# The Total Synthesis of Natural Products

VOLUME 5

Edited by

John ApSimon

*Ottawa–Carleton Institute for Research and Graduate Studies in Chemistry*

*and*

*Department of Chemistry*
*Carleton University, Ottawa*

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# Preface

The art and science of organic synthesis has come of age. This is nowhere more apparent than in the synthetic efforts reported in the natural products area and summarized in the first four volumes of this series.

This present volume describes the synthetic activities reported for a 10-year period only in the sesquiterpene field—evidence enough for the successful efforts of the synthetic organic chemist in recent years. Professor Clayton Heathcock and his colleagues have produced a masterly, timely and important contribution, the breadth of which necessitates a complete volume in the series.

The sixth volume in this series is in an advanced stage of preparation and will contain updating chapters on the subject matter included in the first two volumes together with a description of synthetic efforts in the macrolide field. A seventh volume, covering diterpene synthesis, is in preparation.

JOHN APSIMON

*Ottawa, Canada*
*October 1982*

# Contents

# Total Synthesis of Sesquiterpenes, 1970-79

CLAYTON H. HEATHCOCK, SAMUEL L. GRAHAM, MICHAEL C. PIRRUNG, FRANK PLAVAC, AND CHARLES T. WHITE

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## 1. INTRODUCTION

The first total synthesis of a sesquiterpene was Ruzicka's farnesol synthesis, communicated in 1923.[1] In Volume 2 of this series, we reviewed the sesquiterpene total syntheses which had been published since that time, up to the middle of 1970.[2] That review, covering a 47-year period and including about 300 papers, required 361 pages. In the intervening decade since our initial survey of the field there has been a veritable explosion of activity. In this chapter, we review a further 533 papers dealing with the total syntheses of over 260 different sesquiterpenes. We have made an effort to include all papers dealing with sesquiterpene total synthesis which appeared in the literature through the end of 1979. In addition, we have added a few papers which were inadvertently omitted from the first installment of this review, and have included a few which were either published while the review was under preparation during 1980 or were communicated to us in the form of preprints during that time. Although some of the 1970-1979 papers are improved routes to molecules previously prepared by total synthesis, most of them are new.

The general organization of the earlier review[2] has been followed, with some modification. In general, we have grouped the syntheses according to the number of carbon rings: acyclic, monocyclic, bicyclic, and tri- and tetracyclic. Compounds containing a cyclopropane ring are generally included with the class which would contain the molecule with the cyclopropane ring absent. This arbitrary decision has been made since many of these syntheses are simple extensions of syntheses of a parent with addition of the cyclopropane ring being an additional terminal step. In addition, the review now includes a separate section for sesquiterpene alkaloids.

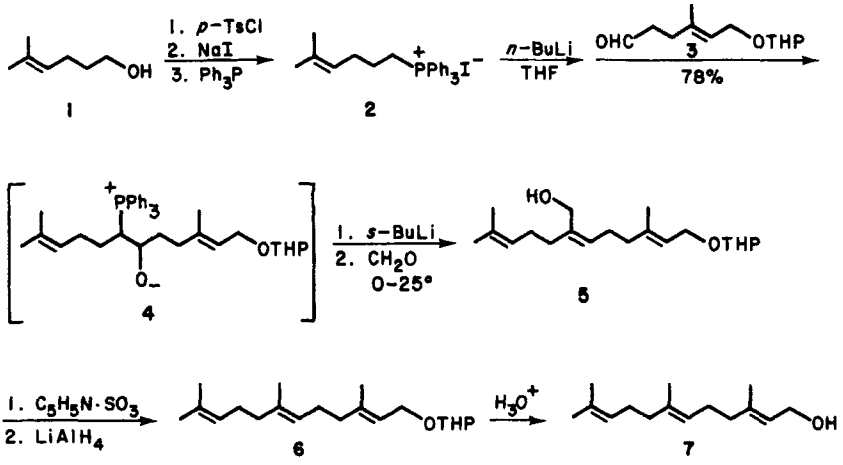
As before, not all relay total syntheses are included. The general rule of thumb is that a relay synthesis is included only if the final product differs in carbon skeleton from the starting material. Thus, conversion of santonin into a germacrane or elemane would be included, but conversion into another eudesmane would not. The core of the review is the flow charts, which outline the syntheses. We have described the syntheses in words, sometimes rather succinctly and sometimes in more detail. We have attempted to point out novel chemistry or unusual synthetic strategy and have sometimes offered a brief critique of the synthesis.

One of the most interesting aspects of a field such as sesquiterpene synthesis is comparison of the various strategies which different workers have employed for a given target. Consequently, we have been more verbose in discussing such comparative syntheses in several cases, such as occidentalol, the vetivanes, the acoranes, the pseudoguaianolides, vernolepin, gymnomitrol, and dendrobine. For the purpose of comparing the efficiency of different syntheses, we generally use the criteria of number of steps, overall yield, and the number of isomer separations required in the synthesis.

## 2. ACYCLIC SESQUITERPENES

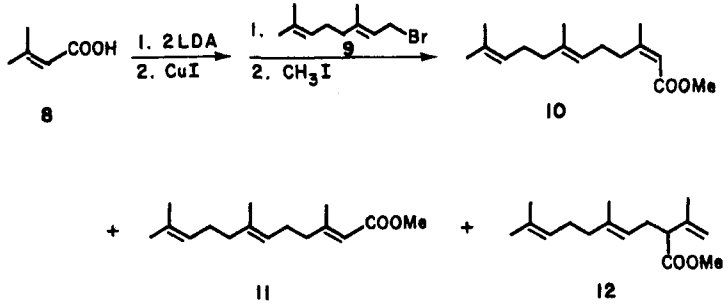
### A. Farnesol and Farnesene

Corey and Yamamoto have reported the elegant synthesis of *trans,trans*-farnesol which is outlined in Scheme 1.[3] The synthesis features a method for stereospecific synthesis of olefins from β-oxido phosphonium ylides and aldehydes.[4] Thus, the phosphorane derived from salt **2** is treated first with aldehyde **3** at low temperature to give the β-oxido phosphonium salt **4**, which is deprotonated and treated with formaldehyde to obtain allylic alcohol **5**, uncontaminated by the *trans,cis*-diastereomer. The allylic hydroxyl is removed by the reduction of the bisulfate ester and the terminal hydroxyl is deprotected to obtain farnesol (**7**).




