# 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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# Contributors to Volume 5

Samuel L. Graham, Department of Chemistry, University of California, Berkeley Clayton H. Heathcock, Department of Chemistry, University of California, Berkeley

Michael C. Pirrung, Department of Chemistry, University of California, Berkeley Frank Plavac, Department of Chemistry, University of California, Berkeley Charles T. White, Department of Chemistry, University of California, Berkeley \_\_\_\_

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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 \_\_\_\_

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# Total Synthesis of Sesquiterpenes, 1970-79

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

Department of Chemistry, University of California, Berkeley, California

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# 1. INTRODUCTION

The first total synthesis of a sesquiterpene was Ruzicka's farnesol synthesis, communicated in 1923.<sup>1</sup> 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.<sup>2</sup> 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<sup>2</sup> 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.

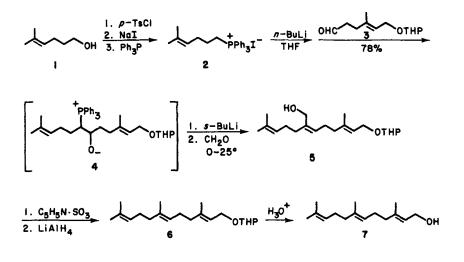
As before, not all relay total syntheses are included. The general rule of thumb is that a relay synthesis is included only if the final product differs in carbon skeleton from the starting material. Thus, conversion of santonin into a germacrane or elemane would be included, but conversion into another 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

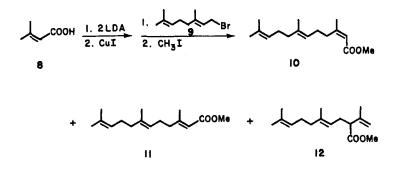
### A. Farnesol and Farnesene

Corey and Yamamoto have reported the elegant synthesis of *trans, trans*-farnesol which is outlined in Scheme 1.<sup>3</sup> The synthesis features a method for stereospecific synthesis of olefins from  $\beta$ -oxido phosphonium ylides and aldehydes.<sup>4</sup> Thus, the phosphorane derived from salt 2 is treated first with aldehyde 3 at low temperature to give the  $\beta$ -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

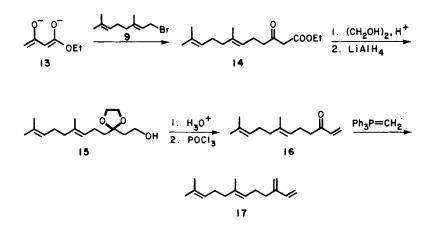
Pitzele, Baran, and Steinman, of Searle Laboratories in Chicago, have studied the alkylation of the dianion of 3-methylcrotonic acid (8), with geranyl bromide (Scheme 2).<sup>5</sup> After addition of the geranyl bromide,



Scheme 2. Searle Synthesis of Methyl Farnesate

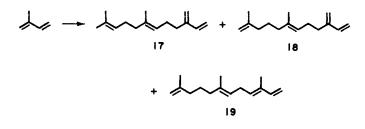
methyl iodide is added to obtain the methyl esters. Isomers 10, 11, and 12 are obtained in a ratio of 2.3:2.1:1.0; methyl farnesate (11) of 89% isomeric purity may be obtained by low pressure chromatography in 26% yield, based on geraniol.

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



Scheme 3. Vig's Synthesis of  $\beta$ -Farnesene

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

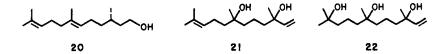


Scheme 4. Otsuka's  $\beta$ -Farnesene Synthesis

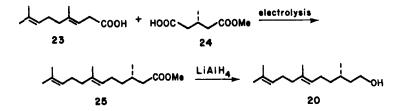
(17) utilizes  $[NiCl(\eta_3-C_3H_5)]_2$ -As $(n-C_6H_{13})_3$  and *t*-BuOK. If the reaction is stopped at 30% conversion of the isoprene,  $\beta$ -farnesene comprises 57% of the product. Unfortunately, preparative glpc is required to separate 17 from its isomers.

### B. Terrestrol, Caparrapidiol, and Caparrapitriol

Terrestrol, (3.5)-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.

