The Total Synthesis
of Natural Products

VOLUME 2

Edited by

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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.

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Contents

THE SYNTHESIS OF MONOTERPENES

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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, bor-
nane, 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, in-
deed, 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. Fin-
ally, there are the "industrial" syntheses, about which a fur-
ther 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 race-
mate, but the correct optical antipode, since we do not know,
a priori, what the physiological differences between the anti-
podes 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 ex-
ercise (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 partic-
ular atom in the molecule in a clear-cut way. For this reason,
such syntheses have been included in this chapter. The liter-
ature 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 exam-
ple, the next section on methylheptenone) are described else-
where in this chapter, in addition to the historical dimeriza-
tion to dipentene. It would naturally be much more useful to
have methods available for the direct dimerization and simul-
taneous 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 telo-
merization 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 phos-
phoric acid telomerization reaction leads to the acetates of
geraniol, lavandulol, and other compounds, besides a complex
mixture of monoterpene hydrocarbons.[5] There are other reac-
tions 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 mix-
ture 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, partic-
ularly of the *Cymbopogon* (lemongrass) species. Some important
terpene syntheses start from it, and it is also the chief prod-
uct 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 ac-
count the fact that it is sensitive to acid,[9,10] and can under-
go 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 electro-
cyclic reactions. One of the earliest of this type is that of
Teisseire, involving the transesterification of ethyl aceto-
acetate 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 de-
tail 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]
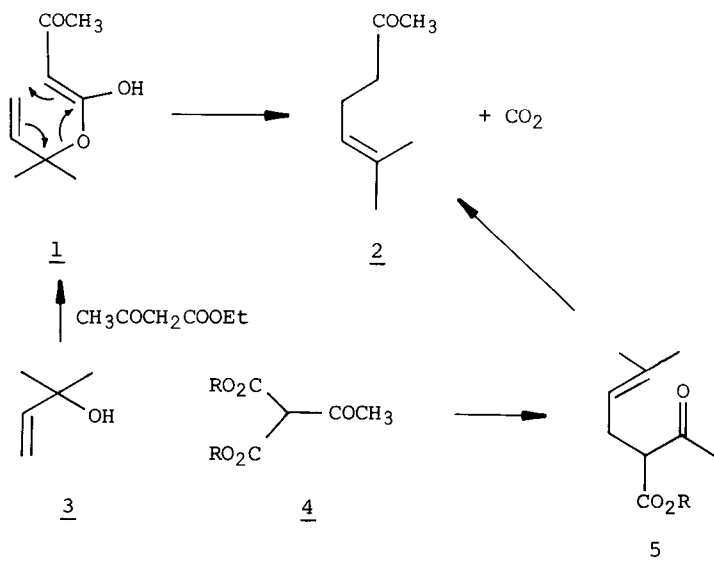

A further variant uses condensation of the allyl alcohol (3) with an acylmalonic ester (4) at 130-200°, when alcohol and carbon dioxide are lost, giving this time a β-ketoester (5) that is convertible to methylheptenone by ketone hydrolysis.[15] This type of procedure forms the basis of one of the best 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]
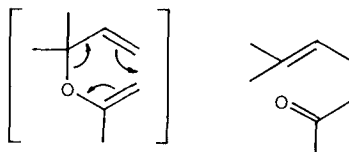
Scheme 1

