The Total Synthesis of Natural Products

VOLUME 5

Edited by

John ApSimon

Ottawa–Carleton Institute for Research and Graduate Studies in Chemistry

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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

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

Department of Chemistry,
University of California,
Berkeley, California

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.

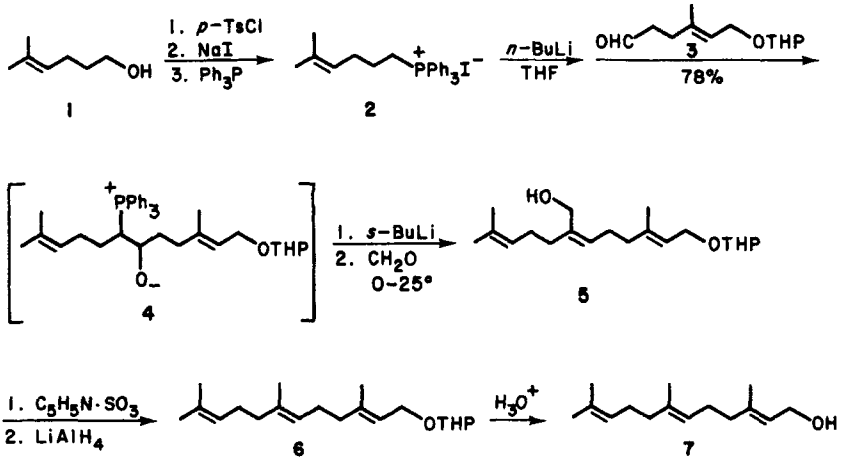
As before, not all relay total syntheses are included. The general rule of thumb is that a relay synthesis is included only if the final product differs in carbon skeleton from the starting material. Thus, conversion of santonin into a germacrane or elemane would be included, but conversion into another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

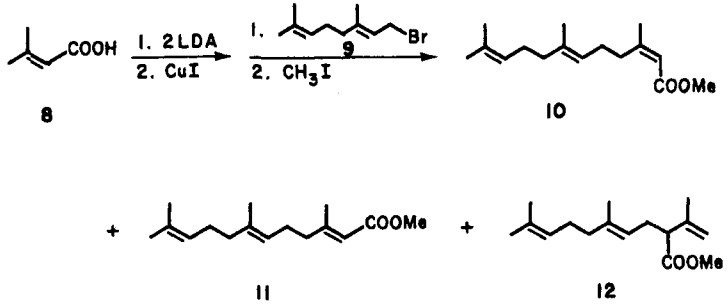
A. Farnesol and Farnesene

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

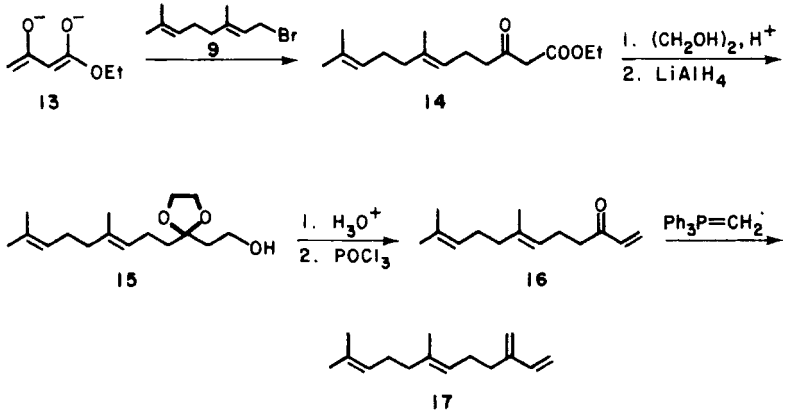
Pitzele, Baran, and Steinman, of Searle Laboratories in Chicago, have studied the alkylation of the dianion of 3-methylcrotonic acid (**8**), with geranyl bromide (Scheme 2).[5] After addition of the geranyl bromide,



