# The Total Synthesis of Natural Products

VOLUME 2

Edited by
John ApSimon

*Department of Chemistry*
*Carleton University,*
*Ottawa*

A WILEY-INTERSCIENCE PUBLICATION

JOHN WILEY & SONS
New York • Chichester • Brisbane • Toronto • Singapore

# THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

# The Total Synthesis of Natural Products

VOLUME 2

Edited by
John ApSimon

*Department of Chemistry*
*Carleton University,*
*Ottawa*

A WILEY-INTERSCIENCE PUBLICATION

JOHN WILEY & SONS
New York • Chichester • Brisbane • Toronto • Singapore

**Library of Congress Cataloging in Publication Data:**

ApSimon, John.
The total synthesis of natural products.
Includes bibliographical references.

1. Chemistry, Organic—Synthesis. I. Title.

QD262.A68 547'.2 72-4075
ISBN 0-471-03252-2 (V.2)

Printed in the United States of America

10 9 8

# Contributors to Volume 2

J. W. ApSimon, Carleton University, Ottawa, Canada
C. H. Heathcock, University of California at Berkeley, Berkeley, California
J. W. Hooper, Bristol Laboratories of Canada, Candiac, P.Q., Canada
D. Taub, Merck, Sharp and Dohme, Rahway, New Jersey
A. F. Thomas, Firmenich SA, Geneva, Switzerland

# Preface

Throughout the history of organic chemistry we find that the study of natural products frequently has often provided the impetus for great advances. This is certainly true in total synthesis, where the desire to construct intricate and complex molecules has led to the demonstration of the organic chemist's utmost ingenuity in the design of routes using established reactions or in the production of new methods in order to achieve a specific transformation.

These volumes draw together the reported total syntheses of various groups of natural products and commentary on the strategy involved with particular emphasis on any stereochemical control. No such compilation exists at present and we hope that these books will act as a definitive source book of the successful synthetic approaches reported to date. As such it will find use not only with the synthetic organic chemist but also perhaps with the organic chemist in general and the biochemist in his specific area of interest.

One of the most promising areas for the future development of organic chemistry is synthesis. The lessons learned from the synthetic challenges presented by various natural products can serve as a basis for this ever-developing area. It is hoped that these books will act as an inspiration for future challenges and outline the development of thought and concept in the area of organic synthesis.

The project started modestly with an experiment in literature searching by a group of graduate students about six years ago. Each student prepared a summary in equation form of the reported total syntheses of various groups of natural products. It was my intention to collate this material and possibly publish it. During a sabbatical leave in Strasbourg in the year 1968-1969, I attempted to prepare a manuscript, but it soon became

apparent that if I was to also enjoy other benefits of a sabbatical leave, the task would take many years. Several colleagues suggested that the value of such a collection would be enhanced by commentary. The only way to encompass the amount of data collected and the inclusion of some words was to persuade experts in the various areas to contribute.

Volume 1 presented six chapters describing the total syntheses of a wide variety of natural products. The subject matter of Volume 2 is somewhat more related, being a description of some terpenoid and steroid syntheses. These areas appear to have been the most studied from a synthetic viewpoint and as such have added more to our overall knowledge of the synthetic process.

A third volume in this series will consider diterpenes and various alkaloids, and suggestions for other areas of coverage are welcome.

I am grateful to all the authors for their efforts in producing stimulating and definitive accounts of the total syntheses described to date in their particular areas. I would like to thank those students who enthusiastically accepted my suggestion several years ago and produced valuable collections of reported syntheses. They are Dr. Bill Court, Dr. Ferial Haque, Dr. Norman Hunter, Dr. Russ King, Dr. Jack Rosenfeld, Dr. Bill Wilson, Mr. D. Heggart, Mr. G. W. Holland, Mr. D. Lake, and Mr. Don Todd. I also thank Professor G. Ourisson for his hospitality during the seminal phases of this venture. I particularly thank Dr. S. F. Hall, Dr. R. Pike, and Dr. V. Srinivasan, who prepared the indexes of Volumes 1 and 2.

JOHN APSIMON

*Ottawa, Canada*
*May 1973*

# Contents

# THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

# THE SYNTHESIS OF MONOTERPENES

A. F. Thomas

*Firmenich SA,*
*Geneva, Switzerland*

## 1. INTRODUCTION

The total synthesis of monoterpenes is not a subject that has attracted a great deal of attention. To be sure, each time some terpenoid curiosity is isolated, there is a certain amount of effort expended to synthesize it, generally as part of a structural "proof," but few chemists have spent much time on attempting to synthesize, say, pinene. One of the reasons for this lack of interest is certainly the vast natural resources of the more complex ring systems (especially the pinane, bornane, and carane systems), so that industry has had little need of total synthesis of these structures and has confined itself to partial syntheses within the systems. These partial syntheses, moreover, are themselves particularly interesting in view of the lability of many of the systems, and have, indeed, often provided the examples for reaction mechanism and stereochemical studies. Supplies of raw materials, however, are not always as easily accessible as they once were and total synthesis from cheaper materials cannot afford to be completely ignored.

