

VOLUME FIVE

**THE
TOTAL SYNTHESIS OF
NATURAL PRODUCTS**

Edited by John ApSimon

The Total Synthesis of Natural Products

VOLUME 5

Edited by

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and

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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

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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 review² 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.

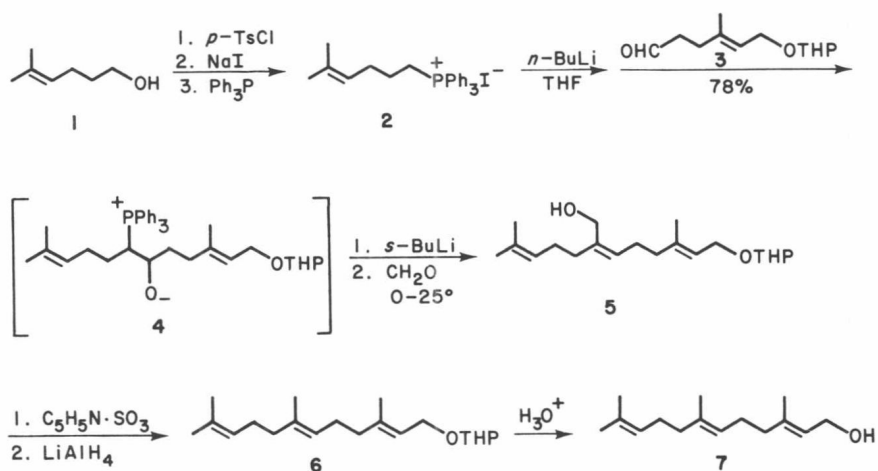
As before, not all relay total syntheses are included. The general rule of thumb is that a relay synthesis is included only if the final product differs in carbon skeleton from the starting material. Thus, conversion of santonin into a germacrane or elemene would be included, but conversion into another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

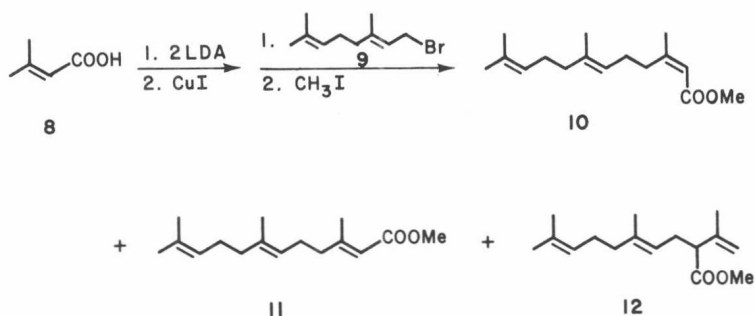
A. Farnesol and Farnesene

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

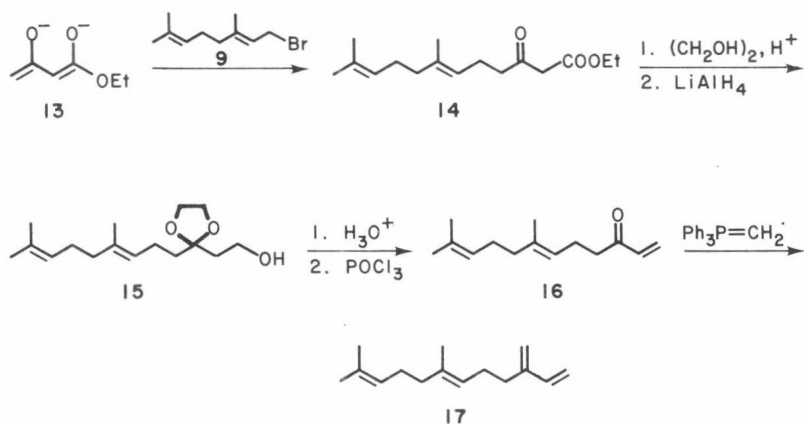
Pitzele, Baran, and Steinman, of Searle Laboratories in Chicago, have studied the alkylation of the dianion of 3-methylcrotonic acid (8), with geranyl bromide (Scheme 2).⁵ After addition of the geranyl bromide,