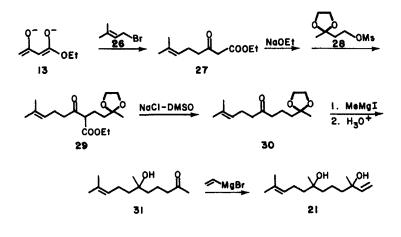


Ahlquist and Ställberg-Stenhagen of the University of Göteborg in Sweden have synthesized both enantiomers of terrestrol by way of the Kolbe electrolysis of homogeranic acid (23) with the enantiomers of monomethyl 3-methylglutarate (24, Scheme 5).<sup>8</sup> Ester 25 is obtained in 8% yield, based on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



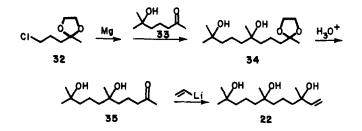
Scheme 5. Ahlquist-Ställberg-Stenhagen Synthesis of Terrestrol

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.<sup>10</sup> 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

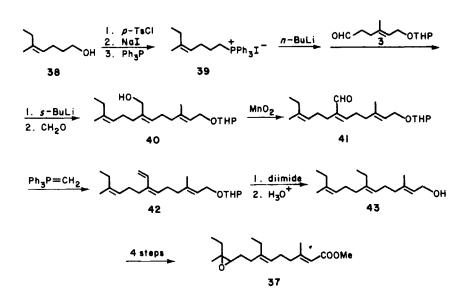
#### **C. Juvenile Hormones**

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.

COOMe 36: R = Me

37: R = Et

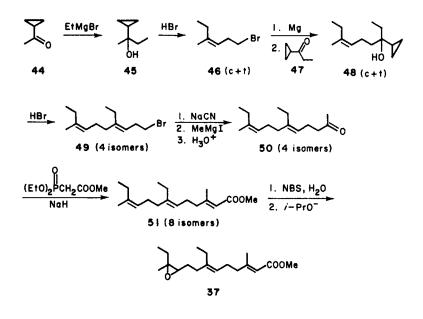
Corey and Yamamoto have utilized the  $\beta$ -oxidophosphonium ylide method for the synthesis of both C<sub>17</sub>- and C<sub>18</sub>-JH, as shown in Scheme 8.<sup>3</sup> Intermediate 40 is converted via aldehyde 41 into tetraene 42, which



Scheme 8. Corey-Yamamoto Synthesis of Juvenile Hormones

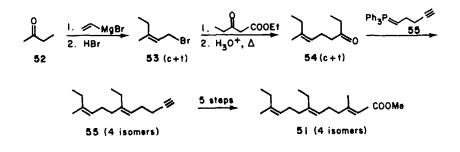
is selectively reduced to obtain alcohol 43. This material has previously been converted into  $C_{18}$ -JH.<sup>11</sup> The  $C_{17}$ -JH 36 is prepared from 40 along the same lines as are used to convert alcohol 5 into farnesol (see Scheme 1).

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.<sup>12a</sup> Their C<sub>18</sub>-JH synthesis had previously been published in preliminary form and was discussed in Volume 2 of this series.<sup>12b</sup> The New Brunswick-Beltsville C<sub>17</sub>-JH synthesis is essentially the same as the Schering synthesis of C<sub>17</sub>-JH.<sup>13</sup> Cochrane and Hanson of the University of Sussex have reported two  $C_{18}$ -JH syntheses.<sup>14</sup> Their first, summarized in Scheme 9, is modeled closely on the Julia nerolidol synthesis.<sup>15</sup> Bromide 46 is obtained as a 3:1



Scheme 9. Juvenile Hormone: Sussex Synthesis A

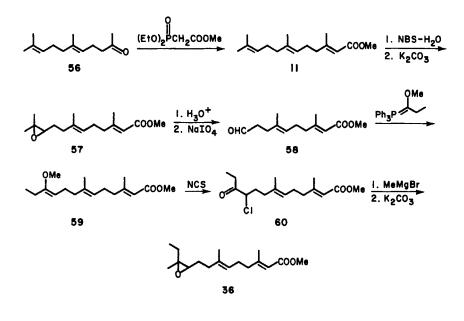
mixture favoring the unnatural E stereoisomer. The second cyclopropyl carbinol solvolysis ( $48 \rightarrow 49$ ) also produces a bad stereoisomer mixture, giving 59% of 3E and 41% of 3Z compounds. Analysis at the stage of dienone 50 showed the ZZ, ZE, EZ, and EE stereoisomers to be present in a ratio of 16:43:11:30. A final Horner-Wadsworth-Emmons olefination ( $50 \rightarrow 51$ ) 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

