TERPENE CHEMISTRY

General Editor

JAMES VERGHESE

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Synthite Industrial Chemicals Private Limited, Kolenchery, Kerala

Tata McGraw-Hill Publishing Company Limited
NEW DELHI

Editorial Supervisor : Usha Tankha
Production Assistant : Anson Babu

Published by Tata McGraw-Hill Publishing Company Limited 12/4 Asaf Ali Road, New Delhi 110 002 and typeset at M/s. Pooja Press & Prakashan Pvt. Ltd. B 167 DDA Sheds, Okhla Industrial Area, Phase I, New Delhi 110 020, and **PRINTED AT SURYA PRINT PROCESS**.

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Preface

Meritorious and well-known monographs dealing with classical terpene chemistry are available. This book has another aim—to afford a short, well-focused glimpse of few of the fascinating phases in the advancing frontiers of this branch of chemistry.

A mighty challenge to the ingenuity of the chemists is the fabrication of sesquiterpenoids in the laboratory. Chapter 1 brilliantly projects the major breakthroughs in this intricate area. Triggered by catalysts, terpenes undergo facile transformations and snapshots of recent developments involving heterogeneous catalysts are presented in Chapter 2. This is followed by a very neat, clear and elegant survey of terpenoid rearrangements in strong acids which are essentially different from those in ordinary acids (Chapter 3). In the concluding chapter the spotlight is on specific aspects of unusual reorganizations of bicyclic monoterpenes induced by light, heat, acid and other electrophiles.

Written by outstanding researchers, it is hoped that this volume will be a valuable source of authoritative information.

The editor acknowledges his deep indebtedness to the contributors. This book is a tribute to the enthusiasm and encouragement of the Board of Directors of Synthite Industrial Chemicals Private Limited.

JAMES VERGHESE

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1

The Synthesis of Sesquiterpenoids from Monoterpenoids

Alan F. Thomas and Yvonne Bessiere

1.1 INTRODUCTION

Before examining the detailed chemical routes leading from monoterpenoids to sesquiterpenoids, we might consider reasons for the synthesis of natural products in general. Perhaps the most obvious reason for any synthesis is to make a substance which is either not found in nature, or not found in sufficient quantities to make extraction an economic proposition. This reason may point towards industrial synthesis. One might, for example, require a certain amount of substance to examine some physical or physiological property. Not only would a small-scale synthesis be sufficient, but closely-related impurities possibly contaminating a natural product, would probably be absent from the synthetic sample, so the property to be examined would be dissociated from any deviation produced by the natural impurities. (This is particularly so in the case of perfumery, where the presence of impurities plays a decisive, and even dominating, role).

A second reason for synthesis has traditionally been as a "confirmation of structure" With the spectral methods of today at the disposal of organic chemists, one might question whether this reason is really as valid as seems to be generally believed.

A third type of synthesis is undertaken to prepare labelled molecules, in the case of terpenoids particularly with ^{2}H or ^{13}C (or their radioactive equivalents ^{3}H and ^{14}C). Here the synthetic strategy is different, since economy is less important.

Occasionally, the discovery, either fortuitously or by design, of a new reaction leads to a desire to use it, and demonstration of its applicability to the synthesis of a natural product can be an impressive way of doing so.

The last reason arises from the natural desire of man to solve puzzles. "If nature can put it together, why can't I!"

Alas, the value of the last type of synthesis is often very limited: even if the conception is ingenious, it is questionable whether the effort is worthwhile if the target substance is readily available.

