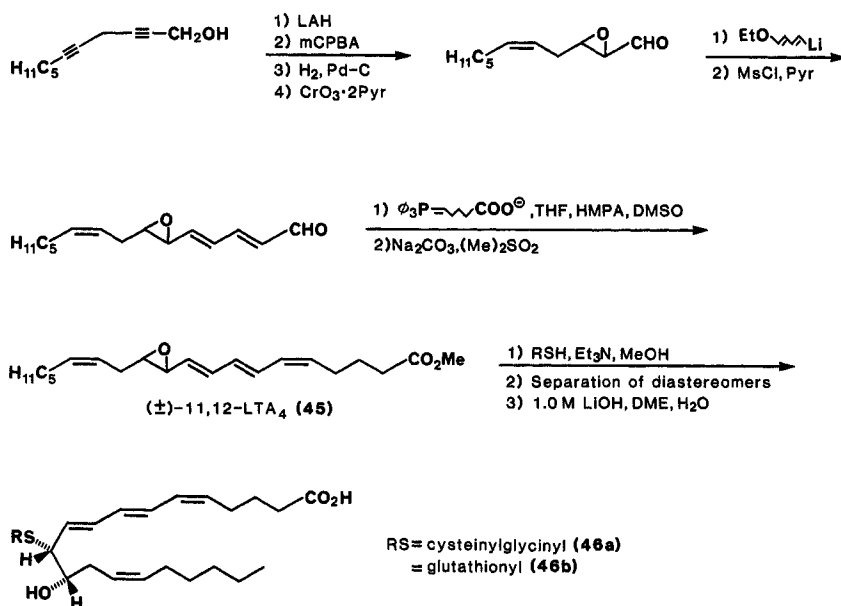
Scheme 5.14. Nonchiral synthesis of 7,8-dehydro analogs of LTA₄ and LTD₄.



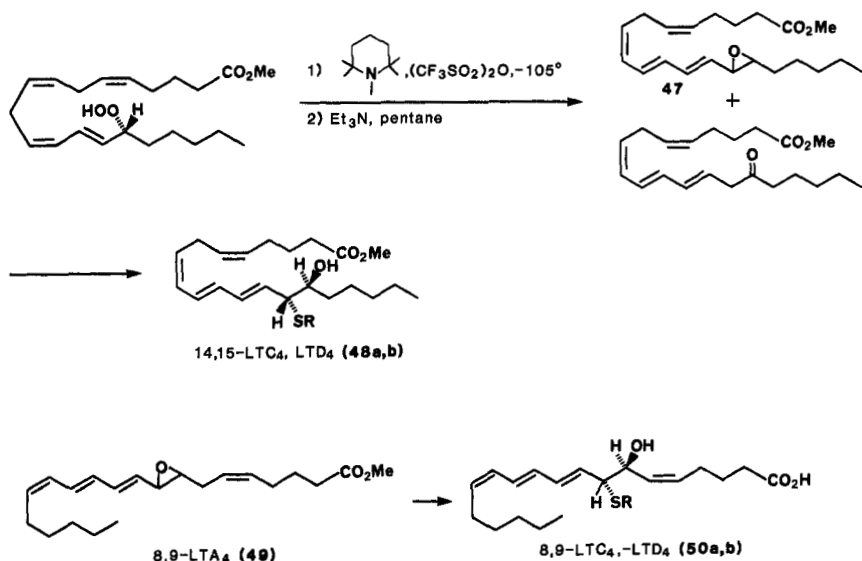
Scheme 5.15. Synthesis of (5*S*)-hydroxy-(12*R,S*)-*S*-glutathionyl-(6,8,10*E*,14*Z*)-eicostetraenoic acids.

(**44a,b**) to determine if they could play a role as a component of natural SRS-A. The compounds were readily prepared from LTA_4 by reaction with protected glutathione under $\text{S}_{\text{N}}1$ -type conditions in the presence of lithium perchlorate (Scheme 5.15).

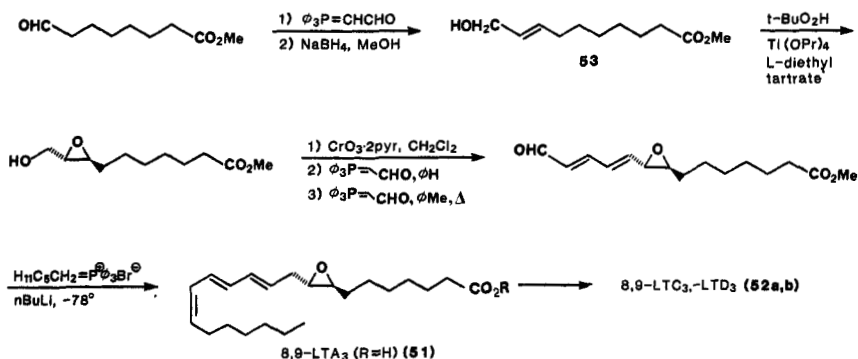
The diastereomers were separated and hydrolyzed to provide the LTC_4 analogs **44a,b**, which were shown to be very much less active ($>1/500$) than LTC_4 . Corey²² also prepared analogs of LTC_4 and LTD_4 (**46a,b**; **48a,b**; **50a,b**) derived from the 11,12- LTA_4 analog **45**, as well as from the methyl (5,8Z,10,12E)-14,15-epoxyeicosatetraenoate (14,15- LTA_4) **47** and from methyl (5,14Z,10,12E),8,9-epoxyeicosa-tetraenoate (8,9- LTA_4) **49**. These positional isomers all had much attenuated activity or no activity when compared with LTD_4 , thus pointing out the importance of the 5,6-substitution in SRS-A (Scheme 5.16a-b).



Scheme 5.16a. Synthesis of 11,12- LTC_4 and - LTD_4 .

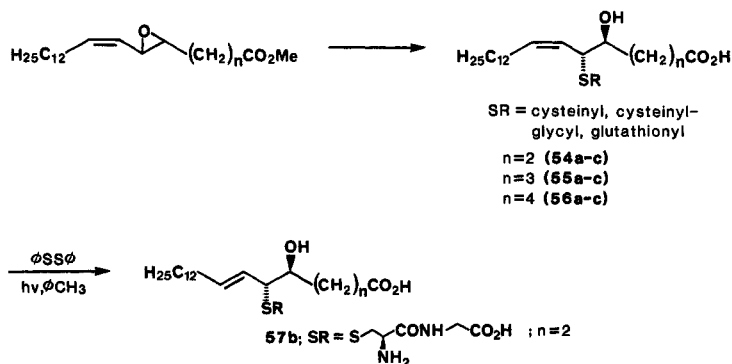
Scheme 5.16b. Synthesis of 14,15-LTC₄, and LTD₄ and 8,9-LTC₄ and -LTD₄.

Workers at Lilly have reported the synthesis of 8,9-LTA₃ (51), 8,9-LTC₃ (52a), and 8,9-LTD₃ (52b),²³ leukotrienes that are reported to be produced from dihomono- γ -linolenic acid in ionophore-stimulated murine mastocytoma cells.²⁴ The natural stereochemistry was assumed to be (8*S*,9*R*,10,12*E*,14*Z*) by analogy with arachidonic acid metabolism in the same cell system. The chiral synthesis was achieved (93% ee) via Sharpless epoxidation of an appropriate allylic alcohol (53) (Scheme 5.17).

Scheme 5.17. Synthesis of 8,9-LTC₃, and -LTD₃.

(5) *Homo- and Nor-Leukotriene Analogs*

Chemists at Smith, Kline and French have prepared a number of 2-nor-9,10,11,12,14,15-hexahydro-leukotriene analogs (**54a–c**, **55a–c**, **56a–c**), some of which are reported to be potent antagonists of SRS-A activity in guinea pig airways and pulmonary artery.²⁵ They observed that the spatial separation of the C-1 carboxy group relative to the hydroxy group in the LTC, D, and E analogs is critical in determining whether an analog is an agonist or an antagonist in this series. Thus LTD and homo-LTD analogs are agonists (**55**, $n = 3$; **56**, $n = 4$), while the nor-derivatives (**54a–c**) are antagonists. The syntheses of these analogs were apparently straightforward with resolution by HPLC after conjugation of the epoxide intermediates with the appropriate thiopeptide. Noteworthy was the photoisomerization of the (6*Z*)-2-nor-LTD₄ (**54b**) to the (6*E*)-2-nor-LTD₄ (**57b**) to provide the otherwise difficult to obtain (*E*)-isomers (Scheme 5.18).

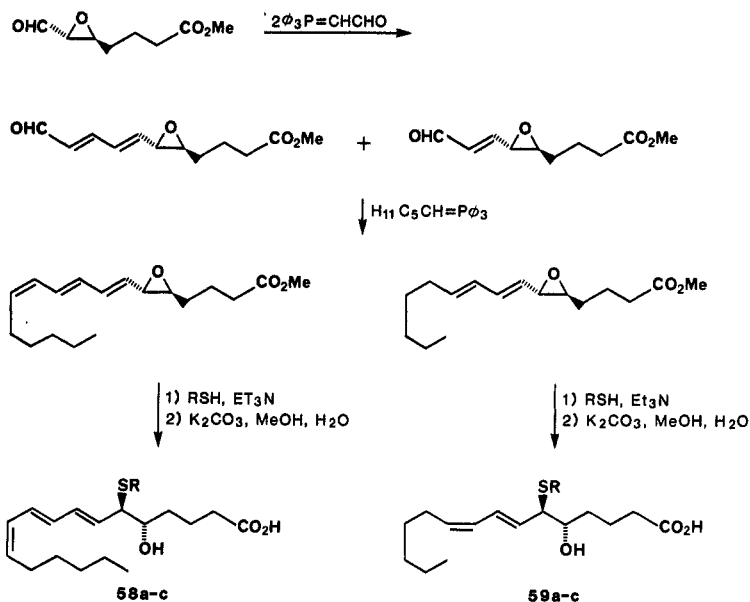


Scheme 5.18. Synthesis of (6*E*)-2-nor-LTD₄ and homologs.

To study the role of chain length on biological activity, Spur and co-workers²⁶ have prepared C-15 (**58a–c**) and C-17 (**59a–c**) leukotriene analogs as potential partial agonists/antagonists of SRS-A (Scheme 5.19).

(6) *Other Analogs of Leukotriene A₄*

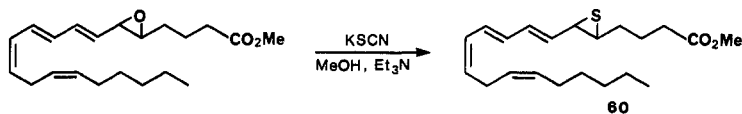
In hopes of discovering inhibitors of either the LTA₄-forming or -degrading enzymes, a number of workers have prepared analogs of LTA₄, where the epoxide function has been replaced with homologous or isosteric groups.



Scheme 5.19. Synthesis of C-15 and C-17 leukotriene analogs.

5,6-Epithia-LTA₄

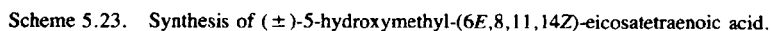
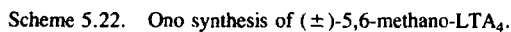
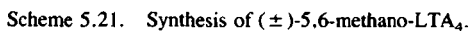
Corey²⁷ prepared the 5,6-epithia-LTA₄ **60** by reaction of racemic LTA₄ with sodium thiocyanate. Spur et al.²⁸ prepared the same compound **60** as well as a number of olefin isomers, partially saturated and unsaturated analogs, from the corresponding epoxides via similar technology (Scheme 5.20). The compounds have shown weak activity as inhibitors of SRS-A biosynthesis.



Scheme 5.20. Synthesis of 5,6-epithia-LTA₄.

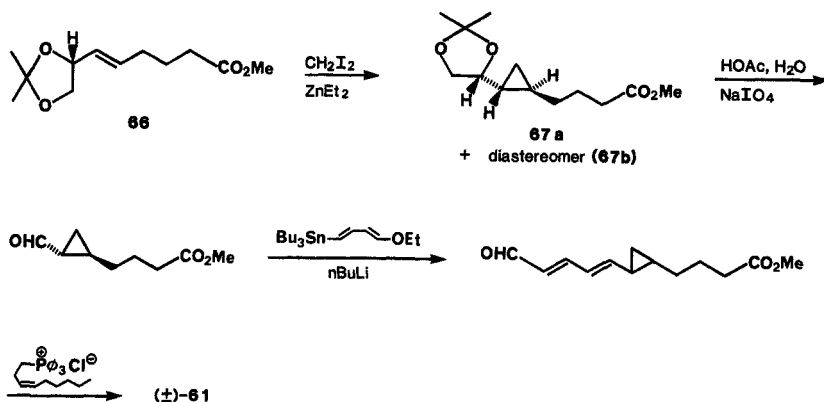
5,6-Methano-LTA₄

Nicolaou²⁹ prepared the 5,6-methano-LTA₄ **61** from reaction of 6-formyl-5,6-methanohexanoate **62** with a novel phosphonate **63** to give the adduct **64** with



predominately the desired (7*E*)-stereochemistry. Subsequent selective reduction of the acetylene function provided the desired analog **61** (Scheme 5.21).

Ono chemists³⁰ prepared the same compound (**61**) as well as the racemic carba-analog of 5-HPETE (**65**) using technology analogous to that utilized before in the synthesis of the corresponding parent compounds (Schemes 5.22 and 5.23). Rokach and co-workers³¹ have prepared the 5,6-methano-LTA₄ [(±)-**61**] analog by reacting the isopropylidene-protected methyl (7*R*-7,8-dihydroxyoct-5*E*)-enoate **66** with diiodomethane and diethylzinc to form the diastereomeric 7,8-methano product **67a,b**. Hydrolysis and cleavage gave the aldehyde **68**, which was converted to the (±)-LTA₄ **61** analog by standard methodology (Scheme 5.24). Although the racemic product was obtained, separation of the diastereomers of **67a,b** prior to cleavage would provide the chiral products if desired.



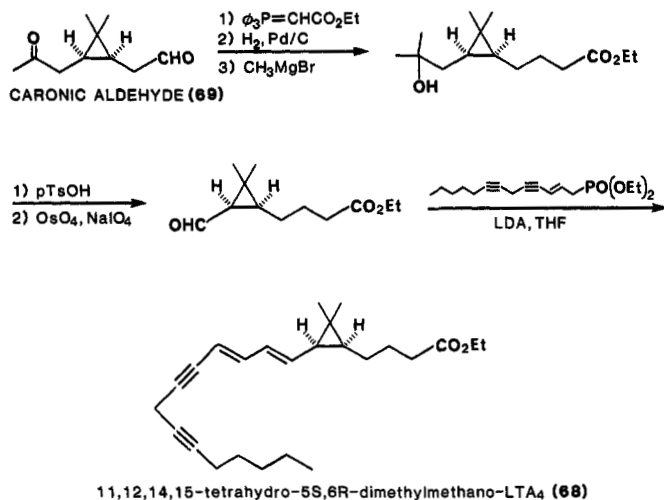
Scheme 5.24. Merck Frosst synthesis of 5,6-methano-LTA₄.

A number of studies have shown the 5,6-methano-LTA₄ **61** to be a selective inhibitor of the 5-lipoxygenase enzyme.^{32,33}

Russian workers have reported the preparation of an unusual 11,12,14,15-tetradehydro-(5*S*,6*R*)-dimethylmethanoleukotriene A₄ analog **68**.³⁴ The compound was prepared in seven steps from the chiral keto aldehyde synthon, caronic aldehyde **69** (Scheme 5.25).

5,6-Aza-LTA₄

Zamboni and Rokach³⁵ converted 5-epi-6-epi-LTA₄ **70** to the 5,6-aza-LTA₄ **71** with the natural LTA₄ stereochemistry in a double inversion process; reaction

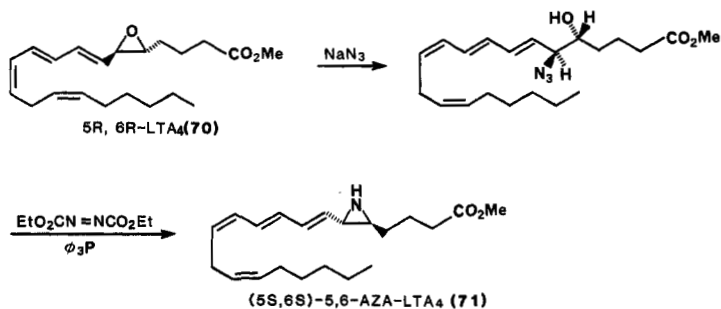


Scheme 5.25. Synthesis of 11,12,14,15-Tetrahydro-(5S,6R)-dimethylmethano-LTA₄.

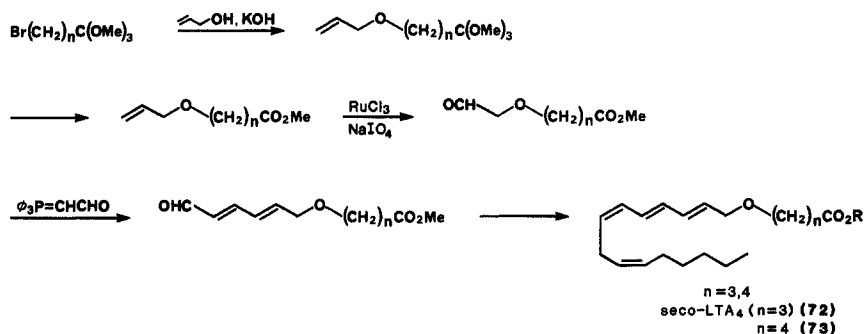
of LTA₄ methyl ester with sodium azide and subsequent reaction with diethylazodicarboxylate and triphenylphosphine (Scheme 5.26).

Seco-Leukotriene A₄

As a further ingenious example of LTA₄ analogs, Syntex researchers³⁶ prepared seco-leukotriene A₄ 72, a compound with structural similarity to LTA₄, but which lacks the reactive epoxide group and is therefore a potential inhibitor of LTB₄ or LTC₄ synthetase enzymes. The synthesis of seco-LTA₄ 72 and a nor-



Scheme 5.26. Synthesis of (5S,6S)-5,6-aza-LTA₄.

Scheme 5.27. Synthesis of seco-LTA₄.

analog **73** are described below in Scheme 5.27. The compound **73** with $n = 4$ is reported inhibit LTB₄ formation in human PMNs.

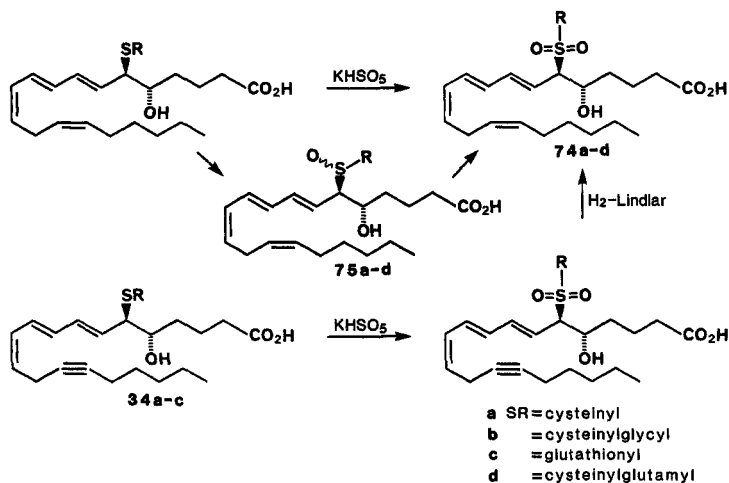
(7) Analogs of LTC₄, LTD₄, and LTE₄ Where the 5-Hydroxy or 6-Peptide Portion Has Been Modified

Many research groups have prepared leukotriene analogs incorporating modifications to the peptide portion, as tools to better understand structure-activity relationships and to aid in the search for effective antagonists and inhibitors.

Oxidized Analogs of LTC₄, D₄, and F₄

One simple modification, with some expectation of a parallel in nature, is the oxidation of the sulfur atom in LTC₄, D₄, or E₄ to the sulfoxide or sulfone. Indeed, the sulfone analog of LTC₄ (**74a**) was proposed by Ohnishi et al.³⁷ as the major component of natural SRS-A, based on a combination of the well-known aryl sulfatase-catalyzed degradation of the natural substance and an apparent molecular ion observed using the field desorption mass spectrometry techniques. To clarify the ambiguities raised by this proposal, Girard and co-workers prepared the sulfone analogs of LTC₄, D₄, and E₄ (**74a-c**)^{38a} and of LTF₄ (**74d**)^{38b} from the parent compounds by direct oxidation with KHSO₅. The reagent converted the leukotrienes first to the diastereomeric sulfoxides **75a-c** and then slowly to the sulfones **74a-d** in 20–25% yield (Scheme 5.28). This reaction was complicated by some degree of overoxidation, apparently epoxidation of the 14,15-double bond. To overcome this side reaction an alternative synthesis was carried out using the 14,15-dehydro-analogs of LTC₄, D₄, and E₄ (**34a-c**), which

could be oxidized to the sulfones without accompanying overoxidation and then hydrogenated over Lindlar catalyst to provide the sulfone analogs **74a-d**. The leukotriene sulfones were only slightly less active than the corresponding sulfides, but were sufficiently different in HPLC retention times from the naturally derived SRS-A components to essentially rule out the possibility that they may be important components of natural SRS-A.



Scheme 5.28. Synthesis of the sulfones of LTC₄, LTD₄, LTE₄, and LTF₄.

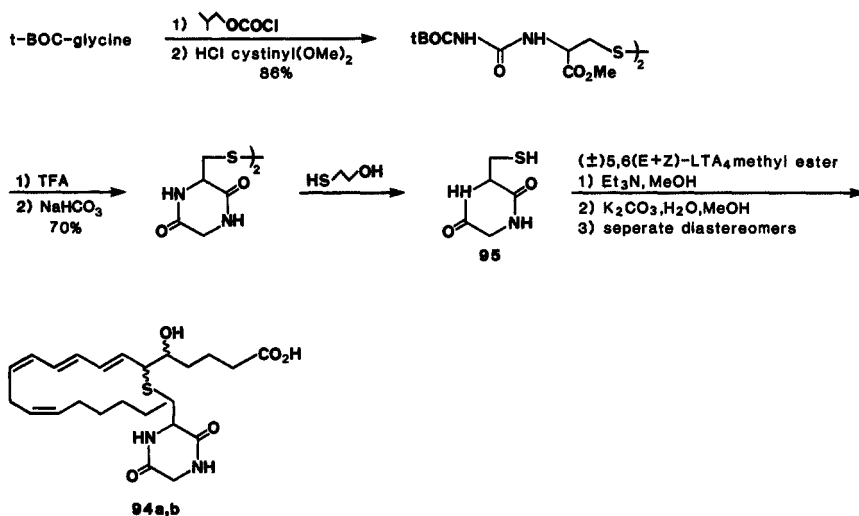
Lewis and co-workers³⁹ reported the preparation of the two diastereomeric sulfoxides of LTC₄ and LTD₄ (**75a,b**) obtained by oxidation of LTC₄ and LTD₄ with buffered sodium periodate. Interestingly, one of the diastereomers (undefined) retained about 10% of the activity of the parent leukotriene D₄, while the other lost essentially all activity. This may reflect a fundamental modification of the peptide conformation brought about by internal hydrogen bonding.

Peptide Analogs

Several research groups have prepared analogs of LTC₄, D₄, E₄, and F₄ where the peptide moiety has been replaced by other peptides or modified amino-acid analogs. Lewis and co-workers³⁹ prepared a large number of such analogs of LTD₄. They explored the role of the carboxy groups in LTD₄ by preparing the mono (**76,77**) and bisamides (**78**), the LTD₄ deamino bisamide **79**, and the LTD₄ monodimethyl amide (glycyl) **80**. They further explored the role of the glycyl

Workers at Ono Pharmaceuticals⁹ have prepared similar analogs. In addition they prepared the bisdimethylamide of LTD₄ **91** and found it to be inactive. The 6-dimethylaminocarboxylpropylthio-analog **92** and the 6-carboxymethylaminopropylthio-analog of LTD₄ **93** were prepared and found to be marginally active (Scheme 5.29).

Bernstein et al. at ICI have recently reported⁴⁰ the preparation of a diketopiperazine analog of LTD₄ (**94a,b**). The compound was prepared by reacting LTA₄ with the diketopeprazine **95** derived from cystinyl-bis-glycine. As a *cis-trans* mixture of racemic LTA₄ epoxides (60:40) was used in this reaction, two pairs of diastereomers were obtained. One diastereomeric pair (**94a**) was about 1/10 as active at LTD₄ while the other (**94b**) was only 1/1000 as active. The authors interpreted these results to indicate that the amide bond in LTD₄ may adopt the *cisoid* geometry in its active conformation (Scheme 5.30).

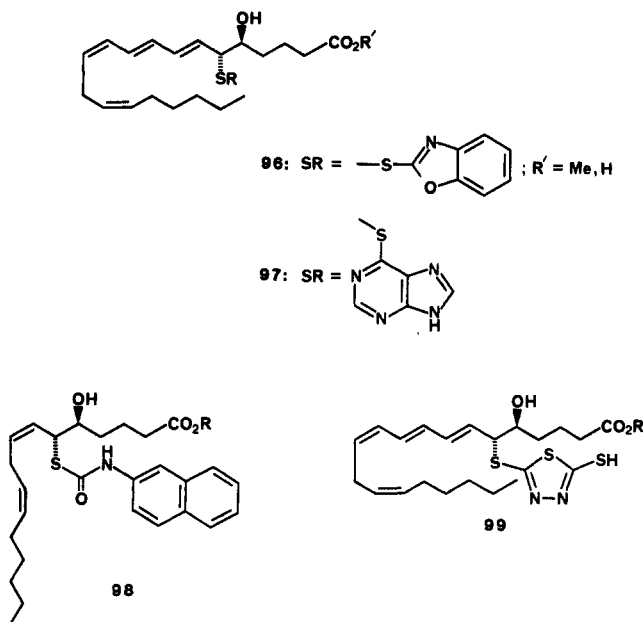


Scheme 5.30. Synthesis of diketopiperazine analogs of LTD₄.

Non-Peptide 6-Substituted Analogs

In the search for potential antagonists of SRS-A and to better understand the requirements of the leukotriene D₄ receptor, several research groups have prepared leukotriene analogs where the peptide portion was replaced with nonpeptide thiols. These were generally prepared in manners analogous to the synthesis of natural leukotrienes, that is, the reaction of the appropriate thiol with LTA₄ or analogous epoxides. In many cases these compounds have only

been reported as part of the patent literature, and little information is available as to their relative biological activity. Suntory chemists⁴¹ prepared a number of analogs using aryl and heterocyclic-thiols (**96–99**) which, except for a 2,5-dimercapto-1,3,4-thiadiazole adduct (**97**) (which retained 10% of the agonist activity of LTD₄), generally lost all activity (Scheme 5.31).



Scheme 5.31. Nonpeptide 6-substituted analogs of LTD₄.

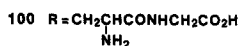
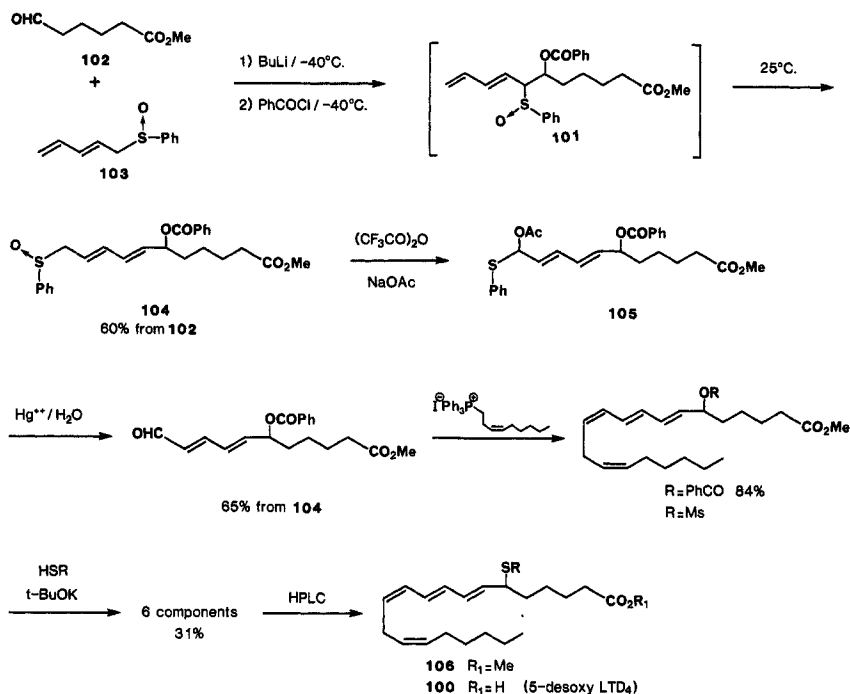
5-Desoxy LTD₄

For purposes of further structure–activity studies, Corey and Hoover have carried out a total synthesis of the 5-desoxy analog of LTD₄ (**100**).⁴² As outlined in Scheme 5.32, when **101** formed *in situ* from **102** and the lithium derivative of **103** was allowed to warm to room temperature, it underwent a double [3,2]-sigmatropic rearrangement to the terminal sulfoxide **104**. After conversion of **104** to **105** by a Pummerer reaction, the full carbon skeleton was assembled by a Wittig reaction. Mesylation and reaction with the potassium salt of *N*-TFA-cysgly-Me gave rise to six compounds in a combined yield of 31%, in sharp contrast to the numerous condensations already described with the epoxide as the leaving group, in which very clean S_N2 displacement occurs. Two of the compounds

were found to be the diastereomeric pair of the desired structure **106**, although the absolute configuration at C-6 was not established. Hydrolysis then yielded the two isomers of **100**, 5-desoxy LTD₄. Both isomers showed less than 1% of the contractile activity of LTD₄ on the guinea pig ileum and parenchymal strips, demonstrating the importance of the C-5 hydroxyl group to biological potency.

B. Analogs of LTB₄

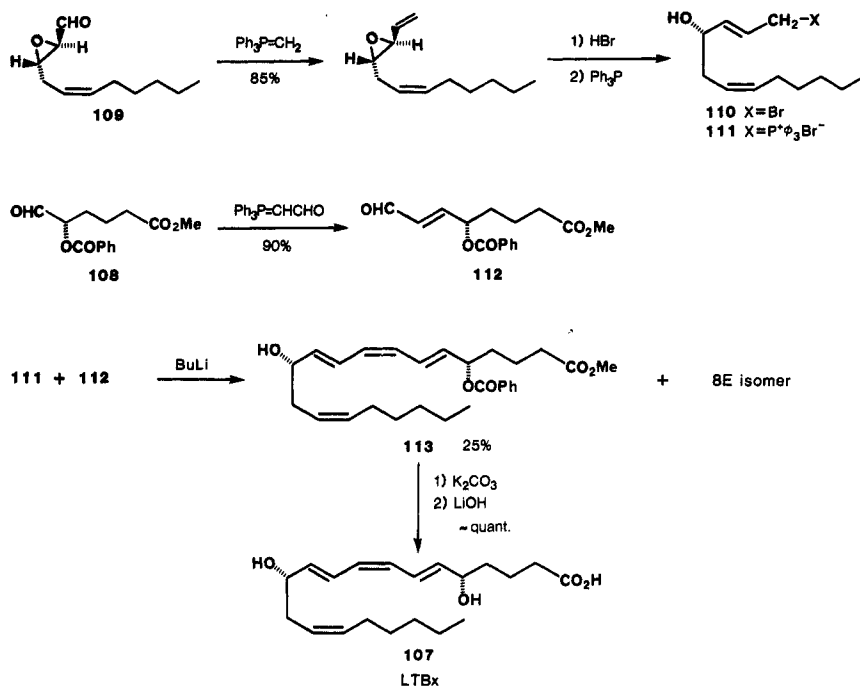
In contrast to the large body of work published on analogs of LTA₄ and the contractile leukotrienes (C₄, D₄, and E₄), relatively little has been reported on analogs of LTB₄.



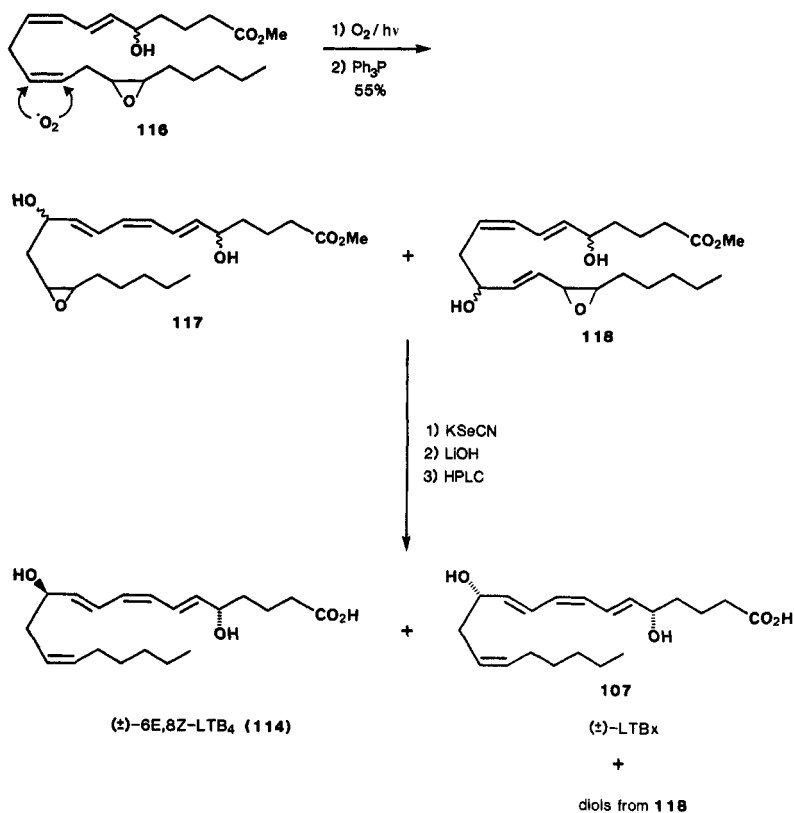
Scheme 5.32. Synthesis of 5-desoxy-LTD₄.

(1) Stereoisomers of LTB_4

Several research groups have, however, prepared stereoisomers and positional isomers of LTB_4 to better understand the structural requirements of biological activity. Two groups have reported total syntheses of LTB_x [5*S*,12*S*-6,10*E*,8,14*Z*]-dihydroxyeicosatetraenoic acid] **107**, a naturally occurring LTB_4 isomer derived from a double lipoxygenation of arachidonic acid (see Scheme 1.4). Corey and co-workers⁴³ prepared the compound in two parts, using the LTB_4 precursor methyl (5*S*)-benzoyloxy-5-formylpentanoate (**108**, see Scheme 3.7), to provide C-1 to C-6. The C-9 to C-20 portion was derived from the previously reported LTB_4 synthon⁴⁴ (2*S*,3*R*)-2,3-epoxy-(5*E*)-undecen-1-al (**109**), via C-1 homologation with methylenetriphenylphosphorane and HBr-induced rearrangement and reaction with the resulting allylic bromide **110** with triphenylphosphine to provide the desired Wittig reagent **111**. Wittig coupling with the C-1 to C-8 aldehyde synthon **112** gave a mixture of isomers of the protected DiHETEs **113**, which after separation and hydrolysis gave the desired LTB_x (**107**) in modest yield (Scheme 5.33).

Scheme 5.33. Synthesis of LTB_x .

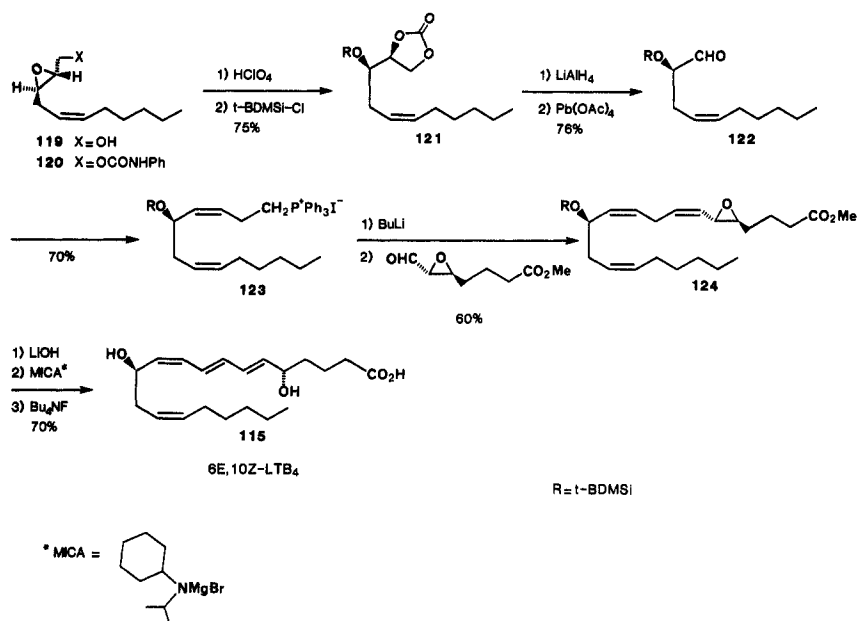
In another report Corey and co-workers⁴⁵ prepared ($\pm$)-LTB_x (**107**) as well as ($\pm$)-(6*E*,8*Z*)-LTB₄ (**114**) and (6*E*,10*Z*)-LTB₄ (**115**). The former two isomers were prepared as shown in Scheme 5.34. The synthesis relied on singlet oxygen addition to the epoxy alcohol **116**, which provided a mixture of epoxy diols (**117** and **118**). Reductive removal of two epoxides of the mixture and subsequent hydrolysis of the ester gave a mixture of racemic LTB_x (**107**) and its 12-*epi*-isomer (**114**).



Scheme 5.34. Synthesis of ($\pm$)-(6*e*,8*Z*)-LTB₄ and ($\pm$)-LTB_x.

Corey prepared the (6*E*,10*Z*)-LTB₄ (**115**) from the previously described epoxy alcohol LTB₄ synthon **119**. Acid-catalyzed rearrangement of the derived phenylcarbonate **120** followed by protection, reductive cleavage of the vicinal carbonate, and cleavage of the resulting diol gave (2*R*)-*t*-butyldimethylsilyloxy-

(4*E*)-decen-1-al (**122**), which was elaborated to the protected triene epoxy alcohol **124**. MICA (Scheme 4.4) catalyzed rearrangement and deblocking gave the (6*E*,10*Z*)-LTB₄ (**115**) (Scheme 5.35).



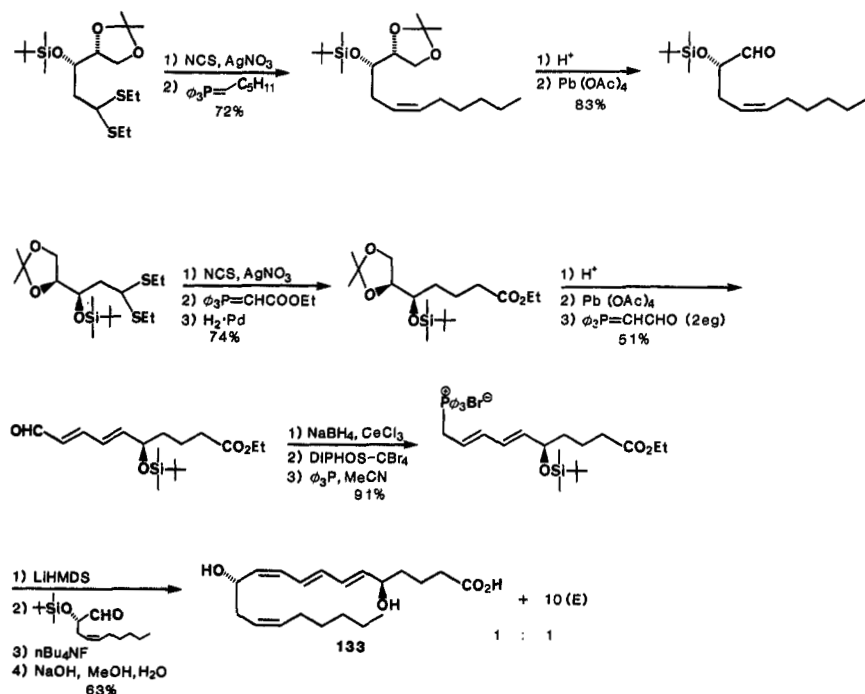
Scheme 5.35. Synthesis of (6*E*,10*Z*)-LTB₄.

The Merck Frosst group has prepared LTB_x (**107**) by a novel route where the key synthon, methyl (6*E*,8*Z*)-10-bromo-6-*t*-butyldimethylsilyloxydecadieneoate (**125**), previously used in the synthesis of 5-HETE,⁴⁶ was converted to the phosphonium salt **126** and reacted with the LTB₄ synthon (2*R*)-*t*-butyldimethylsilyloxy-(4*E*)-decen-1-al (**127**)⁴⁷ to provide a 3:1 mixture of the (10*E*)- and (10*Z*)-adducts **128** and **129**. The unusual preponderance of the *trans*-isomer was attributed to steric hindrance in the normal kinetically favored *erythro* betaine caused by the bulky α -siloxy function (Scheme 5.36).

Both (12*R*)- and (12*S*,6*E*)-LTB₄ (**130**, **131**) are the products of nonenzymatic hydrolysis of LTA₄. They were prepared by Corey and co-workers⁴³ from a common intermediate for the C-1 to C-10 portion (**132**) and from the (+) and (−) forms of malic acid (Scheme 5.37).

Fitzsimmons and co-workers at Merck Frosst prepared (5*R*,12*S*)-dihydroxy-(6,8*E*,10,14*Z*)-eicosatetraenoic acid (**133**), the 5,12-diHETE isomer with the

central triene portion identical to that in LTB_4 , but with the C-1 to C-4 and C-12 to C-20 portions interchanged.⁴⁸ Such a product had been postulated as a possible product of the LTB_4 synthetase enzyme acting on 11,12- LTA_4 . The material, however, showed no biological activity when compared with LTB_4 ⁴⁹ (Scheme 5.38).

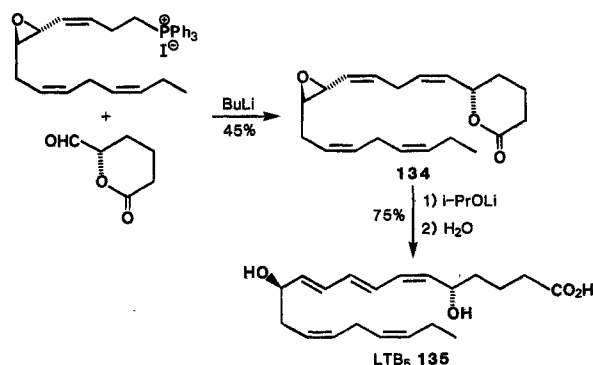


Scheme 5.38. Synthesis of (5*R*,12*S*)-dihydroxy-(6,8*Z*,10,14*E*)-eicosatetraenoic acid.

Lewis et al.⁵⁰ have reported the structural requirements for LTB_4 -like biological activity, measuring *in vitro* neutrophil chemotaxis, as well as guinea pig pulmonary parenchymal strip contractions. Of six stereoisomers studied, *c,t,t*(5*S*,12*R*), *t,c,t*(5*S*,12*S*) and $-(5*R*,12*R*)$, *t,t,c*(5*S*,12*R*), *t,t,t*(5*S*,12*R*), and *t,t,t*(5*S*,12*R*), only the natural stereochemistry isomer 6*c*,8*t*,10*t*(5*S*,12*R*) had significant biological activity. Sirois and co-workers⁵¹ have reported similar findings. Fitzsimmons and Rokach⁵² prepared six analogs of 8,15-dihydroxy-5,9,11,13-eicosatetraenoic acid, possible products analogous to LTB_4 which could be derived from the action of 15-lipoxygenase on arachidonic acid. The synthesis of these analogs is described in Section 4. None of these isomers had significant biological activity.

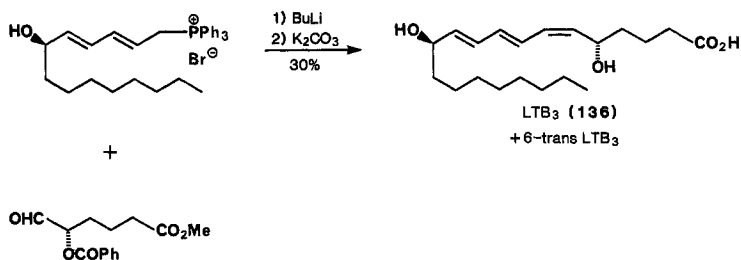
(2) *LTB₅ and LTB₃*

LTB₅ (**135**) has been prepared biosynthetically from eicosapentaenoic acid (EPA)^{16,53} and by total synthesis.⁵⁴ The synthesis was analogous to Corey's previous *LTB₄* synthesis,⁵⁵ with the key step being the potassium isopropoxide catalyzed rearrangement of the epoxy lactone **134** (Scheme 5.39).

Scheme 5.39. Synthesis of *LTB₅*.

LTB₅ has been found to be considerably less active than *LTB₄* both as a chemotactic (one-eighth) and aggregating agent (one-twentieth).

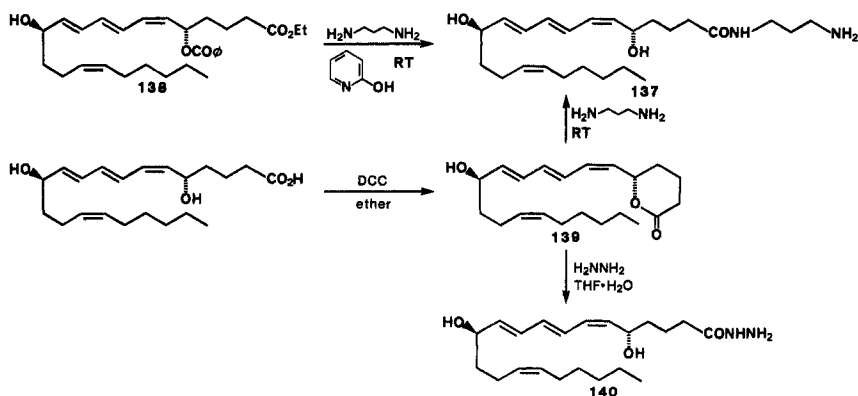
In contrast, *LTB₃* (**136**), recently prepared by Zamboni,⁵⁶ has been shown to be essentially equiactive with *LTB₄*.⁵⁶ However, in spite of its activity, it appears that *LTA₃* is only poorly converted to *LTB₃* by the *LTB₄* synthetase enzyme. The *LTB₃* synthesis was directly parallel to the corresponding *LTB₄* synthesis of Zamboni et al.⁴⁷ (Scheme 5.40). A synthesis of *LTB₃* has also been reported by Spur.⁵⁷

Scheme 5.40. Synthesis of *LTB₃*.

(3) *LTB₄ Amides*

LTB₄ dimethyl amide was prepared from LTB₄ by aminolysis of the corresponding methyl ester.⁵⁸ The compound is reported to be an antagonist of LTB₄-induced neutrophil degranulation.

Young and co-workers⁵⁹ prepared the 3-aminopropylamide of LTB₄ (LTB₄-APA) (**137**) from either **138**, the 5-benzoyloxy ethyl ester synthetic precursor of LTB₄, or from LTB₄ δ -lactone **139**. The LTB₄-APA was used as a reactive intermediate in the preparation of protein conjugates of LTB₄, which are used in the development of a radioimmunoassay for LTB₄ and of fluorescent probes in characterizing the LTB₄ receptor on human leucocytes.⁶⁰ LTB₄-APA (**137**) has been shown to possess about 1% of the aggregating activity of natural LTB₄.⁶¹ The same workers have also prepared LTB₄ hydrazide (**140**) by reaction of LTB₄ δ -lactone with hydrazine (Scheme 5.41).⁵⁹



Scheme 5.41. Synthesis of LTB₄- α -aminopropylamide and LTB₄ hydrazide.

REFERENCES

1. (a) Baker, S.R.; Jamieson, W.B.; Osborne, D.J.; Ross, W.J. *Tetrahedron Lett.* **1981**, 22, 2505. (b) Baker, S.R.; Jamieson, W.B.; McKay, S.W.; Morgan, S.E.; Rackham, D.M.; Ross, W.J.; Shrubsall, P.R. *Tetrahedron Lett.* **1980**, 21, 4123.
2. Corey, E.J.; Niwa, H.; Falck, J.R.; Mioskowski, C.; Arai, Y.; Marfat, A.; In *Advances in Prostaglandin and Thromboxane Research*, Samuelsson, B.; Ramwell, P.W.; Paoletti, R. Eds.; Raven: New York, 1980; Vol. 6, p.19.
3. Rokach, J.; Young, R.N.; Kakushima, M.; Lau, C.K.; Seguin, R.; Frenette, R.; Guindon, Y. *Tetrahedron Lett.* **1981**, 22, 979.
4. Atrache, V.; Pai, J.-K.; Sok, D.-E.; Sih, C.J. *Tetrahedron Lett.* **1981**, 22, 3443.
5. Ernest, I.; Main, A.J.; Menasse, R. *Tetrahedron Lett.* **1982**, 23, 167.
6. Spur, B.; Jendralla, H. *Arch. Pharm. (Weinheim)* **1984**, 317, 651.

7. Drazen, J.M.; Lewis, R.A.; Austen, K.F.; Toda, M.; Brion, F.; Marfat, A.; Corey, E.J.; *Proc. Natl. Acad. Sci. USA*. **1981**, *78*, 3195.
8. Spur, B.; Falsone, G.; Crea, A.; Peters, W.; Koenig, W. *Arch. Pharm. (Weinheim)* **1983**, *316*, 789.
9. Okuyama, S.; Miyamoto, S.; Shimoji, K.; Konishi, Y.; Fukushima, D.; Niwa, H.; Arai, Y.; Toda, M.; Hayashi, M. *Chem. Pharm. Bull.* **1982**, *30*, 2453.
10. Young, R.N.; Kakushima, M.; Frenette, R.; unpublished results.
11. Hammarstroem, S.; In *SRS-A and Leukotrienes*, Piper, P.J. Ed.; Research Studies Press: Chichester, 1981; p. 235.
12. Hammarstroem, S. *J. Biol. Chem.* **1981**, *256*, 2275.
13. Young, R.N.; Coombs, W.; Guindon, Y.; Rokach, J.; Ethier, D.; Hall, R. *Tetrahedron Lett.* **1981**, *22*, 4933.
14. Hammarstroem, S. *J. Biol. Chem.* **1980**, *255*, 7093.
15. Spur, B.; Crea, A.; Peters, W.; Koenig, W. *Arch. Pharm. (Weinheim)* **1984**, *317*, 280.
16. Lee, T.H.; Mencia-Huerta, J.M.; Shih, C.; Corey, E.J.; Lewis, R.A.; Austen, K.F. *J. Biol. Chem.* **1984**, *259*, 2383.
17. Spur, B.; Crea, A.; Peters, W.; Koenig, W. *Arch. Pharm. (Weinheim)* **1983**, *316*, 968.
18. Tolstikov, G.A.; Miftakhov, M.S.; Tolstikov, A.G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1983**, 1452 (C.A. *99*, 158112S).
19. Young, R.N.; Champion, E.; Gauthier, J.Y.; Jones, T.R.; Leger, S.; Zamboni, R.; *Tetrahedron Lett.*, **1986**, *27*, 539.
20. Guindon, Y.; Zamboni, R.; Lau, C.K.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 739.
21. Corey, E.J.; Clark, D.A. *Tetrahedron Lett.* **1980**, *21*, 3547.
22. Corey, E.J.; Goto, G.; Marfat, A. *J. Am. Chem. Soc.* **1980**, *102*, 6607.
23. Baker, S.R.; Boot, J.R.; Morgan, S.E.; Osborne, D.J.; Ross, W.J.; Shrubbsall, P.R. *Tetrahedron Lett.* **1983**, *24*, 4469.
24. Hammarstroem, S. *J. Biol. Chem.* **1981**, *256*, 7712.
25. Gleason, J.G.; Ku, T.W.; McCarthy, M.E.; Weichman, B.M.; Holden, D.; Osborn, R.R.; Zabko-Potapovich, B.; Berkowitz, B.; Wasserman, M.A. *Biochem. Biophys. Res. Commun.* **1983**, *117*, 732.
26. Spur, B.; Crea, A.; Peters, W.; Koenig, W.; *Arch. Pharm. (Weinheim)* **1984**, *317*, 647.
27. Corey, E.J.; Park, H.; Barton, A.; Nii, Y.; *Tetrahedron Lett.* **1980**, *21*, 4243.
28. Spur, B.; Crea, A.; Peters, W.; Koenig, W.; *Arch. Pharm. (Weinheim)* **1984**, *317*, 84.
29. Nicolaou, K.C.; Petasis, N.A.; Seitz, S.P.; *J. Chem. Soc. Chem. Commun.* **1981**, 1195.
30. Arai, Y.; Konno, M.; Shimoji, K.; Konishi, Y.; Niwa, H.; Toda, M.; Hayashi, M. *Chem. Pharm. Bull.* **1982**, *30*, 379.
31. Rokach, J.; Hamel, P.; unpublished results.
32. Koshihara, Y.; Murota, S.; Nicolaou, K.C.; In *Advances in Prostaglandin, Thromboxane and Leukotriene Research*, Samuelsson, B.; Paoletti, R.; Ramwell, P.W. Eds. Raven: New York, 1983; Vol. 11, p. 163.
33. Koshihara, Y.; Murota, S.; Petasis, N.A.; Nicolaou, K.C. *FEBS Lett.* **1982**, *143*, 13.
34. Tolstikov, G.A.; Miftakhov, M.S.; Tolstikov, A.G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1983**, 1451 (C.A. *99*, 158079m).
35. Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1983**, *24*, 331.
36. Patterson, J.W.; Murthy, D.V.K. *J. Org. Chem.* **1983**, *48*, 4413.

37. Ohnishi, H.; Kosuzume, H.; Kitamura, Y.; Yamaguchi, K.; Nobuhara, M.; Suzuki, Y.; *Prostaglandins* **1980**, *20*, 655.
38. (a) Girard, Y.; Larue, M.; Jones, T.R.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 1023. (b) Denis, D.; Charleson, S.; Rackham, A.; Girard, Y.; Larue, M.; Jones, T.R.; Ford-Hutchinson, A.W.; Cirino, M.; Rokach, J. *Prostaglandins*, **1982**, *24*, 801.
39. Lewis, R.A.; Drazen, J.M.; Austen, K.F.; Toda, M.; Brion, F.; Marfat, A.; Corey, E.J. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 4579.
40. Bernstein, P.R.; Krell, R.D.; Snyder, D.W.; Lee, Y.K. *Tetrahedron Lett.* **1985**, *26*, 1951.
41. Cho, H.; Ueda, M.; Funahashi, K.; Koda, K.; *Chem Pharm. Bull.* **1983**, *31*, 3326.
42. Corey, E.J.; Hoover, D.J.; *Tetrahedron Lett.* **1982**, *23*, 3463.
43. Corey, E.J.; Marfat, A.; Hoover, D.J.; *Tetrahedron Lett.* **1981**, *22*, 1587.
44. Corey, E.J.; Marfat, A.; Munroe, J.; Kim, K.S.; Hopkins, P.B.; Brion, F.; *Tetrahedron Lett.* **1981**, *22*, 1077.
45. Corey, E.J.; Hopkins, P.B.; Munroe, J.E.; Marfat, A.; Hashimoto, S.; *J. Am. Chem. Soc.* **1980**, *102*, 7986.
46. Rokach, J.; Guindon, Y.; Zamboni, R.; Lau, C.K.; Girard, Y.; Larue, M.; Perry, R.A.; Atkinson, J.G.; In Abstract Bulletin, 16th Middle Atlantic Regional Meeting (ACS), No. 276, April, 21–23, 1982.
47. Zamboni, R.; Rokach, J.; *Tetrahedron Lett.* **1982**, *23*, 2631.
48. Fitzsimmons, B.J.; Rokach, J.; unpublished results.
49. Evans, J.; Nathaniel, D.; unpublished results.
50. Lewis, R.A.; Goetzl, E.J.; Drazen, J.M.; Soter, N.A.; Austen, K.F.; Corey, E.J.; *J. Exp. Med.* **1981**, *154*, 1243.
51. Sirois, P.; Roy, S.; Borgeat, P.; Picard, S.; Corey, E.J.; *Biochem. Biophys. Res. Commun.* **1981**, *99*, 385.
52. Fitzsimmons, B.J.; Rokach, J.; *Tetrahedron Lett.* **1984**, *25*, 3043.
53. Murphy, R.C.; Pickett, W.C.; Culp, B.R.; Lands, W.E.M.; *Prostaglandins* **1981**, *22*, 613.
54. Corey, E.J.; Pyne, S.G.; Su, W.G.; *Tetrahedron Lett.* **1983**, *24*, 4883.
55. Corey, E.J.; Marfat, A.; Munroe, J.; Kim, K.S.; Hopkins, P.B.; Brion, F.; *Tetrahedron Lett.* **1981**, *22*, 1077.
56. Evans, J.; Zamboni, R.; Nathaniel, D.; Léveillé, C.; Ford-Hutchinson, A.W.; *Prostaglandins*, **1985**, *30*, 981.
57. Spur, B.; Crea, A.; Peters, W.; Koenig, W.; *Arch. Pharm. (Weinheim)* **1985**, *318*, 225.
58. Showell, H.J.; Otterness, I.G.; Marfat, A.; Corey, E.J.; *Biochem. Biophys. Res. Commun.* **1982**, *106*, 741.
59. Young, R.N.; Zamboni, R.; Rokach, J.; *Prostaglandins* **1983**, *26*, 605.
60. Rokach, J.; Hayes E.C.; Girard, Y.; Lombardo, D.L.; Maycock, A.L.; Rosenthal, A.S.; Young, R.N.; Zamboni, R.; Zweerink, H.J.; *Prostaglandins, Leukotrienes Med.* **1984**, *13*, 21.
61. Young, R.N.; Charleson, S.; Evans, J.; Léveillé, C.; Maurice, P.; Nathaniel, D.; unpublished results.

CONCLUSION

The synthesis of the major lipoxygenase-derived products arising from arachidonic acid has now been achieved. A number of the minor components and secondary metabolites of the leukotrienes will undoubtedly be synthesized in the near future, particularly those for which important biological properties may be found.

The synthetic availability of the compounds outlined in this review, especially of LTB₄, LTC₄, LTD₄, and LTE₄, is already proving to be of great value in two major broad areas of investigation. Because of the difficulty of isolating the pure compounds in reasonable amounts, it has been slow work to study and evaluate the actions of these powerful agents in a variety of biological systems. But with the pure synthetic compounds in hand, progress is being rapidly made toward a greater understanding of their functions.⁶⁹

A second major area in which the ready availability of the leukotrienes will undoubtedly prove of great value is in the discovery and development of new drug entities for the treatment of a variety of disease states. The leukotrienes have long been implicated in allergy and inflammation,^{69b} and it seems safe to say that they will be found to play important roles in a variety of other disorders.^{69d} Thus the development of drugs that stimulate, inhibit, or modulate their activities will hopefully prove useful in the treatment or cure of some of these disorders, and the ready accessibility of the pure leukotrienes by synthesis will facilitate the task of the pharmacologist and the medicinal chemist to discover agents that modify their action.

The Synthesis of Monoterpenes 1980–1986

ALAN F. THOMAS

Research laboratory, Firmenich SA, Geneva, Switzerland

YVONNE BESSIÈRE

Borex, Switzerland

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Acknowledgments

References

1. INTRODUCTION

Since the appearance of our earlier chapters on the synthesis of monoterpenes,¹ there has been a renewal of activity in the field. One of the reasons for a heightened interest in monoterpenes in general is because the realization that plants emit very large amounts of volatile materials (more than 70% of the species of trees in North America emit appreciable quantities of hydrocarbons²) has led to a discussion about the fate of these volatile substances, most of which are monoterpenes or isoprene. One study has considered the effect of atmospheric ozone on the isoprene and α -pinene (1–10 ppb) of the forests, discussing the possible consequences of the peroxides and ozonides formed.³ In Australia, the major volatile constituent of the wooded areas is 1,8-cineole from the eucalyptus trees, and some consideration has been given to the chlorination of cineole, which was surmised might occur in chlorinated swimming pools. In fact, it was not possible to detect any of the chlorinated cineoles.⁴ A third, and to some the most far-fetched example of thought along these lines, is the possibility that volatile substances given off by trees under attack by leaf predators could give information to other trees that attack is likely.⁵ This idea of “talking trees” has given rise to further work supporting⁶ and refuting⁷ it, but the voices of the trees are so far not loud enough to convince everybody that they are talking.^{8*}

The close relationship between monoterpenes and insects is, of course, well known, and work has intensified on what attracts, say, bark beetles to appropriate trees. One of the most intriguing aspects is the potentiating effect ethanol has on the aggregation of certain species when in conjunction with the pheromone.⁹ This aspect has little to do with total synthesis, but the discovery of new pheromones and defense secretions certainly has. Many are described in this chapter, but one of the more unusual types is the new cyclopentane structure found by Eisner and Meinwald in pheromones of certain carrion beetles, the synthesis of which is described in the appropriate section (Section 6).¹⁰

Epstein et al. have found a novel skeleton, rothrockane, in an *Artemisia* species (see Section 5.D), these species being already associated with irregular monoterpenoids.

The popular misconceptions about “natural” and “synthetic” products, widely disseminated by the press, have led to a desire to be able to distinguish between the two. This has not yet had much impact on the total synthesis of monoterpenoids; most analysts consider that the optical activity is sufficient measure to determine a “natural.” Nevertheless, a team under G.J. Martin in France has been studying the very small differences in site-specific isotope ratios of natural products, and claim to be able to distinguish not only the differences between, say, synthetic and natural vanillin, but, by using the different isotope

* We are grateful to Dr. P. Greig-Smith for having drawn our attention to the publications quoted in this respect.

ratios found in different regions for ethanol from the transformation of glucose to ethanol, to be able to correlate the geographic origin of wine with the isotope ratio found in its alcohol molecules. One of the first contacts with the monoterpenes that this work has created is mentioned in the section of the bicyclo[3.1.1]heptanes.

Another reason for the increase in interest in monoterpene synthesis is caused by the use of chiral monoterpenes as synthetic auxiliaries. This has led to the study of the chiral synthesis of some monoterpenoids, which is discussed in the relevant sections.

This chapter is organized similarly to the previous ones,¹ although there are some differences within the sections. It does not include topics discussed elsewhere in these volumes (such as ionones, phenolic monoterpenoids, and pheromones that are not directly monoterpenoid).

In the case of monoterpenoids, there must always be an element of personal judgment about what is to be included. Although use of a new reagent to reduce camphor to borneol is undoubtedly the synthesis of a natural product, its inclusion in this chapter would not be likely. On the other hand, if the hydroxylation of a double bond were to produce a newly described glycol, even though the transformation were well-known, we would include it. Between these extremes, there are clearly “twilight” cases that are not easily decided.

Since our last chapter was published,^{1b} there has been only one Specialist Report on monoterpenoids,¹¹ volumes 10 and 11 of this series lacking the monoterpenoid chapter; there have been two subsequent reviews in the journal that replaces the Specialist Periodical Reports.¹² An excellent compendium of naturally occurring monoterpenoids has been published,¹³ as well as a number of other reviews of a more specific nature, for example, on insect pheromones,¹⁴ on microbial transformations of terpenoid compounds,¹⁵ and on particular monoterpenoid skeletons, which are mentioned in the relevant sections of this chapter. The major publication that has appeared since our last chapter is the two-volume handbook of Erman;¹⁶ this contains all the relevant literature up to about 1977 on monoterpenoids, including their synthesis.

We hope that the literature is reasonably complete up to late 1986.

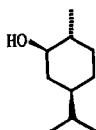
As in the earlier volume, we draw attention to the following errata. Errata to Chapter 1, Volume 2 (see also Vol. 4, p. 453):

- p. 97 Formula **246** is γ -terpineol, not α -.
- p. 182 Ref. 273. The journal should be *J. Am. Chem. Soc.*
- p. 184 Ref. 320. The page number should be 1945.

Errata to Chapter 5, Volume 4:

- p. 475 Line 4 from bottom; for “Christon” read “Christou,” and correct Ref. 180 similarly.

- p. 486 Bottom line. "The aldehyde **239** . . ." actually refers to the *cis*-aldehyde corresponding to formula **235**; **239** is a totally different substance shown on p. 488.
- p. 504 Bottom line. For "Schetter," read "Schletter." and correct Ref. 329 similarly.
- p. 512 The formula for (*S*)-**385** lacks a double bond.
- p. 513 Line 2. (–)-(1*R*,2*R*,4*R*)-carvomenthol is not formula **389** but



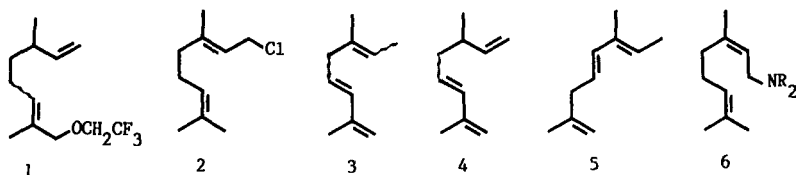
- p. 516 Line 4 from bottom; for *trans* read *cis*.
- p. 534 Line 8; violacene is formula **553**, not **533**.
- p. 542 and heading of p. 543 For "bicyclo[3.1.0]heptane" read ". . . hexane."
- p. 570 Ref. 121; one author is Katzenellenbogen.
- p. 584 Ref. 533; for "Weiter" read "Weiler."

2. TERPENE SYNTHESIS FROM ISOPRENE

There are three reviews of the use of isoprene in terpene synthesis,^{17,18} one of which¹⁸ is in Japanese. There is also an excellent review of the industrial synthesis of isoprene from isobutylene and formaldehyde which also mentions other isoprene syntheses.¹⁹

The dimerization of isoprene, particularly whether head-to-tail or tail-to-tail dimers are formed, has been reviewed by Keim et al.²⁰ Such dimerizations occur in the presence of a nucleophile and a Pd⁰ catalyst. The reaction may be accelerated by the use of ultrasound,²¹ but generally, tail-to-tail dimers are favored. A few conditions have been found that favor the naturally occurring, head-to-tail skeleton. Behr and Keim have shown that use of trifluoroethanol as the nucleophile resulted in a majority of the ethers **1**,²² while the C₁₀ fraction from the telomerization of isoprene with its chlorides yielded up to 54% of geranyl chloride (**2**).²³ Using a more complex Pd catalyst, up to 80% head-to-tail dimers **3** and **4** have been reported.²⁴ Titanium catalysts with diethylaluminum chloride also yielded a majority of 2,6-dimethylocta-1,4,6-triene (**5**).²⁵

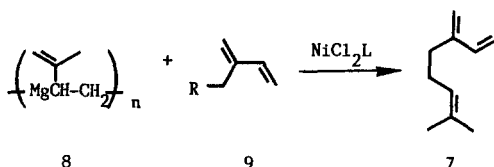
Further studies on the palladium-catalyzed telomerization of isoprene with diethylamine have appeared, one containing the synthesis of a new head-to-head dimer.²⁶ The butyllithium-catalyzed dimerization in the presence of dimethylamine (or diethylamine) remains the best method for preparing



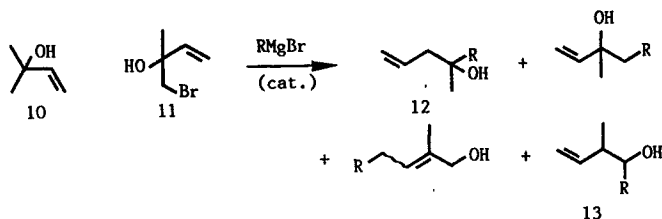
dialkylnerylamines (6) stereoselectively.²⁷ Sodium in the presence of a secondary amine gave myrcene (7), selectively depending on the polar properties of the amine.²⁸

Cyclic dimers of isoprene are also well known, but mostly they do not have naturally occurring skeletons, a Pd^0 catalyst in tetrahydrofuran, for example, yields only 21% of dipentene.²⁹

Isoprene was metalated efficiently with potassium *tert*-butoxide and lithium 2,2,6,6-tetramethylpiperidide,³⁰ and this could lead to synthesis of monoterpenes having a 3-methylene-1-butene unit. Use of isoprene as a 2-methyl-2-butene unit was carried out by direct reaction of magnesium with isoprene,³¹ then the organometallic **8** was treated under various conditions with 2-chloromethyl-1,3-butadiene (**9**, $\text{R} = \text{Cl}$). With nickel catalysts, high yields of myrcene (**7**) were reported.³²

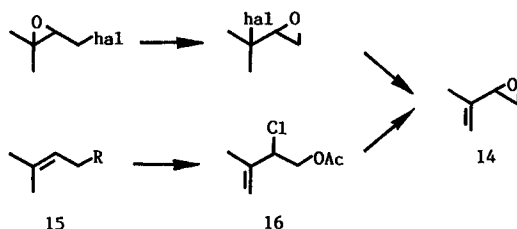


Functionalization of isoprene was discussed earlier (Vol. 4, p. 454) and we mention the continuation of Huisman's studies on the 1,4-addition of sulfonyl chlorides to isoprene,³³ as well as another 1,4-addition of PhSeH .³⁴ Isoprene could also add water, yielding the synthon 2-methyl-3-buten-2-ol (**10**) on treatment of its bis(cyclopentadienyl)zirconium complex with hydrogen peroxide.³⁵ 4-Substituted 2-methyl-2-butenols were obtained from isoprene epoxide and organolithium reagents, added base favoring the production of (*Z*)-isomerism about the double bond.³⁶ Another type of potentially monoterpenoid alcohol was obtained when the bromohydrin **11** (from isoprene and aqueous *N*-bromosuccinimide) reacted with Grignard reagents in the presence of various catalysts. Of the products (Scheme 1), **12** was obtained almost exclusively with Pd^0 , while a CoCl_2 catalyst yielded up to 40% of **13**.³⁷



Scheme 1

Isoprene epoxidized on the vinyl group (1,2-epoxy-3-methyl-3-butene, **14**) would also be an attractive synthon for monoterpenoids if it were more readily accessible. Among the possible preparative methods (Scheme 2), acid-catalyzed isomerization of 2,3-epoxy-1-halo-3-methylbutanes (epoxidized prenyl halides) and dehydrohalogenation of the resulting isomers³⁸ seemed the best route until chlorination of prenyl acetate (**15**, $\text{R} = \text{OAc}$) with hypochlorous acid was published. Dehydration of the mixture of products gave a maximum of the chloroacetate **16**, which yielded the epoxide **14** with sodium hydroxide in methanol.³⁹



Scheme 2

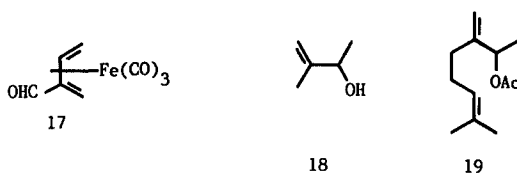
A new isoprene is 2-methylene-3-butenal stabilized as the tricarbonyliron complex **17**, and prepared from isoprene. This has been resolved and reaction with organolithium compounds and cuprates showed inversed diastereoselection.⁴⁰

3. 2,6-DIMETHYLOCTANE DERIVATIVES

A. Hydrocarbons

Since our last survey,^{1b} a few methods for joining prenyl bromide (**15**, $\text{R} = \text{Br}$) directly to 2-bromomethyl-1,3-butadiene (**9**, $\text{R} = \text{Br}$, available from isoprene)

have appeared. Using a bis(cyclooctadienyl)nickel complex, Hegedus et al. obtained myrcene (**7**) in 46% yield.⁴¹ This is, of course, not useful for myrcene, but modifications were used to make other compounds, including ipsenol (see below, **83**). Similar coupling between **15** ($R = \text{Br}$) and **9** ($R = \text{Br}$) has been reported to occur using magnesium oxide in ether⁴² or nickel carbonyl.^{43*} Coupling between **9** ($R = \text{Br}$) and the trimethylstannane **9** ($R = \text{SnMe}_3$) occurred in 94% yield in the presence of zinc chloride in tetrahydrofuran.⁴⁴ More complex is the metalation of 3-methyl-3-buten-2-ol (**18**), the dilithium derivative of which reacted with prenyl bromide (**15**, $R = \text{Br}$) to give, after acetylation with acetyl chloride, the nonnatural acetate **19**. This could be converted to myrcene (**7**) by heating with triethylamine in toluene in the presence of a palladium catalyst.⁴⁵

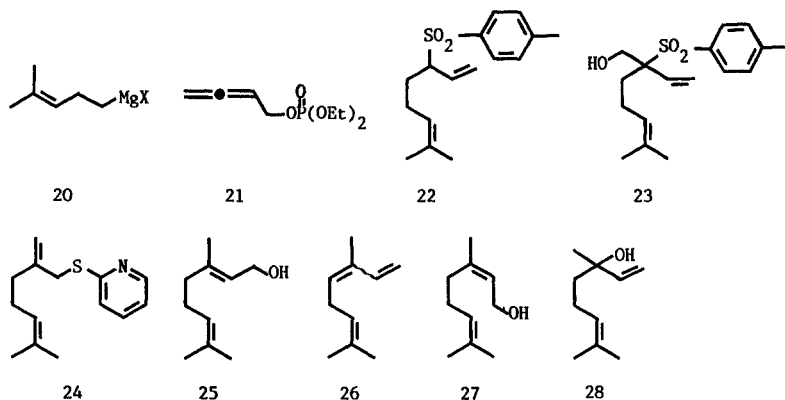


Syntheses of the $C_6 + C_4$ type include reaction of 4-methyl-3-pentylmagnesium halide (**20**) with the phosphate **21**,⁴⁶ or reaction of a copper–magnesium compound corresponding to **20** with a methyl sulfone corresponding to **21**.⁴⁷ Two $C_9 + C_1$ syntheses of myrcene have also been described. One involves use of an activating sulfone group in compound **22** (made by alkylating allyl tolyl sulfone). Metalation with butyllithium enabled formaldehyde to be added, and the resulting alcohol **23** was treated with tributyltin hydride.⁴⁸ The other synthesis involved introduction of the C_1 unit using $n\text{-Bu}_3\text{SnCH}_2\text{I}$ on the metalated C_9 compound **24**.⁴⁹

Conversion of C_{10} alcohols and their derivatives specifically to a single hydrocarbon is still a problem, which a few results will illustrate. Geraniol (**25**) was dehydrated with copper sulfate in 125° to myrcene (**7**) in 25% yield.⁵⁰ Carbodiimides yielded myrcene (**7**) and the two ocimenes (**26**) with geraniol (**25**), while nerol (**27**) gave only cyclic products. Linalool (**28**) gave mostly myrcene under these conditions.⁵¹ With propargylzinc bromide and 5% $\text{Pd}(\text{PPh}_3)_4$ in tetrahydrofuran, Matsushita and Negishi report that geranyl acetate (**25** acetate) gave only the ocimenes (**26**, (E)/(Z) = 75:25), while neryl acetate (**27** acetate) yielded exclusively myrcene (**7**).⁵²

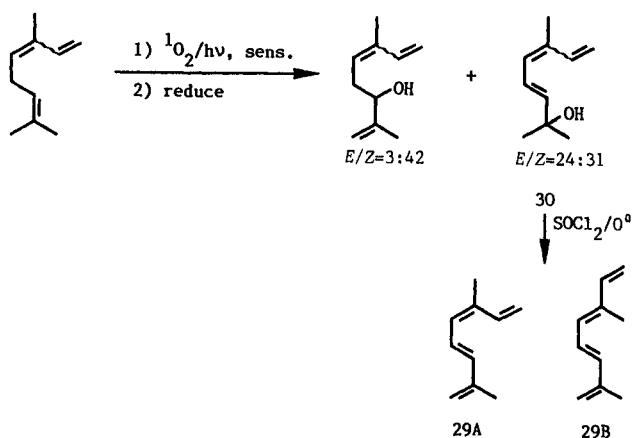
Myrcene labeled with deuterium in the methyl groups has been synthesized.⁵³

* The formula given for nickel carbonyl in *Chem. Abstr.*⁴³ is unlikely.

