# SYNTHETIC STUDIES ON FARNESENE ISOMERS AND HOMOLOGUES FROM THE DUFOUR GLANDS OF ANTS

by

LORNA D. THOMPSON

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Department of Chemistry
University of Keele
Staffordshire

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Abstract

(Z,E)-α-farnesene and its homologues homo-, bishomo- and trishomo-farnesenes had been identified as constituents of the Dufour gland secretion of several species of Myrmica ant. Although farnesene isomers had been found previously in plant and insect sources, the homo-, bishomo- and trishomo-farnesenes were a new group of substances. A general preparative route, that would permit the synthesis of this homologous series, was sought to confirm identification and for biological testing.

A partially stereospecific synthesis of (Z,E)- and (Z,Z)-α--farnesenes, involving a Wittig reaction between 6-methyl-5-hepten-2--one and the ylid from (Z)-4-methyl-3,5-hexadienyltriphenylphosphonium iodide, is described. Although the Wittig reaction was performed under conditions reported to give trans-selective olefin formation, it gave a mixture in which (Z,E)-α-farnesene was the minor component. The ' isomers were separated on a silver nitrate loaded liquid chromatography column. The identity of the natural and synthetic isomers was confirmed.

Two ketones, 7-methyl-6-octen-3-one and 7-methyl-6-nonen-3-one were successfully prepared by a multistage route from 4-chlorobutyryl chloride, the former was used in condensations with the ylid described above. Attempts were made to find optimum conditions for the condensation but yields of (Z,E)- and (Z,Z)-homofarnesenes were poor. The mass spectrum of the (Z,E) isomer, obtained by GC-MS, was identical to that of ant homofarnesene.

Another route to the series, a variation of the Wittig reaction using a sulphoxide reagent, was tried in an attempt to improve the yield of farnesene homologues at the final stage. Trial condensations

of the prepared t-butylsulphoxide reagent with 6-methyl-5-hepten-2--one gave the desired β-hydroxysulphoxide but the elimination step to give farnesene could not be successfully achieved.

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C O N T E N T S

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# INTRODUCTION

## FARNESENES IN MYRMICINE ANTS

### Myrmica rubra

A systematic study of the organic chemicals in the Dufour gland of workers of the common British red ant Myrmica rubra, was started in this department by L.J. Wadhams in 1970. Although this gland has been known since 1841, when it was first recognised by Dufour[1], and is found throughout the order of Hymenoptera, its function still remains unknown. The gland is found in the abdomen, attached by a duct to the sting apparatus. In M. rubra it appears[2] as a clear, pear-shaped sac of approximately one third of the volume of the poison vesicle, and its duct opens, together with the duct from the poison vesicle, at the base of the sting lancet[3].

Wadhams found[4] that the major components of the Dufour gland content were linear hydrocarbons, saturated and unsaturated, in the $C_{13}$-$C_{19}$ range, which were present in microgram quantities. In addition to these linear compounds, three terpenoid hydrocarbons were discovered as minor constituents present in nanogram quantities. These were shown by reaction gas chromatography to be unsaturated and their retention times on polar and non-polar columns showed that they were of low polarity. Their identification however was chiefly by their mass spectra, which were typical of acyclic sesquiterpenes, with the most intense peaks being at low mass (below m/e 100) and the molecular ions weak. The mass spectrum of the first of these compounds showed a molecular ion at m/e 204 and the spectrum was identical to that published by Bergström and Lofqvist[5], which they had identified as that of an isomer of the

sesquiterpene, α-farnesene (**1**, figure 1). The second and third of these sesquiterpene constituents had molecular ions with masses fourteen and twenty eight units higher respectively than the compound assigned the structure of α-farnesene, suggesting that these components were homologues of α-farnesene. These compounds were therefore identified as a homofarnesene, ($C_{16}H_{26}$) and a bishomofarnesene, ($C_{17}H_{28}$) with one and two extra methylene groups respectively.

The mass spectrum of the homofarnesene had a strong peak at m/e 189 ($M^+$ - 29) indicating the presence of an ethyl side-chain. It seemed therefore, that one of the methyl groups at C-3, C-7 or C-11, (see **1**, figure 1), had been replaced by an ethyl group. Similarly, the bishomofarnesene mass spectrum had a strong peak at m/e 203 ($M^+$ - 29), again suggesting the presence of an ethyl side chain.

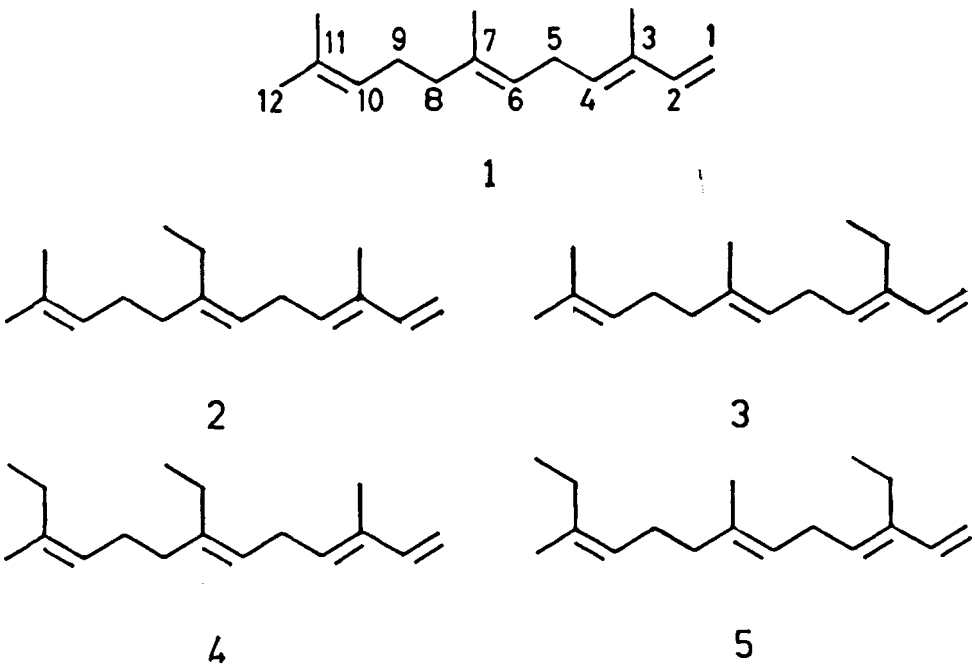



Figure 1

Interpretation of the fragmentation patterns in the mass spectra of the homologues, led to the assignment of the ethyl group to either the C-3 or C-7, but not the C-11 position in the homofarnesene (**2** or **3**, figure 1) and to the C-11 and C-3 or C-7 position in the bishomofarnesene, (**4** or **5**, figure 1).

Four geometrical isomers of α-farnesene are possible and in order to determine which of these was present in the Dufour gland of M. rubra, all four α-isomers plus the two β-farnesene isomers were prepared[6] by dehydration of a mixture of (E)- and (Z)-nerolidol, (**6** and **7**, figure 2), using phosphoryl chloride in pyridine at 70C.

Gas chromatography of the resulting isomeric mixture gave only five peaks corresponding to (Z)-β, (E)-β, (Z,Z)-α, a mixture of (E,Z)-α and (Z,E)-α together, and (E,E)-α-farnesene. The retention time of the natural farnesene from M. rubra, run under the same conditions, showed that it was either (Z,E)- or (E,Z)-α-farnesene but it was not possible to separate completely the (Z,E) and (E,Z) isomers from the synthetic mixture so that reliable mass spectra of the pure isomers could not be obtained. The mass spectra of all four α-farnesene isomers are essentially the same but there are differences in the minor peaks and the relative intensities of some of the peaks. For example the ratio of m/e 135 to m/e 133 is dependent on the configuration of the C-6 double bond. Comparison of the heights of these two peaks in the mass spectrum of the glandular material led to the assignment of an E configuration to this double bond. By a process of elimination therefore the farnesene isomer present in the Dufour gland of M. rubra was identified as (Z,E)-α-farnesene (**8**, figure 3).

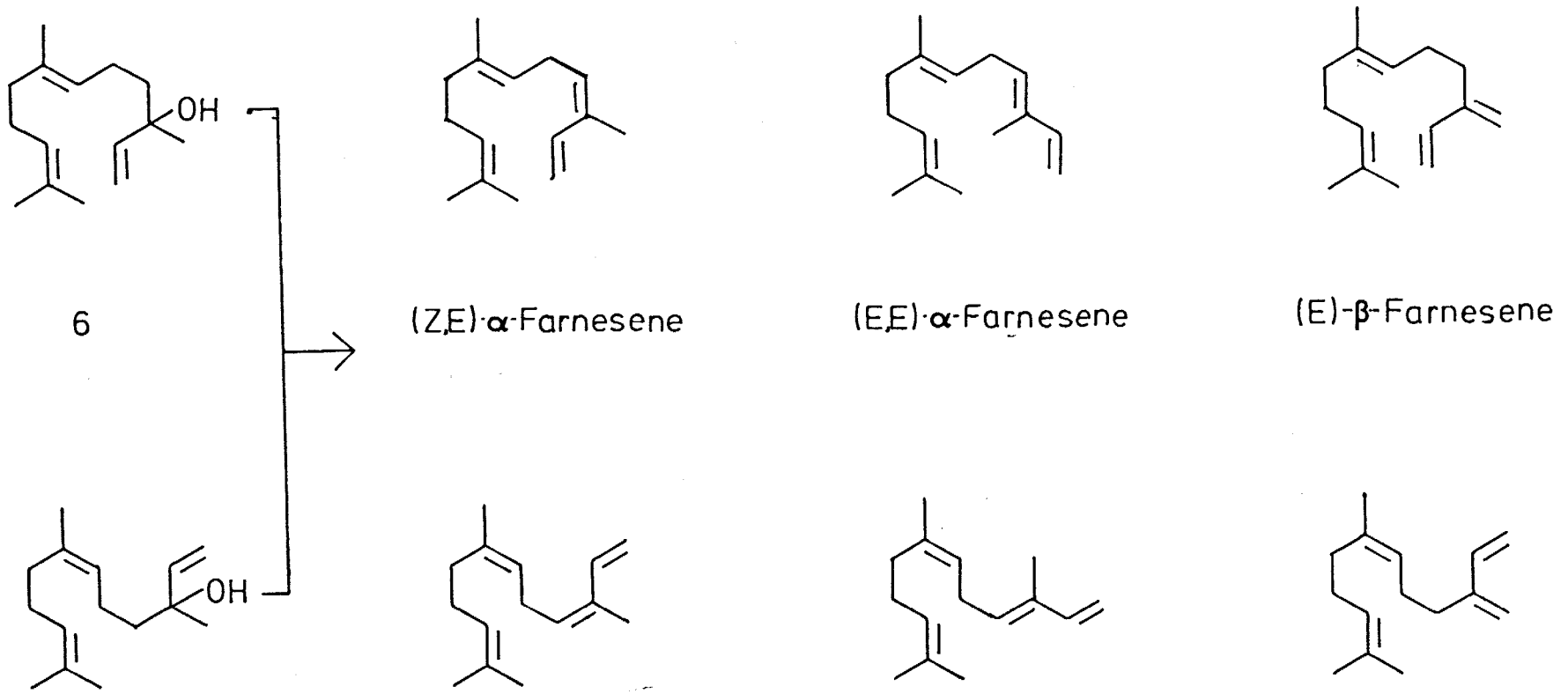

OH
6
(Z,E)-α-Farnesene
(E,E)-α-Farnesene
(E)-β-Farnesene
OH
7
(E,Z)-α-Farnesene
(Z,Z)-α-Farnesene
(Z)-β-Farnesene

Figure 2

Myrmica scabrinodis .

Gas chromatographic investigation of the Dufour gland of another Myrmica ant, M. scabrinodis by K. Parry[7] showed that it contained only four major components rather than more than twenty as in M. rubra. Three of these compounds were found to have the same retention times on gas chromatograph as the α-farnesene, homofarnesene and bishomofarnesene which were minor constituents in M. rubra. The presence of these compounds as major components and the absence of the linear hydrocarbons in the same molecular weight range made M. scabrinodis a better species in which to study the farnesenes. The fourth major component from the Dufour gland of M. scabrinodis was of longer retention time and its mass spectrum showed a molecular ion at m/e 246, fourteen mass units higher than bishomofarnesene. The mass spectrum once again was typical of a sesquiterpene which led to this compound being identified as a farnesene homologue in which the three methyl groups at C-3, C-7 and C-11 had all been replaced by ethyl groups, i.e. trishomofarnesene (**13**, figure 3).

Analysis of the mass spectra of the four farnesenes from M. scabrinodis suggested that they all possessed the (Z,E) arrangement of double bonds and that the extra methylene group was at C-3 or more probably C-7 in homofarnesene (**9** or **10**, figure 3) and at C-11 and C-7 or C-3 in bishomofarnesene (**11** or **12**, figure 3). A further isomeric possibility is introduced at the C-10-C-11 double bond in bis-and tris--homofarnesenes by the presence of the extra methylene at C-11 and the geometry of this double bond has not been determined.

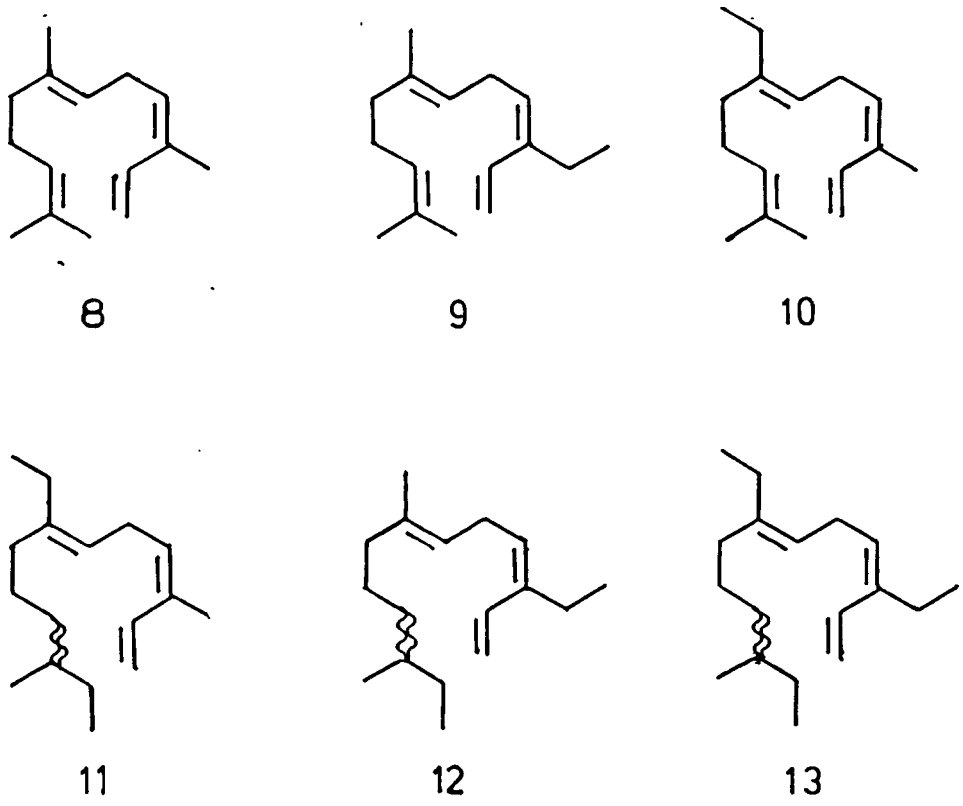



Figure 3.