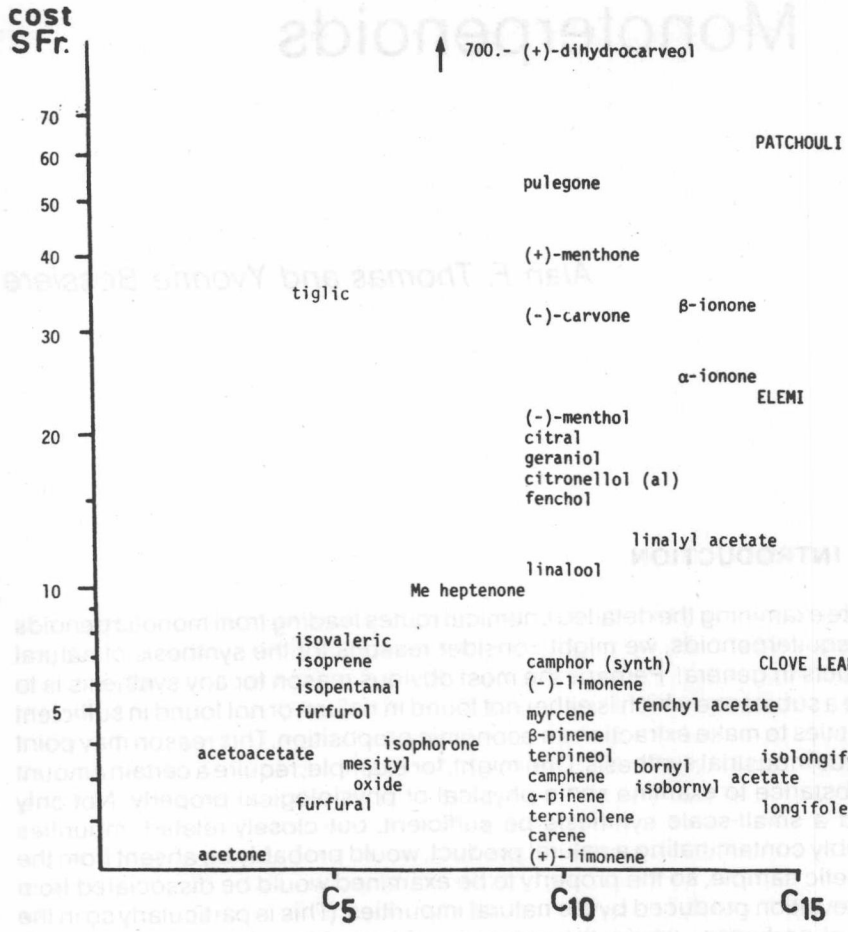


Fig. 1.1 Price of possible synthons for sesquiterpence synthesis. The figures refer to December 1980, and are in Swiss frances per kilogram. Isovaleric means isovaleric acid, etc. Thanks are due to Mr. C.G. Stettler of the purchasing department of Firmenich SA, Geneva, for the information.

The reason why synthesis of sesquiterpenes from monoterpenoids may be interesting is based on the assumption that monoterpenoids are readily available, and, in some cases, very readily available, while sesquiterpenoids are not. Although many sesquiterpenoids could be used, particularly in the perfume and flavour industries, their use is often restricted by inaccessibility. Indeed, the number of industrial sesquiterpenoid syntheses can be counted on one's finger tips—an impressive demonstration of the gulf between academic research and industrial reality!

Figure 1.1 shows the price/kg of possible starting materials for synthesis of sesquiterpenes. These prices relate to 1980, and generally refer to larger amounts (say 100 kg), but the principle does not vary a great deal, and it can be seen at once that there are a considerable number of monoterpenoids that fall into the category of very low-priced substances i.e., "solvent prices". The sesquiterpenes are also given, together with certain oils (in capital letters) from which sesquiterpenoids can be isolated. Thus we can see at once that a synthesis of patchoulol (30% of patchouli oil) starting from dihydrocarvone is not going to be economically feasible. On the other hand, the enormous quantities of carene and α-pinene available provide admirable starting materials for syntheses, especially since chirality is already present.

The considerations about starting materials are compounded—if it is envisaged to scale-up a synthesis—by the propensity of many organic chemists to use unrealistic conditions (such as very low temperatures which are much more costly than high temperatures), solvents whose recovery is difficult (like tetrahydrofuran), and to disregard problems of toxicity (manganese dioxide is difficult to load into a reactor) or pollution (use of mercury salts). These criticisms are not, of course, confined to syntheses of sesquiterpenes alone.