Scheme 2. Searle Synthesis of Methyl Farnesate

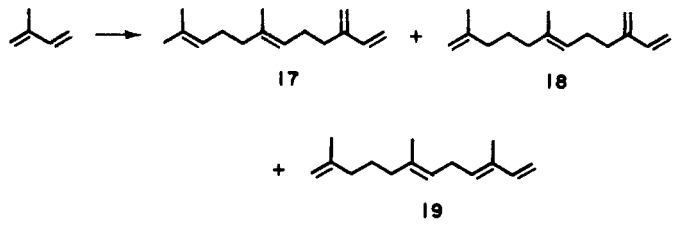
methyl iodide is added to obtain the methyl esters. Isomers **10**, **11**, and **12** are obtained in a ratio of 2.3:2.1:1.0; methyl farnesate (**11**) of 89% isomeric purity may be obtained by low pressure chromatography in 26% yield, based on geraniol.

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

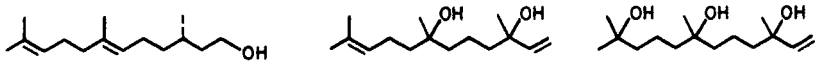


Scheme 4. Otsuka's β-Farnesene Synthesis

(**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.

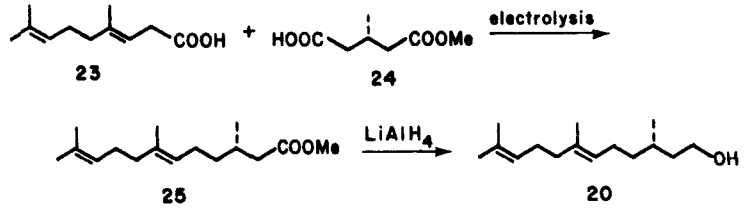
B. Terrestrol, Caparrapidiol, and Caparrapitriol

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.



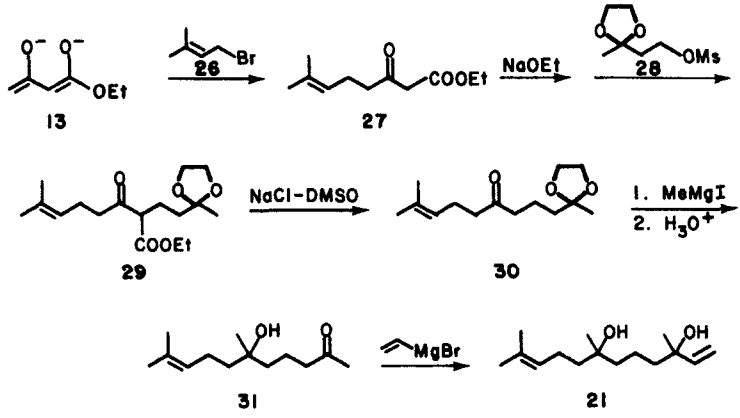
20 21 22

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.



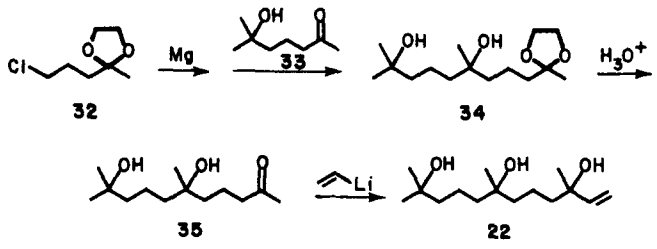
Scheme 5. Ahlquist-Ställberg-Stenhagen Synthesis of Terrestrol

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

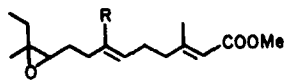
Weyerstahl and Gottschalk, at the Technical University of Berlin, have synthesized caparrapitriol as shown in Scheme 7.[10] As in the Vig synthesis of caparripidiol, the German group makes no mention of a diastereomeric mixture in the addition of vinyllithium to methyl ketone **35**. However, in this 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