Scheme 1. Corey-Yamamoto Synthesis of Farnesol

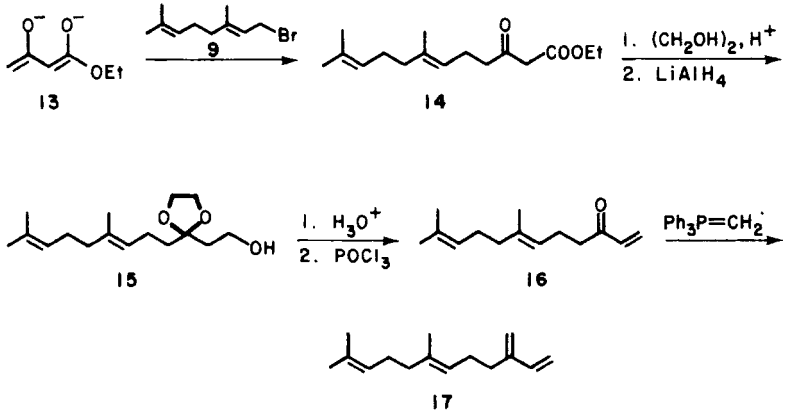
Pitzele, Baran, and Steinman, of Searle Laboratories in Chicago, have studied the alkylation of the dianion of 3-methylcrotonic acid (**8**), with geranyl bromide (Scheme 2).[5] After addition of the geranyl bromide,




Scheme 2. Searle Synthesis of Methyl Farnesate

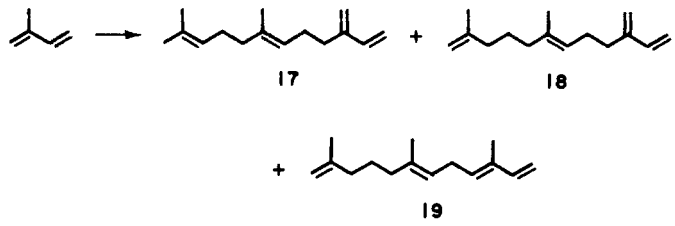
methyl iodide is added to obtain the methyl esters. Isomers **10**, **11**, and **12** are obtained in a ratio of 2.3:2.1:1.0; methyl farnesate (**11**) of 89% isomeric purity may be obtained by low pressure chromatography in 26% yield, based on geraniol.

O. P. Vig and co-workers report a synthesis of β-farnesene (**17**) wherein the dianion of acetoacetic ester is alkylated with geranyl bromide and the resulting β-keto ester transformed into a butadiene unit as shown in Scheme 3.[6] It is not quite clear from their paper just what they synthesized, since both geraniol and β-farnesene are depicted as having *Z* double bonds.




Scheme 3. Vig's Synthesis of β-Farnesene

Otsuka and his co-workers at Osaka University have reported the most direct sesquiterpene synthesis yet—direct trimerization of isoprene (Scheme 4).[7] Several catalysts were found which give a preponderance of the linear trimers **17-19**. The best system for production of β-farnesene

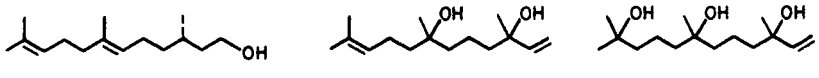



Scheme 4. Otsuka's β-Farnesene Synthesis

(**17**) utilizes $[NiCl(\eta_3\text{-}C_3H_5)]_2\text{-}As(n\text{-}C_6H_{13})_3$ and *t*-BuOK. If the reaction is stopped at 30% conversion of the isoprene, β-farnesene comprises 57% of the product. Unfortunately, preparative glpc is required to separate **17** from its isomers.

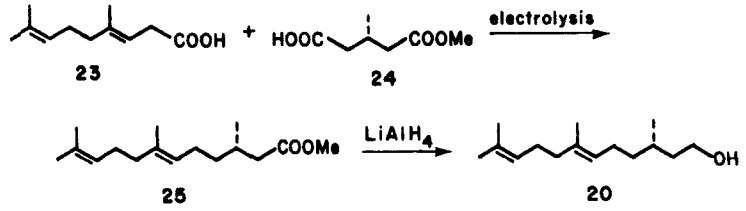
## B. Terrestrol, Caparrapidiol, and Caparrapitriol

Terrestrol, (3*S*)-2,3-dihydrofarnesol (**20**), is the marking perfume of the small bumble bee. Caparrapidiol (**21**) and caparrapitriol (**22**) are plant sesquiterpenes which contain centers of chirality.



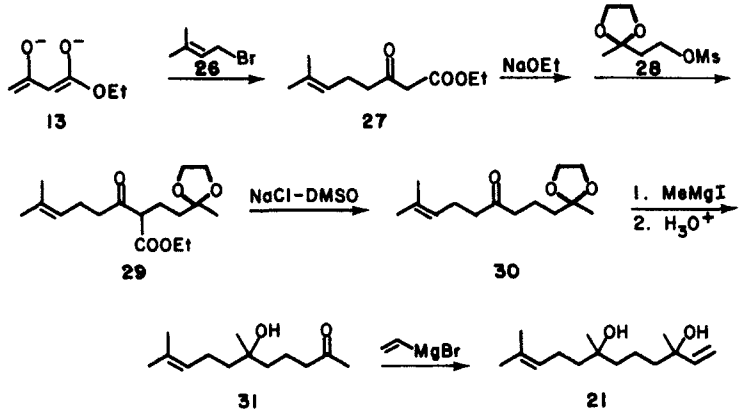

20 21 22

Ahlquist and Ställberg-Stenhagen of the University of Göteborg in Sweden have synthesized both enantiomers of terrestrol by way of the Kolbe electrolysis of homogeranic acid (**23**) with the enantiomers of monomethyl 3-methylglutarate (**24**, Scheme 5).[8] Ester **25** is obtained in 8% yield, based on homogeranic acid.



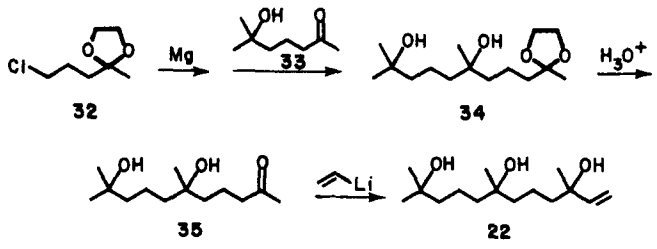

Scheme 5. Ahlquist-Ställberg-Stenhagen Synthesis of Terrestrol

A synthesis of caparrapidiol by O. P. Vig is summarized in Scheme 6.[9] The question of diastereoisomerism in the formation of **21** is not addressed by the authors, who simply state that "...The identity of the synthesized compound was established by comparing its IR and NMR (spectra) with those reported in literature."