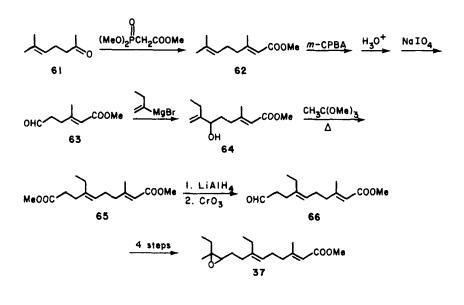
undesired E stereoisomer. The second double bond is introduced by a Wittig reaction, which proceeds in an essentially stereorandom fashion, as expected. The final double bond is introduced by the Corey procedure.<sup>16</sup> Analysis of ester 51 showed it to be an approximately equimolar mixture of 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.<sup>17</sup> 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.<sup>18</sup> 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,<sup>18</sup> Henrick and co-workers were only able to obtain 36 as an 82:18 mixture with its  $C_{10}$ - $C_{11}$  trans isomer.



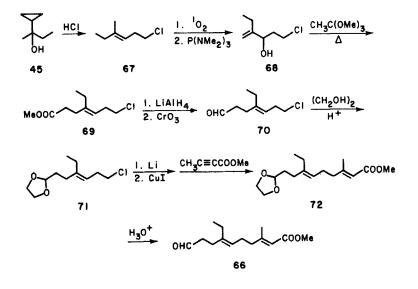
Scheme 11. Zoecon Synthesis of C<sub>17</sub>-JH

The Zoecon group has reported two methods for synthesis of  $C_{18}$ -JH.<sup>19</sup> 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-1-butene to obtain allylic alcohol 64. The C<sub>6</sub> 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<sub>18</sub>-JH

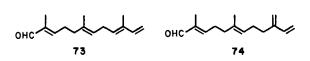
The second Zoecon synthesis (Scheme 13) starts with cyclopropyl carbinol 45, which is solvolyzed to unsaturated chloride 67 as a 3:1 mixture of *E* and *Z* isomers. The mixture of isomers is oxidized by singlet oxygen to obtain allylic alcohol 68 as the major product of a 55:39:6 mixture of isomers. 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.



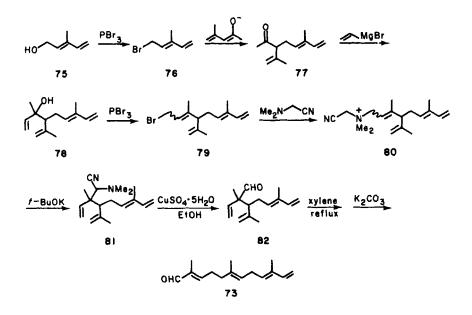
Scheme 13. Second Zoecon Synthesis of C<sub>18</sub>-JH

#### **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



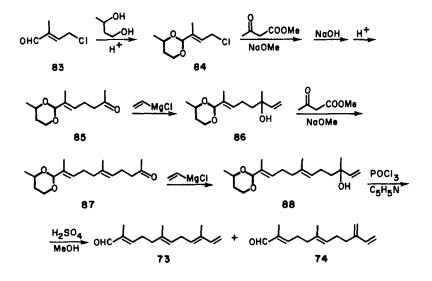
Wuest have reported the stereorational synthesis of the  $\alpha$  isomer (73) which is outlined in Scheme 14.<sup>20</sup> The stereochemistry of the C<sub>9</sub> double bond is assured by the use of the diene alcohol 75 as the starting



Scheme 14. Büchi's *a*-Sinensal Synthesis

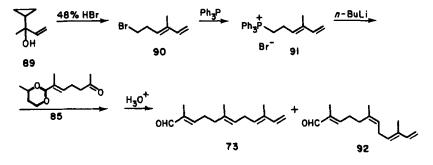
material. The synthesis features a novel [2,3]-sigmatropic rearrangement of the ammonium ylide derived from 80 to form amino nitrile 81 (3:2 mixture of diastereomers). Stereochemistry at the  $C_6$  double bond is established in the final Cope rearrangement; 73 and its 2Z diastereomer are produced in 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.<sup>21</sup> 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).<sup>22</sup>