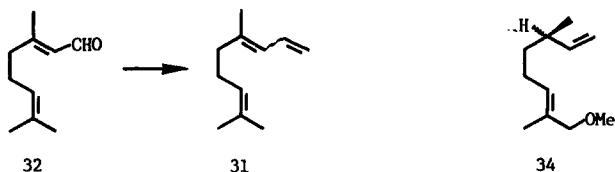


The cosmenes (2,6-dimethyl-1,3,5,7-octatetraenes, **29A**, **29B**) have been synthesized from the ocimenes (**26**). Singlet oxygen followed by reduction of the hydroperoxides obtained yielded a mixture of trienols (Scheme 3), from which the naturally occurring ocimenols (**30**, see below) could be dehydrated with thionyl chloride at 0°. ⁵⁴

Two isomers of a "homocimene" (**31**), were isolated from cardamom oil by Maurer et al. They were synthesized simply by Wittig reaction on citral (**32**). ⁵⁵

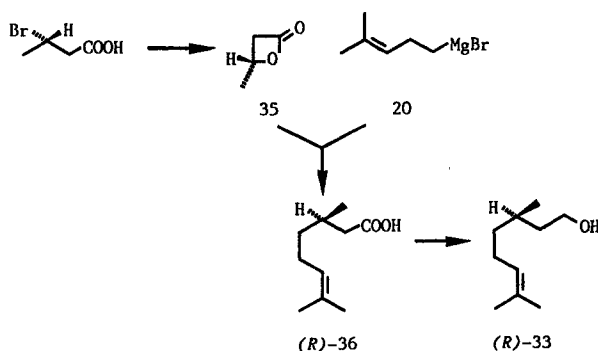


Scheme 3

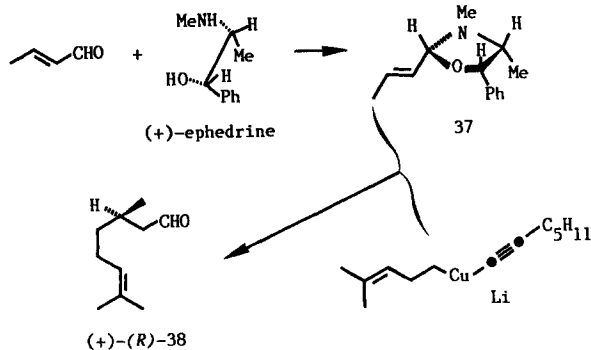


B. Oxygenated 2,6-Dimethyloctanes, One Double Bond: Citronellol, Citronellal, and Citronellic Acid

Since the last report,^{1b} two new esters of citronellol, the geranate and the citronellate, have been found in the European hornet; these are synthesized directly from the constituent acid and citronellol (**33**).⁵⁶ Because of the increased use of optically active citronellol as a chiral starting material, there has been an increase in work aimed at producing one or the other of the isomers synthetically. Using optically active phosphine ligands in the palladium-catalyzed telomerization of isoprene,²⁰ Hidai et al. have made the optically active ether **34**, which was converted to citronellol in three steps. Use of neomenthylidiphenylphosphine as ligand, for example, gave (–)-**34** losing methanol when treated with $\text{NiCl}_2(\text{PBU}_3)_2$; reduction and hydroboration then gave (+)-(*R*)-citronellol (**33**) in 35% optical yield.⁵⁷ Two $\text{C}_6 + \text{C}_4$ routes have also been described. One consists of resolving 3-bromobutyric acid with (*R*)-1-(α -naphthyl)ethylamine, then cyclizing it to the four-membered ring lactone **35**. The latter was converted to citronellic acid (**36**) and then to (+)-(*R*)-citronellol (**33**) (Scheme 4). The (*S*)-acid was also available from the enantiomer of **34**. The other $\text{C}_6 + \text{C}_4$ synthesis consists of forming an optically active addition product from crotonaldehyde and (+) or (–)-ephedrine (Scheme 5). The oxazolidine **37** from (+)-ephedrine will add a C_6 copper compound to give (+)-(*R*)-citronellal (**38**)



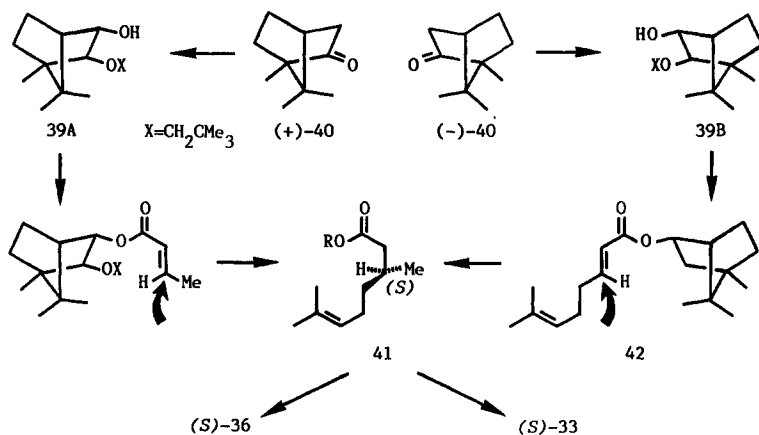
Scheme 4



Scheme 5

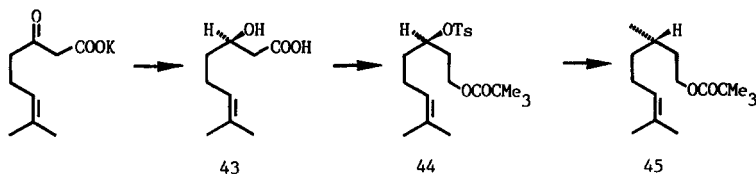
in 40% yield and 85% enantiomeric excess.⁵⁹ (The latter is clearly equivalent to citronellol as a chiral synthon.)

Oppolzer has developed a method of asymmetric synthesis based on the use of the chiral auxiliaries **39A** and **39B** derived respectively from (+)-camphor [(+)-**40**] and (–)-camphor [(–)-**40**].⁶⁰ Crotonylation of **39A** gave the ester that was attacked by 4-methyl-3-pentenyllithium in the presence of copper iodide tributylphosphine and boron trifluoride from only one side of the molecule, the product **41** having the (*S*)-configuration (enantioselectivity 98.5%). The ester **42**—similarly obtainable from **39B**—was methylated under similar conditions, also yielding **41** with 92% enantioselectivity. (*S*)-Citronellic acid [(*S*)-**36**] or (*S*)-citronellol [(*S*)-**33**] were then obtained from **41** by the action of sodium hydroxide or lithium aluminum hydride (Scheme 6).⁶¹ Reduction of potassium



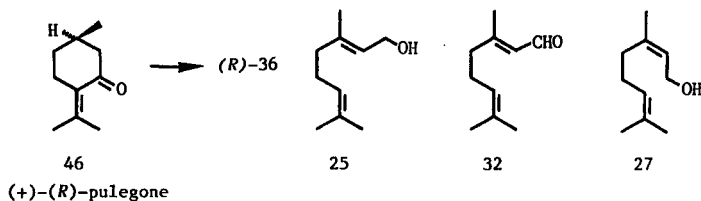
Scheme 6

7-methyl-3-oxo-6-octenoate with baker's yeast yielded the salt of only the (*R*)-acid **43** and this was converted *via* the protected tosylate **44** using lithium dimethyl cuprate to the protected (–)-(*S*)-citronellol **45** (Scheme 7). Naturally occurring pulegone (**46**) has also been transformed to the methyl ester of (+)-(*R*)-citronellic acid [(*R*)-**36**],⁶³ following an earlier method.⁶⁴

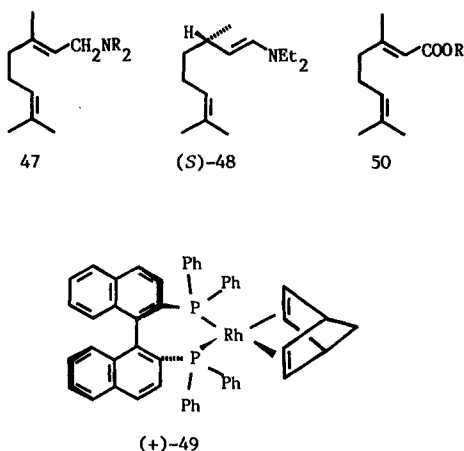


Scheme 7

Methods for chirally reducing the allylic double bond in geraniol (**25**) or the conjugated double bond in citral (**32**) derivatives have also been developed. Achiral reduction is illustrated by use of triphenylphosphinerhodium chloride and triethylsilane, which led to the triethylsilyl enol ether of citronellal (**38**) (with the deuteriated silane, deuterium was introduced),⁶⁵ potassium carbonate in methanol then hydrolyzing the enol ether to citronellal. Similar reduction also occurred with a ruthenium catalyst and trimethoxysilane.⁶⁶ Chiral phosphine ligands attached to rhodium enabled chirality to be introduced during reduction. Thus (*E*)-citral (**32**) has been reduced to (+)-(*R*)-citronellal [(*R*)-**38**], the (*Z*)-isomer of citral yielding (–)-(*S*)-citronellal.⁶⁷ With another chiral phosphine ligand, geraniol (**25**) has been reportedly reduced to (*R*)-citronellol [(*R*)-**33**] and nerol (**27**) to (*S*)-citronellol.⁶⁸ The reaction of citral (**32**) with (+)-ephedrine or L-aspartic acid followed by hydrogenation and liberation of the aldehyde, gave optically active citronellal.⁶⁹ In none of these reductions, however, did the enantiomeric excess exceed 75%, and mostly was between 50 and 60%. Somewhat better was the reduction of diethylgeranylamine (**47**, R = Et) (prepared from myrcene, **7**⁷⁰) which could be made to yield 100% of the enamine (*S*)-**48**



in 96% enantiomeric purity using the catalyst (+)-**49**. The (*Z*)-isomer, diethylnerylamine (**6**, R = Et) (made from isoprene, Vol. 4, p. 455, Ref. 15⁷⁰), gave (*R*)-**48**. Use of the catalyst of the opposite chirality, (–)-**49**, led to the opposite chirality of **48**. This catalyst is good for 7000 turnovers, and is tolerant of hydroxyl groups, so chiral hydroxycitronellal was also made.⁷¹ The same authors have discussed the preparation of 2,2'-bis(diarylphosphino)-1,1'-dinaphthyls such as **49**.⁷²

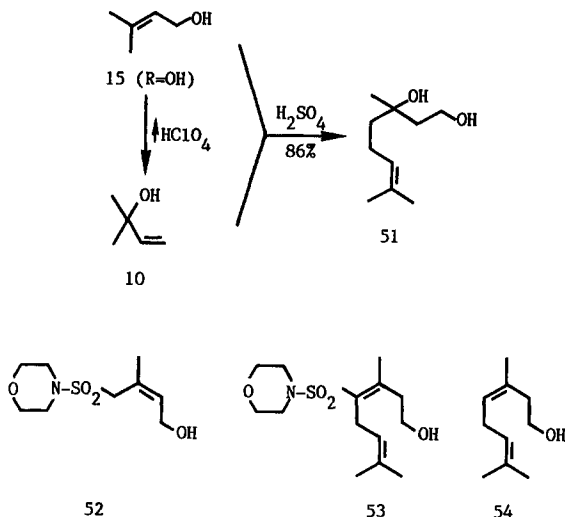


The bioreduction of (*E*)- and (*Z*)-geranic acid salts (**50**, R = metal) to (*R*)- and (*S*)-citronellate has also been reported.⁷³

Julia and Roy have recently investigated the best way of reducing the distal double bond of geraniol (**25**); they suggested addition of hydrogen chloride followed by reduction with zinc borohydride.⁷⁴

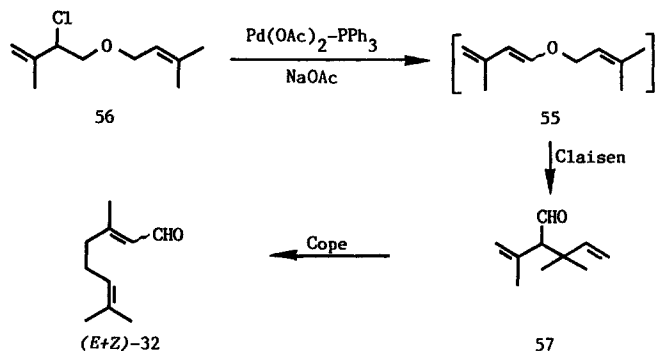
C. Oxygenated 2,6-Dimethyloctanes, Two Double Bonds: Geraniol, Nerol, Citral, Geranic Acid, and Linalool

A few novelties among the $\text{C}_5 + \text{C}_5$ syntheses of this group (Vol. 4, p. 461) include treatment of dimethylacrolein diprenyl acetal with phosphoric acid, which gave a 96% yield of citral (**32**).⁷⁵ Another route from prenol (**15**, R = OH) involved conversion to 2-methyl-3-buten-2-ol (**10**), then addition of **15** (R = OH) to **10** in the presence of sulfuric acid. The diol **51** formed was, however, only dehydrated in poor yield to geraniol (**25**), a mixture of double-bond isomers

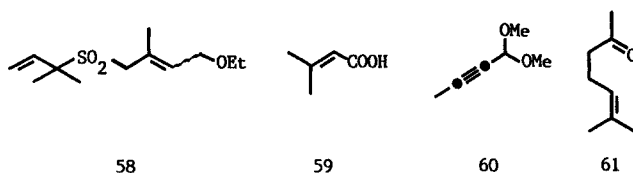


being obtained.⁷⁶ Improvements in the prenylation of isopentenyl derivatives, notably by use of nitromethane as solvent, have been reported⁷⁷ (see also lavandulyl derivatives, below). Activation of an allyl group using a sulfonamide, a well-known approach (cf. Vol. 4, p. 460), was the principle used to make prenyl chloride (**15**, R = Cl) react with the dilithium derivative of **52**.⁷⁸ Under various conditions, the product **53** was reduced to nerol (**27**) or isogeraniol (**54**), the most interesting aspect being that when lithium in ammonia and *tert*-butanol was used, the product was 93% isogeraniol (**54**), while sodium in ammonia and dibenzo-18-crown-6 yielded 96% nerol (**27**).⁷⁹ A synthesis of citral followed a Claisen–Cope route⁸⁰ from the dimethylallyl dienyl ethers **55** made *in situ* from the chloride **56** arising from the reaction of calcium hypochlorite chlorination of bis(dimethylallyl) ether (Scheme 8).⁸¹ The product was 41% (*Z*)- and 59% (*E*)-citral [(*Z*)+(*E*)-**32**] in 66% overall yield—a surprisingly high yield considering that such intermediates as the unconjugated aldehyde **57** obtained after the first Claisen rearrangement frequently undergo conjugation of the double bond β,γ to the aldehyde faster than the Cope rearrangement.^{80,82}

Thermolysis of the sulfone **58** gave 58% of a mixture of geraniol (**25**) and nerol (**27**) ethyl ethers.⁸³ Starting from ‘senecioic’ acid (**59**), Katzenellenbogen has continued studies of the addition of prenyl halides (**15**, R = halogen) to the dianion in presence of copper.⁸⁴ Copper ion also influenced the addition of prenyl bromide (**15**, R = Br) to the anion of the *N*-methylamide of **59**, its presence transforming a yield of 98% of the α -addition product to 83% of the γ -product, geranic acid *N*-methylamide [as a mixture of (*Z*)- and (*E*)-isomers].⁸⁵



Scheme 8



A $\text{C}_6 + \text{C}_4$ synthesis of citral (32) dimethyl acetal consisted of the addition of the copper-lithium compound corresponding to 20 with the acetylenic acetal 60. The reaction occurred at -35°C in 1 hour, and yielded the pure (E)-isomer in 92% yield. Another rather long synthesis involved addition of the lithium derivative corresponding to 20 with 3,4-dichloro-2-butanone. Three conventional steps from the product of this Grignard reaction gave geranyl acetate (25 acetate).⁸⁷

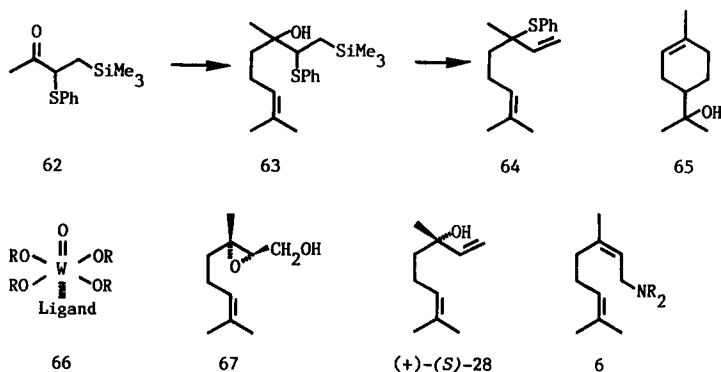
Two methods for converting methylheptenone (61) to geraniol and nerol (25 + 27) have been published, but neither presents an advantage over other well-known methods. One consists of the addition of nitromethane to 61 in the presence of thiophenol, a second carbon atom being then added with formaldehyde.⁸⁸ The other method involves conversion of 61 to 6-methyl-5-heptynyne,⁸⁹ and transformation of this to geraniol by known methods.

Oxidation of geraniol (25) or nerol (27) to citral (57) has been mentioned earlier (Vol. 2, p. 28) as being difficult to carry out specifically. Nerol was oxidized to citral in 92% yield with oxygen catalyzed by tris(triphenylphosphine)ruthenium dichloride (geraniol only gave 67% yield),⁹¹ while somewhat different conditions with another ruthenium catalyst gave citral from geraniol (25) or nerol (27) with considerable retention of the double-bond geometry.⁹² Reduction of citral to geraniol (with no 1,4-reduction) was carried out with the

dimagnesium compound $\text{EtCH}(\text{OMgBr})_2$, prepared from ethylmagnesium bromide and formic acid in tetrahydrofuran.⁹³ Takabe et al. have published yet another paper about the conversion of *N,N*-dimethylgeranylamine (**47**, **6**, $\text{R} = \text{Me}$) to citral through the *N*-oxide; this time they deal with the stereochemistry of the 2,3-double bond (80% retained in the case of the geranyl series, 60% in the neryl series).⁹⁴

A $\text{C}_6 + \text{C}_4$ synthesis of linalool (**28**) and nerol–geraniol has been described by Fleming et al.,⁹⁵ but this is to demonstrate the use of the thiophenyl + trimethylsilyl groups as progenitors of a double bond. Thus the substituted butanone **62** was converted to the geranyl skeleton **63** by a Grignard reaction, and **63** reacted with thionyl chloride and triethylamine in HMPA and lithium chloride to give the thio-derivative **64** of linalool, from which linalool (**28**) or geraniol–nerol were obtained.

A study of the rates of the acid-catalyzed rearrangements between geraniol (**25**), nerol (**27**), and linalool (**28**) (as well as α -terpineol, **65**) has shown that the linalyl cation does not lose its stereochemical identity.⁹⁶ The isomerization of primary to tertiary allyl alcohols is catalyzed by acetylacetone complexes of vanadium(II) or molybdenum(IV),⁹⁷ but it is reported that tungsten ligands of type **66** are more effective, nerol (**27**) or geraniol (**25**) being converted to linalool (**28**) (22–39% in 2 hours) with a selectivity of 92%.⁹⁸ The reverse reaction is, of course, well-known, but a very mild method converts linalyl tosylate to geranyl tosylate [(*E*)/(*Z*) = 87:13] in 95% yield using $\text{Pd}(\text{Ph}_3)_4$ catalyst in tetrahydrofuran/methanol at room temperature overnight.⁹⁹

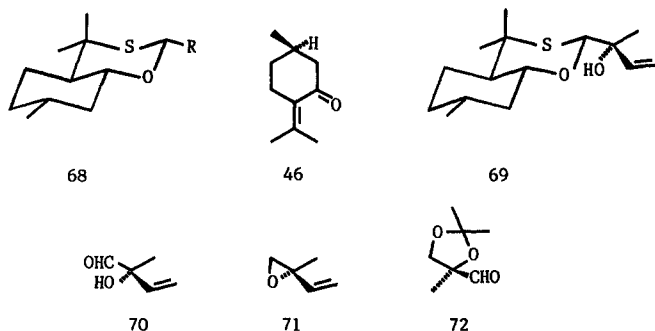


The most interesting conversions of geraniol to linalool would be those introducing chirality in the linalool. This can be effected by using chiral auxiliaries during allylic epoxidation of geraniol. Allylic epoxidation of geraniol is efficiently carried out with *tert*-butyl hydroperoxide in presence of aluminum tri-*tert*-

butoxide, but using a chiral hydroxamic acid as ligand only induced 34% ee.¹⁰⁰ The Sharpless method using L-(+)-diethyl tartrate with *tert*-butyl hydroperoxide, and titanium tetrakisopropoxide gave from geraniol (**25**) 77% of (2*S*,3*S*)-epoxide **67** with 95% ee, while the (2*S*,3*R*)-isomer was obtained from nerol (**27**) with 94% ee.¹⁰¹ This reaction has been realized on crosslinked polystyrene resins, but with this technique, the ee was only 66%.¹⁰² Conversion of **67** to (+)-(*S*)-linalool [(*S*)-**28**] was accomplished by exchanging the hydroxyl group for halide (e.g., iodide, by treating the tosylate with sodium iodide) then either heating in refluxing methanol with zinc dust or treating with butyllithium in tetrahydrofuran at -23°C. Both methods gave high yields of (+)-(*S*)-linalool from bromide or iodide, but the second method must be used for chloride.¹⁰³

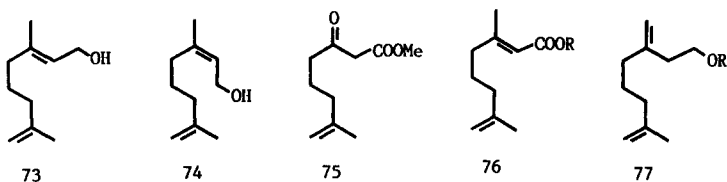
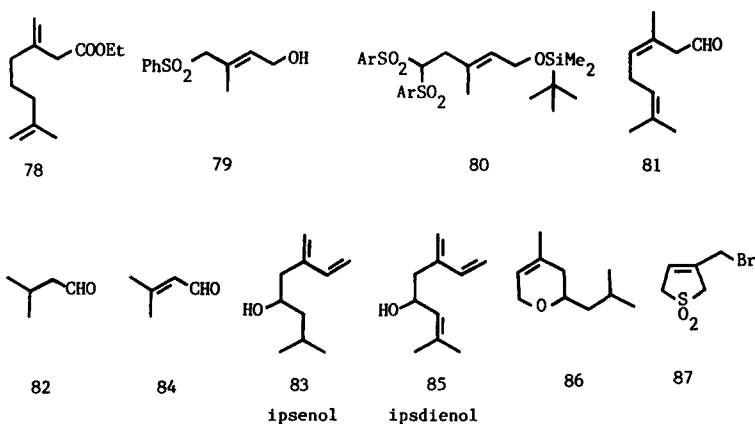
For some years, Eliel has been developing the use of the thioxanes **68** [the parent, **68** (R = H), is readily prepared from (+)-pulegone (**46**)].¹⁰⁴ The acetyl compound **68** (R = Ac) has been used to make (-)-(*R*)-mevalolactone,¹⁰⁵ but here we wish to draw attention to using it to make (+)-(*S*)-linalool [(*S*)-**28**]. Grignard reaction (vinylmagnesium chloride and MgCl₂) gave **69** as the major stereoisomer; the chiral auxiliary group was removed with *N*-chlorosuccinimide and silver nitrate, and the resulting aldehyde **70** was converted to (*R*)-isoprene epoxide (**71**) by the action of potassium hydroxide on the tosylate of **70**. Julia has already converted racemic isoprene epoxide [(±)-**71**] to linalool (Vol. 4, p. 460, Ref. 65),¹⁰⁶ and the route here was similar, although improvements were made.¹⁰⁷ Unfortunately, the (*S*)-isomer of **70** did not crystallize, and neither did its tosylate, but it is clear that the synthesis in principle applies to the other series as well.¹⁰⁷ Indeed, the (*S*)-isomer of **71** was converted to (-)-(*R*)-linalool by Barner and Hübscher, although they did not prepare the epoxide in the same way, but by a Wittig reaction on the chiral protected glycol **72**, followed by ring closure of the monotosylate of the unprotected glycol.¹⁰⁸

Preparation of linalool from other monoterpenoids includes a route from dimethylnerylamine (**6**, R = Me), readily accessible from isoprene (see discussion above). With phenylselenide in the presence of ruthenium, the



dimethylamino group was replaced by phenylselenide,¹⁰⁹ the product being convertible to linalool by the known¹¹⁰ oxidation with hydrogen peroxide. Various routes to geraniol and linalool from myrcene (7) have been described (Vol. 2, p. 18). It is now reported that "autooxidation" of myrcene in dimethylformamide yields mainly linalool (28). (The abstract reports also another "oxidation" in dimethyl sulfoxide that seems equally dubious. Could this abstract refer to dihydromyrcene instead of myrcene?)¹¹¹ A better method is by oxidation of the myrcene complex of zircocene using hydrogen peroxide.³⁵

A word about the synthesis of the α -series, α -geraniol (73) and α -nerol (74), is warranted because they are often intermediates in the synthesis of 1-hydroxylated compounds (e.g., some diols described below). Weiler has continued his exploitation of the dianion of methyl acetoacetate to this end. Instead of prenylation (Vol. 4, p. 461, Ref. 73) he carried out a similar series of operations by alkylating the dianion with 4-bromo-2-methyl-1-butene, thus arriving at compounds of the α -series *via* the keto ester 75, methylating the enol phosphate to 76. He also prepared the double methylene isomer 77 (R = COEt) of geranyl propionate from the intermediate 75.¹¹² The purpose of synthesizing this propionate was to prepare the pheromone of the San Jose scale, *Quadraspidiotus perniciosus*, which is a mixture of the propionates of 73, 74,

 α -geraniol

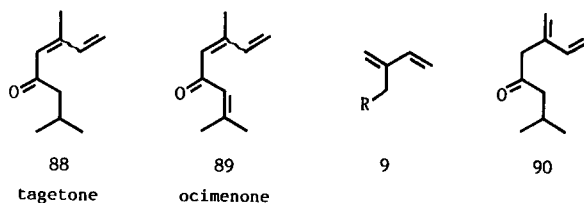
and **77** ($R = H$).¹¹³ Photochemical deconjugation of ethyl α -geranate (**76**, $R = Et$) to the ester **78** has also been examined.¹¹⁴ Julia has adapted an earlier route, using 4-bromo-2-methylbutene in a Grignard reaction with the phenyl sulfone **79** available from isoprene (cf. Vol. 4, p. 454). In the presence of 1% copper acetoacetate, the reaction yielded 80% of α -geraniol (**73**).¹¹⁵ A much more academic route employed $C_6 + C_4$ as the main reaction for building the carbon skeleton between the protected alcohol **80** and isobutenyl ethyl carbonate.¹¹⁶ The most obvious way of passing to the α -series is from the readily available β -series. This can be done *via* the well-known route involving reductive ring opening of the epoxide on the trisubstituted double bond, followed by dehydration (such as Schulte-Elte used in his synthesis of the 2,6-dimethyl-1,4,7-octatrienes, Vol. 2, p. 13, Ref. 49,¹¹⁷). This route has been followed using methanesulfonyl chloride as the dehydrating agent.¹¹⁸ Trifluoroacetic acid was added to the trisubstituted double bond of the β -series, and the resulting ester was also converted to the methylene compound.¹¹⁹

It is reported on dubious evidence that isocitral (**81**) occurs in *origanum* (*Coridothymus capitalus*).¹²⁰ This compound has been known for a long time to be formed in the thermolysis of citral (**57**).¹²¹

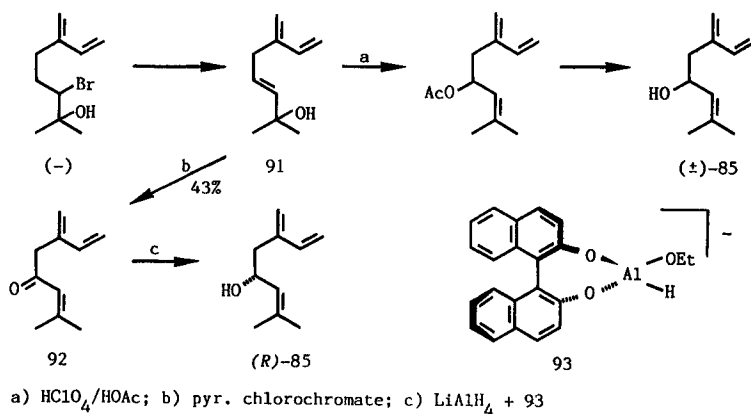
D. 4-Oxygenated 2,6-Dimethyloctanes: Ipsenol, Ipsdienol, Tagetones, and Ocimenones

Reactions with 3-methylbutanal (**82**) (for ipsenol, **83**) or senecio aldehyde (dimethylacrolein, **84**, for ipsdienol, **85**) were discussed previously (Vol. 4, p. 467). Many further publications on the subject have appeared. Isoprene can be tribrominated, first with bromine in carbon tetrachloride, then with *N*-bromosuccinimide. This is one route to 2-bromomethyl-1,3-butadiene (**9**, $R = Br$), obtained from the tribromide with zinc amalgam reduction, but in fact the tribromide reacted directly with the aldehydes **82** or **84** to give ipsenol (**83**) or ipsdienol (**85**).¹²² A reagent used for the reaction of **9** ($R = Br$) with the aldehydes is lithium aluminum hydride in the presence of chromium trichloride;¹²³ alternatively, the bromine atom of **9** ($R = Br$) was exchanged for a dialkylboron group,¹²⁴ or a trimethylsilyl group **9** ($R = SiMe_3$).¹²⁵ In the latter case, the trimethylsilyl ethers of **83** and **85** were obtained first. Another variant of this route employed isoprene directly. This reacted with 3-methylbutanal (**82**) in the presence of dimethylaluminum chloride, although the yield of ipsenol in this case was only 16%, the major product being the dihydropyran **86**.¹²⁶ The same paper also mentions the use of methylenecyclobutane as an isoprene equivalent, but the yield of the addition product with methylbutanal was still only 43%.¹²⁶ This method nevertheless avoids the inconvenient preparation of 2-bromomethyl-1,3-butadiene (**9**, $R = Br$). In addition to the method just mentioned, the latter

compound was made by pyrolysis of the brominated sulfone **87** (made in turn by allylic bromination of the addition product of isoprene and sulfur dioxide), and both **9** ($R = \text{Br}$) and **87** underwent addition of nitriles in the presence of zinc/silver alloy. The products obtained (with 3-methylbutanenitrile and 3-methyl-2-butenenitrile) were the ketones corresponding to ipsenol (**83**) and ipsdienol (**85**), to which they can be reduced. The unconjugated ketones were also rearranged to the conjugated ketones tagetone (**88**) and ocimenone (**89**),

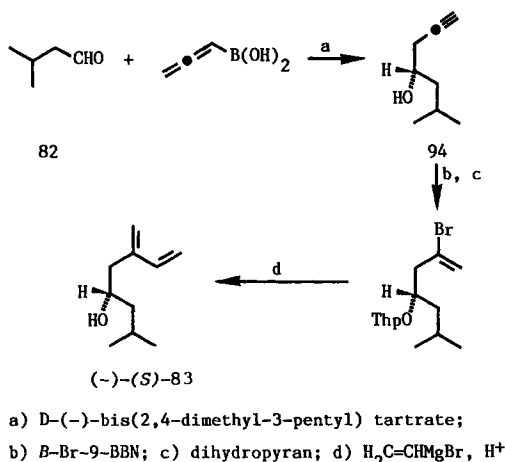


respectively¹²⁷ (see below for these ketones). The trimethylsilyl-substituted isoprene **9** ($R = \text{SiMe}_3$), made from **9** ($R = \text{Cl}$) and trimethylsilylmagnesium chloride in the presence of a nickel catalyst, reacted with 3-methylbutanoyl chloride in the presence of titanium tetrachloride to give the ketone **90** corresponding to ipsenol (**83**). This ketone does not isomerize immediately to the tagetones (**88**), and was reduced with diisobutylaluminum hydride to give ipsenol (**83**).¹²⁸ The same series of reactions was carried out with senecieryl chloride (the acid chloride of **59**) to give ipsdienol (**85**), yields being over 60% from the trimethylsilyl compound **9** ($R = \text{SiMe}_3$).¹²⁸



Scheme 9

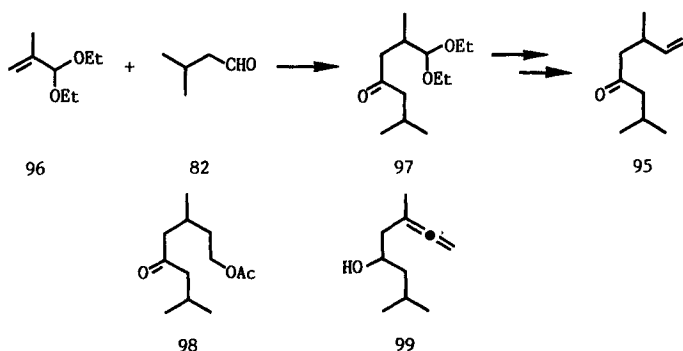
The fact that the unconjugated ketones do not rearrange rapidly was used in a synthesis of chiral ipsdienol (Scheme 9). Rearrangement of the product **91** from the $^1\text{O}_2$ reaction of myrcene (**7**) yields $(\pm)$ -ipsdienyl acetate. If, however, the photooxygenation product was first oxidized, the ketone **92** could be reduced with lithium aluminum hydride and the chiral aluminum complex **93**, when (*R*)-**93** gave $(-)$ -(*R*)-ipsdienol [$(-)$ -**85**], the (*S*)-isomer of **93** yielding $(+)$ -ipsdienol [$(+)$ -**85**].¹²⁹ The natural product **91** was also made by the reaction of myrcene (**7**) with *N*-bromosuccinimide and dehydrobromination of the bromohydrin thus obtained.¹³⁰ An interesting synthesis of chiral $(-)$ -(*S*)-ipsenol [$(-)$ -**83**] used the reaction of methylbutanal (**82**) and allenylboronic acid (made from propargylmagnesium bromide and methyl borate). In the presence of D- $(-)$ -bis(2,4-dimethyl-3-pentyl) tartrate as chiral auxiliary. The chiral product **94** was converted conventionally to $(-)$ -(*S*)-ipsenol (Scheme 10).¹³¹ Sharpless et al. have described how, when racemic ipsdienol [$(\pm)$ -**85**] was epoxidized with their titanium-catalyzed reagent in the presence of D- $(-)$ -diethyl tartrate, only the (*S*)-isomer was epoxidized, leaving a 99% ee of (*R*)-ipsdienol.¹⁰¹



Scheme 10

Actually, the photooxygenation product **91** from myrcene is a pheromone of *Ips amitinus* and has also been prepared by the rearrangement of ipsdienol (**85**) with borofluoric acid.¹³² The acetate of **91** has also been made from myrcene (**7**) by addition of benzenesulfonyl chloride in the first step. (This route was described as a short communication in Vol. 4, p. 469, Ref. 136; further details are now given.¹³³)

Dihydrotagetone (**95**) has been synthesized by dibenzoyl peroxide-initiated radical reaction of 3-methylbutanal (**80**) and the diethyl acetal (**96**) of methacrolein; the product **97** (obtained in 42% yield) could be converted conventionally to dihydrotagetone (**95**).¹³⁴ The same author has described the direct radical addition of **82** to 3-methyl-3-butenyl acetate. The product, **98**, in this case was deacetylated by pyrolysis over ceramic beads to dihydrotagetone (**95**).¹³⁵

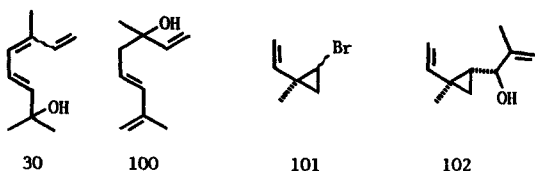


The original method by Cookson et al. for the preparation of the ocimenones (**89**)¹³⁶ has been reexamined by Weyerstahl et al.,¹³⁷ who found that the proportion of (*E*)-**89** to (*Z*)-**89** is 3:1 rather than 9:1, as originally reported. This C₅ + C₅ coupling which Cookson¹³⁶ (and de Villiers et al.¹³⁸) carried out with isoprene and the acid chloride of senecioic acid (**59**) (cf. Vol. 4, p. 47, Refs. 160 and 161), has also been realized by Julia (cf. Vol. 4, p. 473, Refs. 158 and 159), who has published more recent developments.¹³⁹ A Russian patent claims that the oxidation of the allene **99** with pyridinium chlorochromate followed by isomerization with powdered potassium hydroxide gives (*Z*)-tagetone [(*Z*)-**88**] stereoselectively.¹⁴⁰

E. 2-Hydroxy-2,6-dimethyloctadienes and trienes

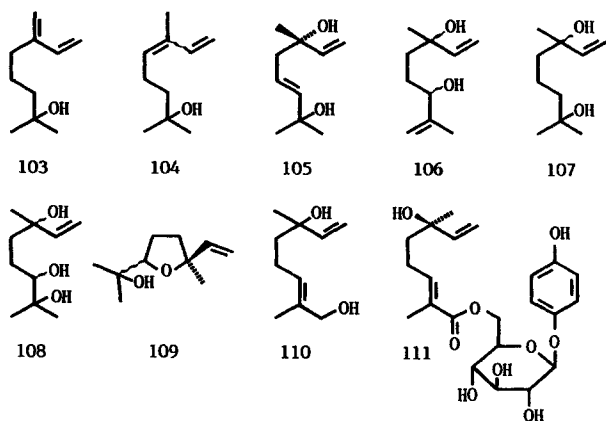
The two compounds **30** have sometimes been called ocimenols. They are naturally occurring in hyacinth,¹⁴¹ lavender, osmanthus, and daphne species, and have been known since 1957.¹⁴² They have been synthesized by photooxygenation of the ocimenes (**26**).⁵⁴

A new synthesis of hotrienol (**100**) starts with the addition of dibromocarbene to isoprene. The dibromocyclopropane was reduced (Bu₃SnH) and the monobromide **101** submitted to a Grignard reaction with methacrolein; the



product, **102**, gave hotrienol (**100**) with acid in tetrahydrofuran.¹⁴³ The cyclopropyl alcohol **102** has also been made from 1-methylcyclopropene and vinylmagnesium bromide, followed by methacrolein.¹⁴⁴

The dihydro-analogs of these compounds are not yet (to our knowledge) reported as naturally occurring, but they are interesting in relation to certain polyhydroxylated compounds mentioned in the next section. They have been made by hydration of diethylnerylamine (**6**, R = Et) or diethylgeranylamine (**47**, R = Et); subsequent removal of the amino group was carried out either by Hofmann elimination from the quaternary salt,¹⁴⁵ or by the action of Pd^{II} with triphenylphosphine¹⁴⁶ or tetra- or pentamethylene diphosphine¹⁴⁷ ligands. The nature of the ligand has a big influence on whether the double bond to be formed will result in alcohols **103** derived from myrcene (**7**), or **104** derived from ocimenes (**26**).



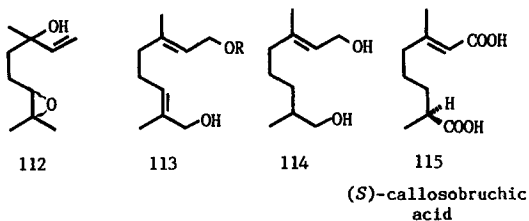
F. Polyoxygenated 2,6-Dimethyloctanes

The hydroxylated linalool **105** has been found in tea;¹⁴⁸ (of the opposite configuration from similar compounds from Ho-oil; Vol. 2, p. 25), and it (without precision of the stereochemistry) has also been found in muscat grapes, where it is

considered as a flavor precursor,¹⁴⁹ together with the diols **106** and **107** and triol **108**.¹⁵⁰ It is not surprising that **106** and **107** have also been found in wine,^{151,152} and ethyl ethers of **105** and other related compounds have been identified.¹⁵² At low pH, some of these compounds cyclize; for example, the triol **108** gives linalool oxides (**109**), and other furanoid and pyranoid monoterpenes are formed in grapes from these compounds.¹⁴⁹ The diol **105** has also been reported as a flavor precursor in elder flowers and berries (without precision of the stereochemistry),¹⁵³ but so far as we are aware, there has been no new synthetic work since we last reported (Vol. 4, p. 465).

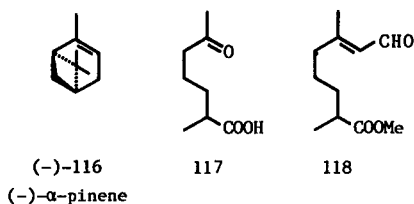
Linalool hydroxylated on the terminal methyl group **110** has been claimed to possess the typical green note of Yuzu oil (*Citrus junos*),¹⁵⁴ but this diol has in fact been known for some time (Vol. 4, p. 465, Refs. 99 and 100),¹⁵⁵ and is without odor,¹⁵⁶ despite the existence of a patent claiming that it has a durable perfume (and flavor).¹⁵⁷ The patent follows the preparation of Enzell et al. (Vol. 4, p. 465, Ref. 99),¹⁵⁸ oxidizing linalyl acetate (**28** acetate) with selenium dioxide. A glycoside, phlebotrichin (**111**), of the (*R*)-acid corresponding to **110** was identified as a bitter substance in *Viburnum phlebotrichum*,¹⁵⁹ but it has not been synthesized. A second group has claimed the opposite configuration of C-6 in compound **111**.¹⁶⁰

Many hydroxylated linalools [including compounds **105**, **106**, **108**, and **110**, both (*Z*)- and (*E*)-isomers], as well as the epoxides of both furanoid (**109**) and pyranoid (see section on pyrans) linalyl oxides, have been identified in papaya fruit (*Carica papaya*). At the same time, the first reported occurrence of the two linalool epoxides (**112**) in nature was made.¹⁶¹ These epoxides are well known to be unstable and easily cyclized (see Vol. 2, p. 165) and have been made by careful peracid oxidation of linalool. An interesting new method has now been described. While the vanadium- or titanium-catalyzed epoxidation of geraniol (**25**) gave the 2,3-epoxide (see above), as does molybdenum-catalyzed epoxidation with hydrogen peroxide,¹⁶² the epoxidation of linalool (**28**) with molybdenum or tungsten peroxo complexes and hydrogen peroxide led, by reaction on the 6,7-double bond, to **112**.¹⁶³

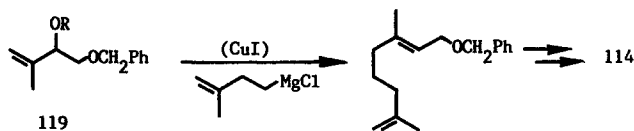


Terminally hydroxylated geraniol **113** ($R = H$) occurs as a glucoside in *Cistanche herba*,¹⁶⁴ and is important as a precursor for loganin and iridodial (see iridoids below); the dihydro analog **114** was recognized some time ago as a sex pheromone of the male African Monarch butterfly, *Danaus chrysippus*,¹⁶⁵ although the absolute stereochemistry remained unknown. The most direct and oldest synthetic route is by the action of selenium dioxide on the isopropylidene system, first studied about 50 years ago,¹⁶⁶ protecting the geraniol as an ester (giving e.g. **113**, $R = Ac$),¹⁶⁵ or by a more recent variant using *tert*-butyl hydroperoxide with a catalytic amount of selenium dioxide.¹⁶⁷

This synthesis has been adapted to make the natural (*S*)-isomer of **114**, reducing the initially formed aldehyde to (*S*)-**114** with baker's yeast.¹⁶⁸ [This same synthesis has been adapted to make (*S*)-callosobruchic acid (**115**), see below]. Julia's synthesis of α -geraniol (**73**) was also extended to make **114** by hydroboration. Hydroboration of **73** with diisopinocampheylborane (made from (–)- α -pinene [(–)-**116**]) gave only a small ee however.¹¹⁵ A synthesis of ($\pm$)-**114** started with the reaction of 2-methylpropiolactone and the ethylene acetal of 3-oxobutylmagnesium bromide. The methyl ester of the acid **117** thus prepared was chain-lengthened by reaction with acetylene and rearrangement with a vanadium catalyst of the ynol thereby obtained. The aldehyde **118** was then reduced with lithium aluminum hydride to **114**.¹⁶⁹

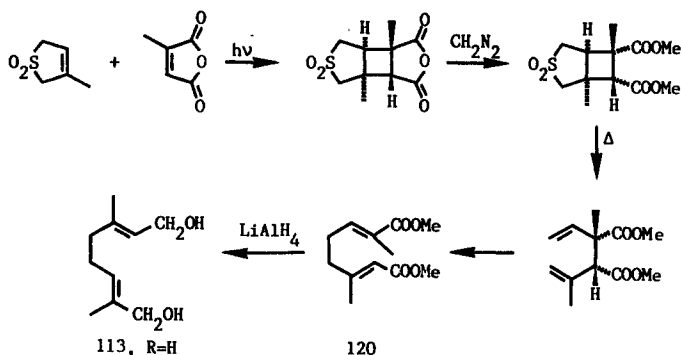


The Monarch butterfly pheromone **114** has also been synthesized by taking advantage of the fact that the phosphonate **119** [$R = PO(OEt)_2$] [prepared by treatment of **119** ($R = H$)¹⁷⁰ with diethyl phosphonyl chloride] reacts with Grignard reagents (in presence of copper iodide) on the terminal double bond. Thus prenylmagnesium chloride (**15**, $R = MgCl$) in the presence of copper iodide gave a mixture of geranyl and neryl benzyl ethers. A similar reaction using isopentenylmagnesium bromide gave the compounds of the α -series, **73** and **74**, as their benzyl ethers. Hydroboration then gave the benzyl ether of the pheromone **114**, from which the benzyl group was removed with lithium in ethylamine (Scheme 11). The (*E*)/(*Z*) ratio in this synthesis was 76:24.¹⁷¹



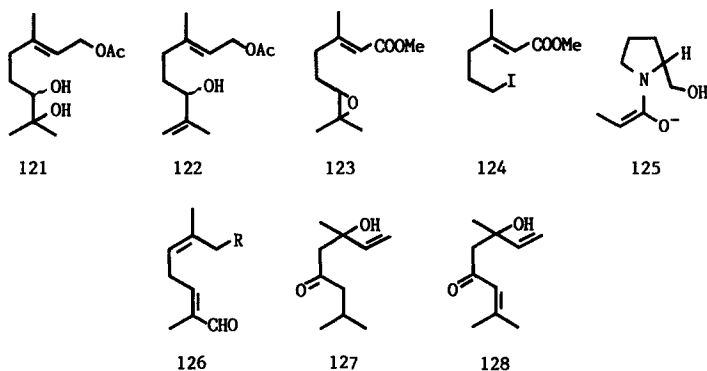
Scheme 11

The sulfone derived from isoprene will add to methylmaleic anhydride in a photochemical reaction (Scheme 12). Conversion of the anhydride to the corresponding diester, and pyrolysis to eliminate sulfur dioxide was followed by thermal rearrangement to the diester **120**, from which the diol **113** ($\text{R} = \text{H}$) was obtained by metal hydride reduction.¹⁷² It might also be pointed out that **113** ($\text{R} = \text{Ac}$) can be epoxidized, and the ring-opened epoxide (the triol monoacetate **121**) dehydrated to the acetate **122**.¹⁷³ The latter has been isolated (together with the corresponding hydroperoxide, the acetate—on the tertiary hydroxyl group—of diol **106**, and some related substances) from a compositae, *Mutisia spinosa*.¹⁷⁴ The intermediate triol monoacetate **121** has also been synthesized in chiral form.¹⁷⁵



Scheme 12

The diacid corresponding to **114** is callosobruchic acid (**115**), and forms part of the copulation release pheromone of the azuki bean weevil, *Callosobruchus chinensis*.¹⁷⁶ Both chiral isomers have been synthesized by Mori et al. from methyl geranate epoxide (**123**). After scission of the epoxide group, the iodide **124** was made conventionally, then the chiral group was introduced using the Evans (*R*)- or (*S*)-prolinol propionamide enolate anion (**125**) (made with lithium diethylamide in tetrahydrofuran on the amide).¹⁷⁷ Removal of the proline group then gave the chiral acids **115**.¹⁷⁸ Both the Monarch butterfly pheromone, (*S*)-**114**,



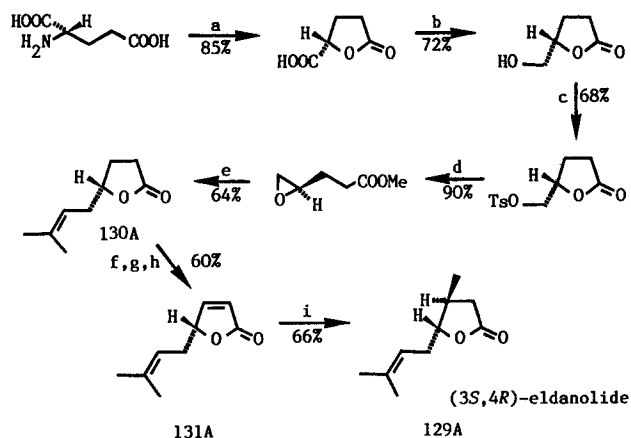
and callosobruchic acid [(*S*)-**115**] have been made by baker's yeast hydrogenation of the double bond of the achiral precursors **126** ($R = \text{CH}_2\text{OAc}$ or COOMe).¹⁶⁸

Synthesis of the hydroxyketones **127** and **128** was discussed in Volume 4 (p. 474, Refs. 163 and 164). The only novelty is that now both have been found in Yuzu (*Citrus junos*) oil, thus making ocimenol definitely naturally occurring.¹⁷⁹

G. 4-Hydroxycitronellic Acid Lactone, Eldanolide

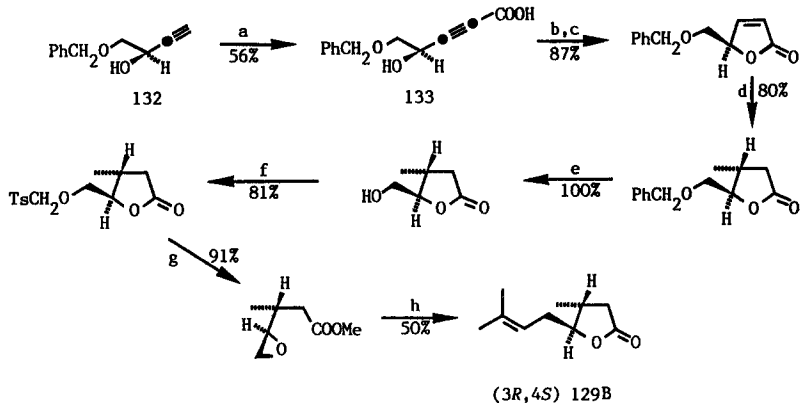
In 1981, the isolation of an isomer of the title product led to its identification as a wing-gland pheromone of the male African sugar cane borer *Eldana saccharina*,¹⁸⁰ and convincing evidence, based on a synthesis of both the (–)-(3*R*,4*S*)- and the (+)-(3*S*,4*R*)-isomers, showed that the latter, **129A**, was the active pheromone.¹⁸¹ The first synthesis of the natural (3*S*,4*R*)-isomer **129A** started from L-(+)-glutamic acid, and is depicted in Scheme 13. This route passes through two compounds, the lactones **130A** and **131A**, that were to be key compounds in later synthetic routes. To make the (3*R*,4*S*)-isomer **129B**, because D-glutamic acid is very expensive, the same authors used a different route from that shown in Scheme 13. The necessary chiral acetylenic alcohol **132** was first made by reduction of the corresponding ketone with lithium aluminum hydride in the presence of (–)-*N*-methylephedrine. When an optical yield of only 55% resulted, resolution of the racemic alcohol **133** (as its acid phthalate with (–)- α -methylbenzylamine) was used. Scheme 14 illustrates the synthesis.¹⁸¹

Another chiral synthesis of eldanolide (**129**) depends on the ready availability of the amide **134** from ethyl (*S*)-lactate.¹⁸² Carefully controlled reaction gave prenylation at the primary position (20:1 compared with tertiary position). A vinylsilane group was then introduced, and migration of this group was carried



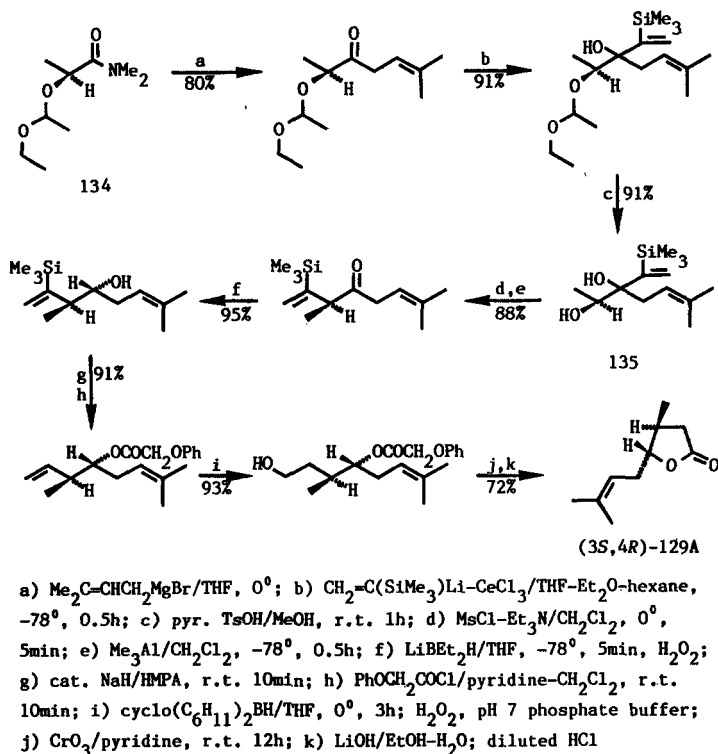
- a) HNO_2 ; b) $\text{BH}_3 \cdot \text{Me}_2\text{S}$; c) TsCl ; d) K_2CO_3 , then MeOH ;
 e) $(\text{Me}_2\text{C=CH})_2\text{CuLi}$; f) LDA ; g) PhSeBr ; h) H_2O_2 ; i) Me_2CuLi

Scheme 13



- a) BuLi , CO_2 ; b) $\text{H}_2/\text{Pd/BaSO}_4$; c) H^+ ; d) Me_2CuLi ; e) H_2/Pd ; f) TsCl ;
 g) K_2CO_3 , MeOH ; h) $(\text{Me}_2\text{C=CH})_2\text{CuLi}$

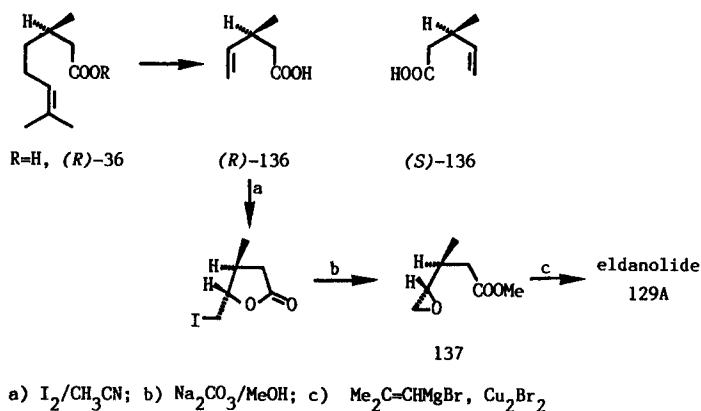
Scheme 14



Scheme 15

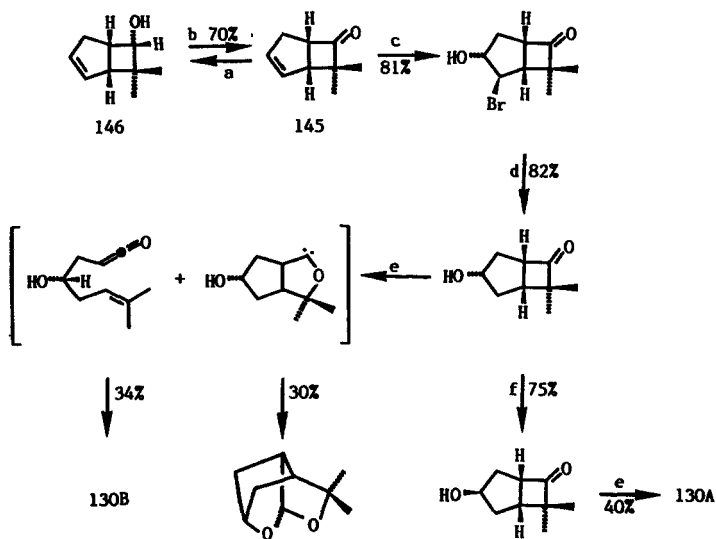
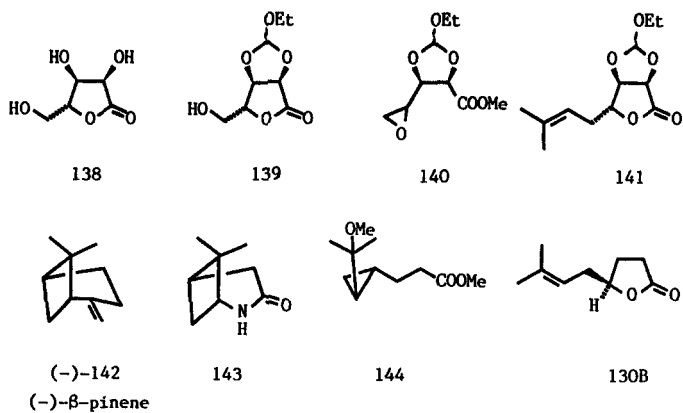
out with trimethylaluminum on the mesylate of the diol **135**. The remainder of the synthesis is shown in Scheme 15, and a parallel synthesis starting with methyl (*R*)-lactate led to the unnatural isomer of eldanolide.¹⁸³

The ready availability of (*R*)-citronellic acid [(*R*)-**36**] has led to syntheses of both natural and unnatural isomers of eldanolide from the same methyl (*R*)-citronellate (Scheme 16).¹⁸⁴ Degradation of the isohexenyl side chain to a vinyl group yielded the acid (*R*)-**136**, iodolactonization ($\text{I}_2/\text{CH}_3\text{CN}$) and treatment with sodium carbonate in methanol gave the epoxide **137** of the corresponding ester. Introduction of the isobutenyl group with isobutenylmagnesium bromide and copper bromide¹⁸⁵ then gave natural eldanolide (**129A**). The unnatural isomer **129B** was made from the epimer (*S*)-**136**, also available from methyl (*R*)-citronellate.¹⁸² The acid (*R*)-**136** has now been made by the action of vinylmagnesium bromide on the (–)-ephedrine amide of crotonic acid followed by removal of the chiral auxiliary with potassium hydroxide, but only in 55% ee.¹⁸⁶



Scheme 16

We come now to the various syntheses consisting of alternative routes to the lactones **130A** and **131A** (for natural eldanolide, **129A**) or **130B** and **131B** for the isomer **129B**. D-Ribonolactone (**138**) has the same chirality at C-4 as that required for natural eldanolide (**129A**), and the synthesis from **138** was effected by protection of the two secondary hydroxyl groups as an acetonide or ortho ester **139**. Action of sodium methoxide on the tosylate of **139** gave the epoxide **140**, which enabled introduction of the four remaining carbon atoms with lithium diisobutenyl cuprate. The yield of the product **141** was only 31% in the case of the ortho ester shown, but if the alternative acetonide route was used, although the yield at this step rose to 67%, it was necessary to replace the acetonide by the same ortho ester group afterward in order to carry out the next step (thermolysis at 240°C of **141**). The chiral lactone **131A** was thereby obtained.¹⁸⁷ The lactone **130B** of the opposite chirality has been made from (–)-β-pinene [(–)-**142**], first converting it into the cyclic amide **143**. The N-nitro derivative of **143** yielded the cyclopropane **144** (90%) with sodium methoxide, which in turn gave the lactone **130B** with *p*-toluenesulfonic acid in refluxing benzene, convertible as before to unnatural (3*R*,4*S*)-eldanolide (**129B**). It was also pointed out that **130** is in principle a good material for the synthesis of the marmelo lactones (see Section 4).¹⁸⁸ An ingenious synthesis of both chiral isomers of eldanolide started from the known (±)-7,7-dimethylbicyclo[3.2.0]hept-2-en-6-one (**145**) (cf. Vol. 2, p. 145)¹⁸⁹ and is depicted in Scheme 17. The initial resolution of the ketone was achieved by incubation of **145** with the fungus *Mortierella ramanniana*, which gives nearly equal quantities of *exo*- and *endo*-alcohols. The (–)-6-*endo*-alcohol **146** was then oxidized back to the now optically active ketone **145**. After the introduction of the *endo*-3-hydroxyl group as shown, the lactone **130B** was

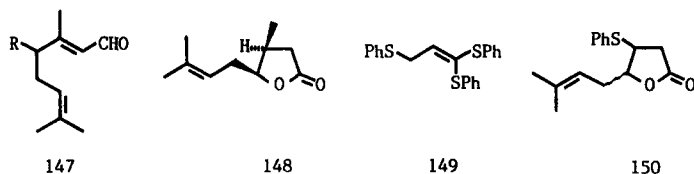


a) *N. Ramanniana*; b) pyr. dichromate; c) MeCONHBr, H₂O, acetone;
 d) Bu₃SnH, azoisobutyronitrile, toluene; e) hv, pentane;
 f) Ph₃P, diethyl azodicarboxylate, PhCOOH, THF, then K₂CO₃, MeOH

Scheme 17

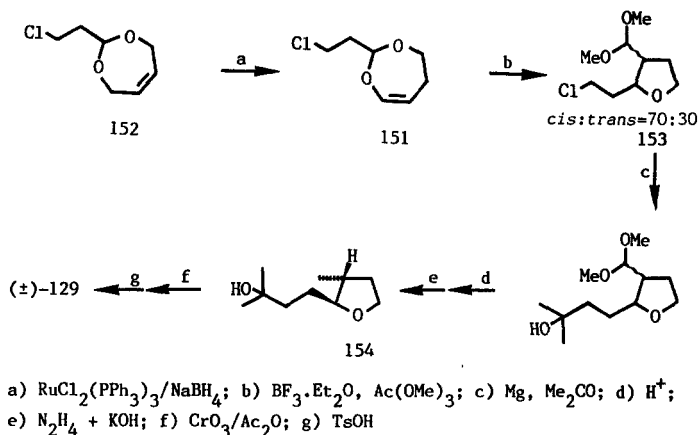
obtained by irradiation. For the other isomer, it was necessary to enantiomerize the 3-hydroxyl group before the irradiation, giving **130A** transformable to natural (3*S*,4*R*)-eldanolide (**129A**).¹⁹⁰

There are some syntheses of racemic eldanolide. One consists of bromination of citral enol acetate with *N*-bromosuccinimide, and treatment of the resulting bromide **147** (*R* = Br) with sodium acetate in HMPA; this gave 46% of the acetate **147** (*R* = OAc).¹⁹¹ Oxidation of the aldehyde function to the acid and reduction of the conjugated double bond gave a mixture of (±)-eldanolide and the *cis*-isomer **148** of eldanolide.¹⁹² The second synthesis consists of forming the skeleton by adding the activated C₃ unit **149** to 4-methyl-3-pentenal. The product underwent cyclization to **150** with trifluoroacetic acid. Loss of thiophenol (1,8-diazabicyclo[5.4.0]undec-7-ene) and addition of the methyl group (lithium dimethyl cuprate) gave (±)-eldanolide [(±)-**129**].¹⁹³ A recent variant employs



methyl propargylate as the C₃ unit, which was added to 4-acetoxy-4-methylpentanal. After partial reduction (Lindlar) and cyclization with *p*-toluenesulfonic acid, (±)-eldanolide was obtained.¹⁹⁴ The third rather long synthesis has as its key step the ring contraction of a 4,5-dihydro-1,3-dioxepin, **151**, prepared by ruthenium-catalyzed rearrangement of the 4,7-dihydro-1,3-dioxepin **152**. The chlorine atom of the resulting tetrahydrofuran **153** was used to introduce the three remaining carbon atoms (Grignard reaction) and the lactone was made by chromium oxide/acetic anhydride oxidation of **154**, a step that gave only 47% yield (Scheme 18).¹⁹⁵

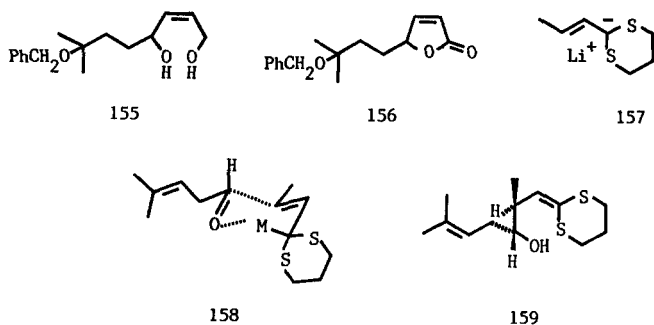
In another synthesis the diol **155** was oxidized with silver carbonate on Celite to the lactone **156** convertible (lithium dimethyl cuprate, debenzylolation, and dehydration) to (±)-eldanolide [(±)-**129**].¹⁹⁶ Finally a synthesis of racemic eldanolide involved coupling of a C₄ unit, **157**, with 4-methyl-3-pentenal. In tetrahydrofuran at -78°C, the reaction occurred at the γ-position to the metal atom (**158**) to yield 72% of the alcohol **159**, which gave 98% (±)-**129** with mercuric chloride.¹⁹⁷



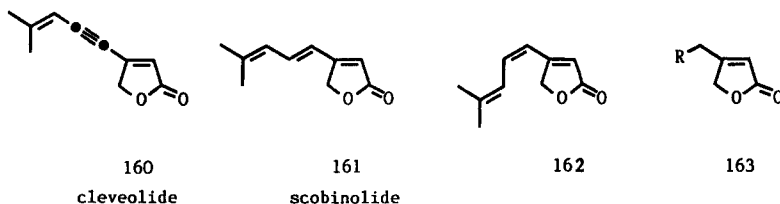
Scheme 18

H. 7-Hydroxydehydrogeranic Acid Lactones: Cleveolide and Scobinolide

In 1981, Bohlmann et al. reported the isolation of the first acetylenic monoterpene, cleveolide (**160**), from the compositae *Senecio clelandii*, a mixture of the dihydro compounds **161** and **162** accompanying it.¹⁹⁸ The (*E*)-isomer, scobinolide (**161**), was also isolated from the fungus *Psathynella scobinacea* by Thaller et al., who also synthesized a mixture of both isomers, **161** and **162**.¹⁹⁹ The



synthesis made use of an improved method for the preparation of the bromomethylbutenolide **163** ($R = Br$),²⁰⁰ best made from diacetoxyacetone and triethylphosphonoacetate; this yielded 63% of the ester $(MeCOCH_2)_2C = CHCOOEt$, which was hydrolyzed to the hydroxybutenolide **163** ($R = Ph_3P^+$) with senecio aldehyde (**84**).¹⁹⁹

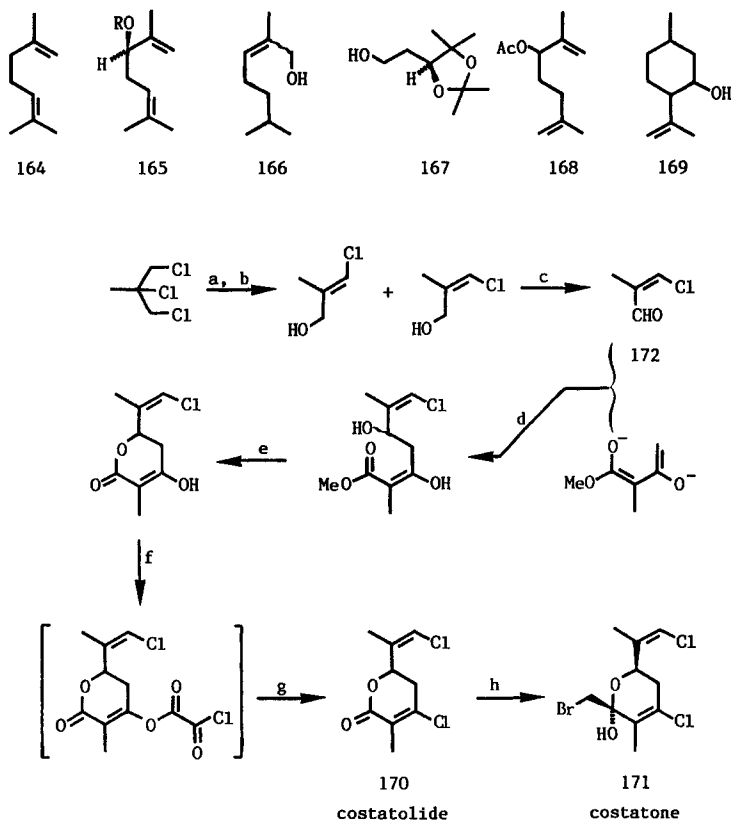


I. Geraniolenes

Geraniolene itself is 2,6-dimethyl-1,5-heptadiene (**164**), and has been made readily by reaction of isoprene with isobutylene in the presence of phosphomolybdic acid, this occurring with 69% selectivity and 56% conversion of isoprene.²⁰²

Under this heading is a small group of “nor”-terpenes, with the 2,6-dimethylheptane skeleton. These include the Comstock mealybug (*Pseudococcus comstockii*) sex pheromone **165** ($R = Ac$), isolated in 1980.^{203,204} Its straightforward syntheses,^{204,205} for example, the Grignard reaction between prenylmagnesium bromide (**15**, $R = MgBr$) and methacrolein,²⁰⁵ gave the racemate. Other syntheses have led to the compound **165** with the natural (+)-(*R*) chirality. Thus Sharpless diethyl tartrate-modified epoxidation¹⁰¹ of the alcohol **166** led to the chiral alcohol **165** ($R = H$), which was then acetylated to yield the pheromone **165** ($R = Ac$).²⁰⁶ Another synthesis starts from the chirally protected triol **167**, made in six steps from L-phenylalanine.²⁰⁷ Oxidation to the corresponding aldehyde and Wittig reaction gave the skeleton of the pheromone, from which **165** ($R = Ac$) was readily obtained.²⁰⁸ The non-naturally occurring isomer **168** of this pheromone has been synthesized from isopulegol (**169**), and is said to mimic the activity of the natural pheromone.²⁰⁹

One of the metabolites isolated from the red alga *Plocamium costatum* is a halogenated cyclized norgeraniolene, costatolide (**170**),^{210,211} and this has been synthesized. It has also been converted to the C_{10} -compound costatone (**171**), isolated from the same alga,²¹⁰ and placed here instead of in the pyran section because of the relationship with costatolide. In a synthesis of the latter, the (*Z*)-orientation of the vinyl chloride group could not be assured by chlorination



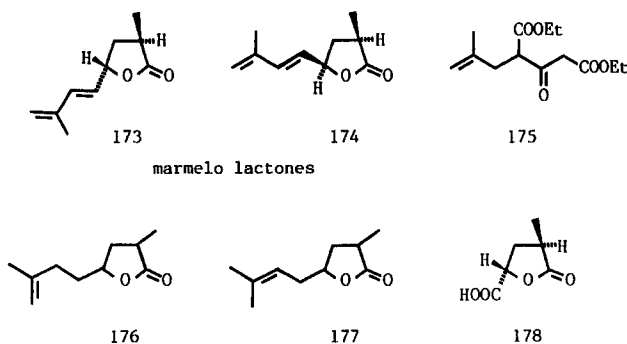
- a) 10% NaOH; b) spinning band distillation; c) MnO₂/ether;
 d) H⁺, -78 - 0°; e) NaOH; f) (COCl)₂, ether; g) DMF, Bu₄NCl;
 h) lithium dicyclohexylamide, BuLi/CH₂Br₂, -78°

Scheme 19

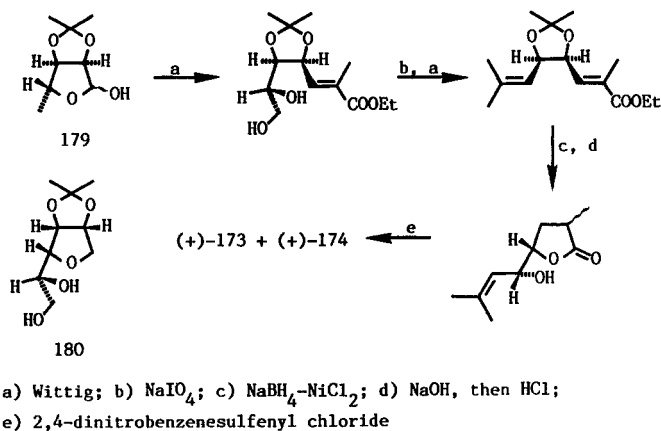
(POCl₃) and dehydrochlorination (dimethylformamide) of propionaldehyde, and the starting material [(Z)-3-chloro-2-methyl-2-propenol] was made as shown in Scheme 19, separating the two chloro compounds of the first step by spinning-band distillation. Reaction of the dianion of methyl methylacetoacetate with the corresponding aldehyde 172 then led to the desired skeleton which was cyclized, and the hydroxyl group was exchanged for a second chlorine atom.²¹² Conversion of costatolide (170) to costatone (171) was effected with lithium dicyclohexylamide and butyllithium with methylene bromide at -78°C (Scheme 19).²¹³

4. TAIL-TO-TAIL DIMETHYLOCTANES: THE MARMELO LACTONES

While mass and IR spectral comparisons are hardly sufficient to warrant the claim for the novel natural product 2,7-dimethyl-2,6-octadienol, said to occur in Egyptian jasmine absolute,²¹⁴ there is no doubt about the natural occurrence of the marmelo lactones (**173**, **174**) isolated from the essential oil of quince (*Cydonia vulgaris* = *C. oblonga*) in 1980.²¹⁵ (This species of quince was described as “Japanese quince,” but should not be confused with the bush known as Japanese quince to European horticulture; this is *C. japonica* and has inedible fruit.) The first synthesis was of the two racemates, and was given in the paper describing their isolation.²¹⁵ Ethyl 2-bromopropionate was allowed to react with the anion of **175**, and after hydrolysis, decarboxylation, and borohydride reduction, the lactone **176** was rearranged with *p*-toluenesulfonic acid to the lactone **177**. This lactone was allylically chlorinated (SO_2Cl_2) and dehydrochlorinated (diazabicycloundecene) to give a mixture of the marmelo lactones (**173**, **174**).²¹⁵ The dehydrogenation of the lactone **177** has also been carried out by electrolysis in water/acetonitrile in the presence of $(\text{PhSe})_2$ and Et_4NBr .²¹⁶ In 1983, the absolute configuration of the marmelo lactones was deduced as (+)-(2*R*,4*S*) for the *trans*- or A isomer **173**, and (–)-(2*R*,4*R*) for the *cis*- or B or *epi*-isomer **174**, by optical²¹⁷ and synthetic means.²¹⁸ The syntheses started from *erythro* or *threo*- γ -methyl-L-glutamic acids. For example, the *erythro*-acid was deaminated with nitrous acid, and the resulting lactone **178** was converted to the corresponding aldehyde by Rosenmund reduction of the acid chloride. A Wittig reaction using $\text{Ph}_3\text{P}=\text{CHC}(=\text{CH}_2)\text{Me}$ gave a mixture of naturally occurring marmelo lactone A (**173**) and the corresponding (*Z*)-isomer.²¹⁸ This route led to about 70% ee, and in order to examine the taste of each isomer, they have all been prepared in high optical purity from sugars.²¹⁹



The (+)-isomers were prepared from 2,3-*O*-isopropylidene-D-ribofuranose (**179**) as shown Scheme 20. A very similar route from 2,3-*O*-isopropylidene-D-mannofuranose (**180**) led to the (–)-isomers. The naturally occurring isomers [(+)-**173** and (–)-**174**] having the (2*R*)-configuration tasted more fruity, the configuration at C-4 having little influence on the taste.