In a further attempt to confirm the identification of the farnesene from M. scabrinodis and M. rubra as (Z,E)-α-farnesene a mixture of (Z)- and (E)-nerolidol was again dehydrated by the method of Anet[6]. However although Parry was able, on the evidence of gas chromatographic retention times, to rule out the possibility that the natural isomer was a β-farnesene or (Z,Z)- or (E,E)-α-farnesene it was less easy to distinguish between (E,Z)- and (Z,E)-α-farnesenes due to their similar retention times and incomplete separation on the capillary columns used.

Parry then tried out a number of different dehydrating agents on nerolidol to see whether it was possible to improve the yield of farnesenes and increase the relative proportions of the (E,Z)- and

(Z,E)-α-farnesenes. He found that by using p-toluenesulphonic acid in refluxing toluene he was able to increase the overall yield of farnesenes to 81% with a higher proportion of the less stable (E,Z) and (Z,E) isomers.

In order to simplify the product mixture produced by the dehydration, the commercially available mixture of nerolidol isomers was separated by preparative gas chromatography and the pure (Z)- and (E)-nerolidols were dehydrated independently using the improved reaction conditions. (E)-Nerolidol gave a mixture of (E)-β-farnesene, (E,E)- and (Z,E)-α-farnesenes, and a cyclized product. (Z)-Nerolidol gave a more complex mixture of (Z)-β-farnesene, (Z,Z)-, (E,Z)- and (E,E)--α-farnesenes, and cyclized products, due to isomerization of the less stable cis double bond. Comparison of the products from the two dehydrations with the Dufour gland material from M. scabrinodis on capillary GC showed that none of the products from (Z)-nerolidol coincided in retention time with the natural isomer. However the retention time of the natural farnesene coincided exactly with that of the (Z,E)-α-farnesene product from dehydration of (E)-nerolidol. A mass spectrum of the pure (Z,E)-α-farnesene could not be obtained since the (Z,E) and (E,Z) isomers were only completely resolvable on capillary columns and no capillary GC-MS facilities were available.

Further Myrmica species

Work by R.P. Evershed in this department on the Dufour gland of two further species of Myrmica, M. ruginodis and M. sabuleti[8] showed that they too contained farnesene and its homologues. M. sabuleti like M. scabrinodis had (Z,E)-α-farnesene, homofarnesene and bishomo-farnesene as major constituents with the third homologue, trishomo-farnesene present in much smaller amounts. M. ruginodis however was

more like M. rubra in that the major components of the Dufour gland content were linear hydrocarbons with α-farnesene, homofarnesene and bishomofarnesene present as only minor constituents.

More recently A.B. Attygalle has studied another three Myrmica species[9] and found that they all contain farnesenes in varying amounts in their Dufour glands. Two of these, M. schencki and M. sulcinodis have farnesenes as major constituents and the third M. rugulosa has them present in minor amounts with more of the linear hydrocarbons. Evershed has also found that M. lobicornis[10] has α-farnesene, homofarnesene and bishomofarnesene as the major components of its Dufour gland content.

Attine species

In addition to these eight species of Myrmica, one species of Acromyrmex, was shown to contain a farnesene homologue[2]. The major component in the Dufour gland of A. octospinosus is homofarnesene. The gland however is very small in this species and the amount of homofarnesene is much less than in the Myrmica species. No α-farnesene was found but it could be present in quantities which are below the limits of detection. Three further Attine species, Atta cephalotes, Atta sexdens sexdens and Atta sexdens rubropilosa were also examined but none of these compounds were found in their Dufour glands.

PHEROMONAL FUNCTION OF DUFOUR GLAND CONTENTS

Although the Dufour gland has been observed and described many years ago, and although it is found throughout the order Hymenoptera, its purpose and function remains unknown. Because of its association with the sting and venom gland it has been suggested that it may provide

a lubricant for the sting lance. The quantity of material produced however seems far more than necessary for that function, and a pheromonal function seems probable, whether or not that is a primary or secondary function of the gland. The Dufour gland content of Myrmica ants has been investigated for pheromonal activity[11,12]. When older workers explore a new foraging area they move slowly and lay down droplets of the Dufour gland content. This induces following workers to move more rapidly and sinuously, exploring the territory for food. This effect is due to the volatile alcohols and carbonyl compounds which are common to all Myrmica species and falls off after a few minutes as these evaporate leaving the higher molecular weight hydrocarbons. These compounds appear to have a territorial marking effect, causing foraging workers to move more slowly over the territory than when the secretion was freshly laid down but more quickly than on new, unmarked territory. Workers of M. rubra and M. scabrinodis are unable to tell whether the freshly deposited secretion was laid by their own or the other species. However when the volatile portion of the secretion (which has almost identical composition in the two species), has evaporated they are able to recognise whether the secretion was laid by their own species. This accords well with the findings that the composition of the less volatile part of the Dufour gland contents is very different in the two species, M. rubra having predominantly linear hydrocarbons and M. scabrinodis predominantly farnesenes. Each of the eight species of Myrmica so far investigated has a distinct blend of hydrocarbons and the workers are presumed to be able to distinguish between the secretion of their own, and that of other species.

## FARNESENES FROM OTHER NATURAL SOURCES

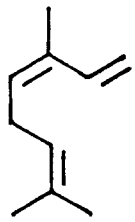
### Plants

While natural β-farnesene has been known for many years and has been shown to have the (E) or trans configuration[13], α-farnesenes have only been isolated comparatively recently. The first reported identification of a natural α-farnesene was in 1966 when Huelin and Murray found that α-farnesene was virtually the only sesquiterpene present in the natural coating of Granny Smith apples[14]. They had originally identified it as β-farnesene[15], but comparison of the UV, NMR, IR and mass spectra of the material from the apples with those of pure β-farnesene, isolated from the essential oil of Matricaria chamomilla[16], showed that they were not the same.

Further work by Murray[17] led him to conclude that the farnesene present in Granny Smith and other varieties of apples, and also in pears and quinces was the 'all-trans' or (E,E)-α-farnesene. This was accompanied by a small proportion of another α-farnesene isomer to which Murray tentatively assigned an (E,Z) configuration. This was shown later by Anet[6] to be incorrect when he synthesised (E,Z)-α-farnesene by dehydration of (Z)-nerolidol and he then assigned the (Z,E) configuration to the minor component from apples and confirmed the assignment of the (E,E) configuration to the predominant isomer.

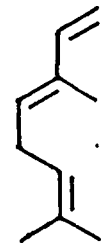
At about the same time as Murray made his assignment[17] of the (E,E) configuration to the major α-farnesene isomer from Granny Smith apples, Sakai and Hirose in Japan reported[18] the isolation and identification of (Z,E)-α-farnesene from the volatile oil of Perilla frutscens f. viridis. Identification was made using the NMR and UV spectra of the isolated farnesene. The presence of a cis double bond in the conjugated diene system was indicated by the absorption maximum

at 238 nm in the UV and the NMR signal at 6.74 ppm for the lone proton of the terminal double bond. These values compare well with those given by Ohloff[19] et al. for cis-β-ocimene (**14**, figure 4) which has a similar diene structure. The assignment of the (Z,E) configuration was again confirmed by Anet[6].



14

cis-β-ocimene



15

trans-β-ocimene

Figure 4

Since the first discovery of a natural α-farnesene by Murray, α-farnesene isomers of undetermined stereochemistry have been identified, particularly in recent years, as constituents of numerous essential oils and other plant materials. In 1980, volume 92 of Chemical Abstracts alone contains twenty one references to α-farnesene only four of which refer to a particular isomer. In cases where the stereochemistry has been assigned, the most common naturally occurring isomer appears to have the most stable, 'all-trans' or (E,E) configuration. (Z,E)-α--farnesene, the isomer found in the Dufour gland of Myrmica ants, in the volatile oil of Perilla and as a minor constituent of apples, has

been identified in plants less frequently, either in conjunction with the more common (E,E) isomer or as the only farnesene present.

The other isomers, (E,Z)- and (Z,Z)-α-farnesenes have not been reported as occurring naturally in plant species.

(E,E)-α-farnesene was identified[20] by Maarse and Van Os in 1973, as a minor constituent of the volatile oil of Origanum vulgare. Identification was based on the IR and mass spectra and the Kovats indices obtained by GC on two different stationary phases. No details were given of how the assignment of the (E,E) configuration was made and no reference was made to the work of Anet[6].

Malingre and Maarse later reported[21] (E,E)-α-farnesene and (E)-β-farnesene as minor components in the essential oil of a species of mint, Mentha aquatica. The farnesenes were again identified by their Kovats indices and mass spectra obtained by GC-MS.

Both (Z,E)- and (E,E)-α-farnesene were found by Collins and Halim[22] in the fruit of Diospyros blancoi or velvet apple, a tree of the Ebony family. The IR and mass spectra of the sole component of the hydrocarbon fraction from the fruit were identical to those of the α-farnesene isolated from varieties of apples, pears and quinces by Murray[17]. Collins and Halim therefore identified the major component from velvet apple as (E,E)-α-farnesene. As in the apples, however, a second α-farnesene was found as a minor component of velvet apple. It was not possible to obtain sufficient of this second isomer to perform the necessary spectral analysis but the mass spectrum was very similar to that of the major (E,E) isomer. Following Murray's tentative identification of the minor isomer from apples as (E,Z)-α-farnesene, this structure was also assigned to the minor component from velvet apple. However, as Anet[6] later showed that Murray's identification was wrong and that the minor component from apples was in fact the (Z,E) isomer

this indicates that the assignment of the (E,Z) configuration to the velvet apple compound was also incorrect and that this too is the (Z,E) isomer.

(E,E)-α-farnesene was found by Shimizu and Yoshihara to be the major component of the essential oil of the fruit of Cydonia oblonga, the Japanese quince[23]. The essential oil obtained by steam distillation of the fruit was analysed by capillary GC and found to contain 58% of the major component, which was isolated by column chromatography on silica gel. Identification as (E,E)-α-farnesene was made by UV, IR, NMR and mass spectrometry. The IR and NMR spectral data were said to coincide exactly with those given by Brieger[24] et al for (E,E)-α--farnesene, prepared by catalytic isomerization of (E)-β-farnesene.

Another Japanese group reported[25] the identification of (EE)-α- and (E)-β-farnesenes in the volatiles of Seri, (Oenanthe stolonifera). The original paper however was not available here and the entry in Chemical Abstracts does not give details of how the farnesene isomers were identified.

Bohlmann and coworkers have identified both (E,E)- and (Z,E)-α--farnesenes several times in various plant species. The identification in each case was made by comparison of the IR and NMR spectra of the isolated compounds with those of authentic material.

The first reported identification of an α-farnesene isomer by this group was in 1977 when (Z,E)-α-farnesene was found[26] in five species of Senecio. The aerial parts of Senecio elegans and S. capitatus and the roots of S. bicolor, S. othonnae, and S. sylvaticus were found to contain this isomer of farnesene.

The (E,E) isomer was first identified[26,27] in 1978 when Bohlmann and Zdero found that the aerial parts of two species of Euryops, E. linearis and E. annae contained (E,E)-α-farnesene. This isomer

was again identified[27] in 1978, in the aerial parts of Eumorphia sericea.

Several further species of Senecio were investigated[29] by Bohlmann's group in 1979 and this time two species, S. mikanoides and S. gathlambanus were found to contain (E,E)-α-farnesene in their aerial parts. This isomer was also found in the aerial parts of Dorinicum macrophyllum[30] and Ligularia macrophylla[31].

Both isomers, (Z,E)- and (E,E)-α-farnesene were identifed[32] by Bohlmann and Abraham as minor components in the aerial parts of another Dorinicum species, D. pardalianches. Finally, (Z,E)-α--farnesene was found in the aerial parts and the roots of Austroeupatorium chaparense[33].

Hendriks and coworkers in 1978 reported[34] that (E,E)-α-farnesene was a minor component of the essential oil of Cannabis sativa. The compound was identified as (E,E)-α-farnesene by GC-MS, the spectrum being compared with those listed[35] in Stenhagen's 'Registry of Mass Spectral Data'. The same compound was also found to be present in the related Humulus lupulus, (hops).

The flowers, leaves and branches of the deciduous tree Meratia praecox were all found[36] to contain (E,E)-α-farnesene when studied by Naya and Kotake. Identification was made by GC-MS and by comparison of IR and NMR spectra with those of authentic samples.

GC retention time and GC-MS were used by a Japanese group in 1979 to identify[37] a component of the peel oil and juice from Citrus Unshiu as (E,E)-α-farnesene. Other citrus oils were also found to contain this farnesene isomer by Moshonas and Shaw in 1980. They identified[38] the (E,E) isomer isolated from distilled lime oil and from cold-pressed Valencia orange peel oil, by comparison of the IR and mass spectra with those of an authentic sample prepared by acid-catalysed dehydration of

farnesol. Previous workers[13] had not found it possible to isolate any α-farnesene isomers from this reaction but Moshonas and Shaw were able to obtain the pure (E,E) isomer by GC on a packed polar column, then rechromatography on a non-polar column to separate it from β-bisabolene. The configurations of the α-farnesene isomers isolated from the dehydration were assigned by comparison of their GC retention times and IR spectra with those given by Anet[6] for all six farnesene isomers.

(E,E)-α-farnesene was reported[39] to be a characteristic component of the essential oil of the leaves of Magnolia stellata but the method of identification was not given in Chemical Abstracts and access to the original journal could not be obtained.

Insects

Although both α-farnesene and especially β-farnesene have been reported frequently as components of various plant materials and essential oils, there are relatively few cases where they have been identified in animal, or particularly insect species.

The first reported isolation of an α-farnesene isomer from an insect was in 1967 when an Australian group[40] found that the sole constituent of the Dufour gland secretion of the Myrmicine ant Aphaenogaster longiceps was identical to the α-farnesene isolated by Huelin and Murray from Granny Smith apples[14]. They were unable to assign configuration on the evidence available but suggested that a trans configuration was most likely in the diene portion of the molecule. This was based on the appearance of the C-2 proton at δ6.3 in the NMR and the UV absorption maximum at 232 nm which correspond to the values reported[19] for trans-β-ocimene (**15**, figure 4) (δ6.30 and $\lambda_{max}$ 232 nm)

rather than for cis-β-ocimene (14, figure 4) (δ6.73 and $\lambda_{max}$ 237 nm). Anet[6] later confirmed that the isomer present in the ants was, like the predominant isomer from apples, (E,E)-α-farnesene.

Shortly after this discovery of (E,E)-α-farnesene in the myrmicine ant, Bergström and Löfqvist identified[41] a different α-farnesene isomer in the Dufour glands of three formicine ants. In their investigations of the slave-keeping ants, Polyergus rufescens and Formica sanguinea and their slaves F. fusca and F. rufibarbis, they discovered that only the last species did not possess α-farnesene in its Dufour gland. Bergström and Löfqvist later identified[5,42] one isomer of α-farnesene as a minor component in the Dufour gland of two further formicine ants, Camponotus ligniperda and Camponotus herculeanus.