On the whole, there are three reasons for synthesis. The first of these has just been mentioned--the preparation of "unusual" monoterpenes that are not readily available from natural sources, with a view to checking the correctness of their structures, examining their properties, and so on. The second type of synthesis is the so-called biogenetic type. These purport to imitate a route that approximates to what is believed to happen in the plant. There are not too many of them, but although they are designed from strictly theoretical viewpoints, they could be extremely important, especially since there is, so far, no good synthetic route to even quite simple monoterpenes that are in large supply in nature. Finally, there are the "industrial" syntheses, about which a further point must be made. The legislation in some countries

is becoming increasingly concerned with whether a compound is known to be naturally occurring or not. Many of the uses of monoterpenes by industry are in perfumes, cosmetics, flavors, and so on, and the idea of the legislators in these fields is that whatever occurs naturally in plant or animal products has been in existence, and possibly in use, for a long time, and so is less likely to be harmful than a new untried substance. Without discussing the merits of this position, it must be remembered that naturally occurring materials are, on the whole, asymmetric, so if an industry wishes to use synthetic compounds that are going to be placed on or in human beings, it may be under some pressure to synthesize not only the racemate, but the correct optical antipode, since we do not know, a priori, what the physiological differences between the antipodes may be. This factor mitigates, to some extent, against the use of purely synthetic starting materials, since total synthesis of optically active substances implies resolution at some stage. Legislation is, unfortunately, not consistent, since patent law does not allow (at least in the United States and Germany) the protection of natural products, no matter what efforts were made to isolate them, assign structures to them, and synthesize them.

There is a fourth type of synthesis that appears from time to time, and which might be called the "building block" type, where the desired molecule is put together by joining small parts of it. Apart from its use as an intellectual exercise (such syntheses are rarely of any industrial use), this approach does have an advantage where labeled molecules are required, since it frequently allows the placing of a particular atom in the molecule in a clear-cut way. For this reason, such syntheses have been included in this chapter. The literature is largely complete up to 1970; more recent work will be found in the "Specialist Periodical Report on Terpenoids and Steroids" (published annually by the Chemical Society, London).

## 2. THE TELOMERIZATION OF ISOPRENE

The ready availability of isoprene makes it an attractive starting point for the synthesis of monoterpenes, and several routes involving the addition of halogen acids (see, for example, the next section on methylheptenone) are described elsewhere in this chapter, in addition to the historical dimerization to dipentene. It would naturally be much more useful to have methods available for the direct dimerization and simultaneous hydroxylation of isoprene, and considerable effort has been put into this aspect, particularly in recent times in

Estonia and Japan. The mixtures obtained are of considerable complexity, and unfortunately much of the work is in journals that are difficult to obtain, including a review of the telomerization using hydrogen chloride (i.e., via the hydrogen chloride adduct).[1] Under these conditions, the $C_{10}$ fraction can contain as much as 45% of geranyl chloride.*[2] Phosphoric acid telomerization of isoprene gives α-terpinene and allo-ocimene as the main $C_{10}$ hydrocarbons, together with geraniol and terpineol.[3,4] In the presence of acetic acid, the phosphoric acid telomerization reaction leads to the acetates of geraniol, lavandulol, and other compounds, besides a complex mixture of monoterpene hydrocarbons.[5] There are other reactions of isoprene that lead to mixtures containing terpenoids, for example, the hydrocarbon will react with magnesium in the presence of Lewis acids, and the complex thus obtained gives adducts with aldehydes but again only as mixtures.[6] Isoprene is also dimerized by lithium naphthalene in tetrahydrofuran to linear monoterpene homologs,[7] passing oxygen through the mixture giving then 30 to 40% of $C_{10}$ alcohols and 30% of $C_{10}$ glycols. Although the alcohols include 10% each of nerol and geraniol, most of the remainder are not natural products.[8]

## 3. 6-METHYLHEPT-5-EN-2-ONE

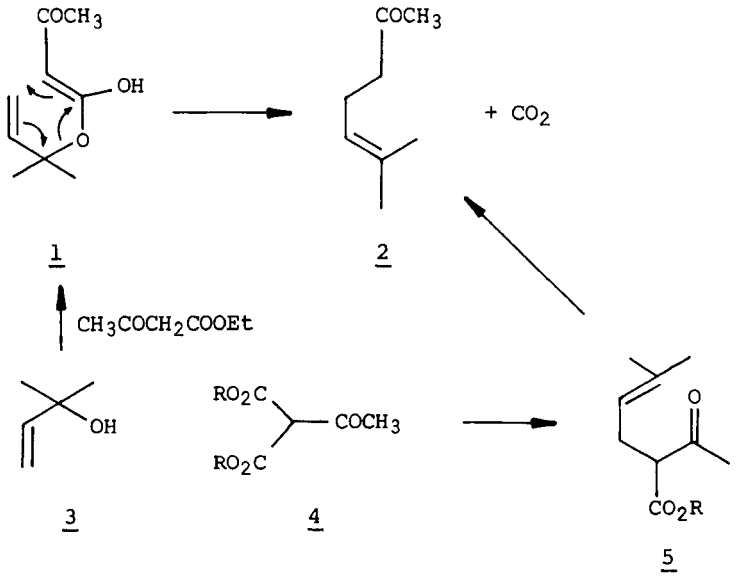
Although not strictly speaking a monoterpene, 6-methylhetp-5-en-2-one (2) is a common constituent of essential oils, particularly of the *Cymbopogon* (lemongrass) species. Some important terpene syntheses start from it, and it is also the chief product from the retro-aldol reaction and certain oxidations of citral and its derivatives. In view of its key position, it has been given a separate section on its synthesis.