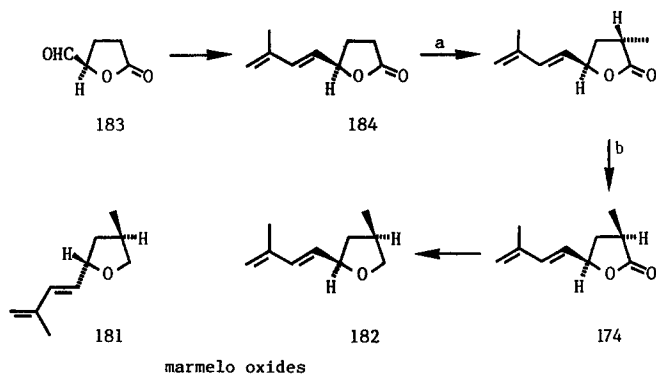


Scheme 20

The marmelo oxides (**181**, **182**) are actually tetrahydrofurans, but are placed here because of their close relationship with the marmelo lactones. They were also isolated from quince, and synthesized from the lactones by reduction.²²⁰ Their absolute configuration was further established by synthesis via the lactones from D-glutamic acid. This was converted to the chiral aldehyde **183**, which, after the side chain had been introduced using a Wittig reaction, gave the lactone **184**, which was then methylated. Lithium diisopropylamide and methyl iodide introduced the methyl group, but in the course of the reaction, 15% of material was epimerized to *epi*-marmelo lactone (**174**). This small proportion was then reduced (LiAlH_4) to *epi*-marmelo oxide (**182**) (Scheme 21).²²¹

5. SUBSTANCES RELATED TO CHRYSANTHEMIC ACID

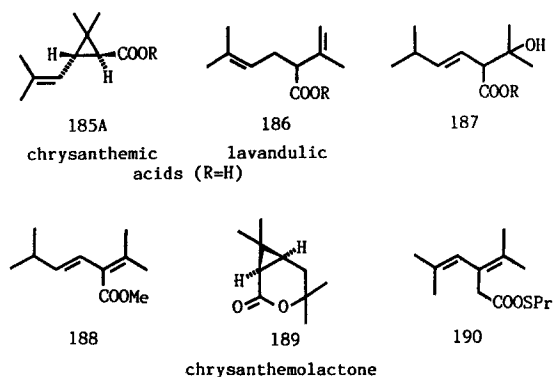
Conversion of chrysanthemic acid (**185**, $\text{R} = \text{H}$) to lavandulic acid (**186**, $\text{R} = \text{H}$) was previously well known (Vol. 4, p. 475, Ref. 171);²²² the action of aqueous sulfuric acid on the methyl ester **185** ($\text{R} = \text{Me}$) yielded mainly the



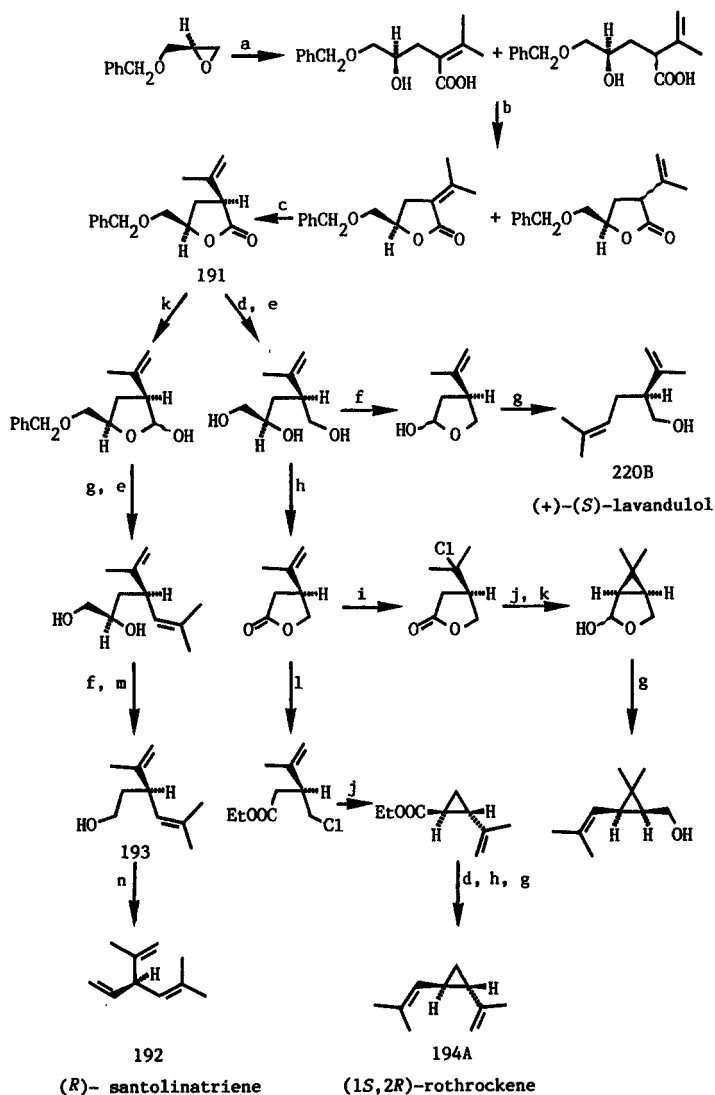
a) lithium diisopropylamide (LDA), MeI; b) LDA

Scheme 21

lavandulyl compound **187**, which subsequently underwent dehydration (to **188**) and lactonization in various ways.^{223*} A most interesting observation is that while the methyl ester **185** ($R = \text{Me}$) will cleanly give **188** with *p*-toluenesulfonic acid, the *n*-propyl thioester of chrysanthemic acid gives **190**, having the santolinyl skeleton.²²⁵ Since the acid-catalyzed rearrangements (of chrysanthemyl and lavandulyl esters) are reversible,²²³ there are means (on paper, at any rate) of going from one to another of the irregular monoterpenoids. There is, however, an ingenious route to four of the five irregular monoterpenoid skeletons—and which is even chiral.²²⁶ The key compound is the lactone **191**, prepared as shown in Scheme 22 from the known²²⁷ (*S*)-*O*-benzylglycidol. The essential step in the



*Some of these lactones, like chrysanthemolactone itself (**189**) have a potent inhibitory effect on germination.²²⁴



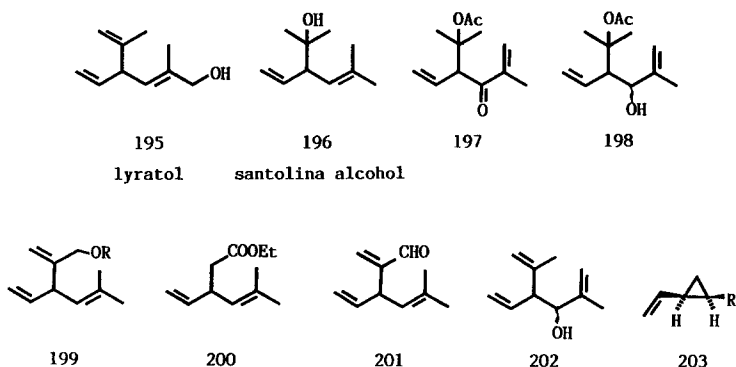
- a) $\text{Me}_2\text{C}=\text{CHCOOH}$ (59) + 2 lithium diisopropylamide (LDA);
 b) toluene, reflux; c) LDA, H^+ ; d) LiAlH_4 ; e) Li/NH_3 ; f) NaIO_4
 g) Wittig; h) pyr. chlorochromate; i) HCl/HOAc ; j) KOtBu ;
 k) DIBAL; l) SOCl_2 , EtOH; m) NaBH_4 ; n) $\text{o-NO}_2\text{C}_6\text{H}_4\text{SeCN}$, oxidize, eliminate

Scheme 22

synthesis of **191** depends on the fact that the enolate of the lactones in the previous step is protonated exclusively from the side of the tetrahydrofuran ring opposite to the benzyloxymethylene substituent.²²⁸ Most of the other steps work in reasonable yield, except the final step to (*R*)-santolinatriene (**192**). This step was effected by formation of the *o*-nitrophenylselenide of the alcohol **193**,²²⁹ then elimination of the selenide oxide, and worked only in 10% yield. It is clear that this scheme does not constitute a suitable preparative path, but it is particularly valuable for firmly establishing the absolute stereochemistry of all the irregular monoterpenoids, especially that of naturally occurring rothrockene,²³⁰ which must be (1*R*,2*S*), the opposite of the (1*S*,2*R*)-rothrockene (**194A**) synthesized.²²⁶

A. The Santolinyl Skeleton

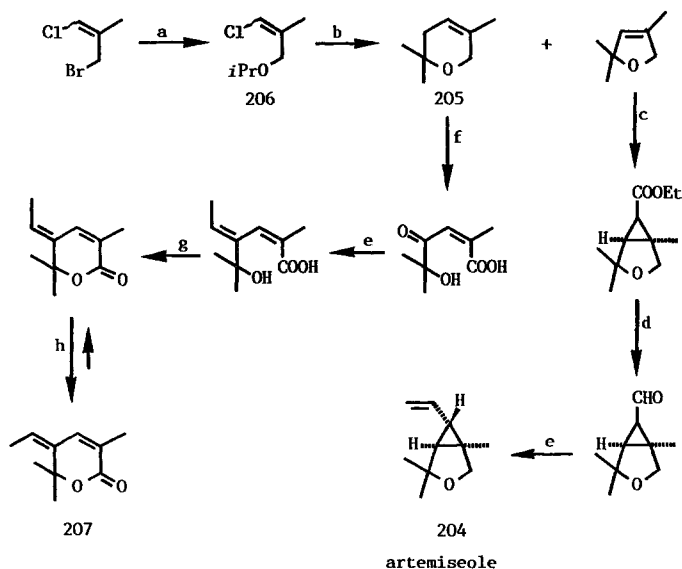
Artemisia species are rich sources of irregular monoterpenes. Thus *Artemisia vulgaris* contains a number of lyratol (**195**) esters, santolina alcohol (**196**) acetate, and the more oxygenated santolina compounds **197** and the two alcohols **198**. The (*Z*)-isomer of lyratol acetate was also found.²³¹ Lyratol (**195**) and its acetate



occur in tansey (*Tanacetum vulgare*),²³² and santolina alcohol (**196**) in *Achillea fragrantissima*.²³³ To make the more oxygenated compounds, lyratol (prepared by Sucrow's procedure, Vol. 2, p. 39, Ref. 140,²³⁴) acetate was photooxygenated, then reduction of the hydroperoxides gave a mixture of the two alcohols **198**. These were not separable on a preparative scale, but were oxidized directly to the ketone **197**.²³¹ A further new alcohol, "neolyratol" (**199**, R = H), was isolated from λ *Artemisia tridentata rothrockii*,²³⁰ its acetate, **199** (R = Ac), from *A. vulgaris*,²³¹ and its 2-methylbutyrate, **199** [R = COCH(Me)Et], from *A. douglasiana*.²³⁵ The synthesis of the alcohol, **199** (R = H), started from

5-methyl-2,4-hexadienol. The vinyl group was introduced by the reaction with ethyl orthoacetate and propionic acid, and the resulting ester **200** was converted to the corresponding aldehyde. The Mannich reaction then yielded the aldehyde **201**, which was reduced to the desired alcohol **199** ($R = H$).²³¹ The photooxygenation product **202** of santolinatriene (**192**) (without specification of the stereochemistry) has been isolated from sagebrush (*A. arbuscula arbuscula*) but was not synthesized.²³⁶ The absolute configuration was not discussed in any of these papers. A short synthesis of santolina alcohol (**196**) needs 1,1-dimethylcyclopropene. The latter will react with vinylmagnesium bromide to give vinylcyclopropylmagnesium bromide (**203**, $R = MgBr$). After Grignard addition of acetone, the alcohol obtained [**203**, $R = C(OH)Me_2$] was converted to santolina alcohol (**196**) with 30% perchloric acid in tetrahydrofuran.¹⁴⁴

Banthorpe and Christou have synthesized "artemiseole"* (**204**) (= arthole, Vol. 4, p. 475, Ref. 177–181) from 3-bromo-1-chloro-2-methylpropene (made from 1-chloro-2-methylpropene with *N*-bromosuccinimide) by the route shown



a) $iPrOH-NaOiPr$; b) $NaOtBu$; c) $N_2CHCOOEt$; d) $NaAlH_4$; e) Wittig;
f) SeO_2 ; g) dipyridyl disulfide/ Ph_3P ; h) $h\nu$

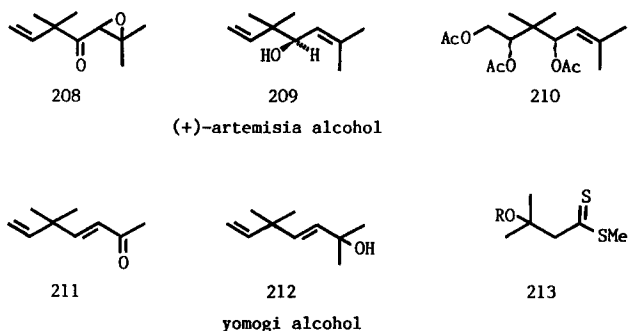
Scheme 23

*The name "artemiseole" is the third that has been given to this compound,¹⁷⁵ but is better than "artemesole" (Vol. 4, p. 475), which bears less relation to the botanical name.

in Scheme 23.²³⁷ The route was not particularly good preparatively, and two isomers of artemiseole were obtained, but an additional bonus was that the dihydropyran **205** obtained during the treatment of the isopropyl ether **206** with sodium *tert*-butoxide (presumably by ether exchange and cyclization of a carbene derived from **206**) could be converted to “chrysanthemum lactone” (**207**),²³⁷ a natural product we discussed previously (Vol. 4, p. 477, Refs. 185 and 186).

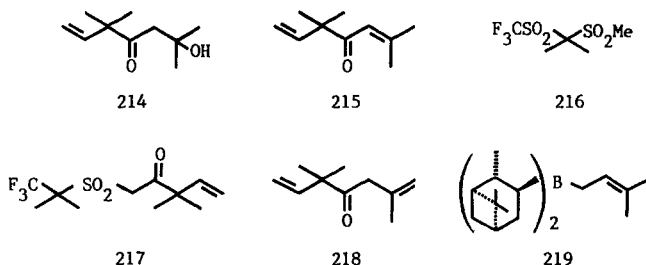
B. The Artemisyl Skeleton

New naturally occurring monoterpenes having the artemisia skeleton include artemisia ketone epoxide (**208**), isolated from *Artemisia vulgaris* and synthesized from prenyl chloride (**15**, R = Cl), and senecioic acid (**59**) chloride under Grignard conditions.^{231,238} (+)-Artemisia alcohol (**209**) has been isolated from *A. herba alba*²³⁹ [the usually encountered form is the (–)-(S)-isomer (–)-**209**]. An incompletely characterized triacetate **210** is also reported from the Brazilian plant *Calea oxylepis*.²⁴⁰



Further details and theoretical treatment have been published about the synthesis of artemisia ketone from trimethylprenylsilane (**15**, R = SiMe₃) and seneciyl chloride (**59** chloride) (Vol. 4, p. 478, Ref. 190).²⁴¹ Other routes employing coupling of a prenyl halide (usually the bromide) with another C₅ unit use “Cr(II)” [with senecio aldehyde (**84**) artemisia alcohol (**209**) was obtained in 88% yield]²⁴² or a graphite–tin alloy.²⁴³ Both the latter two syntheses were modified to prepare the ketone **211**, from which yomogi alcohol (**212**) could be prepared by a Grignard reaction.^{242,243} A C₅ unit, **213** (R = H), was made by addition of methylmagnesium iodide to the product of the addition of carbon disulfide to acetone, and prenyl bromide (**15**, R = Br) was added to the protected alcohol **213** [R = CH(Me)OEt], either via a Grignard reagent of prenyl

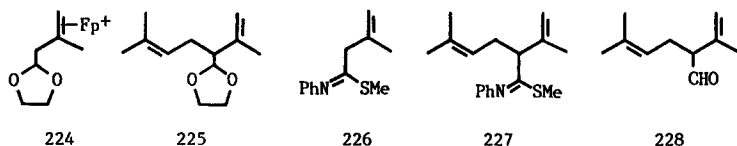
bromide, or by treating the protected alcohol with ethylmagnesium bromide then prenyl bromide. In either case the product was readily converted to the hydroxy ketone **214**, from which artemisia ketone (**215**) was obtained by dehydration with *p*-toluenesulfonic acid in benzene.²⁴⁴ Collonge's original synthesis of artemisia ketone started from 2,2-dimethyl-3-butenoyl chloride, but resulted in poor yields (Vol. 2, p. 41, Refs. 141 and 145), now Hendrickson has shown how this acid chloride reacts with a potentially C₃ unit, **216**, made by the action of methyl iodide and potassium carbonate on mesyl triflone (CF₃SO₂CH₂SO₂Me), which he calls a "nuclear synthon," that is, nucleus of reactivity, capable of rapidly elaborating round it a large product skeleton. The product from the reaction was the sulfone **217**, which underwent a Ramberg-Bäcklund reaction in the presence of sodium hydroxide and a phase-transfer catalyst to give artemisia ketone (**215**).²⁴⁵ It is also reported that 2,2-dimethyl-3-butenic acid will react with methallylmagnesium chloride to give isoartemisia ketone (**218**), which can be isomerized to the natural product **215**.²⁴⁶



The establishment of natural artemisia alcohol from sage as the (*S*)-isomer was announced by Zydowsky and Hill in 1982,²⁴⁷ and an elegant synthesis of both enantiomers by H.C. Brown utilizes the chiral borane **219**, which contains a prenyl group. Reaction of the illustrated enantiomer with senecio aldehyde (**84**) gave the addition product from which (–)-(*S*)-artemisia alcohol [(–)-**209**] was obtained after alkaline peroxide oxidation in 96% ee.²⁴⁸

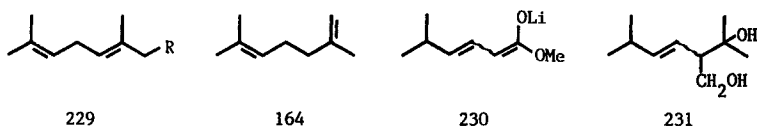
C. The Lavandulyl Skeleton

The arbitrary order in which we had previously taken the noncyclic irregular monoterpenoids (Vol. 2, p. 36; Vol. 4, p. 475) actually masks the fact that the lavandulyl skeleton is central to all of them, including chrysanthemic acid and the recently discovered rothrockyl skeleton. Although chrysanthemates can be converted to the lavandulyl skeleton with methanesulfonic acid,²⁴⁹ the biogenetic



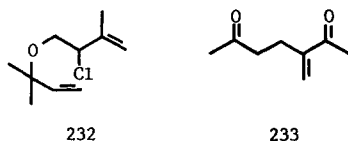
slightly involved treatment (first H_2S , then ethylmagnesium bromide, then CuCl_2 and CuO in acetone) to obtain lavandulal (**228**), which was difficult to purify.²⁵⁸

Another paper has been published on the Garber's $\text{C}_9 + \text{C}_1$ route,²⁵⁹ while the "Prins" route to lavandulol (Vol. 2, p. 46, Refs. 156, 163, and 164; Vol. 4, p. 482, Ref. 214) has received attention. Cookson and Mirza have suggested that the original use of the hydrocarbons **229** ($\text{R} = \text{H}$) and **164** with paraformaldehyde works as well²⁶⁰ as a suggested improvement using the trimethylsilyl compound **229** ($\text{R} = \text{SiMe}_3$);²⁶¹ indeed, it is possible to use the mixture of hydrocarbons, which equilibrates during the reaction.²⁶⁰



Introduction of an isopropyl group α to the carboxyl group of a 5-methylhexanoic acid derivative would lead to the lavandulyl skeleton. This has been carried out by making the lithium enolate (**230**) of methyl 5-methyl-2-hexenoate. After treatment with acetone and reduction of the ester group to a primary alcohol, the diol **231** was obtained.²⁶²

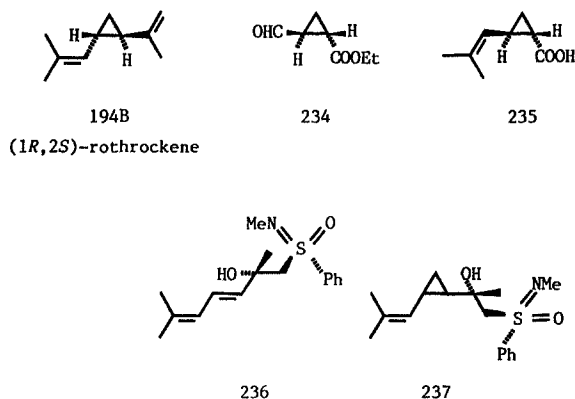
Formation of the lavandulyl skeleton using a sigmatropic rearrangement was known (Vol. 2, p. 44, Ref. 159). A modification consists in heating the chloro ether **232** with " $(\text{Ph}_3\text{P})_4\text{Pd}$ " [$= \text{Ph}_3\text{P} + \text{Pd}(\text{OAc})_2$]. Dehydrochlorination was accompanied by rearrangement to isolavandulal (**221**, $\text{R} = \text{CHO}$),²⁶³ (although it should be remembered that the iso series is not known to be naturally occurring). Isolavandulyl acetate (**221**, $\text{R} = \text{OAc}$) has also been made by double Grignard



addition of methylmagnesium chloride to the diketone **233**, followed by allyl rearrangement and dehydration in acetic anhydride and phosphoric acid.²⁶⁴

D. The Rothrockyl Skeleton

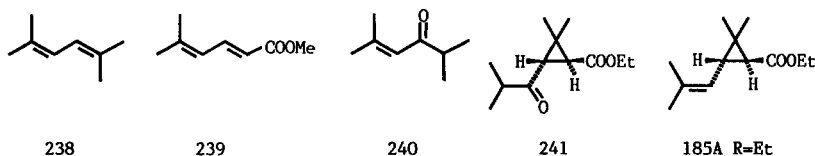
This novel skeleton was found in (1*R*,2*S*)-rothrockene (**194B**), a hydrocarbon isolated from *Artemisia tridentata rothrockii*²³⁰ and synthesized by the same authors by a Wittig reaction on commercial *trans*-2-formylcyclopropylcarboxylate (**234**), followed by a reaction using the salt-free phosphorane $\text{Ph}_3\text{C}=\text{CH}_2$ to complete the isopropenyl group. Epstein et al. also made (1*S*,2*R*)-rothrockene (**194A**) (the opposite of the naturally occurring material) by resolving the acid **235** obtained by hydrolysis of the ester resulting from the first Wittig reaction.²³⁰ The absolute configuration has also been confirmed by the Japanese synthesis referred to above²²⁶ (these authors imply that the chirality of the natural material was in doubt, which does not seem to have been the case), and by an X-ray crystallographic structure determination of the intermediate **236** in another chiral synthesis of rothrockene.²⁶⁵ Starting from 6-methyl-3,5-heptadien-2-one, optically active $\text{PhS}(=\text{O})(\text{Me})=\text{NMe}$ was added to the enolate. The resulting major stereoisomer, **236**, was purified by silica gel chromatography, and the cyclopropane ring, **237**, formed with zinc–silver couple and methylene iodide. To obtain (1*R*,2*S*)-rothrockene (**194B**) from **237**, reduction with aluminum amalgam was employed.²⁶⁵



E. Chrysanthemic Acid and Related Substances

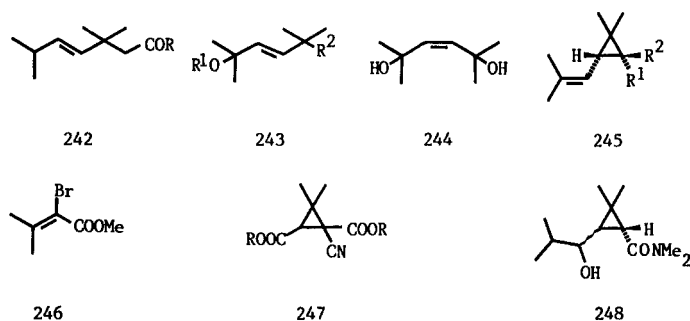
In this section, we have made an attempt at selectivity, in view of the very large amount of literature produced as a result of the commercial interest in chrysanthemic acid and the pyrethroids. In addition to a review in Japanese of the synthesis and reactions of chrysanthemic acid,²⁶⁶ there is an excellent review of the pyrethroid acids with an exhaustive literature list up to 1980.²⁶⁷ We shall only try to complete the latter. Many syntheses are destined as general routes for the preparation of substituted chrysanthemic acids, and those in which the isopropylidene methyl groups are replaced by halogen atoms.

The oldest syntheses of chrysanthemates are those starting from 2,5-dimethyl-2,4-hexadiene (**238**). There have been more papers on the use of rhodium²⁶⁸ or antimony²⁶⁹ to catalyze the addition of diazoacetate and chiral copper complexes to create asymmetry during the addition²⁷⁰ (see Vol. 4, p. 482, Refs. 219–222). The problem with this route is to avoid the use of diazo compounds. An old synthesis of Corey and Jautelat²⁷¹ used the ylide addition of a sulfurane to a suitable precursor (in this case a C₃ unit was added to methyl 5-methyl-2,4-hexadienoate, **239**),²⁷¹ and a recent paper gives details about the addition of ethyl dimethylsulfuranylideneacetate to 2,5-dimethyl-4-hexen-3-one (**240**). This led exclusively to the *trans*-isomer **241**, from which ethyl *trans*-chrysanthemate (**185**, R = Et) was made.²⁷² Other ylide additions are mentioned below.

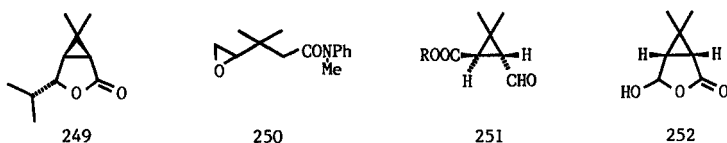


The alcohol corresponding to **240** was mentioned (Vol. 4, p. 484, Ref. 231) as the starting material for Ficini and d'Angelo's synthesis of chrysanthemic acid (**185**, R = H). With triethyl orthoacetate, a Claisen rearrangement led to the ester **242** (R = OEt), which then needed to be oxidized to the precursor **243** (R¹ = H, R² = CH₂COOEt) for cyclopropane ring closure via a carbanion. This synthesis has been further developed.²⁷³ For example, the diacetate of **244** will react with the sodium derivative of PhSO₂CH₂COOMe to give, after double-bond isomerization with Pd(PPh₃)₄, **243** [R¹ = H, R² = CH(COOMe)SO₂Ph]. This can be cyclized with sodium hydride to a mixture of *cis* + *trans* (1:1)

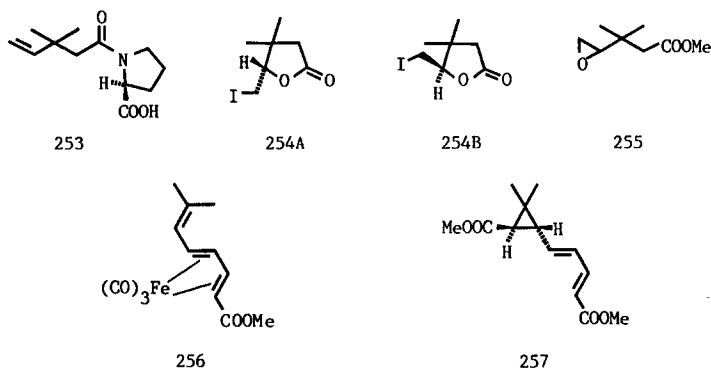
chrysanthemate analogs **245**.²⁷⁴ Other developments used malononitrile derivatives, **243** [$R^2 = \text{CH}(\text{CN})_2$],²⁷⁵ or methyl cyanoacetate derivatives, **243** [$R^2 = \text{CH}(\text{CN})\text{COOMe}$].²⁷⁶ Babler also made synthons for chrysanthemate-like molecules by cyclizing a carbanion onto a double bond, using ethyl 2-bromo-3-methyl-2-butenolate (**246**) as starting material. The latter reacted with methyl or ethyl cyanoacetate in the presence of sodium methoxide to give the cyclopropane **247** directly;²⁷⁷ other related substances have been made by condensing aldehydes with cyanoacetates before cyclizing.²⁷⁸



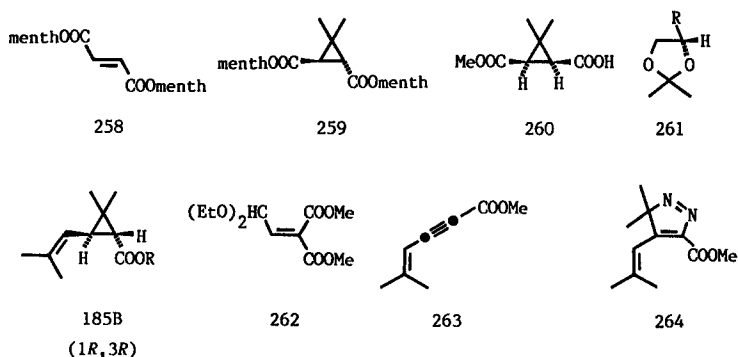
Instead of carbanion attack on a double bond, anion attack on an epoxide can be used to form the cyclopropane, and this is the basis of Snieckus' syntheses. Epoxidation of the amide **242** ($R = \text{NMe}_2$), followed by treatment with lithium diisopropylamide, gave the chrysanthemate skeleton **248** directly (*cis/trans* 1:3). Using the sulfur reagent $\text{Ph}_2\text{S}[\text{OC}(\text{CF}_3)_2\text{Ph}]_2$, the *trans*-isomer of **248** was converted to *trans*-chrysanthemic acid dimethylamide (**245**, $R^1 = \text{H}$, $R^2 = \text{CONMe}_2$), while the *cis*-isomer gave the lactone **249**.²⁷⁹ The synthesis was also carried out using the simpler epoxide **250** (which is, however, not so simple to make) and adding the isopropylidene side chain after cyclization.²⁸⁰ An attempted chiral synthesis of *trans*- (**251**) and *cis*-caronaldehydes (**252**) utilized the chiral amide **253** (from L-proline and 3,3-dimethyl-4-pentenoyl chloride). Iodine in acetonitrile followed by sodium bicarbonate solution gave the (*S*)-iodolactone **254A**, while iodine in aqueous tetrahydrofuran gave the (*R*)-enantiomer **254B**.



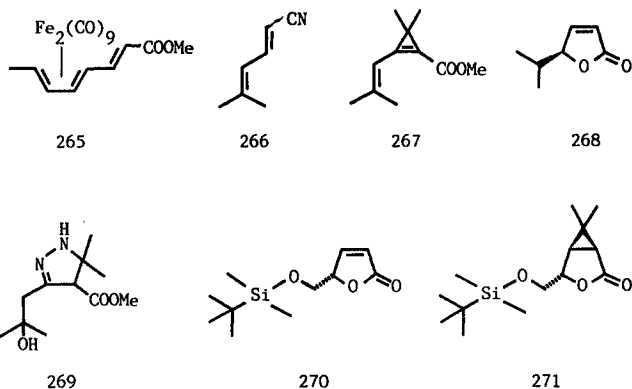
Unfortunately the optical purity was very low in these reactions. Nevertheless, the iodolactones were converted to the epoxides **255**, and these were cyclized to **251** ($R = \text{Me}$) and **252** with lithium hexamethyldisilazane.²⁸¹ The methyl ester **251** ($R = \text{Me}$) has also been made by copper-activated addition of methyl diazoacetate to the tricarbonyliron compound **256**. The product, **257**, was converted to **251** ($R = \text{Me}$) by a reaction sequence including ozonolysis to remove the side chain.²⁸²



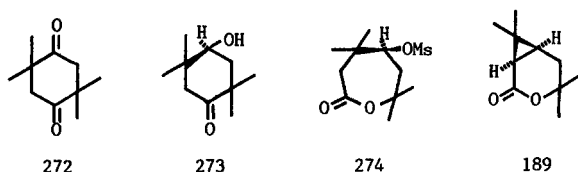
Two developments in the syntheses involving addition of a Me_2C group (with isopropylidenetriphenylphosphorane, Vol. 4, p. 486, Ref. 242) to fumaric acid derivatives have been published, with the idea of synthesizing chiral compounds. De Vos and Krief (whose names were originally attached to the route²⁸³) have used the dimethyl ester **258**, and obtained 74% diastereoisomeric excess (optically pure after one crystallization) of the *trans*-substituted cyclopropane



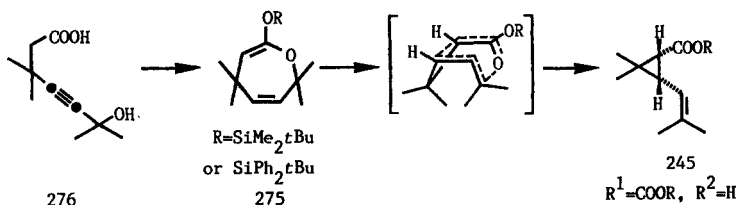
259, readily convertible to methyl *trans*-chrysanthemate (**185**, $R = \text{Me}$).²⁸⁴ They have also resolved *cis*-caronic acid half ester (**260**),²⁸⁵ accessible from maleic anhydride.²⁸³ Another route consisted in having the chirality present at the outset: protected (*R*)-glyceraldehyde **261** ($R = \text{CHO}$) was treated under the Horner-Wittig conditions to give the (*E*)-methyl ester **261** [$R = (E)\text{CH}=\text{CHCOOMe}$], before reaction with isopropylidenetriphenylphosphorane, and thence to (1*R*,3*R*)-chrysanthemic acid (**185B**, $R = \text{H}$).²⁸⁶ In place of the phosphorane, the potassium salt of 2-nitropropane has been used (the substrate this time was **262**).²⁸⁷ The Me_2C group has generally been added by means of diazopropane to an unsaturated compound by Franck-Neumann, who then removed the nitrogen from the resulting pyrazole by irradiation or thermolysis (cf. Vol. 4, p. 484). Thus the acetylenic ester **263** yielded the pyrazole **264**,²⁸⁸ the carbonyliron derivative **265**²⁸⁹ and the nitriles **266** gave dihydropyrazoles.²⁹⁰ Thermolysis of the dihydropyrazoles gave dimethylcyclopropanes, while the pyrazole **264** led by irradiation to a dimethylcyclopropene **267**, which was reduced with diimide to give methyl *cis*-chrysanthemate (**245**, $R^1 = \text{COOMe}$, $R^2 = \text{H}$).²⁸⁸ Diazopropane was also added to the lactone **268**, and nitrogen was removed from the product by irradiation, the cyclopropane being again finally converted to *cis*-chrysanthemate.²⁹¹ The use of diazopropane can be avoided by forming a dihydropyrazole from an unsaturated ketone and hydrazine. The dihydropyrazole **269** then had to be oxidized (MnO_2) before irradiation of the corresponding pyrazole.²⁹² Addition of diazopropane to the butenolide **270** followed by photochemical elimination of nitrogen led to the lactone **271**,²⁹³ the latter being in principle convertible to (1*R*,3*S*)-chrysanthemic acid (**245**, $R^1 = \text{COOH}$, $R^2 = \text{H}$) or its (1*S*,3*R*)-epimer, depending on which side of the lactone ring is to be used for adding an isopropylidene group. By means of a Wittig reaction on the lactol corresponding to **271**, the (1*R*,3*S*)-isomer was made.²⁹⁴



D'Angelo et al. have synthesized *cis*-chrysanthemic acid (**245**, $R^1 = \text{COOH}$, $R^2 = \text{H}$) from 2,2,5,5-tetramethylcyclohexane-1,4-dione (**272**), made from cyclohexane-1,4-dione.^{295,296} One of the keto groups was first converted to an hydroxyl group, either by metal hydride reduction,²⁹⁵ or by using the microorganisms *Curvularia lunata* or *Aspergillus ochraceus* to give the (*S*)-isomer **273**.²⁹⁶ Baeyer–Villiger oxidation (*m*-chloroperbenzoic acid) of the mesylate of **273** then yielded a seven-membered ring lactone **274**, which gave (+)-chrysanthemolactone (**189**) with sodium *tert*-amylate. Conversion of chrysanthemolactone to *cis*-chrysanthemic acid is well documented.²⁹⁶



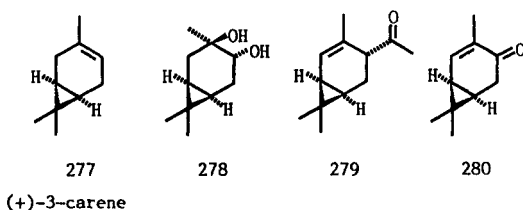
A route that is apparently related to that described in the preceding paragraph has been followed by Funk et al. They prepared the enol ether **275** of the “dehydrated” seven-membered ring lactone corresponding to **274**.²⁹⁷ This lactone resulted from the partial hydrogenation of the acetylenic hydroxy acid **276**. Thermolysis of **275** gave the *cis*-chrysanthemate **245** ($R^2 = \text{H}$) by what was believed to be a concerted reaction (Scheme 24). This step is, of course, not the same as that going from **274** to **189** in the d'Angelo synthesis, which goes through a carbanion retaining the chirality.



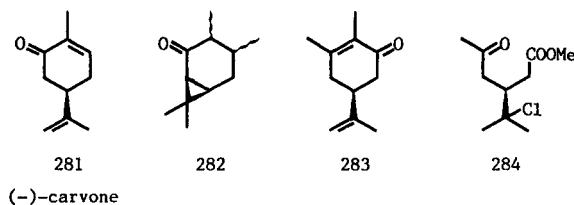
Scheme 24

The most common way of synthesizing (+)-chrysanthemolactone (**189**) is from (+)-3-carene (**277**) (cf. Vol. 2, pp. 55–56). Glycol fission of 3,4-caranediols, for example, occurred best with the *trans*-diol **278**,²⁹⁸ and the products were converted to methyl *cis*-chrysanthemate (**245**, $R^1 = \text{COOMe}$, $R^2 = \text{H}$) generally via the lactone **189**.²⁹⁹ Alternatively one can start from a 2-carene

derivative (Tse-Lok Ho has illustrated this approach with the 3-acetyl-2-carene **279**³⁰⁰ and with 2-carene-4-one, **280**³⁰¹), fission of the double bond (e.g., by ozonolysis) then leading to compounds from which the enantiomer of lactone **189** is accessible. Acetyl-2-carenes like **279** can also be substituted on the ring-carbon atom adjacent to the carbonyl group, making substituted chrysanthemic derivatives available.^{300,302} Further modifications and improvements of routes from carene to *cis*-chrysanthemate derivatives by the Indian workers have been published.³⁰³

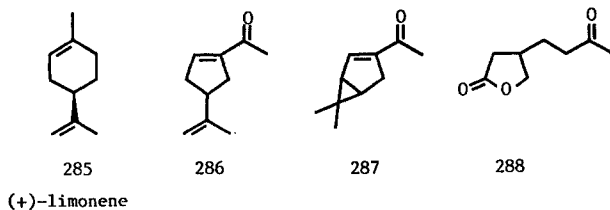


Carvone has also been used as starting material for chrysanthemic acids. One route involves the addition of a methyl group to (–)-carvone (**281**) with lithium dimethyl cuprate, then addition of hydrogen chloride and dehydrochlorination yielded the methylated carvone **282**, which was converted to (–)-chrysanthemolactone (**189** enantiomer) by ring fission with ethyl nitrite and sodium ethoxide, followed by conventional steps.³⁰⁴ The other route involves, first, Grignard addition of a methyl group to the carvone carbonyl group and chromium trioxide oxidation to the methylated carvone **283** [from (–)-carvone]. After addition of hydrogen chloride to the isopropenyl group, ring fission was effected by epoxidation of the double bond and electrolysis, and the product **284** could be converted conventionally to chrysanthemolactone (**189**). The series was followed with both (+)- and (–)-carvone.³⁰⁵

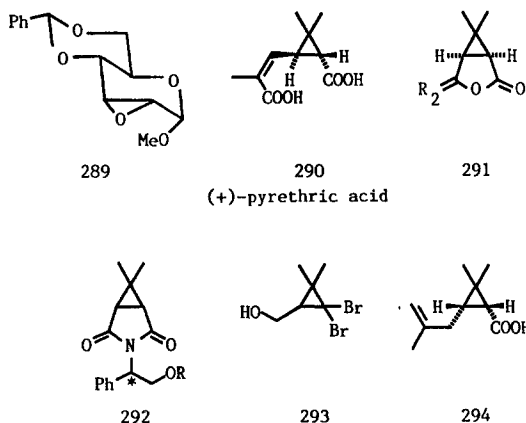


Somewhat long syntheses of chrysanthemic acid from limonene (**285**)³⁰⁶ and α -terpineol (**65**)^{306,307} have been reported. The initial step is in both cases ring

fission at the double bond (with ozone³⁰⁶ or bipyridyl chlorochromate³⁰⁷). The well-known cyclopentenyl methyl ketone **286** from limonene is hydrochlorinated and dehydrochlorinated to form the cyclopropane ring **287**, but treatment of homoterpenyl methyl ketone (**288**, the product of ring fission of α -terpineol) is more complex, and readers are better advised to consult the original papers.



Fitzsimmons and Fraser-Ried have converted the protected glycoside **289** into (+)-(290) and (-)-pyrethric acid. The route is long, and the introduction of the cyclopropane in **289**, using methyl diethylphosphonopropionate [(EtO)₂POCHMeCOOMe] occurred in only 50% yield, but both optical isomers were made from the same intermediate.³⁰⁸

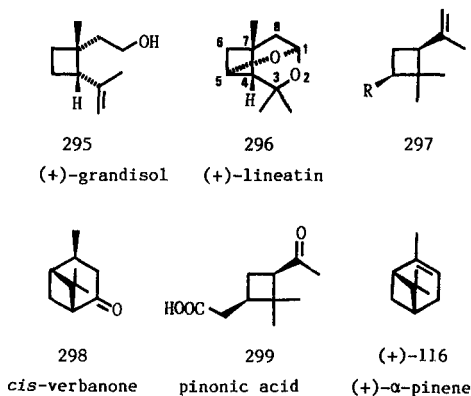


291 ($R_2 = O$). Under acetylation conditions the amide obtained cyclized to the imide **292** ($R = Ac$). One carbonyl group of the corresponding alcohol **292** ($R = H$) was selectively reduced, and after removal of the chiral auxiliary, the chiral lactone **291** ($R = H$) was obtained.³⁰⁹ A rapid route to racemic **291** ($R = H$) consists in the reductive carbonylation of the dibromocyclopropane **293** (from dibromocarbene and prenol) with tetracarbonylnickel in dimethylformamide, when up to 73% of the lactone **291** ($R = H$) can be obtained.³¹⁰

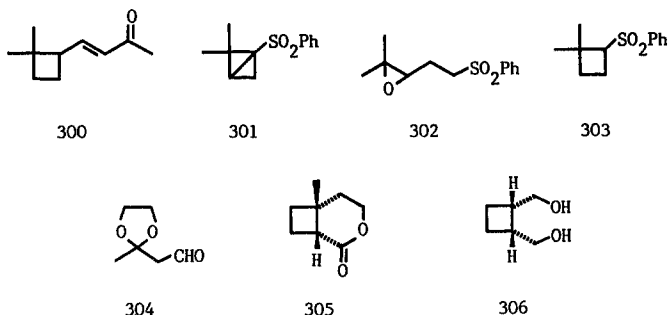
Use of 3,3-dimethylcyclopropene to make *cis*-isochrysanthemic acid (**294**) with 2-methyl-2-propenylmagnesium bromide followed by carbonation was mentioned in Vol. 4 (p. 487, Ref. 244); a new preparation of the cyclopropene and its reaction with prenylmagnesium bromide (**15**, $R = MgBr$) have now been described.³¹¹

6. CYCLOBUTANE MONOTERPENES

Most of the new synthetic work on cyclobutane monoterpenoids concerns the insect pheromone (+)-grandisol (**295**) (Vol. 2, p. 58; Vol. 4, p. 488) and (+)-lineatin (**296**), a pheromone of the Douglas fir beetle, *Trypodendron lineatum* (Vol. 4, p. 489, Ref. 255). There are, however, two other syntheses described, and these will be dealt with first.



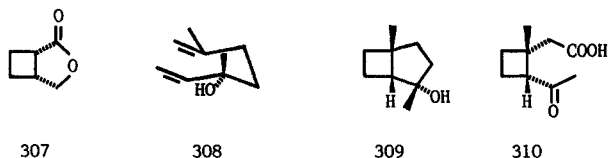
A cyclobutanemethyl acetate, *cis*-planococcyll acetate (**297**, $R = CH_2OAc$), was claimed as a constituent of the citrus mealybug (*Planococcus citri*, Risso) sex pheromone, and was prepared by photolysis of (+)-*cis*-verbanone (**298**) followed by reduction and acetylation of the product **297** ($R = CHO$).³¹² The compound shown is the (+)-(1*R*)-*cis*-isomer; the *trans*- and (–)-isomers were



much less active.³¹² The acetate **297** ($R = \text{CH}_2\text{OAc}$) has also been prepared from pinonic acid (**299**) made by permanganate oxidation of (+)- α -pinene [(+)-**116**]. Degradation of the carboxyl side chain, and Wittig methylenation of the acetyl group then led to the optically active pheromone **297** ($R = \text{CH}_2\text{OAc}$).³¹³

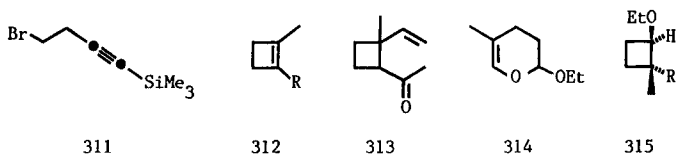
Junionone (**300**) (Vol. 4, p. 488) has been synthesized from 2,2-dimethylbicyclo[1.1.0]butan-1-yl phenyl sulfone (**301**), a compound made from the epoxide **302**.³¹⁴ The synthesis consists in reductive ring opening of **301** to a dimethylcyclobutane activated by a sulfone group, **303**, when the side chain is introduced by the action of 3-oxobutanal ethylene acetal (**304**) on the anion of **303**, and conventional conversion to the required butenone side chain.³¹⁵

The lactone **305** has been used in earlier syntheses of grandisol (**295**); it has now been prepared by a chiral synthesis, taking advantage of the stereoselective oxidation of 1,2-bis(hydroxymethyl)cyclobutane (**306**), which yields the lactone **307** with horse-liver alcohol dehydrogenase. It took seven steps to convert this lactone to **305**.³¹⁶ Oxidative fission of the 5-membered ring of suitably substituted bicyclo[3.2.0]heptanes also constitutes a well-tried route to grandisol, a new method to this skeleton being by irradiation of the dienol **308** (prepared in three steps from 3-chloro-2-methyl-1-propene) in the presence of Cu(I), which led to the alcohol **309**. Ozonolysis of one of the products of dehydration then gave the keto acid **310**,^{317a} transformation of which into grandisol (**295**) was already known (Vol. 4, p. 489, Ref. 260).*



*A new synthesis of optically active **310** leading to optically active grandisol was published too late for inclusion in the text.^{317b}

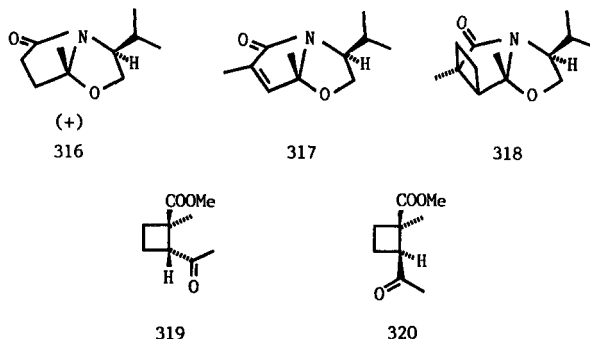
The discovery that 4-bromo-1-trimethylsilyl-1-butyne (**311**) cyclizes with trimethylaluminum in the presence of $\text{Cl}_2\text{Zr}(\eta\text{-C}_5\text{H}_5)_2$ to the cyclobutene **312** ($\text{R} = \text{SiMe}_3$) has been applied to a synthesis of racemic grandisol.³¹⁸ Acetylation of **312** ($\text{R} = \text{SiMe}_3$), followed by addition of $\text{Li}_2\text{Cu}(\text{CH}=\text{CH}_2)_2\text{CN}$ ³¹⁹ gave a 2:1 mixture of *cis*- and *trans*-isomers* of the ketone **313**. These isomers were presumably separated for the continuation of the synthesis, although the note published does not state this. In place of the necessary Wittig reaction on *cis*-**313**, the $\text{Me}_3\text{SiCH}_2\text{MgCl}$ reagent³²⁰ was used to convert **313** to grandisol [$(\pm)$ -**295**].³¹⁸ The authors do not mention whether they also synthesized the *trans*-isomer of grandisol (= fragranol, see Vol. 4, p. 488).



A possible approach to four-membered ring compounds (grandisol is cited particularly in the publication) consists of the treatment of the dihydropyran **314** (product of the reaction between methacrolein and ethyl vinyl ether) with triisobutylaluminum, leading to the alcohol **315** ($\text{R} = \text{CH}_2\text{OH}$), oxidation of which gave the aldehyde **315** ($\text{R} = \text{CHO}$). Although the latter readily reverts to the starting material **314**, it can be isolated and used (especially in the absence of transition metals).³²¹

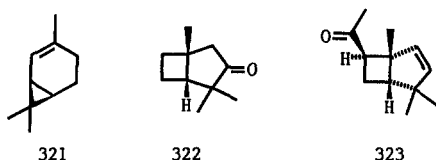
The $[2+2]$ cycloadditions frequently used to prepare cyclobutane monoterpenes have received an extra dimension by Meyers' use of a chiral enone. The amide **316** was prepared by azeotropic removal of water from (+)-(*S*)-valinol and levulinic acid. Introduction of a methyl group through the anion (made with *sec*-BuLi) and oxidation (Ph_2Se_2 then H_2O_2 in pyridine) yielded the chiral enone **317**, which underwent a $[2+2]$ cycloaddition with ethylene to give **318**, from which the chiral auxiliary was removed by acid. This yielded 55% of the fragranol precursor **319**, and 45% of the (–)-grandisol precursor **320**, from which, by conventional steps (Wittig, reduction, cyanide replacement, etc.), (–)-grandisol

*The authors call these (*Z*)- and (*E*)-isomers, but since this is impossible, we presume they mean *cis* and *trans*.



[(-)-**295**] was obtained; the synthesis using (-)-(*R*)-valinol should accordingly lead to (+)-grandisol (**295**). The overall enantiomeric excess was 88%.^{322*}

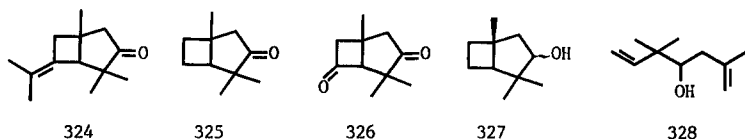
Two methods for preparing the bicyclo[3.2.0]-skeleton are described using 2-carenes. 2-Carene itself (**321**) yielded 1,4,4-trimethylbicyclo[3.2.0]hept-2-ene on irradiation in petroleum ether with a toluene sensitizer,³²³ the latter was converted to grandisol via the 3-ketone **322**. In acetone, irradiation of 3-acetyl-2-carene (**279**) yielded the bicyclo[3.2.0]heptene **323**, in principle also convertible into grandisol.³²⁴



The bicyclic ketone **324**, initially used to prepare lineatin (**296**) (below), has also been converted to the precursor **325** of grandisol (**295**). Ozonolysis of **324** yielded a diketone, **326**, the structure of which was confirmed by X-ray crystallography. Selective reduction of the cyclobutane carbonyl group was effected by borohydride reduction of the specifically formed

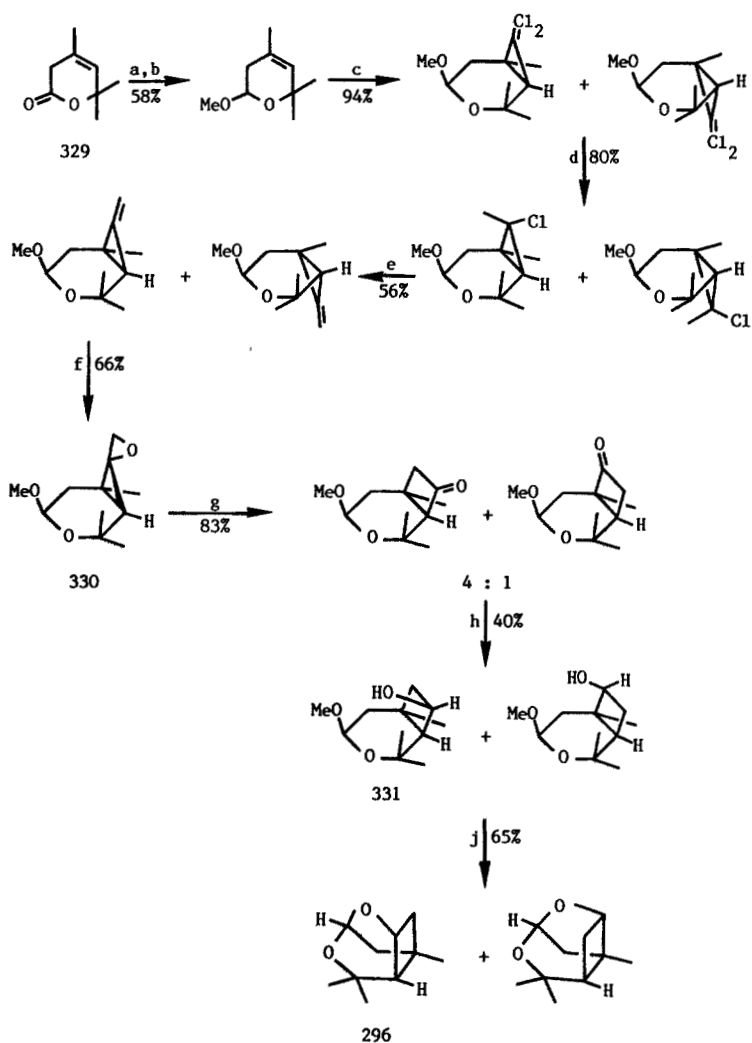
*New syntheses of (+)- and (-)-**320** from optically active ethyl 3-hydroxybutyrate, which led to grandisols of higher rotations than the published values, have been described by Mori (K. Mori, personal communication).

monotosylhydrazone.³²⁵ Conversion of **325** to grandisol (**295**) was described by Wenkert et al. some years ago (Vol. 4, p. 490, Refs. 265 and 266). Rosini et al. have prepared both stereoisomers of the alcohol **327** by irradiation of isoartemisia alcohol (**328**) in the presence of copper(I) trifluoromethanesulfonate.³²⁶ The transformation to **325** and grandisol is evident. (Two known syntheses of **328** are described in this paper.³²⁶)



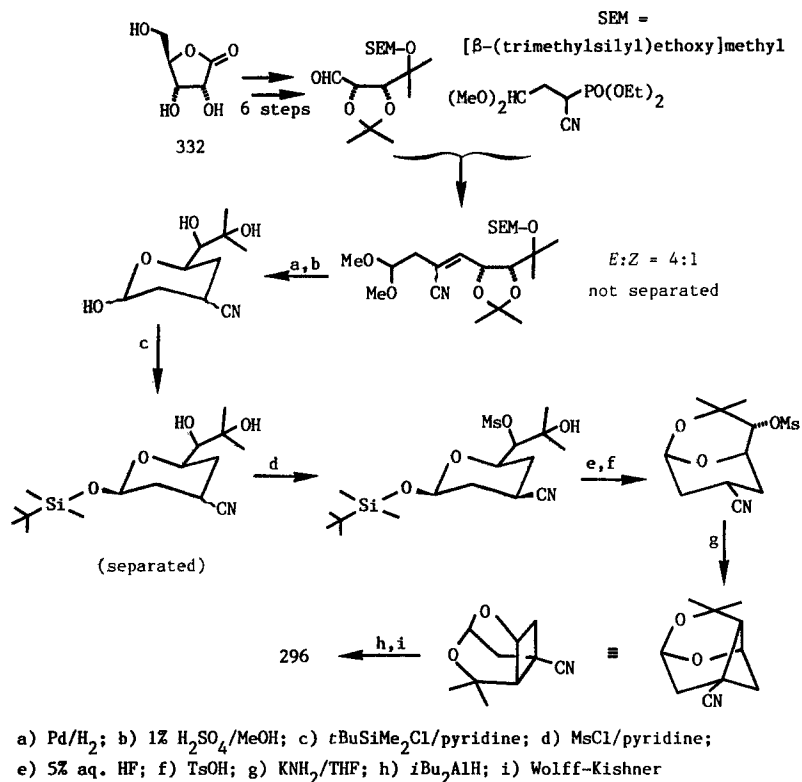
The full paper describing Mori's synthesis of lineatin (**296**) (Vol. 4, p. 489, Ref. 263) has been published.³²⁷ After converting the lactone **329** to ($\pm$)-lineatin using a [2 + 2] cycloaddition,³²⁸ Slessor et al. followed another route from the same lactone **329**, which is readily available by the Lewis acid-catalyzed addition of ketene to mesityl oxide. The route is shown in Scheme 25.³²⁹ In this scheme, the mixture arising from the carbene addition is not separated because, at the stage of the epoxide formation, only the major (desired) isomer **330** was isolated, the other being thermally unstable. The *exo* alcohols obtained in small amounts after the borohydride reduction (step h) were not isolated. To obtain the natural isomer of lineatin [(+)-(1*R*,4*S*,5*R*,7*R*)-**296**] the alcohol **331** was resolved with (–)-(*r*)-1-(1-naphthyl)ethyl isocyanate/triethylamine.³²⁹ The first stereospecific chiral synthesis of (+)-lineatin (**296**) started from D-ribonolactone (**332**), and is illustrated (in somewhat abbreviated form) in Scheme 26; it proceeded in 2.7% overall yield.³³⁰

It was actually in the course of a synthesis of Mori that the true absolute configuration of (+)-lineatin (**296**) was definitely confirmed.³³¹ This started with a [2 + 2] cycloaddition between isoprene and dichloroketene, giving a mixture of two isomeric dichlorocyclobutanones **333** and **334** (3.3:1). After reduction with zinc and acetic acid, the major cyclobutanone **335** was separated. Aldol condensation of the anion of **335** with acetone enabled the isopropyl side chain to be introduced. The later stages of the synthesis of ($\pm$)-lineatin are shown in Scheme 27, and the overall yield was 3.8%. In the course of this synthesis, however, the alcohol **336** was resolved using the chiral hydroxy lactone **252**, available from commercial (1*R*,3*R*)-*cis*-chrysanthemic acid.³³² The ether **337** was shown by X-ray crystallography to have the absolute configuration demonstrated. Since it was related to natural (+)-lineatin, the absolute configuration of the latter was established.³³¹



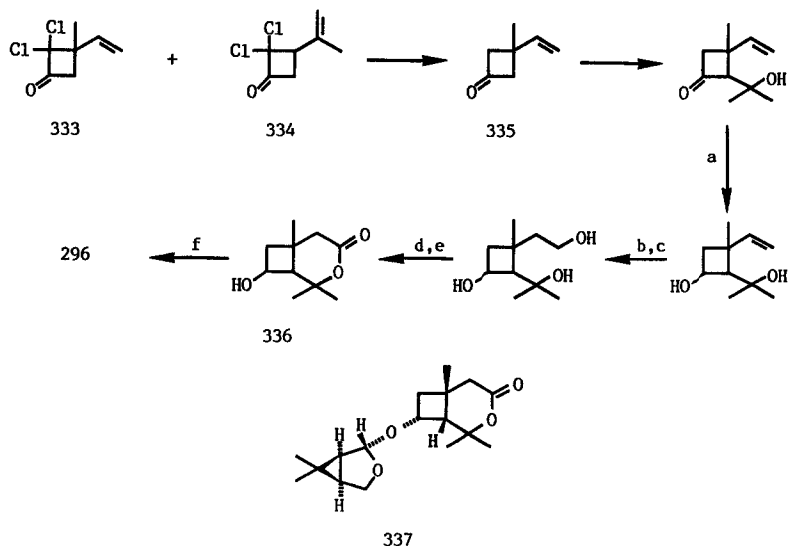
a) LiAlH_4 , THF; b) $(\text{MeO})_3\text{CH}$, NH_4NO_3 ; c) CHCl_3 , NaOH ; d) BuLi , MeI ;
 e) KOtBu/DMSO ; f) $p\text{-NO}_2$ perbenzoic acid, pH 6.4; g) $\text{LiBr/Li}_2\text{CO}_3/\text{MeCN}$;
 h) NaBH_4 ; j) TsOH

Scheme 25



Scheme 26

Two syntheses of (±)-lineatin start from anhydromevalonolactone (5,6-dihydro-4-methyl-2-pyrone, **338**), already used in the synthesis of cyclobutane monoterpenes (cf. Vol. 4, p. 489, Refs. 258 and 259). When the pyrone in acetonitrile saturated with a stream of acetylene was irradiated through Vycor, a 73% yield of the adduct **339** was obtained. After introduction of the *gem*-methyl groups (with methylolithium) and reoxidation (pyridinium chlorochromate), the lactone **340** obtained was hydroborated to yield **336**, together with an isomer with a hydroxyl group at the adjacent position. The alcohol **336** was converted to (±)-lineatin [(±)-**296**] by reduction of its tosylate with diisobutylaluminum hydride, followed by sodium hydride in ether³³³ (a procedure not very different from that used by Mori for converting this same lactone **336** to lineatin). Weiler's synthesis from **338** is broadly similar, except that in the first step he employs a photochemical addition with allene, making it necessary to employ ozonolysis at the point when the *gem*-methyl groups have been introduced (i.e., on the

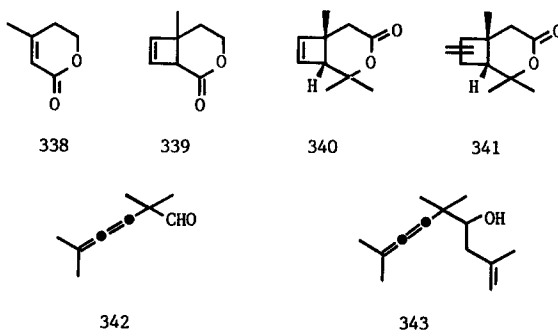


a) $\text{Li}(i\text{Bu})_3\text{BH}$; b) protect OH with $t\text{BuSiMe}_2\text{Cl}$; c) hydroboration-oxidation;
 d) pyr. dichromate; e) remove protection with Bu_4NF ; f) $i\text{Bu}_3\text{AlH}$, HCl

Scheme 27

mixture of isomers **341**) before carrying out the diisobutylaluminum hydride reduction to lineatin.³³⁴

The reaction of 2-methyl-2-propenylmagnesium chloride with the allenic aldehyde **342** (from isobutyraldehyde and 2-methyl-3-butyne-2-ol) gave the precursor **343** for an internal [2 + 2] cycloaddition. After oxidation and irradiation, the bicyclo[3.2.0]heptanone **324** obtained was converted to (±)-lineatin [(±)-

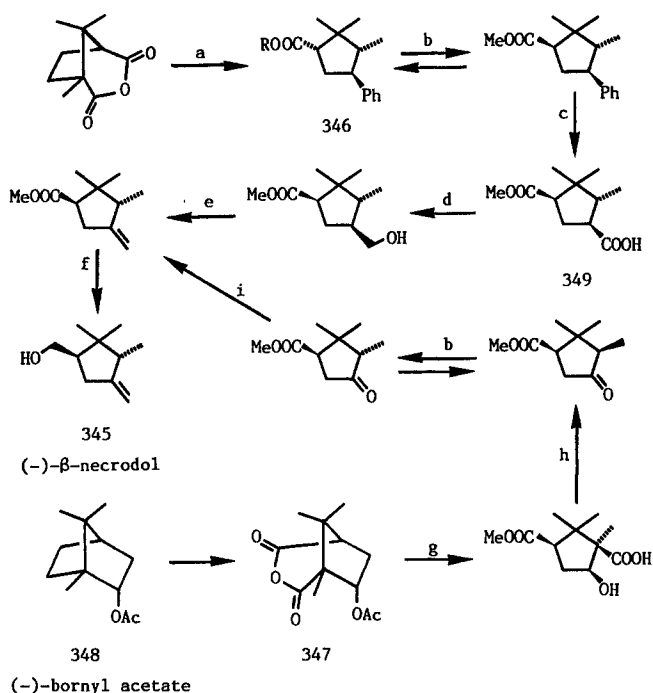


296] by oxidative removal of the isopropylidene group and diisobutylaluminum hydride reduction of the intermediate diketone.³³⁵

7. CYCLOPENTANE MONOTERPENES

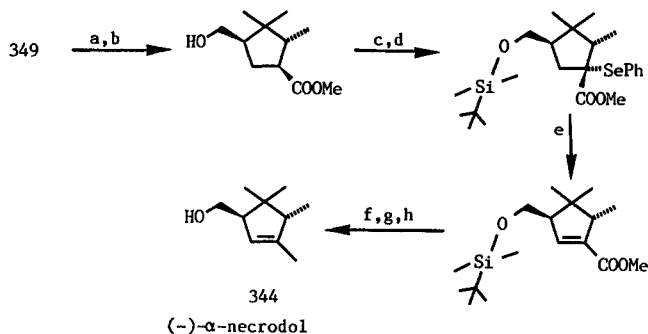
Attention is drawn to two reviews of the iridoids (there were more than 300 isolated in 1980),³³⁶ another of substances isolated from ant glands (which include particularly cyclopentanes and iridoids),³³⁷ a review of secologanin,³³⁸ and finally one about some aspects of the synthesis of iridoids, notably via 1,3,3a,4,7,7a-hexahydrobenzofuran-1-one.³³⁹

Possibly the most exciting cyclopentane monoterpenoid novelty is the discovery by Meinwald et al. of a new skeleton:^{10,340} two derivatives of 1,1,2,3,5-



Scheme 28

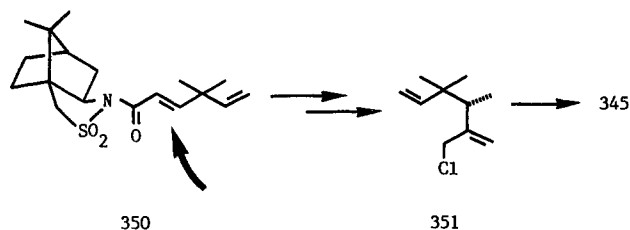
pentamethylcyclopentene, (–)- α - (**344**) and (–)- β -necrodol (**345**) occurring in the defense secretion of the carrion beetle *Necrodes surinamensis*. This skeleton is not derivable by direct cyclization of geranyl pyrophosphate, but could be derived by cyclization of lavandulol (**220**), with which the necrodols co-occur.¹⁰ In the course of a synthesis of the necrodols, phenylcamphoric acid (**346**, R = H), a convenient starting material, was found not to have the stereochemistry published earlier,³⁴¹ but was as shown.³⁴² After epimerization of **346** (R = Me), (–)- β -necrodol (**345**) was synthesized from the epimer, following Scheme 28. The anhydride **347**, obtained from (–)-bornyl acetate (**348**) was also converted to (–)- β -necrodol (**345**). Meinwald was unable to find conditions for rearranging the double bond in (–)- β -necrodol for synthesizing the α -isomer **344**, so a different route starting from acid **349** (Scheme 29) was used.³⁴⁰ It is impossible to do justice to these syntheses in a brief résumé; the many blind alleys are suggested by a glance at the reagents used, and even the determination of the absolute configurations of the natural products was not a trivial matter because of the paucity of material. [This was actually done using the ¹⁹F-NMR signal of the (–)- α -methoxy- α -trifluoromethylphenylacetate of (–)- α -necrodol.]