Scheme 6. Vig's Carrapidiol Synthesis

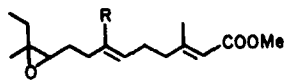
Weyerstahl and Gottschalk, at the Technical University of Berlin, have synthesized caparrapitriol as shown in Scheme 7.[10] As in the Vig synthesis of caparripidiol, the German group makes no mention of a diastereomeric mixture in the addition of vinyllithium to methyl ketone **35**. However, in this case the final triol is obtained as a sharp-melting solid (mp 78-79°C) in 90% yield! Chromatography on starch provides one pure enantiomer of caparripitriol.




Scheme 7. Weyerstahl-Gottschalk Synthesis of Caparrapitriol

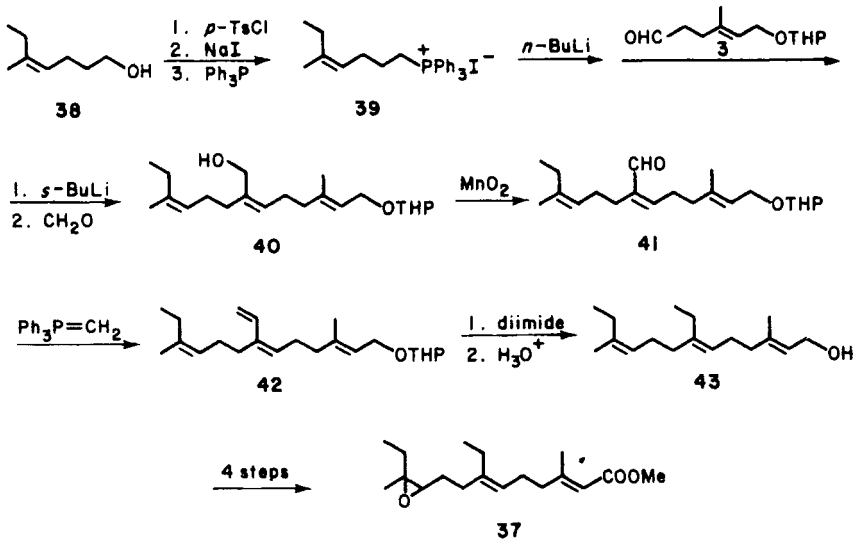
## C. Juvenile Hormones

The $C_{17}$- and $C_{18}$-*Cecropia* juvenile hormones (**36** and **37**) (JH), although not sesquiterpenes, are included because their structures are so similar to those of the acyclic sesquiterpenes. Although **37** was not characterized until 1967 and **36** until 1968, a total of 15 syntheses had been reported by 1972.




**36**: R = Me
**37**: R = Et

Corey and Yamamoto have utilized the β-oxidophosphonium ylide method for the synthesis of both $C_{17}$- and $C_{18}$-JH, as shown in Scheme 8.[3] Intermediate **40** is converted via aldehyde **41** into tetraene **42**, which

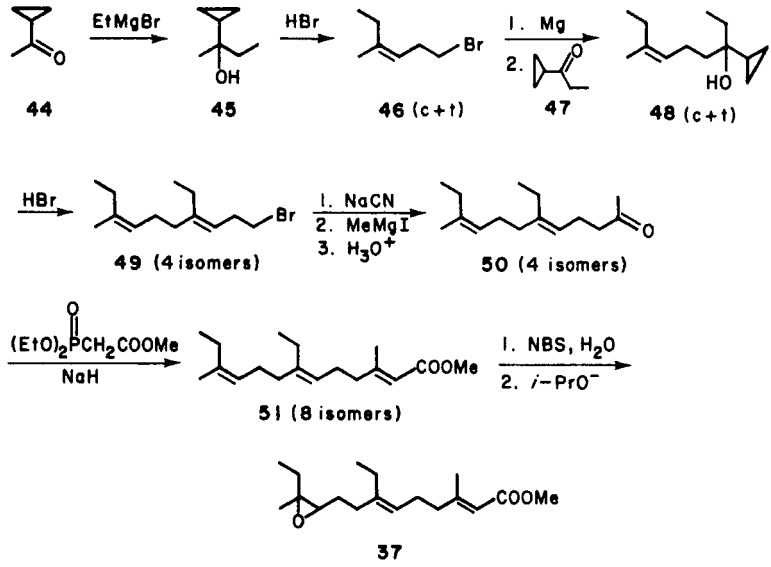



Scheme 8. Corey-Yamamoto Synthesis of Juvenile Hormones

is selectively reduced to obtain alcohol **43**. This material has previously been converted into $C_{18}$-JH.[11] The $C_{17}$-JH **36** is prepared from **40** along the same lines as are used to convert alcohol **5** into farnesol (see Scheme 1).

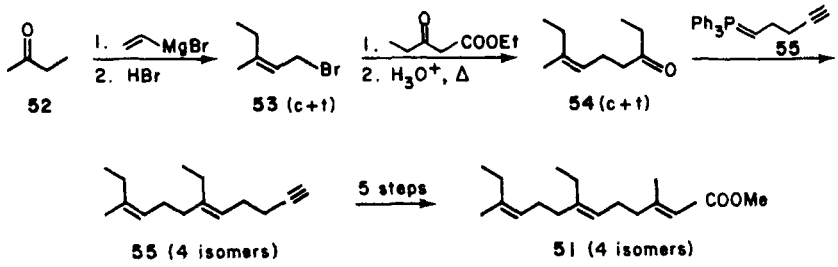
Findlay and MacCay at New Brunswick, and Bowers at the Agriculture Research Service in Beltsville have reported full details of stereorandom syntheses of both **36** and **37**.[12a] Their $C_{18}$-JH synthesis had previously been published in preliminary form and was discussed in Volume 2 of this series.[12b] The New Brunswick-Beltsville $C_{17}$-JH synthesis is essentially the same as the Schering synthesis of $C_{17}$-JH.[13]

Cochrane and Hanson of the University of Sussex have reported two $C_{18}$-JH syntheses.[14] Their first, summarized in Scheme 9, is modeled closely on the Julia nerolidol synthesis.[15] Bromide **46** is obtained as a 3:1