Any synthesis of methylheptenone (2) must take into account the fact that it is sensitive to acid,[9,10] and can undergo cyclizations to hydrogenated xylenes and tetrahydropyrans, for example, during the decomposition of its semicarbazone by acid.[9]

Only the more recent syntheses will be given, and it is interesting that these are all based on some form of electrocyclic reactions. One of the earliest of this type is that of Teisseire, involving the transesterification of ethyl acetoacetate with 2-methylbut-3-en-2-ol (3).[11] The allyl ester (1)

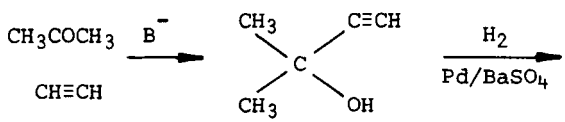
*Formulas of these substances will be found in the sections devoted to more clearly defined syntheses described later. One example of telomerization is also discussed in greater detail in the section devoted to linalool, nerol, and geraniol (p. 17).

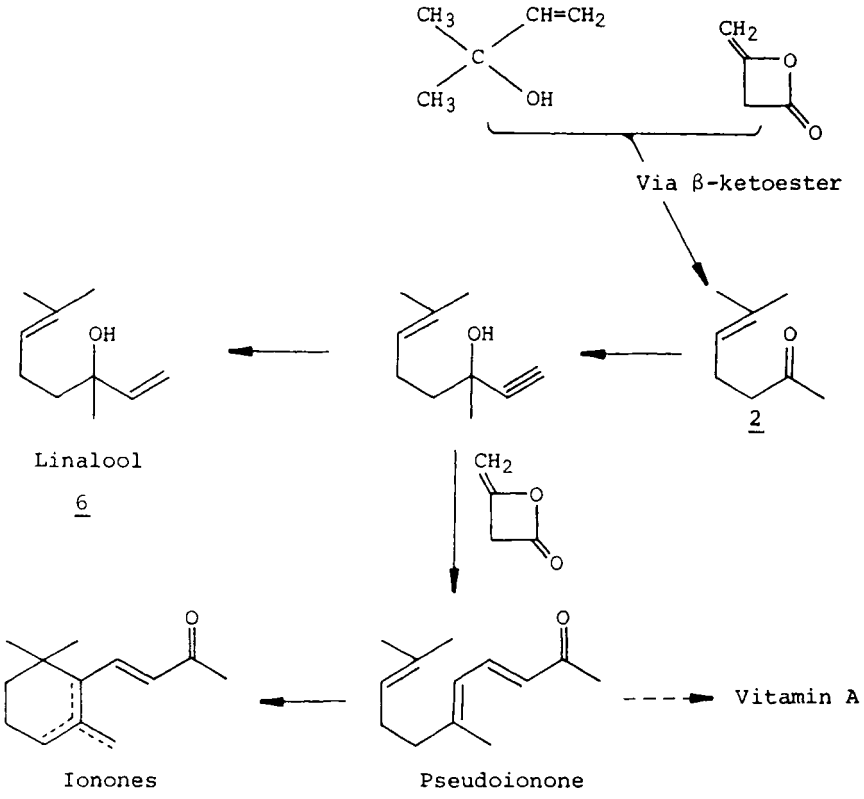
obtained undergoes the Carrol reaction,[12] resulting in a β-ketoacid through a reaction akin to the Claisen rearrangement,[13] and this ketoacid then loses carbon dioxide under the reaction conditions to yield the product (2). An earlier technique for this type of reaction consisted in mixing the alcohol with diketene;[13] when 3 and diketene is added to hot paraffin containing a trace of pyridine, the methylheptenone (2) can be distilled from the mixture.[14]



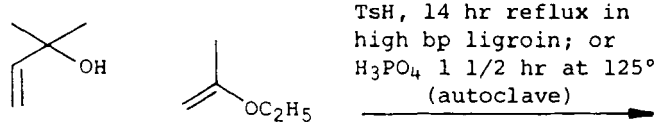

A further variant uses condensation of the allyl alcohol (3) with an acylmalonic ester (4) at 130-200°, when alcohol and carbon dioxide are lost, giving this time a β-ketoester (5) that is convertible to methylheptenone by ketone hydrolysis.[15] This type of procedure forms the basis of one of the best known commercial preparations of methylheptenone (2), required as a vital intermediate for syntheses of linalool (6), the ionones (7), and vitamin A, and which is illustrated in Scheme 1.[16]

Scheme 1

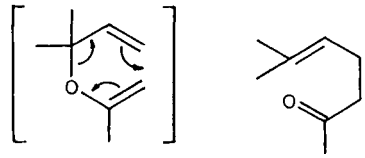





The thermal rearrangement of allyl ethers was described by Julia et al. in 1962,[17] and based on this idea, Saucy and Marbet synthesized methylheptenone from 2-methylbut-3-en-2-ol (3) and ethyl isopropenyl ether (8):[18]