It is hoped that some purpose will be served here by drawing attention to these points, and so introducing a breath of realism into the hurricane of publications about sesquiterpene synthesis. Nevertheless, it must be firmly stated that large-scale industrial use of sesquiterpene synthesis is almost non-existent, and likely to remain so. It is a fact that most sesquiterpenes do not smell, and have practically no physiological action—indeed, those that do have some physiological property appear often to be those whose synthesis is most difficult; few are to be found in this chapter, and none is readily accessible through any type of synthesis.

This chapter should be approached as a source of information about the possible use of monoterpenes, rather than as a compendium of methods for sesquiterpene synthesis, and it is ordered according to the monoterpene skeleton used in the synthesis.

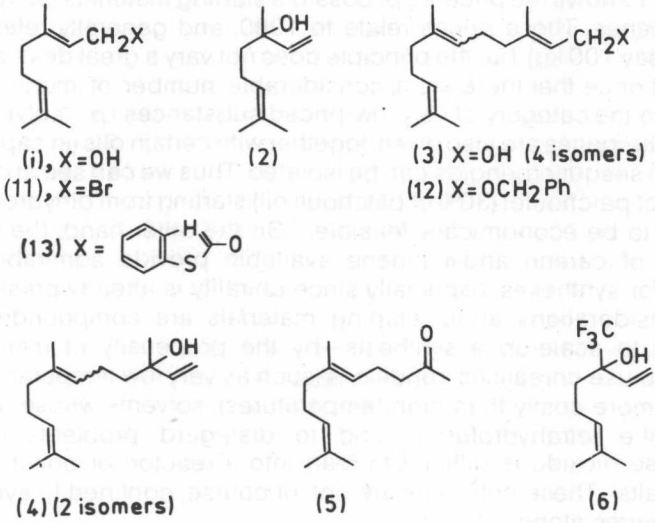
Many totally synthetic routes to sesquiterpenes have been given by Heathcock,[1] and will therefore not be described here in detail.

1.2 SYNTHESIS CLASSIFIED BY TYPE OF SUBSTRATES

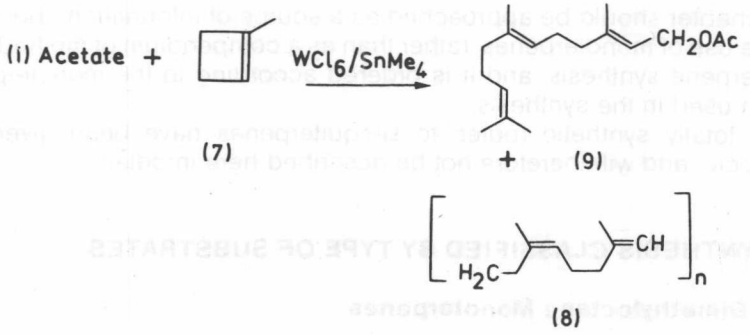
1.2.1 Dimethyloctane Monoterpenes

One of the most straightforward conversions of cheap monoterpenes to sesquiterpenes is possibly the oldest, and certainly one of the most successful commercially. The farnesane skeleton is formed by the

addition of five carbon atoms to geraniol (1) or linalool (2), and such a synthesis of farnesols (3) and nerolidols (4) was described by Ruzicka in 1923,[2] and later developed by Isler *et al.*[3] and Nazarov *et al.*[4], among others. These and similar syntheses[1] employ the oxygenated end of the monoterpene, and usually pass through geranylacetone (5)* When trifluorolinalool (6) was substituted for linalool, the reaction with acetoacetate to give the trifluoro analogue of (5) failed to work, and a different synthesis had to be used.[6]