Scheme 9. Juvenile Hormone: Sussex Synthesis A

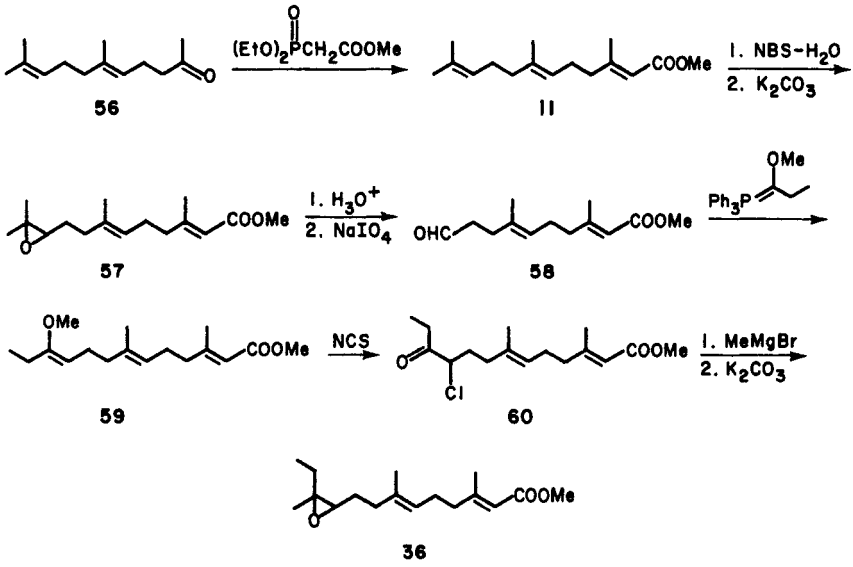
mixture favoring the unnatural E stereoisomer. The second cyclopropyl carbinol solvolysis (**48**→**49**) also produces a bad stereoisomer mixture, giving 59% of *3E* and 41% of *3Z* compounds. Analysis at the stage of dienone **50** showed the *ZZ*, *ZE*, *EZ*, and *EE* stereoisomers to be present in a ratio of 16:43:11:30. A final Horner-Wadsworth-Emmons olefination (**50**→**51**) affords a mixture of all eight stereoisomers, of which the natural *EEZ* isomer is less than 10%. The Sussex group also reports a somewhat more stereoselective synthesis (Scheme 10). The starting unsaturated bromide **53** is prepared as a 3:1 mixture favoring the




Scheme 10. Juvenile Hormone: Sussex Synthesis B

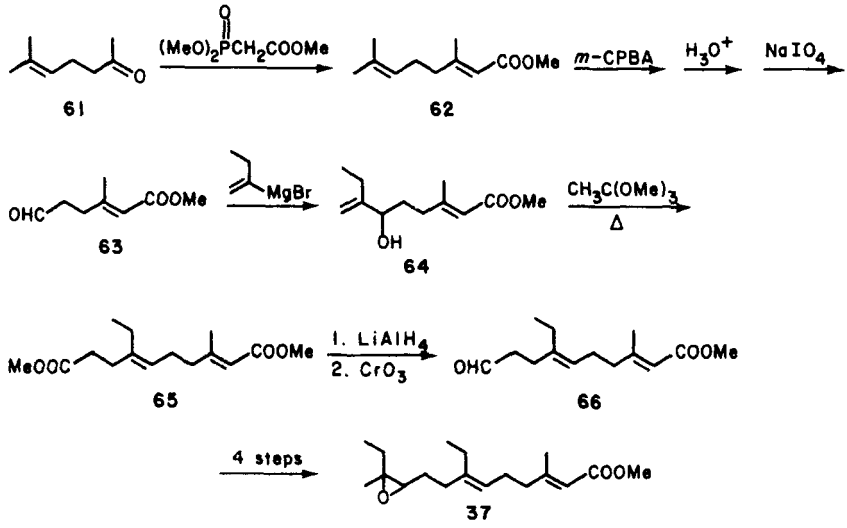
undesired *E* stereoisomer. The second double bond is introduced by a Wittig reaction, which proceeds in an essentially stereorandom fashion, as expected. The final double bond is introduced by the Corey procedure.[16] Analysis of ester **51** showed it to be an approximately equimolar mixture of the four stereoisomers having *2E* stereochemistry. The desired isomer comprised 22% of the mixture.

A Zoecon group headed by C. A. Henrick has prepared the $C_{17}$-JH from *trans*-geranylacetone (**56**) as shown in Scheme 11.[17] This substance is converted into methyl farnesate (**11**), which is then degraded to aldehyde **58**. The epoxide moiety is introduced via chloroketone **60** by a method adapted from Johnson's earlier $C_{18}$-JH synthesis.[18] Since this synthesis starts with *trans*-geranylacetone (**56**), the $C_6$ double bond is homogenous. The $C_2$ linkage is established in the Wadsworth-Emmons reaction. The reaction gives a 2:1 mixture favoring the desired *2E* stereoisomer which is obtained in pure form by distillation. Although the Stanford group originally reported that the epoxide construction occurs with 92% stereoselectivity,[18] Henrick and co-workers were only able to obtain **36** as an 82:18 mixture with its $C_{10}$-$C_{11}$ trans isomer.



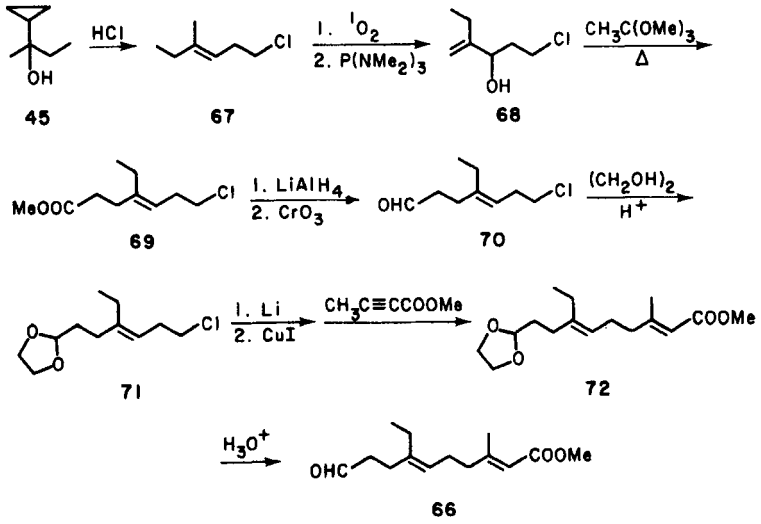

Scheme 11. Zoecon Synthesis of $C_{17}$-JH

The Zoecon group has reported two methods for synthesis of $C_{18}$-JH.[19] The first (Scheme 12) begins with methylheptenone (**61**), which is converted into methyl geranate (**62**). Although this reaction shows only modest stereoselectivity, the *2E* stereoisomer is conveniently isolated in pure form by distillation of the crude product. The terminal double bond is cleaved and the resulting aldehyde is treated with the Grignard reagent derived from 2-bromo-l-butene to obtain allylic alcohol **64**. The $C_6$ double bond stereochemistry is established by Claisen rearrangement (96% stereoselectivity). After selective reduction of the saturated ester function, the synthesis is completed as in Scheme 11. Again, the final hormone is obtained as an 82:18 mixture of cis and trans isomers.