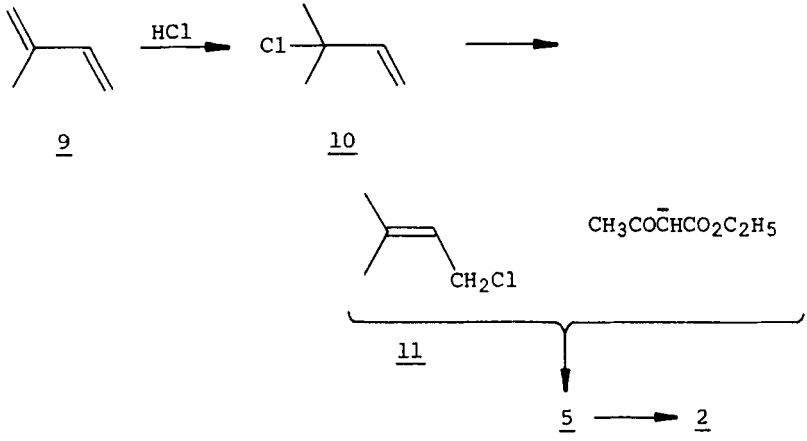



3 8



2

A somewhat more classical approach, namely, building up the molecule by a standard ketone synthesis from a functionalized isoprene is mentioned here particularly in view of the importance of the particular $C_5$ unit involved. The addition of halogen acids to isoprene (9) occurs initially by 1,2-addition, leading to 2-chloro-2-methylbut-3-ene (10) (or its bromo analog when hydrogen bromide is employed). This compound can even be isolated in a relatively pure state provided the addition is not carried through to completion.[19] Under the normal conditions of addition, however, using an excess of acid, the main product is the primary chloride (11). For example, one mole of isoprene and two to three moles of concentrated hydrochloric acid at 0-40° for 1 to 4 hr gives 63% of the primary chloride (11) and 8% of the tertiary chloride (10).[20] Formation of the primary chloride is also favored by elevated temperature and the presence of moisture.[21] Treatment of the sodium derivative of ethyl acetoacetate with the primary chloride (11) thus leads, after conventional hydrolysis and decarboxylation of the β-ketoester (5), to methylheptenone (2).[22] Direct condensation of acetone with the primary chloride (11) is also reported in a Russian patent.[23]

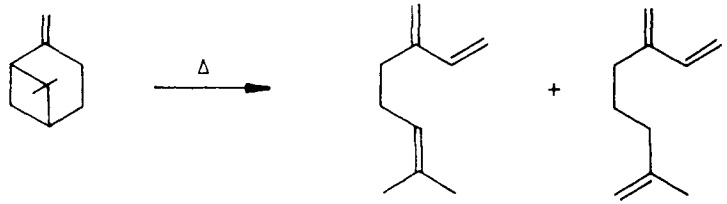


## 4. 2,6-DIMETHYLOCTANE DERIVATIVES

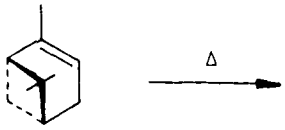
### A. Hydrocarbons

*Myrcene, Ocimene, and Alloocimene*

Both myrcene (12) and ocimene (13a, *cis* and 13b, *trans*) are common constituents of essential oils. In addition, myrcene is made on the industrial scale by pyrolysis of β-pinene (14),[24,25] a reaction that also gives rise to a small amount of α-myrcene (15),[26] not yet reported as a natural product. One of the problems associated with *cis*-ocimene (13a) is its ready transformation to the non-naturally occurring allo-ocimene (16) [the only reported occurrence of the latter in a plant oil has been attributed to rearrangement of *cis*-ocimene (13a) during workup[28]]. Consequently, it is not surprising that pyrolysis of (+)-α-pinene (17) in liquid form over a nichrome wire at 600° gives, in addition to 48% of ocimene, 16.5% of alloocimene (16), together with racemized α-pinene and dipentene (18).[29]*




14 β-Pinene 12 Myrcene 15



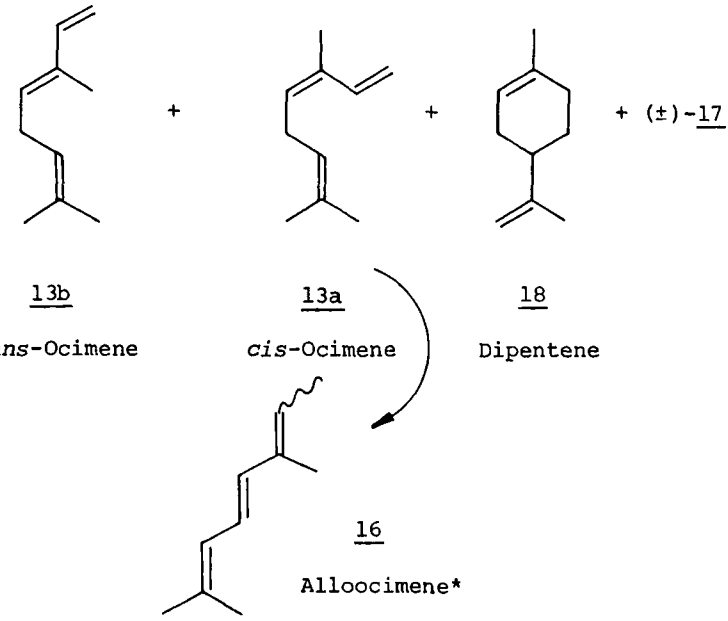

13b + ... (see following page)

17 (+)-α-Pinene

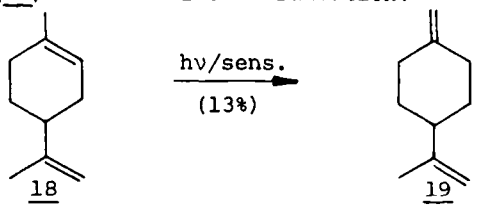
hν

13a ⇌ 13b

*"Dipentene" will be used in this chapter to denote the racemate, "limonene" being reserved for the optically active isomers.