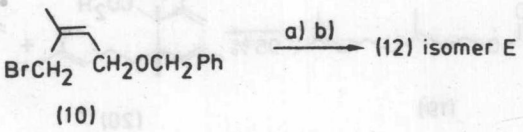


A method that attempted to add an isoprene unit all at once to geranyl acetate (1-acetate) was based on the observation that 1-methylcyclobutene (7) forms a polyisoprene polymer (8) in the presence of tungsten hexachloride in tetramethyltin. In the presence of geranyl acetate, this reaction leads in addition, to 1–2% of farnesyl acetate (9), which can be isolated after precipitating the polymer (8) with methanol.[7] Other Pd(0)-catalyzed alkylations of geranyl and neryl acetates with malonate or phenylsulphonylacetate have been described by Trost.[8]



* Recently, in a synthesis of farnesene-like substances, Fujita *et al.* describe a double bond isomer of (5) as "geranylacetone"[5]. These syntheses do not employ monoterpenes and so fall outside the scope of this chapter.

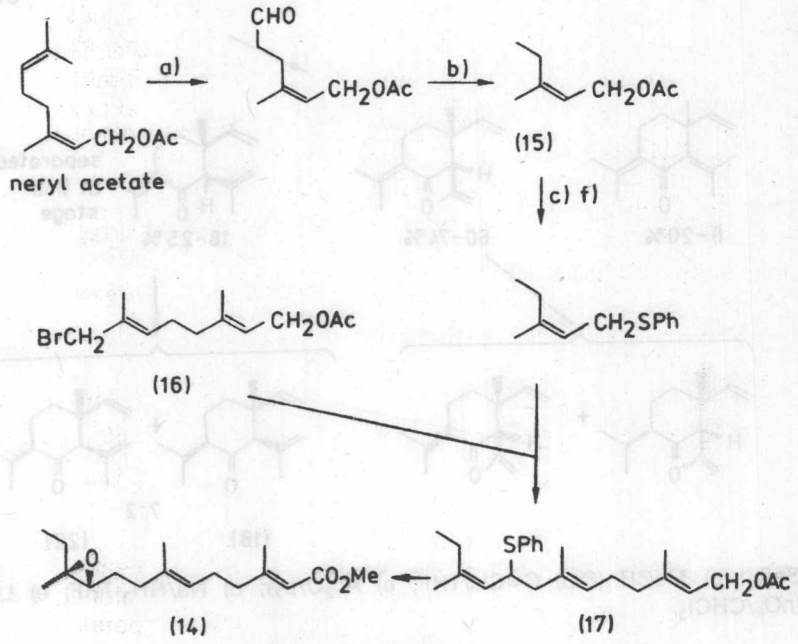
Isoprene itself can be functionalized as the bromoether (10), and the nickel complex of this will react with geranyl bromide (11) to yield farnesyl benzyl ether (12) stereoselectively.[9] The benzothiazole (13) can also be specifically alkylated (with or without allyl rearrangement), but this was not extended to the synthesis of farnesenes.[10]



(10)

a) $Ni(CO)_4$ b) (II)

A particular advantage of using geraniol (1) or its *Z*-isomer, nerol, as starting materials for farnesene syntheses is that they are not only cheap, but available with known configurations of the double bonds.[11] This facet has been exploited in two syntheses of the C_{17} juvenile hormone (14), which depend on the addition of a degraded nerol (15) having a *Z*-double bond, to a functionalized geranyl acetate (16), the product (17) being readily convertible to the hormone (Scheme 1).[12,13]