- a) Li/NH₃; b) CH₂N₂; c) *t*BuSiMe₂Cl; d) *n*BuLi, then PhSeCl;
 e) *m*-Cl-perbenzoic acid, then *i*Pr₂NH; f) LiAl(OEt)₃;
 g) Li/NH₃ on acetate; h) *n*Bu₄NF

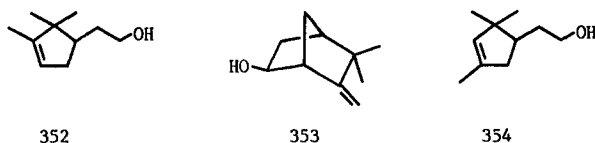
Scheme 29

Another (–)- β -necrodol synthesis has been described by Oppolzer and Schneider.³⁴³ Unfortunately this became known too late for a scheme to be included here, but it depends on a stereoselective addition of methylcopper to a camphor-derived sultamide **350**, occurring from the β -*Re*-bottom face. A further key step was the cyclization of the chloride **351** with activated magnesium and



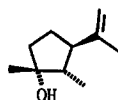
air oxidation of the product, yielding 61% of (1*R*)- β -necrodol (**345**), and (1*S*)-*epi*- β -necrodol.

There are regularly publications concerning the transformation of bornane derivatives [particularly camphor (**40**) oxime] to campholenyl derivatives, but there is no particular interest attached to them as syntheses of natural products. Nevertheless, we mention work on the Beckmann-type rearrangements of camphor oxime,³⁴⁴ and a route to campholenic alcohol (**352**) from the hydroxycamphene **353**.³⁴⁵ γ -Campholenol (**354**) has been identified in *Tanacetum vulgare*,²³² it was already synthesized many years ago.³⁴⁶ Some of the more interesting aspects of the conversion of bromocamphors to campholenic acids (with welcome corrections of the older literature) is being discussed by Money.³⁴⁷

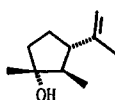


The plinol (**355**), thermal cyclization products of linalool (**28**) (Vol. 2, p. 61, Refs. 208 and 216; Vol. 4, p. 494, Ref. 285), have been synthesized by a new route, starting with Diels–Alder additions to 2,5-dimethylfuran. The adduct with maleic anhydride was said to be *exo*-, **356**,³⁴⁸ although no evidence was given, and the only reference quoted concerning this compound³⁴⁹ does not refer to stereochemistry. The adduct of furan and maleic anhydride is indeed known to be entirely converted to the *exo*-isomer after initial formation of the *endo*-isomer,³⁵⁰ and the NMR signal of the protons at the ring junction of **357** fit better to the known³⁵⁰ figure for *exo*-configuration, so the authors³⁴⁸ are probably correct. Conversion of **356** to the lactone **357**, by catalytic then borohydride reduction, was followed by ring opening (diphenyl sulfide then Raney-nickel-catalyzed hydrogenation) to **358**. The key step was the electrolytic reduction of **358** with sodium methoxide in methanol using graphite electrodes, which yielded

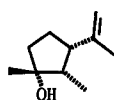
the acetal **359** of a ketone **360**, into which it was converted with acetic acid. Wittig reaction of this ketone yielded plinol C (**355C**), plinol A (**355A**) being obtained by epimerization of ketone **360** before converting the carbonyl to a methylene group. Plinol B (**355B**) was obtained from the *endo*-lactone corresponding to **357**, the required *endo*-adduct of 2,5-dimethylfuran being made by reduction of the 2,5-dimethylfuran adduct with dimethyl acetylenedicarboxylate.³⁴⁸



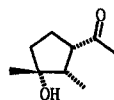
355A
plinol A



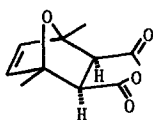
355B
plinol B



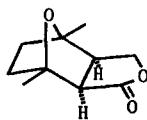
355C
plinol C



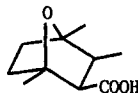
360



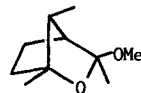
356



357



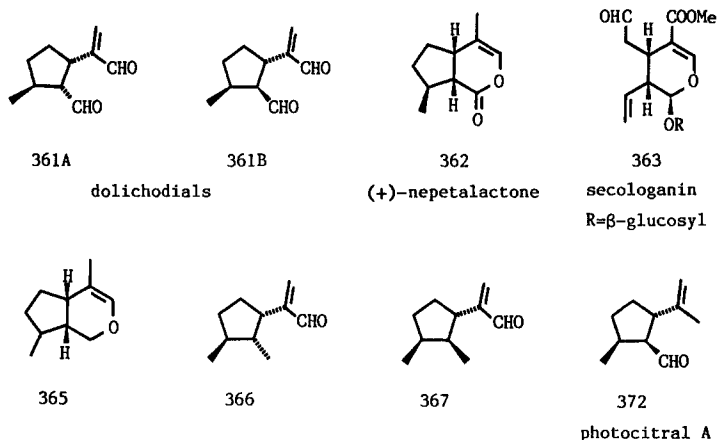
358



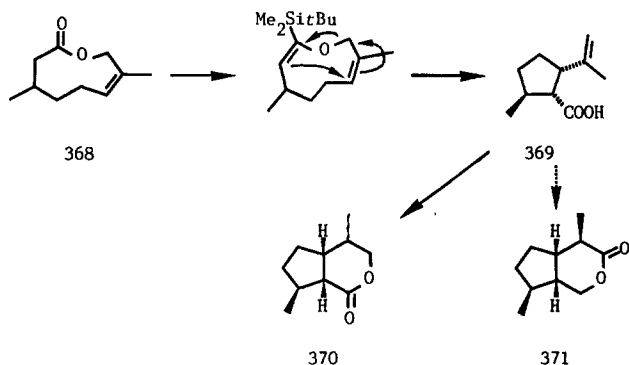
359

A. Iridoids

“10-Hydroxygeraniol” (**113**, R = H) is considered to be the starting point in the biosynthetic route to the dolichodials (**361A**, **361B**), which in turn are implicated in the biosynthesis of nepetalactone (**362**) and other iridoid lactones (cf. Vol. 4, p. 496, and references 351). Other terminally oxygenated 2,6-dimethyloctane terpenes are related to the iridoids; for example, 8-hydroxy-2,6-dimethyl-2,6-octadienal is incorporated into secologanin (**363**, R = β -glucosyl) when administered to *Catharanthus rosea*.³⁵² Some syntheses of iridoids also start from such open-chain compounds, but the link with biogenesis is more than tenuous! Although the enzymic cyclizations probably occur by a mechanism akin to acid catalysis,³⁵² cyclization of 2,6-dimethyl-2,6-octadiene-1,8-dial (dialdehyde corresponding to **113**) only occurs chemically under basic conditions. With very dilute sodium hydroxide in 98% aqueous methanol, an 82% yield of a mixture of dehydroiridodial (**364B**) and chrysomelidial (**364A**) was obtained.³⁵³ Cyclization of optically active 2,6-dimethyl-2-octene-1,7-dial also occurs with *N*-methylaniline and a molecular sieve. This has led to a synthesis of (unnatural) (–)-nepetalactone [(–)-**362**].^{353a} Synthesis of (natural) (+)-**362**, the structure shown, from a somewhat related diathiane has also been briefly reported.^{353b}

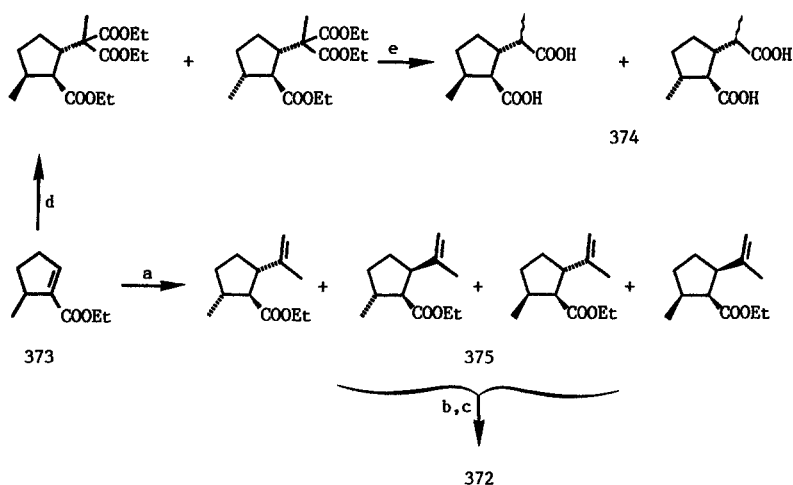


Snider has shown that thermolysis of 2,6-dimethyl-2,7-octadienal at 350°C yielded three compounds, **365–367**, having the iridoid skeleton.³⁵⁴ The lactone **368** was made by cyclization of the corresponding hydroxy acid (“8-hydroxy-citronellic acid”), and its *tert*-butyldimethylsilyl enol ether rearranged in an Ireland-type³⁵⁵ Claisen rearrangement, yielding the iridoid acid **369** after removal of the silyl group with HF in acetonitrile. The latter was converted (by hydroboration–oxidation) into both isomers of dihydronepetalactone (**370**) (erroneously considered to be “unsynthesized” by the authors, who clearly did not read Vol. 4, p. 497). Iridomyrmecin (**371**) is also accessible from **369**³⁵⁶ (Scheme 30).



Scheme 30

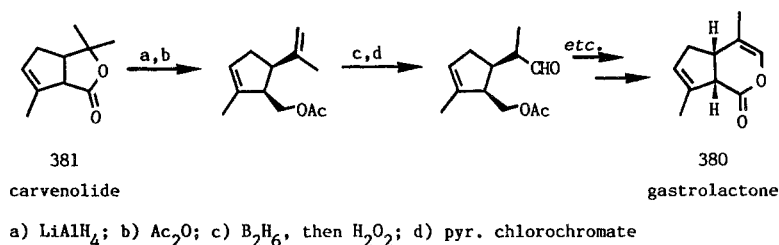
An improvement in the yield of photocitral A (**372**) has been described. Selenium dioxide oxidation of the acetal of **372** gave, after deprotection of the aldehyde group, a 22:78 mixture of **361A** and **361B**,³⁵⁷ but the yield at the selenium oxidation stage was low. Other work relating to the photochemical cyclization of citral (**32**) to photocitral A (**372**) and other compounds (including some novel ones) has also been published.³⁵⁸ Photocitral A itself is implicated in the biosynthesis of the iridoid lactones.³⁵⁹ It has been prepared from ethyl 5-methyl-1-cyclopentenylcarboxylate (**373**), a synthesis "in passing" one might say, because the authors at the same time were synthesizing the nepetalinic acids (**374**) as well as ester of the isomeric acids **375** corresponding to photocitral A (**372**) and its stereoisomers.³⁶⁰



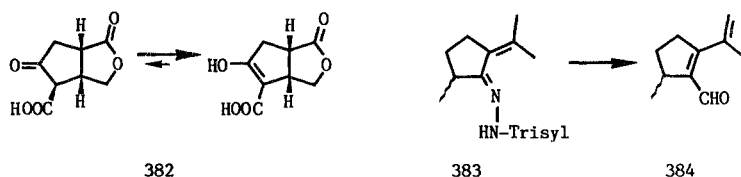
a) $\text{CuI} + \text{CH}_2=\text{C}(\text{Me})\text{MgBr}$; b) LiAlH_4 ; c) pyr. chlorochromate; d) $\text{MeCH}(\text{COOEt})_2$;
 e) hydrolyze, heat

Scheme 31

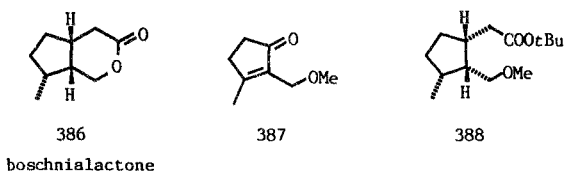
Other new syntheses of the isomers of the dolichodials, chrysomelidial (**364A**) and dehydroiridodial (**364B**), have been published. Methyl 2,4-dioxopentanoate and isoprene react together on irradiation to give two products, one of which, **376**, underwent ring closure to **377** with titanium dichloride (Scheme 32). Both aldehydes were available by this route because the monoacetal **378** equilibrates on aluminum oxide.³⁶¹ Furthermore, the acid of **377** has been resolved as the menthyl ester, making other double-bond isomers available.³⁶² A somewhat



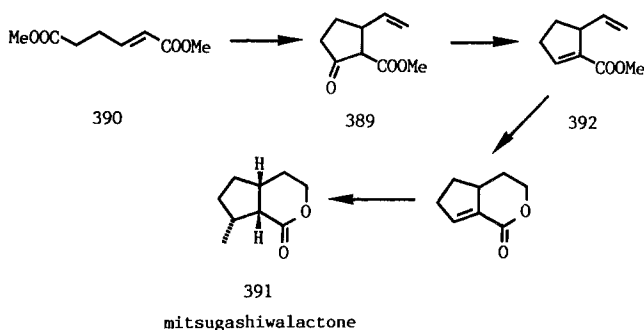
Scheme 33



Instead of cyclization of a dimethyloctane derivative (i.e., having a preformed iridane skeleton), attempts have been made to add suitable groups to a modified cyclopentane, formed from a simpler aliphatic precursor. Thus 2-isopropylidene-5-methylcyclopentanone is available from ethyl adipate (Dieckmann cyclization, then introduction of methyl and isopropylidene groups³⁶⁷) and its triisopropylphenylhydrazone **383** was used for introducing a formyl group (lithiation and dimethylformamide). The resulting conjugated aldehyde **384** is in principle convertible to the aldehyde precursor **385** of chrysomelidial (**364**) isomers, but although the authors of this work were able to introduce a methylthio group into **384**, they were unable to eliminate it to give **385**.³⁶⁸ Further work concerning tosylhydrazones of cyclopentanones has been described by the same authors,³⁶⁹ who have also prepared the noriridoid ($\pm$)-boschnialactone (**386**), by the action of $\text{LiCH}_2\text{COOtBu}$ on the cyclopentenone **387**. Catalytic reduction of the product gave the all-*cis*-isomer **388** from which the lactone **386** was readily accessible.³⁷⁰



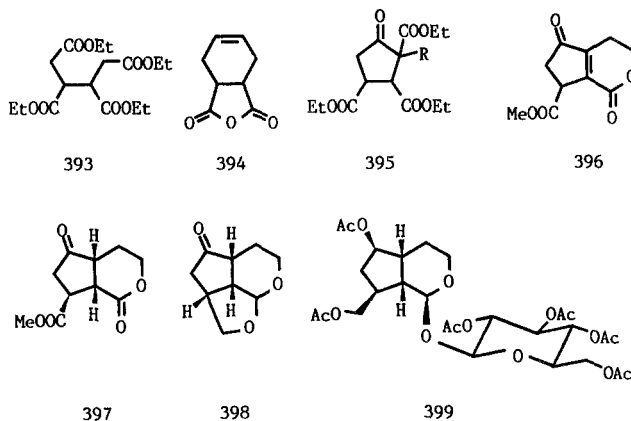
An improved method for the preparation of methyl 2-oxo-5-vinyl-cyclopentanecarboxylate (**389**) by treatment of dimethyl (*E*)-2-hexenedioate (**390**), with the cuprate made from vinyl lithium and copper(I) cyanide (77–85%),³⁷¹ led to a short synthesis of mitsugashiwalactone (**391**) (Scheme 34), another noriridoid isolated from *Boschniaka rossica*.³⁷² Borohydride reduction and dehydration gave methyl 5-vinyl-1-cyclopentenecarboxylate (**392**), and this could be cyclized by hydroboration and extended treatment with hydrogen peroxide—conditions for the highest yield in the cyclization seem to be with hydroboration in base—then a separate acid-catalyzed cyclization. The methyl group was added with lithium dimethyl cuprate.³⁷¹



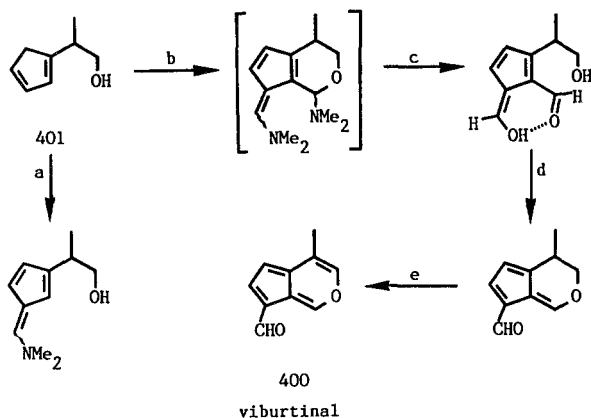
Scheme 34

For many years Obara et al. have been approaching the iridoid skeleton from cyclopentanonecarboxylates. These are available by Dieckmann condensation of, for example, the tetracarboxylate **393** obtained by permanganate oxidation of the Diels–Alder adduct **394** of maleic anhydride and butadiene.³⁷³ Iodoethyl acetate with the anion of **395** ($R = H$) then gave the acetate **395** ($R = CH_2CH_2OAc$), which was cyclized to the lactone **396** by successively, bromination (to **395**, $R = CH_2CH_2Br$) and $CaCO_3$ in dimethylformamide (ester exchange yielding the methyl instead of the ethyl ester).³⁷⁴ The saturated lactone **397**, was then obtained by catalytic hydrogenation,³⁷⁴ or more easily by treatment of **395** ($R = CH_2CH_2OAc$) with 10% sulfuric acid and re-esterifying with diazomethane.³⁷⁵ Careful partial lithium aluminum hydride reduction of the ethylene ketal of **397**, followed by acid cyclization then gave ($\pm$)-tetrahydroanhydroaucubigenone (**398**),³⁷⁴ while transformation of **397** to hexaacetyl tetrahydroaucubin A (**399**) was accomplished by reduction of the keto group with sodium borohydride before carrying out the other reductions and glycosidation.³⁷⁵

Addition of a C_3 unit (ethyl α -bromopropionate) to cyclopentadiene anion forms the start of a synthesis of viburtinal (**400**),³⁷⁶ isolated from *Viburnum* spp.



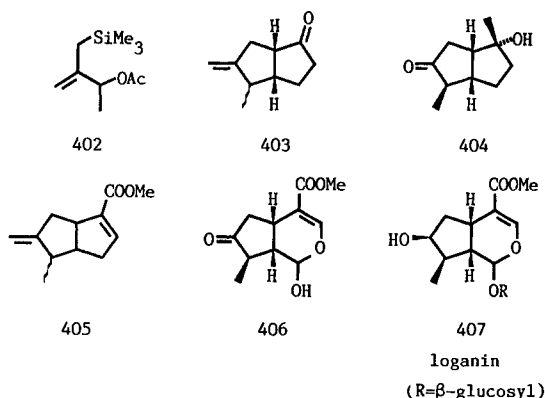
(Caprifoliaceae).³⁷⁷ Lithium aluminum hydride reduction of the ester produced a mixture of the alcohols **401**, and Alazard et al. were able to find conditions under which these alcohols could be doubly formylated (see Scheme 35); a discussion of this interesting reaction has been given.³⁷⁸ Cyclization of the dialdehyde and dehydrogenation completed the synthesis of **400**.³⁷⁶



a) $\text{Me}_2\text{NCH(OMe)}_2$ (1.1 eq.), 1,2-dimethoxyethane (DME), 40° ;
 b) $\text{Me}_2\text{NCH(OMe)}_2$ (5 eq.), DME, 24h reflux; c) 1M NaOH and $(\text{COOH})_2$ in DME (pH 4); d) anhyd. C_6H_6 and anhyd. $(\text{COOH})_2$ cat., 1h reflux; e) dichlorodicyanoquinone (1.5 eq.), anhyd. C_6H_6 , 4h reflux

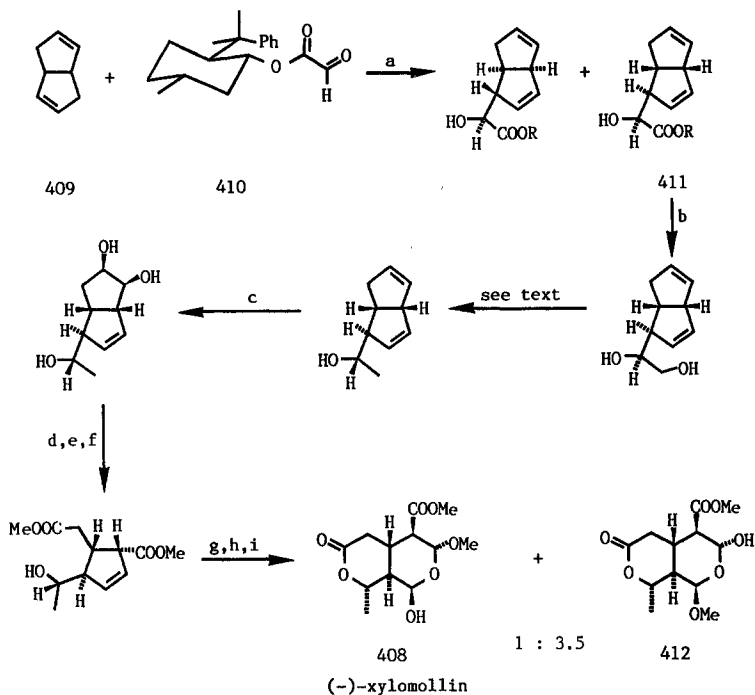
Scheme 35

We have earlier discussed routes to iridoids that depend on oxidative ring opening of a bicyclo[3.3.0]octene (Vol. 4, p. 499). One method of creating this bicyclic system has been exploited by Trost, and consists in the addition of a trimethylsilyl compound (for example **402**) to cyclopentenone in the presence of a palladium catalyst, when 52% of the bicyclo[3.3.0]octanone **403** was obtained. Addition of methyl lithium followed by ozonolysis yielded the bicyclo[3.3.0]octanone **404**, a suitable precursor of chrysomelidial (**364A**).³⁷⁹ From the tosylhydrazone of **403**, it was relatively simple to prepare the unsaturated ester **405**, ozonolysis of which yielded (after zinc reduction) didehydrologanin aglucone (**406**),³⁸⁰ which had already been converted to loganin (**407**, R = β -glucosyl).³⁸¹



Whitesell and Minton have synthesized (–)-xylomollin (**408**), the only *trans*-fused iridoid, from the racemic bicyclic diene **409**. Control of the stereochemistry was effected in the first step by addition of the glyoxylate **410**. The two products were separated and the major one, **411**, was reduced with lithium aluminum hydride. Conversion of the primary alcohol to a methyl group, with concomitant inversion of stereochemistry at the secondary alcohol carbon atom was carried out by protection of the primary alcohol function (*tert*-butyldimethylsilyl), tosylation of the secondary hydroxyl, then removal of the silyl group with formation of an epoxide with inversion, and reduction (LiEt₃BH) of the epoxide. The remaining steps are shown in Scheme 36. It remains to point out that isoxylomollin (**412**) was produced preferentially, and is indeed formed from xylomollin (**408**) slowly in methanolic solution.³⁸²

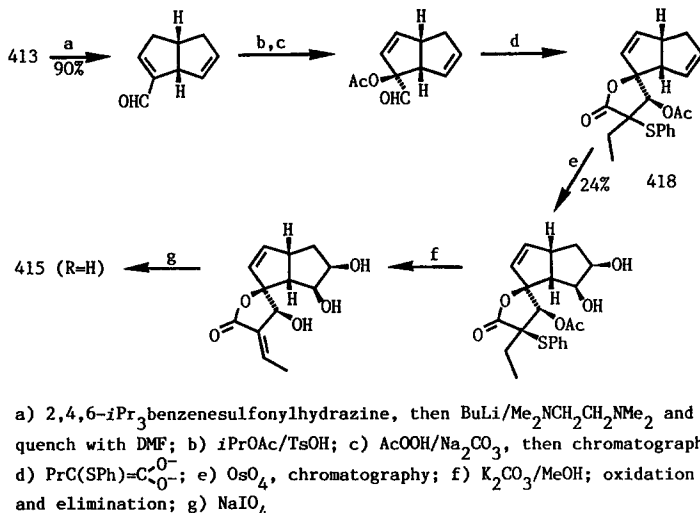
Use of bicyclo[3.3.0]oct-7-en-2-one (**413**), prepared from 1,3-cyclooctadiene, has been mentioned by us (Vol. 4, pp. 501–502, Ref. 314), and a new method for the resolution of its alcohol precursor has been described,³⁸³ so that it is



a) SnCl_4 , -78° ; b) LiAlH_4 ; c) OsO_4 , *N*-methylmorpholine *N*-oxide;
 d) NaIO_4 ; e) Ag_2O ; f) CH_2N_2 ; g) O_3 ; h) $\text{H}_2/\text{C-Pd}$; i) 1 eq. HOAc , MeOH

Scheme 36

available in optically active form. Two syntheses of the biologically active lactone plumericin (**414**) and allamcin (**415**, $\text{R} = \text{H}$) [related to allamandin (**415**, $\text{R} = \text{COOMe}$), and all isolated from *Allamanda* spp.],³⁸⁴ start from this substance. Trost's synthesis of plumericin is outlined in Scheme 37,³⁸⁵ and attention is drawn to the following points. The stereochemistry of plumericin (**414**) was introduced by the chemoselective ring expansion of **416**, when **417** was obtained in nearly 100% diastereoisomeric purity. The ease of the cyclization (merely by buffering the periodate cleavage step) to allamcin (**415**, $\text{R} = \text{H}$) stereospecifically was suggested to represent the biosynthetic pathway, this step being postulated to occur even without enzyme catalysis. The synthesis was carried out on ($\pm$)-**413** but, in principle, synthesis of the separate enantiomers of plumericin (**414**) is possible.³⁸⁵ Conversion of plumericin (**414**) to allamandin (**415**, $\text{R} = \text{COOMe}$) was effected by heating in 0.01*N* perchloric acid at 95 – 100°C for 9 hours, when 31% of plumericin was recovered, 39% was transformed into allamandin, and

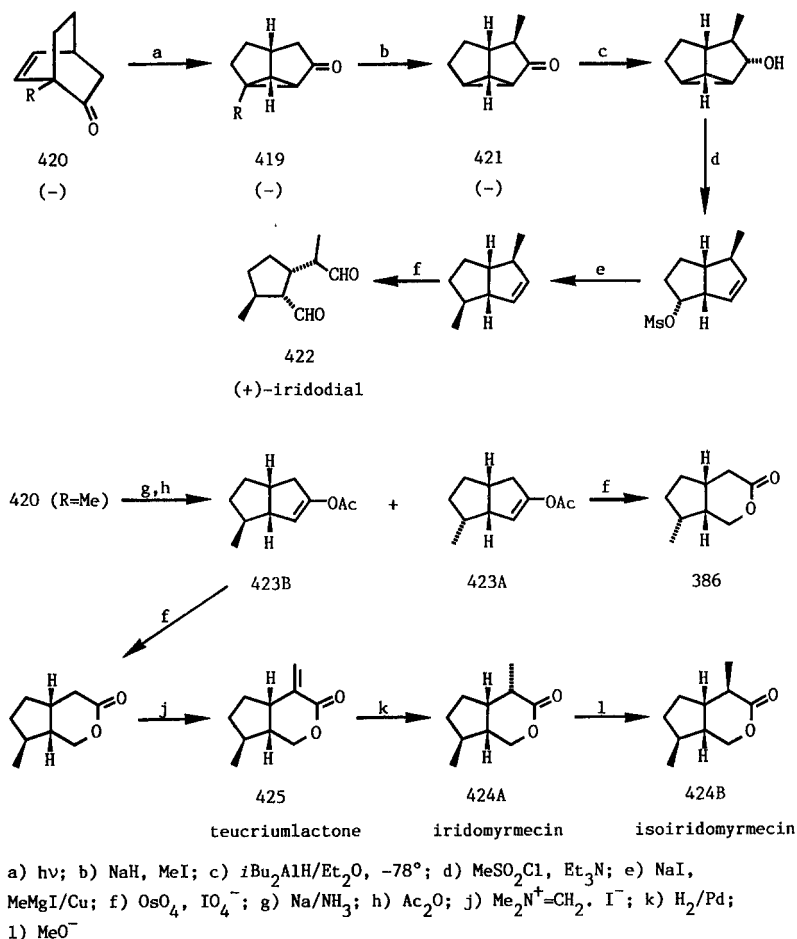


Scheme 38

cleavage and cyclization as before (several routes, one of which is shown in Scheme 38).³⁸⁸

Perhaps the most extensive work based upon the bicyclo[3.3.0]octanones has been associated with their preparation from various tricyclo[3.3.0.0^{2,8}]octane precursors. The formation of the ketone **419** (R = H) by irradiation of bicyclo[2.2.2]oct-5-en-2-one (**420**, R = H) was described in 1971 by Carlson et al.,³⁸⁹ and has been developed by Schaffner and Demuth and their co-workers to provide syntheses of a number of iridoids. They first improved the synthesis and effected the optical resolution of **420** (R = H) using a chiral acetal,³⁹⁰ then showed how the methylation occurred stereospecifically,³⁹¹ converting the product **421** to (+)-iridodial (**422**) (Scheme 39).³⁹² Starting from the methylated bicyclo[2.2.2]octanone **420** (R = Me), they prepared the methylated tricyclo[3.3.0.0^{2,8}]octanone **419** (R = Me), ring opening of which with sodium in liquid ammonia gave, after acetylation, two acetates, **423A** and **423B**, convertible respectively into boschnialactone (**386**) or the iridomyrmecins [**424A** and (iso) **424B**], via teucriumlactone (allodolicholactone, **425**).³⁹³

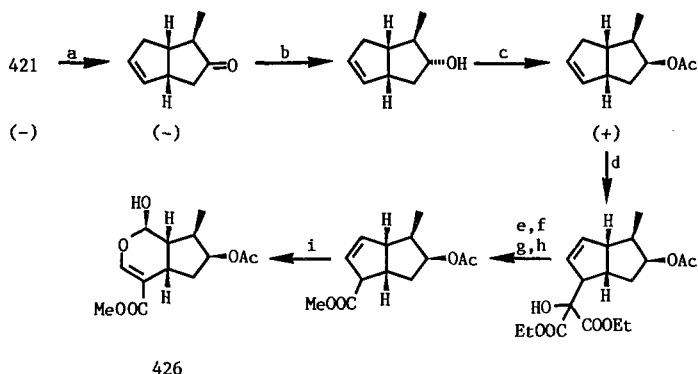
For loganin aglucone-6-acetate (**426**), the synthesis was adapted to use oxidative ring opening of the cyclopentane ring not containing the carbonyl group. Thus the cyclopropane was opened by catalysis with Nafion-Me₃Si (a perfluorinated trimethylsilyl sulfonate resin), as shown in Scheme 40. The synthesis is seventeen steps long from 1,3-cyclohexadiene, and gives enantiomerically pure loganin aglucone-6-acetate (**426**).³⁹⁴ Recently, the same



Scheme 39

group has been examining the irradiation of bicyclo[2.2.2]octenediones, potential precursors for bicyclo[3.3.0]octanediones, but this has been with a view (so far) of making sesqui- rather than monoterpenes.³⁹⁵

($\pm$)-Isoiridomyrmecin (**424B**) has been made by a somewhat different route, but along the same lines as Scheme 39, by Wender and Dreyer. Irradiation of benzene and vinyl acetate gave their starting material, the tricyclo[3.3.0.0^{2,8}]octenyl acetate **427**. This was converted (via the alcohol and the corresponding ketone) to **428** (= dehydro-**421**). Introduction of the methyl group in the unsaturated ring occurred with Me_2CuLi . Two products were

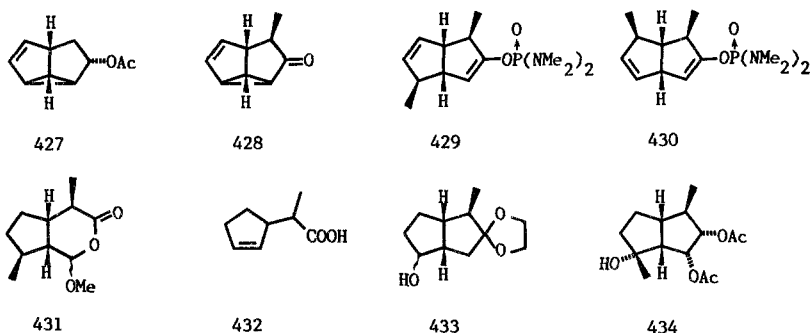


- a) Nafion-Me₃Si, toluene, 80°; b) NaBH₄; c) Et₄NOAc on mesylate;
 d) OC(COOEt)₂, TiCl₄; e) 10% KOH; f) NaIO₄/pyridine; g) CH₂N₂;
 h) Ac₂O/pyridine; i) OsO₄, then NaIO₄

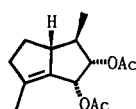
Scheme 40

obtained, isolated as their enol phosphoramides **429** and **430**, the former of which, after catalytic reduction and ozonolysis, gave the acetal **431**, reducible by NaBH₃CN to isoiridomyrmecin (**424B**).³⁹⁶

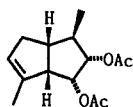
Kon and Isoe have also been examining routes from tricyclo[3.3.0.0^{2,8}]octanes,³⁹⁷ but the latter were prepared by an alternative route from the diazoketone made from the cyclopentenylpropionic acid **432**. This yielded the tricyclic ketone **421**,³⁹⁸ but as a mixture of both possible isomers. On treatment with formic acid and ketalization, the major product obtained was **433**. The fact that the hydroxyl group is present as both stereoisomeric forms is unimportant, because oxidation and treatment with methyl lithium yielded (±)-**404**, also prepared by Trost (see



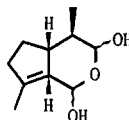
above), and converted to chrysomelidial (**364A**) by first introducing a double bond in place of the carbonyl group (Shapiro reaction), then oxidation of this double bond (OsO_4), yielding **434** after acetylation, together with another isomer and a little triacetate. Dehydration of **434** ($\text{POCl}_3/\text{pyridine}$) gave two diacetates, **435** and **436**, the glycol from **435** then being oxidized with NaIO_4 to chrysomelidial (**364A**). (The other glycol, after oxidation, required treatment with acetic acid to liberate chrysomelidial from the internal acetal **437**.)³⁹⁷ In a



435

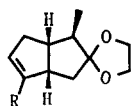


436

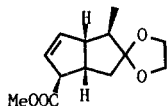


437

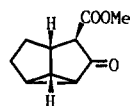
later paper (but with a dearth of experimental detail) the same authors have described a route to ($\pm$)-dehydrologanin aglucone (**406**) from **433**.³⁹⁹ Oxidation to the corresponding ketone was followed by treatment of the ketone tosylhydrazone with butyllithium, trapping the vinyl anion produced with either dimethylformamide to give the aldehyde **438** ($\text{R} = \text{CHO}$), or with methyl chloroformate to yield the ester **438** ($\text{R} = \text{COOMe}$). Kinetic protonation of the enolate of the ester **438** ($\text{R} = \text{COOMe}$) yielded the unsaturated ester **439**, which could then undergo oxidative ring fission to yield ($\pm$)-didehydrologanin aglucone (**406**).³⁹⁹



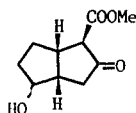
438



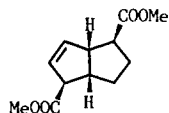
439



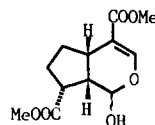
440



441



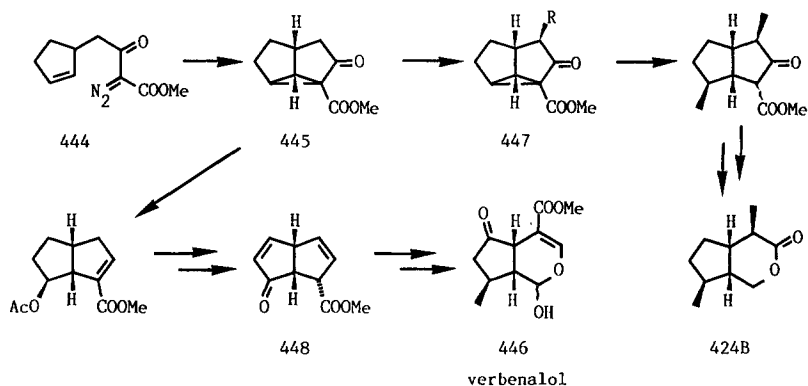
442



443

Another modification consists in introducing an ester group into **419** ($\text{R} = \text{H}$), giving **440**. Ring opening with formic acid gave the formate of **441**, the keto group of which was deoxygenated via the thioketal. Oxidation of the

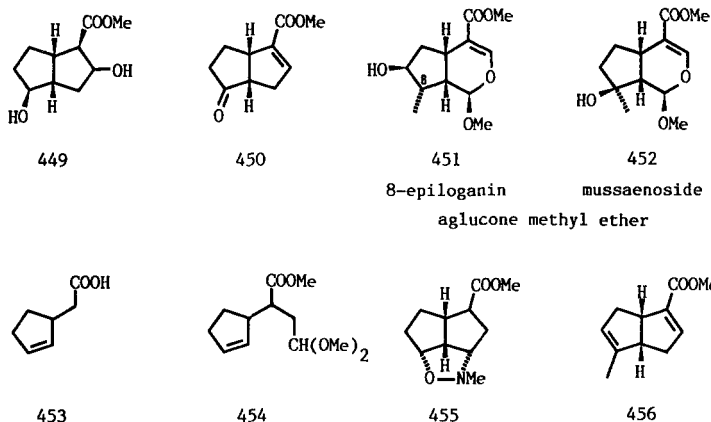
hydroxyl group of **441** yielded a ketone and dehydration of the cyanhydrin of the latter gave an unsaturated nitrile. Hydrolysis of this and deconjugation as before gave the diester **442**, which was converted as usual by oxidative ring fission to forsythide aglucone dimethyl ester (**443**).⁴⁰⁰



Scheme 41

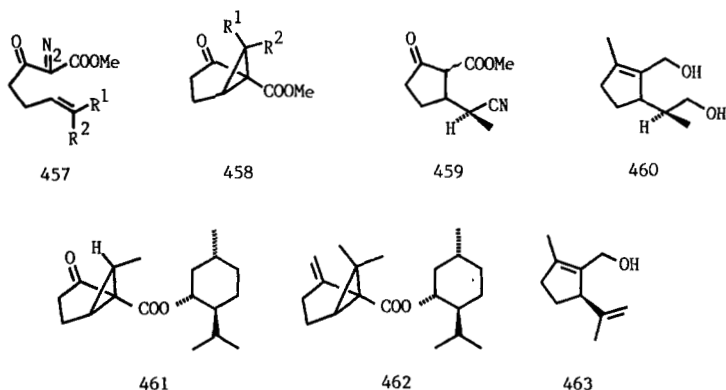
Vandewalle et al. have also used routes to several iridoids that pass through a tricyclo[3.3.0.0^{2,8}]octane, prepared by adapting the Doering³⁹⁸ procedure. Refluxing the diazoketo ester **444** in toluene with Cu(II) acetylacetonate gave the ester **445**,⁴⁰¹ which was used to prepare ($\pm$)-isoiridomyrmecin (**424B**) and verbenalol (**446**).⁴⁰² We have not described this in full detail in Scheme 41 because many of the steps are similar to those already described, for example, ring opening of the ester **447** ($R = Me$) with lithium dimethyl cuprate to put in simultaneously the other methyl group. In the route to ($\pm$)-verbenalol (**446**), the double bond had to be deconjugated from the ester group. Instead of using kinetic protonation (Isoe et al., see above) Vandewalle et al. used bromination-dehydrobromination (*N*-bromosuccinimide then zinc), separating the two isomeric esters to obtain only the required one, **448**.⁴⁰² The same group also prepared the diester **447** ($R = COOMe$) by the action of methyl carbonate on the anion of **445**.⁴⁰³ Ring opening with sulfuric and acetic acid, then cyanoborohydride reduction yielded the ester **449**, from which the keto ester **450** was obtainable. The latter had already been prepared by a somewhat longer route, and converted to 8-epiloganin (**451**) or musaenoside (**452**) aglucone methyl ether.⁴⁰⁴ This alternative route is of some interest additionally because of the method by which the bicyclo[3.3.0]octane skeleton was prepared. 2-Cyclopenten-1-ylacetic acid (**453**) was alkylated as the dianion with

iodoacetaldehyde dimethyl acetal, and the product esterified to give **454**.* Treatment of the liberated aldehyde with *N*-methylhydroxylamine gave the bicyclo[3.3.0]octane **455** directly. Grignard addition of methylmagnesium iodide to **450** and dehydration yielded the ester **456**. From the latter, Markovnikov or anti-Markovnikov addition of water to the double bond in the methylcyclopentene half of the molecule, and oxidative ring fission of the other half, led to **452** or **451**.



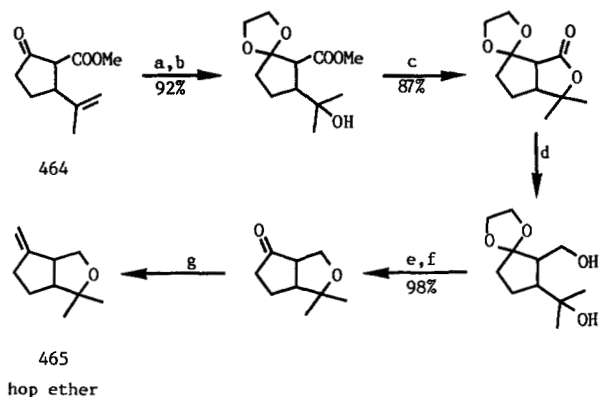
Another approach to cyclopentanes through a bicyclic compound used the nucleophilic⁴⁰⁶ or thermal⁴⁰⁷ ring opening of bicyclo[3.1.0]hexanones which were made by the reaction of copper sulfate with diazo- β -keto esters **457**, leading to the bicyclic keto esters **458**.⁴⁰⁶ Following this route, Nakayama et al. opened the cyclopropane ring of **458** ($R^1 = H$, $R^2 = Me$) with sodium cyanide in dimethyl sulfoxide, when they obtained 72% of the cyclopentanone **459**. After introduction of a methyl group and various metal hydride reductions, they prepared ($\pm$)-dehydroiridodiol (**460**). Furthermore, they were able to resolve **458** ($R^1 = H$, $R^2 = Me$) through the menthyl ester **461**, thereby preparing both optical isomers of dehydroiridodiol (**460**).⁴⁰⁸ Following a similar route, Paquette et al. introduced the menthol chiral auxiliary before making the diazoketo ester (**457**, menthyl ester in place of methyl) then, after cyclization, separated the isomers **462** from a Wittig reaction. Acid ring opening and reductive removal of menthol gave the alcohol **463**⁴⁰⁹ (corresponding to the chrysomelidial precursor **385**).

*Vandewalle comments on the low reactivity of iodoacetaldehyde dimethyl acetal, particularly with the ester of **453**. This low reactivity is, in fact, documented,⁴⁰⁵ and one of us spent a few unsuccessful weeks trying to alkylate dimethyl malonates with this acetal many years ago, which makes us admire the 30% yield Vandewalle quotes for reaction with **453** ester dianion!



Using the thermal ring opening of **458** ($R^1 = R^2 = \text{Me}$) Johnson et al. obtained the cyclopentane β -keto ester **464** which they converted into hop ether (**465**) following Scheme 42. By using the chiral phosphorus organolithium compound **466** [from (+)-(*R*)- α -(1-naphthyl)ethylamine] in step g of Scheme 42, they were able to isolate two chiral adducts, which they converted to both stereoisomers of hop ether,⁴¹⁰ thereby showing that the natural product isolated from Japanese hops (see Vol. 4, p. 496) was of very low chirality.

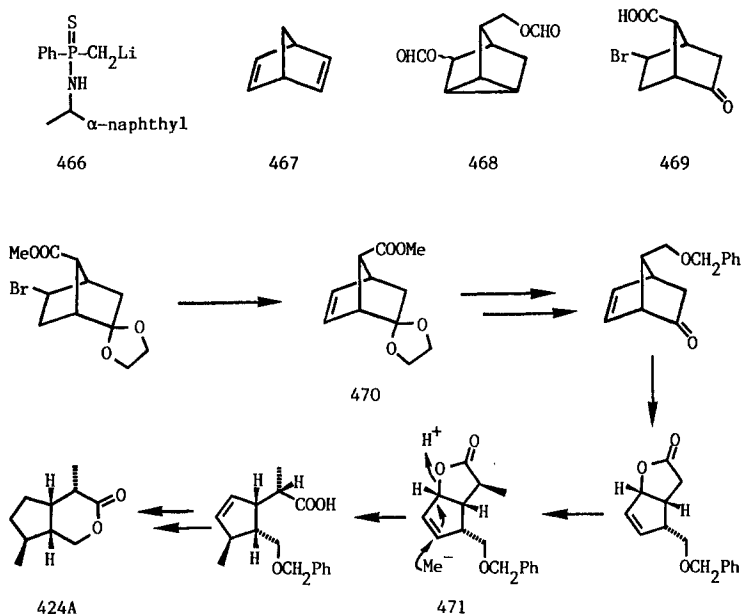
Access to cyclopentanes by fission of one half of a bicyclo[2.2.1]heptane has long been used as a route to iridoids. A more recent example is Grieco's synthesis



a) $\text{HOCH}_2\text{CH}_2\text{OH} + \text{H}^+$; b) $\text{Hg}(\text{OAc})_2$, then NaBH_4 ; c) KOtBu ;
d) LiAlH_4 ; e) TsCl/pyridine ; f) TsOH/acetone ; g) **466**

Scheme 42

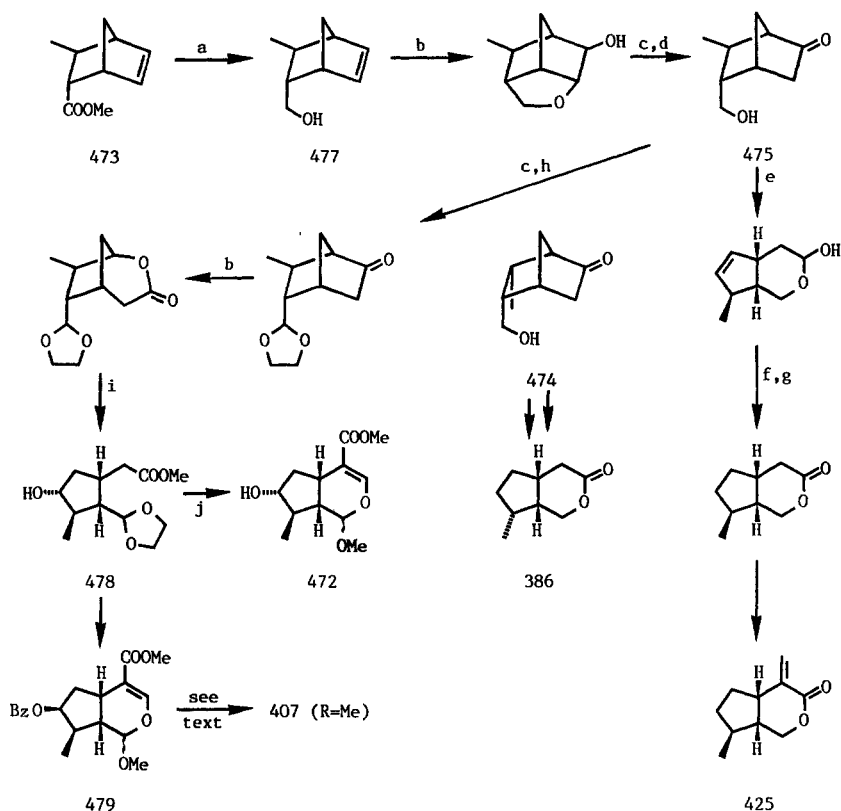
of ($\pm$)-iridomyrmecin (**424A**).⁴¹¹ Norbornadiene (**467**) yields a mixture of tricyclic formates from a Prins reaction (formaldehyde in acetic acid) and these can be converted (hydrolysis, oxidation, and HBr in acetic acid) to the keto acid **469**.⁴¹² The ethylene acetal methyl ester of **469** was Grieco's starting material (Scheme 43). The action of 1,8-diazabicyclo[5.4.0]undec-7-ene in dimethylformamide not only dehydrobrominated but also rearranged the ester to be *syn* to the protected ketone **470**.⁴¹³ Lithium aluminum hydride reduction and Baeyer-Villiger oxidation of the benzyl ether of the deprotected ketone gave a lactone, the anion of which could be methylated stereospecifically to **471**. Reaction of the latter with lithium dimethyl cuprate occurred exclusively in the S_N2' mode, giving an acid with the correct stereochemistry for ready conversion to iridomyrmecin (**424A**).⁴¹¹



Scheme 43

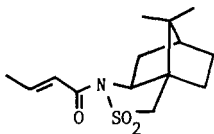
Vandewalle et al. have also used oxidative ring opening of one side of a norbornanone to prepare a number of iridoids, culminating in a synthesis and correction of the structure of specionin. At first they described the synthesis of teucrium lactone (**425**) and a loganin precursor (**472**) from the Diels-Alder adduct **473** of cyclopentadiene and methyl (*E*)-crotonate (Scheme 44).⁴¹⁴ The same paper describes the preparation of the all-*endo*-isomer **474** of ketone **475**, from

which boschnialactone (**386**, having the 8-methyl group in the opposite configuration from **425**) was prepared by a similar route to that followed for **425**.⁴¹⁴ The synthesis of **472** was greatly improved by using the Oppolzer technique⁴¹⁵ for preparing a π -face-differentiated dienophile (in this case **476**), where the cyclopentadiene can only react on one face in the presence of TiCl_4 , leading to the chiral alcohol **477**. The route to **478** was then as shown in Scheme 44,⁴¹⁶ and conversion to (-)-1-*O*-methylloganin aglucone (**407**, $\text{R} = \text{Me}$) was carried out by treatment with diethyl azodicarboxylate, triphenylphosphine, and benzoic acid,⁴¹⁷ when the (+)-benzyl ester **479** was obtained in 76% yield. As



a) LiAlH_4 ; b) *m*-Cl-perbenzoic acid; c) $(\text{COCl})_2$, DMSO, Et_3N ; d) Al/Hg ; e) 250 nm/MeCN, 17h; f) pyr. chlorochromate; g) Pd/H_2 ; h) trans-acetalization; i) $\text{NaOMe}-\text{MeOH}$; j) protect OH, KO^tBu -lithium isopropylcyclohexylamide, acid work-up, and heating with TsOH

Scheme 44



476

before, formylation was effected with lithium isopropylcyclohexylamide and potassium *tert*-butoxide with methyl formate. Acid-catalyzed ring closure and debenzoylation then gave the loganin aglucone methyl ether (**407**, R = Me).⁴¹⁶

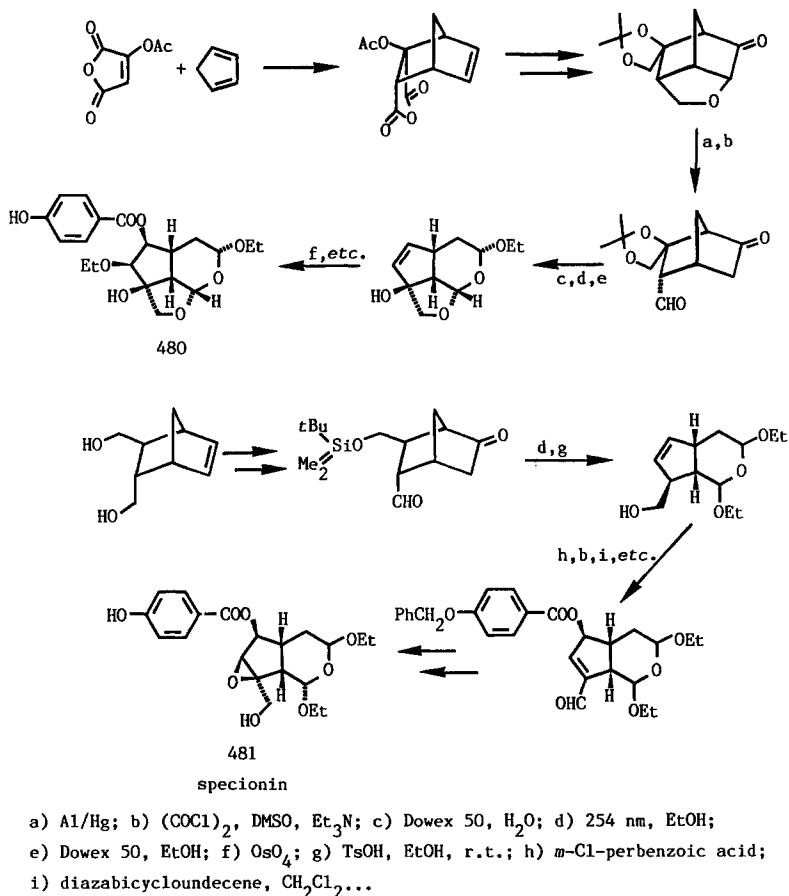
This approach was then extended to the synthesis of structure **480** (Scheme 45),⁴¹⁸ a compound believed to represent the structure of specionin, an insect antifeedant isolated from the leaves of *Catalpa speciosa*, Warder.⁴¹⁹ It turned out that **480** was not identical to specionin, and after correctly predicting the structure **481**,⁴¹⁸ they went on to synthesize it (Scheme 45).⁴²⁰

The great advantage of the type of approach used by Vandewalle is that a variety of stereochemistries of different substituents around a bicyclo[2.2.1]heptane skeleton is accessible using different Diels-Alder reactions, making a stereo-specific approach to many iridoids possible by relatively simple manipulations of the functional groups.

The nor-iridoid boonein (**482**), isolated from *Alstonia boonei*,⁴²¹ has been synthesized using as key step the ring expansion of a 7-chlorobicyclo[3.2.0]heptan-6-one (cf. Vol. 4, p. 498).⁴²² Cycloaddition of methylchloroketene and cyclopentadiene gave the starting material **483**.⁴²³ Ring expansion with diazomethane gave the bicyclo[3.3.0]octanone **484**, which was converted into boonein (**482**) following Scheme 46. The lithium aluminum hydride reduction of **484** gave readily separable isomeric alcohols **485** in the ratio of 1.8:1 (A/B); the undesired one, **485B**, could be reoxidized to **484** and reused.⁴²²

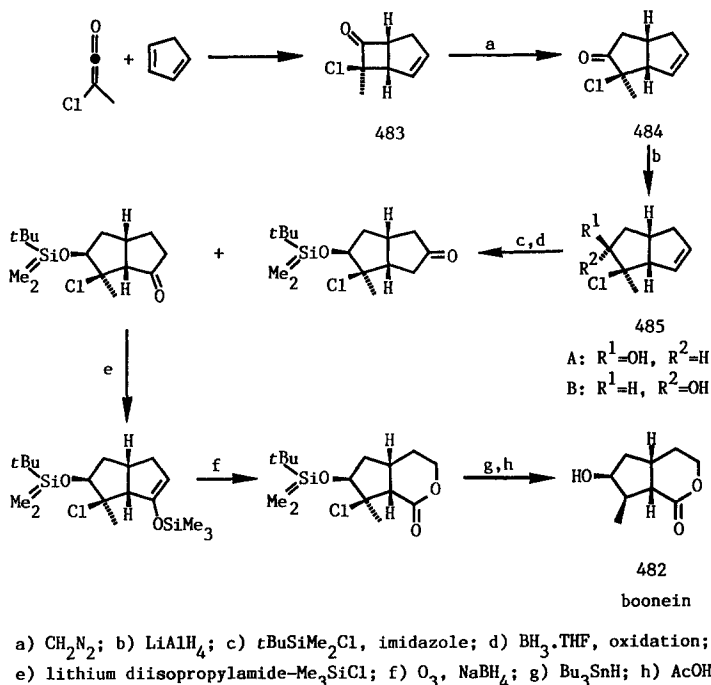
B. Secoiridoids

Attention was drawn at the beginning of the section on cyclopentanes to the review by Tietze on the biogenetic position of secologanin (**363**, R = β -glucosyl).³³⁸ In this review, Tietze again draws attention to the difficulties of laboratory glycosidation, but later in the same journal, reports a new method for converting iridoid acetates to their glucoside tetraacetates.⁴²⁴ There is still much discussion concerning the biological pathway of the fission of loganin (**407**, R = β -glucosyl) to secologanin (**363**, R = β -glucosyl); Hutchinson et al. have reported a method for carrying out the reverse reaction using magnesium and trimethylsilyl chloride in tetrahydrofuran.⁴²⁵ Sweroside (**486**, R = β -glucosyl)

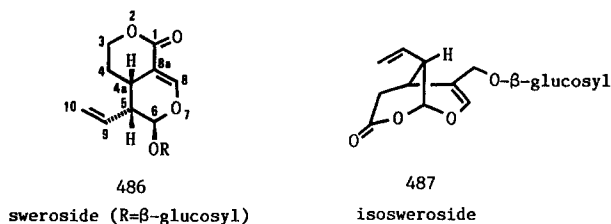


Scheme 45

(the numbering given is according to *Chem. Abstr.*, but is not universal, see, e.g., Ref. 426) is difficult to convert to the aglucone without epimerization at C-5, but the groups of Hutchinson and Tietze have now shown how this can be done, and have fully characterized all the stereoisomers of sweroside aglucone methyl ether (**486**, R = Me) at C-5 and C-6,⁴²⁷ most useful information for the synthesis of secoiridoids. Although we do not give a list of all new, unsynthesized, iridoids, the isolation of isosweroside (**487**) with a novel skeleton and an unusual position for the sugar, from *Sambucus ebulus*, L. (Caprifoliaceae)⁴²⁶ provides an intriguing synthetic target.

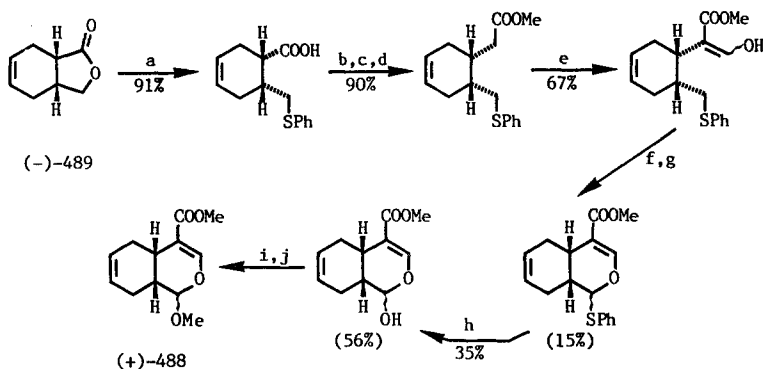


Scheme 46



The total synthesis of (–)-1-*O*-methylsweroside aglucone (**486**, R = Me) has been described by Ikeda and Hutchinson.⁴²⁸ We briefly mentioned (Vol. 4, p. 504) an earlier synthesis of the racemate of **486** (R = Me) by Hutchinson et al.,⁴²⁹ and the key intermediate, **488**, is the same, but now it has been prepared in optically active form. The starting material was (–)-**489**, made either by enzymatic *in vitro* oxidation of (±)-cyclohexene-4,5-bismethanol,⁴³⁰ or enantiotropic hydrolysis of the corresponding diesters with pig-liver esterase.⁴³¹ Two one-carbon homologations and a Pummerer reaction then converted this material

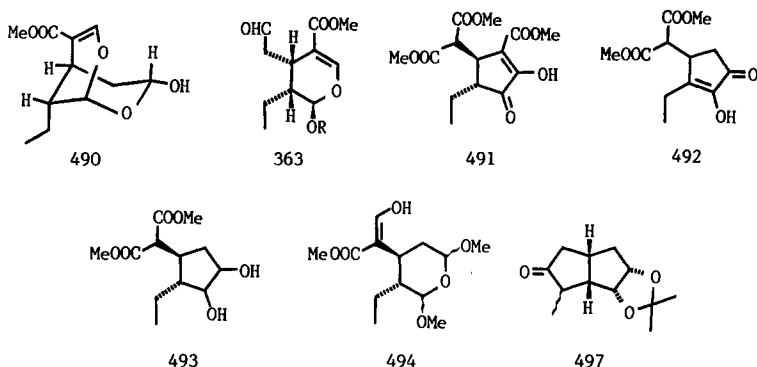
to ($\pm$)-**488**, in which all the asymmetric centers of sweroside aglucone are present (Scheme 47). Conversion of **488** to **486** ($R = \text{Me}$) was by the methods described earlier,⁴²⁹ but at the time, the aglucone could not be made from sweroside (**486**, $R = \beta\text{-glucosyl}$) because of the C-5 epimerization referred to above, so the authors made their material for comparison from (–)-loganin (**407**, $R = \beta\text{-glucosyl}$).⁴²⁸



- a) LiSPh , 1.05 eq., DMF, reflux, 4h; b) $(\text{COCl})_2$, benzene, r.t., 1.5h;
 c) CH_2N_2 , Et_2O , r.t., 4h; d) Ag_2O catalyst, MeOH, reflux, 20min;
 e) lithium diisopropylamide, 1.05 eq., THF, -50° , 1h; then HCOOEt , 1.5 eq., -50° , 1h; f) NaIO_4 , 1 eq., MeOH/THF/ H_2O (6:3:4), r.t., overnight;
 g) 2,6-lutidine, trifluoroacetic acid, 3 eq., $-15 - 0^\circ$, 1h;
 h) HgCl_2 , 3 eq., MeCN/ H_2O (3:1), reflux, 20h; i) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, MeOH, r.t., 1h;
 j) allyl- O-SiMe_3 (excess), Tf-O-SiMe_3 catalyst, CH_2Cl_2 , $-20 - 0^\circ$, 3h

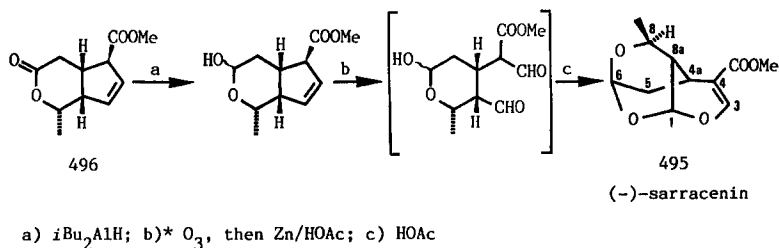
Scheme 47

Dihydrosecologanin aglucone (**490**) is not naturally occurring, but Brown and Jones hope to extend their synthesis of it to secologanin aglucone (**363**, $R = \text{H}$, as cyclic acetal).⁴³² Treatment of methyl (*E*)-hexenoate successively with base and dimethyl oxalate then dimethyl malonate yielded the cyclopentane **491**. Refluxing with acetic acid was selective for the decarboxylation of the β -keto ester, and although the *trans*-stereochemistry was lost at this stage, **492**, it was regained after reduction of **492** with sodium borohydride, when almost a single glycol, **493**, was formed. Sodium periodate oxidative cleavage and partial reduction of the diester with diisobutylaluminum hydride gave a mixture of acetals **494** which was converted (in only 40% yield) to ($\pm$)-dihydrosecologanin aglucone (**490**) by acid in tetrahydrofuran.⁴³²



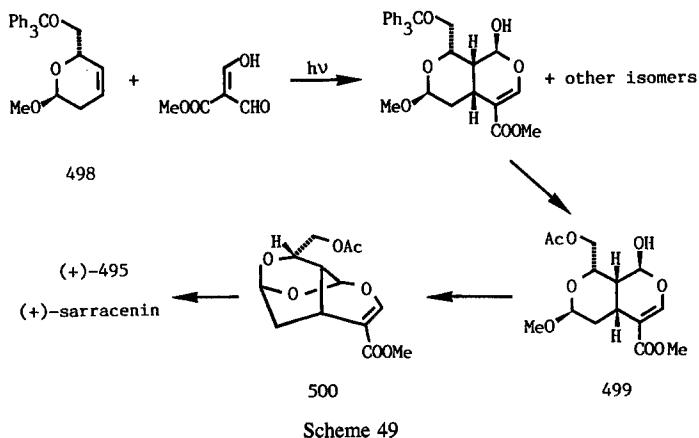
Tietze has synthesized $[10-^{13}\text{C}]$ secologanin (**363**, $\text{R} = \beta\text{-glucosyl}$, with ^{13}C at vinyl CH_2 position) by protection of the aldehyde group of unlabeled secologanin, fission of the vinyl double bond, putting back the methylene group with a labeled Wittig reagent, and deprotection.⁴³³

Whitesell's synthesis of $(\pm)$ -sarracenin $[(\pm)\text{-}495]$ (Vol. 4, p. 501, Ref. 314) has been published in full.⁴³⁴ It is worthwhile noting certain difficulties reported at the end of the synthesis involving the apparently simple steps shown in Scheme 48. Partial reduction of the lactone function in **496** with diisobutylaluminum hydride requires two equivalents, the first of which is taken up by complexation with the carbomethoxy group. Even with this problem solved, the yield of sarracenin $[(\pm)\text{-}495]$ from **496** was only 15%, and it is impossible to see where the loss was because of the instability of the intermediate compounds.⁴³⁴ Because both epimers of **497** were available in an earlier step toward **496**, Whitesell also synthesized the as yet unnatural episarracenin with an epimeric 8-methyl group.⁴³⁴

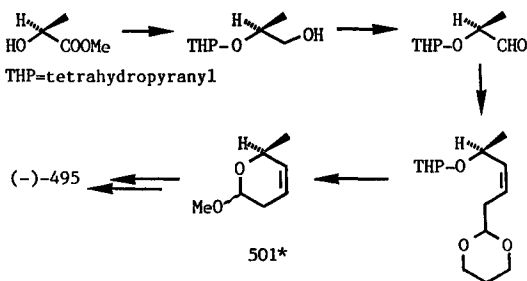


Scheme 48

*The scheme in the paper gives " OsO_4 , NMO" for this step, but the text and experimental section mention only ozonolysis.

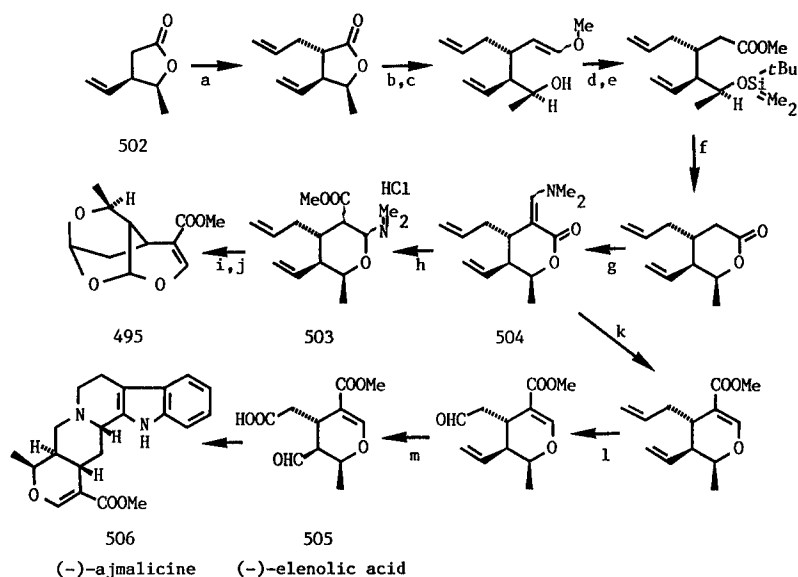


The first synthesis of optically active sarracenin reported was actually of the unnatural (+)-isomer, and used the compound **498** (available from galactose by an undescribed route) as the chiral starting material (Scheme 49). The photoreaction of the first step is analogous to the original Büchi loganin synthesis (Vol. 2, p. 82, Ref. 238), and the desired isomer (32%) was separated from the others before changing the protecting groups and cyclizing the compound **499** with perchloric acid in acetic acid (77% yield of **500**). The latter was converted to (+)-sarracenin [(+)-**495**] via the tosylate.⁴³⁵ The same photochemical approach was used by Baldwin and Crimmins to make natural (–)-sarracenin [(–)-**495**]. They made their starting material **501** from methyl lactate following Scheme 50. The two isomers of **501** obtained were separated by chromatography, and the *trans*-isomer made to undergo the photochemical reaction as before. The crude



*There is an obvious mistake in the text concerning the NMR spectra of the two isomers of **501**.

photoproducts were not isolated, but cyclized with *p*-toluenesulfonic acid in methylene chloride, when the major isomer obtained was sarracenin (**495**), the next most important was 8-episarracenin, and there were two other bis-acetals not fully characterized.⁴³⁶ Although the yield of the natural product was not very high, the beauty of the synthesis lies in its brevity. Baldwin and Crimmins draw attention to the disparity between the various optical rotations recorded for (–)-sarracenin;⁴³⁶ their own value (-20.9°) lies close to the value quoted by Takano et al., who have published a rather long synthesis of (–)-sarracenin starting from D-glucose.⁴³⁷ The conversion of glucose to the required chiral methyl vinyl γ -lactone **502** was very tedious, but they later published a shorter route from methyl lactate,⁴³⁸ the first three steps of which are the same as those used by Baldwin and Crimmins. The route from **502** to sarracenin is shown in Scheme 51. The product **503** of the penultimate step (just before the ozonolysis) was not purified.⁴³⁷ The compound **504** was also used by the same group in a synthesis of (–)-elenolic acid (**505**).⁴³⁸ We have already referred to the interest secoiridoids

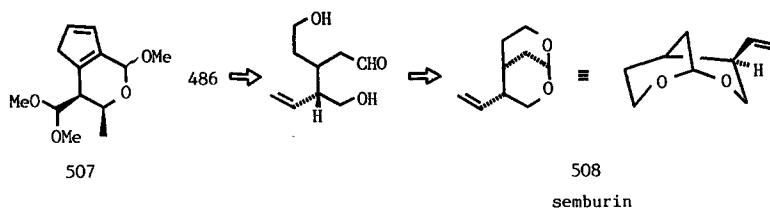


a) lithium diisopropylamide, CH₂=CHCH₂Br, THF, –78°; b) *i*Bu₂AlH, CH₂Cl₂, –78°; c) Ph₃P⁺CH₂OMe.Cl[–], KOtBu, glyme, r.t.; d) *t*BuSiMe₂Cl/imidazole, DMF, r.t.; e) pyr. chlorochromate, CH₂Cl₂, r.t.; f) *p*-TsOH, MeOH, reflux; g) Me₂NCH(OMe)₂, 170°; h) 5% HCl–MeOH, r.t.; i) O₃, MeOH, –78°, then Me₂S; j) 90% aq. HOAc, 80°; k) HCl/Et₂O; H₂SO₄–MeOH, reflux; l) OsO₄, then Pb(OAc)₄; m) CrO₃; OsO₄/NaIO₄

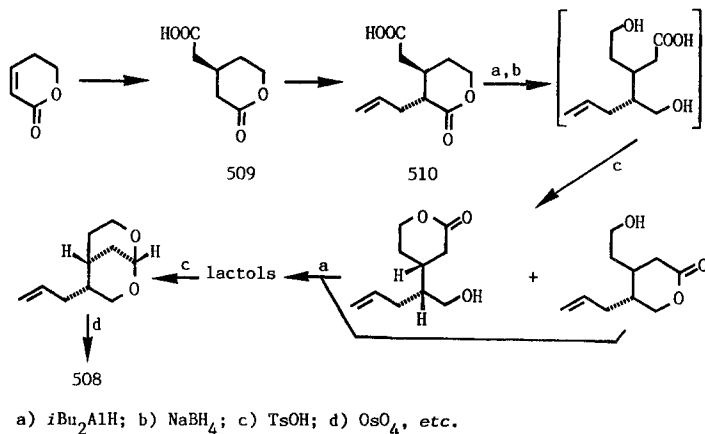
Scheme 51

have in respect to the biogenesis of alkaloids, and we recall that, for example, (–)-elenolic acid can be readily converted to (–)-ajmalicine (**506**).^{342,343}

Tixidre et al. have discussed possible routes to elenolic acid (**505**) from compound **507**.^{440,378}

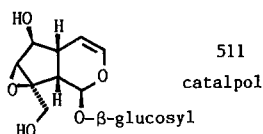


Semburin (**508**) is related to the congeneric sweroside (**486**, R = β -glucosyl),⁴⁴¹ and was isolated from *Swertia japonica*.⁴⁴² (Called “semburi” or “senburi” in Japanese, this plant is sold for its bitterness.⁴⁴³) The synthesis of the racemate has been carried out from 2-penten-5-olide, which yielded 40% of the acid **509** after malonic ester synthesis. Like some of the syntheses already mentioned, use was made here of the more stable allyl group as a function that will be used later to prepare a less stable group, in this case the vinyl group, which the authors did not believe would resist the transformation they were planning. This allyl group was introduced conventionally via the dianion of **509**, and yielded two isomers, the major one being the desired **510**. The conversion of this to semburin (**508**) is shown in Scheme 52.⁴⁴¹



Scheme 52

The reader who has had the courage to read through the whole of this section on iridoids will no doubt have been struck by the length of the syntheses (see our comments in Vol. 4, p. 453); it is clear that practically none of them could be considered for large-scale production, despite the interest such compounds have, pharmaceutically, in their own right, and as materials for syntheses of pharmaceutically active alkaloids. It is therefore of interest to know to what extent there are readily available iridoids that can be transformed to others. Although this is not “total synthesis,” we might draw attention to the fact that catalpol (**511**) has been isolated in 100-g lots from *Picrorhiza kurrooa* (Scrophulariaceae), and can be converted to substances of interest for cyclopentanoid natural products.⁴⁴⁴



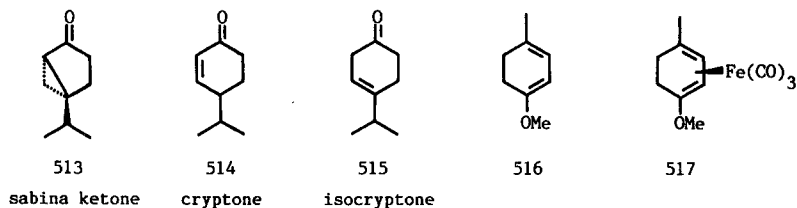
8. *p*-MENTHANES

A. Hydrocarbons

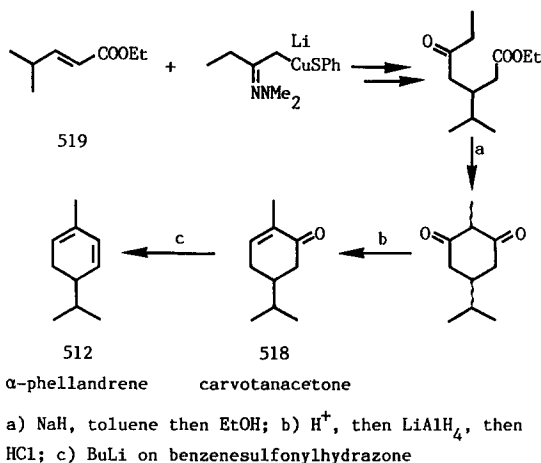
Clearly the synthesis of menthadienes is now following the law of diminishing returns, but a few aspects, particularly concerning chirality, still arise from time to time.