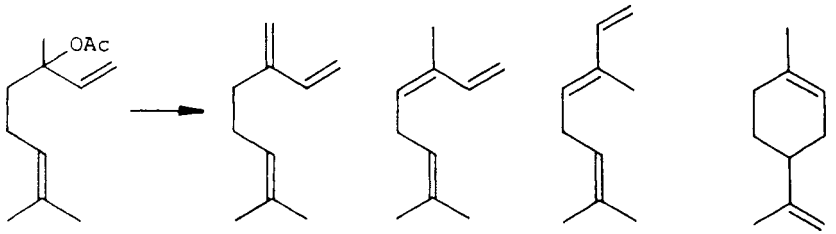



Isomerization of α-pinene (17) to ocimene can also occur photochemically,[30,31] and Kropp has investigated this and related reactions.[32] Direct irradiation of α-pinene in low yield was already known to give a product contaminated by dipentene (18) and other products.[33] Sensitized irradiation of α-pinene in xylene or xylene-methanol was now found to give only *cis*-ocimene (13a) after short reaction times, but with longer periods of irradiation an equilibrium between *cis*- and *trans*-ocimene is set up, although the product is never seriously contaminated with dipentene (18),[32] as is the case with the pyrolytic and γ-ray radiolytic conversions of α-pinene to ocimene.[34] This photochemical reaction of α-pinene is somewhat unexpected in giving no β-pinene, unlike the similar reaction of dipentene (18), that gives a 13% yield of p-mentha-1(7),8-diene (19) on sensitized irradiation.[32]




*For a detailed discussion of the various stereoisomeric alloocimenes, see Crowley.[27]

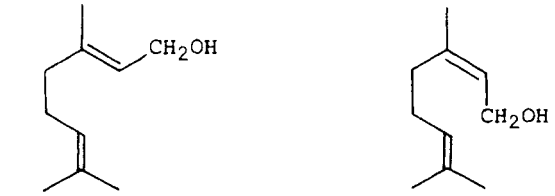
Total synthesis of both myrcene (12) and ocimene (13) generally involves pyrolysis of a suitable alcohol or acetate. The most easily available are probably the derivatives of linalool (Scheme 1), treated in more detail later, but which is easily made by reaction of sodium acetylide on methylheptenone.[35] Linalool itself (6) has been known for some years to give myrcene (12) by treatment with iodine at 140-150°,[36,37] but the acetate (20) can be pyrolyzed alone,[37] while loss of acetic acid occurs over Chromosorb P* at temperatures as low as 140°, to give the following amounts of the different hydrocarbons:[39]




20 43% 20% 35% 2%

12 13a 13b 18

Pyrolysis of various other acetates to give ocimenes and myrcene has also been described.[26,38] Dehydration of geraniol (21) or nerol (22) (related to linalool allylically) in the presence of potassium hydroxide at 200° for 10 minutes† also gives 60% of myrcene and other products, including allo-ocimene.[41]




Geraniol Nerol

21 22

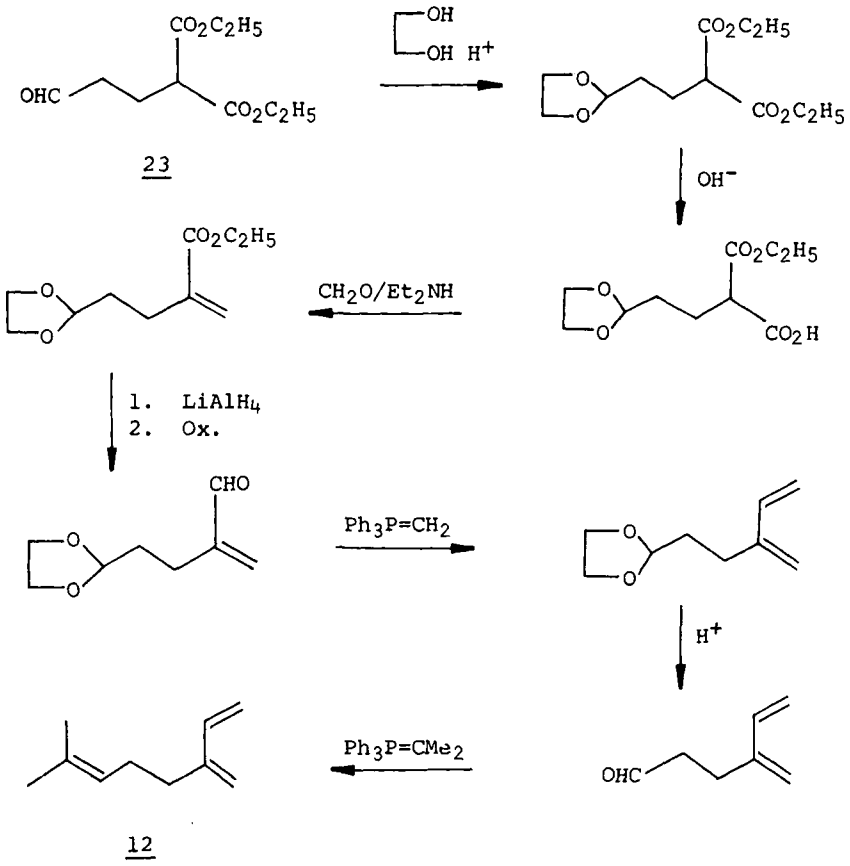
12 + 16 + other products

*In view of the instability of linalyl acetate on certain supports, it is always chromatographed in the author's laboratory on Chromosorb-W, on which it is stable up to 200°.