Scheme 12. First Zoecon Synthesis of $C_{18}$-JH

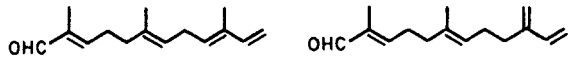
The second Zoecon synthesis (Scheme 13) starts with cyclopropyl carbinol **45**, which is solvolyzed to unsaturated chloride **67** as a 3:1 mixture of *E* and *Z* isomers. The mixture of isomers is oxidized by singlet oxygen to obtain allylic alcohol **68** as the major product of a 55:39:6 mixture of isomers. After separation of the mixture, **68** is subjected to Claisen rearrangement using the orthoacetate method to obtain chloroester **69**. As usual, the stereoselectivity in this reaction is excellent, only 4% of the *Z* stereoisomer is produced. The $C_2$-$C_3$ double bond geometry is established by adding the cuprate derived from **71** to methyl 2-butynoate to obtain **66**.




Scheme 13. Second Zoecon Synthesis of $C_{18}$-JH

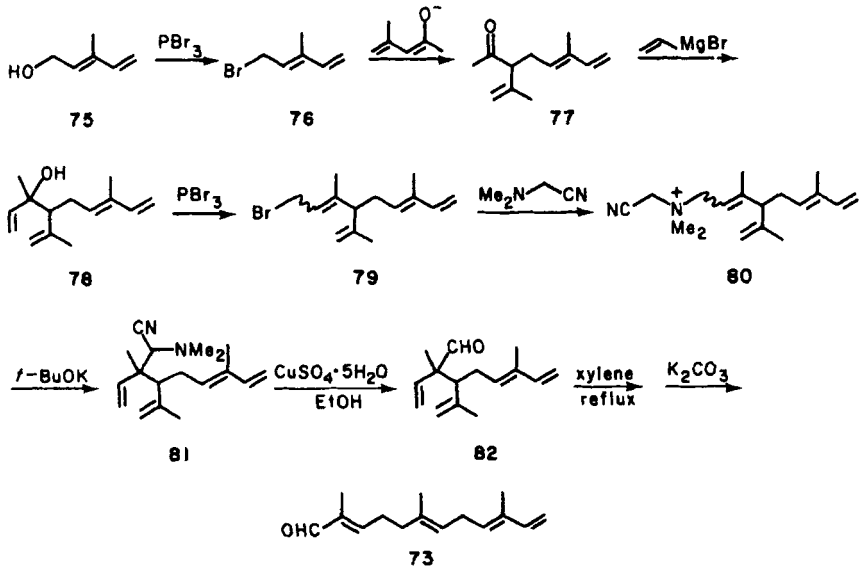
## D. Sinensals

The sesquiterpene aldehydes $\alpha$- and $\beta$-sinensal (**73** and **74**) are important contributors to the aroma and taste of Chinese orange oil. Büchi and




**73** **74**

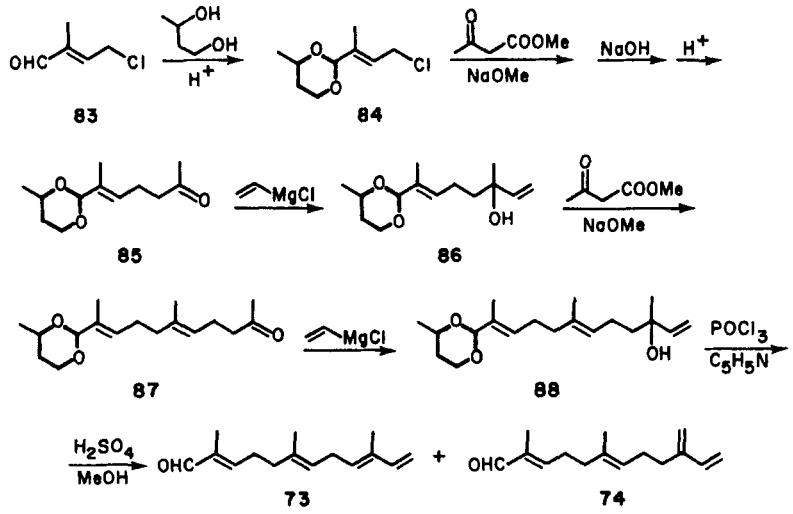
Wuest have reported the stereorational synthesis of the $\alpha$ isomer (**73**) which is outlined in Scheme 14.[20] The stereochemistry of the $C_9$ double bond is assured by the use of the diene alcohol **75** as the starting




Scheme 14. Büchi's $\alpha$-Sinensal Synthesis

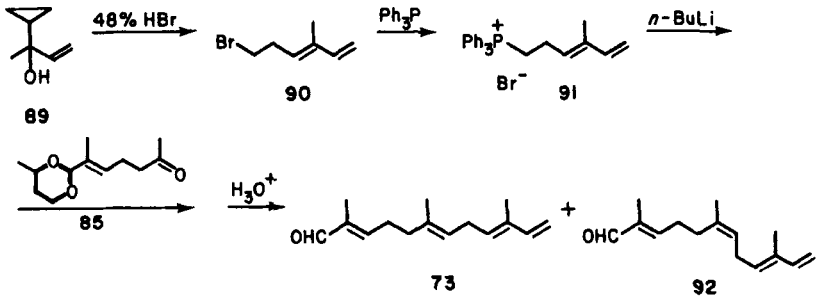
material. The synthesis features a novel [2,3]-sigmatropic rearrangement of the ammonium ylide derived from **80** to form amino nitrile **81** (3:2 mixture of diastereomers). Stereochemistry at the $C_6$ double bond is established in the final Cope rearrangement; **73** and its *2Z* diastereomer are produced in a 2:3 ratio. The latter isomer is quantitatively isomerized to the more stable *2E* isomer **73** by heating with potassium carbonate.