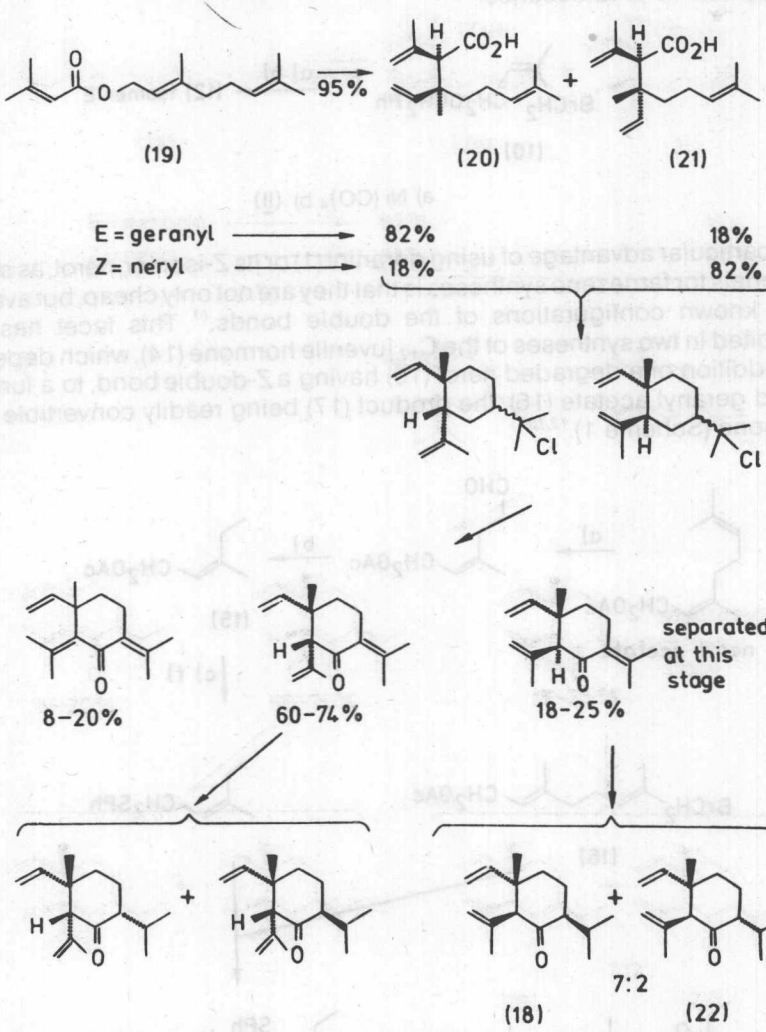


a) O_3 then Me_2S; b) $(PPh_3)_3RhCl$; c) MeOH-K_2CO_3; d) MeLi; e) TsCl; f) PhS^-

Scheme 1

Fráter's ingenious synthesis of shyobunone (18) employs a geranyl (or neryl) ester (19) that already contains the extra isoprene unit linked to oxygen. Rearrangement of the ester enolate yields the *erythro* (20) and *threo* (21) acids, the chlorides of which can be rearranged to the desired carbon

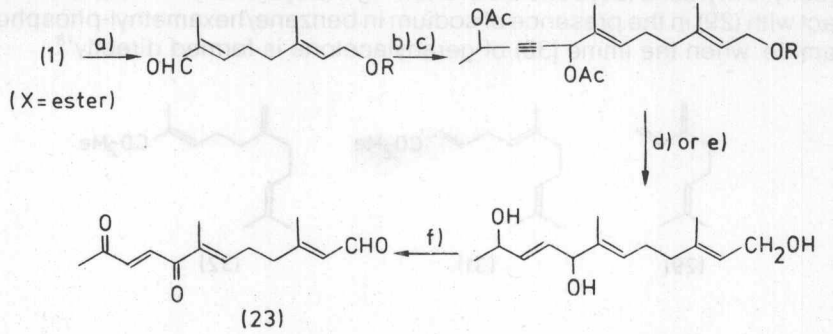
skeleton. Replacement of the chlorine atom by hydrogen yields the four isomers of shyobunone (18), and the synthesis enabled the correct structure of epishyobunone (22) to be established (it was previously given the structure of one of the other isomers) (see Scheme 2).[14]



a) SeO_2; b) MeCH (OLi) C≡CLi/THF; c) Ac_2O/pyr; d) Na/NH_3-THF; e) $LiAlH_4$; f) $MnO_2/CHCl_3$.