†This technique, developed by Ohloff[40] has recently been re-examined by Bhati both for alcohol dehydration and isomerization (see below, under menthone).

A recent synthesis of myrcene on the "building block" principle (i.e., putting one unit together with another in logical sequence until the desired molecule is reached) has been described by Vig et al.[42] It starts with ethyl 2-carbethoxy-5-formyl butanoate (23) and follows Scheme 2.

Scheme 2




23

12

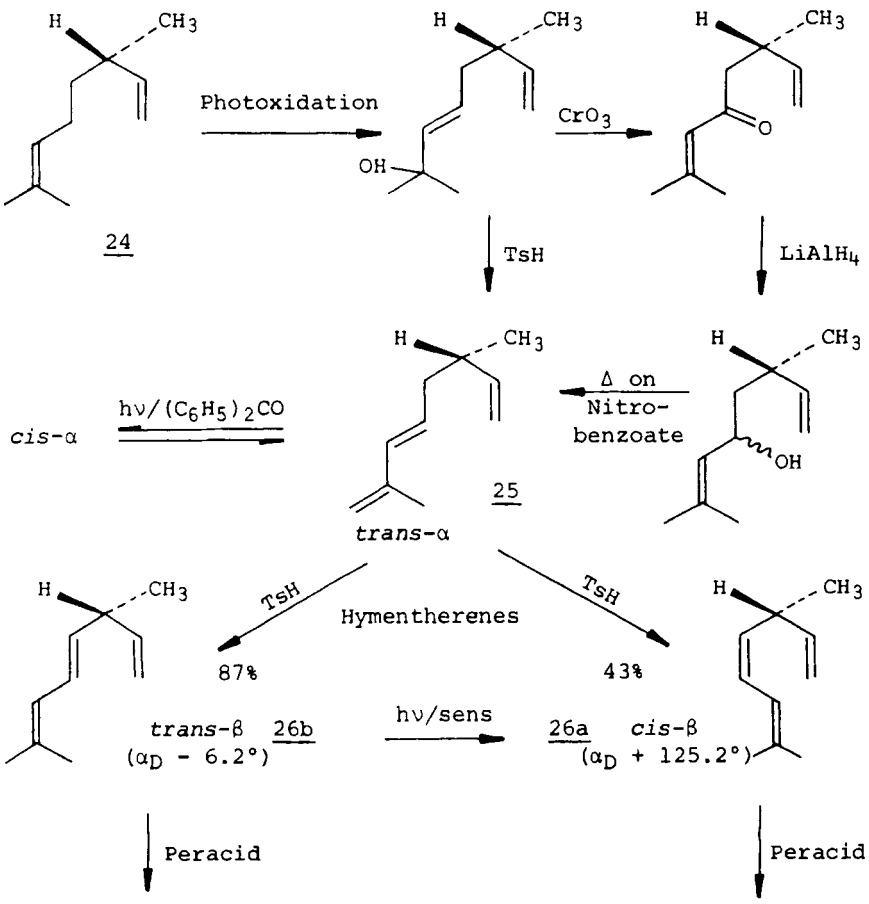
*Hymentherene and Achillene*

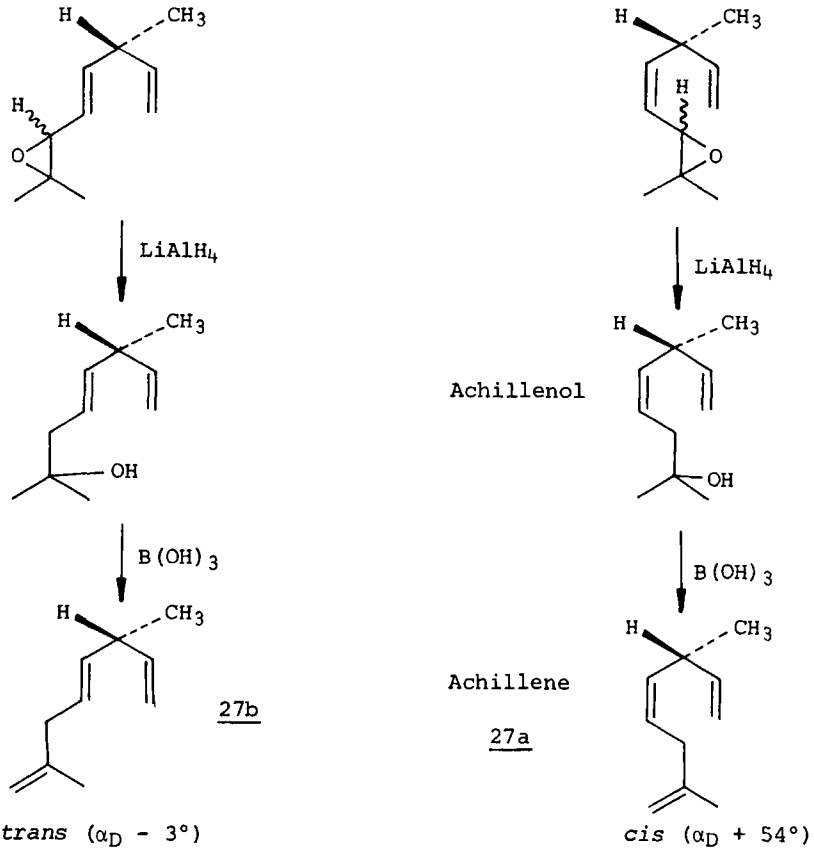
2,6-Dimethylocta-2,4,7-triene (26) was originally reported as a natural product, and given the name hymentherene;[43] later, however, it turned out that the substance isolated was a mixture of two known monoterpenes.[44] The name has been retained in this chapter for convenience, and also because it is still possible that the substance will be found in nature. The