More recently, both (E,E)- and (Z,E)-α-farnesenes have been isolated[43] from the trail pheromone of the red imported fire ant, Solenopsis invicta. Identification of the (Z,E) isomer was made by comparison of UV, IR, NMR and mass spectra with those of synthetic material from the dehydration of nerolidol. The (E,E) isomer was identified by its GC retention time on two columns compared with synthetic material.

In addition to their identification in ants, farnesene isomers have also been found in bees and aphids. All four α-farnesene isomers were found[44] to be minor components of the Dufour gland secretion of three species of Andrena bees (Hymenoptera, Apidae), Andrena bicolour, A. helvola, and A. haemorrhoa. Three further species, A. denticulata, A. nigroaenea, and A. carbonaria, were found to contain three α-farnesene isomers. Identification was made by GC-MS.

The first report of a farnesene isomer being found in aphids, was in 1972 when Bowers identified the alarm pheromone of several species of aphid as (E)-β-farnesene. The rose aphid (Macrosiphum rosae), the pea aphid (Acyrthosiphon pisum), the greenbug aphid (Schizaphis graminum), and the cotton aphid (Aphis gossypii), were all found to have (E)-β-farnesene as their alarm pheromone. This was also the first report of a farnesene isomer showing pheromonal activity.

A further species of aphid, Myzus persicae, the green peach aphid was later reported by Edwards[46] and his coworkers, and by Wientjens[47] and his coworkers, to have (E)-β-farnesene as its alarm pheromone. The latter group also found this farnesene isomer to be the alarm pheromone for three species of grain aphid, Macrosiphum (sitobion) avenae, Rhopalosiphum padi and Metopolophium dirhodum.

All six aphids of the subfamily Aphidinae were also found[48] by Nault and Bowers to produce (E)-β-farnesene as alarm pheromone.

More recently in 1980, in a study of six species of aphid, Pickett and Griffiths discovered[49] that in addition to (E)-β-farnesene, the green peach aphid Myzus persicae has two α-farnesene isomers, (E,E)- and (Z,E)-α-farnesene as components of the alarm pheromone. They also reported that (E)-β-farnesene is a major component of the alarm pheromone of another species of aphid, Phorodon humuli.

It is interesting to note that during work on this thesis, a reference was found to a Japanese review[50] entitled, "Studies on the substances possessing pheromonal activities in insects". The review was not available here but the entry in Chemical Abstracts states that, "the roles of farnesene, germacrene, verbenyl acetate and their analogues as alarm or sex pheromones are discussed".

## COMPOUNDS IN INSECTS STRUCTURALLY RELATED TO FARNESENE

### Insect Juvenile Hormones

A series of sesquiterpenoids with structures similar to farnesene and its homologues have also been isolated from various insect species. They are the juvenile hormones (JHO, I, II, III, figure 5) which are the hormones that induce the retention of juvenile characteristics during moulting.

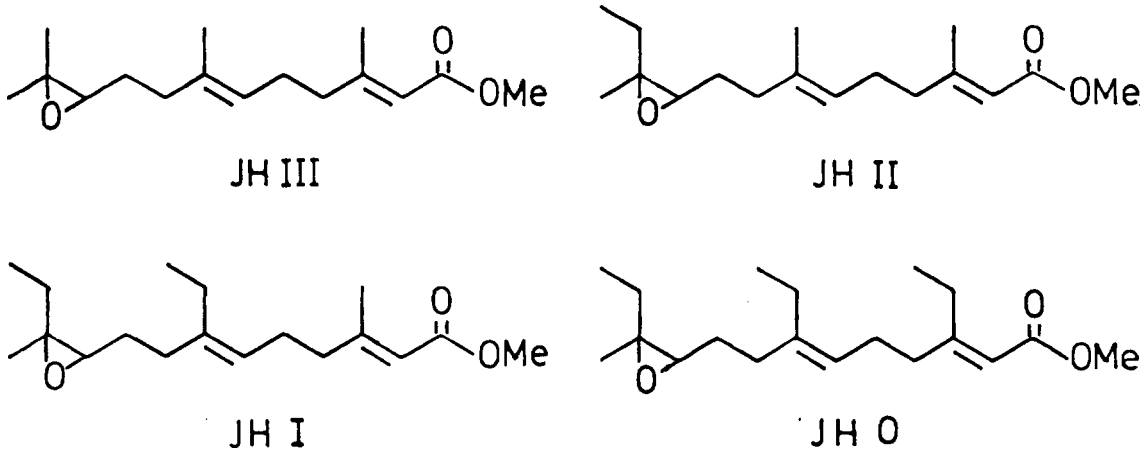



Figure 5

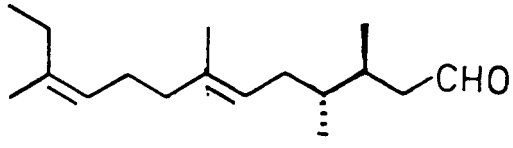
JHI was the first to be isolated[51] from the silk moth, Hyalophora cercropia and its structure was identified[52] as methyl-10,11-epoxy-7--ethyl-3-methyl-2,6-tridecadienoate i.e. the two extra methylene groups are at C-7 and C-11.

A second juvenile hormone, JHII was later identified[53] in H. cercropia and this was found to have the extra methylene group at C-11, unlike the equivalent farnesene homologue, homofarnesene where it is at C-3 or, more probably, C-7. This hormone was also found to be present[54] in the tobacco hornworm moth Manduca sexta, in conjunction with the simplest member of the series JHIII, which like farnesene has no extra methylene groups.

The series was completed by the recent discovery[55] of JHO, the equivalent of trishomofarnesene, in eggs of Manduca sexta.

Ant trail substances

The trail pheromone of the Pharaoh's ant Monomorium pharaonis, was shown[56] to be a bishomofarnesene compound, faranal (**16**, figure 6), which has extra methylene groups at C-11 and C-4.

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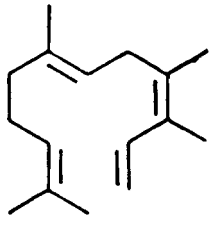

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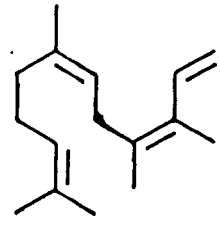

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Figure 6

Two isomers of a homofarnesene with the extra methylene group in a different position from that found in Myrmica ants, have recently been identified[43] as components of the trail pheromone of the ant, Solenopsis invicta. They are (Z,E)- and (Z,Z)-3,4,7,11-tetramethyl--1,3,6,10-dodecatetraene (**17** and **18**, figure 6); the extra methylene group being at the C-4 position.

GENERAL APPROACH TO SYNTHESIS OF FARNESENE AND ITS HOMOLOGUES

In order to confirm the assignment of structures and stereochemistry made for farnesene and its homologues, synthetic compounds were required for comparison with the natural materials. Pure synthetic compounds would also be useful for testing for biological activity.

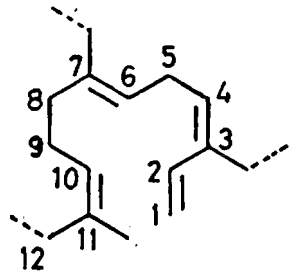


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Figure 7

Structural Considerations

If we study the structure of the ant farnesene (**19**, figure 7), there are several points to be considered when selecting a synthetic route to these compounds. The structure is that of a branched-chain hydrocarbon with four double bonds. One of these double bonds, at the C-3 position, has a cis or (Z) configuration and another, at the C-7 position, a trans or (E) configuration. We therefore need either to synthesise these double bonds stereospecifically or to be able to separate completely the desired isomer from the mixture produced in the synthesis. The double bond which is required to have a cis configuration is also part of a conjugated diene system with the terminal or C-1 double bond. Dienes are particuarly susceptible to autoxidation so reaction conditions have to be chosen carefully to prevent this once the diene is formed and also to prevent isomerization of the C-3 double bond to the more stable trans configuration.

There is an isolated methylene group at the C-3 position of farnesene between the C-1 to C-4 diene system and the C-6 double bond. This methylene group being allylic to two double bonds is an active site and may easily form an ion or radical. Also isomerization along the chain could occur to bring the diene system into conjugation with the C-6 double bond, forming an allofarnesene structure (**20**, figure 8). This is reported[18] to occur quantitatively when (Z,E)-α-farnesene is passed through a carbowax 20M GC column at high temperature (200°C).

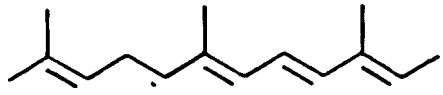

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Figure 8

Three of the four double bonds in the molecule are trisubstituted. Two of these need to be synthesised stereospecifically for all the homologues and the third, at C-10, has no possibility of isomerism in the case of farnesene and homofarnesene, but for the higher homologues cis and trans isomers are possible and the stereochemistry at this double bond has not yet been assigned in the natural ant materials. The fact that the equivalent juvenile hormones, JHI and JHO (figure 5) have been shown to have a cis or (Z) epoxide group at the C-10-C-11 position and faranal (16, figure 6), the bishomosesquiterpenoid from Pharaoh's ant, has a (Z) double bond at this position, makes it likely that the bis-and tris-homofarnesenes will also have a (Z) double bond here.

In order to determine which isomer is present in the ants we need to be able to prepare both isomers, each free from contamination by the other. Trisubstituted double bonds are generally more difficult to prepare than disubstituted and while a number of methods have been reported for the stereospecific or stereoselective formation of cis and trans disubstituted double bonds, some of which will be discussed in detail later, the possibilities for trisubstituted double-bonds are more limited.

The final point to consider in approaching the synthesis of α-farnesene and its homologues is that we do need to synthesise all

four compounds and therefore a general synthetic route to farnesene, which can also be adapted for each of the homologues is to be preferred.

Formation of trisubstituted double bonds

A key reaction in any synthesis of α-farnesene is the formation of trisubstituted double bonds. Traditional methods of forming double bonds involve elimination of water or hydrogen halides from alcohols or alkyl halides respectively. To form trisubstituted double bonds by this approach, tertiary alcohols or halides would be required, and these in fact are more reactive towards elimination than either primary or secondary alcohols or halides.

A well known method of preparing alcohols is the Grignard reaction, in which a Grignard reagent (**22**, figure 9), formed by reaction of magnesium with an alkyl halide (**21**), reacts with a carbonyl compound (**23**).

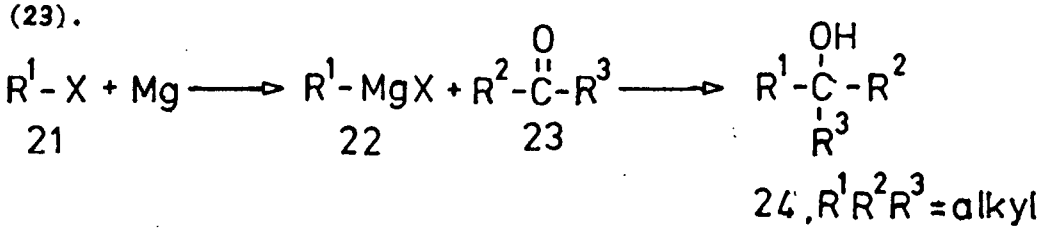



Figure 9

The major disadvantage of the use of eliminations to form alkenes is that the hydrogen eliminated can come from any one of the carbons attached to the one bearing the hydroxyl group. This means that for a tertiary alcohol (**24**, figure 9), where the three alkyl groups, $R_1$, $R_2$ and $R_3$ are different, three isomeric elimination products are possible. Elimination generally occurs to give the most stable alkene, but mixtures are often formed.

An alternative approach to the use of the Grignard reaction followed by dehydration, which does not have this disadvantage is the Wittig[57] reaction, in which the carbonyl group of an aldehyde or ketone is replaced specifically by a carbon-carbon double bond. The reaction involves nucleophillic attack on the carbonyl carbon by a phosphorus ylid (**25**, figure 10) or alkylidene phosphorane (**26**), to form a betaine (**27**). This then undergoes elimination of triphenylphosphine oxide (**28**) to give the olefin (**29**).

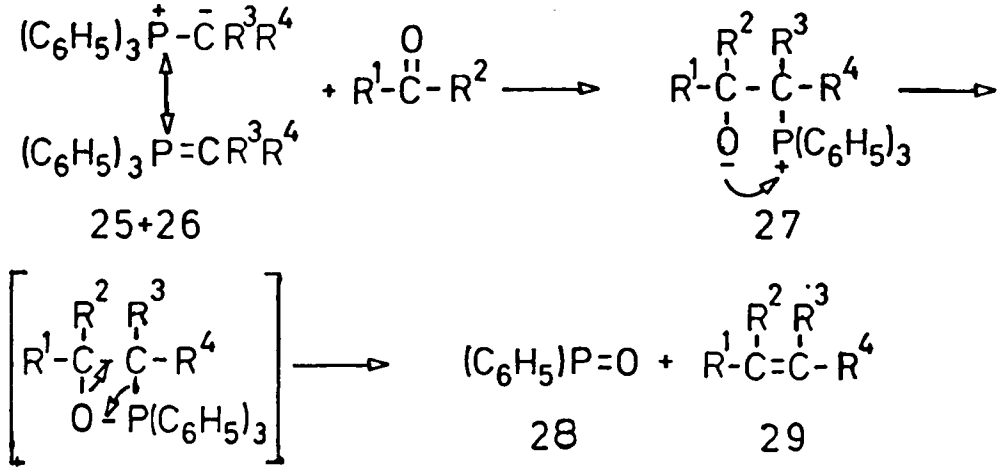


Figure 10

The ylid (**25**), is formed by the action of a base on a triphenylalkyl phosphonium salt (**32**, figure 11), which in turn is prepared by reaction of triphenylphosphine (**30**) with an alkyl halide (**31**).

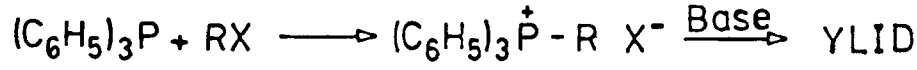


Figure 11

To use the Wittig reaction to form a trisubstituted double bond we need either to have a ketone as the carbonyl component or to use the phosphonium salt of a secondary alkyl halide. Both methods have their

disadvantages. Although the Wittig reaction is widely quoted in textbooks as being a useful general method with aldehydes or ketones, in pratice, when one looks at specific examples they are almost always aldehydes or highly activated ketones. Ketones are much less reactive towards ylids than aldehydes and when reaction of triphenyl phosphine with a secondary halide is attempted, elimination competes with substitution, as a result of which olefins may be formed.

In spite of these difficulties the Wittig reaction is a very useful method for the formation of double bonds and has been the subject of several reviews, including those by Trippet[58], and Maercker[59] and more recently by House[60], and Pommer[61]. Other double bond forming reactions such as reduction of triple bonds are not generally applicable to trisubstituted double bonds. Corey, however has developed a procedure[62] involving lithium aluminium hydride reduction of propargylic alcohols, followed by iodination and reaction with lithium dialkylcopper reagents, which allows the stereospecific formation of trisubstituted double bonds from triple bonds. Corey's use of this in the synthesis of juvenile hormones[63,64] will be discussed in greater detail later.