Scheme 2

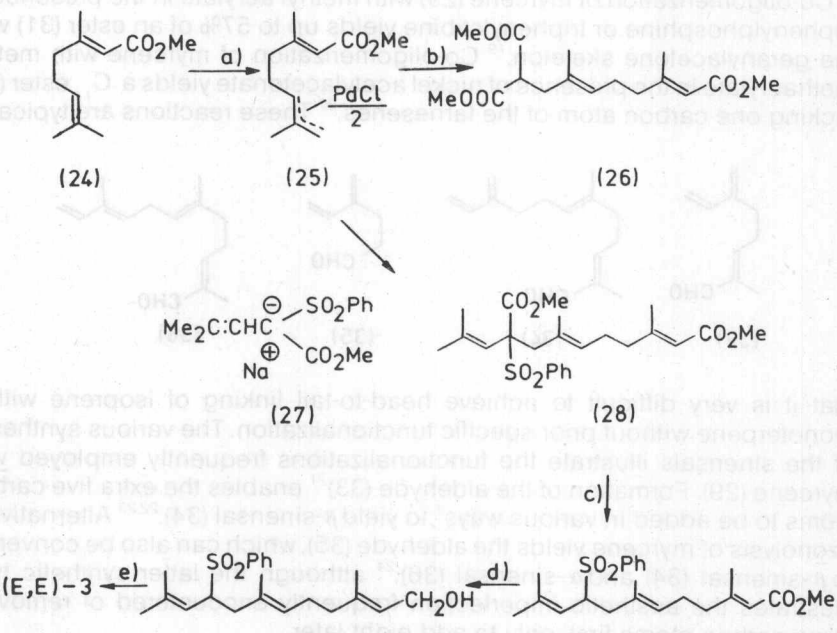
Functionalization of geraniol derivatives at the hydrocarbon end of the chain with selenium dioxide was used in two syntheses, on very similar lines, of the norsesquiterpenoid gyrinidal (23) (isolated from the "whirligig" beetle), one starting from geranyl acetate (1, X = OAc),[15] and the other from geranyl mesitoate (1, X = OOC )[16] (Scheme 3).



a) SeO_2; b) MeCH (OLi) C≡CLi/THF; c) Ac_2O/pyr; d) Na/NH_3–THF; e) $LiAlH_4$; f) $MnO_2/CHCl_3$.

Scheme 3

Somewhat more original is the approach of Trost and Weber, who functionalized the hydrocarbon end of methyl geranate (24) as a palladium chloride complex (25). This reacts with carbanions, such as malonate (to give 26) or the sulphone-activated ester (27) to give (28) the latter being convertible to farnesol (3) (Scheme 4).[17]

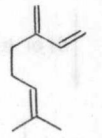


a) PdCl, NaCl, $CuCl_2$, NaOAc, HOAc; b) Na malonic ester; c) LiI. $3H_2O$, NaCN in DMF 120°; d) i-Bu_2AlH in PhMe + hexane,—40 to O°; e) Li in $EtNH_2$ at—78°.

Scheme 4

Probably the most popular hydrocarbon employed for preparing farnesenes is myrcene (29). A very simple method of adding a C_3 functionalized unit

directly to myrcene (29) consists in allowing the cyclohexylimine of acetone to react with (29) in the presence of sodium in benzene/hexamethyl-phosphoric triamide, when the imine (30) of geranylacetone is formed directly[18].



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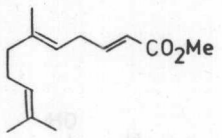

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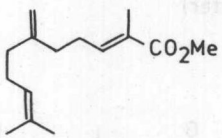

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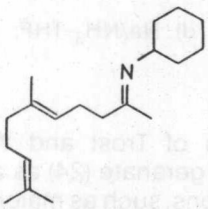
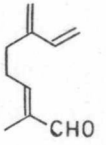


(30)

Co-oligomerization of myrcene (29) with methyl acrylate in the presence of triphenylphosphine or triphenylstibine yields up to 57% of an ester (31) with the geranylacetone skeleton.[19] Co-oligomerization of myrcene with methyl methacrylate in the presence of nickel acetylacetonate yields a C_{14} ester (32) lacking one carbon atom of the farnesenes.[20] These reactions are typical in



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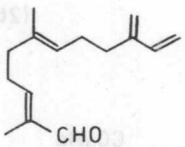