A BASF group headed by Werner Hoffmann has reported a synthesis which affords a mixture of the two sinensals, as well as modifications which allow the production of either pure isomer.[21] The first synthesis (Scheme 15) begins with chloroaldehyde **83**, which contains the eventual $C_2$ double bond. The chain is elaborated to **88** by two cycles of the basic Nazarov-Ruzicka-Isler synthesis (vinyl Grignard, Carroll reaction).[22]



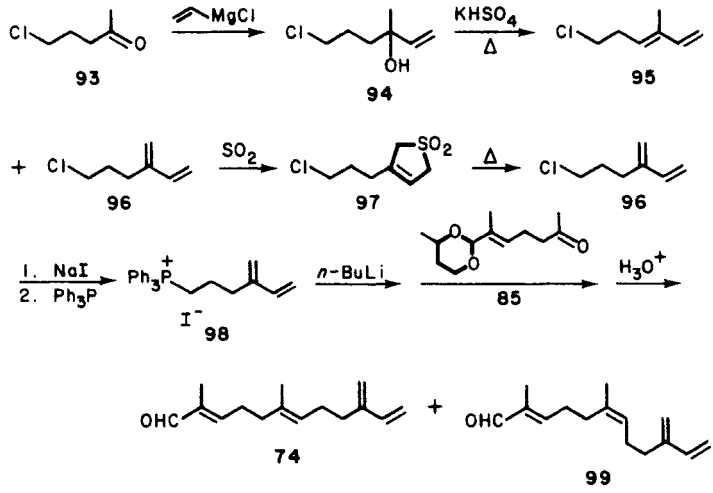

Scheme 15. First BASF Synthesis of Sinensals

Dehydration of **88**, followed by deprotection of the aldehyde affords $\alpha$- and $\beta$-sinensals in a ratio of 2:1. The *E*/*Z* ratio at the $C_9$ double bond in **73** is not stated. A modified synthesis which yields no $\beta$-sinensal is shown in Scheme 16. The $C_7$-$C_{12}$ segment is assembled as shown, using



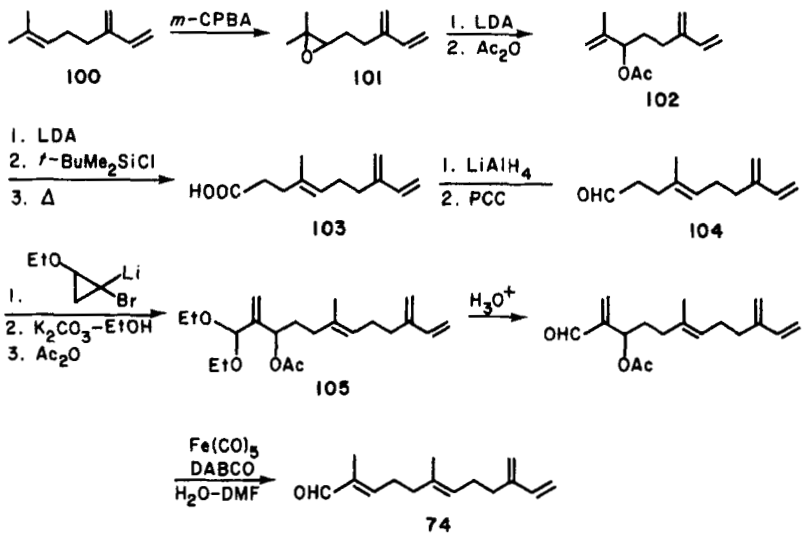

Scheme 16. BASF Synthesis of Pure $\alpha$-Sinensal

the Julia method. Bromo diene **90** is obtained as an 85:15 mixture of stereoisomers favoring the desired *E* isomer. The final Wittig coupling affords α-sinensal (**73**) as a 1:1 mixture with its $C_6$ diastereomer **92**. The other BASF modification (Scheme 17) leads to β-sinensal (**74**), uncontaminated by α-sinensal, again as a 1:1 mixture with the $C_6$-diastereomer (**99**). The required bis-unsaturated halide **96** is isolated from a 7:3 mixture of **95** and **96** by formation of the sulfolene **97**. The remainder of the synthesis follows the same lines as are used to prepare the α isomer.



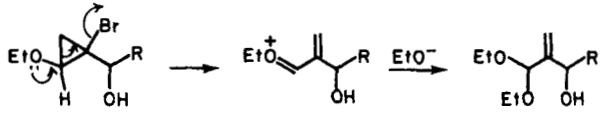

Scheme 17. BASF Synthesis of Pure β-Sinensal

A final synthesis of β-sinensal, from Hiyama's group in Kyoto, is summarized in Scheme 18.[23] The synthesis starts with myrcene, a frequently-used precursor for the preparation of β-sinensal. After oxidation of the more reactive trisubstituted double bond, epoxide **101** is subjected to Crandall-Rickborn isomerization to an allylic alcohol, which is




Scheme 18. Hiyama Synthesis of β-Sinensal

acetylated and subjected to Claisen rearrangement to obtain **103**, apparently with good stereoselectivity. The terminal unsaturated aldehyde function is introduced by a method developed in Hiyama's group, whereby the carbanion derived from 1,1-dibromo-2-ethoxycyclopropane is added to aldehyde **104** at low temperature (-95°C). The resulting adduct (**106**) is solvolyzed in basic ethanol to obtain the unsaturated acetal:

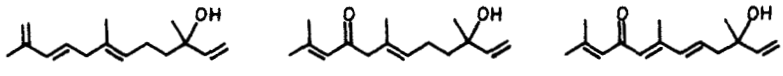



106

The synthesis of β-sinensal is completed by reductive removal of the acetoxy function, which occurs with double bond isomerization to the more stable position.

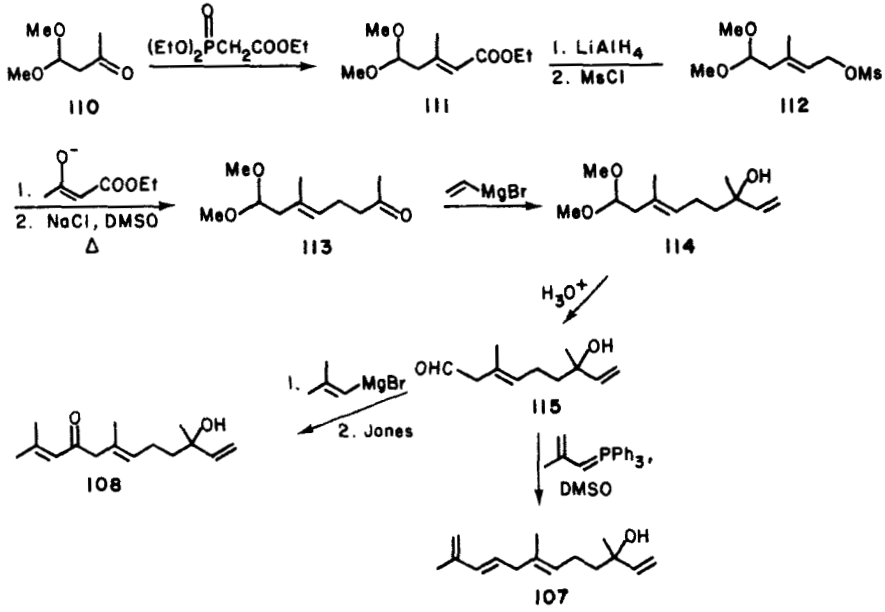
## E. Fokienol, Oxonerolidol, and Oxodehydronerolidol

Fokienol (**107**), 9-oxonerolidol (**108**), and 9-oxo-5,8-dehydronerolidol (**109**) are relatives of the simpler nerolidol.[24] Fokienol is a stereochemically more complex problem than is nerolidol, since it may exist as four racemates.