Previous syntheses of farnesene

Farnesene itself has been synthesised by several methods, none of which are applicable to synthesis of the higher homologues. Also none of the methods used allowed the desired (Z,E)-α-farnesene to be obtained completely free from contamination by other isomers. The synthesis of farnesene as a mixture of isomers by dehydration of nerolidol[6] has been mentioned previously, but even when conditions were varied[7] to give more of the (Z,E) isomer it was still not possible to separate this isomer completely. Also to make this synthesis of

general use, the necessary homologues of nerolidol would have to be obtained.

(E,E)-α-farnesene has been prepared[24], free from contamination by other isomers, by rhodium chloride catalysed isomerization of (E)-β-farnesene. The same workers also reported[24] that dehydration of farnesol does not give any isolable α-farnesene, but this was later disproved when Mashonas and Shaw[38] used this method to prepare all four α-farnesene isomers.

A Japanese group also obtained[65] (E,E)-α-farnesene from (E,E)--farnesol by a process involving opening of an oxiran ring using an organoaluminium reagent, but when this procedure was carried out using (Z,E)-farnesol, β-farnesene was obtained. A non-stereospecific synthesis of α-farnesene was carried out by an Indian group[66]. This started from citral (**33**, figure 12), and involved use of Wittig and modified Wittig reactions.

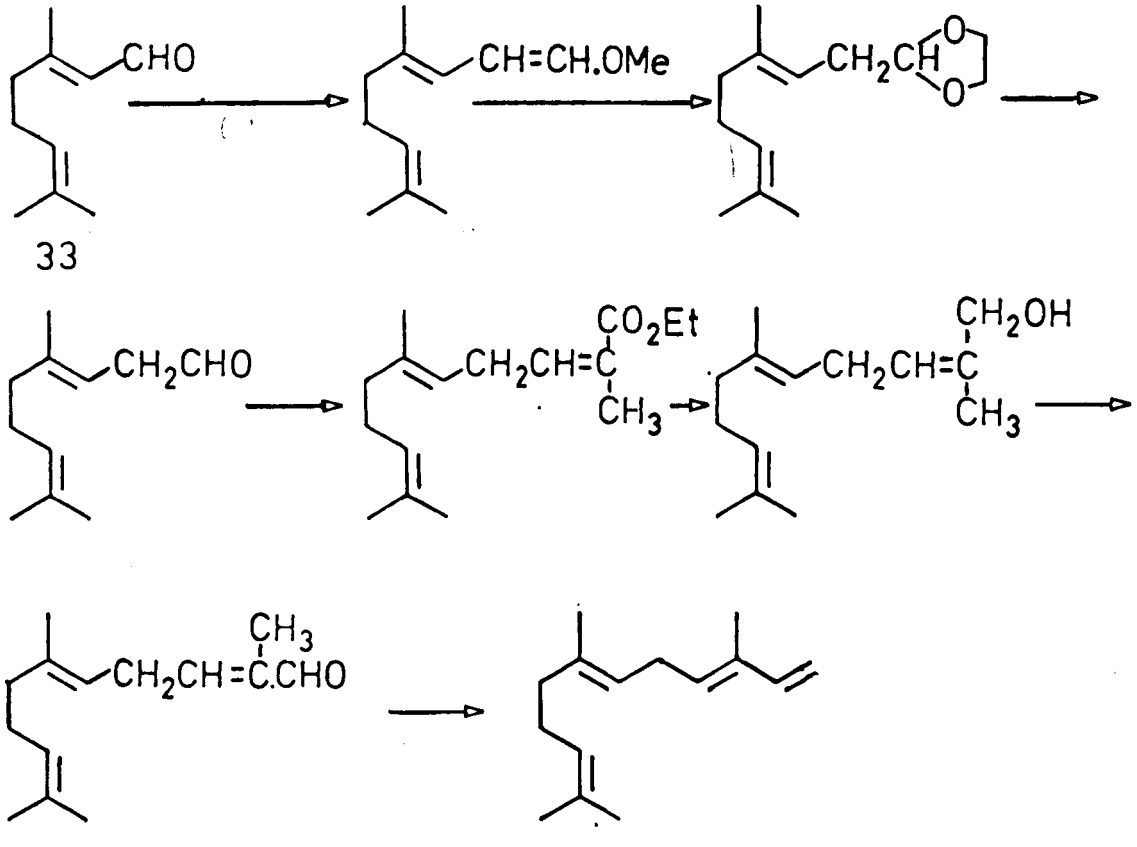
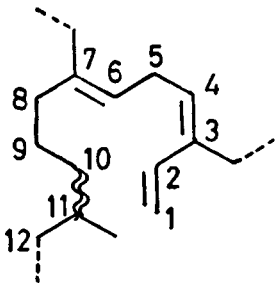



Figure 12

More recently cathodic reduction of farnesyltriphenylphosphonium bromide was found[67] to give α-farnesene as the major product. As already mentioned, these methods are only applicable to farnesene itself and are non-stereospecific, or give the most stable (E,E)-α--farnesene isomer. Whereas what is needed here is a general, preferably stereospecific, route to farnesene which can also be used for the homologues, the critical points being the formation of the trisubstituted double bonds and the prevention of autoxidation, or isomerization of the diene system once it is formed.

Juvenile Hormone Syntheses

A number of syntheses of the insect juvenile hormones, whose structural similarity to farnesene and its homologues has already been discussed, have been published and it was thought that these might be of some assistance in developing a synthetic route to the farnesenes. Although the two series of compounds are similar in structure however, there are certain differences which make farnesene and its homologues a more difficult synthetic problem. For example as mentioned earlier, the isolated methylene group at the C-5 position makes farnesene (**34**, figure 13) susceptible to isomerization, or the formation of an ion or radical. In the juvenile hormone (**35**, figure 13), the C-5 methylene is only allylic to one double bond and therefore less reactive, and isomerization of the double bonds into conjugation cannot occur. Also the juvenile hormone structure is less readily autoxidised since it does not contain the conjugated diene system of farnesene. In addition to this, farnesene has one cis double bond whereas the juvenile hormones have the more stable 'all-trans' arrangement.



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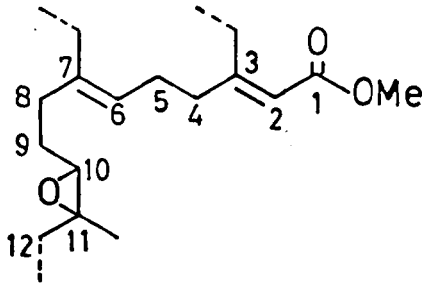
Farnesene



35

Juvenile Hormone

Figure 13

A number of elegant schemes for the stereospecific synthesis of the $C_{17}$ and $C_{18}$ juvenile hormones (equivalent to homo- and bishomo-farnesenes) have been devised by Corey and his coworkers. Two of these have already been mentioned[43,64] briefly as involving the stereospecific conversion of propargylic alcohols to trisubstituted olefinic carbinols via organoaluminium and copper reagents. The first of these[63] has several novel features including the fact that it commences from an aromatic precursor, p-methoxytoluene (**36**, figure 14).

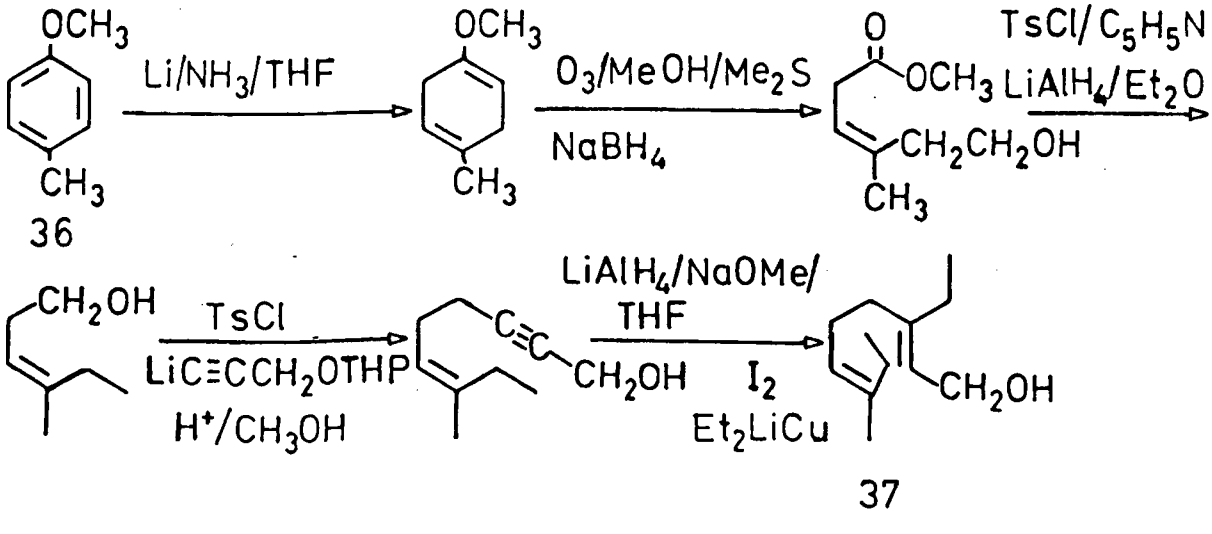



Figure 14

This route however would not be suitable for a general synthesis of farnesene and its homologues because it would only be applicable for the homologues with an ethyl group at C-4 i.e. bis and tris-homofarnesenes. Also it would be a rather lengthy synthesis as there are several steps involved in reaching the alcohol (**37**) and several more steps in converting this to farnesene. The second[64] of Corey's syntheses involving propargylic alcohols also starts from a novel precursor, a δ-lactone (**38**, figure 15) and leads to the formation of the same, 3-ethyl-7-methyl-trans, cis-$^{2,6}$-nonadiene-1-ol (**37**) as the previous synthesis. The same arguments against the suitability of the method for farnesene synthesis apply in this second case.

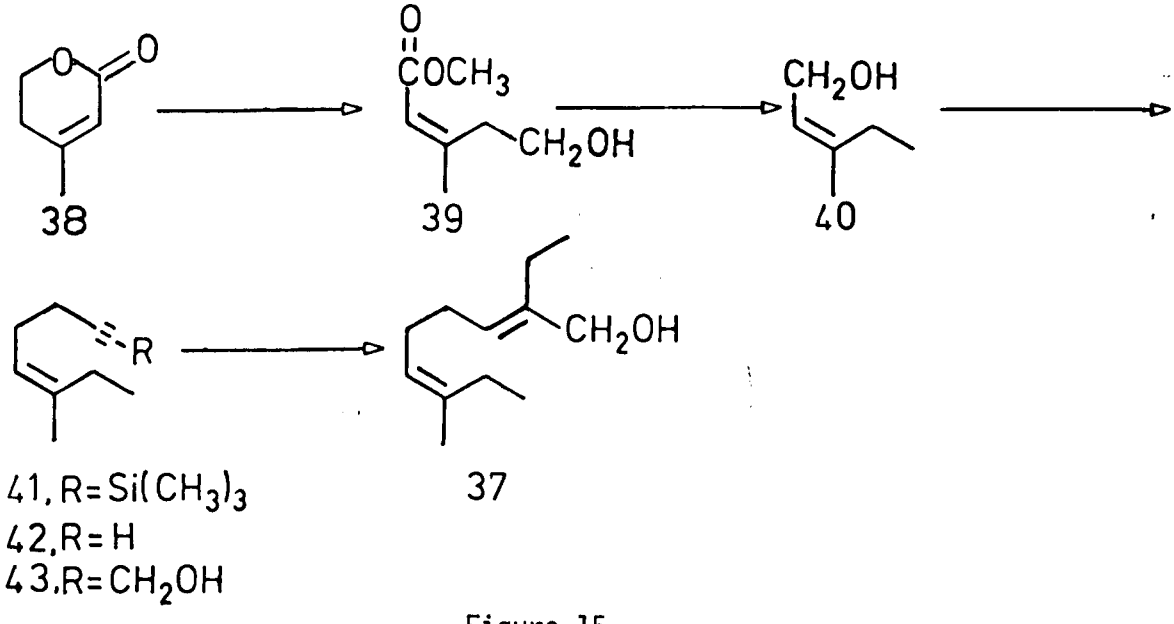
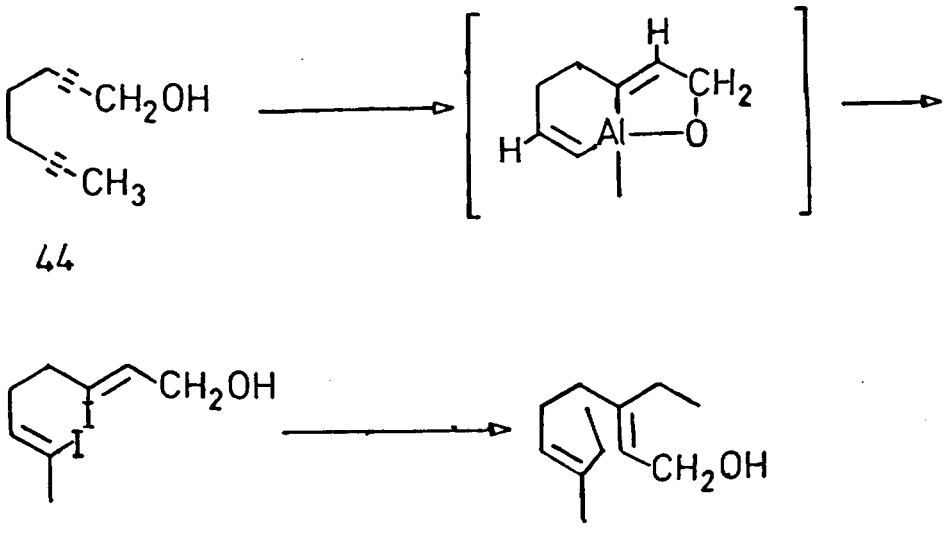



Figure 15

The alcohol (**37**) was also prepared[64] by Corey's group by a method which would permit the introduction of a methyl rather than an ethyl group at the C-11 position of farnesene. In this case the starting material was octa-2,6-diyne-1-ol (**44**, figure 16).




44

Figure 16

Using this method it would be possible to introduce two methyl groups or two ethyl groups. However for homofarnesene, one methyl group (at C-11) and one ethyl group (at C-7) are required and this would be difficult to achieve by this route.

A non-stereospecific juvenile hormone synthesis allowing structural variation in the alkyl residues and starting from cylcopropyl methyl ketone (**45**) was reported by Cochrane and Hanson and is outlined (below) in figure 17.