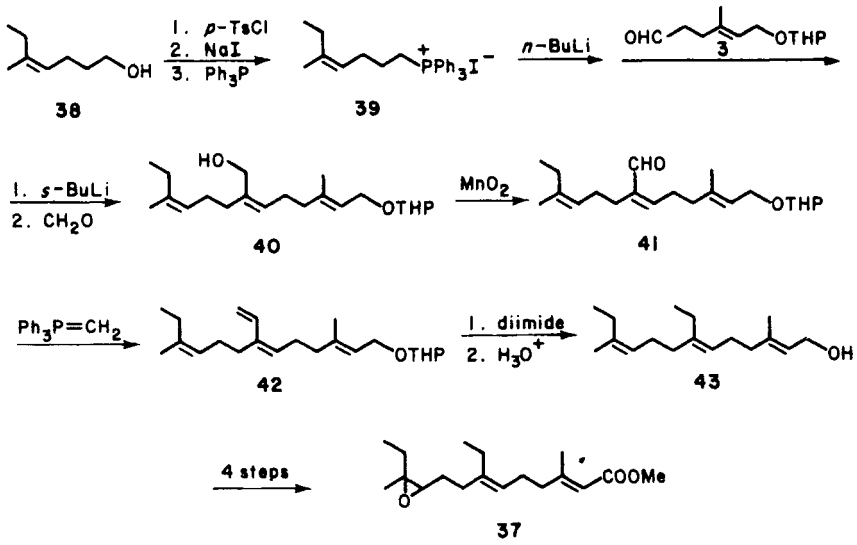
C. Juvenile Hormones

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

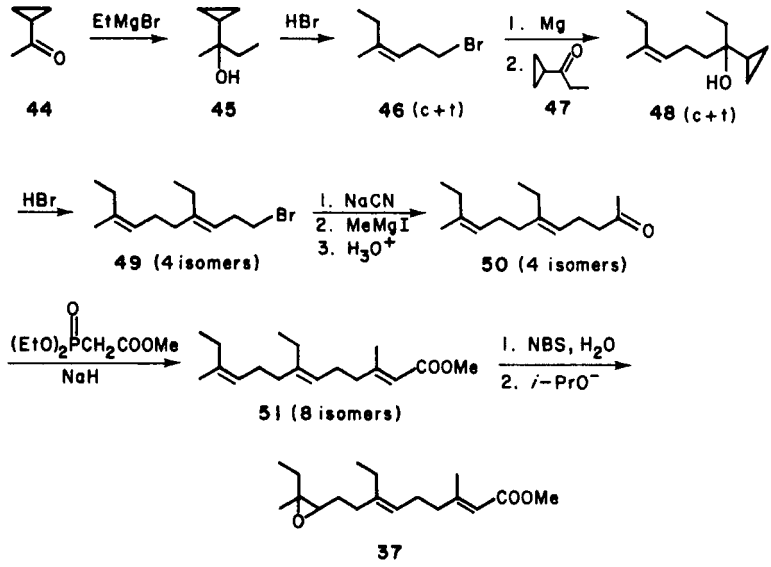


Scheme 8. Corey-Yamamoto Synthesis of Juvenile Hormones

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).

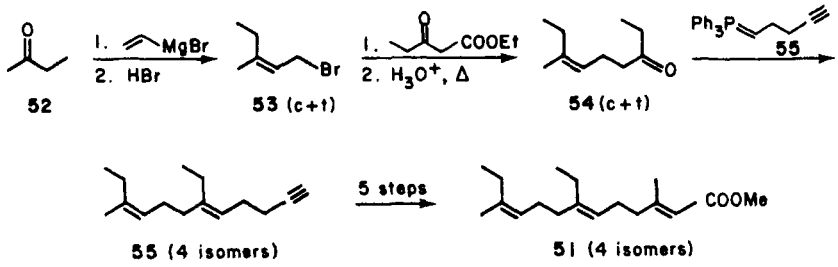
Findlay and MacCay at New Brunswick, and Bowers at the Agriculture Research Service in Beltsville have reported full details of stereorandom syntheses of both **36** and **37**.[12a] Their C_{18}-JH synthesis had previously been published in preliminary form and was discussed in Volume 2 of this series.[12b]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