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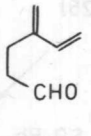

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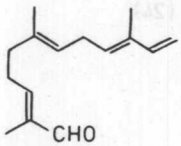
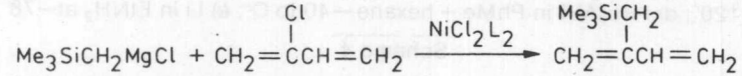


(36)

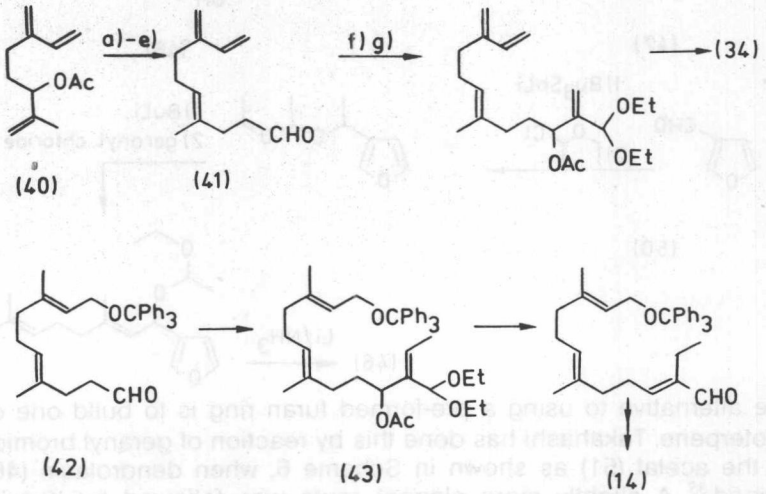
that it is very difficult to achieve head-to-tail linking of isoprene with a monoterpene without prior specific functionalization. The various syntheses of the sinensals illustrate the functionalizations frequently employed with myrcene (29). Formation of the aldehyde (33)[21] enables the extra five carbon atoms to be added in various ways[1] to yield β-sinensal (34).[22,23] Alternatively, ozonolysis of myrcene yields the aldehyde (35), which can also be converted to β-sinensal (34) and α-sinensal (36),[24] although the latter synthetic type illustrates the aesthetic imperfection frequently encountered of removing three carbon atoms first, only to add eight later.



(37) (38) (39)

The reaction of the Grignard reagent (37) from chloromethyltrimethylsilane and chloroprene (38) in the presence of a catalytic amount of dihalodiphosphinenickel (II) yields an isoprene equivalent (39) which reacts with aldehydes and acid chlorides.[25] Although it has not been extended to sesquiterpene synthesis, clearly (39) ought to react with (33) or the corresponding acid chloride to yield sinensal derivatives.

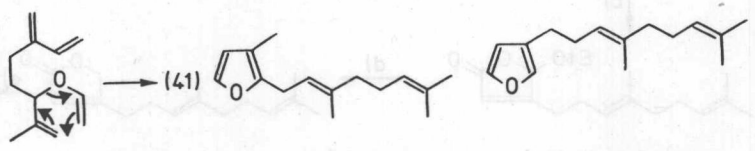
Methods of functionalizing myrcene at C_3 as in the acetate (40) have been known for a long time,[26] and (40) can be used to make the aldehyde (41)[27]—an intermediate in the Büchi-Wüest β-sinensal synthesis.[23] Recently, this aldehyde has been converted to β-sinensal in a different way (Scheme 5). The use of different precursors, (42), (43), leads to one of the juvenile hormones (14).[27] This synthesis is again, unfortunately, despite the ingenuity of its