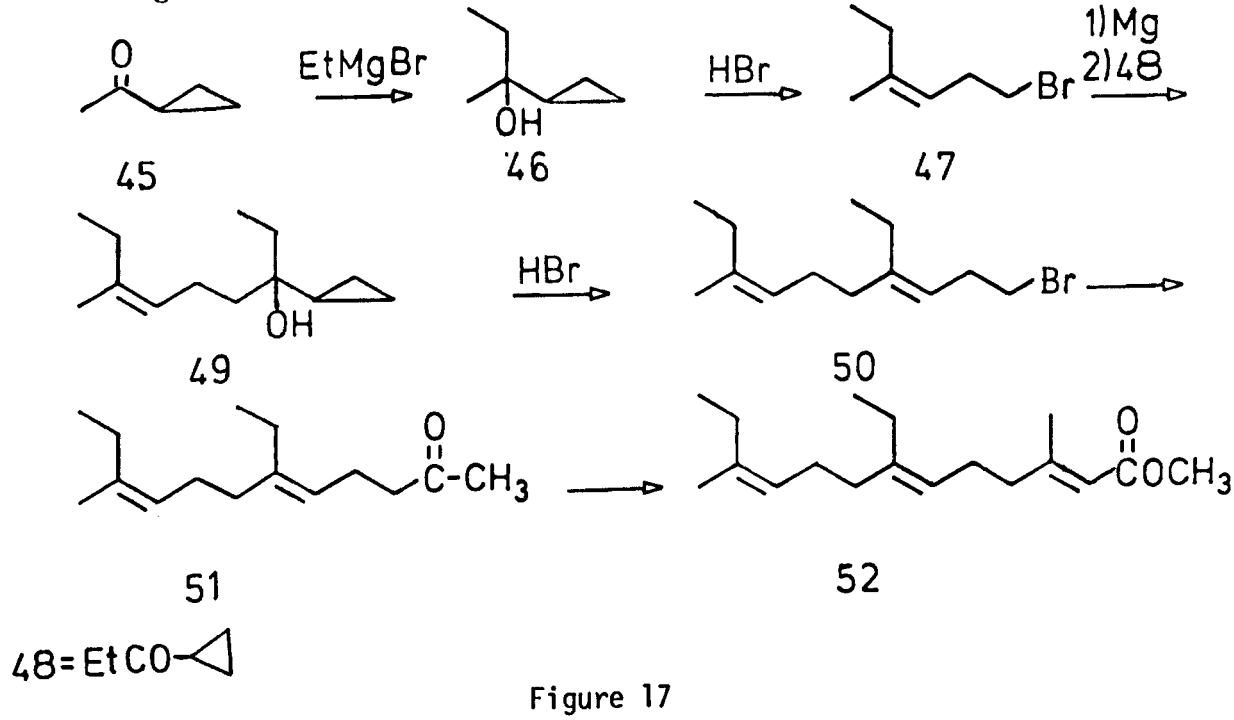



Figure 17

The synthesis makes use of the procedure reported[69] by Julia's group in which cyclopropyl methyl ketone is treated with a Grignard reagent and the resulting cyclopropyl carbinol is then cleaved with 48% hydrobromic acid. In the juvenile hormone synthesis cyclopropyl methyl ketone was treated with ethyl magnesium bromide to give 2-cyclopropylbutan-2-ol (**46**), which on cleavage with hydrobromic acid yielded 1-bromo-4-methylhex-3-ene (**47**) as a mixture of cis and trans isomers. This bromide was then used in a further Grignard reaction with cyclopropyl ethyl ketone (**48**) to give the cyclopropyl alcohol (**49**). Acid-cleavage then gave the bromide (**50**), again as a mixture of isomers. Conversion to the nitrile and treatment with methyl magnesium iodide produced the ketone (51) which had been reported as an intermediate in a number of other juvenile hormone syntheses[70]. To complete the synthesis a modified Wittig reaction using the anion of diethyl methoxy carbonyl methyl phosphonate was carried out on the ketone to give the ester (**52**) which after epoxidation yielded the juvenile hormone JHI. A comparable synthetic route was reported briefly by another group[71].

As already stated this route allows variation in the alkyl side--chains so that if it were possible to adapt it for farnesene synthesis all the homologues could be made. To make farnesene by this method, the bromide (**50**) would have to be converted either to the organomagnesium derivative (**53**, figure 18) for use in a Grignard reaction or to the phosphonium salt (**54**) for use in a Wittig reaction. In each case the ketone used would be methyl vinyl ketone.

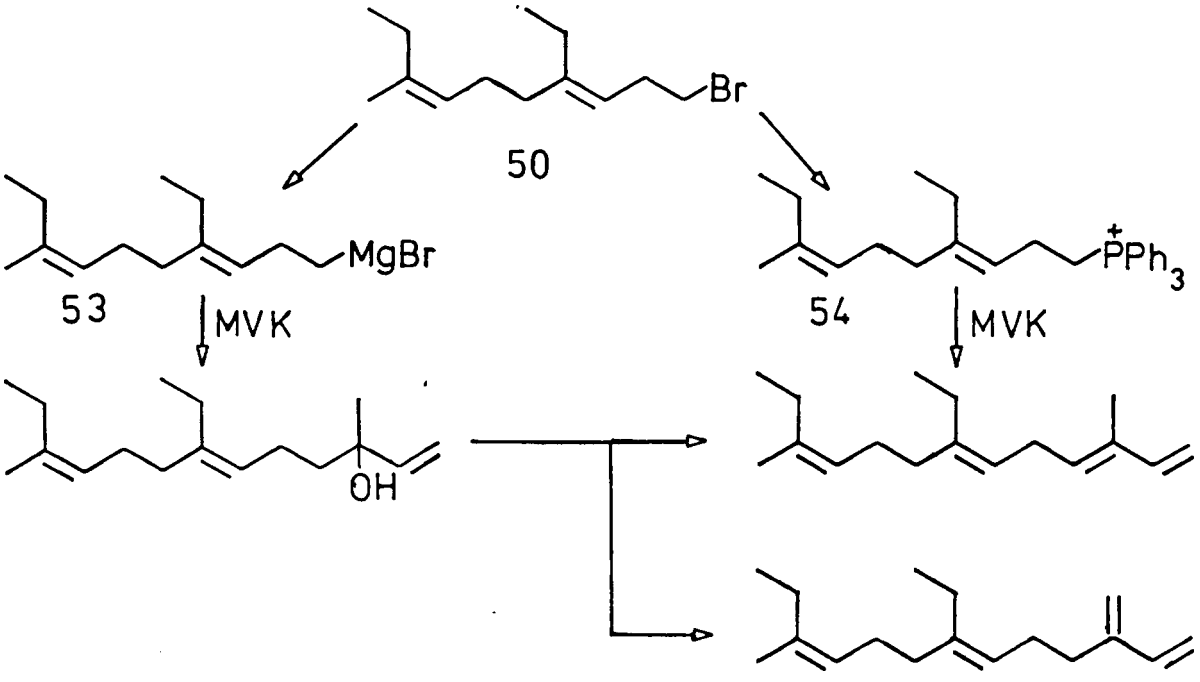



Figure 18

Both possibilities have disadvantages. The Grignard route would give a mixture of α- and β-farnesene which the Wittig method would not. The Wittig reaction, on the other hand, involves use of basic reaction conditions which might tend to polymerize the rather unstable methyl vinyl ketone and there are no reports in the literature of the use of this ketone in Wittig reactions.

In the light of the various caveats listed above and using the experience gained from a study of the successful syntheses of the juvenile hormones described in the literature, a generalized synthesis of farnesene and its homologues was attempted in the work described in this thesis.

# DISCUSSION

The main aim of the present work was to investigate synthetic routes to the α-farnesene and its homologues which are found in the Dufour gland of Myrmicine ants. The pure synthetic compounds were required to confirm the identification of the natural materials, which at that time was based only on GC retention times and mass spectral data, and for use in behavioural studies with the ants. A general synthesis was sought which, with suitable modifications to the starting materials, would be applicable to all the compounds.

Although the synthetic routes to juvenile hormones, described in the introduction, were available as models, none of these were directly applicable to the synthesis of farnesene. The choice initially seemed to be limited to two methods of forming trisubstituted double bonds, the Wittig reaction, and Corey's procedure for conversion of propargylic alcohols to trisubstituted olefinic carbinols via organoaluminium and copper reagents. Neither method was without drawbacks but the better known Wittig reaction was taken as first choice because of the greater difficulties involved in handling the organo-copper reagents. The Wittig reaction was chosen because it allows the carbon-oxygen double bond of an aldehyde or ketone to be replaced specifically with a carbon-carbon double bond. This is in contrast to the more traditional method of double-bond formation via a Grignard reaction to form a carbinol which is then dehydrated, often giving a mixture of double bond isomers.

## First Wittig route to farnesene

The first Wittig route to farnesene which was tried is outlined in figure 19 (Route A). It involves formation of a secondary phosphonium salt for use in a Wittig reaction with β-chloropropionaldehyde followed

by preparation of the phosphonium salt (**58**) of the resulting chlorodiene (**57**) for a final Wittig reaction with the commercially available ketone, 6-methyl-5-hepten-2-one (**59**).

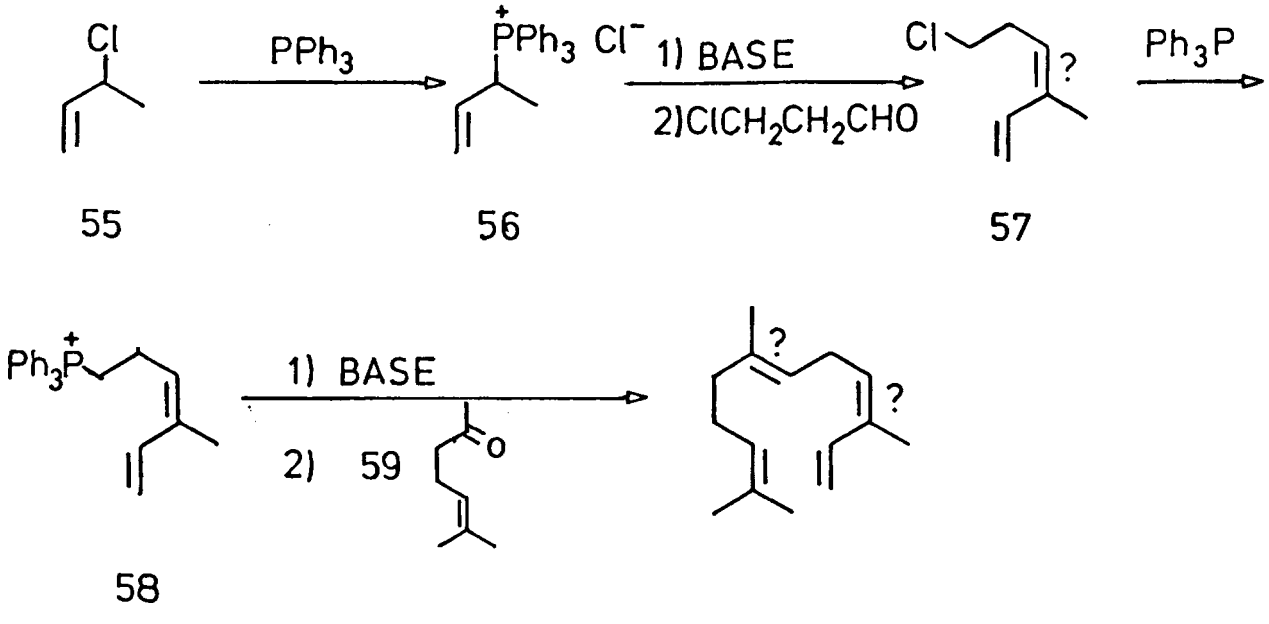



Figure 19

The first step in this synthesis was the reaction of 3-chloro-1--butene (**55**) with triphenylphosphine to form the phosphonium salt (**56**). This was attempted by refluxing together equimolar proportions of triphenylphosphine and 3-chloro-1-butene in dimethyl formamide and a crystalline salt was obtained. (m.p. 216-220$^{o}$) For the next stage in the synthesis which was a Wittig reaction, β-chloropropionaldehyde was required and this was prepared by bubbling hydrogen chloride gas through acrolein[72]. Attempts to prepare the chlorodiene (**57**) by the Wittig reaction between the prepared salt and β-chloropropionaldehyde using sodium ethoxide as the base did not give the required product. Further examination of the $^{1}$H NMR spectrum of the salt suggested that it was not the expected secondary phosphonium salt formed by direct replacement of chlorine with triphenylphosphine but a rearranged primary salt (**60**)

formed by $S_N2'$ attack of triphenylphosphine at the double bond as shown in figure 20.

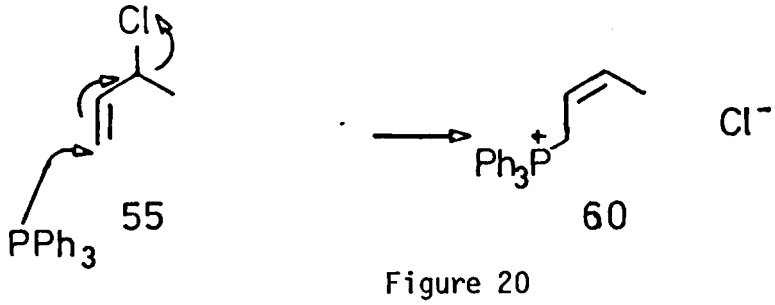



Figure 20

To confirm that this had occurred the same salt was prepared directly from crotylbromide (1-bromo-but-2-ene) and triphenylphosphine. Melting points of the two salts could not be compared as one was a chloride and the other a bromide but the $^1H$ NMR spectra were identical; each having a three-proton signal at δ 1.2 for the methyl group, a two proton signal at δ 3.45 for the methylene group and a two proton multiplet between δ 4.7-5.7 for the two alkene protons. The desired salt (**56**, figure 19) would be expected to have a spectrum quite different from this. There would be three protons in the alkene region instead of two, since it has a terminal double bond, and a one proton signal for the proton on the carbon attached to phosphorus. Farnesene synthesis by route A was not pursued since the necessary phosphonium salt could not be prepared.

Second Wittig route to farnesene

An alternative, slightly longer route again involving Wittig reactions was chosen for the second attempt at farnesene synthesis. (Route B, figure 21). This, like route A, makes use of the ketone, 6-methyl-5-hepten-2-one (**59**) but this time the phosphonium salt (**63**) it reacts with is that of β-bromopropionaldehyde ethylene acetal (**62**). The scheme is completed by a crossed aldol condensation of the aldehyde (**64**), formed by this Wittig reaction, with propionaldehyde

to give the aldehyde (**65**) followed by a second Wittig reaction with methylene triphenylphosphorane.