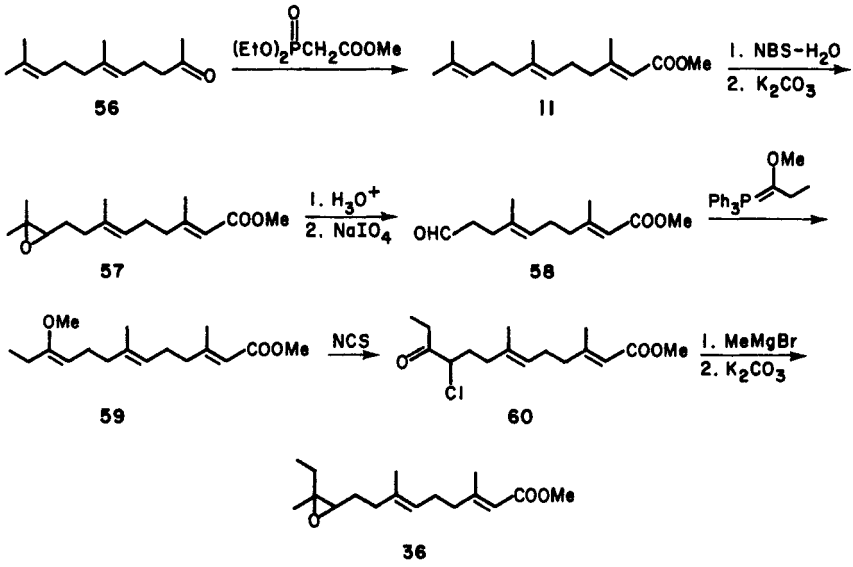
mixture favoring the unnatural E stereoisomer. The second cyclopropyl carbinol solvolysis (**48**→**49**) also produces a bad stereoisomer mixture, giving 59% of *3E* and 41% of *3Z* compounds. Analysis at the stage of dienone **50** showed the *ZZ*, *ZE*, *EZ*, and *EE* stereoisomers to be present in 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

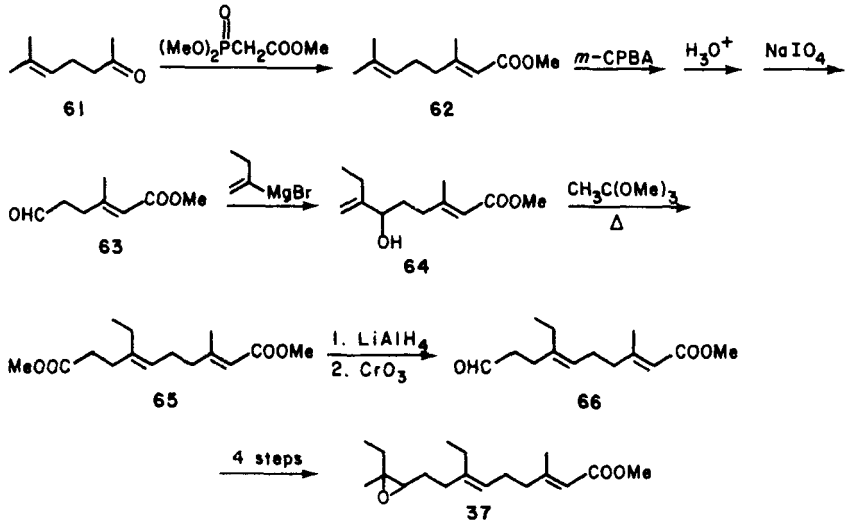
undesired *E* stereoisomer. The second double bond is introduced by a Wittig reaction, which proceeds in an essentially stereorandom fashion, as expected. The final double bond is introduced by the Corey procedure.[16] Analysis of ester **51** showed it to be an approximately equimolar mixture of the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