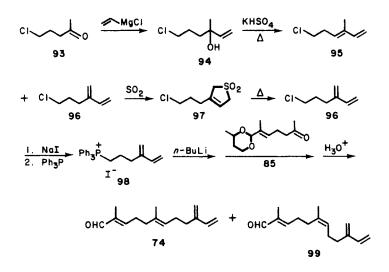
Scheme 15. First BASF Synthesis of Sinensals

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<sub>9</sub> double bond in 73 is not stated. A modified synthesis which yields no  $\beta$ -sinensal is shown in Scheme 16. The C<sub>7</sub>-C<sub>12</sub> segment is assembled as shown, using



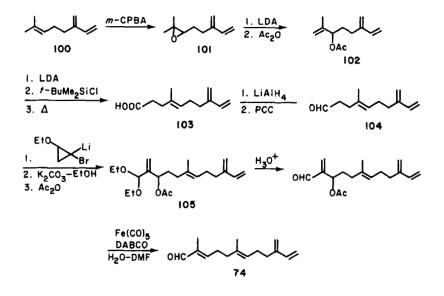
Scheme 16. BASF Synthesis of Pure  $\alpha$ -Sinensal

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  $\alpha$ -sinensal (73) as a 1:1 mixture with its C<sub>6</sub> diastereomer 92. The other BASF modification (Scheme 17) leads to  $\beta$ -sinensal (74), uncontaminated by  $\alpha$ -sinensal, again as a 1:1 mixture with the C<sub>6</sub>-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  $\alpha$  isomer.



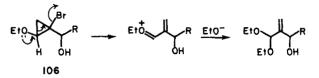
Scheme 17. BASF Synthesis of Pure  $\beta$ -Sinensal

A final synthesis of  $\beta$ -sinensal, from Hiyama's group in Kyoto, is summarized in Scheme 18.<sup>23</sup> The synthesis starts with myrcene, a frequently-used precursor for the preparation of  $\beta$ -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  $\beta$ -Sinensal

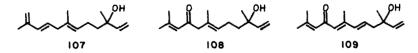
acetylated and subjected to Claisen rearrangement to obtain 103, apparently with good stereoselectivity. The terminal unsaturated aldehyde function is introduced by a method developed in Hiyama's group, whereby the carbanion derived from 1,1-dibromo-2ethoxycyclopropane is added to aldehyde 104 at low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



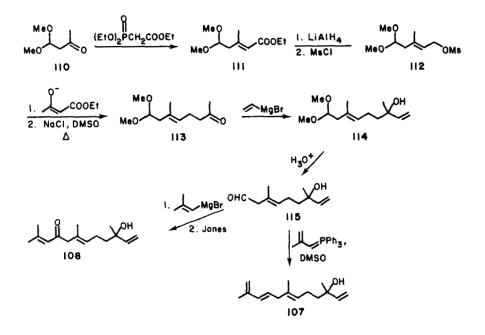
The synthesis of  $\beta$ -sinensal is completed by reductive removal of the acetoxy function, which occurs with double bond isomerization to the more stable position.

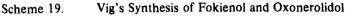
### E. Fokienol, Oxonerolidol, and Oxodehydronerolidol

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



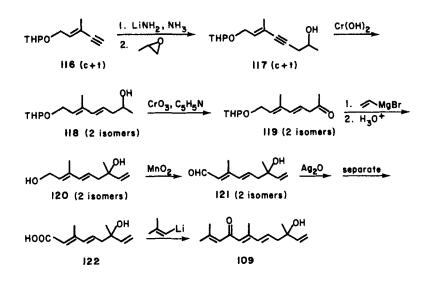
O. P. Vig's synthesis of racemic fokienol is outlined in Scheme  $19.^{25}$ The synthesis begins with a Wadsworth-Emmons reaction of keto acetal 110, which affords unsaturated ester 111 as a 60:40 mixture of E and Z

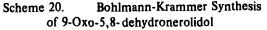




stereoisomers. Vig separates the mixture and carries on only with the correct 2*E* diastereomer, which is elaborated by straightforward steps into aldehyde 115. The most impressive step in this synthesis is the Wittig reaction on the  $\beta$ , $\gamma$ -unsaturated aldehyde 115, which is reported to 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.