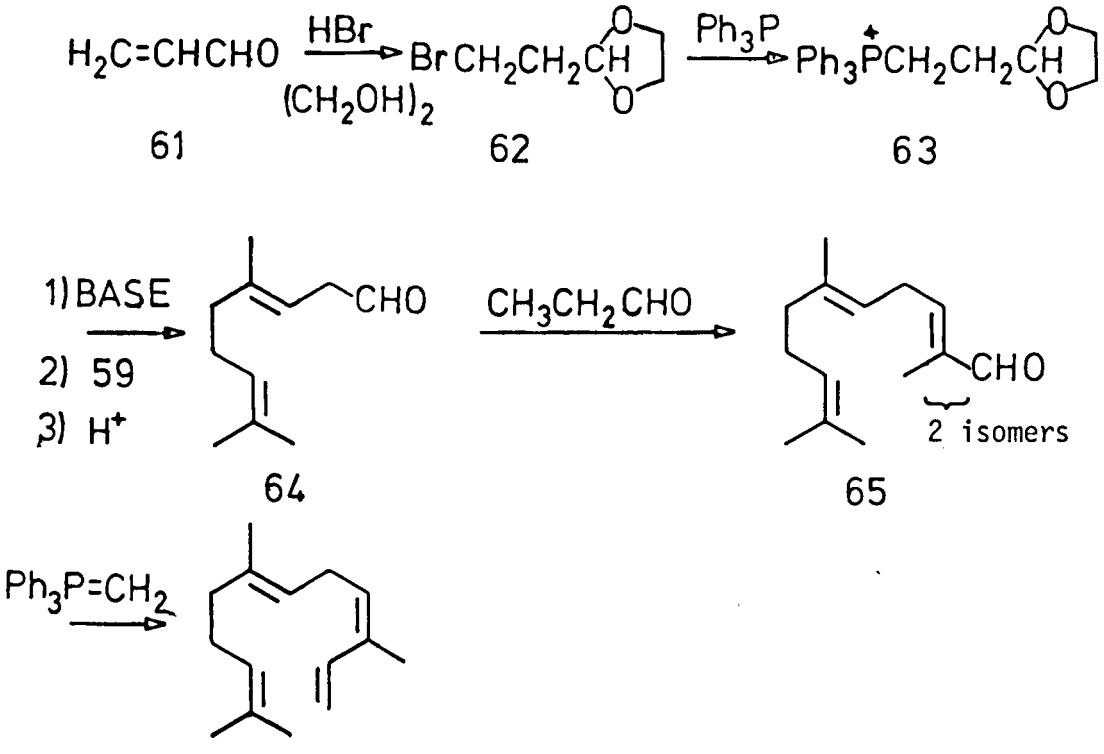


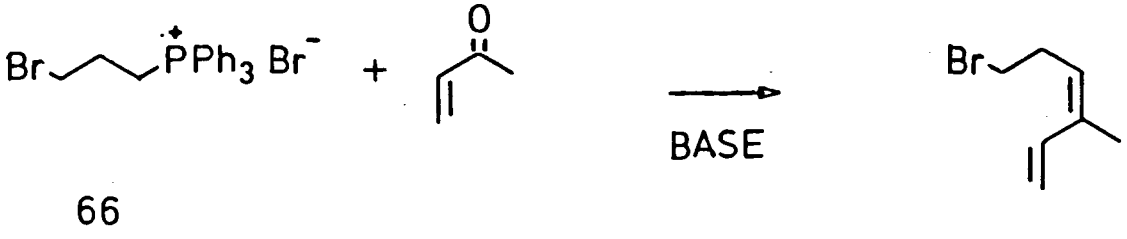

Figure 21

β-Bromopropionaldehyde ethylene acetal (**62**) was prepared in 46% yield by adding acrolein (**61**) to a solution of hydrogen bromide in ethylene glycol[73] at 5-10 °C. The $^1$H NMR spectrum of the product, with a one proton triplet at δ 4.9 for the C-H next to two oxygens, a four proton singlet at δ 3.85 for the methylene's of the acetal group, a two proton triplet at δ 3.4 for the methylene group next to bromine and a two proton multiplet at δ 2.2 for the central $-CH_2-$ group, shows that the desired bromo-acetal was formed. The product was not very stable and darkened quite rapidly on standing, possibly due to hydrolysis producing traces of HBr which would cleave the acetal leaving the free aldehyde. Attempts to carry out the next stage of the reaction sequence, formation of a phosphonium salt (**63**) from the bromo-acetal (**62**) were not successful. Refluxing the bromo-acetal with triphenyl

phosphine in benzene, toluene and xylene gave an oil in each case. It was thought that hydrolysis of the bromoacetal might be causing the problem so potassium carbonate was added to the reaction mixture in toluene to neutralize any HBr formed but an oil was formed as before. The $^1H$ NMR spectrum of the oil was recorded and this suggested that some of the desired salt could be present since it contains phenyl absorptions, a single peak at δ 3.85 for the acetal group, a triplet at δ 5.0 for the -CH- group, and broad absorptions at δ 2.0 and 3.5 for the two $-CH_2-$ groups. It was not possible however to purify and crystalize the salt for use in a Wittig reaction. This meant that route B also had to be abandoned at this point and an alternative sought.

Synthesis via a dihalide

In the planned synthesis via route A (figure 18), the C-3 double bond of farnesene was to be made by a Wittig reaction between the terminal four-carbon unit, in the form of a phosphonium salt, and the central three-carbon unit, in the form of a carbonyl compound. The possibility was now considered of interchanging the positions of these functional groups so that the carbonyl group was on the terminal C-4 fragment as shown in figure 22.




66

Figure 22

It would not be possible to carry out this reaction however because the phosphonium salt, 3-bromopropyltriphenylphosphonium bromide (**66**), is unstable[74] under the basic conditions necessary for a Wittig reaction, and rearranges to give cyclopropyltriphenylphosphonium bromide, (67, figure 23).

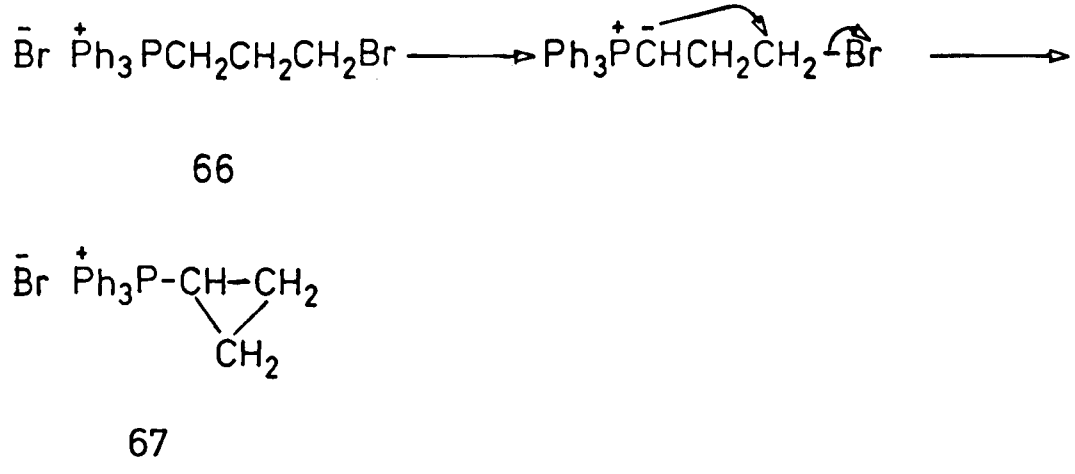


Figure 23

This rearrangement could be prevented by starting from 3-bromopropan--1-ol instead of 1,3-dibromopropane and protecting the hydroxyl group as a tetrahydropyranyl derivative. This would make the reaction sequence rather lengthy since the tetrahydropyranyl group would have to be removed after the Wittig reaction and the hydroxyl group then replaced with a bromide in order to form the phosphonium salt required for the second Wittig reaction with 6-methyl-5-hepten-2-one.

Another method of preventing this rearrangement of the salt would be to form the bis-phosphonium salt (**69**) of the 1,3-dibromopropane (**68**). The mono-salt is formed by reaction of the bis-halide with triphenyl phosphine in a non-polar solvent such as benzene[75] or xylene[74]. The mono-salt is insoluble in these solvents and precipitates out as it is formed. If however, the reaction is carried out in a polar solvent such as dimethyl formamide[75,76], the mono-phosphonium salt stays in solution and can react with a second equivalent of triphenylphosphine to give the bis-phosphonium salt (**69**, figure 24).

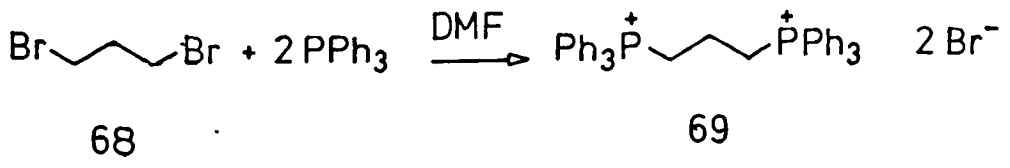



Figure 24

To use this salt (**69**) in the synthesis of farnesene, the two ends must react with different ketones; methyl vinyl ketone (**71**, figure 25) and 6-methyl-5-hepten-2-one (**59**). If both reactions were to be carried out simultaneously by adding two equivalents of base to form the bis-ylid (**70**), followed by the two ketones together, a mixture of three products could be formed in addition to cis and trans isomers.

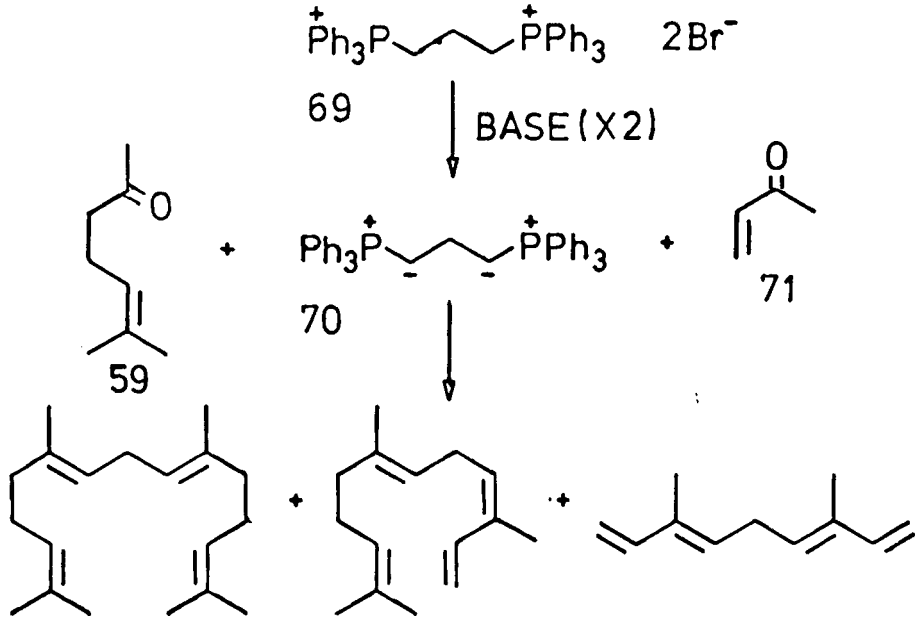



Figure 25

The possibility was therefore considered, of adding only one equivalent of base to the salt (**69**), to form an ylid at one end only and allowing this to react with one of the ketones (**59** or **71**) to form an intermediate monophosphonium salt which could then be used in a second Wittig reaction with the other ketone as shown in figure 26.

The bis-phosphonium salt (**69**) was prepared in 90% yield by refluxing 1,3-dibromopropane (**68**) with two equivalents of triphenyl phosphine in dimethylformamide for 30 minutes.

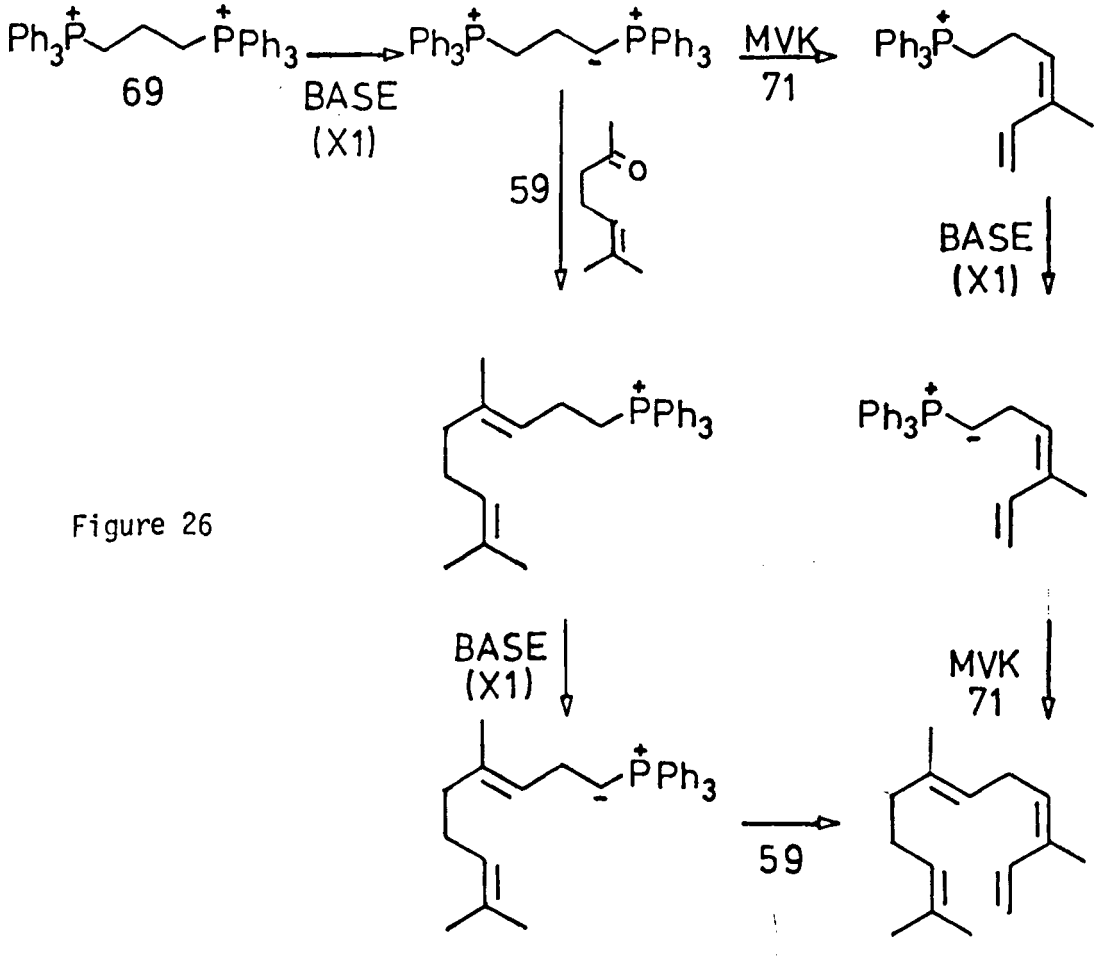



Figure 26

Cis double bonds from Wittig reactions

The C-3 to C-4 double bond of farnesene, which was to be formed by the Wittig reaction between the bis-salt and methyl vinyl ketone, has a cis configuration in the isomer present in the Myrmica ants. A study of the literature was therefore made to find a suitable method for producing a stereospecifically cis product from the Wittig reaction. Rossi, in his review[77] on 'Synthesis of Achiral components of Insect pheromones' refers to a number of stereoselective syntheses of disubstituted double bonds with the cis configuration. Of these methods, the one used by Bestmann[78] and co-workers to produce

(7Z,11Z)-7,11-hexadecadien-1-yl acetate, 94% stereoisomerically pure seemed the most suitable. The method involved use of sodium bis-(trimethylsilyl)amide as the base in Wittig reactions which were carried out at -78 °C. The same base was used by Bestmann's group to obtain 98% cis products[79] in the synthesis of (Z)-9-dodecenyl acetate, (Z)-9-tetradecenyl acetate and the corresponding acid. All of these reactions were carried out in tetrahydrofuran as solvent. The reason for using this base is to obtain "lithium salt-free" ylid solutions based on the findings of Bergelson and co-workers who reported that the presence of lithium salts augments the yield of trans-product when a Wittig reaction is carried out in a non-polar solvent with a non-stabilized ylid. In the absence of lithium salts the cis isomer predominates in such cases.