107 108 109

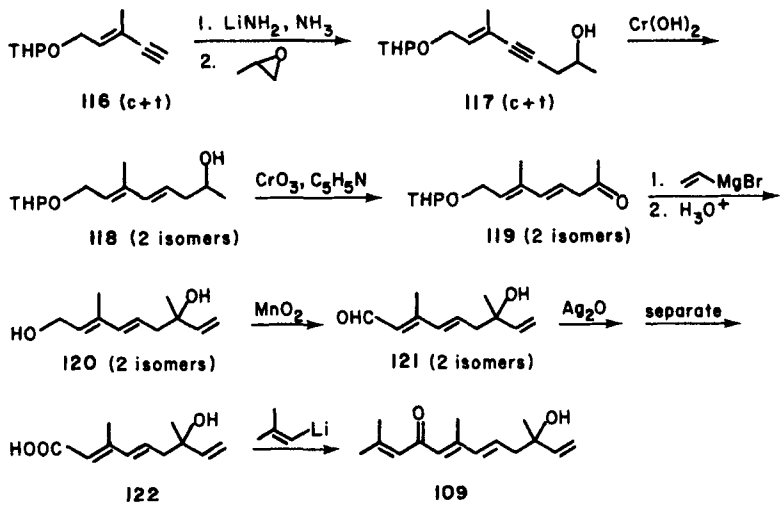
O. P. Vig's synthesis of racemic fokienol is outlined in Scheme 19.[25] The synthesis begins with a Wadsworth-Emmons reaction of keto acetal **110**, which affords unsaturated ester **111** as a 60:40 mixture of *E* and *Z*




Scheme 19. Vig's Synthesis of Fokienol and Oxonerolidol

stereoisomers. Vig separates the mixture and carries on only with the correct 2*E* diastereomer, which is elaborated by straightforward steps into aldehyde **115**. The most impressive step in this synthesis is the Wittig reaction on the $\beta,\gamma$-unsaturated aldehyde **115**, which is reported to occur stereospecifically, in good yield, and without enolization or prior conjugation of the unsaturated aldehyde, to give **107**. Aldehyde **115** is converted into oxonerolidol (**108**) by Grignard addition and oxidation.

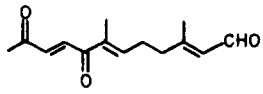
Bohlmann and Krammer have synthesized 9-oxo-5,8-dehydronerolidol (**109**) as shown in Scheme 20.[26] The synthesis starts with the protected unsaturated alcohol **116**, which was used as a mixture of cis and trans isomers. The eventual $C_5$ double bond is established by reduction of acetylene **117** by chromous hydroxide. The mixture of $C_7$ stereoisomers is separated by chromatography after preparation of acid **122**. The synthesis is completed by reaction of the correct stereoisomer with 2-methyl-1-propenyllithium.




Scheme 20. Bohlmann-Krammer Synthesis of 9-Oxo-5,8-dehydronerolidol

## F. Gyrindal

The norsesquiterpene gyrindal (**123**) is a defense secretion of the whirligig water beetle. Its synthesis has been reported by Meinwald, Opheim, and Eisner, of Cornell[27] and by Miller, Katzenellenbogen, and Bowles,

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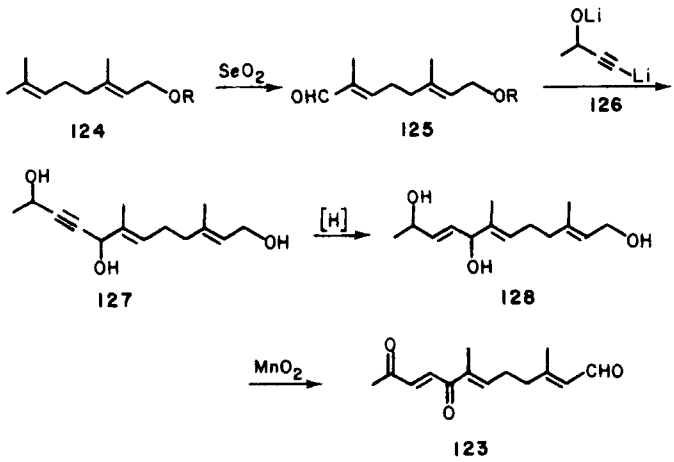
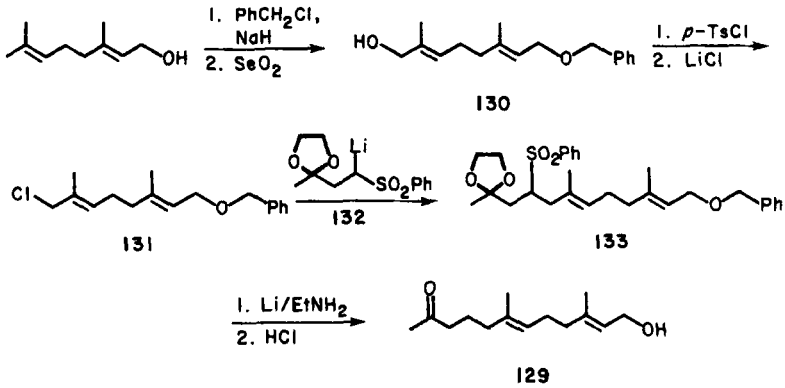
of Illinois.[28] The two syntheses, which are essentially identical, are outlined in Scheme 21. They differ only in the protecting group used for geraniol—the Cornell group employed the acetate whereas the Illinois group used the mesitoate—and in the method used for reducing the triple bond—the Cornell group used $Li/NH_3$ whereas the Illinois group used $LiAlH_4$—NaOMe. The Illinois team reports a much higher overall yield (9.6% vs. 1.7%).