related *cis*-2,6-dimethylocta-1,4,7-triene (27a) has been isolated from *Achilla filipendulina* by Dembitskii et al.[45,46]

Early syntheses of "B-hymentherene" were unsuccessful[47,48] and the first time the substance was certainly isolated is by Schulte-Elte,[49] who started from the known[47] (6S)-(+)-2,6-dimethylocta-1,3,7-triene (25), the (6S)-configuration of the positively rotating isomer of this substance having been established previously by correlation with (-)-*trans*-pinane.[50,51] Heating this triene ("*trans*-α-hymentherene," (25) in benzene and a catalytic amount of *p*-toluenesulfonic acid gave the thermodynamically more stable β-isomers (26a, 26b). The full synthesis from 2,6-dimethylocta-2,7-diene[50] (24) is shown in Scheme 3, which also gives the synthesis of natural

Scheme 3



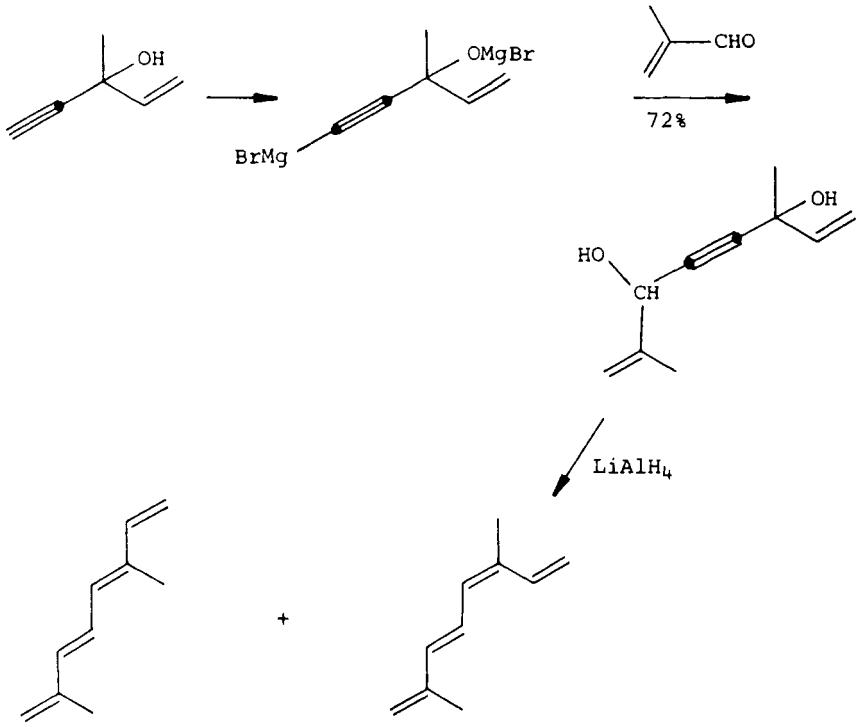



achillene (27a) that Schulte-Elte achieved from *cis*-β-hymentherene (26a).[49] Although the reaction of *p*-toluenesulfonic acid on *trans*-α-hymentherene (25) leads to only 3% of the natural *cis*-configuration about the C-4 double bond, irradiation of the *trans*-compound (26b) in the presence of a sensitizer leads to a mixture containing 43% of the *cis* compound (26a).[49] Achillenol [the alcohol obtained immediately before achillene (27a) in the synthesis] has also been reported recently as a natural product,[52] but the rotation does not agree with Schulte-Elte's synthetic material.[49]

*Cosmene*

The only natural monoterpene tetraene is cosmene, 2,6-dimethylocta-1,3,5,7-tetraene (29a), isolated from *Cosmos bipinnatus*, Cav., and other compositae by Sörensen and Sörensen.[53] The

hydrocarbon was synthesized by Nayler and Whiting by the route shown from 3-methylpent-1-en-4-yn-3-ol (28).[54] It is believed that the natural isomer is all-*trans*, (29a) and while the disubstituted ethylene is fairly well established as *trans*, the evidence for the trisubstituted ethylene is not so certain, in fact Nayler and Whiting state that their crude synthetic product contained two isomers (29a and 29b) about this double bond, recrystallization improving the purity.[54]