The statement “ α -phellandrene (**512**) racemate is unknown”^{*} has recently appeared;⁴⁴⁵ evidently some referees have not read our earlier chapter, which contains leading references. Racemic α -phellandrene was first prepared by Wallach in 1908 (who gave a small rotation, but stated that he suspected it to be practically racemic). This particular phellandrene was made by the action of acid on (–)-sabina ketone (**513**), which led to the mixture of cryptone (**514**) and isocryptone (**515**), racemized because of the intermediate carbocation. Grignard reaction on cryptone (**514**) and dehydration then gave racemic α -phellandrene [(±)-**512**],⁴⁴⁶ any rotation probably arising from impurities. A more recent preparation is mentioned by Thompson.⁴⁴⁷ The latter is based on the “Birch’s complexes” with tricarbonyliron (see Vol. 4, p. 508, Refs. 352 and 353), and it is notable that the reaction of the enol methyl ether (**516**) of 4-methyl-3-cyclohexenone with carbonyliron having a chiral ligand led to the chiral complex **517**, which was converted to chiral α -phellandrene with

^{*}What the authors probably meant was “not well described recently,” which is quite true.



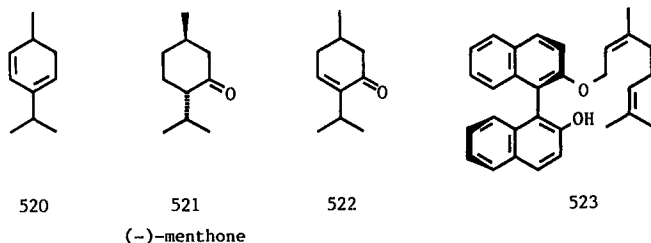
isopropylcadmium followed by removal of the tricarbonyliron, but the enantiomeric excess is low.^{448,449} Returning to the synthesis of racemic α -phellandrene (**512**) referred to above,⁴⁴⁵ the hydrocarbon was prepared by the Shapiro reaction (butyllithium on the benzenesulfonylhydrazone) from carvotanacetone (**518**), made from ethyl 4-methyl-2-pentenoate (**519**) following Scheme 53.⁴⁴⁵ [A more rapid route to **518** is by catalytic reduction of racemic carvone, ($\pm$)-**281**.] The same paper gives a method for the synthesis of 2,4-menthadiene (**520**)* (not a natural product, so far as we are aware) from (–)-menthone (**521**). Bromination and dehydrobromination gave 4-menthene-3-one (**522**) from which the Shapiro reaction again gave the desired hydrocarbon, (+)-2,4-menthadiene.⁴⁴⁵ (See also the preparation of piperitone from menthone given below.)



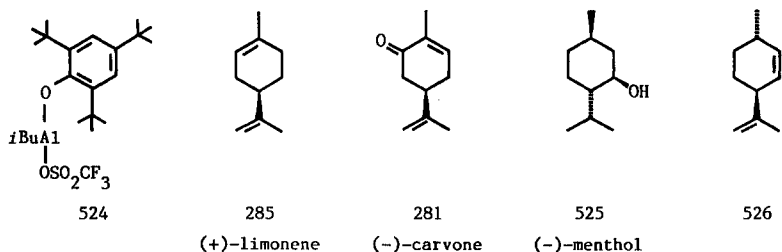
Scheme 53

*In this case, the authors say that **520** “has not been synthesized in racemic form”, a statement that is true so far as “usable synthesis” is meant. The racemate has been mentioned by Bates et al., who also prepared a Diels–Alder adduct, but gave a description neither of the hydrocarbon nor of the adduct.⁴⁵⁰

Isomerization is discussed in a paper treating the catalytic hydrogenation of menthadienes (including α -phellandrene) over phenanthrene- $\text{Cr}(\text{CO})_3$ in cyclohexane. This reaction is accelerated by (–)-menthone and attempts were therefore made to introduce asymmetry.⁴⁵¹

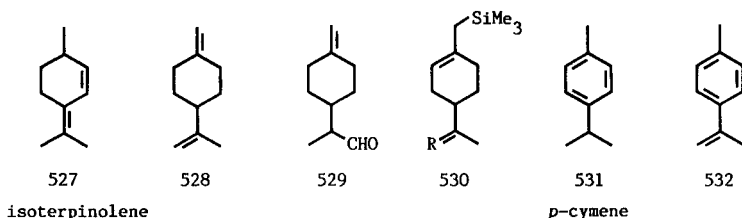


Yamamoto et al. have been trying to synthesize limonene by a “biomimetic” cyclization of nerol (**37**) derivatives. The principle is to use the chiral derivative **523** and an alkylaluminum. After much experimentation,⁴⁵² the best conditions were with the reagent **524** in CCl_3F , when 77% ee of (+)-limonene (**285**) was obtained.⁴⁵³ It is widely believed still that the Wolff–Kishner reduction of optically active carvone (**281**) will yield optically active limonene (e.g., see Ref. 16, p. 152), a reaction reported by Friedman and Miller.⁴⁵⁴ This was already doubtful (Friedman and Miller gave no experimental evidence), since Jeger et al. had shown in 1950 that the Wolff–Kishner reaction with α,β -unsaturated ketones displaces the double bond,⁴⁵⁵ but Akhila and Banthorpe have now shown conclusively that (–)-carvone (**281**) yields ($\pm$)-limonene [$\pm$ -**285**] by the Wolff–Kishner reaction.⁴⁵⁶



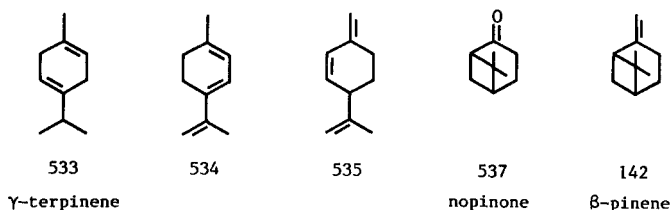
It is important to be aware of syntheses of even nonnaturally occurring menthadienes, because these are so often intermediates to some more valuable substances. Thus one route from 3-carene (**277**) to menthol (**525**) starts with

opening of the cyclopropane with sodium to *trans*-2,8-menthadiene (**526**). Further treatment with sodium (on sodium carbonate or alumina) rearranged the latter to isoterpinolene [2,4(8)-menthadiene (**527**)].⁴⁵⁷ 1(7),8-Menthadiene (**528**) is a potential intermediate for 1(7)-menthen-9-al (**529**),⁴⁵⁸ although this aldehyde is also not yet reported in nature. The diene **528** was made, for example, by a Wittig-type reaction on the Diels–Alder adduct **530** (R = O) of methyl vinyl ketone and 2-trimethylsilyl-1,3-butadiene (**9**, R = SiMe₃). Treatment of **530** (R



= CH₂) with cesium fluoride in dimethyl sulfoxide yielded ($\pm$)-limonene [($\pm$)-**285**], while methanolic hydrogen chloride gave **528**.⁴⁵⁹ Menthadienes are also often implicated in reactions of other terpenes; for example, *p*-cymene (**531**) and α ,4-dimethylstyrene (**532**) are implicated in the off-odor of stale lemons, and arise from cyclization of citral (**32**) in the presence of citric acid (via a number of menthadienols).⁴⁶⁰ A more “synthetic” aspect of the cyclization of dimethyloctane monoterpenes to menthanes can be found in some of the reactions of myrcene (**7**). On heating with zinc chloride and sodium and potassium chloride, myrcene yielded ($\pm$)-limonene [($\pm$)-**285**] and γ -terpinene (**533**), fused nitrates and nitrites giving isoterpinolene (**527**).⁴⁶¹ A metal oxide catalyst on alumina and H₂S with myrcene (**7**) at 450°C yielded up to 76% of *p*-cymene (**531**).⁴⁶²

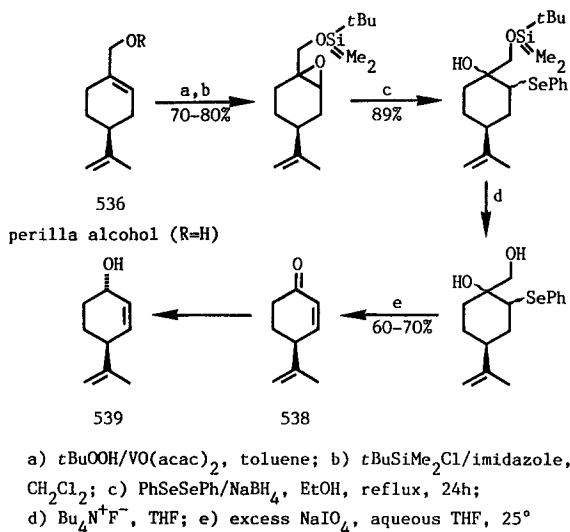
The only well-authenticated menthatriene isolated from natural sources is still the triene **534** (cf. Vol. 2, p. 91; recently also identified from curly parsley, *Petroselinum hortense*⁴⁶³ and *Petroselinum crispum*⁴⁶⁴). We should, however, mention the preparation of the nonnatural 1(7),2,8-menthatriene (**535**) from perilla alcohol (**536**, R = H) via a Claisen rearrangement of the ether **536** (R = 2-oxo-3,5,7-trimethyl-3,5,7-cycloheptatrienyl).⁴⁶⁵



B. Oxygenated Derivatives of Menthanes

(1) The 1-, 4-, and 8-Oxygenated Menthanes

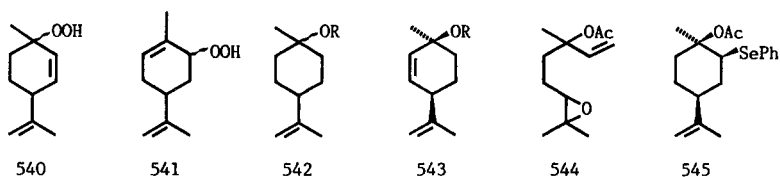
One of the problems in the synthesis of the C₉-monoterpenoid cryptone (**514**) is the suppression of the accompanying isocryptone (**515**) (Vol. 2, p. 98). Nopinone (**537**), prepared from β -pinene (**142**), can be ring-opened with either ethylaluminum dichloride⁴⁶⁶ or fluorosulfonic acid at -70°C ⁴⁶⁷ to give only ($\pm$)-cryptone (**514**). The “previously unreported”⁴⁶⁸ 4-isopropenyl-2-cyclohexanone (**538**) was actually first prepared by Sato et al.⁴⁶⁹ from 2-cyclohexenol. Epoxidation and dehydration led to 3,4-epoxycyclohexene which, on treatment with lithium isopropenylcuprocyanide gave the alcohol **539**. This was then oxidized to the ketone **538**. Stevens and Albizati made **538** by addition of a methylene group to the acetyl carbonyl group in 4-acetylcyclohexanone. Somewhat more interesting is their synthesis of the (*R*)-isomer of **538** from (–)-perilla alcohol (**536**, R = H) following Scheme 54.⁴⁶⁸



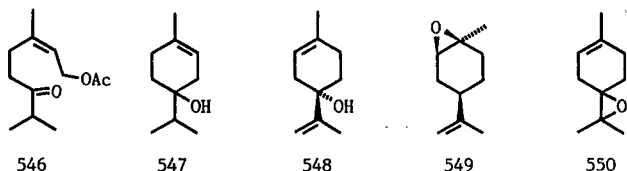
Scheme 54

One of the easiest direct routes to 1-oxygenated menthanes is by direct oxidation of limonene (**285**). Autoxidation gives a mixture of 1- (**540**) and 2-hydroperoxides (**541**), and all of these have now been separated and characterized.⁴⁷⁰ Photochemical addition of methanol to give the β -terpineol

methyl ethers (**542**, R = Me) has now been published in *Organic Syntheses*.⁴⁷¹ Various microorganisms (*Diplodia*, *Corynespora*, *Fusarium*, *Giberella*, etc.) will oxidize limonene to the 1,2-diols (see below), and these were dehydrated to *cis*-2,8-menthadien-1-ol (**543**, R = H) (the starting material for the synthesis of the tetrahydrocannabinols, see also Vol.2, p. 95).⁴⁷² The acetate **543** (R = Ac) has also been made from linalyl acetate epoxide (**544**) after epoxide opening with benzene selenolate. Cyclization with trifluoroacetic acid then yielded the product **545** that was converted to **543** (R = Ac) by hydrogen peroxide.⁴⁷³

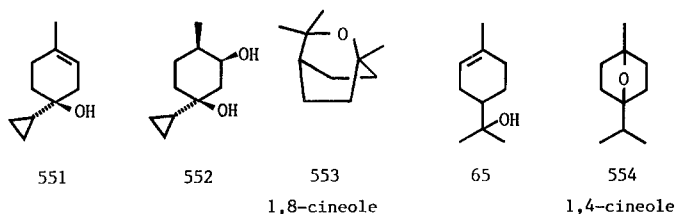


The reaction of a ketone with an allyl acetate in the presence of samarium iodide catalyzed by palladium (Pd⁰) has been applied to an intramolecular addition. The keto acetate **546** [prepared from neryl acetate (**27** acetate)] was cyclized to 1-menthen-4-ol ("4-terpinenol" **547**) in 62% yield using 5 mol% of Pd(PPh₃)₄.⁴⁷⁴ Separation of the (+)- and (-)-isomers of **547** has been achieved on Chirasil-Val columns.⁴⁷⁵ The synthesis by Delay and Ohloff of optically active 1,8-menthadien-4-ol (**548**) (Vol. 4, p. 511, Ref. 382) encountered difficulties when it was carried out on a larger scale. They then attempted to

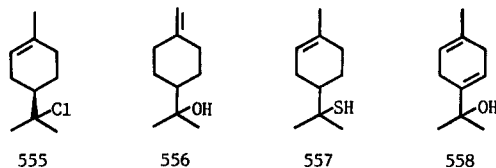


oxidize *cis*-limonene epoxide (**549**) with *tert*-butyl hydroperoxide in the presence of selenium dioxide, removing the epoxide subsequently with zinc-acetic acid reduction. Although somewhat better, the yield was still disappointing.⁴⁷⁶ Using the ring opening of terpinolene epoxide (**550**) to yield (±)-**548** (Vol. 2, p. 100, Refs. 323 and 325; Vol. 4, p. 511, Ref. 377), it is a little tricky to achieve reproducibly high yields. A recent study has examined a number of solvents and acids, and it seems that the best for this particular reaction is *p*-toluenesulfonic acid in acetone for 1 hour, giving 70% of **548**.⁴⁷⁷

The unusual cyclopropane **551** was isolated [probably as the (*S*)-isomer] from *Pistacia vera*, together with the hydrated analog **552**; **551** was synthesized by Grignard reaction of cyclopropylmagnesium bromide with 4-methyl-3-cyclohexenone, and the diol **552** by lithium aluminum reduction of the epoxide of **551**.⁴⁷⁸



Synthesis of the menthane tertiary alcohols from other terpenes is also well known. 1,8-Cineole (**553**) (the major constituent of *Eucalyptus stageriana* oil) can be made to yield either ($\pm$)-(α)- (**65**) or β -terpineol (**542**, R = H), by acid-catalyzed ring opening under various conditions in the presence of synthetic zeolites. Similarly 1,4-cineole (**554**) gave **542** (R = H) or 1-menthen-4-ol (**547**).⁴⁷⁹ (Synthesis of the cineoles is discussed below.) The oldest method for preparing α -terpineol (**65**) is by the action of aqueous acid on α - (**116**) or β -pinene (**142**), but it is not always realized that citric acid in ethanol is enough to effect this at 38°C for several weeks.⁴⁸⁰ The hydration of limonene (**285**) also has a long history, and it has now been shown that in sodium lauryl sulfate up to 97% of α -terpineol can be achieved.⁴⁸¹ The latter experiment depends on the formation of micelles, and is only convenient for small-scale work at present. Otherwise, the direct conversion of limonene to α -terpineol has always been a lower yielding process than that starting from turpentine (pinenes). One way of circumventing the difficulties is by addition of HCl to limonene first. In the presence of zinc oxides or salts, the chloride **555** was converted to terpineol or its esters.⁴⁸² (Prepared in this way, α -terpineol should be optically active, unlike that made by direct hydration.⁴⁸³)



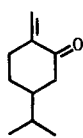
δ -Terpineol (**556**) has been found in *Lavandula latifolia*,⁴⁸⁴ and with somewhat less evidence, reported in *Coridothymus capitatus*.⁴⁸⁵ It was synthesized by hydration of β -pinene (**142**) in the presence of mercury, a method due to Fétizon and described below (perilla alcohol).⁴⁸⁴

The very powerfully smelling (grapefruit) 1-menthene-8-thiol (**557**), isolated from grapefruit, was synthesized by direct hydrosulfuration of limonene (**285**).⁴⁸⁶

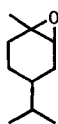
1,4-Menthadien-8-ol (**558**) has been reported as a new natural product from olibanum resin.⁴⁸⁷ This compound had already been synthesized in a routine manner by Hoppmann and Weyerstahl in 1974, from the methyl ester of 4-methyl-1,4-cyclohexadienecarboxylic acid (from isoprene and propargylic acid).⁴⁸⁸

(2) The 2-Oxygenated Menthanes

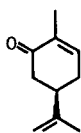
For many years the formula **559** for "santolinenone" has been suspect. The last nail in its coffin has finally been driven by Guella et al., who, after disposing of a certain amount of published rubbish, have synthesized **559** from 1-menthene epoxide (**560**), by ring opening (lithium diisopropylamide) and oxidation (silver carbonate on Celite). They carefully described **559**, the corresponding alcohols, and the dimer of **559**,⁴⁸⁹ so there is no further excuse for inadequate characterization of this pseudo-product.



559

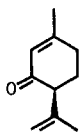


560



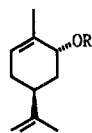
281

(-)-carvone



561

(-)-isopiperitenone

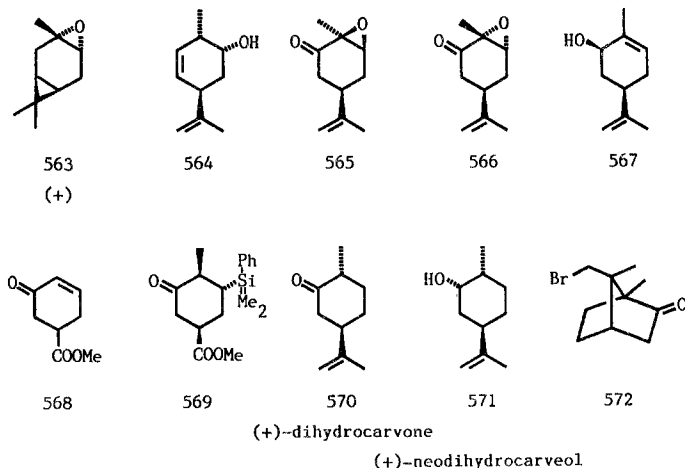


562

(+) -trans- carveol

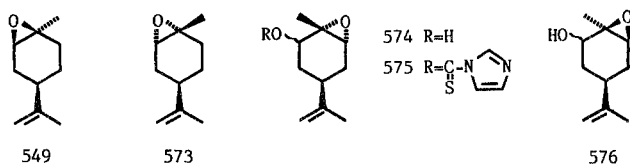
The importance of carvone (**281**) to the flavor industry, and as a chiral substance readily available in both enantiomeric forms, besides being a useful vehicle when an α,β -unsaturated ketone is required, means that the literature is very large. In the sense of novel syntheses, however, there is a welcome shrinkage. Perhaps the best evidence for the importance of **281** is that the direct synthesis from orange peel (i.e., (+)-limonene, **285**) is now suggested for an undergraduate experiment.⁴⁹⁰ It can also directly be made biologically from either α - (**116**) or β -pinene (**142**) by cultivating *Pseudomonas* spp. in their

presence.⁴⁹¹ Most chemical oxidations of limonene lead not only to carvone (**281**) but also to isopiperitenone (**561**). Thus Collin's reagent and *tert*-butyl hydroperoxide with hexacarbonylchromium both gave only slightly more **281** than **561**.⁴⁹² Surprisingly efficient (considering that Wacker conditions rarely give clean products in high yields on a laboratory scale) is the oxidation of limonene (**285**) in the presence of palladium chloride and cupric chloride in acetic acid, which was made to yield 63% of *trans*-carveyl acetate (**562**, R = Ac).⁴⁹³ Several routes from 3-carene epoxide (**563**) to (+)-carvone [(+)-**281**] have been described by Sukh Dev's group,⁴⁹⁴ one of these routes passing through 5,8-menthadien-2-ol (**564**) and the corresponding unconjugated ketone. The carvone epoxide (**565**) has been isolated from *Catasetum maculatum*. The epoxide obtained from carvone (**281**) is mostly (94:6) the other one, **566**, and synthesis of **565** is better effected by epoxidation of *cis*-carveol (**567**), then oxidation with chromium trioxide in pyridine.⁴⁹⁵ A development of Fleming's synthesis of carvone (**281**) from 2-methylcyclohexanone (Vol. 4, p. 514, Ref. 398) has appeared. The starting material was methyl 5-oxo-3-cyclohexenecarboxylate (**568**). The methyl group was introduced next to the carbonyl group by quenching the addition product from **568** and $(\text{PhMe}_2\text{Si})_2\text{CuLi}$ with methyl iodide giving **569**, then the isopropyl group was formed with methyllithium on the ethylene acetal of **569**. The remainder of the synthesis is straightforward.⁴⁹⁶



The widely occurring reduced carvones are formed (in 100% optical purity) by reduction with various microorganisms. A most interesting point is that each stage in the reduction is accompanied by a fall in the toxicity. For example, (–)-carvone (**281**) was reduced by *Tetrahymena pyriformis* successively to (+)-

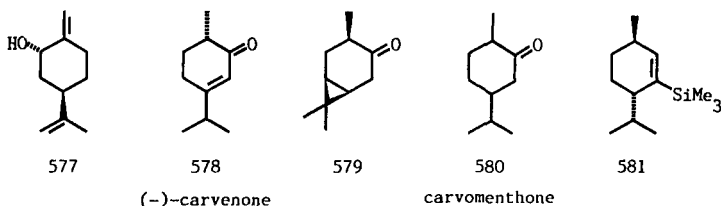
dihydrocarvone (**570**) and (+)-neodihydrocarveol (**571**) with a slight decrease each time in the toxicity.⁴⁹⁷ This same sequence also occurred in the presence of cultured cells of *Nicotiana tabacum*.⁴⁹⁸ We have already referred to many chemical methods of carrying out such reductions (Vol. 2, p. 105; a recent example, with sodium borohydride in pyridine, was carried out on what was amusingly termed a "large scale" of 24 g!⁴⁹⁹). Another recent reduction using hydrosilylation catalyzed by an optically active rhodium catalyst talks of "asymmetric induction" in the reduction of (-)-(*R*)-carvone to the carveols.⁵⁰⁰ It is unclear what is meant. Specific reduction of carvone has been effected by the addition of thiophenol, giving an equatorial methyl group. Subsequent lithium aluminum reduction, reductive elimination of the sulfur group (Li in PrNH_2), and reoxidation of the alcohol gave (+)-dihydrocarvone (**570**).⁵⁰¹ It is probably easier to carry this reduction out with "NaHTe" (made by the action of tellurium on sodium borohydride). This yielded 99% of a single isomer, **570**, from (-)-carvone (**281**).⁵⁰² The same group has shown that reduction of (+)-carvone [(+)-**281**] with tetracarbonylhydridoferrate gives (-)-dihydrocarvone [(-)-**570**] in ethanol, and a quantitative yield of (-)-neodihydrocarveol [(-)-**571**] in tetrahydrofuran.⁵⁰³ The bromocamphor **572** was converted to a mixture of the two stereoisomers of dihydrocarvone with sodium-potassium alloy in ether or electrochemically,⁵⁰⁴ but a preparation of the *trans*-isomer of **570** occurred during a chemical purification of limonene *cis*-epoxide (**549**) from the mixture of limonene epoxides. This mixture was allowed to rearrange with acid. The *trans*-epoxide **573** rearranged more rapidly, yielding *trans*-**570**, and the *cis*-epoxide **549** can be distilled pure.⁵⁰⁵ Optically pure (+)-*trans*-carveol (**562**, $\text{R} = \text{H}$) has been made from the epoxides of carveols (**574**) having the isopropenyl and methyl groups *cis*, through the thiocarbonylimidazolidine derivative **575**. Refluxing with tributyltin hydride in benzene yielded **562** ($\text{R} = \text{H}$), while similar treatment of the epoxides **576**, with the *trans*-alkyl groups, yielded a complex mixture but which still contained some *cis*-carveol.⁵⁰⁶



Limonene *cis*-epoxide (**549**) is favored by employing molybdenum-catalyzed epoxidation of limonene, and it undergoes *trans*-diaxial opening with sodium phenylselenide. Both the ring-opened selenides were readily converted to *trans*-1(7),8-menthadien-2-ol (**577**).⁵⁰⁷ In Volume 2(p.110) we have noted the common

route to **577** by rearrangement of perilla alcohol (**536**, $R = H$) derivatives. Another route has employed the tributylstannane **536** ($R = SnBu_3$) derived from perilla alcohol.⁵⁰⁸

Many terpenoids in the correct oxidation state having also an oxygen atom at C-2 are converted to carvenone (**578**) with sulfuric acid. The epoxide (**563**) of 3-carene also undergoes this reaction, yielding the (–)-isomer **578**, the (+)-isomer being obtained from (–)-4-caranone (**579**).⁵⁰⁹



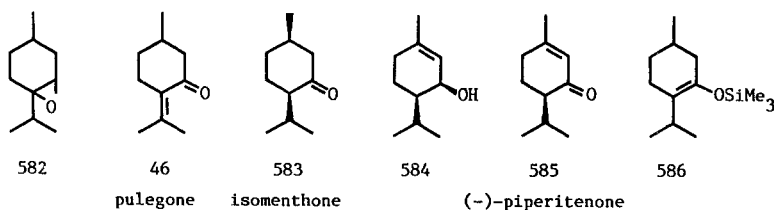
Finally, the conversion of menthone (**521**), to carvomenthone (**580**), via epoxidation of the trimethylsilyl derivative **581**, ring opening, and desilylation, should be mentioned.⁵¹⁰

(3) The 3-Oxygenated Menthanes

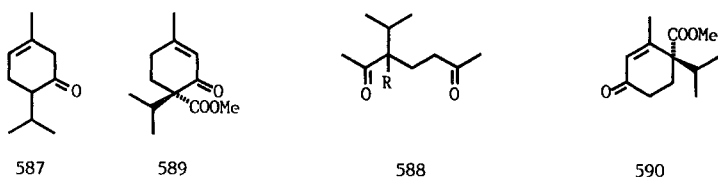
A much needed description of all isomers of the (–)-menthol (**525**) and (–)-menthone (**521**) series has been given, including the preparation and properties of the pure isomers, separation of the ketones, and specific reduction of these.⁵¹¹ The one-step nucleophilic inversion of the hydroxyl group of (–)-menthol (**525**),⁵¹² has received some development.⁵¹³ A number of Indian patents deal with the conversion of 2,8-menthadiene (**526**) to menthol (**525**), usually by addition of an hydrogen halide to the 8,9-double bond, epoxidation, then reduction.⁵¹⁴ Hydroxylation of 2- or 3-menthenes has also been described,⁵¹⁵ the route presumably involving an epoxide intermediate. 3-Menthene epoxide (**582**) has been converted in 72% yield to menthone by electrolysis, that is, using “electrogenerated acid” (electrolysis, $LiClO_4$, CH_2Cl_2), to effect the rearrangement.⁵¹⁶

Reduction of the more unsaturated 3-oxygenated menthanes is a well-known route to menthones; thus treatment of pulegone (**46**) with cyclooctadiene and an iridium catalyst yielded 61% menthone (**521**) and 39% isomenthone (**583**).⁵¹⁷ *cis*-Piperitol (**584**) was also converted to isomenthone (**583**) by treatment with low-valence cobalt complexes coordinated with phosphines.⁵¹⁸

Usually, however, the interest is more to go from the cheaper menthone to the more expensive piperitone (**585**). The (–)-(*R*)-isomer **585** is isolated from

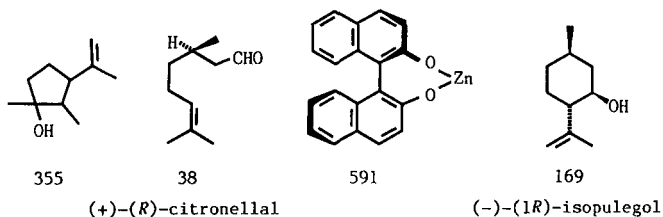


Eucalyptus dives, but the (+)-(*S*)-isomer has been isolated from *Mentha piperita*.⁵¹⁹ Photooxygenation of menthone trimethylsilyl enol ether (**581**) gave 82% of (+)-piperitone [(+)-**585**]. (The tetrasubstituted trimethylsilyl enol ether **586** gave 4-menthen-3-one, **522**, under the same conditions.)⁵²⁰ Metge and Bertrand have also described a route from menthone, consisting in treating α,α' -dibrominated menthone with zinc in ethanol. From the various ethoxymenthones thus obtained, 4-menthen-3-one (**522**), piperitone (**585**), and 1-menthen-5-one (**587**) were prepared.⁵²¹ Attention is drawn to a useful modification by Kreiser and Below of the original Walker synthesis of piperitone (Vol. 2, p. 119, Ref. 380). They converted the intermediate **588** ($R = \text{COOMe}$) into the piperitone-4-carboxylate (**589**) with HCl and trimethylsilyl chloride after 16 hours at room temperature, or to the *o*-menthane analog **590** with piperidine acetate in refluxing benzene.⁵²² The diketone **588** ($R = \text{H}$) has also been prepared from crude plinol (**355**) by ozonolysis of the cyclopentene obtained after hydrogenation and dehydration of **355**.⁵²³

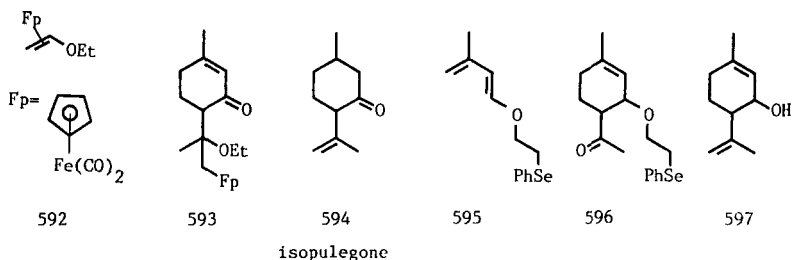


A very efficient way of converting optically active citronellals (**38**) into optically active isopulegols (**169**) is by use of the chiral reagent **591**, which is superior to other Lewis acids. The reaction is not controlled by the reagent, but only by the configuration of the citronellal. Thus (+)-(*R*)-citronellal (**38**) gave (1*R*)-isopulegol (**169**), (-)-(*S*)-citronellal giving the (1*S*)-isomer of **169**⁵²⁴ (see also menthane-3,9-diols below).

Direct addition of an isopropenyl group to a methylcyclohexenone has been realized using the cyclopentadienyldicarbonyliron compound **592**. The anion of 3-methyl-2-cyclohexenone thus gave **593**. Fluoroboric acid at -78°C followed



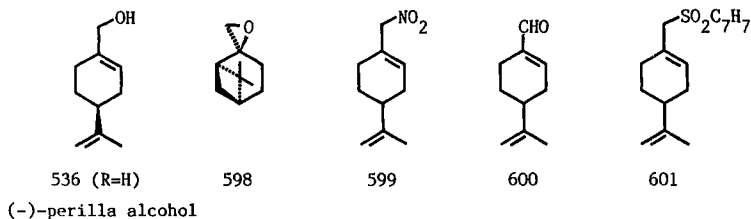
by tetraethylammonium bromide in methylene chloride to remove the cyclopentadienyliron group then gave isopiperitenone (**561**). Starting from 5-methyl-2-cyclohexenone gave a mixture of pulegone (**46**) and isopulegone (**594**).⁵²⁵ The oxygenated isoprene **595**, prepared by a Wittig reaction (isobutenyltriphenylphosphonium halide and $\text{PhSeCH}_2\text{CH}_2\text{OCHO}$), produced the Diels–Alder adduct **596** with methyl vinyl ketone. A second Wittig reaction added the methylene group needed for isopiperitenol (**597**). Removal of the phenylselenoethyl group (sodium periodate) and oxidation completed a lengthy route to isopiperitenone [$(\pm)$ -**562**].⁵²⁶



(4) The 7-Oxygenated Menthanes

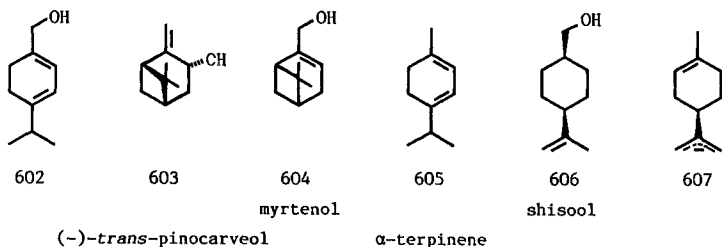
The most common way of preparing the derivatives of perilla alcohol (**536**, $\text{R} = \text{H}$) is from pinenes (Vol. 2, p. 126), and several methods for ring opening of β -pinene epoxide (**598**) [this is the epoxide of $(-)$ - β -pinene (**142**) leading to $(-)$ -perilla alcohol (**536**, $\text{R} = \text{H}$)] have been published. The problem is always to have an adequate yield in the reaction, because acid conditions also cause extensive double-bond rearrangement. Formic acid in acetic anhydride led to a mixture of the formate and acetate of perilla alcohol, but the yield did not exceed 50%.⁵²⁷ More efficient was the use of trichloroacetic acid in the presence of A-4 Zeolite, which yielded **536** with 84% selectivity.⁵²⁸ Fétizon has described ring opening with mercuric salts followed by acid dehydration to give 90% of

perilla alcohol from the pinene epoxide,⁵²⁹ but in two laboratories, we were never able to achieve the yields published, and indeed had difficulty in attaining even 30% (the remainder being the usual rearranged products).⁵³⁰ The best method published seems to be that of Delay, consisting in treatment of the epoxide **598** with catalytic amounts of ammonium nitrate in nitromethane.⁵³¹ (See also, below, the ring opening of **598** to 1-menthene-7,8-diol.)



One can also start directly from β -pinene (**142**). This was opened to the nitro compound **599** with nitrous acid, titanium tetrachloride then giving perilla aldehyde (**600**).⁵³² Photochemical addition of *Se*-phenyl *p*-toluenesulfonate to β -pinene yielded an addition product in 91% yield, oxidative deselenylation of which gave 94% of the 7-substituted menthadiene **601**, but the latter was not converted to the oxygenated menthadiene.⁵³³

1,3-Menthadien-7-ol (**602**) was mentioned as long ago as 1879, when it was believed to have been isolated from Roman camomile (*Anthemis nobilis*) and called "anthemol."⁵³⁴ [No subsequent analysis of Roman camomile mentions it, and the only isomeric alcohols found were (-)-*trans*-pinocarveol (**603**)⁵³⁵ and myrtenol (**604**), which occurs as such and in a number of esters.⁵³⁶] Now the compound has at least been synthesized by Schlosser et al. from α -terpinene (**605**). Reaction of fluorodimethoxyborane with the potassium anion from **605**, followed by oxidation, gave "anthemol" (**602**).⁵³⁷ If it really is a natural product, we do not believe it occurs in Roman camomile!

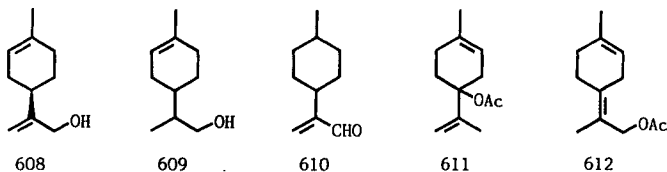


A better method for the hydrogenation of perilla alcohol (**536**, $R = H$) to shisool (**606**) than the one described in Volume 4 (p. 520, Ref. 450) is using copper–chromium or copper–zinc catalyst and hydrogen. The major product at 80–150°C is said to be the *cis*-isomer **606**, higher temperatures (up to 240°C) giving the *trans*-isomer.⁵³⁸

(5) The 9-Oxygenated Menthanes

A simple access to 9-oxygenated menthanes (which ought to have appeared in Vol. 4) is by oxidation of the anion **607**, obtained by metalation of limonene with butyllithium in *N,N,N',N'*-tetramethylethylenediamine, when optically active 1,8-menthadien-9-ol (**608**) was obtained.⁵³⁹ An alternative involved addition of phenyl sulfide to **607**, followed treatment with trimethyl phosphite in methanol.⁵⁴⁰

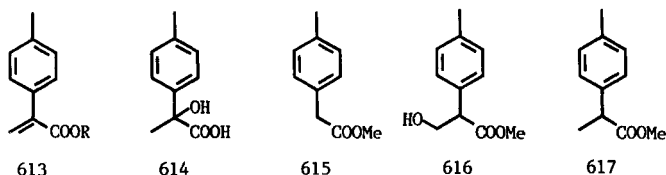
The (naturally occurring, Vol. 2, p. 129, Ref. 413) more reduced alcohol **609** has been prepared by a modification of the “old” Ziegler method,⁵⁴¹ namely by hydroalumination of limonene with aluminum and hydrogen at 160°C and 100 atmospheres, followed by oxidation.⁵⁴² A new hydroborating agent, thexylchloroborane-dimethyl sulfide, has been used with limonene (**285**), allowing only monohydroboration (unlike, for example, $BH_2Cl \cdot SMe_2$, with which dihydroboration occurs). This allowed clean preparation of **609** and of the corresponding aldehyde (the latter in 68% yield after oxidation).⁵⁴³ The aldehyde **610**, not natural, so far as we are aware, has been prepared by lead tetraacetate oxidation of the corresponding alcohol⁵⁴⁴ (available from 8-menthene via the anion).



9-Oxygenated 1,4(8)-menthadienes are probably best synthesized by allylic rearrangement of 1,8-menthadien-4-yl acetate (**611**), which produced a 1:10 mixture of **611** and **612** in 88% yield with catalytic amounts of $Pd(MeCN)_2Cl_2$.^{545*}

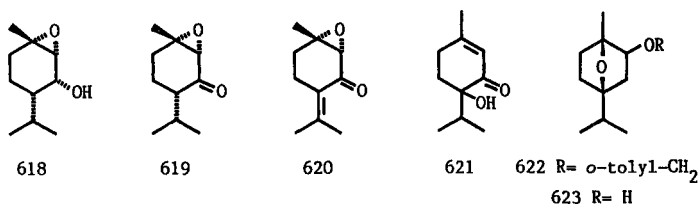
*Only the (*Z*)-isomer of **612** is shown in the paper. The reagent is highly (*E*)-specific, but this refers to aliphatic chains. Probably **612** is a mixture of both isomers.

There are two new approaches to the 9-carboxylic acid **613**, R = H. One consists in the reaction of dichlorocarbene with 4-methylacetophenone. The initially formed dichloroepoxide reacted with sodium hydroxide, and the main product from the reaction was the hydroxyacid **614**, which underwent dehydration to **613** (R = H). The latter formed dimers in boiling water.⁵⁴⁶ Methyl (4-methylphenyl)acetate (**615**) reacted with formaldehyde, and the product **616** was dehydrated to **613** (R = Me). Hydrogenation over rhodium then gave the ester **617**, which is also the product of hydroformylation of **615**.⁵⁴⁷



(6) *Menthane Ethers: Epoxides, Cineoles, Cyclic Peroxides, Menthofuran Derivatives*

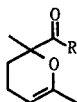
cis-Piperitol epoxide (**618**) (Vol. 4, p. 516; an error in our text states that it was *trans*-piperitol epoxide) has been made by Chinese workers, who subsequently oxidized it to piperitone epoxide (**619**).⁵⁴⁸ The latter has been isolated, together with piperitenone epoxide (**620**), from *Calamintha sepeta*, subsp. *glandulosa*, and reported to isomerize to 4-hydroxy-1-menthen-3-one (**621**) during isolation.⁵⁴⁹ Both epoxides **619** and **620** have long been known as natural products and synthesized.⁵⁵⁰



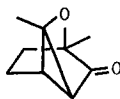
The only derivative of 1,4-cineole (**554**) we feel constrained to mention is not even a natural product. As a herbicide, however, Cynmethylin (**622**) will doubtless soon be present in the environment.⁵⁵¹ It was synthesized by epoxidation of 1-menthen-4-ol (**547**),⁵⁵² using vanadium-catalyzed *tert*-butyl hydroperoxide,



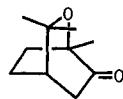
624



625



626

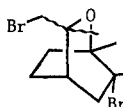


627

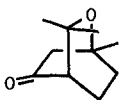
then treatment of the epoxide with acid to yield 2-*exo*-hydroxycineole (**623**), which was converted to the ether with 2-methylbenzyl chloride.⁵⁵³

The 2,5-endoperoxide **624** has been isolated from *Callilepis laureola* (Compositae),⁵⁵⁴ and was synthesized from α -phellandrene (**512**), when both stereoisomers of **624** were formed.

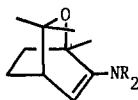
Two new preparations of 1,8-cineole (**553**) [the biogenesis of which from geraniol (**25**) in *Rosmarinus officinalis* has been elucidated⁵⁵⁶] have been recorded. A Diels–Alder adduct **625** (R = Me) of methyl vinyl ketone and isopropenyl methyl ketone was converted to the diazoketone (R = CH=N₂) with diethyl oxalate/base, then toluenesulfonyl azide, and treatment of the latter with [Rh(OAc)₂]₂ in methylene chloride at room temperature for five minutes converted it in very high yield to the tricyclic compound **626**. Lithium dimethylcuprate then yielded the ketone **627**,⁵⁵⁷ conversion of which to 1,8-cineole (**553**) was known.⁵⁵⁸ The other 1,8-cineole synthesis was a by-product of an observation which enabled the two stereoisomers of limonene 1,2-epoxide to be separated. The *cis*-epoxide **549** was brominated to stereoisomers of a dibromocineole **628**, under conditions when the *trans*-epoxide did not react, and could be distilled pure afterward. The dibromo compound **628** yielded 1,8-cineole (**553**) with tributyltin hydride.⁵⁵⁹



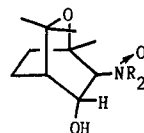
628



629



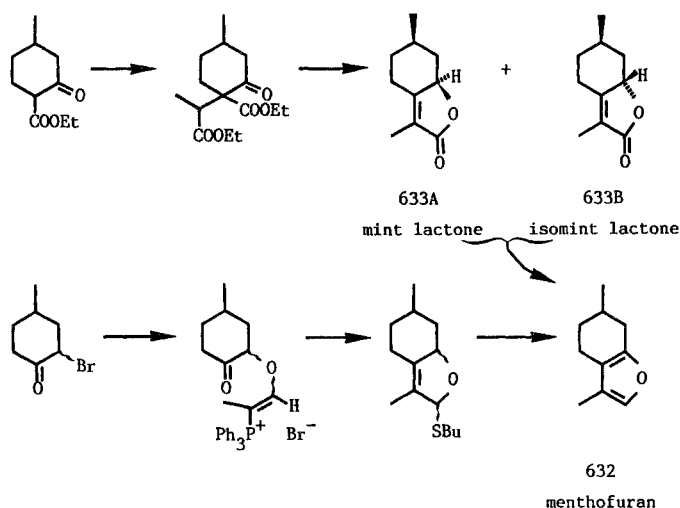
630



631

The ketone **629** has been isolated from peony flowers.⁵⁶⁰ It had already been synthesized several times; for example, by hydroboration of the enamine **630** of the isomeric ketone **627**, then Cope elimination of the *N*-oxide **631** of the amino alcohol.⁵⁶¹ Chromyl acetate oxidation of 1,8-cineole (**553**) led first to **629**; further oxidation gave diketones.⁵⁶² *Aspergillus niger* also gave some **629**, although the main products were the corresponding alcohols.⁵⁶³

Another synthesis of menthofuran (**632**) from ethyl 2-oxo-4-methylcyclohexanecarboxylate (Vol. 4, p. 520, Refs. 440 and 445) consists in adding the side chain using ethyl 2-iodopropionate and sodium hydride in dimethylformamide. The product yielded the butenolides, mint and isomint lactones (**633A**, **633B**) (see below), after refluxing 4 days with concentrated hydrochloric acid (65% yield), and the mixture was reduced to menthofuran (**632**) with lithium aluminum hydride (Scheme 55).⁵⁶⁴ Garst and Spencer have carried out a three-step synthesis of menthofuran (**632**) from 2-bromo-4-methylcyclohexanone (made from 4-methylcyclohexanone). (α -Formylethylidene)triphenylphosphorane [$\text{Ph}_3\text{P} = \text{C}(\text{Me})\text{CHO}$] was alkylated on the oxygen atom with the bromoketone, and the presumed product was directly cyclized with 1-butanethiol anion. The thioacetal was oxidized with mercuric sulfate, again without isolation of an intermediate, to menthofuran, in 49% overall yield from 4-methylcyclohexanone (Scheme 55).⁵⁶⁵

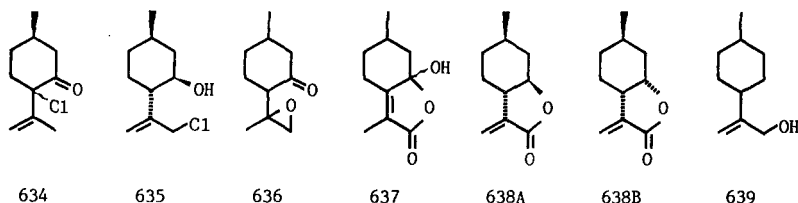


Scheme 55

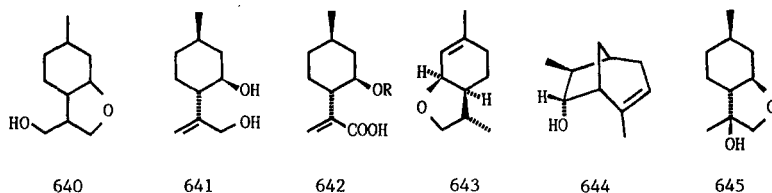
Further methods for making menthofuran (**632**) from pulegone (**46**) or isopulegol (**169**) consist in treatment with iodine and barium hydroxide, or *N*-bromosuccinimide and sodium hydroxide (these methods giving rather poor yields),⁵⁶⁶ or using the Wolinsky two-phase chlorination method with hypochlorous acid: pulegone (**46**) gave 75% of the chloroketone **634** from which menthofuran (**632**) was obtained with triethylamine or aluminum chloride. The chlorinated isopulegol **635** must be oxidized before the triethylamine treatment.⁵⁶⁷ The epoxide of isopulegol (**169**) was oxidized with chlorine to isopulegone

epoxide (**636**) and the latter converted to menthofuran (**632**) with hydrochloric acid.⁵⁶⁸

(-)-Mint lactone (**633A**) and (+)-isomint lactone (**633B**) have been isolated from *Mentha piperita*,⁵⁶⁹ and one synthesis of the mixture is mentioned above (Scheme 55). In fact they were already made in 1967 by the photooxygenation of menthofuran (**632**),⁵⁷⁰ but have now also been made by oxidation of menthofuran with chromic oxide. The initial product, **637** (also prepared by the photooxygenation method⁵⁷⁰), reported in oils of the *Mentha* species, was dehydrated then hydrogenated to the mint lactones (**633A**, **633B**).⁵⁶⁹ Another synthesis of the mint lactones involves addition of a propionic acid side chain to 4-methylcyclohexanone;⁵⁷¹ unfortunately, we had access only to the inadequate abstract for this work.



The isomers **638** of the mint lactones have also been synthesized. Brocksom and Ferreira started from 8-menthen-10-ol (**639**) (made by rearrangement of 8-menthene epoxide). Hydration of the double bond and lead tetraacetate oxidation gave the hydroxylactones **640**, which were converted to **638** by dehydration and oxidation.⁵⁷² Starting from (-)-(1*R*)-isopulegol (**169**), Bal and Pinnick hydroxylated it to **641**. The secondary alcohol was protected, then the primary alcohol was oxidized to the corresponding acid, giving an intermediate **642** that could be transformed to either **638A** (with dicyclohexylcarbodiimide) or **638B** (with diethyl azodicarboxylate and triphenylphosphine).⁵⁷³

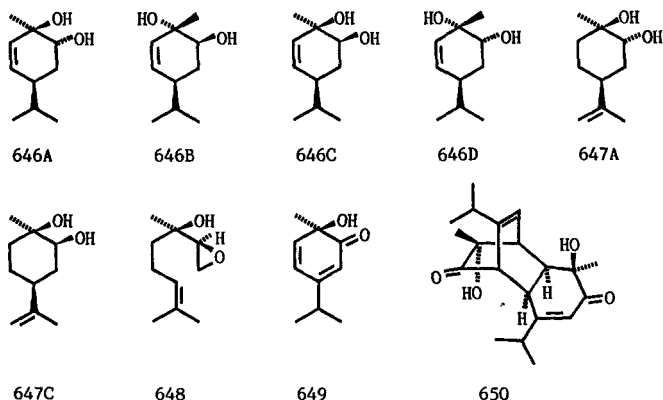


In the late 1970s, a number of independent laboratories isolated an ether from dill (*Anethum graveolens*⁵⁷⁴ or *Anethum sowa*⁵⁷⁵), to which structure **643** (but without stereochemistry) was attributed, this structure being supported by obtaining four stereoisomers on catalytic reduction of menthofuran (**632**), one of which was the same as the reduction product of **643**.⁵⁷⁶ Brunke and Rojahn prepared all the isomers of **643** from (+)-(**285**) and (-)-limonene, making the 1-menthen-9-ols (**609**) stereospecifically, then carrying out photooxygenation and cyclization. They thereby showed that the natural product was related to (+)-limonene* and must therefore have the structure shown.⁵⁷⁷ Two of the isomers (**643** and the one with the epimeric methyl group, both as racemates) were prepared by the reaction of the acetate of 2,6-dimethyl-2,6-octadienol (**113**, R = Ac) with boron trifluoride etherate, the other components from this reaction being the bicyclic alcohol **644**.⁵⁷⁸ The latter authors also converted the dill ethers to menthofuran (**632**).

Brocksom et al. have shown that isopulegols (e.g., **169**) can be oxidized to the hydroxy ether **645** by thallium triacetate, without loss of stereochemistry.⁵⁷⁹

(7) The Dioxygenated Menthanes

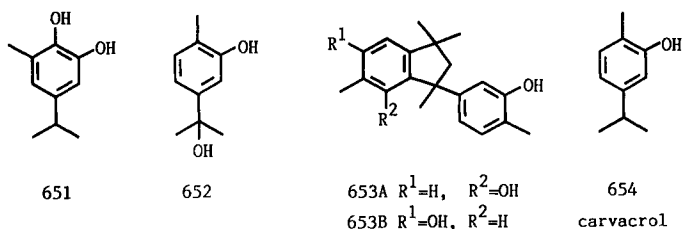
All the stereoisomers of the 5-menthene-1,2-diols (**646A-D**) are naturally occurring. The first one, **646A**, has been known for some time to occur in *Eucalyptus dives*,⁵⁸⁰ the three other diols were identified from the most polar fraction of *Chenopodium multifidum* oil.⁵⁸¹ The isomer **646A** can be obtained by microbial hydroxylation of (+)-(*S*)-phellandrene (**512**) with *Corynespora*



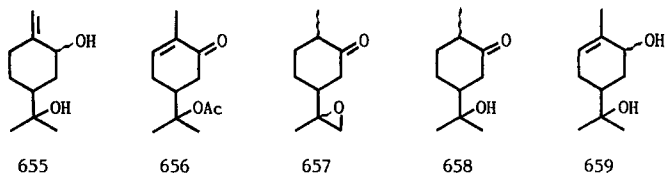
* The formulas of (+)- and (-)-limonene are reversed in this paper, but the conclusions are correct.

cassiicola; various 1,2-diols from other menthadienes (e.g., 4-menthenediols from γ -terpinene, **533**) are also described.⁵⁸² Using limonene as the substrate, 80% of the *trans*-1,2-diol **647A** was reported,⁵⁸³ the latter diol also being one of the major products of the electrochemical oxidation of limonene on a graphite electrode.⁵⁸⁴ Sharpless et al. have published an ingenious synthesis of the isomer **647C** by the reaction of linalool *erythro*-epoxide (**648**) with triethyl vanadate. The *threo*-epoxide decomposes under these conditions; the hydroxyl group presumably assists delivery of the metal to the epoxide function.⁵⁸⁵

The more oxidized 1,2-oxygenated menthadiene **649** dimerizes readily, and the dimer **650** has been isolated from the heartwood of *Callitris macleayana*. Thermolysis of the dimer results in methyl migration, and the structure **651** of the *m*-menthane obtained was confirmed by synthesis.⁵⁸⁶ This work led Carman and Van Dongen to an unexpected observation⁵⁸⁷ concerning a diol, **652**, that Patwardhan and Gupta had isolated (together with the 8-methyl ether and the dehydrated analog) from *Lavandula gibsonii*.⁵⁸⁸ The Indian workers noted that **652** dimerized when a CDCl_3 solution was allowed to stand for several weeks, and they attributed structure **653A** to this dimer.⁵⁸⁸ Carman found that the acetate of compound **649** (available by the action of lead tetraacetate on carvacrol, **654**—the Wessely reaction⁵⁸⁹) gave, on treatment with ethanolic sulfuric acid, a dimer that was identical with the major product from the dimerization of **652**, namely **653B**, and that the other dimer, **653A**, was only present to the extent of 10%.⁵⁸⁷

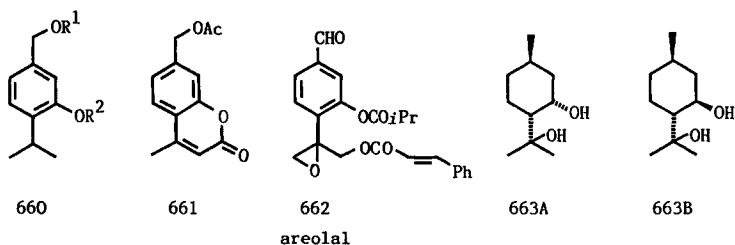


The synthesis of 1(7)-menthene-2,8-diols (**655**) has been mentioned (Vol. 4, p. 526, Ref. 503); the two isomers have now been isolated from *Osmitopsis asteriscoides*.⁵⁹⁰ The known acetate **656**, an insect repellent, has been isolated from *Mentha haplocalyx* oil,⁵⁹¹ and a review of synthetic methods has been published by Verghese.⁵⁹² In this connection, attention is drawn to a method for reducing an epoxide in the presence of a ketone, by reaction with phenyl telluride anion, PhTe^- , then triphenyltin hydride. The dihydrocarvone epoxides (**657**) yielded the hydroxydihydroketone **658** corresponding to **656**.⁵⁹³ Note also



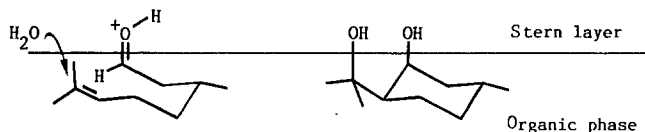
the bioconversion of α -terpineol (**65**) to the sobrerols (**659**) with cultured cells of *Nicotiana tabacum*.⁵⁹⁴

The naturally occurring thymol derivative **660** ($R^1 = \text{COiPr}$, $R^2 = \text{Me}$) has been synthesized by Sanghvi and Rao, using base reaction with the functionalized coumarin **661** (see Vol. 4, p. 522, Ref. 471), to obtain the diol **660** ($R^1 = R^2 = \text{H}$) and then functionalizing the latter.⁵⁹⁵ A more complex synthetic goal (not yet achieved) would be the synthesis of areolal (**662**) reported to occur as the racemate in roots of *Piptotrix areolare* (Compositae).⁵⁹⁶

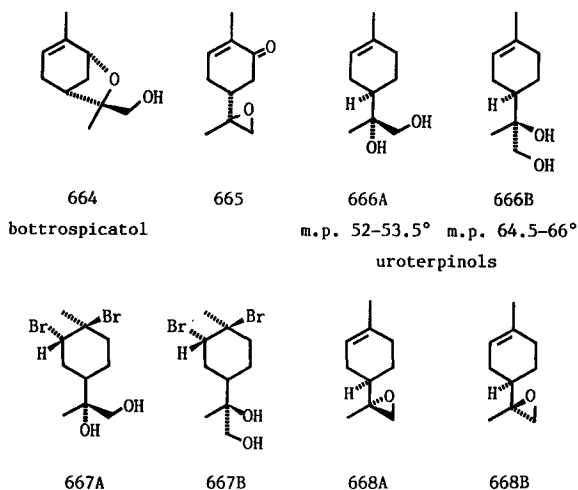


The allelopathic* diols **663A** and **663B** were isolated as racemates from *Eucalyptus citriodora*.⁵⁹⁷ The optically active substances have been synthesized by acid-catalyzed cyclization of citronellal, a reaction known since 1897,⁵⁹⁸ (+)-(R)-citronellal (**38**) giving (+)-**663A** and (-)-**663B** as drawn.⁵⁹⁹ It has now been shown that 0.038M sodium dodecyl sulfate in the cyclization reaction medium favors the formation of **663A**, the intermediate for this isomer (Scheme 56) not having the hydroxyl group in the organic phase.⁶⁰⁰ A related compound, bottrospectol (**664**), has been isolated from cultures of *Streptomyces bottropensis*; this, too, is allelopathic. A mixture of the two isomers (about C-8) was synthesized from (-)-carvone epoxide (**665**). Borohydride reduction to carveol epoxide, then treatment with acid, gave both isomer of **664**.⁶⁰¹

* Allelopathic: inhibiting seed germination of another species.



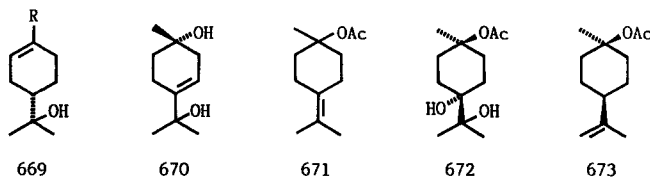
It will be recalled that there was some confusion about the stereochemistry of the uroterpinols (**666A**, **666B**) (Vol. 4, pp. 525–526), and that the stereochemistry attributed by Kergomard and Verschambre⁶⁰² was questioned because it did not correlate with the stereochemistry of the bisabolols into which **666A** and **666B** were converted. A very careful study by Carman et al. has now vindicated Kergomard, whose stereochemistries were correct. The mixture of uroterpinols (**666**) is not separable, neither are the dibromides **667** obtained by bromination of **666**. The *p*-nitrobenzoates of **666** are not separable, but Carman was able to separate the *p*-nitrobenzoates of the dibromides **667**. The stereochemistry was then demonstrated by X-ray crystallography, and the dibromide *p*-nitrobenzoates separately converted to the *p*-nitrobenzoates of the uroterpinols, from which the diols **666A** and **666B** were isolated crystalline. The



NMR spectra were very different, and the lower-melting isomer (m.p. 52–53.5°C) was assigned structure **666A**.⁶⁰³ In a later paper, Carman et al. show how the isomer **666A** can be obtained from the higher boiling isomer [the

(4*R*,8*R*)-isomer] of limonene 8,9-epoxide (**668A**), the other epoxide (4*R*,8*S*) **668B** leading to **666B**, using in both cases tetramethylammonium hydroxide in dimethyl sulfoxide for 36 hours at 35–40°C.⁶⁰⁴ The discrepancy about bisabolol remains, but that is not the concern of this chapter.

An early synthesis of optically active oleuropic acid (**669**, R = COOH) from β -pinene epoxide (**598**), involving initial ring opening with carbonic acid (Vol. 2, p. 135, Ref. 408) to 1-menthene-7,8-diol (**669**, R = CH₂OH), has been much improved, particularly the steps concerning oxidation of the 7-hydroxyl group of **669** (R = CH₂OH).⁶⁰⁵ In view of the high yields claimed in a somewhat similar ring opening of **598** (see above, section on the 7-oxygenated menthanes), it is notable that the authors of the oleuropic acid synthesis only claim 65% in the step to **669** (R = CH₂OH).⁶⁰⁵ This same diol, **669** (R = CH₂OH), has been found among the products of the biotransformation of α -terpineol (**65**) with cultured cells of *Nicotiana tabacum*.⁵⁹⁴

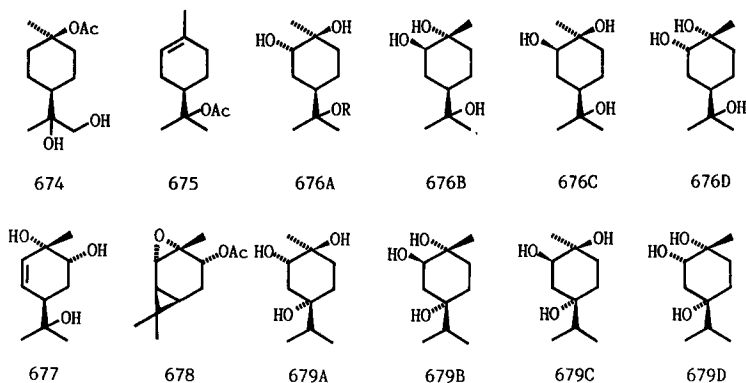


Access to 3-menthene-1,8-diol (**670**), one of the minor products isolated (as its 1-acetate) from incubation of γ -terpenyl acetate (**671**) with a suspension of cultured *Nicotiana tabacum* cells,⁶⁰⁶ was conveniently achieved by reduction of piperitenone epoxide (**620**) with lithium aluminum hydride.⁶⁰⁷

(8) The Trioxygenated and the Polyoxygenated Menthanes

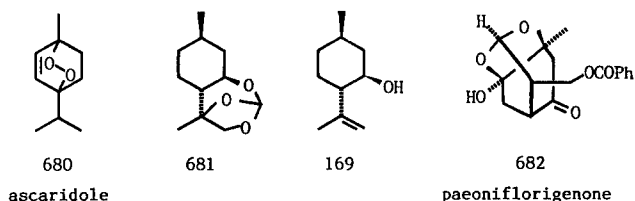
We have mentioned several times the work Hirata and Suga have been carrying out on the oxygenation of various monooxygenated menthanes with cultured cells of *Nicotiana tabacum*. A particularly interesting result is the production of stereospecifically oxygenated menthanetriol derivatives. For example, γ -terpinyl acetate (**671**) yields mainly the 1,4,8-triol 1-acetate **672**, the structure of which was confirmed by X-ray crystallography.⁶⁰⁶ β -Terpinyl acetate (**673**) gives the 1,8,9-triol 1-acetate **674**,⁶⁰⁸ and ($\pm$)- α -terpinyl acetate [($\pm$)-**675**] was reported to give the ($\pm$)-1,2,8-triol 8-acetate **676A** (R = OAc).⁶⁰⁹ In a study of the oxidation of (+)- α -terpineol [(+)-**65**, corresponding to **675**], Carman and Fletcher have shown that the products from the performic oxidation are the two *trans*-glycols **676A** (R = H) and **676B**. The *cis*-hydroxylating agent, potassium

permanganate, yields cleanly in aqueous solution the *cis*-glycol **676C**, the fourth glycol **676D** being obtained when *tert*-butanol is present in the permanganate oxidation. With this, the Australian authors have clarified the confused stereochemistry of the 1,2,8-triols;⁶¹⁰ it is only a pity that the acetate **676A** (R



= Ac) of the Japanese workers has not been checked against the now clear configurations of the triols. The 5-menthenetriol **677** related to **676D** has been made by base treatment of 4 α -acetoxy-2-carene epoxide (**678**).⁶¹¹ The 1,2,4-triol **679A**, already reported as a natural product (Vol. 4, p. 572, Ref. 505), has been isolated from the pyrolysate of ‘‘Aden’’ incense (from *Boswellia carteri*). The stereoisomers **679C** and **679D** were again synthesized as comparison products.⁶¹² The racemates of all four menthane-1,2,4-triols (**679**) and some 1,3,4-triols have been prepared from ascaridole (**680**) by De Pascual Teresa et al.⁶¹³ (For the optically active triols, see Ref. 614.)

The ortho ester **681** of menthane-3,8,9-triol has been isolated from *Mentha piperita* and synthesized from (–)-isopulegol (**169**). Osmium tetroxide oxidation

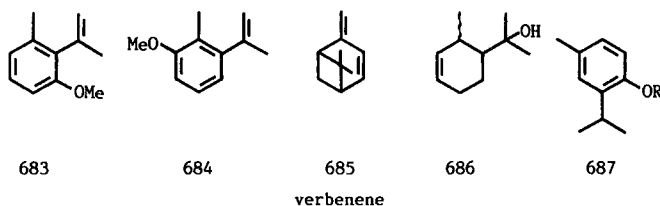


of the latter gave the triol that was converted to **681** with ethyl orthoformate. Alternatively, the epoxyacetate of isopulegol can be treated with alumina.⁶¹⁵

The pentaoxygenated menthane paeoniflorigenone (**682**) has been isolated from roots of *Paeonia albiflora*,⁶¹⁶ as has another related compound,⁶¹⁷ but these have not been synthesized.

9. *o*-MENTHANES

There is still little synthetic work toward the main terpenes of the *o*-menthane group (see Vol. 4, p. 527). Synthesis of the methyl ether **683** and its isomer **684** from, respectively, 2-methoxy-6-methylbenzoic acid and 3-methoxy-2-methylbenzoic acid showed that the substance isolated by Bohlmann from *Piqueria trinervia*⁶¹⁸ was **683**, and not **684**, as he had believed.⁶¹⁹



The pyrolysis of verbenene (**685**) leading to *o*-menthatrienes, has been reexamined,⁶²⁰ and a number of *o*-menthadienes and two stereoisomers of an “*o*-terpineol” (**686**) have been prepared from a Diels–Alder reaction between 1,3-pentadiene and methyl acrylate, with subsequent Grignard addition.⁶²¹

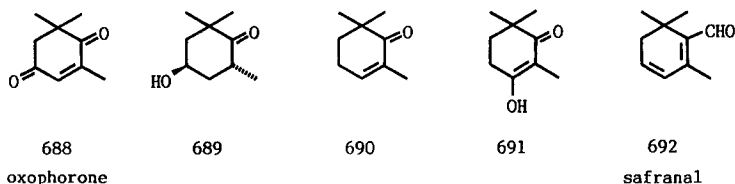
10. *m*-MENTHANES

Verghese has published a review about this class.⁶²² Authentically naturally occurring *m*-menthanes are “*m*-thymol” (**687**, R = H) and its methyl ether **687** (R = Me), isolated from various *Calea* species^{623,240} as well as the isobutyl ether **687** (R = *i*Bu) from *Athrixia elata*.⁶²⁴ Paknikar has synthesized **687** (R = H) by Grignard reaction of 2-hydroxy-5-methylacetophenone.⁶²⁵

11. TRI- AND TETRAMETHYLCYCLOHEXANES

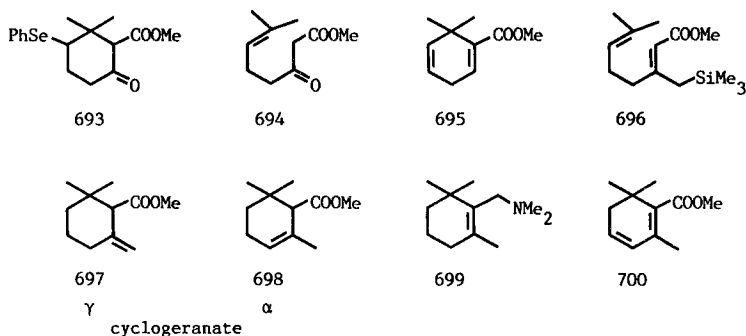
The known oxophorone **688** occurs in longjug tea.⁶²⁶ It is made by oxidation of isophorone, and a study of the chlorination products of the related alcohol **689** has been made.⁶²⁷

Access to key materials for synthesis in this group has been possible for some years by reaction of acrolein with 2-methyl-3-pentanone in presence of *p*-toluenesulfonic acid, distilling off the water formed during the reaction, and leading to 2,6,6-trimethyl-2-cyclohexenone (**690**).⁶²⁸ Alternatively, 2-methyl-3-pentanone reacts with methyl acrylate in the presence of base (sodium methoxide/methanol in xylene) to give 92% of the diketone **691** (probably as the enol).⁶²⁹

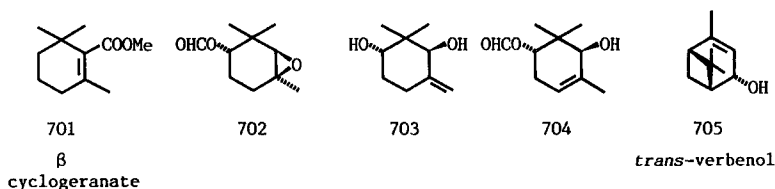


The full paper of the phenyl selenide-mediated cyclization of geranyl acetate (**25** acetate) (cf. Vol. 4, p. 529, Ref. 532a) has appeared; the product was converted to safranal (**692**).⁶³⁰ This reaction required two steps: one for the addition of the selenium reagent, and one for cyclization. Alderdice and Weiler carried out both steps at once by using PhSeCl in the presence of aluminum chloride. The product **693**, from the keto ester **694**, was then methylated (lithium dimethyl cuprate on the enol phosphate) and deselenized to **695**.⁶³¹ The keto ester **694** has been converted (as its enol phosphate) to the trimethylsilyl derivative **696** with trimethylsilylmethylmagnesium chloride. Cyclization of **696** with stannic chloride results in a 7:1 ratio of methyl γ - (**697**) to α -cyclogeranate (**698**), the trimethylsilyl group exerting an unexpectedly large effect on the cyclization.⁶³² (The use of **696** for the synthesis of karahana ether is described later in this section.) Usually, cyclization of methyl geranate (**50**, R = Me) results in more α -cyclogeranate (**698**); for example, the new technique of using electrogenerated acid for cyclization gives a ratio of 89:11 of **698** to **697**.⁶³³ Geranylamines (**6**, **47**) were also cyclized to β -cyclogeranylamines (e.g., **699**) with concentrated hydrochloric acid⁶³⁴ or 40% sulfuric acid;⁶³⁵ 2,4,4-trimethyl-3-methylenecyclohexene and 1,1-dimethyl-2,3-bis(methylene)cyclohexane have been prepared from **699**.⁶³⁵

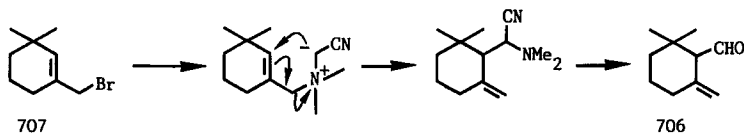
Methyl β -safranate (**700**) is readily prepared from methyl β -cyclogeranate (**701**), by epoxidation and opening of the epoxide with Filtrol®.⁶³⁶ If there is no activa-



tion, epoxide opening with Filtrol® stops at the allyl alcohol stage. For example, the epoxide **702** opened in two different ways: to the diol **703** of the γ -series with lithium diisopropylamide, and to the monoformate **704** of the α -series with Filtrol®.⁶³⁷ The latter reaction was actually used to make the optically active compounds **703** and **704**, the starting material **702** being prepared from *trans*-verbenol (**705**) by pyrolysis then epoxidation with concomitant Baeyer–Villiger rearrangement.⁶³⁸ It may be recalled that Hunt and Lythgoe prepared γ -cyclocitral

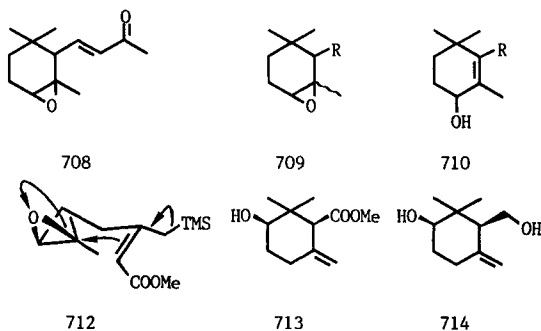


(**706**) from the bromide **707** (see Vol. 4, p. 531, Ref. 551). Another way of carrying out the conversion of **707** to **706** is by the reaction of dimethylaminoacetonitrile in dimethylformamide in the presence of potassium carbonate (Scheme 57); the rearrangement observed is similar to that used by Mori in his karahana ether synthesis (see below). A second step (silver nitrate in a mixed-solvent system) was needed to convert the aminonitrile to the aldehyde **706**.⁶³⁹

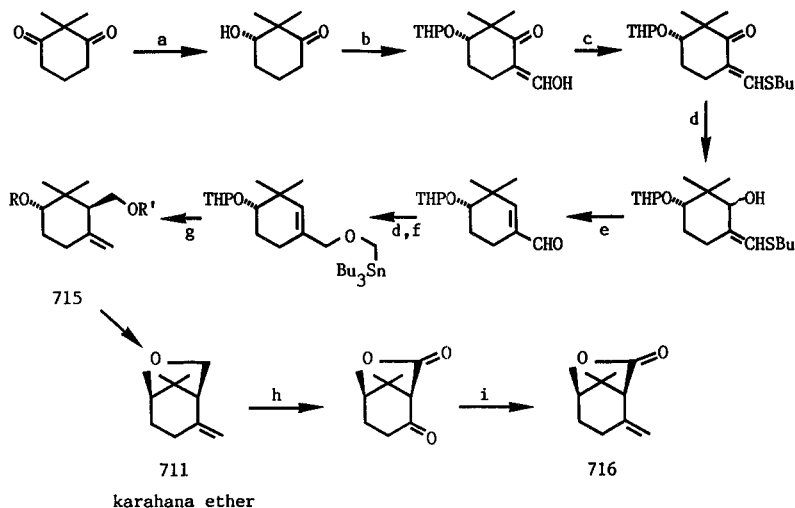


Scheme 57

We have mentioned the ozonolysis of β -ionone leading to β -cyclocitral (Vol. 4, p. 531, Ref. 550). The principle has now been extended to the epoxide (**708**) of α -ionone, and from the epoxides obtained [those of α -cyclocitral (**709**, R = CHO) or methyl α -cyclogeranate (**709**, R = COOMe)], the hydroxylated compounds **710** (R = CHO)⁶⁴⁰ and **710** (R = COOMe)⁶⁴¹ have been prepared.