Scheme 21. Synthesis of Gyrindal

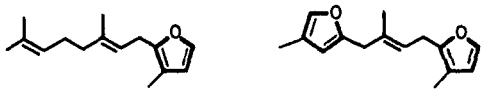
Kato et al., have described the synthesis of oxocrinol (**129**),[29] a norsesquiterpene from marine algae (Scheme 22). The synthesis is conceptually identical to the synthesis of geranylgeraniol by Altman, Ash, and Marson.[30] Altman's (*E,E*)-allylic chloride **131** was coupled with sulfone anion **132**. After reductive cleavage of the sulfone moiety and deprotection, oxocrinol (**129**) was obtained in 18% overall yield.




Scheme 22. Kato's Synthesis of Oxocrinol

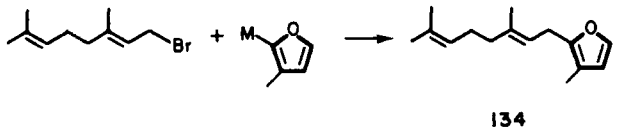
## G. Sesquirosefuran and Longifolin

Sesquirosefuran (**134**) and longifolin (**135**) are the first 2,3-substituted furans in the sesquiterpene series. Sesquiterpene **134** has been prepared by three groups.[31-33] All three syntheses rely on coupling geranyl



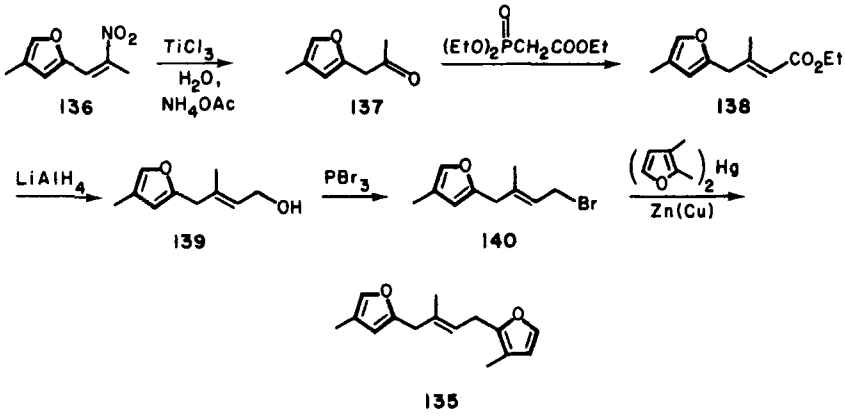

134 135

bromide with a 3-methyl-2-furylmetallic reagent (Scheme 23). The exact reagents employed have been the furyllithium,[31] the *bis*-furylmercury,[32] and the furylmagnesium bromide.[33] The highest coupling yield (40%) is




Scheme 23. Synthesis of Sesquirosefuran

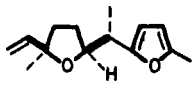
reported for the furyllithium reagent. A related synthesis of longifolin (**135**) is outlined in Scheme 24.[34] The final coupling proceeds in only 4% yield.




Scheme 24. Synthesis of Longifolin

## H. Davanafurans

The davanafurans (**141-144**) are a set of stereoisomeric farnesene derivatives which contribute to the characteristic odor of Davana oil. The principal component is isomer **141**. Thomas and Dubini have synthesized



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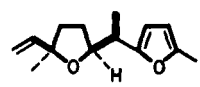

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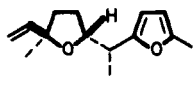

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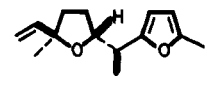

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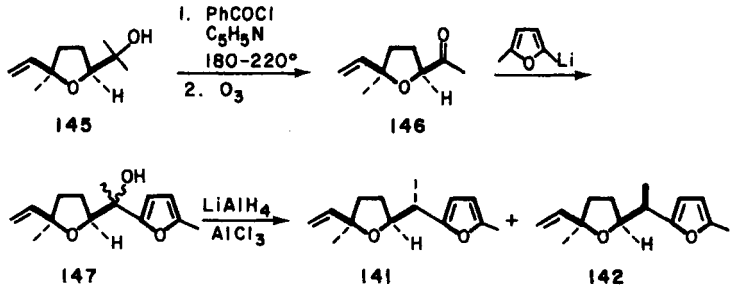
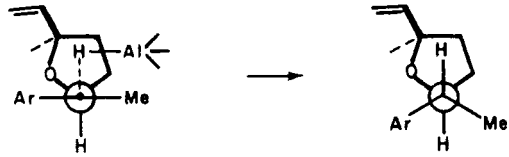
the four isomers starting with linalool oxides of known stereochemistry.[35] The synthesis of isomers **141** and **142** is summarized in Scheme 25. The (−)-*cis*-linalyl oxide **145** is converted by standard methods into the cis ketone **146**, which is treated with 5-methyl-2-furyllithium to obtain a mixture of unstable tertiary alcohols. The alcohol mixture is hydrogenolyzed using $LiAlH_4$-$AlCl_3$ to obtain a mixture of **141** and **142** in a ratio of 4:1. Similar transformation of (+)-*trans*-linalyl oxide affords

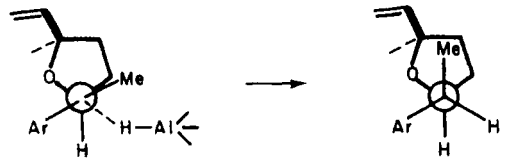



Scheme 25. Thomas-Dubini Synthesis of Davanafurans

**143** and **144** in a ratio of 3:1. Although the absolute stereostructures of the davanafuran group are established by their synthesis from linalool of known absolute configuration, the relative stereochemistry within the cis and trans pairs is still open to question. That is, does the major natural diastereomer correspond to **141** or **142**? The major product of the reduction shown in Scheme 25 is identical with the major natural davanafuran. Thomas and Dubini argue that the major product in this reduction should have structure **141** on the basis of transition state **148**. However, the alternate formulation **149**, which leads to **142**, would seem to be more consistent with the Cram-Felkin model for asymmetric induction.




148 141

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## I. Dendrolasin, Neotorreyol, Torreyal, Ipomeamarone, Freelingyne, and Dihydrofreelingyne

The common structural unit in this group of sesquiterpenes is the β-substituted furan ring. Several syntheses of dendrolasin (**150**), neotorreyol (**151**), torreyal (**152**), and ipomeamarone (**153**) were recorded in our original review.[36] The first three present the challenge of double bond stereochemistry. In ipomeamarone there is the similar problem of achieving cis,trans selectivity about the tetrahydrofuran ring. Freelingyne (**154**) and dihydrofreelingyne (**155**) are much more challenging synthetic targets. In addition to their highly unsaturated nature, both