Sodium bis( trimethylsilyl) amide was prepared as a white solid from hexamethyldisilazane and sodamide in refluxing benzene[81].

$$NaNH_2 + [Si(CH_3)_3]NH \xrightarrow[\text{Benzene}]{} NaN[Si(CH_3)_3] + NH_3\uparrow$$

The reaction of the monoylid of the bisphosphonium salt (**57**) with methyl yinyl ketone had already been attempted in this department (unpublished results) without success, using both sodium hydride and sodium ethoxide as base. The lack of success was thought to be due to polymerization of the unstable ketone in the presence of base and so rather than repeat this reaction with the newly prepared silylamide it was decided first to test the suitability of this base for use with the bisphosphonium salt (**69**) by attempting the reaction of this salt with the other ketone, 6-methyl-5-hepten-2-one (**59**). The possibility that a Wittig reaction with methyl vinyl ketone might prove impracticable

would not rule out the use of the bis-salt for farnesene synthesis because the terminal four-carbon unit could still be added in two stages. This could be achieved in two ways. The bis-salt (**69**) could be reacted with the ketone (**59**) to give an intermediate salt (**72**, figure 27) which after a second Wittig reaction with puruvaldehyde dimethyl acetal (**73**) and removal of the protecting group would give the aldehyde (**74**). This could then be used in a final Wittig reaction with methylenetriphenylphosphorane (**75**) to give farnesene.

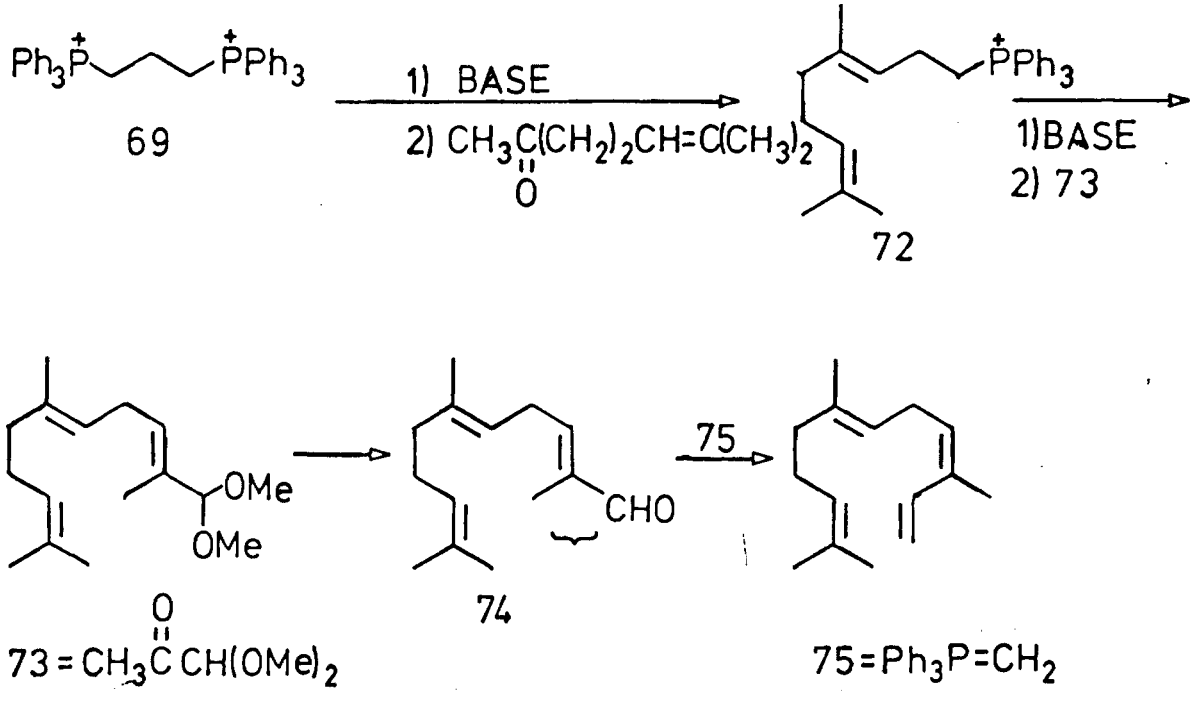



Figure 27

Alternatively, after reaction of the bis-salt (**69**) with 6-methyl-5-hepten-2-one, the intermediate salt (**72**) could be used in a second Wittig reaction with chloro-, bromo- or iodo-acetone (**76**, X = Cl, Br or I). The product (**77**) from this, could then be used to form another salt (**78**) for a Wittig reaction with formaldehyde (**79**), to give farnesene as outlined in figure 28.

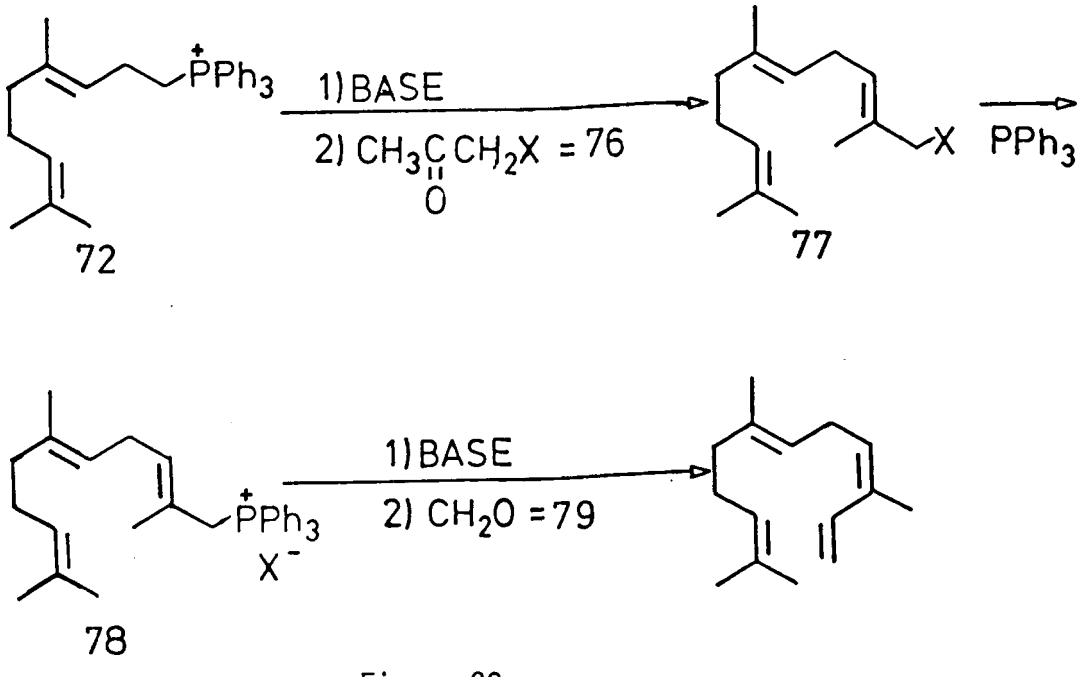



Figure 28

Of the two possible approaches, the former would be preferable since pyruvaldehyde dimethylacetal (**72**) is commercially available whereas the halogen-substituted acetone (**75**) would have to be synthesised first and bromoacetone especially is unstable.

The reaction of the bis-salt with 6-methyl-5-hepten-2-one using the silylamide as base was first attempted in tetrahydrofuran, with cooling to -78 °C before addition of the ketone, as described by Bestmann[79]. This did not yield any of the desired monophosphonium salt and large amounts of the bis-salt were recovered. Repeating the reaction at room temperature using dimethoxyethane as solvent was also unsuccessful. To ascertain that the prepared silylamide was suitable for use in a Wittig reaction a simple salt, n-butyltriphenylphosphonium bromide was prepared and a small-scale trial reaction of this with cyclohexanone was carried out using the silylamide as base. This did yield the expected product and further attempts were then made to use the base for a Wittig reaction with the bis phosphonium salt. This

time however cyclohexanone was used as it is a more reactive ketone than the 6-methyl-5-hepten-2-one. None of the desired product was obtained and the bisphosphonium salt was recovered in each. case.

Since all attempts to carry out Wittig reactions on the mono-ylid had failed, and there were no reports in the literature of this having been done, this approach was abandoned and the possibility was considered of forming the bisylid instead although this would lead to a mixture of products being formed. Trial reactions were carried out using the salt with two equivalents of n-butyl lithium as base and the red colouration produced suggested that the bis-ylid had been formed. Addition of two equivalents of cyclohexanone caused the colour to disappear but on working up large amounts of bisphosphonium salt were recovered and no product could be detected. Examination of the various reports[75,76,82-88] in the literature of the use of this salt in Wittig reactions revealed that yields were generally very low and it was therefore decided to abandon this route entirely. An additional factor influencing this decision was that trial Wittig reactions of methylvinyl ketone with the ylid from n-butyltriphenylphosphonium bromide had suggested that this ketone was unsuitable for use in such reactions and the terminal four-carbon unit would therefore have to be added in two stages as described above.

Adaptation of juvenile hormone synthesis

In the search for an alternative synthetic route, one of the juvenile hormone syntheses discussed in the introduction was reconsidered. This was the synthesis by Cochrane and Hanson[68], which was based on Julia's procedure[69] for opening cyclopropyl rings with hydrobromic acid. Using this method the C-4 to C-12 portion of the α-farnesene structure could be synthesised as a bromodiene (**83**, figure 29) in four steps

from cyclopropyl methyl ketone (**39**). The route, outlined in figure 29, involves treatment of cyclopropyl methyl ketone (**39**) with the Grignard reagent, methyl magnesium iodide to give the cyclopropyl carbinol (**80**), which after treatment with hydrobromic acid as described by Julia[69] gives the homoallylic bromide (**81**). Conversion

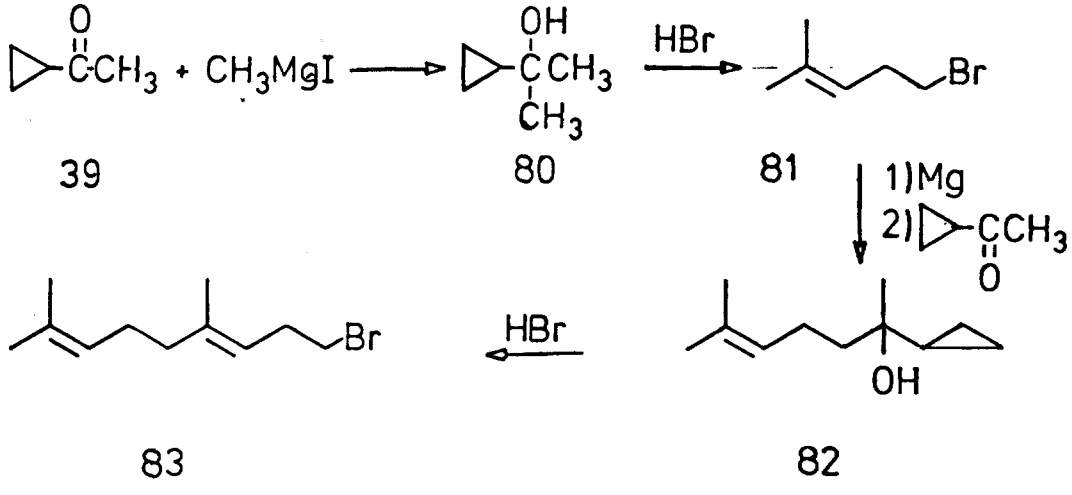



Figure 29

of this to the Grignard reagent and reaction with cyclopropyl methyl ketone yields a second cyclopropyl carbinol (**82**) which is cleaved with hydrobromic acid to give the bromodiene (**83**).

The most direct way of converting this to α-farnesene would be to convert the bromide to the corresponding phosphonium salt by reaction with triphenylphosphine, and then carry out a Wittig reaction between the ylid formed from this salt and methylvinylketone. However previous attempts to use this ketone in a Wittig reaction had proved unsuccessful due to its polymerization in the presence of base and no reports of its use in this type of reaction could be found in the literature. An alternative to this would be to convert the bromide (**83**) to a Grignard reagent before treatment with methyl vinyl ketone to give nerolidol which could be dehydrated to give farnesene. The disadvantages of this method are that a mixture of α- and β-farnesenes would be obtained and

also of double bond isomers in which the desired (Z,E)-α-farnesene would be only a minor component.

As neither the Wittig nor the Grignard method of attaching the terminal four-carbon unit, in the form of methylvinyl ketone, were favourable one of the two-stage processes described above would have to be used. In both cases the bromide (83) would need to be converted to its phosphonium salt (72, figure 27) with triphenylphosphine. The most favourable of these methods, outlined in figure 27, involved reaction of the phosphonium salt (72) with pyruvaldehyde dimethyl acetal (73) and removal of the acetal protecting group to give an aldehyde (74) which after a second Wittig reaction with methylene triphenylphosphorane (75) would give farnesene. The other method also involved two Wittig reactions. The first between the phosphonium salt (72) and a halo-acetone (76) to give a triene-halide (77) which after conversion to the phosphonium salt (78) would be used in the second Wittig reaction with formaldehyde (see figure 28).

Route via bromodiene

The C-6 to C-12 fragment of α-farnesene however was readily available as 6-methyl-5-hepten-2-one (59) which had been used in the previous attempts at farnesene synthesis. This could be used to prepare α-farnesene by a Wittig reaction if the bromodiene (84, figure 30), was available and could be converted to the phosphonium salt (85).

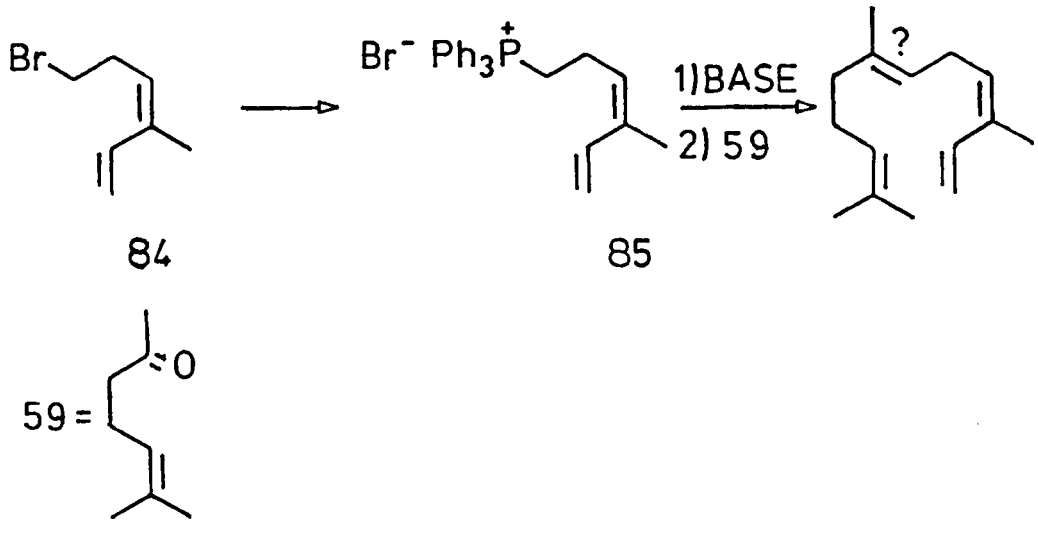



Figure 30

It was thought that it might be possible to prepare this bromo-diene (84) from cyclopropylmethyl ketone (**39**) by a modification of Julia's procedure which was used in the juvenile hormone synthesis. In this case the Grignard reagent which would need to be used would by vinyl magnesium bromide (**86**, figure 31). Addition of this to cyclopropyl methyl ketone should give the cyclopropyl methyl vinyl carbinol (**87**) which on treatment with hydrobromic acid should rearrange to give the desired 6-bromo-3-methylhexa-1,3-diene (**84**).