Via β-ketoester

Linalool

6

2

Ionones

7

Pseudoionone

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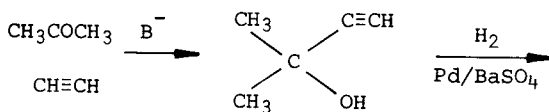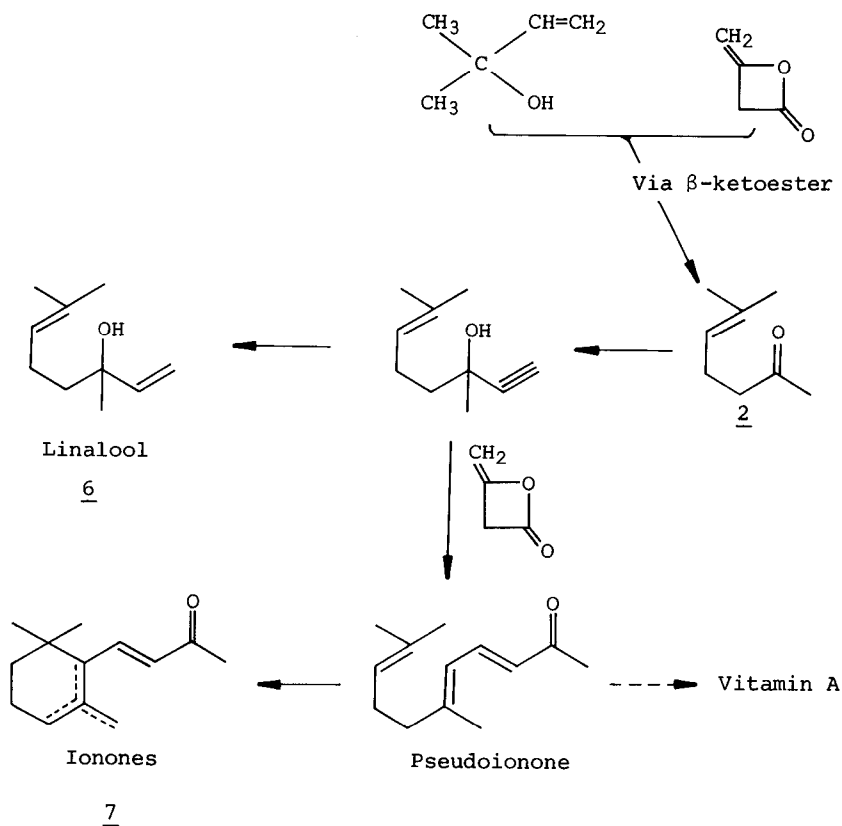
The thermal rearrangement of allyl ethers was described by Julia et al. in 1962,[17] and based on this idea, Saucy and Marbet synthesized methylheptenone from 2-methylbut-3-en-2-ol (3) and ethyl isopropenyl ether (8):[18]

3   8

TsH, 14 hr reflux in
high bp ligroin; or
H₃PO₄ 1 1/2 hr at 125°
     (autoclave)
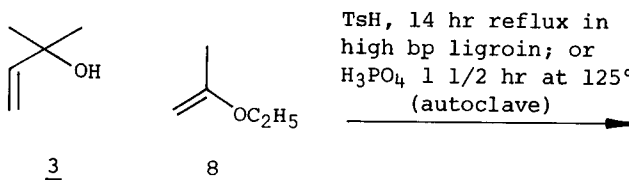
$$\underline{2}$$

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]
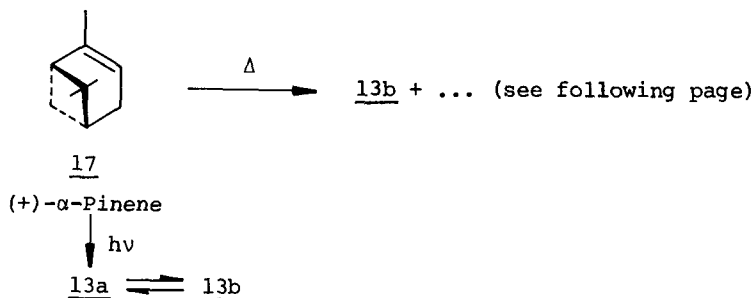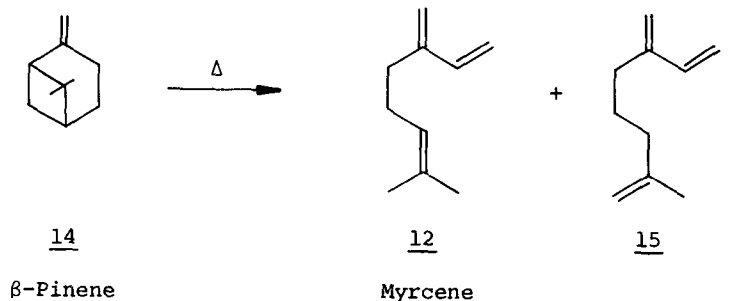
$$\underline{9} \qquad \underline{10}$$