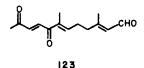
Bohlmann and Krammer have synthesized 9-oxo-5,8-dehydronerolidol (109) as shown in Scheme 20.<sup>26</sup> The synthesis starts with the protected unsaturated alcohol 116, which was used as a mixture of cis and trans isomers. The eventual  $C_5$  double bond is established by reduction of acetylene 117 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.



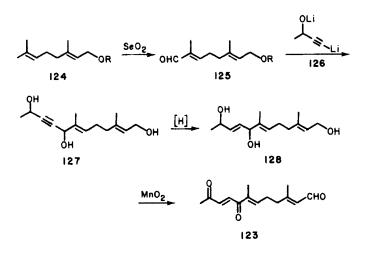


### F. Gyrindal

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<sup>27</sup> and by Miller, Katzenellenbogen, and Bowles,

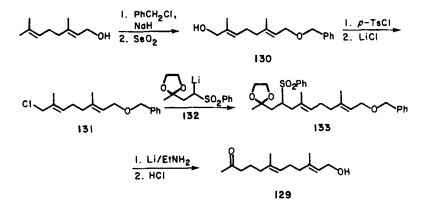


of Illinois.<sup>28</sup> The two syntheses, which are essentially identical, are outlined in Scheme 21. They differ only in the protecting group used for geraniol—the Cornell group employed the acetate whereas the Illinois group used the mesitoate—and in the method used for reducing the triple bond—the Cornell group used Li/NH<sub>3</sub> whereas the Illinois group used LiAlH<sub>4</sub>—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),<sup>29</sup> a norsesquiterpene from marine algae (Scheme 22). The synthesis is conceptually identical to the synthesis of geranylgeraniol by Altman, Ash, and Marson.<sup>30</sup> 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.



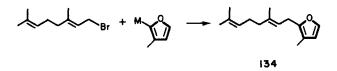
Kato's Synthesis of Oxocrinol Scheme 22.

#### 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.<sup>31-33</sup> All three syntheses rely on coupling geranyl

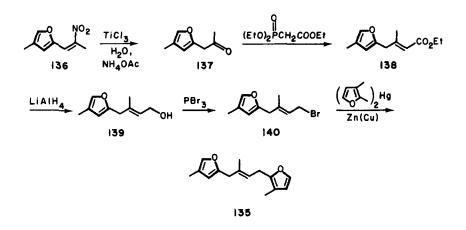


bromide with a 3-methyl-2-furylmetallic reagent (Scheme 23). The exact reagents employed have been the furyllithium,<sup>31</sup> the *bis*-furylmercury,<sup>32</sup> and the furylmagnesium bromide.<sup>33</sup> The highest coupling yield (40%) is



Scheme 23. Synthesis of Sesquirosefuran

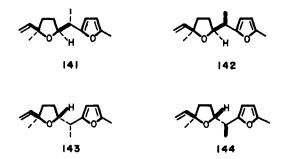
reported for the furyllithium reagent. A related synthesis of longifolin (135) is outlined in Scheme 24.<sup>34</sup> The final coupling proceeds in only 4% yield.



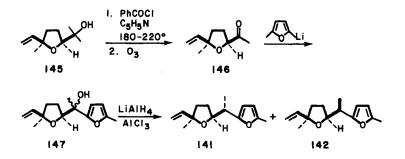
Scheme 24. Synthesis of Longifolin

#### 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

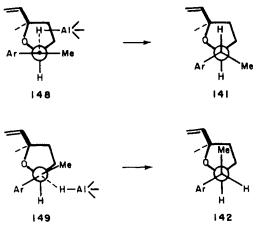


the four isomers starting with linalool oxides of known stereochemistry.<sup>35</sup> The synthesis of isomers 141 and 142 is summarized in Scheme 25. The (-)-*cis*-linally oxide 145 is converted by standard methods into the cis ketone 146, which is treated with 5-methyl-2-furyllithium to obtain a mixture of unstable tertiary alcohols. The alcohol mixture is hydrogenolyzed using LiAlH<sub>4</sub>-AlCl<sub>3</sub> to obtain a mixture of 141 and 142 in a ratio of 4:1. Similar transformation of (+)-*trans*-linally 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.



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

The common structural unit in this group of sesquiterpenes is the  $\beta$ substituted furan ring. Several syntheses of dendrolasin (150), neotorreyol (151), torreyal (152), and ipomeamarone (153) were recorded in our original review.<sup>36</sup> 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