Racemic kaharana ether [(±)-**711**] has been synthesized by Armstrong and Weiler from the trimethylsilane **696**. Its epoxide cyclizes (figure **712**) when treated with dry SnCl_4 or BF_3 -etherate to give the *cis*-ester **713**, which was reduced to the diol **714**, a known intermediate for karahana ether.⁶⁴² The synthesis by Mori and Mori of (1*S*,5*R*)-karahana ether (**711**), although long, is very important because the chirality was carefully checked along the route, and the product obtained was estimated to be at least 98.4% optically pure. The synthesis is shown in Scheme 58, and a few points must be made; step b had to be carried out on the protected alcohol to avoid racemization. When the Moris arrived at **715** (R = THP, R' = H), they did not yet know what the relative configuration would be. Finding that it was the wrong one for direct cyclization, they adopted two techniques for converting RO to one ester (tosyl), and R'O to a different ester, so that they could then effect an intramolecular $\text{S}_{\text{N}}2$ displacement of the tosyloxy group by a $-\text{CH}_2\text{O}^-$ at C-1. The better route was with R = Ts and R' = Ac, [made from the tetrahydropyranyl ether acetate **715** R = THP, R' = Ac), and *p*-toluenesulfonic acid in methanol]. The karahana ether (**711**) was also converted to karahana lactone (**716**),⁶⁴³ and the latter compared directly with the sample of karahana lactone originally isolated from Japanese hops. The "natural" lactone was found to be almost racemic. The possibility clearly exists that karahana lactone is an artifact,⁶⁴³ and Mori has suggested that the optical rotation of natural products should be determined at the time of their isolation⁶⁴⁵ — a sentiment with which we heartily agree, if only it were always possible!



a) baker's yeast; b) $\text{HCOOEt}/\text{NaOMe}$, on THP-ether; c) BuSH/TsOH ; d) NaBH_4 ; e) $\text{HgCl}_2/\text{CdCO}_3$ (dehydrates); f) NaH , then $\text{Bu}_3\text{SnCH}_2\text{I}$; g) BuLi ([2,3]-sigmatropic rearrangement); h) $\text{RuCl}_3/\text{NaIO}_4$; i) Wittig

Scheme 58

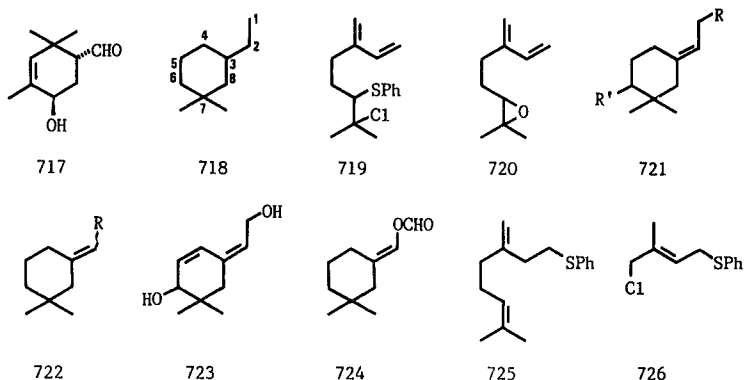
A new ferulol derivative (cf. Vol. 4, p. 533), **717** (absolute stereochemistry unknown), has been identified in a Mongolian species, *Artemisia rutifolia*, but not synthesized.⁶⁴⁶ Related compounds are known from other *Artemisia* species.

12. ETHYLDIMETHYLCYCLOHEXANES

A. Ochtodanes

The name "ochtodane" was proposed by Fenical et al. in 1980 for the 1-ethyl-3,3-dimethylcyclohexane skeleton (**718**) derived from the numerous halogenated and oxygenated derivatives isolated from the red alga *Ochtodes crockeri*⁶⁴⁷ and other seaweeds (cf. Vol. 4, p. 534).⁶⁴⁸ A review including marine terpenoids has been published.⁶⁴⁹

The skeleton can be synthesized from myrcene (**7**) (brominative cyclization was mentioned in Vol. 4, p. 534, Ref. 583), either by reaction with benzenesulfonyl chloride (giving **719**), or by epoxidation (to **720**) before cyclizing with SnCl_4 or trifluoroacetic acid. The cyclized products **721** ($\text{R} = \text{OCOCF}_3$ or Cl , $\text{R}' = \text{OH}$ or SPH) were converted to the boll-weevil pheromone **722** (R

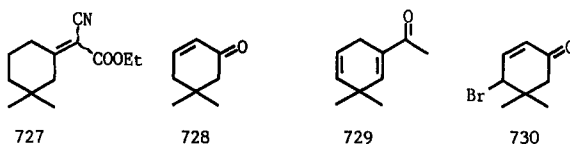


= CHO), and to the (*Z*)-diol **723**,⁶⁵⁰ which had been isolated from *Ochtodes crockeri*.

In the course of the synthesis of the boll-weevil pheromones **722** ($R = \text{CHO}$ and $R = \text{CH}_2\text{OH}$) (Vol. 4, p. 534, Ref. 578), Hedin et al. found that the acids **722** ($R = \text{COOH}$) and the (*Z*)-acetate (*Z*)-**722** ($R = \text{CH}_2\text{OAc}$), were pheromone inhibitors, as was the enol formate **724**.⁶⁵¹ This fact is particularly important because the last named compound, **724**, was formed to the extent of 50% in a sample of the pheromone (*E*)-**722** ($R = \text{CHO}$) that had been standing for 4 years.⁶⁵¹

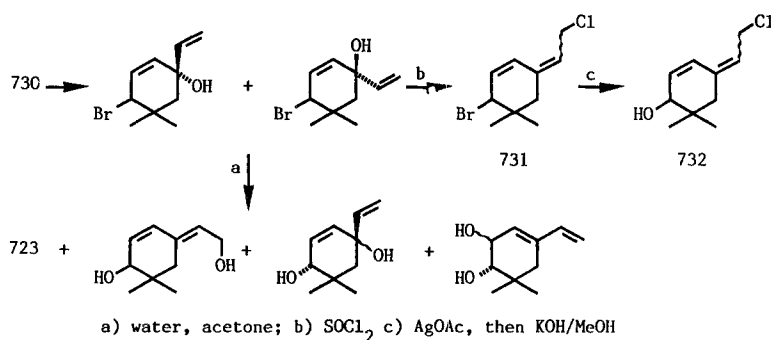
The thioether **725**, formally the addition product of myrcene (**7**) and thiophenol, was made from prenylmagnesium chloride (**15**, $R = \text{MgCl}$) and the chlorothioether **726**. Formic acid caused cyclization of **725** to a mixture of double-bond isomers of ochtodene-1-thioethers, which were converted to the corresponding ochtodene-1-ols. The latter were oxidized to the aldehydes, which were equilibrated by base to the boll-weevil aldehydes **722** ($R = \text{CHO}$).⁶⁵²

A complement to the various routes to derivatives of **722**, starting from 3,3-dimethylcyclohexanone (Vol. 4, pp. 534–535), is the reaction of the latter with ethyl cyanoacetate. The products **727** were hydrolyzed with lithium chloride (sodium chloride in the text!) in aqueous dimethyl sulfoxide to **722** ($R = \text{CN}$), but the yield given is only 53%, much dimethylcyclohexanone being recovered.⁶⁵³



Many of the naturally occurring octodanes have a double bond in the ring, and the most direct way to 5,5-dimethyl-2-cyclohexenone (**728**) is from the enol ether of dimedone by lithium aluminum hydride reduction.⁶⁵⁴ The cyclohexenone can then be used directly to introduce a C₂ unit; it was also reduced catalytically to the previously mentioned 3,3-dimethylcyclohexanone.⁶⁵⁵ Treatment of the ozonolysis product from 3-carene (**277**) with sodium ethoxide also led to a ketone, **729**, that might be a useful starting material.⁶⁵⁶

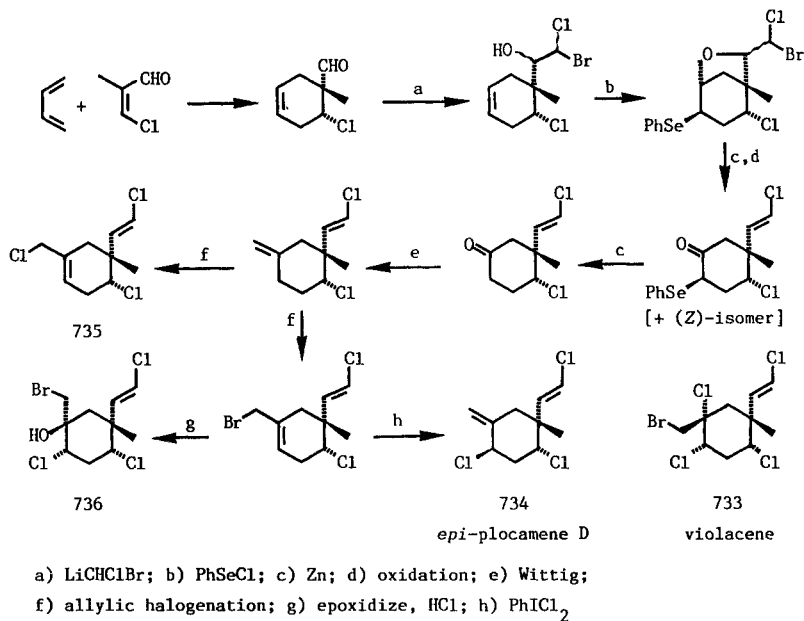
A series of octodanes occurring in *Ochtodes rockeri* has been synthesized from **728**. Bromination with *N*-bromosuccinimide gave the unstable bromoketone **730**, which was treated at once with vinylmagnesium bromide. The products (Scheme 59) were hydrolyzed with water and acetone to the various octodenediols shown, these being identical with the natural products. Alternatively, the chlorobromides **731** underwent replacement of the bromine atom specifically with silver acetate and then methanolic potassium hydroxide, the (*E*)-chloroalcohol (*E*)-**732** being identical with the natural product.⁶⁵⁷



Scheme 59

B. Other Ethyldimethylcyclohexanes

Violacene (**733**), the plocamenes, and other related polyhalogenated compounds, all isolated from algae,⁶⁴⁹ are the only naturally occurring 1-ethyl-1,3-dimethylcyclohexanes. A start has been made on a synthesis of violacene (**733**), which has resulted in the synthesis of *epi*-plocamene D (**734**), and its allylically rearranged trichloride **735**, which is also naturally occurring. The route is shown in Scheme 60, but the way to an epimer of violacene was blocked when Williard and de Laszlo were unable to replace the hydroxyl group of compound **736**.⁶⁵⁸

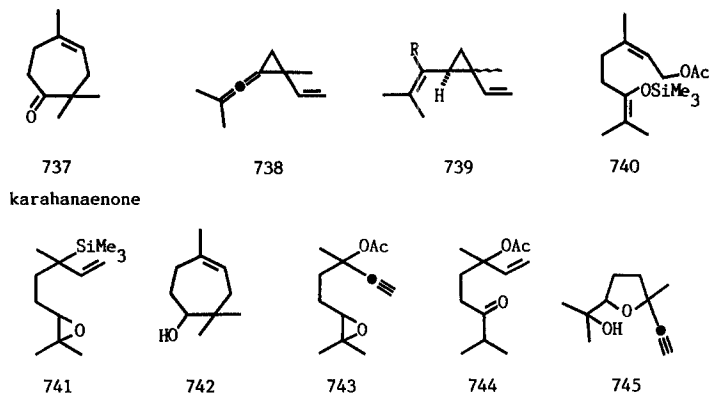


Scheme 60

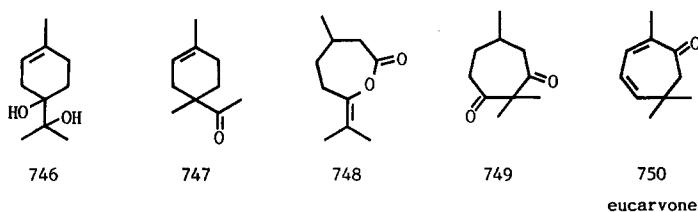
13. THE CYCLOHEPTANES

A. Trimethylcycloheptanes

Many of the synthetic principles involved in recent preparations of karahanaenone (**737**) were discussed in Vol. 4 (p. 536). Isoprene and the carbene $\text{Me}_2\text{C}=\text{C}=\text{C}:$ give the cyclopropane **738**, and the latter will react with thiophenol to give two isomers **739** ($\text{R} = \text{SPh}$) of a sulfur analog of the trimethylsilyloxycyclopropane **739** ($\text{R} = \text{OSiMe}_3$), known to rearrange thermally to a cycloheptadiene (Vol. 4, p. 537, Ref. 600). The interesting point is that *cis*-**739** ($\text{R} = \text{SPh}$) undergoes this rearrangement at 25°C, while the *trans*-isomer requires 160°C. Karahanaenone is obtained after desulfurizing with aqueous mercuric chloride in acetonitrile at reflux for 12 hours.⁶⁵⁹ Further studies of the cyclization of the nerol derivative **740** have been made.⁶⁶⁰ Geraniol (**25**) has been converted into the trimethylsilyl epoxide **741**, and this cyclizes to karahanaenol (**742**),⁶⁶¹ also a natural product. Use of electrogenerated acid has been mentioned;⁶³³ in another paper, the same group has used electrogenerated perchloric acid to open dehydrolinalyl acetate epoxide (**743**) to the corresponding ketone. The oxolinaelyl acetate **744** gave karahanaenone (**737**) on pyrolysis at 200°C. In fact, the epoxide

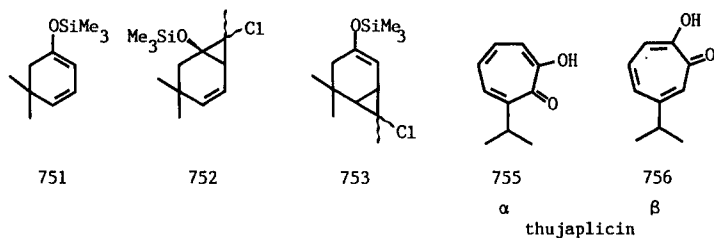


743 was also made electrochemically, converted to the tetrahydrofuran **745** with sodium hydroxide, and **745** was also transformed into karahanaenone (**737**).⁶⁶² The diol **746** was converted with boron trifluoride-etherate into a 7:3 mixture of karahanaenone (**737**) and its double-bond isomer, 4,7,7-trimethyl-3-cycloheptenone.⁶⁶³ The authors made **746** by titanium chloride–magnesium amalgam-activated coupling of acetone with 4-methyl-3-cyclohexenone, but the diol **746** is more readily accessible from terpinolene epoxide (**550**).⁶⁶⁴ In the rearrangement of **746**, one might have expected some methyl rearrangement to the natural product **747** (Vol. 4, p. 534, Ref. 580), but none was observed.⁶⁶³



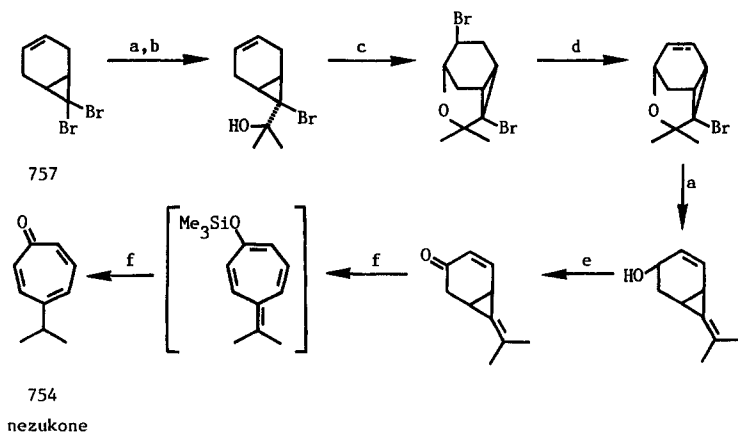
Pulegone (**46**) undergoes a Baeyer–Villiger reaction with *m*-chloroperbenzoic acid, and the product, **748**, can be rearranged to the cycloheptanedione **749** with diethylaluminum phenyl sulfide, this dione being a potential source of substances related to karahanaenone (**737**).⁶⁶⁵

A synthesis of eucarvone (**750**) starts from the trimethylsilyl enol ether (**751**) of 5,5-dimethyl-2-cyclohexenone. Methylchlorocarbene gave two adducts, **752** and **753**. After removal of the silyl groups (methanol), refluxing with methanolic triethylamine gave 62% eucarvone (**750**).⁶⁶⁶



B. Isopropylcycloheptanes

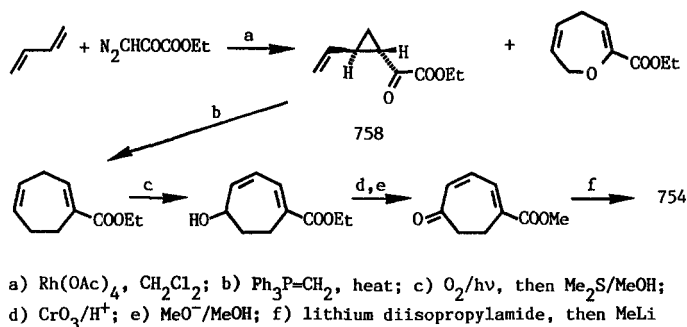
The full paper of Itoh et al. about the cyclization of a 3-isopropylallyl alcohol onto a double bond, with $\text{TiCl}_4\text{-PhNHMe}$, to give a cycloheptenyl chloride (Vol. 4, p. 540, Ref. 615) has been published,⁶⁶⁷ and further extensions of Noyori's synthesis of nezukone (**754**) and α - (**755**) and β -thujaplicin (**756**) ('hinokitiol,' Vol. 4 p. 539, Refs. 611–614) starting from tetrabromoacetone and 2-isopropylfuran, have been reported.⁶⁶⁸ A chemically ingenious, but economically impossible, synthesis of nezukone (**754**) is shown in Scheme 61. This starts from the addition product **757** of dibromocarbene to 1,4-cyclohexadiene. The poor yield (45%) in the early stages (quenching the lithiated **757** with acetone) is also unfortunate. The other stages, however, work in surprisingly high yield.⁶⁶⁹



- a) BuLi ; b) acetone, HMPT-THF ; c) N -bromosuccinimide;
 d) 1,5-diazabicyclo[4.3.0]non-5-ene (DBN); e) pyr. dichromate;
 f) $\text{Li cyclohexylisopropylamide/HMPT-THF}$; treat solution with BuLi and Me_3SiCl , quench with Bu_4NF

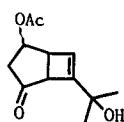
Scheme 61

Without the disadvantage of using diazo compounds in the first step, Wenkert's latest monoterpenoid syntheses would be most efficient approaches, and in any case represent novel routes to well-known materials. Nezukone (**754**) was the result of examining the reaction between butadiene and diazopyruvic ester catalyzed by rhodium tetraacetate. The major product of the addition was the cyclopropane **758** (Scheme 62). It was known that divinylcyclopropanes could be thermolyzed to cycloheptadienes (Vol.4, p.537, Ref.600). The Wittig product from **758** thus gives a cycloheptadiene, and subsequent steps are shown in the scheme. The last step involves Grignard addition to the ester function of the enolate, then loss of water and redistribution of the double bonds.⁶⁷⁰ (Further examples of the use of diazo compounds will be found under perillene in the section on furans.)

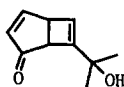


Scheme 62

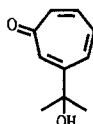
Isopropylcycloheptanes have already been synthesized from isopropyl-substituted bicyclo[3.2.0]heptanes (Vol. 4, p. 539, Ref. 610), but these were usually with isopropyl on the cyclopentane of the bicyclic starting materials. Now Cavazza and Pietra have prepared the bicyclo[3.2.0]heptenone **759**, formed with the isopropyl group on the cyclobutene side by laser irradiation of 2-methyl-3-butyne-2-ol in the presence of 4-acetoxy-2-cyclopentenone. Aluminum oxide resulted in the loss of acetic acid (to **760**) and, on irradiation with UV light, the tropone **761** was formed. After dehydration (SOCl_2), the product was converted to β -dolabrin (**762**) by known methods (given in Vol. 4, p. 540, Ref. 616).⁶⁷¹ Irradiation of 3-isopropyl-2-cyclopentenone and acetylene gives another isopropylbicyclo[3.2.0]heptenone **763**, and 6-isopropyltricyclo[4.1.0.0^{2,7}]heptan-3-one (**764**); the latter was converted to nezukone (**754**) by selenium dioxide oxidation in *tert*-butanol, the poor yield ($\approx 20\%$ overall) being offset by the rapidity of performing only two steps.⁶⁷²



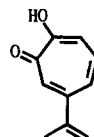
759



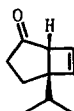
760



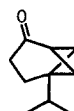
761



762

 β -dolabrin

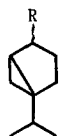
763



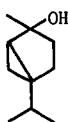
764

14. BICYCLO[3.1.0]HEXANES: THE THUJANES

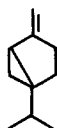
The new natural product **765** ($R = \text{CHO}$) is reported to occur in juniper,⁶⁷³ but there is no information about stereochemistry or synthesis. The corresponding acid **765** ($R = \text{COOH}$) was said to occur in carrots.⁶⁷⁴ Diterpene acid esters of sabinene hydrate (**766**) have been isolated from flowers of *Helianthus annulus*.⁶⁷⁵



765

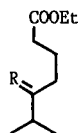


766

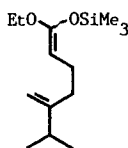


767

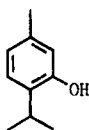
sabinene



768

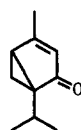


769



770

thymol



771

umbellulone

A useful sabinene (**767**) synthesis has been described by Rousseau and Slougui. The keto ester **768** ($R = \text{O}$) was prepared conventionally from ethyl 4-methyl-3-oxopentanoate and converted to the methylene compound **768** ($R = \text{CH}_2$) by a Wittig reaction. The trimethylsilylketene acetal **769** was then treated with bromoform and diethylzinc in pentane, yielding 70% of the ester **765** ($R =$

COOEt), which (via the corresponding alcohol tosylate) can be converted to sabinene (**767**).⁶⁷⁶

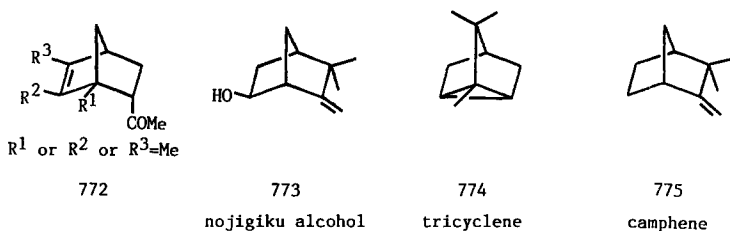
Norin et al. have also found that irradiation of thymol (**770**), in trifluoromethanesulfonic acid, with 254- or 300-nm wavelength, gives a mixture of products (rearranged and disproportionated phenols) including 5% pulegone (**46**) and 10% umbellulone (**771**).⁶⁷⁷ Even at 10% yield, such a simple process is almost worthwhile on a small scale.

Finally another version of the carbenoid addition to 2-cyclopentenone [using $\text{LiC}(\text{SPh})_3$] has been published.⁶⁷⁸

15. BICYCLO[2.2.1]HEPTANES

The interest of the early synthetic and structural conundrums posed by camphor (**40**) (cf. Vol. 2, p. 149) are well illustrated in a profile of Julius Bredt.⁶⁷⁹

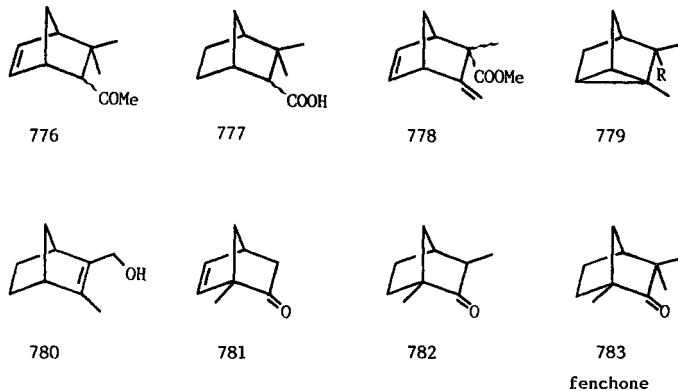
Three unusual bicyclo[2.2.1]heptenes, **772**, have been characterized from lavender oil; there is nothing spectacular about their synthesis, since they are merely the Diels–Alder adducts of methyl vinyl ketone and the methylcyclopentadiene isomers.⁶⁸⁰



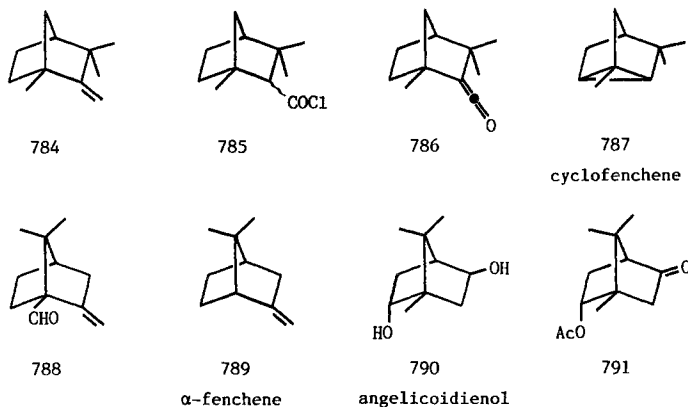
A new synthesis of nojigiku alcohol (**773**) (Vol. 4, p. 554) starts from tricyclene (**774**) and we should perhaps recall the preparation of the latter from camphor (**40**) tosylhydrazone and sodium methoxide in decalin.⁶⁸¹ [Tricyclene is also produced in other reactions leading to camphene (**775**), such as the reaction of 3-bromocamphor with methylaniline.⁶⁸²] The new synthesis consists in anodic oxidation with triethylamine in acetic acid, and yields 76% of **773**, with 8% of the *endo*-isomer and 11% of diols.⁶⁸³ Oxidation of tricyclene (**774**) with lead tetraacetate also gives nojigiku alcohol (**773**), but as a minor (16%) product, the main product being camphor (**40**).⁶⁸⁴ Tricyclene having a plane of symmetry, these methods all lead to racemic **773**.

The Diels–Alder approach to bicyclo[2.2.1]heptanes is still giving rise to much work. We might mention the catalysis of the reaction between

cyclopentadiene and mesityl oxide (Vol. 2, p. 151, Ref. 511). All Lewis acids except TiCl_4 favored *exo*- over *endo*-products,⁶⁸⁵ as indeed does the uncatalyzed reaction (Vol. 2, p. 152, Refs. 514 and 515). The products, **776**, would be useful for the preparation of camphanic acid (**777**) derivatives, were it not that the *exo*- and *endo*-isomers of **777** are difficult to separate.⁶⁸⁶ The best way of making *endo*-camphanic acid (*endo*-**777**) is by oxidation of camphene (**775**) with hydrogen peroxide in ethyl formate⁶⁸⁷ or formic acid.⁶⁸⁶ Another Diels–Alder reaction led to the unsaturated esters **778** [from cyclopentadiene and the allenic carboxylate, $\text{CH}_2=\text{C}=\text{C}(\text{Me})\text{COOMe}$];⁶⁸⁸ bromination and reductive debromination of **778** gave the ester **779** ($\text{R} = \text{COOMe}$), which was converted to teresantalol (**779**, $\text{R} = \text{CH}_2\text{OH}$).⁶⁸⁹ Addition of cyclopentadiene and 2-butynoic esters, followed by reduction, gave the alcohol **780**, which was not actually used for the synthesis of monoterpenoids.⁶⁹⁰ The reaction between methylcyclopentadienes and chloroacrylonitrile, followed by hydrolysis, gave a number of methylbicyclo[2.2.1]hepten-2-ones, of which **781** was the major one, and was separated from the others by distillation. After catalytic reduction, the 1-methylbicyclo[2.2.1]heptan-2-one yielded, on methylation with lithium cyclohexylisopropylamide and methyl iodide, 1,3-dimethylbicyclo[2.2.1]heptan-2-one (“fenchosantenone,” **782**), a second methylation giving fenchone (**783**), but in only 30% yield.⁶⁹¹



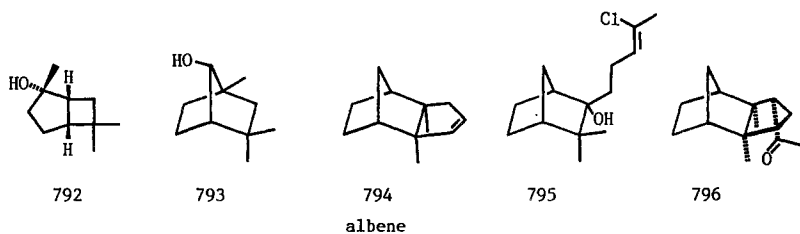
From fenchone (**783**), methylmagnesium iodide and dehydration yielded Wallach's "homofenchene" (**784**),⁶⁹² which was in turn converted to the acid chloride **785**. The latter formed the ketene **786** in 19% yield when heated with triethylamine in benzene at 130–140°C,⁶⁹³ and the ketene underwent an unusual photoreaction. In pentane, the carbene insertion product cyclofenchene (**787**) was formed, but at -60°C in methanol, another reaction competed with the



more normal methanol addition, and the aldehyde **788** was the main product, further photolysis leading to α -fenchene (**789**) by photodecarbonylation.⁶⁹⁴

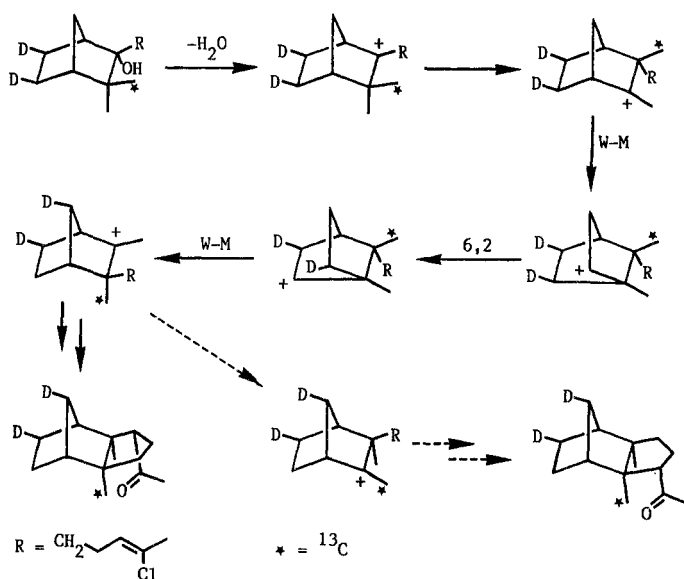
A hydroxyborneol (angelicoidienol, **790**) was isolated from *Pleurospermum angelicoides*;⁶⁹⁵ it was identical with the diol synthesized by Money et al. in 1979 by remote oxidation of bornyl acetate (**348**) with chromic oxide in acetic anhydride and acetic acid; this yielded 40% of the ketone **791**, metal hydride reduction of which gave the diol **790**.⁶⁹⁶

For the synthesis of many bicyclo[2.2.1]heptanes, it is useful to know something of the various bromocamphors; attention is drawn to the papers of Money⁶⁹⁷ (the 1986 paper giving a history) in this respect. Attention is also drawn to the synthesis of the system from linalool (**28**). Irradiation of the latter



with a (quartz) 450-W Hanovia lamp in the presence of Cu(I) trifluoromethanesulfonate and benzene in ether gave the bicyclo[3.2.0]heptane **792** which, after treatment with trifluoroacetic acid and hydrolysis, was converted to the hydroxyfenchene **793** (not natural). The isomer with a *syn*-hydroxyl group was also prepared.⁶⁹⁸

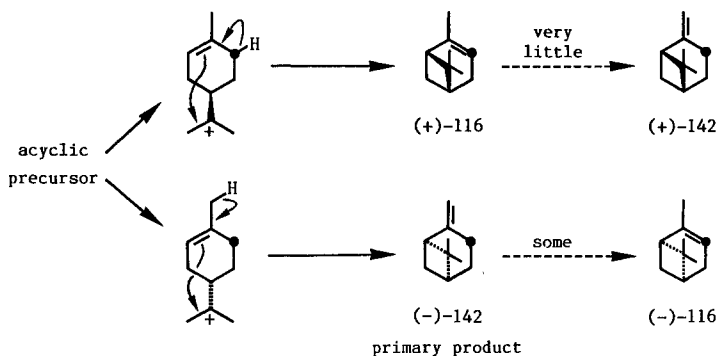
In the course of two earlier syntheses of albene (**794**) (Vol. 4, p. 550), there was a question of the apparent *endo*-3,2-methyl shift in going from chiral **795** to **796**, in which the chirality was greatly reduced. By examining the behavior of doubly labeled (deuterium and ^{13}C) **795**, Baldwin and Barden found that there was no *endo*-3,2-methyl shift; the major pathway involved an *exo*-methyl shift first, then a series of Wagner–Meerwein rearrangements (Scheme 63), with a minor route (shown in the scheme by dotted arrows) leading to the compound of opposite chirality.⁶⁹⁹



Scheme 63

A new synthesis of albene (**794**) depends on a palladium-catalyzed [3 + 2] cycloaddition of 3-acetoxy-2-(trimethylsilylmethyl)propene (**797**) to the norbornene diester **798** which, in this case, takes place in exclusively *exo*-fashion. (With the norbornadiene corresponding to **798**, the stereochemical mode of addition is less uniform.) Conversion of the product **799** to albene (**794**) turned out to be less straightforward than the appearance of **799** might suggest, and the route that finally worked best is shown in Scheme 64.⁷⁰⁰

It has long been known that $(-)\text{-}\beta\text{-pinene}$ [$(-)\text{-}142$] occurs widely in *Pinus* (and other) species, as a relatively pure optical isomer, while $(+)\text{-}\alpha\text{-pinene}$ [$(+)\text{-}116$], with which it co-occurs, exhibits much wider variations in optical purity. In a beautifully clear paper, Banthorpe et al. have shown, by feeding experiments with labeled mevalonic acid, that the acyclic precursor to the pinene skeleton first gives two menthene carbocations which, in turn, cyclize to $(+)\text{-}\alpha$ [$(+)\text{-}116$] or $(-)\text{-}\beta$ -pinene [$(-)\text{-}142$]. Very little of the former isomerizes to $(+)\text{-}\alpha$ -pinene, but larger amounts of $(-)\text{-}\beta$ -pinene isomerize to $(-)\text{-}\alpha$ -pinene, giving rise to the differing optical activities observed for α -pinene (Scheme 65).⁷⁰⁵ The relevance of this to synthetic work is that it is always a problem to obtain $(+)\text{-}\beta$ - or α -pinene in optically pure form for conversion to other compounds, and this gives another impetus (in addition to the commercial one of the higher price of β -pinene) to study the interconversion of the pinenes. In this connection, see the convenient procedure for upgrading commercial $(+)\text{-}$ and $(-)\text{-}$ pinene of Brown et al.⁷⁰⁶

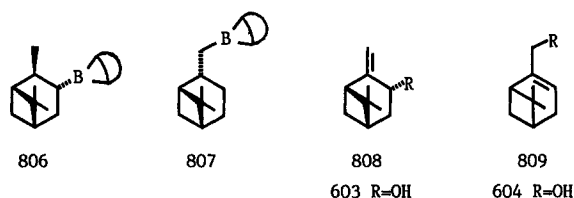


Scheme 65

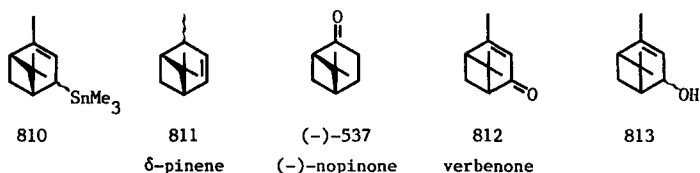
Before leaving the biogenesis of the pinenes, we draw attention to work showing the natural isotope effect between deuterium and hydrogen leading to a depletion of deuterium at specific positions in the $(-)\text{-}\alpha$ -pinene molecule, measured by natural-abundance deuterium NMR spectroscopy. A correlation with the optical activity was also discussed.⁷⁰⁷

A simple conversion of $(+)\text{-}\alpha$ - to $(+)\text{-}\beta$ -pinene has been effected through the addition product with 9-BBN (9-borabicyclo[3.3.1]nonane). *B*-3-Pinanyl-9-BBN (**806**) undergoes exceptionally rapid olefin-alkyl group exchange; after 30 hours reflux in diglyme it has reached equilibrium, the major component being the myrtenyl derivative **807**, from which $(+)\text{-}\beta$ -pinene [$(+)\text{-}142$] is liberated with benzaldehyde. From $(+)\text{-}\alpha$ -pinene of 92% optical purity, $(+)\text{-}\beta$ -pinene of

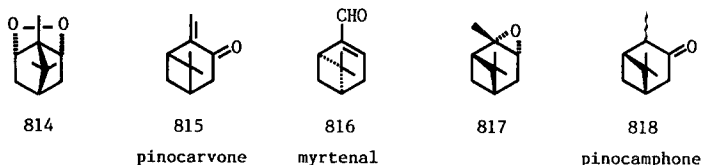
86% optical purity was obtained.⁷⁰⁸ Conversion of α - to β -pinene has been realized via the hydroperoxide **808** ($R = \text{OOH}$) from the sensitized photooxygenation of α -pinene, or its reduction product, *trans*-pinocarveol (**603**), both of which yielded 40% β -pinene with lithium aluminum hydride in the presence of titanium tetrachloride.⁷⁰⁹ This situation must be more complex, however, because the hydroperoxides **808** ($R = \text{OOH}$) and **809** ($R = \text{OOH}$) already equilibrate in hexane at 40°C, the resulting mixture containing about 70% of the myrtenyl isomer **809** ($R = \text{OOH}$).⁷¹⁰ α -Pinene (**116**) gives 59% of myrtenyl trimethylstannane (**809**, $R = \text{SnMe}_3$) with butyllithium in tetramethylethylenediamine followed by trimethyltin chloride, and the stannane gives 85% α -pinene with methanolic hydrogen chloride containing 4% water.⁷¹¹



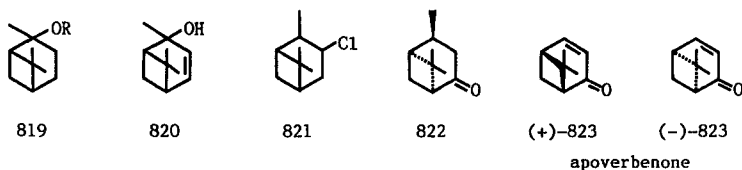
Russian workers have used this reaction (from a *cis/trans* mixture or pure *trans*-(+)-4-methylstannylpinane, **810**) to make the two isomers of δ -pinene (**811**). There is little difference in the behavior of the stereoisomers of **810**, the *cis*-isomer of **811** being always the major product.⁷¹² It is possible to introduce cyclopentadienyldicarbonyliron (Fp) into the α -pinene skeleton [via myrtenyl chloride (**809**, $R = \text{Cl}$)], and the compound **809** ($R = \text{Fp}$) forms a complex with HBF_4 , the action of sodium iodide on the latter liberating β -pinene (**142**) in 52% yield.⁷¹³ The ready availability of *trans*-pinocarveol (**603**) from (+)- α -pinene [(+)-**116**] has led to its use in the preparation of (-)-nopinone [(-)-**537**] by ozonolysis, then removal of the hydroxyl group ($\text{Cr}_2\text{Cl}_2 + \text{aqueous HCl}$ on mesylate). The other optical isomer of nopinone [(+)-**537**] is available from the common (-)- β -pinene [(-)-**142**]. A Wittig reaction on (-)-**537** led to the uncommon (+)- β -pinene [(+)-**142**].⁷¹⁴



Of the many papers about the direct oxidation of pinenes to make natural products, we have selected a few that, in our opinion, offer some advantage in the preparation of these oxygenated pinanes. Autoxidation of α -pinene in the presence of cuprous iodide and α,α' -dipyridyl at 50°C under 100 psi pressure of air is reported to lead in a 40% conversion to verbenone (**812**),⁷¹⁵ autoxidation in sulfolane is claimed to effect higher conversions.⁷¹⁶ These methods avoid the use of lead salts. Pd(II)-catalyzed oxidation gives verbenone and verbenols (**813**), but conversions are low.⁷¹⁷ In the last type of reaction, β -pinene usually gives a mixture of *trans*-pinocarveyl (**808**) and myrtenyl (**809**) derivatives (e.g., with PdCl₂ and *tert*-butyl hydroperoxide in acetic acid).⁷¹⁸ Sharpless et al. have pointed out that their selenium dioxide-catalyzed oxidation of β -pinene with *tert*-butyl hydroperoxide gives, in addition to >90% of *trans*-pinocarveol (**603**), small amount of *tert*-butyl ethers of pinocarveol and myrtenol (**808** and **809**, R = OCM₃)⁷¹⁹ The photooxygenation of α -pinene is well known (cf. Vol. 2, p. 157, Ref. 546 and 547); it has been shown that in the presence of protic solvents (aqueous acetonitrile), some rearrangement (to **814**) and ring opening (to menthenes) occur, dioxygenated products being isolated after reduction.⁷²⁰ The most useful new aspect of photooxygenation is the production of the unsaturated ketones by including catalytic amounts of 4-dimethylaminopyridine in the acetic anhydride-pyridine mixture employed. Thus photooxygenation of α -pinene under these conditions rapidly gives 97% of pinocarvone (**815**) and β -pinene gives, somewhat more slowly, 58% of myrtenal (**816**)⁷²¹ — surely the quickest way of making these substances on a small scale. Barton and Crich have obtained 95% of pinocarvone (**815**) from oxidation of β -pinene with 8-pyridinoselenic anhydride.⁷²²

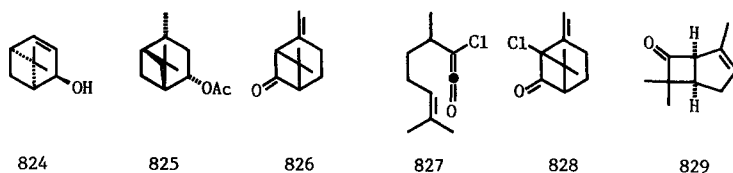


The ready accessibility of α -pinene epoxide (**817**) is frequently the reason for its use to make other compounds. A most interesting claim is that with 1 mol% of aluminum isopropoxide at 100–120°C, *trans*-pinocarveol (**603**) is obtained, while 5 mol% of the reagent at 140–170°C gives pinocamphone (**818**).⁷²³ Kane et al. have used the pinanyl oxides *cis*- and *trans*-**819** (R = K) to open α -pinene epoxide (**817**). These alkoxides are made from dimethylsulfinylpotassium and *cis*-pinanol (**819**, R = H) (the product of autoxidation of pinane; *cis* here means from *cis*-pinane, therefore with the *trans*-hydroxyl group) and are among the



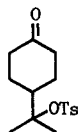
most basic alkoxides known. They yield *trans*-pinocarveol (**603**) and **820** with α -pinene epoxide (**817**) and are also very efficient for dehydrochlorinating **821** to δ -pinene (**811**).⁷²⁴

Verbanone and its derivatives are normally made by oxidation of α -pinene [usually (+)-**116**]; when Takayanagi and Nishino required (–)-*trans*-verbanone (**822**), they used a synthetic procedure starting from (+)-apoverbenone [(+)-**823**] accessible from the (–)- β -pinene series. The Wharton reaction (hydrazine hydrate) with the (*trans*)-epoxide of **823** yields **824**, which can be oxidized to (–)-apoverbenone [(–)-**823**], from which **822** was obtained by reaction with lithium dimethyl cuprate. [This work was actually to prepare verbanyl acetates, the (1*R*,2*R*,5*R*)-series of which notably (+)-**825** is active as pheromone mimics in the cockroach *Periplaneta americana*, while the (1*S*,2*S*,5*S*)-series from **822** are inactive.]⁷²⁵



Total synthesis of the pinane skeleton from the acid chloride of geranic acid (**50**, R = H) has been carried out by Snider et al. Refluxing with triethylamine in toluene gave 43% of the isomer **826** of chrysanthenone (**801**). This compound was converted into chrysanthenone (**801**) with palladium on calcium carbonate and hydrogen, and α -pinene (**116**) resulted from a Wolff–Kishner reaction on **801**.⁷²⁶ Snider's first paper on this work reported the conversion of **827** to the chloropinane **828** in 55% yield, but when the chlorine atom in **827** was replaced by hydrogen, the reaction did not work.⁷²⁷ Probably the filifolone (**829**) synthesis from chrysanthenone (**801**) (see Vol. 4, p. 542, Ref. 621) involves **826** as an intermediate.⁷²⁶

Another total synthesis of nopinone [(±)-**537**] involves cyclization of the tosylate **830** (cf. Vol. 4, p. 552, Ref. 695). The latter was prepared conventionally from ethyl 4-oxocyclohexanecarboxylate.⁷²⁸



830



831



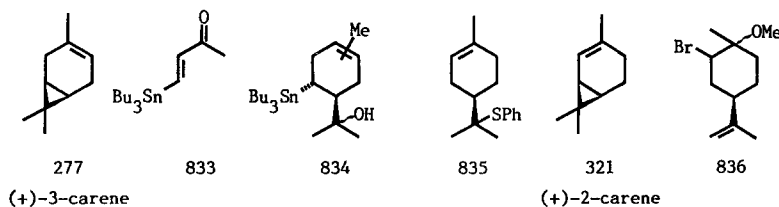
832

Both α - and β -pinenes labeled with ^{14}C on the C-2 methyl group have been made by a Wittig reaction on nopinone (**537**).⁷²⁹ This is a better route than using a Grignard reaction; Grignard reactions with nopinone give notoriously bad yields, and dehydration of the pinanol (**819**, $\text{R} = \text{H}$) obtained only works reasonably well with thionyl chloride in pyridine, as Stenström and Skattebøl found when preparing α -pinene deuteriated in the C-2 methyl group.⁷³⁰ We also like to draw attention to the preparation of the *syn*-deuteriomethylpinene (**831**, $\text{R} = \text{CD}_3$), prepared from the known⁷³¹ ether **832**. The latter can be converted to **831** ($\text{R} = \text{CH}_2\text{OH}$) (the isomer of the natural product **800**) with acetic anhydride in pyridine followed by lithium aluminum hydride. The deuteriated pinene **831** ($\text{R} = \text{CD}_3$) was obtained after oxidation to the acid **831** ($\text{R} = \text{COOH}$) and conventional reductions using deuteriated reagents.⁷³²

17. BICYCLO[4.1.0]HEPTANES

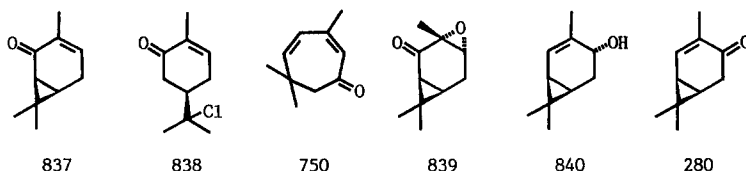
Akhila and Banthorpe have studied the biogenesis of 3-carene (**277**) in *Pinus silvestris*.⁷³³

There are two new syntheses of the carenes, both of which involve cyclopropane ring closure from an 8-substituted menthene. In the first, the menthene was synthesized from isoprene and the ketone **833** by a Diels–Alder reaction, the extra methyl group being introduced with methyllithium. A mixture of positional and stereoisomers **834** was thus obtained, which yielded ($\pm$)-3-carene [($\pm$)-**277**] with thionyl chloride.⁷³⁴ This synthesis is adaptable to the homologs of carene by varying the starting materials, but does not give optically active products, of course. Julia's synthesis, however, yields optically active 2-carene (**321**) from limonene, both 2-carenes being available because both limonenes are available. The synthesis depends on the cyclization of 8-phenylthio-1-menthene [the (–)-isomer is shown, **835**] with butyllithium in tetramethylethylenediamine, when 86% of (+)-2-carene (**321**) is obtained. The thioether (–)-**835** was prepared from (+)-limonene (**285**) by first protecting the 1,2-double bond with *N*-bromosuccinimide and methanol. After addition of thiophenol (catalyzed by perchloric acid) to the product **836**, the double-bond protection was removed with zinc in ethanol.⁷³⁵ The necessity for syntheses of this kind is because

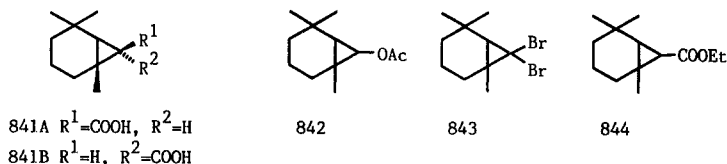


3-carene, the readily available natural source of the group, is only available in one enantiomeric form.

Wiemer et al. have re-examined the route to 3-caren-2-one (**837**) by reaction of carvone hydrochloride (**838**) with base.⁷³⁶ The difficulty here is to prevent the formation of eucarvone (**750**), which is known since the time of Wallach to be the preferred product of the reaction. Using one equivalent of sodium hydroxide in 25% aqueous dimethyl sulfoxide, they were able to isolate 42% of the optically active 4-caren-2-one (**837**) from (–)-carvone hydrochloride (**838**) with formation of only 17% of eucarvone (**750**). Epoxidation of **837** gave **839** (also available directly from **838** with basic hydrogen peroxide), and Wharton rearrangement (hydrazine hydrate) then yielded the carenol **840**, oxidized to 2-caren-4-one (**280**). Thus, since both carvones are available, all possible optically active carenones are also available.⁷³⁶



Some bicyclo[4.1.0]heptanes that are not caranes occur in labdanum. These are the two acids **841A** and **841B** and the acetate **842**.^{673,737} They are presumably carotenoid breakdown products, related to other C_{11} compounds likewise occurring in labdanum.⁷³⁷ All have been synthesized from 1,3,3-trimethylcyclohexene. Addition of dibromocarbene yields the dibromo compound **843**, from which **842** is obtained by partial reduction and acetate exchange, while addition of ethyl diazoacetate to the cyclohexene yields the esters **844** (the stereochemistry is a little vague in the paper cited⁶⁷³), from which the acids **841** are obtained. The *endo*-acid **841B** has the peculiar property of not reacting with diazomethane.⁷³⁷



18. FURAN MONOTERPENOIDS

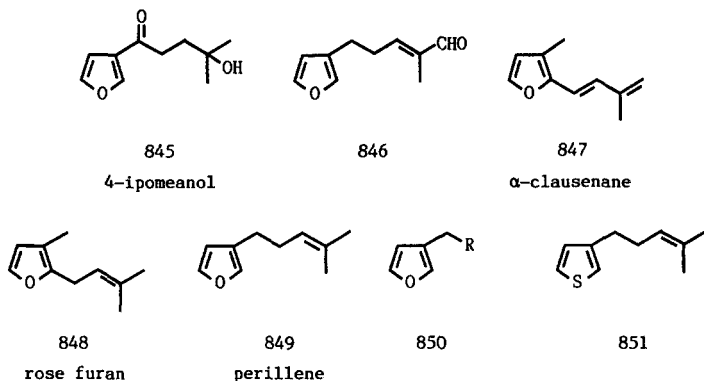
The decision of what should be placed in this section is not obvious. Actually all monoterpene furan derivatives could be classed as oxygenated dimethyloctanes, but so could most other monoterpenoids, and it is to lessen the load in other sections that we include this one. We should point out that we have already discussed eldanolide, menthofurans, marmelo lactones, and oxides, and the 7-hydroxygeranic acid derivatives, cleveolide and scobinolide.

A. 3-Substituted and 3-Methyl-2-substituted Furans

Synthetic activity in this group arises for several reasons. Besides the usual interest in the synthesis of natural products, some of the members are associated with biological activity: 4-ipomeanol (**845**), for example, causes bovine pulmonary toxicity, like some other related furyl ketones for which toxicity studies have been carried out.⁷³⁸ *Perilla frutescens* ("egoma" in Japanese) is used in Japanese food, and is also a cause of bovine pulmonary toxicity;⁷³⁹ this plant contains several furan monoterpenoids⁷⁴⁰ (cf. Vol. 4, p. 559, Ref. 736). Perillenal (**846**) is a pheromone of the pine sawfly *Neodiprion sertifer*.⁷⁴¹ There are also a number of sesqui- and higher terpenoids containing furan units, for which the monoterpene analogs represent good starting materials, or models for the higher terpenoids.

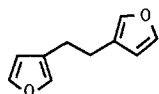
α -Clausenane is now believed to be **847**, related to rose furan (**848**) with which it co-occurs in *Clausia willdenovii*,⁷⁴² rather than being a dehydroperillene (perillene = **849**); we are unsure of the status of "lepalene" (see Vol. 4, p. 559, Ref. 534a).

Syntheses of perillene (**849**) starting from preformed 3-substituted furans are the most common. Preparation of the alcohol **850** ($R = \text{OH}$) is possible from diethyl furan-3,4-dicarboxylate by partial hydrolysis and thermolysis, the monocarboxylate then being reduced with lithium aluminum hydride. Conversion of this alcohol to a halide is more difficult to carry out in high yield; Tanis has suggested that the best conditions for making the chloride **850** ($R = \text{Cl}$) are with mesyl chloride and lithium chloride in *s*-collidine and dimethylformamide.⁷⁴³ The Grignard reagent **850** ($R = \text{MgCl}$) was coupled

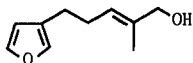


with prenyl chloride (**15**, $R = Cl$) in the presence of Kochi's catalyst (Li_2CuCl_4) to give 85% of perillene (**849**).⁷⁴³ The Grignard reagent **850** ($R = MgBr$) also reacted with prenyl diethyl phosphate [**15**, $R = OPO(OEt)_2$] in the presence of cuprous iodide, giving perillene (**849**) accompanied by some isomeric furans formed by reaction at C-2 and/or allylic addition.⁷⁴⁴ The same route was used to make thiaperillene (**851**),⁷⁴⁴ a compound isolated from hops (Vol. 4, p. 559, Ref. 735). Baker et al. used **850** ($R = Br$) in a reaction with π -1,1-dimethylallylnickel bromide complex; unfortunately the yield of perillene was only 15%, the major compound being the "dimer" **852**.⁷⁴⁵ The *p*-toluenesulfonate **850** ($R = OTs$) was prepared from the alcohol **850** ($R = OH$) using not pyridine, but powdered sodium hydroxide and *p*-toluenesulfonyl chloride in ether,* and without isolating the tosylate, lithium diprenyl cuprate was added [made from triphenylprenylstannane (**15**, $R = SnPh_3$)], when perillene was obtained in 15% yield.⁷⁴⁷ The tributylstannane **850** ($R = SnBu_3$) was also converted to perillene (**849**) with prenyl bromide and butyllithium. The same authors oxidized their perillene to the alcohol **853** with selenium dioxide,⁷⁴⁸ a reaction that Kramp and Bohlmann reported as giving poor yields.⁷⁴⁹ Using addition of $PhSCl$ to perillene, followed by oxidation (H_2O_2 , cat. SeO_2) and removal of the sulfur with trimethyl phosphite, Kramp and Bohlmann claimed better results. The reaction of the bromide **850** ($R = Br$) (made in this case from the alcohol and PBr_3 in tetrahydrofuran–pyridine and used *in situ*) with the copper dienolate of tiglic or angelic acid led to the ester **854**, which was transformed to the alcohol **853** and perillenal (**846**). In this reaction, the chloride **850** ($R = Cl$) did not give satisfactory results.⁷⁵⁰

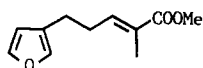
*This method of preparing tosylates of allyl alcohols, then using them *in situ* was first described by Wenkert and Mylari, but not published directly.⁷⁴⁶



852

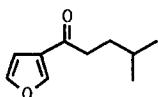


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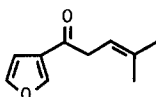


854

Synthesis of some of the oxygenated perillenes, perilla ketone (**855**), egoma ketone (**856**), and isoegoma ketone [(*E*)-**857**], all occurring in *Perilla frutescens*, has been effected from furan-3-carbonitrile (**858**), prepared either from 3-bromofuran and cuprous cyanide or from 3-furoic acid and benzene-1,3-dicarbonitrile. Reaction of the nitrile **858** with isoamylmagnesium bromide gave moderate yields of perilla ketone (**855**) after hydrolysis. The double bond of isoegoma ketone [(*E*)-**857**] was introduced by reaction of **855** with phenylselenenyl chloride then oxidation (H_2O_2), and the double bond of **857** was deconjugated to give egoma ketone (**856**) with potassium *tert*-butoxide in *tert*-butanol.⁷⁵¹ We were happy to note from this work that the methoxy compound **859**, reported earlier to occur in *Perilla frutescens*, is, as we suggested (Vol. 4, p. 559), most probably an artefact. The reaction of isopropylmagnesium chloride with acetylene in the presence of cuprous chloride in tetrahydrofuran yields magnesium isopentenylcupric chloride with a (*Z*)-double bond. This organocuprate reacted with the acid chloride of 3-furoic acid in the presence of Pd^0 to give (*Z*)-**857** [not natural but with a better odor than the (*E*)-isomer], which was isomerized to isoegoma ketone [(*E*)-**857**] with acid. This route is a rapid one-pot synthesis of **857** which is useful on a small scale.⁷⁵²

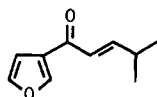


855



856

egoma ketone

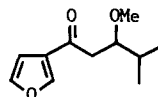


(E)-857

isoegoma ketone



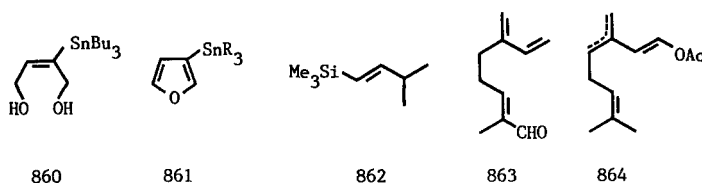
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859

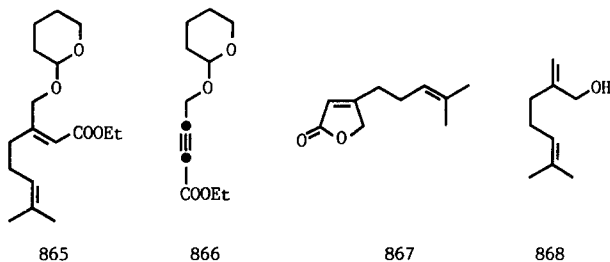
We have pointed out that the difficulty of any route to furanoid compounds using 3-bromofuran for making 3-furyllithium is the access of this starting material (Vol. 4, p. 557). It is true that it is commercially available, but it is prohibitively expensive. Fleming and Taddei have certainly made a great improvement from the laboratory point of view, by using the reagent $\text{Bu}_3\text{SnCuSMe}_2\cdot\text{LiBr}$ and butyne-1,4-diol; this yielded the diol **860**, which was oxidized (pyridinium chlorochromate) to the tributylstannane **861** ($\text{R} = \text{Bu}$) in 81% yield. Like 3-bromofuran, **861** can be converted to 3-furyllithium with butyllithium in tetrahydrofuran at -78°C .⁷⁵³ This route is still not easily amenable to large-scale

production, so cheap routes from **861** ($R = \text{Bu}$) are still some distance off. Nevertheless, Stille's synthesis of egoma ketone (**856**), consisting of the carbonylative coupling of **861** ($R = \text{Me}$) with prenyl chloride, carbon monoxide at 50 psig pressure, and bis(dibenzylideneacetone)palladium + triphenylphosphine,⁷⁵⁴ should be just as good with **861** ($R = \text{Bu}$) and cheaper than using 3-bromofuran as the starting material for making the stannane (as did Stille). Fleming's route to 3-furyllithium can be used for making 3-furoic acid, of course, by adding carbon dioxide to the lithio compound.⁷⁵³ 3-Furoyl chloride reacts with the trimethylsilane **862**, giving isoegoma ketone [(E) -**857**] in 65% yield—another reasonably rapid approach on a small scale.⁷⁵⁵



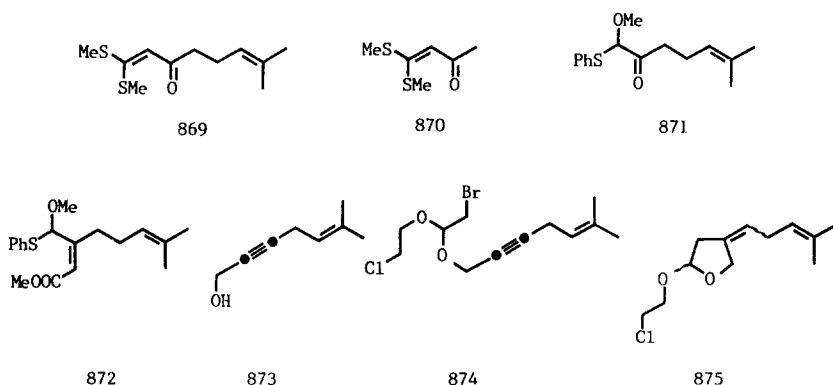
Routes to furan monoterpenes from other monoterpenoids are well known, and the photooxygenation route from myrcene (**7**) to perillene (**849**) was discussed in Vol. 4 (p. 561). Using the aldehyde **863** led, by the same route ($^1\text{O}_2$, then ferrous ion) to perillenal (**846**).⁷⁵⁶ The simplest reported preparation of perillene (**849**) from a dimethyloctane monoterpenoid precursor is certainly the autoxidation of citral enol acetates (**864**), yielding 11% of a mixture of perillene (**849**) and rose furan (**848**) after passing air through a chloroform solution for 24 hours.⁷⁵⁷

Construction of the suitably substituted geranic acid for making the furan ring has been effected too. For example, Poulter et al. have prepared the substituted geranate **865** by reaction of 4-methyl-3-pentenylcopper with the acetylenic ester **866**.⁷⁵⁸ The ester **865** then underwent cyclization in the presence of acid to the lactone **867**, related to scobinolide (**161**), and the action of acid on the lactol produced from **867** with diisobutylaluminum hydride gave perillene (**849**).⁷⁵⁸ The lactone **867** has also been prepared by a slightly different method; the C_9 alcohol **868** was made (in poor yield) from isobutenol and prenyl chloride with butyllithium. The extra carbon atom was introduced by the action of sodium cyanide on the epoxide of **868**, and hydrolysis of the cyano group followed by dehydration yielded the lactone **867**.⁷⁵⁹ The dimethylthioacetal of **867** has been used to synthesize perillene (**849**). This thioacetal was made from the suitably substituted ketene thioacetal **869** and dimethylsulfonium methylide. Thus the ketene thioacetal **870** (readily prepared from acetone, carbon disulfide, and sodium amylate, followed by methylation⁷⁶⁰) can be prenylated with lithium

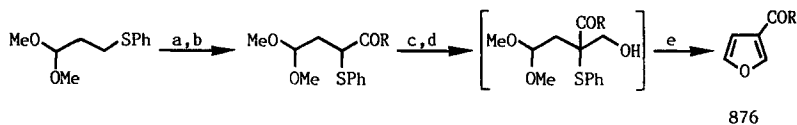


diisopropylamide and prenyl bromide (**15**, $R = \text{Br}$) to yield the desired ketene thioacetal **869**, which is to undergo the reaction with dimethylsulfonium methylide. The thioacetal of **867** is then hydrolyzed with acetic acid (to the 2-methylthiofuran) and desulfurized with Raney nickel to yield perillene (**849**).⁷⁶¹

Dimethylamides react with the carbanion from methoxymethyl phenyl sulfide, MeOCH_2SPh , and in this way the compound **871** was made from *N,N*-dimethyl-5-methyl-4-hexenamide in 76% yield. (The amide was prepared by unreported means from prenyl bromide, which seems unlikely.) Addition of a C_2 unit to **871** using the Wittig–Horner reaction (methyl diethylphosphonoacetate) gave the required carbon framework **872** which, after reduction of the ester group ($i\text{Bu}_2\text{AlH}$) and treatment with *p*-toluenesulfonic acid, gave perillene (**849**), the last stage yielding only 60%.⁷⁶²



An ingenious reaction by Stork and Mook consists of forming the C-3,C-4 bond of the furan ring, all the other carbon atoms being built beforehand. The starting material is the acetylenic alcohol **873** (propynol and prenyl chloride),



a) BuLi; b) $\text{RCON}(\text{CH}_2)_2$; c) lithium diisopropylamide; d) HCHO; e) heat, toluene

Scheme 66

which readily forms the acetal **874** with $\text{BrCH}_2\text{CH}(\text{Br})\text{OCH}_2\text{CH}_2\text{Cl}$ and dimethylaniline in methylene chloride. Reductive cyclization to **875** occurred with tributyltin hydride, and deacetalization with *p*-toluenesulfonic acid then gave perillene (**849**).⁷⁶³

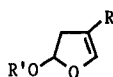
Scheme 66 shows a route for making 3-substituted furyl ketones. The group R is, for example, $\text{CH}=\text{CHCHMe}_2$, when isoegoma ketone (**857**) is obtained. In order to prepare ipomeanin (**876**, $\text{R} = \text{CH}_2\text{CH}_2\text{COMe}$), the amide used in the first step must be the keto amide $\text{MeCOCH}_2\text{CH}_2\text{CON}(\text{CH}_2)_2$ (which was protected as the ethylene thioacetal).⁷⁶⁴ Wenkert's diazo-addition techniques have been used to achieve synthesis of ethyl 3-furoate (**877**, $\text{R} = \text{COOEt}$) and furyl-3-carbaldehyde (**877**, $\text{R} = \text{CHO}$) in only two steps. For ethyl 3-furoate, the diazo compound from ethyl formylacetate **878** ($\text{R} = \text{COOEt}$) was used with either vinyl acetate or butyl vinyl ether, and for the other the diazo compound from malondialdehyde **878** ($\text{R} = \text{CHO}$) with vinyl acetate. These reactions were carried out using rhodium tetraacetate as catalyst. The products of the addition, **879**, were pyrolyzed if $\text{R}' = \text{OAc}$, or treated with acid in carbon tetrachloride if $\text{R}' = \text{Bu}$, when the products **877** were obtained. For the synthesis of perillene (**849**), compound **879** ($\text{R} = \text{CHO}$, $\text{R}' = \text{Bu}$) was prepared by the method described. It was found to react by "backside" addition with prenyllithium (**15**, $\text{R} = \text{Li}$), and in order to have the perillene skeleton, addition of the lithium derivative of phenyl prenyl sulfone was required, yielding **879** [$\text{R} = \text{CH}(\text{OH})\text{CH}(\text{SO}_2\text{Ph})\text{CH}=\text{CMe}_2$], which, after acid treatment and reductive removal of the sulfone group, yielded perillene (**849**). From the reverse addition, the isomer **880** of perillene (not yet, so far as we know, naturally occurring) was prepared.⁷⁶⁵



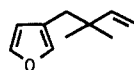
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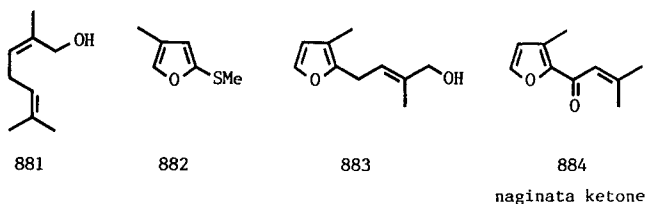


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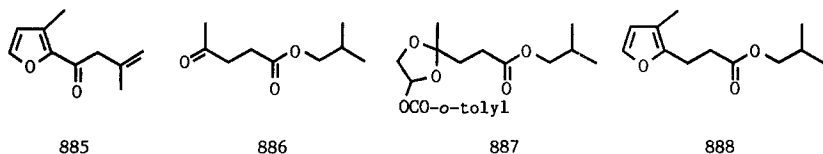
880

Many of the papers already mentioned in the context of perillene also speak of the preparation of rose furan (**848**), such as the autoxidation of citral enol acetate,⁷⁵⁷ the ketene thioacetal method,⁷⁶¹ and the route starting from isobutenol.⁷⁵⁹ The latter required the alcohol **881**, an isomer of **868**, which was prepared by prenylation of isobutenylthiophenol. Allylic epoxidation and epoxide opening with sodium cyanide followed the same route as for perillene, but the yield (19%) of rose furan was again low.⁷⁵⁹ The ketene thioacetal route was adapted by making the simpler furan **882** from **870** and dimethylsulfonium methylide, then prenylating **882** (butyllithium and prenyl bromide) and desulfurizing with Raney nickel.⁷⁶¹ Kramp and Bohlmann also speak of rose furan (**848**),⁷⁴⁹ but they prepared it by Schlosser's method⁷⁶⁶ (Vol. 4, p. 557, Ref. 726), and their contribution here is limited to an examination of the selenium dioxide oxidation to the alcohol **883**, which they required for further elaboration to feryl diterpenes.⁷⁴⁹