Cosmene + 29b

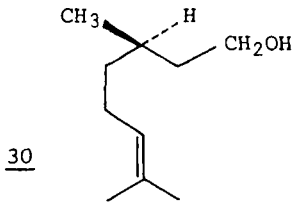
29a

B. Alcohols

*Citronellol*

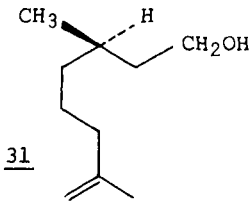
3,7-Dimethyloct-6-en-1-ol is one of the most widely distributed monoterpene alcohols both as the alcohol and the corresponding acetate. It occurs naturally in both (+)- and (-)-forms, almost always as the β-form (i.e., isopropylidene, e.g., 30),

although isolated reports of the α-form (31) occurring in nature do exist. In this connection, it is worth mentioning the confusion in the literature about the terms "rhodinol" and "rhodinal." The older literature refers to a mixture, but later it has been held that citronellol and "rhodinol" are identical.[55,56] Eschinazi[57] and Naves and Frey[58] consider "rhodinol" to be (+)-α-citronellol (31), and "rhodinal" to be the corresponding α-aldehyde. On the other hand, Chemical Abstracts refers to "rhodinol" as 3,7-dimethyloct-6-en-1-ol, but "rhodinal" as 3,7-dimethyloct-7-en-1-ol.[59] It is the author's opinion that the name should no longer be used at all, and all references be made to citronellol, α-citronellol and citronellal.




30

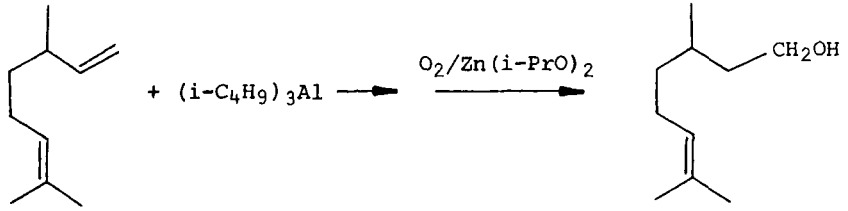
(+)-Citronellol




31

(+)-α-Citronellol

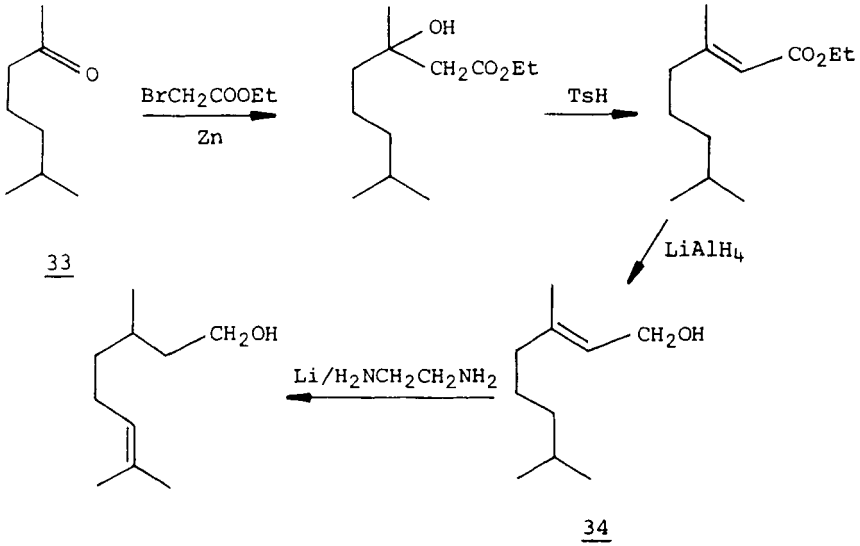
Syntheses of citronellol are commercially important because supplies of the natural material are insufficient, and since geraniol is available from myrcene (see below), there are many syntheses described in the literature from geraniol or geranic acid by reduction (see Ref. 44 for a list), and these largely conventional syntheses will not be mentioned here. Somewhat more interesting is the synthesis from 2,6-dimethylocta-2,7-diene (32) using tri-isobutylaluminum then oxidizing[51] (the presence of zinc isopropoxide being beneficial[60]), this reaction being the equivalent of a hydroboration.




32

Another synthesis is important as an illustration of the

use of N-lithioethylenediamine to displace double bonds. This reagent is mentioned below in similar connections, and, in the synthesis of citronellol, it was found that dihydrogeraniol (34), made from 6-methylheptan-2-one (33) via a Reformatsky reaction[61] is converted in 70% yield to citronellol.[62]




33

34

All the syntheses of citronellol from geraniol result, of course, in the racemate, while the most important natural diastereomer is the (-)-form, and synthetic approaches to the chiral form are rare.

*Linalool, Nerol, and Geraniol**

Together with citronellol, these alcohols and their acetates constitute the most widely distributed monoterpene alcohols in nature. Geraniol is not only of some value in itself, but also as an intermediate to citronellol which is more useful to

*A detailed discussion of the allyl rearrangements occurring between linalool and the other two alcohols, recognized to occur in the last century[63] will not be given since it belongs properly to the domaine of physical organic chemistry.