$$CH_3COCHCO_2C_2H_5$$

$$\underline{11}$$

$$\underline{5} \longrightarrow \underline{2}$$
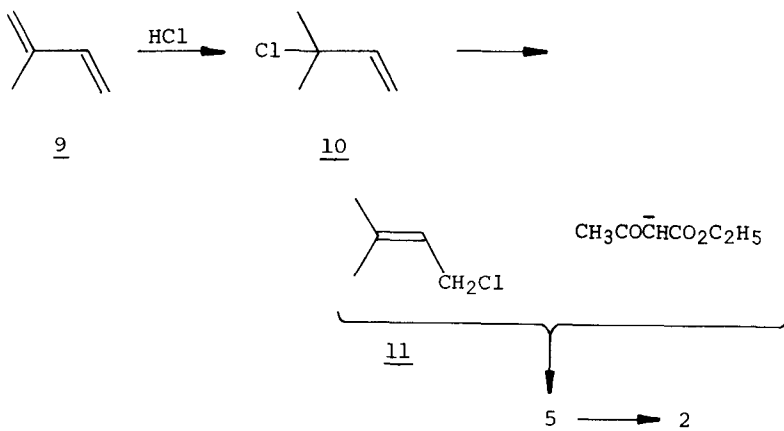
4.   2,6-DIMETHYLOCTANE DERIVATIVES

A.   Hydrocarbons
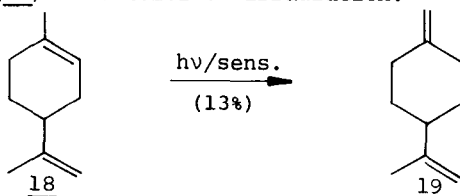
Myrcene, Ocimene, and Alloocimene

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	12	15
β-Pinene	Myrcene	

17
(+)-α-Pinene

13b + ... (see following page)

| hν

13a ⇌ 13b

---

*"Dipentene" will be used in this chapter to denote the race-
mate, "limonene" being reserved for the optically active iso-
mers.

13b	**13a**	**18**	
trans-Ocimene	*cis*-Ocimene	Dipentene	

16
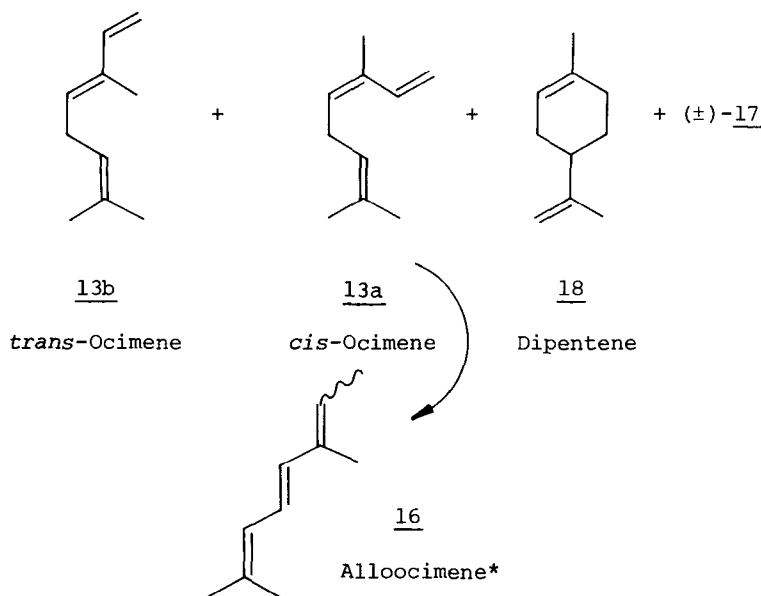
Alloocimene*

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]

hν/sens.