There has been further study of the direct prenylation of 3-methylfuran (cf. Vol. 2, p. 161, Ref. 558; Vol. 4, p. 557, Ref. 724) using 3-chloro-3-methyl-1-butene or the corresponding trifluoroacetate and zinc halides or silver trifluoroacetate. Rose furan was indeed obtained, but was accompanied by the 2,4-disubstituted furan.⁷⁶⁷

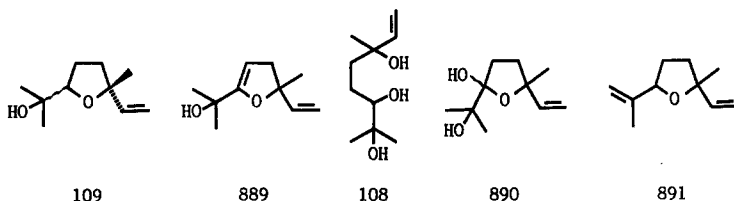
Naginata ketone (**884**) was prepared by Calas et al., using the same principle as for making isogoma ketone (**857**). 3-Methyl-2-furoyl chloride reacted with trimethyl(2-methylpropenyl)silane in the presence of titanium tetrachloride to give 60% of naginata ketone (**884**), together with 30% of the unconjugated isomer **885** and a small amount of the addition product of naginata ketone and hydrogen chloride. The two by-products were converted to naginata ketone (**884**) by refluxing in benzene containing triethylamine.⁷⁵⁵



Meier and Scharf have reexamined the "Marckwald fission" as a route to rose furan (**848**). This reaction concerns the acid-catalyzed addition of water, generally to furfurylidene ketones, to give 1,4-diketones,⁷⁶⁸ and was greatly developed by Robinson in the 1930s as a possible route to steroids.⁷⁶⁹ However, ring opening of the simple furfurylideneacetone gives a poor yield, and after some trials, Meier and Scharf found that action of hydrogen chloride in isobutanol on furfuryl alcohol gave acceptable yields of the keto ester **886**. "Protection" of the keto group as the ethylene acetal (the term is used here more from habit than as an exact description) was followed by oxidation with *tert*-butyl per-*o*-toluate. The oxidized compound **887** (in 70% yield!) was pyrolyzed, when 37% of the ester **888** was obtained, together with the isomer having a 2-methyl group and the large substituent at C-3. Rose furan (**848**) was prepared from **888** by Grignard addition followed by dehydration with *p*-toluenesulfonic acid.⁷⁷⁰

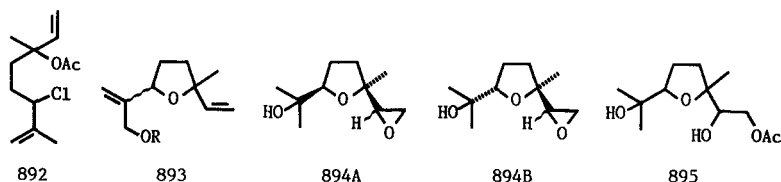
B. 2,2,5-Substituted Furans

The linalool oxides (**109**) are probably the oldest known of this group (Vol. 2, p. 165). They have been isolated after the action of *Streptomyces albus* on linalool (**28**), the optical activity at C-2 of the furan is the same as that of the starting linalool. This work also points out that rotations of the linalool oxides are different when measured neat or in solution.⁷⁷¹ The oxidized linalool oxide **889** has been found in grape juice. It was synthesized by the action of silver carbonate on the dihydroxylinalool **108** (also occurring in grape juice), and dehydrating the hemiacetals **890** thus formed.⁷⁷²

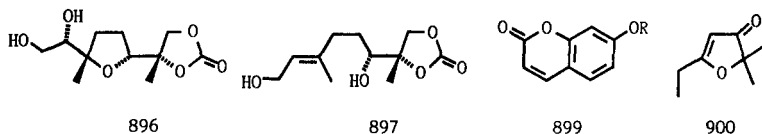


There are many compounds closely related to natural products that are associated with novel syntheses. Dehydrated linalool oxide **891**, for example, is conveniently made by chlorination of linalool acetate (**28** acetate) with calcium hypochlorite, then cyclization of the allyl chloride **892** with sodium hydroxide and Aliquat 336 in methanol.⁷⁷³ Once obtained **891** was converted to the dehydrogenated lilac alcohols **893** (R = H). The monoepoxides (on the isopropenyl group) were transformed in a mixture of diacetates that were pyrolyzed to the acetates **893** (R = Ac).⁷⁷⁴ Linalool oxide epoxides (**894**) have

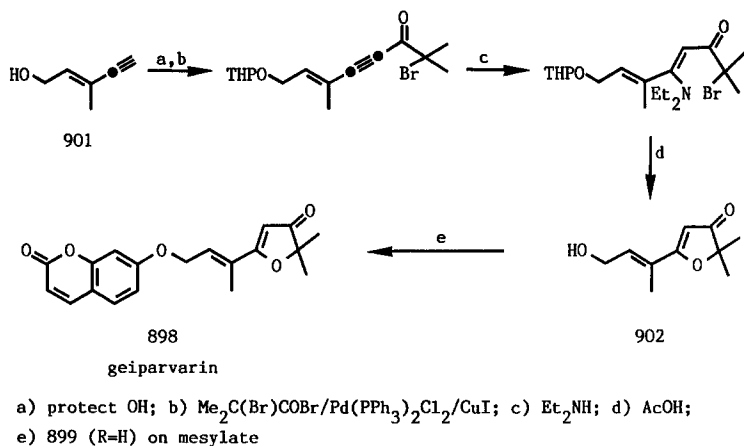
been prepared by permanganate oxidation of geranyl (or neryl) chloride (**2**) (carbon dioxide acidity was used). The chlorohydrins obtained were converted to the epoxides **894** with powdered potassium hydroxide in ether. This method gives the *cis*-epoxides **894A** (one isomer from geranyl and one from neryl chloride), all four isomers being available by double epoxidation of geranyl acetate (**25** acetate), followed by treatment with aqueous hydroxide.⁷⁷⁵ Geranyl acetate was also oxidized by ruthenium(IV) oxide in aqueous acetonitrile and carbon tetrachloride to give the glycol acetates **895** and a little of the corresponding ketone.⁷⁷⁶



Attention is drawn to the synthesis the oxygenated linalool oxide **896**. This compound (and other stereoisomers) is not a naturally occurring monoterpene, but a fragment required in the synthesis of a calcium ion-selective ionophore, ionomycin, and was made from hydroxygeranyl acetate (**113**, R = Ac), then Sharpless conditions for introducing a chiral epoxide were used. The vital step is the cyclization of **897** by epoxidizing again under Sharpless conditions (titanium tetrakisopropoxide and diethyl tartrate) when the product **896** is obtained.⁷⁷⁷

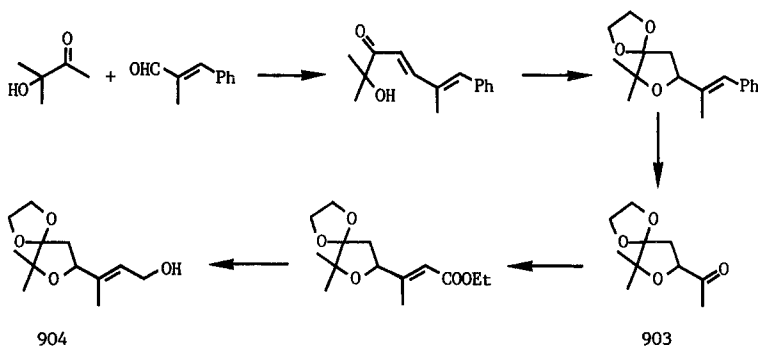


Geiparvarin (**898**) isolated from *Geijera parviflora*,⁷⁷⁸ reported to have antitumor properties, was first synthesized by Smith et al., who thereby also established the stereochemistry of the double bond.⁷⁷⁹ The synthesis consisted of the aldol addition of the aldehyde **899** (R = CH₂CHO), prepared from umbelliferone (**899**, R = H), to 5-ethyl-2,2-dimethyl-2*H*-furan-3-one (**900**) when both isomers of **898** were obtained, the (*E*)-isomer being identical to the natural product.⁷⁷⁹ The synthesis of Jackson and Raphael (Scheme 67) starts with the acetylenic alcohol **901**, once readily available, but no longer, because of the hazards associated with its handling (cf. Vol. 4, p. 558, Ref. 733). The



Scheme 67

tetrahydropyranyl derivative of **901** was converted to the monoterpene precursor **902** of geiparvarin, the mesylate of **902** being treated with umbelliferone (**899**, R = H) to give geiparvarin (**898**).⁷⁸⁰ Another synthesis of geiparvarin (**898**) depended on the availability of the protected tetrahydrofuranone **903**. The latter was prepared (Scheme 68) by aldol condensation of α -methylcinnamaldehyde with 3-hydroxy-3-methyl-2-butanone. Protection of the keto group was accompanied by cyclization to the tetrahydrofuran, and ozonolysis (O_3 , then Me_2S) removed the unsaturated side chain.⁷⁸¹ From **903**, preparation of the monoterpene precursor **904** was simply effected by a Horner–Wittig reaction followed by metal hydride ($i\text{Bu}_2\text{AlH}$) reduction. Umbelliferone (**899**, R = H)

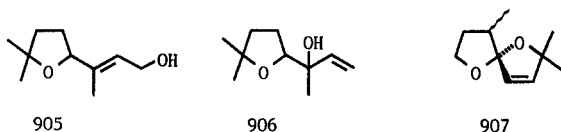


Scheme 68

was introduced after exchanging the hydroxyl group in **904** for chlorine, and the protecting group was hydrolyzed with acetic acid. Finally the double bond missing for geiparvarin (**898**) was introduced with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, not the cheapest of reagents).⁷⁸²

A compound somewhat related to **902**, the alcohol **905**, has been isolated from peppermint and synthesized from 2,6-dimethyl-5,7-octadien-2-ol (called ocimenol by the authors). The action of peracetic acid on the latter gave the furan **906**, and allylic rearrangement with phosphorus tribromide followed by replacement of the bromide with potassium acetate gave the (*E*) + (*Z*) acetates of **905**.⁷⁸³

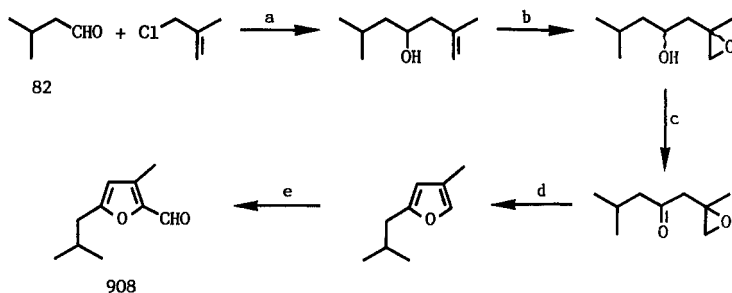
Some tetrahydrofuran analogs to rose furan have been synthesized by Hoepfner and Weyerstahl, but none was as interesting a perfume as rose furan.⁷⁸⁴



C. Other Furans

Two new, apparently isoprenoid 1,6-dioxaspiro[3.5]nonanes **907** have been isolated from geranium,⁷⁸⁵ but have not been synthesized.

A new furancarbaldehyde **908** has been isolated by Maurer and Hauser from the essential oil of *Tagetes glandulifera*, and was synthesized following Scheme 69.⁷⁸⁶



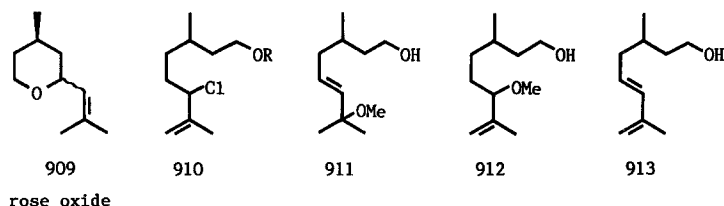
- a) Mg, ether, 10–15°, 3h; b) *m*-Cl-perbenzoic acid, CH_2Cl_2 , 25°, 5h;
 c) pyr. dichromate, CH_2Cl_2 , 25°, 15h; d) 2N H_2SO_4 , pentane, 25°, 1h;
 e) POCl_3 , DMF, 15–25°, 4h

Scheme 69

19. PYRAN MONOTERPENOIDS

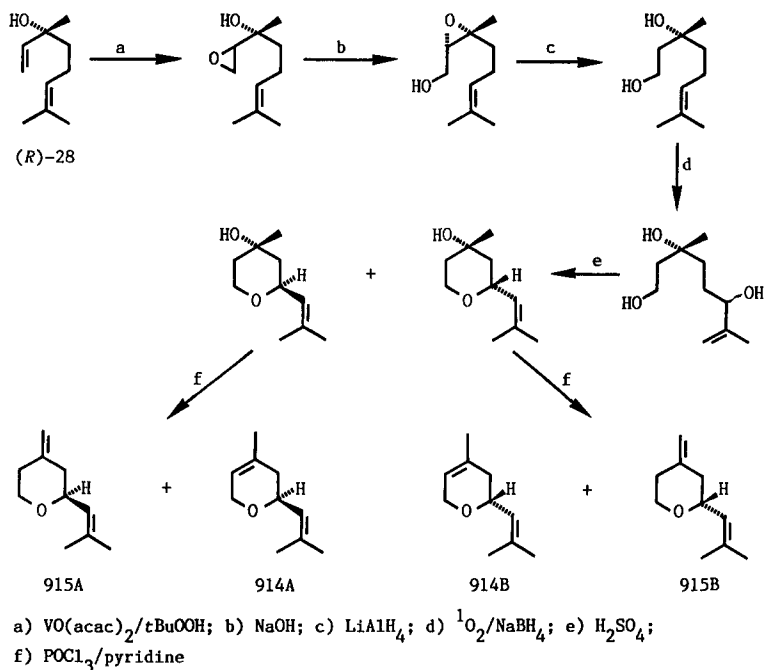
Nearly all the synthetic work in this group concerns the preparation of rose oxide, a review of which has appeared in Polish.⁷⁸⁷

There is still a little work continuing on the old route to rose oxide (**909**) from a citronellol (**33**) derivative. Wolinsky et al. used their two-phase chlorination with hypochlorous acid which, with citronellol (**33**) or its acetate, yielded the chlorinated compound **910** (R = H) or its acetate **910** (R = Ac). Treatment of the latter, first with base (to remove hydrogen chloride), then sulfuric acid (to cyclize), gave a mixture of the two stereoisomers of rose oxide (**909**).⁷⁸⁸ Anodic oxidation of citronellol (**33**) has been mentioned (Vol. 4, p. 565, Ref. 770); a new development using diphenyl diselenide and tetraethylammonium bromide in methanol resulted in an electrooxidative oxyselelenation–deselenation sequence, and the isolated product (89% yield) was the methoxylated citronellol **911**. (A similar reaction was used for marmelo lactone, see Section 4.)²¹⁶ A slightly different anodic alkoxylation of citronellol in alcohol containing sodium benzenesulfonate gave (in methanol) 54% of the isomer **912** of **911**. To obtain rose oxide (**909**), **912** was treated in ethanol with tributylphosphinepalladium chloride and sodium methoxide, which eliminated methanol, and the dehydrocitronellol **913** was cyclized with sulfuric acid.⁷⁸⁹ Further work on the anodic cyclization of citronellol (**33**) has also been published.⁷⁹⁰



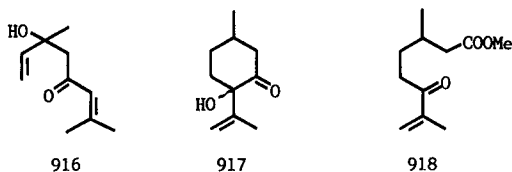
Ohloff et al. have synthesized the optically active nerol oxides (**914A** and **914B**) from (–)-(R)-linalool [(R)-**28**] following the route in Scheme 70. In the last step, dehydration with phosphorous oxychloride in pyridine, some of the exocyclic isomers **915** were produced.⁷⁹¹ Reduction of the nerol oxides (**914**) and the isomers **915** to rose oxide (**909**) were mentioned in Vol. 4 (p. 565, Refs. 123 and 773), and some specific conditions to furnish a maximum of the *cis*-isomer of **909** from **915** have been given,⁷⁹² the *cis*-isomer being the more powerful smelling.⁷⁹¹

The hydroxyocimene **916** (Vol. 4, p. 474, Ref. 163) has been converted to nerol oxides (**914**) by the action of sulfuric acid on the diol obtained from **916** with lithium aluminum hydride.⁷⁹³

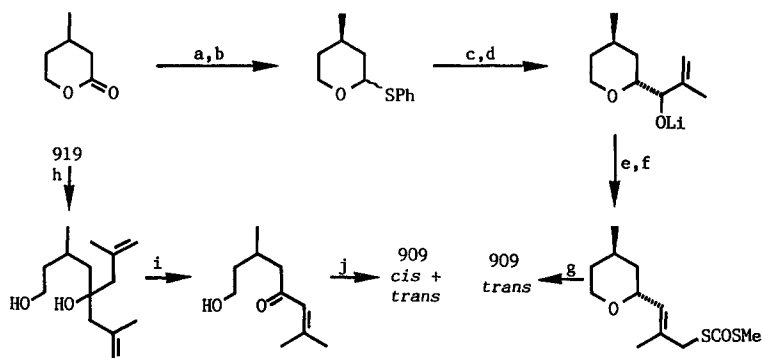


Scheme 70

4-Hydroxy-8-menthenone (**917**) [obtainable from pulegone (**46**) epoxide, Vol. 4, p. 525, Ref. 496] has been converted by electrolysis in methanol-lithium perchlorate at 8°C to the keto ester **918**, a useful starting material for the preparation of rose oxide (**909**). The subsequent route employed by Torii et al. was reduction of the keto group ($\text{NaBH}_4/\text{CeCl}_3$), followed by chlorination and dehydrochlorination. The alcohol **913** was then produced by reduction with lithium aluminum hydride and cyclized with sulfuric acid, giving 83% *cis*- and 9% *trans*-**909**.⁷⁹⁴



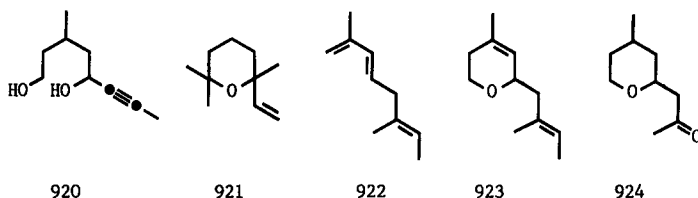
Some methods for preparing rose oxide from 3-methyl-5-pentanolide (**919**) have been developed. One is specific for *trans*-rose oxide (*trans*-**909**), which the authors of the work seem to believe is more valuable in perfumery than the *cis*-isomer.⁷⁹⁵ Actually the reason most syntheses give a maximum of the *cis*-isomer is because that is the one needed in perfumery.⁷⁹¹ It is true that the method (which we depict in Scheme 71) is a "two-flask" one,⁷⁹⁵ but it suffers from very great disadvantages, precluding it from any idea of scale-up. First, it employs expensive reagents, one of which (tributyltin hydride) has a molecular weight of 291 for making a product of molecular weight 154, and five equivalents are required. Second, hexamethylphosphoric triamide (HMPT) is used as a solvent, and this substance is carcinogenic. Third, the reagent carbon disulfide requires special precautions because of its highly flammable nature. Fourth, all steps are run at -78°C . Fifth, it is almost impossible to purify perfumery materials when sulfur-containing compounds have been used in their preparation—and two such are employed here. Even refluxing methyl iodide has its problems! Scheme 71 illustrates a contrasting synthesis from the same starting material, **919**. Addition of **919** and isobutenyl chloride simultaneously to magnesium (the Barbier conditions) yielded 92% of the bis-addition product. One isobutenyl unit was removed by strong base in dimethylformamide (DMF), then reduction to the alcohol and cyclization with potassium bisulfate gave a 4:1 (*cis/trans*) mixture of the rose oxides (**909**).⁷⁹⁶



- a) $i\text{Bu}_2\text{AlH}$ /toluene, -78° ; b) $\text{PhSH}/\text{BF}_3 \cdot \text{OEt}_2$, -78° ;
 c) lithium 1-(dimethylamino)naphthalenide/THF, -78° ; d) methacrolein;
 e) HMPT/ CS_2 , -78° ; f) MeI, reflux; g) 5 eq. Bu_3SnH ,
 azobis(isobutyronitrile)/toluene; h) $\text{CH}_2=\text{C}(\text{Me})\text{CH}_2\text{Cl}/\text{Mg}$;
 i) KOtBu/DMF , then acidify; j) LiAlH_4 , then KHSO_4

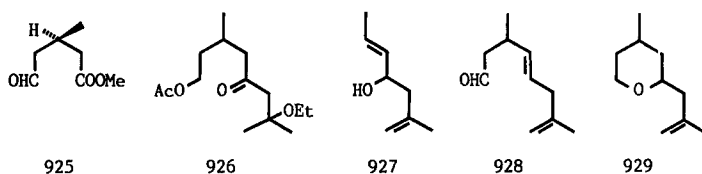
Scheme 71

In a third synthesis of rose oxide (**909**) from the lactone **919**, addition of propynyllithium, followed by borohydride reduction, gave the diol **920**, to which the additional methyl group was added with lithium dimethyl cuprate. Hydrolysis and treatment with silver nitrate yielded the rose oxides (**909**).⁷⁹⁷ This same paper describes a related synthesis of the naturally occurring 2,2,6-trimethyl-6-vinylpyran (**921**)⁷⁹⁷ (Vol. 2, p. 167).



Yamamoto and Nakamura have reported a synthesis of rose oxide from the dimer **922** of isoprene. Prins reaction (formaldehyde) yielded the dihydropyran **923**, which underwent specific ozonolysis and hydrogenation to the known (and naturally occurring) ketone **924**.⁷⁹⁸ Conversion of the latter to rose oxide (**909**) is well known (Vol. 2, p. 168, Ref. 586).

(-)-Menthone (**521**) has been converted to the chiral compound (*R*)-**925** in eight steps [chiral 3-methylcyclopentanone was also converted to (*R*)-**925** in three steps]. This compound, (*R*)-**925**, can then be transformed conventionally to chiral rose oxides,⁷⁹⁹ but this long route does not seem advantageous over that described above.⁷⁹¹



Further studies on the $C_5 + C_5$ route to rose oxide (**909**) mentioned in Vol. 4 (p. 565, Ref. 773) include the radical addition of 3-methyl-3-butenyl acetate to 3-ethoxy-3-methylbutanal. This led to 40% of the ketone **926**, which can be converted to rose oxides (*cis/trans* 9:1) by reduction ($NaBH_4$), hydrolysis, and acid cyclization.⁸⁰⁰ Russian workers have examined (and with variously substituted homologs) the reaction between 3-methylbutanal (**82**) and 4,4-

dimethyl-1,3-dioxane. In acid, this mixture loses formaldehyde and water to yield dihydronerol oxide (**86**) and a double-bond isomer, but rose oxide was not mentioned in this work.⁸⁰¹ Hydrogenated rose oxides have also been synthesized from dihydronaginata ketone (dihydro-**884**) by high pressure reduction followed by treatment with aluminum oxide at 255°C and hydrogenation.⁸⁰²

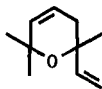
More original is the Claisen rearrangement of the vinyl ether of alcohol **927** (made by Grignard addition of isobutenylmagnesium chloride to 2-butenal), which yielded 58% of the aldehyde **928**, needing only reduction to the alcohol before acid cyclization to iso-rose oxide (**929**) and rose oxide (**909**).⁸⁰³

In a paper concerning the aluminum chloride-catalyzed Diels–Alder reaction between 4-methyl-1,3-pentadiene (piperylene) and the nitrile **930**, rose oxide is mentioned, but the authors do not describe the synthesis.⁸⁰⁴

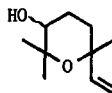
The unsaturated pyran **931** has been identified in clary sage oil by Maurer and Hauser. They synthesized it by base-catalyzed elimination of the mesylate of pyranoid linalyl oxide **932**.⁸⁰⁵



930



931



932

Acknowledgments

Our greatest thanks goes to Wolfgang Giersch (who had to cope not only with the subject but also the illegibility of the first draft) and Arnold Uijttewaai, whose numerous suggestions we frequently followed. Ferdinand Näf, Roger Snowden, and Bruno Maurer also made invaluable recommendations and corrections. Thanks also are due to Sina Escher and Professor Ernie Wenkert for unpublished work, and to Professor Jerry Meinwald for unpublished work and for a most pleasant discussion accompanied by the Brandenburg Concertos numbers 4 and 5.⁸⁰⁶

REFERENCES

1. (a) Thomas, A.F. In *The Total Synthesis of Natural Products*; ApSimon, J.W., Ed.; Wiley-Interscience: New York, 1973; Vol. 2, p. 1. (b) Thomas, A.F. Bessière Y., In *The Total Synthesis of Natural Products*; ApSimon, J.W. Ed.; Wiley Interscience: New York, 1981; Vol. 4, p. 451.

2. Rasmussen, R.A. *J. Air Pollut. Control Assoc.* **1972**, 22, 537.
3. Gäb, S.; Hellpointer, E.; Turner, W.V.; Korte, F. *Nature* **1985**, 316, 535; Griesbaum, K.; Zwick, G. *Chem. Ber.* **1986**, 119, 229.
4. Carman, R.M.; Fletcher, M.T. *Aust. J. Chem.* **1983**, 36, 1483.
5. Rhoades, D.F. In *Plant Resistance to Insects*, Hedin, P.A., Ed.; Am. Chem. Soc. 1983; *Am. Nat.* **1985**, 125, 205.
6. Baldwin, I.T.; Schultz, J.C. *Science* **1983**, 221, 277.
7. Williams, K.S.; Myers, J.H. *Oecologia (Berlin)* **1984**, 63, 166; Fowler, S.V.; Lawton, J.H. *Am. Nat.* **1985**, 126, 181.
8. Greig-Smith, P. *New Sci.* **1986**, 110, 33.
9. Klimetzek, D.; Köhler, J.; Vité, J.P.; Kohnle, U. *Naturwissenschaften* **1986**, 73, 270, and literature quoted therein.
10. Eisner, T.; Meinwald, J. *Psyche* **1982**, 89, 357; Eisner, T.; Deyrup, M.; Jacobs, R.; Meinwald, J. *J. Chem. Ecol.* **1986**, 12, 1407.
11. Banthorpe, D.V.; Branch, S.A. In *Terpenoids and Steroids*; Hanson, J.R., Ed.; (Specialist Periodical Reports), The Royal Society of Chemistry: London, 1983; p. 3.
12. Grayson, D.H. *Nat. Prod. Rep.* **1984**, 1, 319; Carson, M.S.; Grayson, D.H. *Nat. Prod. Rep.* **1986**, 3, 251.
13. Dev, S.; Narula, A.P.S.; Yadav, J.S. *CRC Handbook of Terpenoids, Monoterpenoids* (2 vols.); CRC Press: Boca Raton, FL, 1982.
14. Baker, R.; Herbert, R.H. *Nat. Prod. Rep.* **1984**, 1, 299.
15. Krasnobajew, V. In *Biotechnology*; Rehm, H.-J.; Reed, G., Eds.; Verlag Chemie: Weinheim, 1984; Vol. 6a, p 97.
16. Erman, W.F. *Chemistry of the Monoterpenoids*, Dekker: New York, 1985.
17. (a) Cainelli, G.; Cardillo, G. *Acc. Chem. Res.* **1981**, 14, 89. (b) Gerber, R.; Stegemann, H.; Gaube, W. *Militzer Ber.* **1981**, 7.
18. Nishida, T.; Fujita, Y. *Kagaku no Ryoiki* **1983**, 37, 506.
19. Helin, M.; Davidson, M. *Inf. Chim.* **1980**, [206], 163.
20. Keim, W.; Behr, A.; Röper M.; In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F.G.A., Eds.; Pergamon: Oxford, 1982; Vol. 8, p. 399. See also Berger, R.; Gaube, W. *J. Prakt. Chem.* **1985**, 327, 643.
21. Fujita, T.; Watanabe, S.; Suga, K.; Sugahara, K.; Tsuchimoto, K. *Chem. Ind. (London)* **1983**, 167.
22. Behr, A.; Keim, W. *Chem. Ber.* **1983**, 116, 862.
23. Erm, A.; Heinvali, M.; Valimae, T.; Laats, K. *Eesti NSV Tead. Akad. Toim. Keem.* **1981**, 30, 56.
24. Neibecker, D.; Touma, M.; Tkatchenko, I. *Synthesis* **1984**, 1023.
25. Kaufmann, T.; Ennen, J.; Berghus, K. *Tetrahedron Lett.* **1984**, 25, 1971.
26. Keim, W.; Röper, M.; Schieren, M. *J. Mol. Catal.* **1983**, 20, 139.
27. (a) Takabe, K.; Katagiri, T.; Tanaka, J. *Tetrahedron Lett.* **1972**, 4009; *Chem. Lett.* **1977**, 1025. (b) Anderson, T.; Moberg, C. *Organometallics* **1985**, 4, 1083.
28. Barton, J.; Hrubes, M.; Kaspár, M.; Ružická, V. *Collect. Czech. Chem. Commun.* **1983**, 48, 2361.
29. Goliaszewski, A.; Schwartz, J. *Tetrahedron* **1985**, 41, 5779.

30. Klusener, P.A.A.; Hommes, H.H.; Verkruijsse, H.D.; Brandsma, L. *J. Chem. Soc., Chem. Commun.* **1985**, 1677.
31. Yasuda, H.; Nakano, Y.; Natsukawa, K.; Tani, H. *Macromolecules* **1978**, *11*, 586.
32. Kajihara, Y.; Ishikawa, K.; Yasuda, H.; Nakamura, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3035.
33. Burger, J.J.; Chen, T.B.R.A.; de Waard, E.R.; Huisman, H.O. *Tetrahedron* **1980**, *36*, 723.
34. Brown, R.S.; Eyley, S.C.; Parsons, P.J. *J. Chem. Soc., Chem. Commun.* **1984**, 438.
35. Yasuda, H.; Nagasuna, K.; Asami, K.; Nakamura, A. *Chem. Lett.* **1983**, 955 (cf. also *Organometallics* **1982**, *1*, 388).
36. Tamura, M.; Suzukamo, G. *Tetrahedron Lett.* **1981**, *22*, 577.
37. Araki, S.A.; Ohmura, M.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1607.
38. Gevorgyan, A.A.; Kazaryan, P.I.; Avakyan, S.V. *Khim. Geterosikl. Soedin.* **1983**, 125; *Chem. Abstr.* **1983**, *98*, 197907.
39. Suzuki, S.; Fujita, Y.; Kobayashi, Y.; Sato, F. *Synth. Commun.* **1986**, *16*, 491; *Tetrahedron Lett.* **1986**, *27*, 69.
40. Frank-Neumann, M.; Martina, D.; Heitz, M.P. *J. Organomet. Chem.* **1986**, *301*, 61.
41. Hegedus, L.; Varaprath, S. *Organometallics* **1982**, *1*, 259.
42. Oprean, I.; Ciupe, H.; Rosca, I.L.; Rom. Pat., RO 70,112; *Chem. Abstr.* **1982**, *97*, 24039.
43. Oprean, I.; Ciupe, H.; Ginsca, L.; Rom. Pat., RO 77,595; *Chem. Abstr.* **1983**, *99*, 176104.
44. Godshalx, J.P.; Stille, J.K. *Tetrahedron Lett.* **1983**, *24*, 1905.
45. Carpita, A.; Bonaccorsi, F.; Rossi, R. *Tetrahedron Lett.* **1984**, *25*, 5193.
46. Djahanbini, D.; Cazes, B.; Goré, J. *Tetrahedron Lett.* **1984**, *40*, 3645.
47. Kleijn, H.; Westmijze, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 340.
48. Ueno, Y.; Sano, H.; Aoki, S.; Okawara, M. *Tetrahedron Lett.* **1981**, *22*, 2675.
49. Ochiai, M.; Tada, S.; Sumi, K.; Fugita, E. *Tetrahedron Lett.* **1982**, *23*, 2205.
50. Hoffman, R.V.; Bishop, R.D.; Fitch, P.M.; Hardenstein, R. *J. Org. Chem.* **1980**, *45*, 917.
51. Moreno Manas, M.; Trins, A.; Trivino, A.; Virgili, A. *An. Quím., Ser. C* **1980**, *76*, 58.
52. Matsushita, H.; Negishi, E. *J. Org. Chem.* **1982**, *47*, 4161.
53. Hendry, L.B.; Piatek, B.; Browne, L.E.; Wood, D.L.; Byers, J.A.; Fish, R.H.; Hicks, R.A. *Nature* **1980**, *284*, 485.
54. Lamparsky, D. In *Essential Oils and Aromatic Plants*; Baerheim Svendsen, A.; Scheffer, J.J.C., Eds.; Dr. W. Junk Publishers: Dordrecht, 1985; p. 79.
55. Maurer, B.; Hauser, A.; Froidevaux, J.-C. *Tetrahedron Lett.* **1986**, *27*, 2111.
56. Wheeler, J.W.; Ayorinde, F.O.; Greene, A.; Duffield, R.M. *Tetrahedron Lett.* **1982**, *23*, 2071.
57. Hidai, M.; Mizuta, H.; Yagi, H.; Nagai, N.; Hata, K.; Uchida, Y. *J. Organomet. Chem.* **1982**, *232*, 89.
58. Sato, T.; Kawara, T.; Nishizawa, A.; Fujisawa, T. *Tetrahedron Lett.* **1980**, *21*, 3377. See also Fujisawa, T.; Sato, T.; Kawara, T.; Noda, A.; Obinata, T. *Tetrahedron Lett.* **1980**, *21*, 2553.
59. Mangeney, P.; Alexakis, A.; Normant, J.F. *Tetrahedron Lett.* **1983**, *24*, 373.
60. Oppolzer, W.; Chapuis, C.; Guo, M.D.; Reichlin, D.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4781.
61. Oppolzer, W.; Moretti, R.; Godel, T.; Meunier, A.; Löher, H. *Tetrahedron Lett.* **1983**, *24*, 4971.

62. (a) Hirama, M.; Noda, T.; Itô, S. *J. Org. Chem.* **1985**, *50*, 127. (b) Hirama, M.; Jpn. Kokai Tokkyo Koho, JP 60,190,737, [85,190,737]; *Chem. Abstr.* **1986**, *104*, 225060.
63. Jackman, L.M.; Lange, B.C. *J. Org. Chem.* **1983**, *48*, 4789.
64. Plešek, J. *Collect. Czech. Chem. Commun.* **1957**, *22*, 644.
65. Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390.
66. Matsumoto, H.; Hoshino, Y.; Nagai, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1279.
67. Dang, T.P.; Aviron-Violet, P.; Collenille, Y.; Varagnat, J. *J. Mol. Catal.* **1982**, *16*, 51.
68. Inoue, S.; Osada, M.; Koyano, K.; Takaya, H.; Noyori, R. *Chem. Lett.* **1985**, 1007.
69. Kortvelyessi, G. *Acta Chim. Acad. Sci. Hung.* **1985**, *119*, 347.
70. Takabe, K.; Yamada, T.; Katagiri, T. *Synth. Commun.* **1983**, 297.
71. (a) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumbobayashi, H.; Taketani, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc.* **1984**, *106*, 5208. (b) Tani, K.; Yamagata, T.; Tatsuno, Y.; Yamagata, Y.; Tomita, K.; Akutagawa, S.; Kumobayashi, H.; Otsuka, S. *Angew. Chem. Int. Ed.* **1985**, *24*, 217.
72. Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumbobayashi, H.; Taketani, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.
73. Simon, H.; Bader, J.; Günther, H.; Neumann, S.; Thanos, J. *Angew. Chem. Int. Ed.* **1985**, *24*, 539.
74. Julia, M.; Roy, P. *Tetrahedron* **1986**, *42*, 4991.
75. Nissen, A.; Rebafka, W.; Aquila, W. (BASF); Eur. Pat., Appl. 21,074 (publ. Jan. 7, 1981).
76. Babin, D.; Fourneron, J.-D.; Julia, M. *Bull. Soc. Chim. Fr.* **1980**, 588.
77. Julia, M.; Schmitz, C. *Tetrahedron* **1986**, *42*, 2485.
78. Moiseenkov, A.M.; Polunin, E.V.; Semenovskiy, A.V. *Tetrahedron Lett.* **1979**, 4759. See also Moiseenkov, A.M.; Polunin, E.V.; Zaks, I.M.; Semenovskiy, A.V. *Dokl. Akad. Nauk SSSR* **1977**, *236*, 124.
79. Moiseenkov, A.M.; Polunin, E.V.; Semenovskiy, A.V. *Angew. Chem. Int. Ed.* **1981**, *20*, 1057.
80. Thomas, A.F. *J. Am. Chem. Soc.* **1969**, *91*, 3281.
81. Suzuki, S.; Fujita, Y.; Nishida, T. *Tetrahedron Lett.* **1983**, *24*, 5737.
82. Julia, S.; Julia, M.; Linarès, H. *Bull. Soc. Chim. Fr.* **1962**, 1960.
83. Julia, M.; Lavé, D.; Mulhauser, M.; Ramirez-Muñoz, M.; Uguen, D. *Tetrahedron Lett.* **1983**, *24*, 1783.
84. Savu, P.M.; Katzenellenbogen, J.A. *J. Org. Chem.* **1981**, *46*, 239.
85. Majewski, M.; Mpango, G.B.; Thomas, M.T.; Wu, A.; Snieckus, V. *J. Org. Chem.* **1981**, *46*, 2029.
86. Alexakis, A.; Commerçon, A.; Coulentianos, C.; Normant, J.F. *Tetrahedron* **1984**, *40*, 715.
87. Mathew, K.K.; Raman, P.S.; Bhargavi Antharjanam, T.G. *Indian J. Chem., Sect. B.* **1981**, *20*, 340.
88. Ono, N.; Kaimura, A.; Kaji, A. *Tetrahedron Lett.* **1984**, *25*, 5319.
89. Negishi, E.; King, A.O.; Klima, W.L.; Patterson, W.; Silveira, Jr., A. *J. Org. Chem.* **1980**, *45*, 2526.
90. Okukado, N.; Negishi, N. *Tetrahedron Lett.* **1978**, 2357, and literature quoted in Ref. 2.
91. Matsumoto, M.; Ito, S. *J. Chem. Soc., Chem. Commun.* **1981**, 907.
92. Minami, I.; Yamada, M.; Tsuji, J. *Tetrahedron Lett.* **1986**, *27*, 1805.
93. Babler, J.H.; Invergo, B.J. *Tetrahedron Lett.* **1981**, *22*, 621.

94. Takabe, K.; Yamada, T.; Katagiri, T. *Chem. Lett.* **1982**, 1987.
95. Fleming, I.; Paterson, I.; Pearce, A. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 256.
96. Cori, O.; Chayet, L.; Perez, L.M.; Bunton, C.A.; Hachey, D. *J. Org. Chem.* **1986**, 51, 1310.
97. Matsubara, S.; Okazoe, T.; Oshima, K.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1983**, 24, 3741; *Bull. Chem. Soc. Jpn.* **1985**, 58, 844.
98. Hosogai, T.; Fujita, Y.; Ninagawa, Y.; Nishida, T. *Chem. Lett.* **1982**, 411.
99. Inomata, K.; Murata, Y.; Kato, H.; Tsukahara, Y.; Kinoshita, H.; Kotake, H. *Chem. Lett.* **1985**, 931.
100. Takai, K.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, 56, 3791.
101. (a) Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.* **1980**, 102, 5974. (b) Martin, V.S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Sharpless, K.B. *J. Am. Chem. Soc.* **1981**, 103, 6237. (c) See also review: Sharpless, K.B.; Berens, C.H.; Katsuki, T.; Lee, A.W.M.; Martin, V.S.; Takatani, M.; Viti, S.M.; Walker, F.J.; Woodward, S.S. *Pure Appl. Chem.* **1983**, 55, 589.
102. Farrell, J.; Alexis, M.; Trecarten, M. *Nouv. J. Chim.* **1983**, 7, 449.
103. Nicolaou, K.C.; Duggan, M.E.; Ladduwahetty, T. *Tetrahedron Lett.* **1984**, 25, 2069.
104. Eliel, E.L.; Lynch, J.E. *Tetrahedron Lett.* **1981**, 22, 2855.
105. Eliel, E.L.; Soai, K. *Tetrahedron Lett.* **1981**, 22, 2859.
106. Julia, M.; Uguen, D. *Bull. Soc. Chim. Fr.* **1976**, 513.
107. Ohwa, M.; Kogure, T.; Eliel, E.L. *J. Org. Chem.* **1986**, 51, 2599.
108. Barner, R.; Hübscher, J. *Helv. Chim. Acta* **1983**, 66, 880.
109. Murahashi, S.-I.; Yano, T. *J. Am. Chem. Soc.* **1980**, 102, 2456.
110. (a) Sharpless, K.B.; Lauer, R.F. *J. Am. Chem. Soc.* **1973**, 95, 2697. (b) See also Warpehoski, M.A.; Chabaud, B.; Sharpless, K.B. *J. Org. Chem.* **1982**, 47, 2897.
111. Nomura, M.; Fujihara, Y.; Matsubara, Y. *Nippon Kagaku Kaishi* **1980**, 779; *Chem. Abstr.* **1980**, 93, 186568.
112. Alderdice, M.; Spino, C.; Weiler, L. *Tetrahedron Lett.* **1984**, 25, 1643.
113. Anderson, R.J.; Gieselmann, M.J.; Chinn, H.R.; Adams, K.G.; Henrick, C.A.; Rice, R.E.; Roelofs, W.L. *J. Chem. Ecol.* **1981**, 7, 695.
114. Lombardo, D.A.; Weedon, A.C. *Tetrahedron Lett.* **1986**, 27, 5555.
115. Julia, M.; Verpeaux, J.-N. *Tetrahedron* **1983**, 39, 3289.
116. Ferroud, D.; Gaudin, J.M.; Genet, J.P. *Tetrahedron Lett.* **1986**, 27, 845.
117. Schulte-Elte, K.H.; Gadola, M. *Helv. Chim. Acta* **1971**, 54, 1095.
118. Szantay, C.; Novak, L.; Kis-Tamás, A.; Majoros, B.; Ujváry, I.; Jurak, F.; Poppe, L.; Hung. Teljes, HU 24,595; *Chem. Abstr.* **1983**, 99, 122703.
119. Streinz, L.; Wimmer, Z.; Roshka, G.K.; Ischchenko, R.I.; Romanuk, M.; Kovalev, B. *Collect. Czech. Chem. Commun.* **1985**, 50, 2174.
120. Sandra, J.M.; Cuñat, P. *Phytochemistry* **1980**, 19, 89.
121. Ohloff, G. *Tetrahedron Lett.* **1960**, 10.
122. Martínez, A.G.; Marco Contelles, J.L. *Synthesis* **1982**, 742.
123. Hiyama, T.; Okuda, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, 55, 561.
124. Bubnov, Y.N.; Etinger, M.Yu. *Tetrahedron Lett.* **1985**, 26, 2797.
125. Hosomi, A.; Araki, Y.; Sukarai, H. *J. Org. Chem.* **1983**, 48, 3122.
126. Snider, B.B.; Rodini, D.J.; Kirk, T.C.; Cordova, R. *J. Am. Chem. Soc.* **1982**, 104, 555.

127. Rousseau, G.; Drouin, J. *Tetrahedron* **1983**, *39*, 2308.
128. Sakurai, H.; Hosomi, A.; Saito, M.; Sasaki, K.; Iguchi, H.; Sasaki, J.; Araki, Y. *Tetrahedron* **1983**, *39*, 883.
129. Baeckström, P.; Björkling, F.; Högberg, H.-E.; Norin, T. *Acta Chem. Scand., Ser. B* **1983**, *37*, 1.
130. Schulze, K.; Haufe, G.; Kohler, G. *Z. Chem.* **1980**, *20*, 293.
131. Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Soc.* **1986**, *108*, 483.
132. Francke, W.; Sauerwein, P.; Vité, J.P.; Klimetzek, D. *Naturwissenschaften* **1980**, *67*, 147.
133. Masaki, Y.; Hashimoto, K.; Sakuma, K.; Kaji, K. *J. Chem. Soc., Perkin Trans. I* **1984**, 1289.
134. Tsukasa, H. *Yakugaku Zasshi* **1982**, *31*, 615.
135. Tsukasa, H. *Yakugaku Zasshi* **1984**, *33*, 233.
136. Adams, D.R.; Bhatnagar, S.P.; Cookson, R.H.; Tuddenham, R.M. *J. Chem. Soc., Perkin Trans. I* **1975**, 1741.
137. Weyerstahl, P.; Zombik, W.; Gansau, C. *Liebigs Ann. Chem.* **1986**, 422.
138. de Villiers, D.J.J.; Gabers, C.F.; Laurie, R.N. *Phytochemistry* **1971**, *10*, 1359.
139. Guittet, E.; Julia, S. *Synth. Commun.* **1981**, *11*, 709.
140. Badanyan, Sh.O.; Vorskanyan, S.A.; Chobanyan, Zh.A.; USSR Pat., SU 1,133,256 (Appl. Jan. 7, 1985); *Chem. Abstr.* **1985**, *103*, 54333.
141. Kaiser, R.; Lamparsky, D. *Parf. Cosmét. Arômes* **1977** (17), 71; **1977** (18), 102; see also Ref. 54.
142. Nazarov, I.N.; Krasnaya, Zh.A.; Makin, S.M. *Dokl. Akad. Nauk SSSR* **1957**, *114*, 553; *Chem. Abstr.* **1958**, *52*, 235.
143. Moiseenkov, A.M.; Czeskis, B.A.; Bolesov, I.G.; Zhurina, G.R.; Jernstedt, K.; Ahlgren, G. *Chem. Scripta* **1982**, *19*, 182; *Chem. Abstr.* **1982**, *97*, 56024.
144. (a) Czeskis, B.A.; Moiseenkov, A.M.; Rudashevskaya, T.Yu.; Nesmeyanova, O.A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1982**, 2548. (b) Moiseenkov, A.M.; Czeskis, B.A.; Semenovskiy, A.V. *J. Chem. Soc., Chem. Commun.* **1982**, 109.
145. Chalk, A.J.; Magennis, S.A.; Wertheimer, V., Proc. 1st China–Japan–US Trilateral Seminar on Organometallic Chemistry, Fundamentals of Research on Organometallic Chemistry, 1980, p. 851 (Reinhold: New York, 1982; *Chem. Abstr.* **1982**, *97*, 182664).
146. Chalk, A.J.; Wertheimer, V.; Magennis, S.A. *J. Mol. Catal.* **1983**, *19*, 189.
147. Kumobayashi, H.; Mitsuhashi, S.; Akutagawa, S.; Ohtsuka, S. *Chem. Lett.* **1986**, 157.
148. Etoh, H.; Ina, K.; Iguchi, M. *Agric. Biol. Chem.* **1980**, *44*, 2999.
149. Williams, P.J.; Strauss, C.R.; Wilson, B. *J. Agric. Food Chem.* **1980**, *28*, 766.
150. Williams, P.J.; Strauss, C.R.; Wilson, B. *Phytochemistry* **1980**, *19*, 1137.
151. Rapp, A.; Knipser, W.; Engel, L. *Vitis* **1980**, *19*, 226; *Chem. Abstr.* **1981**, *94*, 82103.
152. Strauss, C.R.; Wilson, B.; Rapp, A.; Guentert, M.; Williams, P.J. *J. Agric. Food Chem.* **1985**, *33*, 706.
153. Eberhardt, R.; Pfannhauser, W.Z. *Lebensm.-Unters. Forsch.* **1985**, *181*, 97.
154. Awano, K.; Watanabe, I.; Yanai, T.; Furuhashi, A.; Kogami, K.; Hayashi, K.; 9th International Congress on Essential Oils, Singapore 1983, Abstracts, p. 46.
155. Battersby, A.R.; Brown, S.H.; Payne, T.G. *Chem. Commun.* **1970**, 827.
156. (a) Escher, S., Ph.D. Thesis, ETH Zürich, 1972. (b) See also Escher, S.; Loew, P.; Arigoni, D. *Chem. Commun.* **1970**, 823.

157. T. Hasegawa Co. Ltd.; Jpn. Kokai Tokkyo Koho, JP 58 140,032; *Chem. Abstr.* **1984**, 100, 22323.
158. Behr, D.; Wahlberg, I.; Nishida, T.; Enzell, C.R. *Acta. Chem. Scand., Ser. B* **1978**, 32, 228.
159. Hase, T.; Iwagawa, T.; Mutnesada, K. *Phytochemistry* **1982**, 21, 1434.
160. Takido, M.; Fukuhara, K.; Yamanouchi, S.; Takahashi, S. *Phytochemistry* **1983**, 22, 223.
161. Winterhalter, P.; Katzenberger, D.; Schreier, P. *Phytochemistry* **1986**, 25, 1347.
162. (a) Bortolini, O.; Di Furia, F.; Modena, G. *J. Mol. Catal.* **1983**, 19, 319. (b) Bortolini, O.; Conte, V.; Di Furia, F.; Modena, G. *J. Mol. Catal.* **1983**, 19, 331.
163. Arcoria, A.; Ballistreri, F.P.; Tomaselli, G.A.; Di Furia, F.; Modena, G. *J. Org. Chem.* **1986**, 51, 2374.
164. Kobayashi, H.; Komatsu, J. *J. Pharm. Soc. Jpn.* **1983**, 103, 508.
165. Meinwald, J.; Thompson, W.R.; Eisner, T.; Owen, D.F. *Tetrahedron Lett.* **1971**, 3485.
166. Delaby, R.; Dupin, E. *Bull. Soc. Chim. Fr.* **1938** (5), 931.
167. Armstrong, R.J.; Weiler, L. *Can. J. Chem.* **1983**, 61, 2530.
168. Gramatica, P.; Giardina, G.; Speranza, G.; Manitto, P. *Chem. Lett.* **1985**, 1395.
169. Fujisawa, T.; Sato, T.; Kawara, T.; Noda, A. *Tetrahedron Lett.* **1982**, 23, 3193.
170. Terao, S.; Shiraiishi, M.; Kato, K. *Synthesis* **1984**, 969.
171. Araki, S.; Butsugan, T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 969.
172. (a) Williams, J.R.; Lin, C. *J. Chem. Soc., Chem. Commun.* **1981**, 752. (b) Williams, J.R.; Lin, C.; Chodosh, D.F. *J. Org. Chem.* **1985**, 50, 5815.
173. Eschenmoser, W.; Uebelhart, P.; Eugster, C.H. *Helv. Chim. Acta* **1983**, 66, 82.
174. Zdero, C.; Bohlmann, F.; King, R.M.; Robinson, H. *Phytochemistry* **1986**, 25, 509.
175. Meier, H.; Uebelhart, P.; Eugster, C.H. *Helv. Chim. Acta* **1986**, 69, 106.
176. Tanaka, K.; Ohsawa, K.; Honda, H.; Yamamoto, I. *J. Pestic. Sci.* **1981**, 6, 75.
177. Evans, D.A.; Takacs, J.M. *Tetrahedron Lett.* **1980**, 21, 4233.
178. Mori, K.; Ito, T.; Tanaka, K.; Honda, H.; Yamamoto, I. *Tetrahedron* **1983**, 39, 2303.
179. Kitahara, T.; Takagi, Y.; Matsui, M. *Agric. Biol. Chem.* **1980**, 44, 897.
180. Kunesch, G.; Zagatti, P.; Lallemand, J.-Y.; Debal, A.; Vigneron, J.-P. *Tetrahedron Lett.* **1981**, 22, 5271.
181. (a) Vigneron, J.-P.; Méric, R.; Larchevêque, M.; Debal, A. *Tetrahedron Lett.* **1982**, 23, 5051. (b) Vigneron, J.-P.; Méric, R.; Larchevêque, M.; Debal, A.; Lallemand, J.-Y.; Kunesch, G.; Zagatti, P.; Gallois, M. *Tetrahedron* **1984**, 40, 3521.
182. Suzuki, K.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett.* **1984**, 25, 1817.
183. Suzuki, K.; Ohkuma, T.; Tsuchihashi, G. *Tetrahedron Lett.* **1985**, 26, 861.
184. Uematsu, T.; Umemura, T.; Mori, K. *Agric. Biol. Chem.* **1983**, 47, 597.
185. Huynh, C.; Derguini-Bouméchal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, 1503.
186. Whittaker, M. *Chem. Ind. (London)* **1986**, 463.
187. Ortuno, R.M.; Mercé, R.; Font, J. *Tetrahedron Lett.* **1986**, 27, 2519.
188. Yokoyama, Y.; Yunokihara, M. *Chem. Lett.* **1983**, 1245.
189. Rey, M.; Roberts, S.M.; Dieffenbacher, A.; Dreiding, A.S. *Helv. Chim. Acta* **1970**, 53, 417.
190. Davies, H.G.; Roberts, S. M.; Wakefield, B. J.; Winders, J.A. *J. Chem. Soc., Chem. Commun.* **1985**, 1166.
191. Iriye, R.; Yorifuji, T.; Takeda, N.; Tatematsu, A. *Agric. Biol. Chem.* **1984**, 48, 2923.

192. Iriye, R. *Agric. Biol. Chem.* **1985**, 49, 2775.
193. Dziadulewicz, E.; Gallagher, T. *Tetrahedron Lett.* **1985**, 26, 4547.
194. Barua, N.C.; Schmidt, R.R. *Synthesis* **1986**, 891.
195. Frauenrath, H.; Philipps, T. *Tetrahedron* **1986**, 42, 1135.
196. Chakraborty, T.K.; Chandrasekaran, T. *Tetrahedron Lett.* **1984**, 25, 2891.
197. Fang, J.M.; Hong, B.-C. *Synth. Commun.* **1986**, 16, 523.
198. Bohlmann, F.; Zdero, C.; King, R.M.; Robinson, H. *Phytochemistry* **1981**, 20, 2425.
199. Gadir, S.A.; Smith, Y.; Taha, A.A.; Thaller, V. *J. Chem. Res. (S)* **1986**, 102.
200. Martin, R.; Chapelo, C.B.; Svanholt, K.L.; Dreiding, A.S. *Helv. Chim. Acta* **1976**, 59, 2724.
201. Gadir, S.A.; Smith, Y.; Taha, A.A.; Thaller, V. *J. Chem. Res. (S)* **1986**, 222.
202. Nippon Zeon Co. Ltd.; Jpn. Kokai Tokkyo Koho, JP 59 36,626 (84 36,626); *Chem. Abstr.* **1984**, 101, 7481.
203. Negishi, T.; Uchida, M.; Tamaki, Y.; Mori, K.; Ishiwatori, T.; Asano, S.; Nakagawa, K. *Appl. Ent. Zool.* **1980**, 15, 328.
204. Bierl-Leonhart, B.A.; Moreno, D.S.; Schwarz, M.; Foster, H.S.; Plimmer, J.R.; DeVilbiss, E.D. *Life. Sci.* **1980**, 27, 399.
205. Uchida, M.; Nakagawa, K.; Negishi, T.; Asano, S.; Mori, K. *Agric. Biol. Chem.* **1981**, 45, 369.
206. Mori, K.; Ueda, H. *Tetrahedron* **1981**, 37, 2581.
207. Terashima, S.; Tseng, C.C.; Hayashi, M.; Koga, K. *Chem. Pharm. Bull.* **1979**, 27, 758.
208. Nakagawa, N.; Mori, K. *Agric. Biol. Chem.* **1984**, 48, 2799.
209. Shankaram, K.; Rao, A.S. *Ind. J. Chem., Sect. B* **1982**, 21, 542.
210. Stierle, D.B.; Wing, R.M.; Sims, J.J. *Tetrahedron Lett.* **1976**, 4455.
211. Kazlauskas, R.; Murphy, P.T.; Quinn, R.J.; Wells, R.J. *Tetrahedron Lett.* **1976**, 4451.
212. Williard, P.J.; Grab, L.A.; de Laszlo, S.E. *J. Org. Chem.* **1983**, 48, 1123.
213. Williard, P.J.; Grab, L.A. *Tetrahedron Lett.* **1984**, 25, 5009.
214. Nofal, M.A.; Ho, C.-T.; Chang, S.S. *Perfum. Flavor.* **1982**, 6 (6), 24.
215. Tsuneya, T.; Ishihara, M.; Shiota, H.; Shiga, M. *Agric. Biol. Chem.* **1980**, 44, 957.
216. Torii, S.; Uneyama, K.; Ono, M. *Tetrahedron Lett.* **1980**, 21, 2653.
217. (a) Ishihara, M.; Tsuneya, T.; Shiota, H.; Shiga, M.; Yokoyama, Y. *Agric. Biol. Chem.* **1983**, 47, 2121. (b) Nishida, Y.; Konno, M.; Ohru, H.; Meguro, H. *Agric. Biol. Chem.* **1986**, 50, 187.
218. Nishida, Y.; Ohru, H.; Meguro, H. *Agric. Biol. Chem.* **1983**, 47, 2123; **1984**, 48, 1211.
219. Konno, M.; Nishida, Y.; Ohru, H.; Meguro, H. *Agric. Biol. Chem.* **1986**, 50, 1665.
220. Tsuneya, T.; Ishihara, M.; Shiota, H.; Shiga, M. *Agric. Biol. Chem.* **1983**, 47, 2495.
221. Nishida, Y.; Fukushima, Y.; Ohru, H.; Meguro, H. *Agric. Biol. Chem.* **1984**, 48, 1217.
222. Otieno, D.A.; Pattenden, G.; Popplestone, C.R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 196.
223. Goldschmidt, Z.; Crammer, B.; Ikan, R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2697.
224. Crammer, B.; Goldschmidt, Z.; Ikan, R.; Spiegelstein, H. *J. Agric. Food Chem.* **1985**, 33, 1148.
225. Elmore, N.F.; Roberts, J.E.; Whitham, G.H. *J. Chem. Res. (S)* **1985**, 98.
226. Takano, S.; Tanaka, M.; Seo, K.; Hiram, M.; Ogasawara, K. *J. Org. Chem.* **1985**, 50, 931.
227. Takano, S.; Seya, K.; Goto, E.; Hiram, M.; Ogasawara, K. *Synthesis* **1983**, 116.
228. Takano, S.; Kudo, J.; Takahashi, M.; Ogasawara, K. *Tetrahedron Lett.* **1986**, 27, 2405.
229. Grieco, P.A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, 41, 1485.

230. (a) Epstein, W.W.; Gaudioso, L.A. *J. Org. Chem.* **1982**, *47*, 175. (b) Epstein, W.W.; Gaudioso, L.A.; Brewster, G.B. *J. Org. Chem.* **1984**, *49*, 2748.
231. Näf-Müller, R.; Pickenhagen, W.; Willhalm, B. *Helv. Chim. Acta* **1981**, *64*, 1424.
232. Héthelgi, E.; Tétényi, P.; Kettenes-van der Bosch, J.J.; Salemink, C.A.; Heerma, W.; Versluis, C.; Kloosterman, J.; Sipma, G. *Phytochemistry* **1981**, *20*, 1847.
233. Aboutabe, E.A.; Soliman, F.M.; El-Zalabani, S.M.; Brunke, E.J.; El-Kersh, T.A. *Sci. Pharm.* **1986**, *54*, 37.
234. Sucrow, W. *Tetrahedron Lett.* **1970**, 4725.
235. Bohlmann, F.; Ates, N.; Jakupovic, J.; King, R.M.; Robinson, H. *Phytochemistry* **1982**, *21*, 2691. Called "lavandulol 2-methylbutyrate" in this paper; another incorrect name ("santolinyl 2-methylbutyrate") was given in an erratum: *Phytochemistry* **1983**, *22*, 1531.
236. Epstein, W.W.; Gaudioso, L.A. *Phytochemistry* **1984**, *23*, 2257.
237. Banthorpe, D.V.; Christou, P.N. *J. Chem. Soc., Perkin Trans. 1* **1981**, 105.
238. Näf-Müller, R.; Näf, F.; Morris, A.F.; Swiss Pat., 648,838 (applied for June 11, 1981, granted April 15, 1985).
239. Segal, R.; Breuer, A.; Feuerstein, I. *Phytochemistry* **1980**, *19*, 2761.
240. Bohlmann, F.; Bapuji, M.; King, R.M.; Robinson, H. *Phytochemistry* **1982**, *21*, 1164.
241. Délérís, G.; Pillot, J.P.; Rayez, J.C. *Tetrahedron* **1980**, *36*, 2215. See also Délérís, G.; Dunoguès, J.; Calas, R. *J. Organomet. Chem.* **1976**, *116*, C 45.
242. Hiyama, T.; Okuda, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561.
243. Boldrini, G.P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umanironchi, A. *J. Organomet. Chem.* **1985**, *280*, 307.
244. Masson, S.; Thuillier, A. *Tetrahedron Lett.* **1982**, *23*, 4087.
245. Hendrickson, J.B.; Boudreaux, G.J.; Palumbo, P.S. *J. Am. Chem. Soc.* **1986**, *108*, 2358.
246. Watanabe, S.; Fujita, T.; Suga, K.; Masamura, S.; Hamatani, Y. *Yakugaku Zasshi* **1983**, *32*, 389; *Chem. Abstr.* **1983**, *99*, 176091.
247. (a) Zydowsky, T.M.; Hill, R.K. American Chemical Society Meeting, Kansas City, September 1982, Abstr. Orgn. 71. (b) Zydowsky, T.M. *Diss. Abstr. Int. B.* **1982**, *43*, 1855; *Chem. Abstr.* **1983**, *98*, 48820.
248. Brown, H.C.; Jadhav, P.K. *Tetrahedron Lett.* **1984**, *25*, 1215.
249. Suzukamo, G.; Fukao, M.; Tamura, M. *Tetrahedron Lett.* **1984**, *25*, 1595.
250. Babin, D.; Fourmeron, J.D.; Harwood, L.M.; Julia, M. *Tetrahedron* **1981**, *37*, 325.
251. Julia, M.; Schmitz, C. *Bull. Soc. Chim. Fr.* **1986**, 630.
252. Wolf, J.P.; Pfander, H. *Helv. Chim. Acta* **1986**, *69*, 62.
253. Kramer, A.; Pfander, H. *Helv. Chim. Acta* **1982**, *65*, 293.
254. Johansen, J.E.; Liaaen-Jensen, S. *Tetrahedron Lett.* **1976**, 955.
255. Fráter, G. *Helv. Chim. Acta* **1979**, *62*, 2825.
256. Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417.
257. Celebuski, J.; Rosenblum, M. *Tetrahedron* **1985**, *41*, 5741.
258. Masson, S.; Mothes, V.; Thuillier, A. *Tetrahedron* **1984**, *40*, 1573.
259. Du Preez, H.E.; Garbers, C.F.; Steenkamp, J.A. *S. Afr. J. Chem.* **1980**, *33*, 21; *Chem. Abstr.* **1981**, *94*, 15882.
260. Cookson, R.C.; Mirza, N.A. *Synth. Commun.* **1981**, *11*, 299.
261. Ueno, Y.; Aoki, S.; Okawara, M. *J. Chem. Soc., Chem. Commun.* **1980**, 683.

262. Shirley, I.; Smith, I.H.; Whiting, D.A. *Tetrahedron Lett.* **1982**, 23, 1501.
263. The Kurakai Co. Ltd.; Jpn. Kokai Tokkyo Koho, JP 59 106,434 (granted 84 106,434); *Chem. Abstr.* **1984**, 101, 171559.
264. Miyakoshi, T.; Saito, S. *Yakugaku Zasshi* **1982**, 31, 113.
265. Barbachyn, M.R.; Johnson, C.R.; Glick, M.D. *J. Org. Chem.* **1984**, 49, 2746.
266. Suzukamo, G. *Yoki Gosei Kagaku Kyokaishi* **1982**, 40, 930.
267. Arlt, D.; Jautelat, M.; Lantzsch, R. *Angew. Chem. Int. Ed.* **1981**, 20, 703.
268. Demonceau, A.; Noels, A.F.; Anciaux, A.J.; Hubert, A.J.; Teyssié, P. *Bull. Soc. Chim. Belg.* **1984**, 93, 949.
269. Stufflebene, G.; Lorenz, K.T.; Bauld, N.L. *J. Am. Chem. Soc.* **1986**, 108, 4234.
270. Aratani, T.; Yoneyoshi, A.; Nagase, T. *Tetrahedron Lett.* **1982**, 23, 685.
271. Corey, E.J.; Jautelat, M. *J. Am. Chem. Soc.* **1967**, 89, 3912.
272. Rama Rao, A.V.; Narayana Rao, M.; Garyali, K. *Synth. Commun.* **1984**, 14, 557.
273. Ficini, J.; Falou, S.; d'Angelo, J. *Tetrahedron Lett.* **1983**, 24, 375.
274. Genêt, J.P.; Piau, F.; Ficini, J. *Tetrahedron Lett.* **1980**, 21, 3183.
275. Genêt, J.P.; Piau, F. *J. Org. Chem.* **1981**, 46, 2414.
276. Genêt, J.P.; Balabane, M.; Charbonnier, F. *Tetrahedron Lett.* **1982**, 23, 5027.
277. Babler, J.H.; Invergo, B.J. *Tetrahedron Lett.* **1981**, 22, 2743.
278. Babler, J.H.; Spina, K.P. *Tetrahedron Lett.* **1985**, 26, 1923.
279. Majewski, M.; Snieckus, V. *Tetrahedron Lett.* **1982**, 23, 1343.
280. Majewski, M.; Snieckus, V. *J. Org. Chem.* **1984**, 49, 2682.
281. Takano, S.; Sato, N.; Akiyama, M.; Ogasawara, K. *Heterocycles* **1985**, 23, 2859. See also Takano, S.; Kasahara, C.; Ogasawara, K. *Heterocycles* **1982**, 19, 1443.
282. Monpert, A.; Martelli, J.; Grée, R.; Carrié, R. *Nouv. J. Chim.* **1983**, 7, 345.
283. Devos, M.J.; Denis, J.N.; Krief, A. *Tetrahedron Lett.* **1978**, 1847.
284. De Vos, M.J.; Krief, A. *Tetrahedron Lett.* **1983**, 24, 103.
285. (a) De Vos, M.J.; Krief, A. *J. Am. Chem. Soc.* **1982**, 104, 4282. (b) Krief, A.; U.S. Pat., 4,487,955; *Chem. Abstr.* **1986**, 105, 24468.
286. Mulzer, J.; Kappert, M. *Angew. Chem. Int. Ed.* **1983**, 22, 63.
287. Krief, A.; Hevesi, L.; Chaboteaux, G.; Mathy, P.; Sevrin, M.; De Vos, M.J. *J. Chem. Soc., Chem. Commun.* **1985**, 1693.
288. Franck-Neumann, M.; Drietrich-Buchecker, C. *Tetrahedron Lett.* **1980**, 21, 671.
289. Franck-Neumann, M.; Martina, D.; Heitz, M. P. *Tetrahedron Lett.* **1982**, 23, 3493.
290. Franck-Neumann, M.; Miesch, M. *Bull. Soc. Chim. Fr.* **1984**, 362.
291. Franck-Neumann, M.; Sedrati, M.; Vigneron, J.-P.; Bloy, V. *Angew. Chem. Int. Ed.* **1985**, 24, 996.
292. Franck-Neumann, M.; Miesch, M. *Tetrahedron Lett.* **1982**, 23, 1409; see also Fr. Pat., 79 22,559.
293. Mann, J.; Thomas, A. *J. Chem. Soc., Chem. Commun.* **1985**, 737.
294. Mann, J.; Thomas, A. *Tetrahedron Lett.* **1986**, 27, 3533.
295. d'Angelo, J.; Revial, G. *Tetrahedron Lett.* **1983**, 24, 2103.
296. (a) Buisson, D.; Azerad, R.; Revial, G.; d'Angelo, J. *Tetrahedron Lett.* **1984**, 25, 6005. (b) d'Angelo, J.; Revial, G.; Azerad, R.; Buisson, D. *J. Org. Chem.* **1986**, 51, 40.

297. (a) Funk, R.L.; Munger, J.D., Jr. *J. Org. Chem.* **1985**, *50*, 707. (b) See also Funk, R.L.; Abelman, M.M.; Munger, J.D., Jr. *Tetrahedron* **1986**, *42*, 2831.
298. Hendrich, A.; Piątkowski, K. *Pol. J. Chem.* **1984**, *58*, 73.
299. (a) Mane, B.M.; Gore, K.G.; Kulkarni, G.H. *Indian J. Chem., Sect. B* **1980**, *19*, 605. (b) Bhat, N.G.; Mane, B.M.; Kulkarni, G.H.; Mitra, R.B. *Indian J. Chem., Sect. B* **1981**, *20*, 204.
300. Ho, T.-L., *Synth. Commun.* **1983**, *13*, 761.
301. Ho, T.-L.; Din, Z.U. *Synth. Commun.* **1980**, *10*, 921.
302. Mitra, R.B.; Mahamulkar, B.G.; Kulkarni, G.H. *Synthesis* **1984**, 428.
303. (a) Mitra, R.B.; Khanra, A.S.; Deshmukh, A.R.A.S. *Indian J. Chem., Sect. B* **1981**, *20*, 436. (b) Bhat, N.G.; Joshi, G.D.; Gore, K.G.; Kulkarni, G.H.; Mitra, R.B. *Indian J. Chem., Sect. B* **1981**, *20*, 558. (c) Naik, R.H.; Kulkarni, G.H. *Indian J. Chem., Sect. B* **1983**, *22*, 859. (d) Naik, R.H.; Bhat, N.G.; Kulkarni, G.H. *Indian J. Chem., Sect. B* **1983**, *22*, 1209. (e) Naik, R.H.; Kulkarni, G.H.; Mitra, R.B. *Indian J. Chem., Sect. B* **1985**, *24*, 154.
304. Ho, T.-L.; Din, Z.U. *Synth. Commun.* **1982**, *12*, 257.
305. Torii, S.; Inokuchi, T.; Oi, R. *J. Org. Chem.* **1983**, *48*, 1944.
306. Ho, T.-L.; Liu, S.-H. *Synth. Commun.* **1982**, *12*, 995.
307. Kuchibhotla, U.; Chakraborty, T.K.; Chandrasekaran, S. *Indian J. Chem., Sect. B* **1984**, *23*, 1216.
308. Fitzsimmons, B.J.; Fraser-Ried, B. *Tetrahedron* **1984**, *40*, 1279.
309. Mukaiyama, T.; Yamashita, H.; Asami, M. *Chem. Lett.* **1983**, 385.
310. Hirao, T.; Harano, Y.; Yamana, Y.; Hamada, Y.; Nagata, S.; Agawa, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1341.
311. Nesmeyanova, O.A.; Rudashevskaya, T.Y.; Dyachenko, A.I.; Savilova, S.F.; Nefedov, O.M. *Synthesis* **1982**, 296.
312. Bierl-Leonhardt, B.A.; Moreno, D.S.; Schwarz, M.; Fargerlund, J.; Plimmer, J.R. *Tetrahedron Lett.* **1981**, *22*, 389. See also Moroe, T.; Komatsu, A.; Matsui, H.; Nagashima, H.; Tujima, N.; Jpn. Kokai Tokkyo Koho, JP 70 19,696; *Chem. Abstr.* **1970**, *73*, 66127.
313. Wolk, J.L.; Goldschmid, Z.; Dunkelblum, E. *Synthesis* **1986**, 347.
314. Gaoni, Y. *J. Org. Chem.* **1982**, *47*, 2564.
315. (a) Gaoni, Y. *Tetrahedron Lett.* **1982**, *23*, 5219. (b) Gaoni, Y.; Tomažič, A. *J. Org. Chem.* **1985**, *50*, 2948.
316. Jones, J.B.; Finch, M.A.W.; Jakovac, I.J. *Can. J. Chem.* **1982**, *60*, 2007.
317. (a) Rosini, G.; Marotta, E.; Petrini, M.; Ballini, R. *Tetrahedron* **1985**, *41*, 4633; *Parf., Cosmét., Arômes* **1986**, *67*, 54. (b) Demuth, M.; Palomer, A.; Sluma, H.-D.; Dey, A.K.; Krüger, C.; Tsay, Yi-Hung *Angew. Chem. Int. Ed.* **1986**, *25*, 1117.
318. Negishi, E.; Boardman, L.D.; Tour, J.M.; Sawada, H.; Rand, C.L. *J. Am. Chem. Soc.* **1983**, *105*, 6344.
319. Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J. *Tetrahedron Lett.* **1982**, *23*, 3755.
320. Chan, T.H.; Chang, E. *J. Org. Chem.* **1974**, *39*, 3264.
321. Menicagli, R.; Malanga, C.; Lardicci, L.; Pecunioso, A. *J. Chem. Res. (S)* **1983**, 124.
322. Meyers, A.I.; Fleming, S.A. *J. Am. Chem. Soc.* **1986**, *108*, 306.
323. Sonawane, H.R.; Nanjundiah, B.S.; Udaya Kumar, M. *Tetrahedron Lett.* **1984**, *25*, 2245.
324. Sonawane, H.R.; Naik, V.G.; Nanjundiah, B.S.; Purohit, P.C. *Tetrahedron Lett.* **1983**, *24*, 3025.