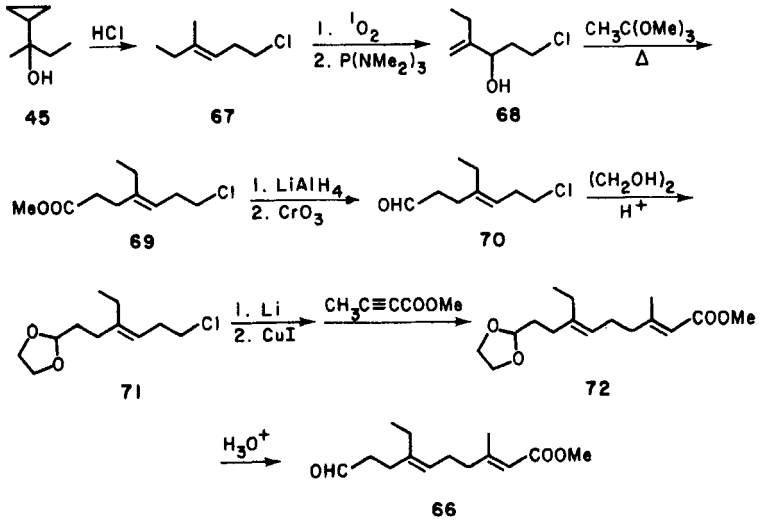
Scheme 11. Zoecon Synthesis of C_{17}-JH

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

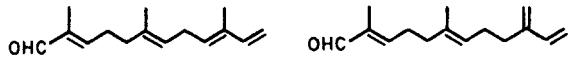
The second Zoecon synthesis (Scheme 13) starts with cyclopropyl carbinol **45**, which is solvolyzed to unsaturated chloride **67** as a 3:1 mixture of *E* and *Z* isomers. The mixture of isomers is oxidized by singlet oxygen to obtain allylic alcohol **68** as the major product of a 55:39:6 mixture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

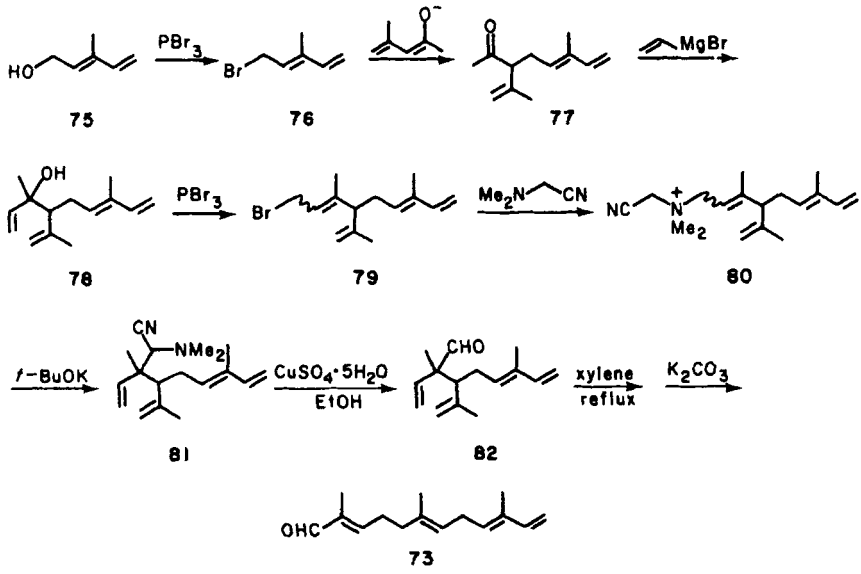
D. Sinensals

The sesquiterpene aldehydes α- and β-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 α 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 α-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]