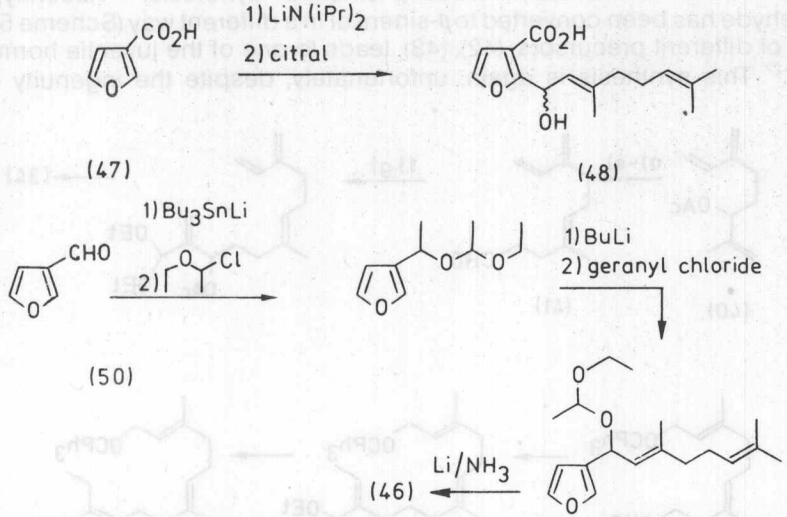
a) LiN $(iPr)_2$, $tBuMe_2SiCl$; b) 70°; c) $PhCH_2N^+Me_3F^-$/aq. MeOH; d) $LiAlH_4$; e) pyr, HCl—CrO_3; f) Br/BuLi; g) H_2SO_4 aq.; h) $NaCNBH_3$.

Scheme 5

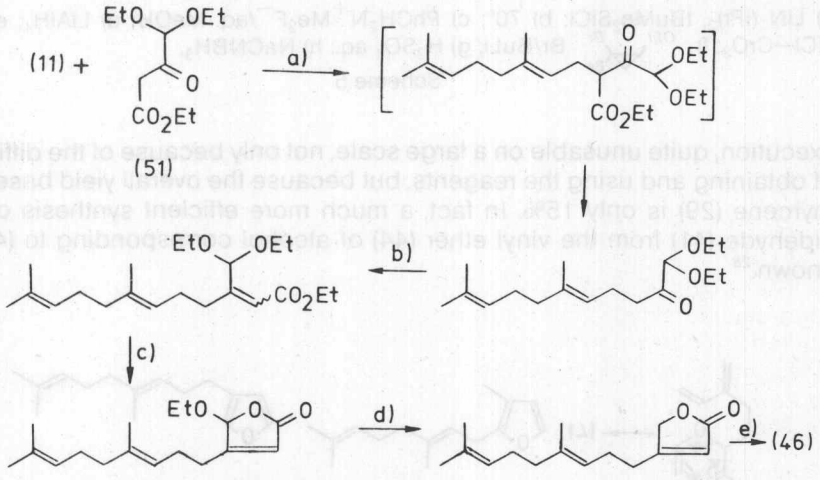
execution, quite unusable on a large scale, not only because of the difficulty of obtaining and using the reagents, but because the overall yield based on myrcene (29) is only 15%. In fact, a much more efficient synthesis of the aldehyde (41) from the vinyl ether (44) of alcohol corresponding to (40) is known.[28]



The furanoid sesquiterpenes like sesquirosefuran (45), dendrolasin (46) and their oxygenated derivatives are farnesene oxides, and extensions of some of the methods already described can be employed in their synthesis. The simplest way of preparing (45), for example, is probably by reaction of geranyl bromide (11) with a metallated 3-methylfuran (both lithium[29] and mercury[30] have been used). 3-Furoic acid (47) can be dimetallated, and the reaction of this dianion with citral yields (48).[31] Still has made dendrolasin (46) by the reaction of geranyl chloride on the metallated acetal (49) derived from 3-furfural (50).[32]



The alternative to using a pre-formed furan ring is to build one onto a monoterpene. Takahashi has done this by reaction of geranyl bromide (11) with the acetal (51) as shown in Scheme 6, when dendrolasin (46) was obtained.[33] A slightly more elegant route was followed by Kondo and



a) NaOEt; b) $(EtO)_3PCH_2CO_2Et$; c) H^+ /UV; d) $NaBH_4$; e) li—Bu_2AlH.

Scheme 6