325. Rømming, C.; Skattebøl, L.; Stenstrøm, Y. *Acta Chem. Scand., Ser. B.* **1986**, *40*, 434.
326. Rosini, G.; Geier, M.; Marotta, E.; Petrini, M.; Ballini, R. *Tetrahedron* **1986**, *42*, 6027.
327. Mori, K.; Sasaki, M. *Tetrahedron* **1980**, *36*, 2197.
328. Borden, J.H.; Handley, J.R.; Johnston, B.D.; MacConnell, R.; Silverstein, R.M.; Slessor, K.N.; Swigar, A.A.; Wong, D.T. *J. Chem. Ecol.* **1979**, *5*, 681.
329. Slessor, K.N.; Oelschlager, A.C.; Johnston, B.D.; Pierce, H.D., Jr.; Grewal, S.K.; Wickermesinghe, L.K.G. *J. Org. Chem.* **1980**, *45*, 2290.
330. Kandil, A.A.; Slessor, K.N. *J. Org. Chem.* **1985**, *50*, 5649.
331. Mori, K.; Uematsu, T.; Minobe, M.; Yanagi, K. *Tetrahedron Lett.* **1982**, *23*, 1921; *Tetrahedron* **1983**, *39*, 1735.
332. Martel, J.J.; Demoute, J.P.; Tèche, A.P.; Tessier, J.R. *Pestic. Sci.* **1980**, *11*, 188.
333. White, J.D.; Avery, M.A.; Carter, J.P. *J. Am. Chem. Soc.* **1982**, *104*, 5486.
334. MacKay, W.R.; Ounsworth, J.; Sum, P.-E.; Weiler, L. *Can. J. Chem.* **1982**, *60*, 872.
335. Skattebøl, L.; Stenstrøm, Y. *Tetrahedron Lett.* **1983**, *24*, 3021; *Acta Chem. Scand., Ser. B* **1985**, *39*, 291; PCT Int. Appl., WO 84 03,703; *Chem. Abstr.* **1985**, *103*, 71552.
336. (a) El-Naggar, L.J.; Beal, J.F. *J. Nat. Prod.* **1980**, *43*, 649. (b) Buzogany, K.; Cucu, V. *Farmacia (Bucharest)* **1983**, *31*, 129.
337. Attygalle, A.B.; Morgan, E.D. *Chem. Soc. Rev.* **1984**, *13*, 245.
338. Tietze, L.-F. *Angew. Chem. Int. Ed.* **1983**, *22*, 828.
339. Hutchinson, C.R. *Kagaku Zokan (Kyoto)* **1983**, 41.
340. Jacobs, R.T.; Feutrill, G.; Meinwald, J.; unpublished work; personal communication from Meinwald, J.
341. Bird, C.W.; Yeong, Y.C. *Tetrahedron* **1974**, *30*, 321.
342. Jacobs, R.; Feutrill, G.; Meinwald, J. *Tetrahedron Lett.* **1983**, *24*, 2441.
343. Oppolzer, W.; Schneider, P. *Helv. Chim. Acta* **1986**, *69*, 1817.
344. (a) Kozlov, N.G.; Pehk, T.I. *Zh. Org. Khim.* **1982**, *18*, 1118. (b) Vandemark, M.R.; Scornavacca, A.M. *Org. Prep. Proced. Int.* **1981**, *13*, 395. (c) Brunner, H.; Becker, R. *Angew. Chem. Int. Ed.* **1985**, *24*, 703.
345. Yadav, J.S.; Patil, D.G.; Krishna, R.R.; Chawla, H.P.S.; Dev, S. *Tetrahedron* **1982**, *38*, 1003.
346. Boyle, P.H.; Cocker, W.; Grayson, D.H.; Shannon, P.V.R. *J. Chem. Soc. C* **1971**, 2136.
347. Hutchinson, J.H.; Money, T.; Piper, S.E. *Can. J. Chem.* **1986**, *64*, 854.
348. Imagawa, T.; Matsuura, K.; Murai, N.; Akiyama, T.; Kawanisi, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3020.
349. Diels, O.; Olsen, S. *J. Prakt. Chem.* **1940**, *156*, 285.
350. Lee, M.W.; Herndon, W.C. *J. Org. Chem.* **1978**, *43*, 518.
351. (a) Bellesia, F.; Grandi, R.; Pagnoni, U. M.; Pinetti, A.; Trave, R. *Phytochemistry* **1984**, *23*, 83. (b) Uesato, S.; Ueda, S.; Kobayashi, K.; Miyanchi, M.; Itoh, H.; Inouye, H. *Phytochemistry* **1986**, *25*, 2309, and references cited therein.
352. (a) Battersby, A.R.; Thompson, M.; Glüsenkamp, K.-H.; Tietze, L.-F. *Chem. Ber.* **1981**, *114*, 3430. (b) See also Uesato, S.; Kanomi, S.; Iida, A.; Inouye, H.; Zenk, M.H. *Phytochemistry* **1986**, *25*, 839. (c) Uesato, S.; Ogawa, Y.; Inouye, H.; Saiki, K.; Zenk, M.H. *Tetrahedron Lett.* **1986**, *27*, 2893. (d) Fretz, H.; Woggon, W.-D. *Helv. Chim. Acta* **1986**, *69*, 1959; and references cited therein.
353. Bellesia, F.; Ghelfi, F.; Pagnoni, U.M.; Pinetti, A. *Tetrahedron Lett.* **1986**, *27*, 381.
- 353a. Schreiber, S.L.; Meyers, H.V.; Wiberg, K.B. *J. Am. Chem. Soc.* **1986**, *108*, 8274.

- 353b. Denmark, S.E.; Sternberg, J.A. *J. Am. Chem. Soc.* **1986**, *108*, 8277.
354. Snider, B.B.; Duncia, J.V. *J. Org. Chem.* **1980**, *45*, 3461.
355. Ireland, R.E.; Mueller, R.H.; Willard, A.K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
356. Abelman, M.M.; Funk, R.L.; Munger, J.D., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 4030; see also Ref. 297.
357. Beaupin, C.; Rossi, J.C.; Vidal, J.P.; Girard, J.P.; Passet, J. *Phytochemistry* **1980**, *19*, 1541.
358. (a) Wolff, S.; Barany, F.; Agosta, W.C. *J. Am. Chem. Soc.* **1980**, *102*, 2378. (b) Wolff, S.; Agosta, W.C. *J. Am. Chem. Soc.* **1983**, *105*, 1292. (c) Yoshioka, M.; Ishii, K.; Wolf, H.R. *Helv. Chim. Acta* **1980**, *63*, 571.
359. Grandi, R.; Pagnoni, U.M.; Pinetti, A.; Trave, R. *J. Chem. Res. (S)* **1984**, 194.
360. Sakai, T.; Morita, K.; Matsumara, C.; Sudo, A.; Tsuboi, S.; Takeda, A. *J. Org. Chem.* **1981**, *46*, 4774.
361. (a) Takeshita, H.; Hatsui, T.; Kato, N.; Masuda, T.; Tagoshi, H. *Chem. Lett.* **1982**, 1153. (b) Kato, N.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1574.
362. Kato, N.; Nakanishi, K.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1109.
363. Jones, T.H.; Blum, M.S.; Fales, H.M. *Tetrahedron Lett.* **1980**, *21*, 1701.
364. Blum, M.S.; Wallace, J.B.; Duffield, R.M.; Brand, J.M.; Fales, H.M.; Sokolski, E.A. *J. Chem. Ecol.* **1978**, *4*, 47.
365. Jones, T.H.; Blum, M.S. *Tetrahedron Lett.* **1981**, *22*, 4373.
366. Gais, H.-J.; Lukas, K.L.; Ball, W.A.; Braun, S.; Lindner, H.J. *Liebigs Ann. Chem.* **1986**, 687.
367. Cornubert, R.; Borrel, C. *Bull. Soc. Chim. Fr.* **1930**, 301.
368. Caille, J.C.; Farnier, M.; Guilard, R. *Can. J. Chem.* **1986**, *64*, 824.
369. Caille, J.C.; Farnier, M.; Guilard, R.; Aubry, A.; Lecomte, C. *Can. J. Chem.* **1986**, *64*, 831.
370. Caille, J.C.; Tabyaoui, B.; Guilard, R.; Bellamy, F.D. *Synth. Commun.* **1985**, *15*, 669.
371. Nugent, W.A.; Hobbs, F.W., Jr. *J. Org. Chem.* **1986**, *51*, 3376.
372. Sakan, T.; Murai, F.; Isoe, S.; Hyeon, S.B.; Hayashi, S. *J. Chem. Soc. Jpn., Pure Chem. Sect.* **1969**, *90*, 507.
373. (a) Kurosawa, K.; Obara, H. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 528. (b) Kurosawa, K.; Obara, H.; Uda, H. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 530.
374. Kimura, H.; Obara, H.; Takahashi, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3661.
375. Obara, H.; Kimura, H.; Tanaka, Y. *Chem. Lett.* **1985**, 1139.
376. Brayer, J.-L.; Alazard, J.-P.; Thal, C. *J. Chem. Soc., Chem. Commun.* **1983**, 257.
377. (a) Godeau, R.P.; Rossi, J.C.; Fouraste, I. *Phytochemistry* **1977**, *16*, 604. (b) Godeau, R.P.; Pélissier, Y.; Fouraste, I. *Trav. Soc. Pharm. Montpellier* **1978**, *38*, 343.
378. Alazard, J.-P.; Brayer, J.-L.; Tixidre, A.; Thal, C. *Tetrahedron* **1984**, *40*, 695.
379. Trost, B.M.; Chan, D.M. *J. Am. Chem. Soc.* **1981**, *103*, 5972.
380. (a) Trost, B.M.; Nanninga, T.N. *J. Am. Chem. Soc.* **1985**, *107*, 1293. (b) See also Trost, B.M. *Angew. Chem. Int. Ed.* **1986**, *25*, 1.
381. Büchi, G.; Carlson, J.A.; Powell, J.E., Jr.; Tietze, L.-F. *J. Am. Chem. Soc.* **1973**, *95*, 532.
382. Whitesell, J.K.; Minton, M.A. *J. Am. Chem. Soc.* **1986**, *108*, 6802.
383. (a) Whitesell, J.K.; Minton, M.A.; Felman, S.W. *J. Org. Chem.* **1983**, *48*, 2193. (b) See also Kuritani, H.; Takaoka, Y.; Shingu, K. *J. Org. Chem.* **1979**, *44*, 452.
384. Abe, F.; Mori, T.; Yamanchi, T. *Chem. Pharm. Bull.* **1984**, *32*, 2947. For the history of the structure and biological activity (antitumor) see references in Kupchan, S.M.; Dessertine, A.L.; Blayblock, B.T.; Bryan, R.F. *J. Org. Chem.* **1974**, *39*, 2477.

385. Trost, B.M.; Balkovec, J.M.; Mao, M.K.-T. *J. Am. Chem. Soc.* **1983**, *105*, 6755; *J. Am. Chem. Soc.* **1986**, *108*, 4974.
386. Trost, B.M.; Balkovec, J.M. *Tetrahedron Lett.* **1985**, *26*, 1807.
387. Trost, B.M.; Mao, M.K.-T.; Balkovec, J.M.; Buhlmayer, P. *J. Am. Chem. Soc.* **1986**, *108*, 4965.
388. Parkes, K.E.B.; Pattenden, G. *Tetrahedron Lett.* **1986**, *27*, 1305.
389. Givens, R.S.; Oettle, W.F.; Coffin, R.L.; Carlson, R.G. *J. Am. Chem. Soc.* **1971**, *93*, 3957.
390. Demuth, M.; Raghavan, P.R.; Carter, C.; Nakano, K.; Schaffner, K. *Helv. Chim. Acta* **1980**, *63*, 2434.
391. Demuth, M.; Chandrasekhar, S.; Nakano, K.; Raghavan, P.R.; Schaffner, K. *Helv. Chim. Acta* **1980**, *63*, 2440.
392. Ritterskamp, P.; Demuth, M.; Schaffner, K. *J. Org. Chem.* **1984**, *49*, 1155.
393. (a) Schaffner, K.; Demuth, M. *Chimia* **1981**, *35*, 437. (b) Demuth, M.; Schaffner, K. *Angew. Chem. Int. Ed.* **1982**, *21*, 820.
394. Demuth, M.; Chandrasekhar, S.; Schaffner, K. *J. Am. Chem. Soc.* **1984**, *106*, 1092.
395. Demuth, M.; Ritterskamp, P.; Weigt, E.; Schaffner, K. *J. Am. Chem. Soc.* **1986**, *108*, 4149.
396. Wender, P.A.; Dreyer, G.B. *Tetrahedron Lett.* **1983**, *24*, 4543.
397. Kon, K.; Isoe, S. *Tetrahedron Lett.* **1980**, *21*, 3399.
398. Doering, W. von E.; Fossel, E.T.; Kaye, R.L. *Tetrahedron* **1965**, *21*, 25.
399. Kon, K.; Isoe, S. *Helv. Chim. Acta* **1983**, *66*, 755.
400. Takemoto, T.; Isoe, S. *Chem. Lett.* **1982**, 1931.
401. Callant, P.; De Wilde, H.; Vandewalle, M. *Tetrahedron* **1981**, *37*, 2079.
402. Callant, P.; Ongena, R.; Vandewalle, M. *Tetrahedron* **1981**, *37*, 2085.
403. Callant, P.; De Wilde, H.; Storme, P.; Vandewalle, M. *Bull. Soc. Chim. Belg.* **1984**, *93*, 489.
404. Storme, P.; Callant, P.; Vandewalle, M. *Bull. Soc. Chim. Belg.* **1983**, *92*, 1019.
405. Bayer, O. In *Methoden der Organische Chemie* (Houben-Weyl), Springer Verlag, 1954; Vol. 7, Part 1, p. 374.
406. Tsunemoto, D.; Araki, N.; Kondo, K. *Tetrahedron Lett.* **1977**, 109.
407. Trost, B.M.; Vladuchick, W.C. *J. Org. Chem.* **1979**, *44*, 148.
408. Nakayama, M.; Ohira, S.; Takata, S.; Fukuda, K. *Chem. Lett.* **1983**, 148.
409. Roberts, R.A.; Schüll, V.; Paquette, L.A. *J. Org. Chem.* **1983**, *48*, 2076.
410. Johnson, C.R.; Elliot, R.C.; Meanwell, N.A. *Tetrahedron Lett.* **1982**, *23*, 5005.
411. Grieco, P.A.; Srinivasan, C.V. *J. Org. Chem.* **1981**, *46*, 2591.
412. Peel, R.; Sutherland, J.K. *J. Chem. Soc., Chem. Commun.* **1974**, 151.
413. Grieco, P.A.; Williams, E.; Tanaka, H.; Gilman, S. *J. Org. Chem.* **1980**, *45*, 3537.
414. Callant, P.; Storme, P.; Van der Eycken, E.; Vandewalle, M. *Tetrahedron Lett.* **1983**, *24*, 5797.
415. Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397.
416. Vandewalle, M.; Van der Eycken, J.; Oppolzer, W.; Vullioud, C. *Tetrahedron* **1986**, *42*, 4035.
417. Mitsunobu, O. *Synthesis* **1981**, 1.
418. Van der Eycken, E.; Callant, P.; Vandewalle, M. *Tetrahedron Lett.* **1985**, *26*, 367.
419. Chang, C.C.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1983**, 605.
420. Van der Eycken, E.; Van der Eycken, J.; Vandewalle, M.; *J. Chem. Soc., Chem. Commun.* **1985**, 1719.

421. Marini-Bettolo, G.B.; Nicoletti, M.; Messana, I.; Patamia, M.; Galeffi, C.; Ogukawa, G.; Portalone, G.; Vaciago, A. *Tetrahedron* **1983**, 39, 323. This is probably the same lactone as was described by Goodson, J.A.; Henry, T.A. *J. Chem. Soc.* **1925**, 127, 1640.
422. Lee, T.V.; Toczek, J.; Roberts, S.M. *J. Chem. Soc., Chem. Commun.* **1985**, 371.
423. Rey, M.; Roberts, S.M.; Dieffenbacher, A.; Dreiding, A.S. *Helv. Chim. Acta* **1970**, 53, 417.
424. Tietze, L.-F.; Fischer, R. *Angew. Chem. Int. Ed.* **1983**, 22, 888.
425. Ikeda, T.; Yne, S.; Hutchinson, C.R. *J. Org. Chem.* **1985**, 50, 5193.
426. Gross, G.-A.; Sticher, O. *Helv. Chim. Acta* **1986**, 69, 1113.
427. Ikeda, T.; Hutchinson, C.R.; Meier, H.; Tietze, L.-F. *Tetrahedron Lett.* **1984**, 25, 2427.
428. Ikeda, T.; Hutchinson, C.R. *J. Org. Chem.* **1984**, 49, 2837.
429. Hutchinson, C.R.; Mattes, K.C.; Nakane, M.; Partridge, J.J.; Uskokovic, M.R. *Helv. Chim. Acta* **1978**, 61, 1221.
430. Jakovic, I.J.; Goodbrand, H.B.; Lok, K.P.; Jones, J.B. *J. Am. Chem. Soc.* **1982**, 104, 4659.
431. Schneider, M.; Engel, N.; Hönicke, P.; Heinemann, G.; Görisch, H. *Angew. Chem. Int. Ed.* **1984**, 23, 142.
432. Brown, R.T.; Jones, M.F. *J. Chem. Soc., Chem. Commun.* **1985**, 699. See also the synthesis of ($\pm$)-elenolide by the same authors, *J. Chem. Soc., Chem. Commun.* **1986**, 1818.
433. Tietze, L.-F.; Henke, S. *Angew. Chem. Int. Ed.* **1981**, 20, 970.
434. Whitesell, J.K.; Matthews, R.S.; Minton, M.A.; Helbling, A.M. *J. Am. Chem. Soc.* **1981**, 103, 3468.
435. Tietze, L.-F.; Glüsenkamp, K.-H.; Nakane, M.; Hutchinson, C.R. *Angew. Chem. Int. Ed.* **1982**, 21, 70.
436. Baldwin, S.W.; Crimmins, M.T. *J. Am. Chem. Soc.* **1982**, 104, 1132.
437. Takano, S.; Morikawa, K.; Hatakeyama, S. *Tetrahedron Lett.* **1983**, 24, 401.
438. Hatakeyama, S.; Saijo, K.; Takano, S. *Tetrahedron Lett.* **1985**, 26, 865.
439. MacKellar, F.A.; Kelly, R.C.; van Tamelen, E.E.; Dorschel, C. *J. Am. Chem. Soc.* **1973**, 95, 7155.
440. Tixidre, A.; Alazard, J.-P.; Thal, C. *Tetrahedron Lett.* **1983**, 24, 3323.
441. Ohfuné, Y.; Takaki, K.; Kameoka, H.; Sakai, T. *Chem. Lett.* **1982**, 209.
442. Takaki, K.; Kameoka, H. *Chem. Lett.* **1981**, 1257.
443. Tanaka, T. In *Cyclopedia of Edible Plants of the World*, Nakao, S., Ed.; Keigaku: Tokyo, 1976.
444. (a) Weinges, K.; Haremsa, S.; Huber-Patz, U.; Jahn, R.; Rodewald, H.; Irngartinger, H.; Jaggy, H.; Melzer, E. *Liebigs Ann. Chem.* **1986**, 46. (b) Weinges, K.; Brunner, D. *Liebigs Ann. Chem.* **1986**, 54.
445. Paquette, L.A.; Doehner, R.F., Jr. *J. Org. Chem.* **1980**, 45, 5105.
446. Wallach, O. *Liebigs Ann. Chem.* **1908**, 359, 265.
447. Thompson, D.J. *J. Organomet. Chem.* **1976**, 108, 381.
448. Birch, A.J.; Raverty, W.D.; Stephenson, G.R. *J. Chem. Soc., Chem. Commun.* **1980**, 857.
449. Birch, A.J.; Raverty, W.D.; Stephenson, G.R. *Organometallics* **1984**, 3, 1075.
450. Bates, R.B.; Caldwell, E.S.; Klein, H.P. *J. Org. Chem.* **1969**, 34, 2615.
451. Le Maux, P.; Dabard, R.; Simonneaux, G. *J. Organomet. Chem.* **1983**, 241, 37.
452. (a) Sakane, S.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, 105, 6154. (b) Maruoka, K.; Yamamoto, H. *Angew. Chem. Int. Ed.* **1985**, 24, 668.
453. Sakane, S.; Fujiwara, J.; Marouka, K.; Yamamoto, H. *Tetrahedron* **1986**, 42, 2193.

454. Friedman, L.; Miller, J.G. *Science* **1971**, *172*, 1044.
455. Fisher, R.; Lardelli, G.; Jeger, O. *Helv. Chim. Acta* **1950**, *33*, 1335.
456. Akhila, A.; Banthorpe, D.V. *Indian J. Chem., Sect. B.* **1980**, *19*, 998.
457. Misra, A.N.; Sarma, M.R.; Soman, R.; Dev. S.; Indian Pat., 146,047, 146,086; *Chem. Abstr.* **1980**, *93*, 8330.
458. Morris, A.F.; Delay, F.; Gautschi, F.; Thomas, A.F.; Giersch, W.F.; Boschung, A. (Firmenich SA), Eur. Pat. Appl., EP 92,031, Oct. 26, 1983.
459. Hosomi, A.; Iguchi, H.; Sasaki, J.; Sakurai, H. *Tetrahedron Lett.* **1982**, *23*, 551.
460. Kimura, K.; Iwata, I.; Nishimura, H. *Agric. Biol. Chem.* **1982**, *46*, 1387.
461. Nomura, M.; Fujihara, Y. *Yakugaku Zasshi* **1982**, *31*, 107.
462. Ryashenteva, M.A.; Belanova, E.P.; Minachev, Kh.M.; Emel'yanov, M.M.; Semenovskii, A.V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1980**, 1659; *Chem. Abstr.* **1980**, *93*, 150395.
463. Vernon, F.; Richard, H.M.J. *Lebensm.-Wiss. Technol.* **1983**, *16*, 32.
464. MacLeod, A.J.; Snyder, C.H.; Subramanian, G. *Phytochemistry* **1985**, *24*, 2623.
465. Takeshita, H.; Nametsuka, H.; Uchida, K. *Chem. Lett.* **1982**, 1061.
466. Snider, B.B.; Rodini, D.J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872.
467. Coxon, J.M.; Hydes, G.J.; Steel, P.J. *Tetrahedron* **1985**, *41*, 5213.
468. Steven, R.V.; Albizati, K.F. *J. Org. Chem.* **1985**, *50*, 632.
469. Sato, T.; Gotoh, Y.; Watanabe, M.; Fujisawa, T. *Chem. Lett.* **1983**, 1533.
470. Jones, B.B.; Clark, B.C., Jr.; Iacobucci, G.A. *J. Chromatogr.* **1980**, *202*, 127; duplicated in *Tetrahedron* **1981**, *37*, suppl. n° 1, 405.
471. Tise, F.P.; Kropp, P.J. *Org. Synth.* **1983**, *61*, 112.
472. Abraham, W.R.; Stumpf, B.; Kieslich, K.; Ger. Offen., 3,239,545; *Chem. Abstr.* **1984**, *101*, 130923, Ger. Offen., 3,243,090.
473. Kametani, T.; Kurobe, H.; Nemoto, H. *J. Chem. Soc., Chem. Commun.* **1980**, 762.
474. Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 1195.
475. Koppenhoefer, B.; Allmendinger, H.; Nicholson, G. *Angew. Chem. Int. Ed.* **1985**, *24*, 48.
476. Ohloff, G.; Giersch, W.; Näf, R.; Delay, F. *Helv. Chim. Acta* **1986**, *69*, 698.
477. Gurudutt, K.N.; Pasha, M.A.; Ravindranath, B. *Indian J. Chem., Sect. B.* **1985**, *24*, 820.
478. Mangoni, L.; Monaco, P.; Previtera, L. *Phytochemistry* **1982**, *21*, 811.
479. Nomura, K.; Fujihara, Y. *Nippon Kagaku Kaishi* **1985**, 217; *Curr. Abstr. Chem.* **1985**, 385, 763.
480. Watanabe, A.; Iwata, I. *Eiyo to Shokuryo* **1980**, *33*, 305; *Chem. Abstr.* **1981**, *95*, 23155.
481. Link, C.M.; Jansen, D.K.; Sukenik, C.N. *J. Am. Chem. Soc.* **1980**, *102*, 7798. This paper checked a number of earlier publications on the same subject and now seems authoritative.
482. Anandaraman, S.; Gurudutt, K.N.; Natarajan, C.P.; Ravindranath, B. *Tetrahedron Lett.* **1980**, *21*, 2189.
483. Wallach, O. *Liebigs Ann. Chem.* **1906**, *350*, 141.
484. De Pascual-Teresa, J.; Caballero, E.; Caballero, C.; Machin, G. *Phytochemistry* **1983**, *22*, 1033.
485. Sandra, J.M.; Cufat, P. *Phytochemistry* **1980**, *19*, 89.
486. (a) Demole, E.; Enggist, P.; Ohloff, G. *Helv. Chim. Acta* **1982**, *65*, 1785. (b) Demole, E.; Enggist, P. (Firmenich SA), Eur. Pat. Appl., EP 54,847; *Chem. Abstr.* **1982**, *97*, 150593.
487. Maupetit, P. *Perfum. Flavor.* **1984**, *9*, 19.
488. Hoppmann, A.; Weyerstahl, P. *Chem. Ber.* **1974**, *107*, 1102.
489. Guella, G.; Cavazza, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1984**, *67*, 1248.

490. Rothenberger, O.S.; Krasnoff, S.B.; Rollins, R.B. *J. Chem. Educ.* **1981**, *57*, 741.
491. Rhodes, P.M.; Vinskill, N. (Pfizer Inc.), Eur. Pat., 77,682, Oct. 21, 1981.
492. Pearson, A.J.; Chen, Y.-S.; Han, G.-R.; Hsu, S.-Y.; Ray, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 267. This paper also claims that the NMR spectrum of isopiperitone is incorrect in the literature.
493. Heumann, A.; Reglier, M.; Waegell, B. *Angew. Chem. Int. Ed.* **1982**, *21*, 366.
494. Shastri, M.H.; Patil, D.G.; Patil, V.D.; Dev, S. *Tetrahedron* **1985**, *41*, 3083.
495. Lindquist, N.; Battiste, M.A.; Whitten, W.M.; Williams, N.H.; Strekowski, L. *Phytochemistry* **1985**, *24*, 863.
496. Ager, D.J.; Fleming, I.; Patel, S.K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2520.
497. (a) Kergomard, A.; Renard, M.F.; Verschambre, H. *Agric. Biol. Chem.* **1982**, *46*, 97. (b) Kergomard, A.; Renard, M.F.; Verschambre, H.; Grolière, C.-A.; Dupy-Blanc, J. *Agric. Biol. Chem.* **1986**, *50*, 487.
498. Hirata, T.; Hamada, H.; Aoki, T.; Suga, T. *Phytochemistry* **1982**, *21*, 2209. (b) Suga, T.; Hirata, T.; Hamada, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2865.
499. Raucher, S.; Hwang, K.-J. *Synth. Commun.* **1980**, *10*, 133.
500. Kugure, T.; Ojima, I. *J. Organomet. Chem.* **1982**, *234*, 249.
501. Solladié, G.; Hutt, J. *Bull. Soc. Chim. Fr.* **1986**, 643.
502. Yamashita, M.; Kato, Y.; Suemitsu, R. *Chem. Lett.* **1980**, 847.
503. Yamashita, M.; Miyoshi, K.; Okada, Y.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1329.
504. Hamon, D.P.G.; Richards, K.R. *Aust. J. Chem.* **1983**, *36*, 109.
505. Cardenas, C.G.; Din, Z.U. (SCM Corp.); U.S. Pat., 4,296,257; *Chem. Abstr.* **1982**, *96*, 85796.
506. Barton, D.H.R.; Motherwell, R.S.H.; Motherwell, W.B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2263.
507. Rickards, R.W.; Watson, W.P. *Aust. J. Chem.* **1980**, *33*, 451.
508. Ueno, Y.; Sano, H.; Okawara, M. *Synthesis* **1980**, 1011.
509. Grayson, D.H. *Proc. Roy. Irish Acad., Sect. B* **1983**, 85.
510. Fristad, W.E.; Bailey, T.R.; Paquette, L.A. *J. Org. Chem.* **1980**, *45*, 3028.
511. Haut, S.A. *J. Agric. Food Chem.* **1985**, *33*, 278.
512. Mitsonobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427.
513. Rollin, P. *Synth. Commun.* **1986**, *16*, 611.
514. (a) C.S.I.R.; Indian Pat., 147,337, Feb. 2, 1980; *Chem. Abstr.* **1981**, *94*, 15919. (b) Bhavana Chemicals Ltd.; Indian Pat., 151,863, Aug. 20, 1983; *Chem. Abstr.* **1984**, *100*, 210211.
515. (a) Pande, B.S.; Sarma, M.R.; Soman, R.; Dev, S.; Indian Pat., 150,529. (b) Soman, R.; Dev, S.; Indian Pat., 150,447; *Chem. Abstr.* **1983**, *99*, 88417, 88418.
516. Uneyama, K.; Isimura, A.; Fujii, K.; Torii, S. *Tetrahedron Lett.* **1983**, *24*, 2857.
517. Suggs, J.W.; Cox, S.D.; Crabtree, R.H.; Quirk, J.M. *Tetrahedron Lett.* **1981**, *22*, 303.
518. Kumobayashi, H.; Taketomi, H.; Akutagawa, S. (Takasago Perfumery Co. Ltd.); Jpn. Kokai Tokkyo Koho, 80 02,627, Jan. 10, 1980; *Chem. Abstr.* **1980**, *93*, 26589.
519. Burbott, A.J.; Hennessey, J.P., Jr.; Johnson, W.C., Jr.; Loomis, W.D. *Phytochemistry* **1983**, *22*, 2227.
520. Friedrich, E.; Lutz, W. *Chem. Ber.* **1980**, *113*, 1245.
521. Metge, C.; Bertrand, C. *C. R. Hebd. Séances Acad. Sci., Ser. C* **1980**, *291*, 255.
522. Kreiser, W.; Below, P. *Tetrahedron Lett.* **1981**, *22*, 429.

523. Ho, T.-L. (S.C.M. Corp.), U.S. Pat., 4,463,194, Feb. 26, 1982.
524. Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1985**, 26, 5535; *Tetrahedron* **1986**, 42, 2203.
525. Chang, T.C.T.; Rosenblum, M. *J. Org. Chem.* **1981**, 46, 4103.
526. Mandai, T.; Osaka, K.; Kawagishi, M.; Kawada, M.; Otera, J. *Synth. Commun.* **1984**, 14, 797.
527. Surburg, H.; Mondon, A. *Chem. Ber.* **1981**, 114, 118.
528. Nomura, M.; Fujihara, Y. *Nippon Kagaku Kaishi* **1985**, 990; *Curr. Abstr. Chem.* **1985**, 375431.
529. (a) Bluthe, N.; Ecoto, J.; Fétizon, M.; Lazare, S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1747. (b) Fétizon, M.; Ecoto, J.; Lazare, S.; Eur. Pat. 21,952, June 19, 1979.
530. Delay, F.; Thomas, A. F.; unpublished work.
531. Delay, F.; Swiss Pat., Appl. n° 5671, Nov. 28, 1984; Ger. Offen., 3,541,939; *Chem. Abstr.* **1986**, 105, 97053.
532. Francisco, C.G.; Freire, R.; Hernández, R.; Melián, D.; Salazar, J.A.; Suárez, E. *J. Chem. Soc., Perkin Trans. 1* **1984**, 459.
533. Kang, Y.-H.; Kice, J.L. *J. Org. Chem.* **1984**, 49, 1507.
534. Fittig, R.; Köbig, J. *Liebigs Ann. Chem.* **1879**, 195, 92.
535. Chrétien-Bessière, Y.; Peyron, L.; Bénezet, L.; Garnerio, J. *Bull. Soc. Chim. Fr.* **1970**, 381.
536. Thomas, A.F.; unpublished work.
537. Schlosser, M.; Bosshardt, H.; Walde, A.; Stähle, M. *Angew. Chem.* **1980**, 92, 302.
538. Watanabe, Y.; Hirose, K.; Jpn. Kokai Tokyo Koho, 80 20,755.
539. (a) Crawford, R.J.; Erman, W.F.; Broaddus, C.D. *J. Am. Chem. Soc.* **1972**, 94, 4298. (b) Erman, W.F.; Broaddus, C.D. (Proctor and Gamble); U.S. Pat., 3,658,925, April 25, 1972.
540. Suemune, H.; Isawaka, G.; Ueno, K.; Sakai, K. *Chem. Pharm. Bull. (Tokyo)* **1984**, 32, 4632.
541. Ziegler, K.; Krupp, F.; Zosel, K. *Liebigs Ann. Chem.* **1960**, 629, 241.
542. Kuchin, A.V.; Tolstikov, G.A.; Yurev, V.P.; Ponomarenko, V.I.; Kurilenko, G.N.; Nurusev, R.A.; Akhmetov, L.I. *Zh. Obshch. Khim.* **1980**, 50, 911.
543. Brown, H.C.; Kulkarni, S.U.; Pandu Rao, C.; Patil, V.D. *Tetrahedron* **1986**, 42, 5515.
544. Brocksom, T.J.; Ferreira, J.T.B. *J. Chem. Res. (S)* **1980**, 412.
545. Oehlschlager, A.C.; Mishra, P.; Dhami, S. *Can. J. Chem.* **1984**, 62, 791.
546. Ikeda, Y.; Manda, E. *Yakugaku Zasshi* **1982**, 31, 830; *Chem. Abstr.* **1982**, 97, 72029.
547. Takeuchi, K.; Sugi, Y.; Matsuzaki, T.; Arakawa, H.; Bando, K. *Chem. Ind. (London)* **1985**, 446.
548. Jiang, Z.; Liu, C. *Huaxue Xuebao* **1981**, 281.
549. DePooter, H.L.; DeBuyck, L.F.; Schamp, N.M. *Phytochemistry* **1986**, 25, 691.
550. Reitsema, R.H. *J. Am. Chem. Soc.* **1956**, 78, 5022.
551. (a) Lee, P.W.; Stearns, S.M.; Powell, W.R.; Stoutamire, D.W.; Payne, G.B.; Woodward, M.D.; Burton, W.B.; Silveira, E.J.; Ehmann, A. *J. Agric. Food Chem.* **1986**, 34, 162. (b) Peterson, L.W.; Woodward, M.D.; Foster, J.P.; Lee, P.W.; Gross, J.R., Shell Chemical Co., Technical Information, 1983. (c) Payne, G.B.; Soloway, S.B.; Powell, J.E.; Roman, S.A.; Kollmeyer, W.D. (Shell Chemical Co.); Eur. Pat. Appl., 81,893, June 22, 1983; *Chem. Abstr.* **1983**, 99, 212423.
552. Ohloff, G.; Uhde, G. *Helv. Chim. Acta* **1965**, 48, 10.
553. Mulder, A.J. (Shell Int. Res.); Eur. Pat. Appl., EP 135,225; *Chem. Abstr.* **1985**, 103, 178157.
554. Bohlmann, F.; Zdero, C. *Phytochemistry* **1982**, 21, 139.

555. (a) Schenck, G.O.; Kinkel, K.G.; Mertens, W.J. *Liebigs Ann. Chem.* **1953**, 584, 125. (b) Turner, J.A.; Herz, W. *J. Org. Chem.* **1977**, 42, 1895.
556. Orsini, F.; Pelizzoni, F. *Gazz. Chim. Ital.* **1980**, 110, 553.
557. Adams, J.; Belley, M. *Tetrahedron Lett.* **1986**, 27, 2075.
558. Wilson, C.W., III; Shaw, P.E. *Aust. J. Chem.* **1975**, 28, 2529.
559. Davies, S.G.; Polywka, M.E.C.; Thomas, S.E. *J. Chem. Soc., Perkin Trans. I* **1986**, 1277.
560. Kumar, N.; Motto, M. G. *Phytochemistry* **1986**, 25, 250.
561. Bondavalli, F.; Schenone, P.; Ranise, A.; Lanteri, S. *J. Chem. Soc., Perkin Trans. I* **1980**, 2626.
562. De Martinez, M.V.; De Venditti, F.G.; De Fenik, I.J.S.; Catalan, C.A.N. *An. Assoc. Quím. Argent.* **1982**, 70, 137.
563. Nishimura, H.; Noma, Y. *Agric. Biol. Chem.* **1982**, 46, 2601.
564. Tsuboi, S.; Shimozuma, K.; Takeda, A. *J. Org. Chem.* **1980**, 45, 1517.
565. Garst, M.E.; Spencer, T.E. *J. Org. Chem.* **1983**, 48, 2442.
566. Taneja, S.C.; Dhar, K.L.; Atal, C.K. *Indian J. Chem., Sect. B* **1980**, 19, 714.
567. Hegde, S.G.; Beckwith, D.; Doti, R.; Wolinsky, J. *J. Org. Chem.* **1985**, 50, 894.
568. Din, Z. U.; Ho, T.-L.; Traynor, S. G. (SCM Chemicals); U.S. Pat., 4,240,969, Dec. 23, 1980; *Chem. Abstr.* **1981**, 95, 7510.
569. Takahashi, K.; Someya, T.; Muraki, S.; Yoshida, T. *Agric. Biol. Chem.* **1980**, 44, 1535.
570. Foote, C.S.; Wuesthoff, M.T.; Wexler, S.; Burstain, I.G.; Denny, R.; Schenck, G.O.; Schulte-Elte, K.-H. *Tetrahedron* **1967**, 23, 2583.
571. Fujita, T.; Watanabe, S.; Mihar, K.; Itoh, K.; Sugahara, K. *J. Chem. Technol. Biotechnol. Chem. Technol., Sect. A* **1985**, 35, 57; *Chem. Abstr.* **1985**, 103, 88089.
572. Brocksom, T.J.; Ferreira, J.T.B. *Synth. Commun.* **1981**, 11, 105.
573. Bal, B.S.; Pinnick, H.W. *Heterocycles* **1981**, 16, 2091.
574. (a) Bélafi-Réthy, K.; Kerényi, E.; Kolta, R. *Acta Chim. Acad. Scient. Hungaricae* **1974**, 83, 1. (b) Bélafi-Réthy, K.; Kerényi, E. *Ibid.* **1977**, 94, 1. (c) Scheffer, J. J. C.; Koedam, A.; Baerheim-Svendsen, A. *Saertryk av Meddeleser fra Norsk Farm.* **1977**, 39, 161.
575. Chou, J.S.-T.; Iwamura, J.I. *T'ai-wan K'o Hsueh* **1978**, 32, 131; *Chem. Abstr.* **1979**, 91, 52719.
576. Göckeritz, D.; Poggendorf, A.; Schmidt, W.; Schubert, D.; Pohloudek-Fabini *Pharmazie* **1979**, 34, 846.
577. Brunke, E.J.; Rojahn, W. *Dragoco Rept.* **1984**, 67.
578. Kitagawa, I.; Tsuji, S.; Nishikawa, F.; Shibuya, H. *Chem. Pharm. Bull. (Tokyo)* **1983**, 31, 2639.
579. Ferraz, H.M.C.; Brocksom, T.J.; Pinto, A.C.; Abia, M.A.; Zocher, D.H.T. *Tetrahedron Lett.* **1986**, 27, 811.
580. (a) Blumann, A.; Della, E.W.; Henrick, C.A.; Hogkins, J.; Jeffries, P.R. *Aust. J. Chem.* **1962**, 15, 290. (b) Stolow, R. D.; Sachdev, K. *Tetrahedron* **1965**, 21, 1889; *id.*, *J. Org. Chem.* **1971**, 36, 960.
581. De Pascual Teresa, J.; Torres, C.; González, M.S.; Grande, M.; Bellido, I.S. *Phytochemistry* **1983**, 22, 2749.
582. Abraham, W.R.; Stumpf, B.; Kieslich, K.; Ger. Offen., 3,338,196, May 2, 1985; *Chem. Abstr.* **1985**, 103, 176997.
583. Abraham, W.R.; Stumpf, B.; Kieslich, K.; Ger. Offen., 3,239,545.

584. Montiel, V.; Lopez-Segura, M.; Aldaz, A.; Grande, M.; Barba, F. *Electrochim. Acta* **1984**, 29, 1123.
585. Morgans, D.J., Jr.; Sharpless, K.B.; Traynor, S.G. *J. Am. Chem. Soc.* **1981**, 103, 462.
586. Carman, R.M.; Van Dongen, J.M.A.M. *Aust. J. Chem.* **1984**, 37, 2607.
587. Carman, R. M.; Van Dongen, J.M.A.M. *Aust. J. Chem.* **1986**, 39, 817.
588. Patwardhan, S.A.; Gupta, A.S. *Phytochemistry* **1983**, 22, 2080.
589. Rotermund, G.W. In *Methoden der Organischen Chemie*, Müller, E., Ed.; Houben-Weyl; Vol. IV/1b, p. 242.
590. Bohlmann, F.; Zdero, C.; Jakupovic, J.; Rourke, J.P. *Liebigs Ann. Chem.* **1985**, 2342.
591. Ding, D.; Sun, H. *Zhiwu Xuebao* **1983**, 25, 62; *Chem. Abstr.* **1983**, 99, 43303.
592. Verghese, J. *PAFAI J.* **1983**, 5, 27.
593. Clive, D.L.J.; Chittattu, G.J.; Farina, V.; Kiel, W.A.; Menchen, S.M.; Russel, C.G.; Singh, A.; Wong, C.K.; Curtis, N.J. *J. Am. Chem. Soc.* **1980**, 102, 4438.
594. Suga, T.; Aoki, T.; Hirata, T.; Lee, Y.S.; Nishimura, O.; Utsumi, M. *Chem. Lett.* **1980**, 229.
595. Sanghvi, Y.S.; Rao, A.S. *Indian J. Chem., Sect. B* **1980**, 19, 952.
596. Hernández, J.D.; Román, L.U.; Rodríguez M., Espinera, J.; Joseph-Nathan, P. *Phytochemistry* **1986**, 25, 1743.
597. (a) Nishimura, H.; Kaku, K.; Nakamura, T.; Fukazawa, Y.; Mizutani, J. *Agric. Biol. Chem.* **1982**, 46, 319. (b) Nishimura, H.; Nakamura, T.; Mizutani, J. *Phytochemistry* **1984**, 23, 2777.
598. (a) Barbier, P.; Leser, G. *C. R. Hebd. Séances Acad. Sci.* **1897**, 124, 1308. (b) Zimmerman, H.E.; English, J. *J. Am. Chem. Soc.* **1953**, 75, 2367, give a historical summary of the reaction.
599. Naves, Y.-R.; Ochsner, P. *Helv. Chim. Acta* **1964**, 47, 51.
600. Clark, B.C., Jr.; Chamblee, T.S.; Iacobucci, G.A. *J. Org. Chem.* **1984**, 49, 4557.
601. Nishimura, H.; Hiramoto, S.; Mizutani, J.; Noma, Y.; Furusaki, A.; Matsumoto, T. *Agric. Biol. Chem.* **1983**, 47, 2697.
602. Kergomard, A.; Verschambre, H. *Tetrahedron* **1977**, 33, 2215.
603. Carman, R.M.; Greenfield, K.L.; Robinson, W.T. *Aust. J. Chem.* **1986**, 39, 21.
604. Carman, R.M.; De Voss, J.J.; Greenfield, K.L. *Aust. J. Chem.* **1986**, 39, 441.
605. Pellegata, R.; Ventura, P.; Villa, M.; Palmisano, G.; Lesma, G. *Synth. Commun.* **1985**, 15, 165.
606. Lee, Y.S.; Hirata, T.; Suga, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2475.
607. Shimizu, S.; Shibata, H.; Karasawa, D.; Mori, K. *Shinshu Daigaku Nogakubu Kiyo* **1983**, 20, 219; *Chem. Abstr.* **1984**, 101, 55354.
608. Suga, T.; Lee, Y.S.; Hirata, T. *Bull. Chem. Soc. Jpn.* **1983**, 56, 784.
609. Hirata, T.; Lee, Y.S.; Suga, T. *Chem. Lett.* **1982**, 671.
610. Carman, R.M.; Fletcher, M.T. *Aust. J. Chem.* **1984**, 37, 2129.
611. Naik, R.H.; Joshi, G.D.; Kulkarni, G.H. *Indian J. Chem., Sect. B* **1986**, 25, 306.
612. Pailer, M.; Scheidl, O.; Gutwillinger, H.; Klein, E.; Obermann, H. *Monatsh. Chem.* **1981**, 112, 987.
613. De Pascual Teresa, J.; Torres, C.; González, M.S.; Bellido, I.S. *An. Quím., Ser. C* **1983**, 79 (3 suppl. 1), 442; *Chem. Abstr.* **1985**, 102, 62442.
614. Garsida, P.; Halsall, T.G.; Hornby, G.M. *J. Chem. Soc., Ser. C* **1969**, 716.
615. Koepsel, M.; Krempel, A.; Surburg, H.; Progress in Essential Oil Research, Proceedings 16th International Symposium Essential Oils; Brunke, E.-J., Ed.; 1985, 241; *Chem. Abstr.* **1986**, 105, 115037.

616. Shimizu, M.; Hayashi, T.; Morita, N.; Kiuchi, F.; Noguchi, H.; Iitaka, Y.; Sankawa, U. *Chem. Pharm. Bull. (Tokyo)* **1983**, *31*, 577.
617. Hayashi, T.; Shinbo, T.; Shimizu, M.; Arisawa, M.; Morita, N.; Kimura, M.; Matsuda, S.; Kikuchi, T. *Tetrahedron Lett.* **1985**, *26*, 3699.
618. Bohlmann, F.; Suwita, A. *Phytochemistry* **1978**, *17*, 560.
619. Sangaiah, R.; Rao, G.S.K. *Tetrahedron Lett.* **1981**, *22*, 1843.
620. Bazyl'chik, V.V.; Fedorov, P.I.; Skakovskii, E.D.; Vinogradov, L.I. *Zh. Org. Khim.* **1981**, *17*, 320; cf. Thomas, A.F.; Willhalm, B.; Ohloff, G. *Helv. Chim. Acta* **1969**, *52*, 1249.
621. Bazyl'chik, V.V.; Fedorov, P.I.; Klyuev, N.A.; Dank, E.K. *Zh. Org. Khim.* **1985**, *21*, 1450.
622. Verghese, J. *Perfum. Flavor.* **1980**, *5* (June-July), 47.
623. Bohlmann, F.; Gupka, R.K.; Jakupovic, J.; King, R.M.; Robinson, H. *Phytochemistry* **1982**, *21*, 2899.
624. Bohlmann, F.; Wallmeyer, M.; Jakupovic, J. *Phytochemistry* **1982**, *21*, 1806.
625. Dinge, A.S.; Kirtany, J.K.; Paknikar, S.K. *Indian J. Chem., Sect. B.* **1981**, *20*, 245.
626. Kawakami, M.; Yamanishi, T. *Agric. Biol. Chem.* **1983**, *47*, 2077.
627. Widmer, E.; Zell, R.; Lukáč, T.; Casadei, M.; Schönholzer, P.; Broger, E.A. *Helv. Chim. Acta* **1981**, *64*, 2405.
628. (a) Baumann, M.; Hoffmann, W. (BASF); Ger. Offen., 2,547,223, Oct. 22, 1975; *Chem. Abstr.* **1977**, *87*, 134868. (b) Baumann, M.; Hoffmann, W.; Nürrenbach, A. *Liebigs Ann. Chem.* **1979**, 1945.
629. Baumann, M.; Hoffmann, W. (BASF); Ger. Offen., 3,112,056; *Chem. Abstr.* **1983**, *98*, 34307. See also Maini, P.N.; Sammes, M.P. *Synth. Commun.* **1984**, *14*, 731, for a similar preparation of the homolog without the C-2 methyl group.
630. Kametani, T.; Suzuki, K.; Kurobe, H.; Nemoto, H. *Chem. Pharm. Bull. (Tokyo)* **1981**, *29*, 105. See also Jpn. Kokai Tokkyo Koho, JP 81 77,236; *Chem. Abstr.* **1982**, *96*, 20298.
631. Alderdice, M.; Weiler, L. *Can. J. Chem.* **1981**, *59*, 2239. This paper can be considered a continuation of that cited as Ref. 533 in Vol. 4, about which we apologize to Prof. Weiler for misspelling his name.
632. Armstrong, R.J.; Weiler, L. *Can. J. Chem.* **1983**, *61*, 2530.
633. Uneyama, K.; Isimura, A.; Torii, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1859.
634. Kane, B.J.; Von Genk, R.A. (SCM Chemicals); U.S. Pat., 4,244,890, Jan. 13, 1981.
635. Takabe, K.; Yamada, T.; Katagiri, T. *Chem. Ind. (London)* **1980**, 540.
636. Schulte-Elte, K.H.; Egger, B.; Müller, B. (Firmenich SA); Eur. Pat. Appl., EP 46,606; *Chem. Abstr.* **1982**, *97*, 24036.
637. Escher, S.; Giersch, W.; Ohloff, G. *Helv. Chim. Acta* **1981**, *64*, 943.
638. Ohloff, G. *Angew. Chem. Int. Ed.* **1970**, *9*, 743, gives leading references; see also Joulain, D.; Rouessac, F. *Chem. Commun.* **1972**, 314.
639. Stella, L. *Tetrahedron Lett.* **1984**, *25*, 3457.
640. He, Ju-Fang; Wu, Yu-Lin *Synth. Commun.* **1985**, *15*, 95.
641. Brooks, D.W.; Kennedy, E. *J. Org. Chem.* **1983**, *48*, 277.
642. Armstrong, R.J.; Weiler, L. *Can. J. Chem.* **1983**, *61*, 214; **1986**, *64*, 584.
643. Mori, K.; Mori, H. *Tetrahedron*, **1985**, *41*, 5487.
644. Naya, Y.; Kotake, M. *Tetrahedron Lett.* **1968**, 1645.
645. Mori, K.; Tamura, H. *Tetrahedron* **1986**, *42*, 2643.

646. Huneck, S.; Zdero, C.; Bohlmann, F. *Phytochemistry* **1986**, *25*, 883.
647. Paul, V.J.; McConnell, O.J.; Fenical, W. *J. Org. Chem.* **1980**, *45*, 3401.
648. Crews, P.; Myers, B.L.; Naylor, S.; Clayson, E.L.; Jacobs, R.S.; Staal, G.B. *Phytochemistry* **1984**, *23*, 1449.
649. Naylor, S.; Hanke, F.J.; Manes, L.V.; Crews, P. *Fortsch. Chem. Nat.* **1983**, *44*, 189.
650. Masaki, Y.; Hashimoto, K.; Sakuma, K.; Kaji, K. *Tetrahedron Lett.* **1982**, *23*, 1481; *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3466.
651. Hedin, P.A.; Burks, M.L.; Thompson, A.C. *J. Agric. Food Chem.* **1985**, *33*, 1011.
652. Mandai, T.; Mizobuchi, K.; Kawada, M.; Otera, J. *J. Org. Chem.* **1984**, *49*, 3403.
653. Ghosh, A.; Banerjee, U.K.; Venkateswaran, R.V. *J. Chem. Res. (S)* **1986**, 148.
654. Frank, R.L.; Hall, H.K. *J. Am. Chem. Soc.* **1950**, *72*, 1645.
655. Wawrzęńczyk, C.; Lochyński, S. *Monatsh. Chem.* **1985**, *116*, 99.
656. Lochyński, S.; Wawrzęńczyk, C.; Walkowicz, M.; Góra, J. *Perfum. Favor.* **1985**, *10* (6), 7, give a review of such methods.
657. Zegarski, J.; Howard, B.M. *Tetrahedron Lett.* **1985**, *26*, 1363.
658. Williard, P.G.; de Laszlo, S.E. *J. Org. Chem.* **1985**, *50*, 3738.
659. Cairns, P.M.; Crombie, L.; Pattenden, G. *Tetrahedron Lett.* **1982**, *23*, 1405.
660. Itoh, A.; Oshima, K.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2050.
661. Wang, D.; Chan, T.-H. *J. Chem. Soc., Chem. Commun.* **1984**, 1273.
662. Uneyama, K.; Date, T.; Torii, S. *J. Org. Chem.* **1985**, *50*, 3160.
663. Bhushan, V.; Chandrasekaran, S. *Chem. Lett.* **1982**, 1537.
664. Thomas, A.F.; Dubini, R. *Helv. Chim. Acta* **1974**, *57*, 2084.
665. Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 99.
666. Blanco, L.; Slougui, N.; Rousseau, G.; Conia, J.M. *Tetrahedron Lett.* **1981**, *22*, 645.
667. Itoh, A.; Saito, T.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1456.
668. Noyori, R.; Hayakawa, Y. *Tetrahedron* **1985**, *41*, 5879.
669. Banwell, M.G.; Gravatt, G. Lance; Rickard, C.E.F. *J. Chem. Soc., Chem. Commun.* **1985**, 514.
670. Wenkert, E.; Greenberg, R.S.; Kim, H.-S.; unpublished observations (personal communications from E. Wenkert).
671. Cavazza, M.; Pietra, F. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2283.
672. Cavazza, M.; Guerriero, A.; Pietra, F. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2005.
673. de Rijke, D.; Ter Heide, R.; Boelens, H. *Perfum. Flavor.* **1982**, *7* (February/March), 31.
674. Novák, M. *Phytochemistry* **1985**, *24*, 858.
675. Pyrek, J. St.; *Lloydia—J. Nat. Prod.* **1984**, *47*, 822.
676. Rousseau, G.; Slougui, N. *J. Am. Chem. Soc.* **1984**, *106*, 7283.
677. Baeckström, P.; Jacobsson, U.; Kontek, B.; Norin, T. *J. Org. Chem.* **1985**, *50*, 3728.
678. Cohen, T.; Yu, L.-C. *J. Am. Chem. Soc.* **1983**, *105*, 2811.
679. Kauffman, G.B. *J. Chem. Educ.* **1983**, *60*, 341.
680. Kaiser, R.; Lamparsky, D. *Helv. Chim. Acta* **1984**, *67*, 1184.
681. Shapiro, R.H.; Duncan, J.H.; Clopton, J.C. *J. Am. Chem. Soc.* **1967**, *89*, 1442.
682. Giumanini, A.G.; Musiani, M.M. *J. Prakt. Chem.* **1980**, *322*, 423.
683. (a) Matsubara, Y.; Uchida, T.; Ohnishi, T.; Kanehira, K.; Fujita, Y.; Hirashima, T.; Nishiguchi, I. *Tetrahedron Lett.* **1985**, *26*, 4513. (b) Matsubara, Y.; Hirashima, T.; Nishiguchi, I.; U.S. Pat., 4,510,025, Appl. Aug. 24, 1983; *Chem. Abstr.* **1985**, *103*, 27090.

684. Iwamuro, H.; Kanehiro, M.; Okabe, O.; Matsubara, Y. *Nippon Nogeikagaku Kaishi* **1983**, 57, 1097.
685. Bachner, J.; Huber, U.; Buchbauer, G. *Monatsh. Chem.* **1981**, 112, 679.
686. Buchbauer, G.; Vitek, R.; Hirsch, M.C.; Kurz, C.; Cech, B.; Vas, E.M. *Monatsh. Chem.* **1982**, 113, 1433.
687. Boelens, H.; Ter Heide, R. (Naarden); Ger. Offen., 2,944,412, Netherlands Appl. November 3, 1978; *Chem. Abstr.* **1981**, 94, 30959.
688. Ismail, Z.M.; Hoffmann, H.M.R. *J. Org. Chem.* **1981**, 46, 3549.
689. Monti, H.; Raffin, D. *C. R. Hebd. Séances Acad. Sci., Ser. C* **1984**, 299, 539.
690. Simmross, F.-M.; Weyerstahl, P. *Liebigs Ann. Chem.* **1981**, 1089.
691. Buchbauer, G.; Rohner, H.C. *Liebigs Ann. Chem.* **1981**, 2093; see also other methylated bicyclo[2.2.1]heptanones in Dworan, E.; Buchbauer, G. *Chem. Ber.* **1981**, 114, 2357.
692. Wallach, O. *Liebigs Ann. Chem.* **1907**, 353, 209.
693. Carlsen, L.; Egsgaard, H.; Schaumann, E.; Mrotzek, H.; Klein, W.-R. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1557.
694. Kirmse, W.; Spaleck, W. *Angew. Chem. Int. Ed.* **1981**, 20, 776.
695. Mahmood, U.; Singh, S.B.; Thakur, R.S. *Phytochemistry* **1983**, 22, 774.
696. Allen, M.S.; Darby, N.; Salisbury, P.; Sigurdson, E.S.; Money, T. *Can. J. Chem.* **1979**, 57, 733.
697. (a) Dadson, W.M.; Lam, M.; Money, T.; Piper, S.E. *Can. J. Chem.* **1983**, 61, 343. (b) Hutchinson, J.H.; Money, T.; Piper, S.E. *Can. J. Chem.* **1986**, 64, 854.
698. Avasthi, K.; Salomon, R.G. *J. Org. Chem.* **1986**, 51, 2556.
699. Baldwin, J.E.; Barden, T.C. *J. Am. Chem. Soc.* **1983**, 105, 6656.
700. Trost, B.M.; Renaut, P. *J. Am. Chem. Soc.* **1982**, 104, 6668.
701. De Pascual Teresa, J.; Urones, J.G.; Fernandez, A. *Phytochemistry* **1983**, 22, 2753.
702. Bhatt, S.K.; Sthapak, J.K.; Singh, K.U. *Fitoterapia* **1984**, 55, 183; *Chem. Abstr.* **1985**, 102, 119402.
703. Bohlmann, F.; Zdero, C. *Phytochemistry* **1982**, 21, 2543.
704. Birgersson, G.; Schlyter, F.; Lofquist, J.; Bergström, G. *J. Chem. Ecol.* **1984**, 10, 1349.
705. Banthorpe, D.V.; Ekundayo, O.; Njar, V.C.O. *Phytochemistry* **1984**, 23, 291.
706. Brown, H.C.; Jadhav, P.K.; Desai, M.C. *J. Org. Chem.* **1982**, 47, 4583.
707. Martin, G.J.; Janvier, P.; Akoka, S.; Mabon, F.; Jurczak, J. *Tetrahedron Lett.* **1986**, 27, 2855.
708. Midland, M.M.; Petre, J.E.; Zderic, S.A.; Kazubski, A. *J. Am. Chem. Soc.* **1982**, 104, 528.
709. Min, Y.-F.; Zhang, B.-W.; Cao, Y. *Synthesis* **1982**, 875.
710. Brill, W.R. *J. Chem. Soc., Perkin Trans. 2* **1984**, 621.
711. Andrianome, M.; Delmond, B. *J. Chem. Soc., Chem. Commun.* **1985**, 1203.
712. Kashin, A.N.; Bakunin, V.N.; Beletskaya, I.P.; Reutov, O.A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1981**, 1180.
713. Araki, S.; Hatano, M.; Butsugan, Y. *J. Org. Chem.* **1986**, 51, 2126.
714. Lavallée, P.; Bouthillier, G. *J. Org. Chem.* **1986**, 51, 1362.
715. Bhaduri, S.; Mahandru, M.M.; Brit. Pat., 2,078,223, Appl. June 17, 1980; *Chem. Abstr.* **1982**, 95, 218066.
716. Nomura, M.; Fujihara, Y. *Kinki Daigaku Kogakubu Kenkyu Hokoku* **1980**, 14, 7; *Chem. Abstr.* **1981**, 95, 220152.

717. Dimitrov, D.; Sirakova, V.; Angelov, V.; Stefanova, R. *Khim. Ind. (Sofia)* **1984**, 56, 54.
718. Uemura, S.; Fukuzawa S.; Toshimitsu, A.; Okano, M. *Tetrahedron Lett.* **1982**, 23, 87.
719. Warpehoski, M.A.; Chabaud, B.; Sharpless, K.B. *J. Org. Chem.* **1982**, 47, 2897.
720. Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1980**, 21, 2417.
721. Mihelich, E.D.; Eickhoff, D.J. *J. Org. Chem.* **1983**, 48, 4135.
722. Barton, D.H.R.; Crich, D. *Tetrahedron* **1985**, 41, 4359.
723. Scheidl, F. *Synthesis* **1982**, 728; Ger. Offen., 3,143,226 and 3,143,227.
724. (a) Kane, B.J.; Marcelin, G.; Traynor, S.G. *J. Org. Chem.* **1980**, 45, 895. (b) Traynor, S.G.; Kane, B.J.; Coleman, J.B.; Cardenas, C.G. *ibid.* 900. (c) Kane, B.J.; Traynor, S.G. (SCM Chemicals); U.S. Pat., 4,289,917; *Chem. Abstr.* **1982**, 96, 6905.
725. Takayanagi, H.; Nishino, C. *Nippon Kagaku Kaishi* **1981**, 629; *Chem. Abst.* **1981**, 95, 94150.
726. Kulkarni, Y.S.; Snider, B.B. *J. Org. Chem.* **1985**, 50, 2809.
727. Snider, B.B.; Hui, R.A.H.F.; Kulkarni, Y.S. *J. Am. Chem. Soc.* **1985**, 107, 2194. See also Kulkarni, Y.S.; Burbaum, B.W.; Snider, B.B. *Tetrahedron Lett.* **1985**, 26, 5619.
728. Murthi, G.S.S.; Mazumder, A. *Indian J. Chem., Sect. B.* **1981**, 20, 339.
729. Najar, V.C.O.; Banthorpe, D.V. *J. Label. Comp. Radiopharm.* **1985**, 22, 615.
730. Stenström, Y.; Skattebøl, L. *Acta Chem Scand., Ser. B* **1980**, 34, 131.
731. Gibson, T.; Erman, W.F. *J. Am. Chem. Soc.* **1969**, 91, 4771.
732. Borden, W.T.; Lee, J.G.; Young, S.D. *J. Am. Chem. Soc.* **1980**, 102, 4841.
733. Akhila, A.; Banthorpe, D.V. *Phytochemistry* **1980**, 19, 1691.
734. Kadow, J.F.; Johnson, C.R. *Tetrahedron Lett.* **1984**, 25, 5255.
735. Fourneron, J.D.; Harwood, L.M.; Julia, M. *Tetrahedron* **1982**, 38, 693.
736. Maas, D.D.; Blagg, M.; Wiemer, D.F. *J. Org. Chem.* **1984**, 49, 853.
737. Escher, S.; personal communication.
738. Garst, J.E.; Wilson, B.J. In *Oxygen and Oxy-Radicals in Chemistry and Biology*; Rodgers, M.A.J.; Powers, E.L., Eds.; Academic: New York; 1981, p. 507.
739. Wilson, B.J.; Garst, J.E.; Linnalary, R.D.; Doster, A.R. In *Effects of Poisonous Plants on Livestock*, Keeler, R.R.; Van Kempen, K.R.; James, L.F., Eds.; Academic: New York; 1978, p. 311.
740. Koezuka, Y.; Honda, G.; Tabata, M. *Phytochemistry* **1986**, 25, 859.
741. Ahlgren, G.; Bergström, G.; Löfqvist, J.; Jansson, A.; Norin, T. *J. Chem. Ecol.* **1979**, 5, 309.
742. Subba Rao, G.S.R.; Ravindranath, B.; Sashi Kumar, V.P. *Phytochemistry* **1984**, 23, 399.
743. (a) Tanis, S.P. *Tetrahedron Lett.* **1982**, 23, 3115. (b) Tanis, S.P.; Herrinton, P.M. *J. Org. Chem.* **1983**, 48, 4572.
744. Araki, S.; Butsugan, Y. *Chem. Lett.* **1982**, 177; *Bull. Chem. Soc. Jpn.* **1983**, 56, 1446.
745. Baker, R.; Ekanayake, N.; Johnson, S.A. *J. Chem. Res. (S)* **1983**, 74.
746. Wenkert, E.; Mylari, B.L.; quoted in Stork, G. and Borch, R. *J. Am. Chem. Soc.* **1964**, 86, 936.
747. Wiley, R.A.; Choo, H.-Y.; McClellan, D.M. *J. Org. Chem.* **1983**, 48, 1106.
748. Burka, L.T.; Felice, T.J.; Jackson, S.W. *Phytochemistry* **1981**, 20, 647.
749. Kramp, W.; Bohlmann, F. *Liebigs Ann. Chem.* **1986**, 226.
750. Bernasconi, S.; Colombo, M.; Jommi, G.; Sisti, M. *Gazz. Chim. Ital.* **1986**, 116, 69.
751. Garst, J.E.; Wilson, B.J. *J. Agric. Food Chem.* **1984**, 32, 1083.
752. Jabri, N.; Alexakis, A.; Normant, J.F. *Tetrahedron* **1986**, 42, 1369.

753. Fleming, I.; Taddei, M. *Synthesis* **1985**, 898.
754. Sheffy, F.K.; Godschalx, J.P.; Stille, J.K. *J. Am. Chem. Soc.* **1984**, *106*, 4833.
755. Pillot, J.-P.; Benneteau, B.; Dunoguès, J.; Calas, R. *Tetrahedron Lett.* **1980**, *21*, 4717.
756. Baeckström, P.; Okecha, S.; de Silva, N.; Wijekoon, D.; Norin, T. *Acta Chem. Scand., Ser. B* **1982**, *36*, 31.
757. Tada, M.; Chiba, K.; Hashizume, T. *Agric. Biol. Chem.* **1982**, *46*, 819.
758. Poulter, C.D.; Wiggins, P.L.; Plummer, T.L. *J. Org. Chem.* **1981**, *46*, 1532.
759. Takano, S.; Morimoto, M.; Satoh, S.; Ogasawara, K. *Chem. Lett.* **1984**, 1261.
760. Thuillier, A.; Vialle, J. *Bull. Soc. Chim. Fr.* **1962**, 2182.
761. Okazaki, R.; Negishi, Y.; Inamoto, N. *J. Chem. Soc., Chem. Commun.* **1982**, 1055; *J. Org. Chem.* **1984**, *49*, 3819.
762. Mandai, T.; Takeshita, M.; Mori, K.; Kawada, M.; Otera, J. *Chem. Lett.* **1983**, 1909.
763. Stork, G.; Mook, Jr., R. *J. Am. Chem. Soc.* **1983**, *105*, 3720.
764. Watanabe, E.; Imai, N.; Inomata, K.; Kinoshita, H.; Kotake, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3225.
765. Wenkert, E.; Ferreira, V.; Hoffmann, M.; Kim, H.-S.; unpublished observations (personal communication from Wenkert, E.).
766. Nguyen Dinh L.; Schlosser, M. *Helv. Chim. Acta* **1977**, *60*, 2085.
767. Ismail, Z.M.; Hoffmann, H.M.R. *Angew. Chem. Int. Ed.* **1983**, *22*, 719.
768. Markwald, W. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2811.
769. (a) Robinson, R. *J. Chem. Soc.* **1938**, 1390. (b) Birch, A.J.; Jaeger, R.; Robinson, R. *J. Chem. Soc.* **1945**, 582.
770. Meier, L.; Scharf, H.-D. *Liebigs Ann. Chem.* **1986**, 731.
771. David, L.; Verschambre, H. *Tetrahedron Lett.* **1984**, *25*, 543.
772. Dimitriadis, E.; Williams, P.J. *Chem. Ind. (London)* **1984**, 108.
773. Naegeli, P., (Givaudan SA); Eur. Pat., EP 131,254; *Chem. Abstr.* **1985**, *103*, 53948.
774. Taiyo Perfumery Co.; Jpn. Kokai Tokkyo Koho, 82 82382, May 22, 1983; *Chem. Abstr.* **1983**, *97*, 216521.
775. Amouroux, R.; Folefoc, G.; Chastrette, F. Chastrette, M. *Tetrahedron Lett.* **1981**, *22*, 2259; cf. Klein, E. and Rjahn, W. *Tetrahedron* **1965**, *21*, 2353.
776. Carlsen, P.H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. *J. Org. Chem.* **1981**, *46*, 3936.
777. Wuts, P.G.M.; D'Costa, R.; Butler, W. *J. Org. Chem.* **1984**, *49*, 2582.
778. Lakey, F.N.; MacLeod, J.K. *Aust. J. Chem.* **1967**, *20*, 1943.
779. Jerris, P.J.; Smith III, A.B. *Tetrahedron Lett.* **1980**, *21*, 711.
780. Jackson, R.F.W.; Raphael, R.A. *Tetrahedron Lett.* **1983**, *24*, 2117.
781. Guthrie, A.E.; Semple, J.E.; Joullié, M.M. *J. Org. Chem.* **1982**, *47*, 2369.
782. Chen, K.M.; Joullié, M.M. *Tetrahedron Lett.* **1984**, *25*, 393.
783. (a) Sakurai, K.; Takahashi, K.; Yoshida, T. *Agric Biol. Chem.* **1983**, *47*, 1249. (b) Takasago Perfumery Co., Ltd.; Jpn. Kokai Tokkyo Koho, 57 130,981-983, Aug. 13, 1982; *Chem. Abstr.* **1983**, *98*, 54243.
784. Hoepfner, W.; Weyerstahl, P. *Liebigs Ann. Chem.* **1986**, 99.
785. Kaiser, R. *Helv. Chim. Acta* **1984**, *67*, 1198.
786. Maurer, B.; Hauser, A. *Tetrahedron Lett.* **1984**, *25*, 1061.

787. Góra, J.; Kaminska, J.; Smigiełski, K. *Pollena: Tluszcze, Srodki, Piorace Kosmet.* **1982**, 26, 32; *Chem. Abstr.* **1983**, 98, 132125.
788. Hegde, S.G.; Vogel, M.K.; Saddler, J.; Hinyo, T.; Rockwell, N.; Haynes, R.; Oliver, M.; Wolinsky, J. *Tetrahedron Lett.* **1980**, 21, 441.
789. Suzukamo, G.; Takano, T.; Tamura, M.; Ikimi K. (Sumitomo Chemical Co., Ltd.); Eur. Par. Appl., EP 21,769, Jan. 7, 1981; Jpn. Appl., JP 79 77,919, June 19, 1979; *Chem. Abstr.* **1981**, 95, 43412.
790. Góra, J.; Smigiełski, K.; Zachara, A.; Socha, A.; Szelejewski, W.; Brud, W.; Pilecki, M.; Wolinsky, A.; Pol. Pat., 119,185; *Chem. Abstr.* **1983**, 99, 176103.
791. Ohloff, G.; Giersch, W.; Schulte-Elte, K.H.; Enggist, P.; Demole, E. *Helv. Chim. Acta* **1980**, 63, 1582.
792. Hoffmann, W. (BASF); Ger. Offen., DE 3,150,234, June 30, 1983; *Chem. Abstr.* **1983**, 99, 122709.
793. Hasegawa, T. Co. Ltd.; Jpn. Kokai Tokkyo Koho, JP 80 55,126; *Chem. Abstr.* **1980**, 93, 239702.
794. Torii, S.; Inokuchi, T.; Oi, R. *J. Org. Chem.* **1982**, 47, 47.
795. Cohen, T.; Lin, M.-T. *J. Am. Chem. Soc.* **1984**, 106, 1130.
796. Snowden, R.L.; Muller, B.L.; Schulte-Elte, K.H. *Tetrahedron Lett.* **1982**, 23, 335.
797. Audin, P.; Doutheau, A.; Gore, J. *Bull. Soc. Chim. Fr.* **1984**, 297.
798. Yamato, T.; Nakamura, M.; 7th International Congress Essential Oils, Tokyo, 1977, Abstracts p. 287; *Chem. Abstr.* **1980**, 92, 129093.
799. Takano, S.; Masuda, K.; Ogasawara, K. *Heterocycles* **1981**, 16, 1509.
800. Toyotama Perfumery Co., Ltd.; Jpn. Kokai Tokkyo Koho, JP 59 29860; *Chem. Abstr.* **1984**, 101, 90762.
801. Romanov, N.A.; Kantor, E.A.; Musavirov, R.S.; Karakhanov, R.A.; Rakhmankulov, D.L. *Zh. Org. Khim.* **1981**, 17, 1762.
802. Liu, C.T.; Chang, C.H.; Chou, T.L. *J. Heterocycl. Chem.* **1984**, 21, 129.
803. Ho, T.-L.; Din, Z.U. *Synth. Commun.* **1982**, 12, 1099.
804. Ismail, Z.M.; Hoffmann, H.M.R. *Angew Chem. Int. Ed.* **1982**, 21, 859.
805. Maurer, B.; Hauser, A.; 9th International Congress on Essential Oils, Singapore, 1983, Proceedings, Vol 3, p. 69.
806. Bach, J.S.; Brandenburg Concertos n° 4 BWV 1049 and n° 5 BWV 1050, C.F. Peters, Leipzig, 1850.

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