(13%)

18   **19**

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

Total synthesis of both myrcene (12) and ocimene (13) gen-
erally 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 methyl-
heptenone.[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
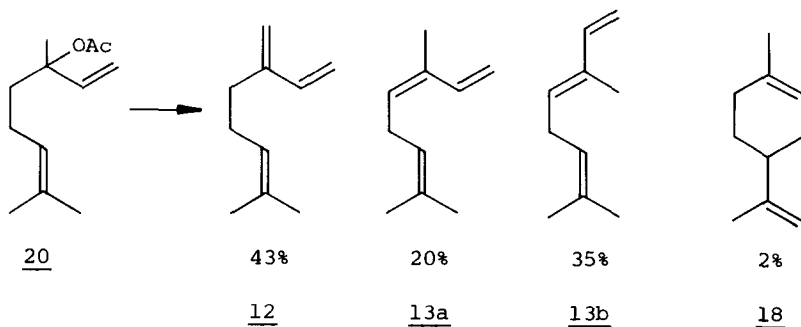
Pyrolysis of various other acetates to give ocimenes and myr-
cene has also been described.[26,38] Dehydration of geraniol
(21) or nerol (22) (related to linalool allylically) in the
presence of potassium hydroxide at 200° for 10 minutes† also
gives 60% of myrcene and other products, including allo-
ocimene.[41]

Geraniol
21

Nerol
22

12 + 16 + other products
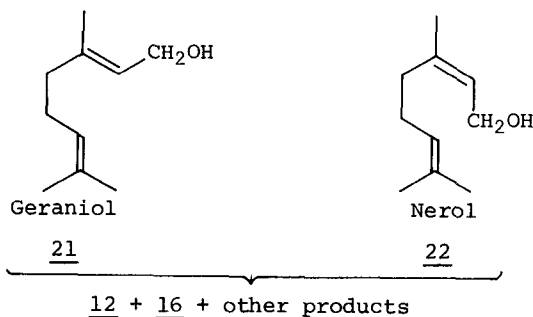
*In view of the instability of linalyl acetate on certain sup-
ports, it is always chromatographed in the author's laboratory
on Chromosorb-W, on which it is stable up to 200°.
†This technique, developed by Ohloff[40] has recently been re-
examined by Bhati both for alcohol dehydration and isomeriza-
tion (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
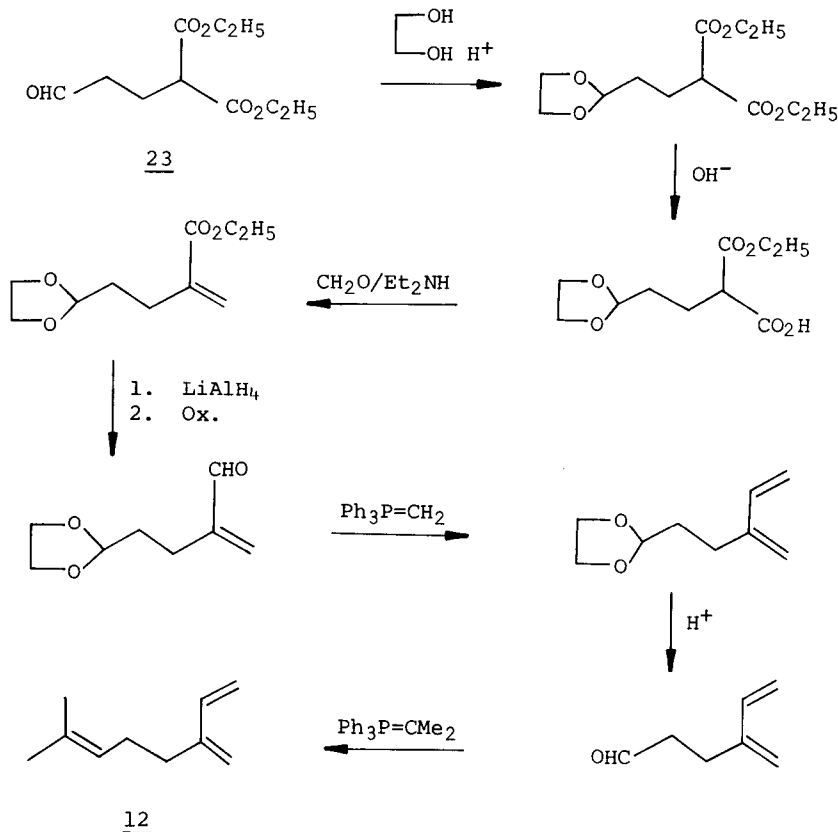
Hymentherene and Achillene

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