Scheme 2. Searle Synthesis of Methyl Farnesate

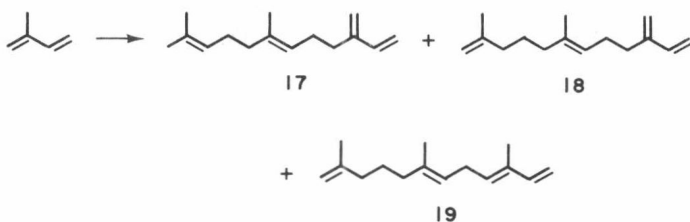
methyl iodide is added to obtain the methyl esters. Isomers **10**, **11**, and **12** are obtained in a ratio of 2.3:2.1:1.0; methyl farnesate (**11**) of 89% isomeric purity may be obtained by low pressure chromatography in 26% yield, based on geraniol.

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

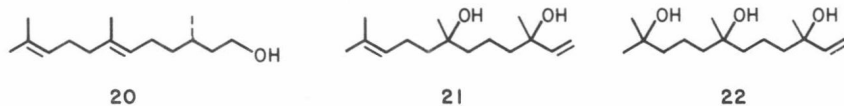


Scheme 4. Otsuka's β -Farnesene Synthesis

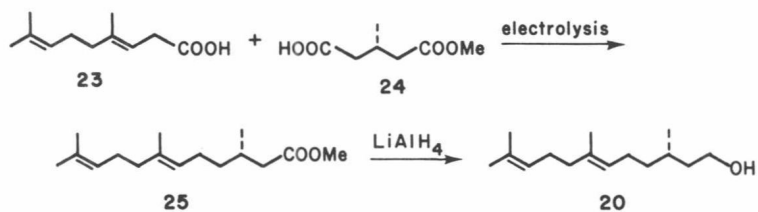
(17) utilizes $[\text{NiCl}(\eta_3\text{-C}_3\text{H}_5)]_2\text{-As}(n\text{-C}_6\text{H}_{13})_3$ and $t\text{-BuOK}$. If the reaction is stopped at 30% conversion of the isoprene, β -farnesene comprises 57% of the product. Unfortunately, preparative glpc is required to separate 17 from its isomers.

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.

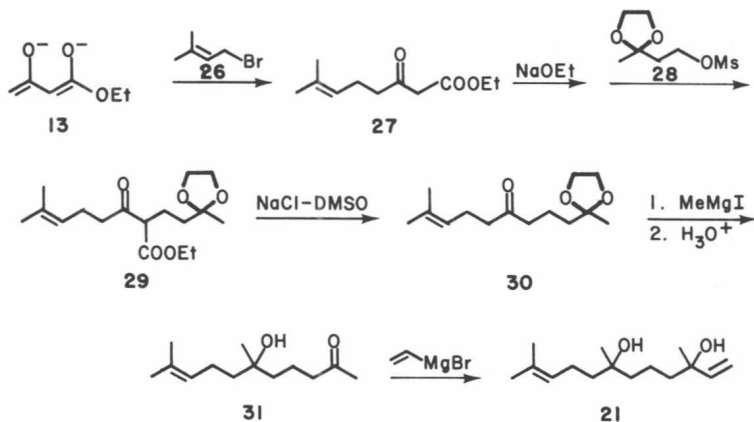


Ahlquist and Stållberg-Stenhagen of the University of Göteborg in Sweden have synthesized both enantiomers of terrestrol by way of the Kolbe electrolysis of homogeranic acid (23) with the enantiomers of monomethyl 3-methylglutarate (24, Scheme 5).⁸ Ester 25 is obtained in 8% yield, based on homogeranic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



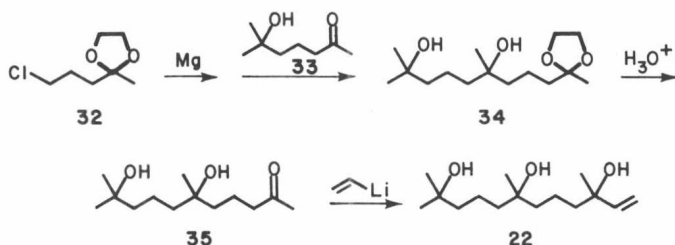
Scheme 5. Ahlquist-Ställberg-Stenhagen Synthesis of Terrestrol

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 vinyl lithium 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 caparrapitriol.



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.