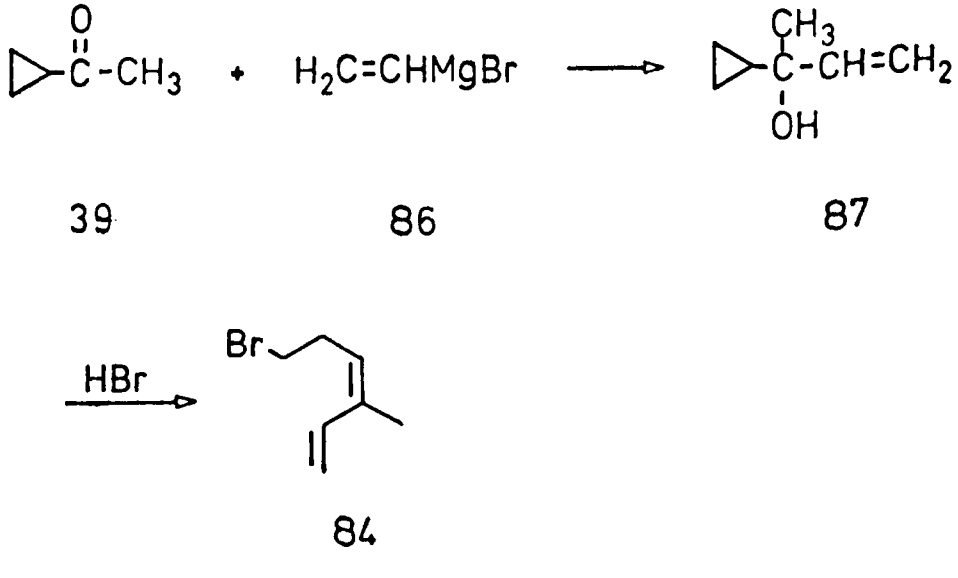



Figure 31

A survey of the literature revealed that Julia's group had in fact carried out both of these stages in good yields[89]; 83% for the addition of the Grignard to cyclopropyl methyl ketone and 85% for the cleavage of the cyclopropyl ring. In addition to this, a German group had used this method to prepare[90] the bromodiene (**84**) and had also converted it to the phosphonium salt (**85**) in their synthesis of sinensal (**90**, figure 32). The phosphonium salt was suspended in THF and heated with n-butyl-lithium in hexane to form the ylid. Addition of the methyl ketone, (**88**, figure 31) which has a structure similar to that of the ketone to be used in the farnesene synthesis, 6-methyl-5-hepten--2-one (**59**), gave a 65% yield of the acetal (**89**). Removal of the protecting group then gave the desired aldehyde sinensal (**90**).

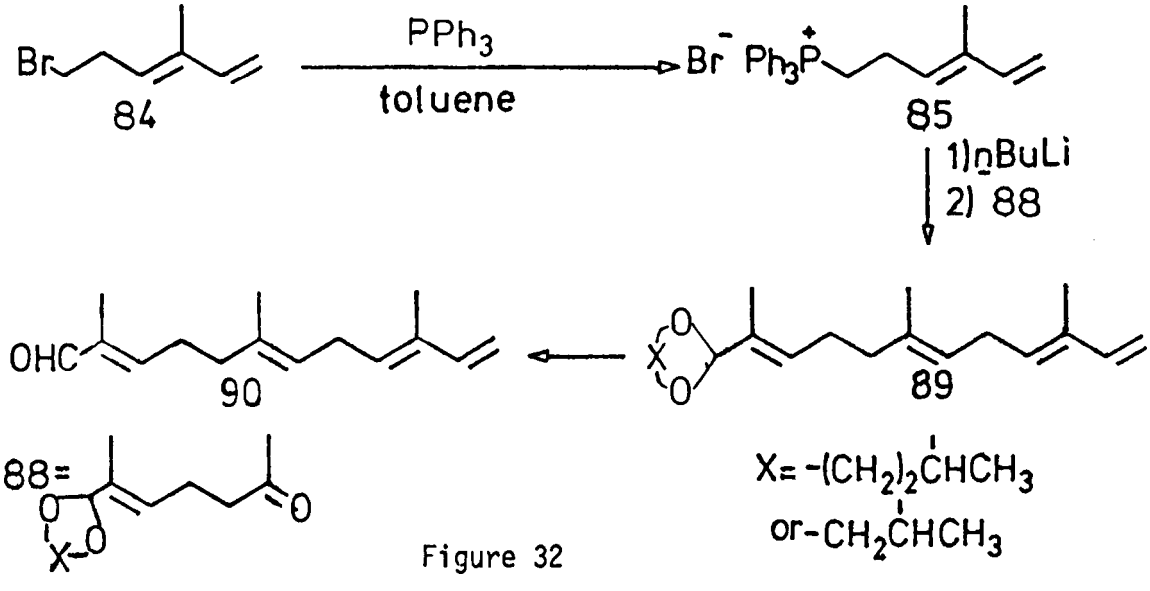



Figure 32

The preparation of 6-bromo-3-methyl-hexa-1,3-diene (**84**) by Julia's method from cyclopropylmethyl ketone and its conversion to the phosphonium salt for a Wittig reaction with 6-methyl-5-hepten-2-one seemed like a promising route to the synthesis of α-farnesene. The proposed scheme involved only four stages from commercially available starting materials; treatment of cyclopropyl methyl ketone with the Grignard reagent from yinyl bromide, rearrangement of the resulting carbinol (**71**) with hydro-

bromic acid to give the bromodiene (**84**), conversion of this to the phosphonium salt and finally a Wittig reaction with 6-methyl-5-hepten--2-one (**59**). The basic scheme is outlined in figure 33.

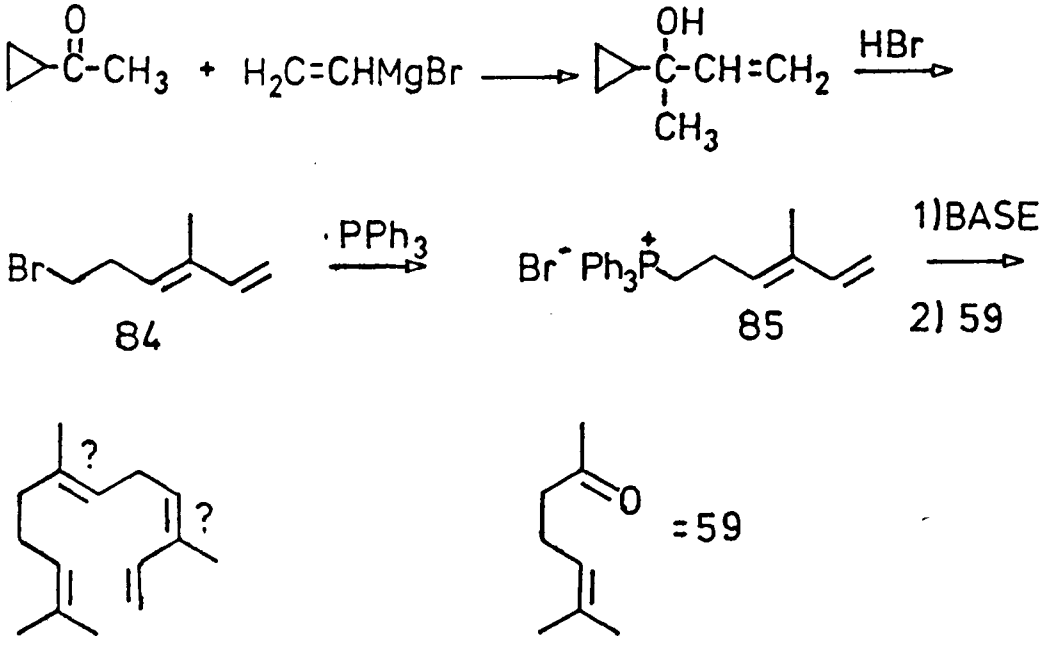



Figure 33

In the first attempt to use this route to farnesene a modification of Julia's procedure was tried. McCormick and Barton had reported[91] briefly that opening of the cyclopropyl ring could be achieved using magnesium bromide or iodide in refluxing ether instead of the hydrobromic acid used by Julia's group. The advantage of this method is that magnesium halides, being much milder reagents than hydrobromic acid, would be less likely to attack the olefinic linkage in the product. Also it was thought that it should be possible to achieve the two-stage conversion of cyclopropyl methyl ketone to the bromodiene (**84**) without isolating the intermediate tertiary carbinol (**87**).

In an attempt to use this procedure to prepare the bromodiene, cyclopropylmethyl ketone in ether was added to the prepared vinyl Grignard in tetrahydrofuran as described by Julia[89]. After the mixture

had been left to stand overnight, magnesium bromide was added with more ether before boiling under reflux for one hour. No bromodiene was obtained from this reaction and a large amount of cyclopropyl methyl ketone was recovered with some of the cyclopropylmethylvinyl carbinol (**87**). This recovery of starting material was probably due to loss of the very volatile vinyl bromide from the reaction mixture during initial formation of the Grignard reagent.;

The synthesis of the cyclopropylmethylvinyl carbinol was repeated as before, but this time the product was isolated at this stage. The yield of carbinol was low and it was contaminated with the starting ketone, again probably due to loss of vinyl bromide. No further attempt was made to use McCormick and Barton's method for ring-opening due to lack of information about the experimental conditions necessary for this reaction. This step was successfully achieved using hydrobromic acid as described by Julia[89] giving the bromodiene as a mixture of *cis*- and *trans* isomers.

Stereochemistry of the bromodiene

The presence of the two isomers in the product was revealed by the $^1$H NMR spectrum (figure 34) which showed two signals for the protons of the methyl group at δ 1.73 and 1.81, and two overlapping doublet of doublets for the $C_2$ proton, centred at δ 6.28 and 6.60. Assignment of the two methyl group signals to their respective isomers was based on data given by Babler *et al.*, who prepared[92] a mixture of the *cis*- and *trans*-bromodienes by treatment of the carbinol (**71**) with lithium bromide and *p*-toluenesulphonic acid in glacial acetic acid. They give a value of δ 1.83 for the methyl group of the *cis* product and δ 1.77 for the *trans*. Also Julia gives[89] values of 1.79 (cis) and 1.71 p.p.m. (trans) for the diene alcohol prepared from the bromide, and notes that several

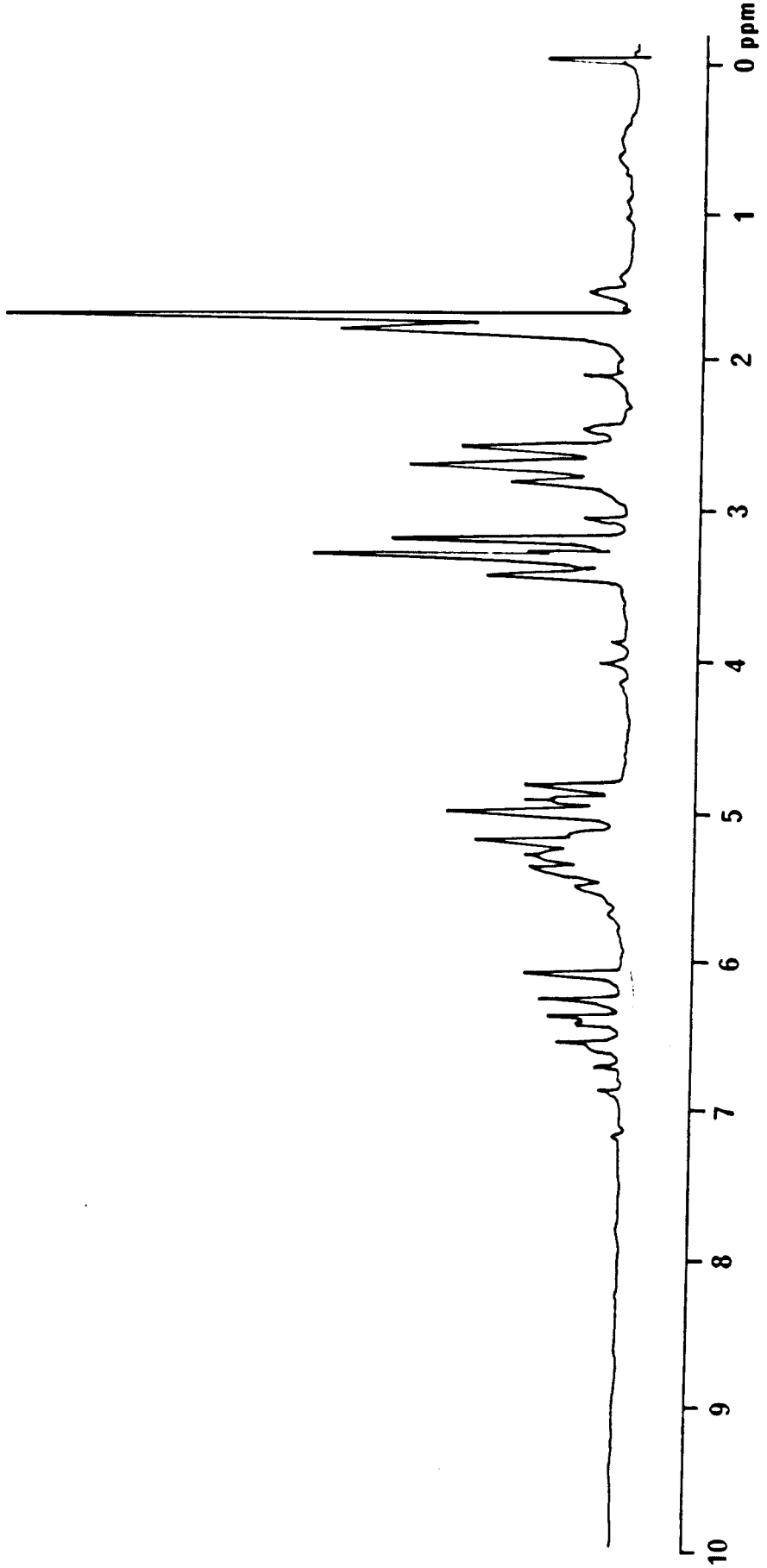



Figure 34

$^1$H NMR spectrum of (Z)- and (E)-6-bromo-3-methylhexa-1,3-diene

authors[93-95] have remarked that there is a shift of 0.07-0.08 p.p.m., to lower field, for the methyl group signal of such systems in moving from the cis to the trans isomer. This shift was also noted by Mori *et al*[70].

The two overlapping doublets of doublets for the proton on C-2 could be assigned to their respective isomers by comparison with the values given[19] for the cis- and *trans*-β-ocimenes by Ohloff *et al*. The similarity of the diene system of the β-ocimenes to that of α-farnesene and also therefore to that of the bromodiene, was discussed earlier in the introduction to this thesis, where the structures of the β-ocimenes are given (**14** and **15**, figure 4).

Integration of the $^{1}H$ NMR spectrum of the bromodiene mixture showed that the *cis* isomer required for the synthesis of (Z,E)-α-farnesene, was the minor component. The ratio of *trans* to *cis* product was estimated to be approximately 2:1, which was in good agreement with the values obtained by Julia by measurement of GC peak areas of 65% *trans*, 35% *cis*, for the corresponding alcohol or acetate prepared from the bromide. Baumann and his coworkers however estimated from the $^{1}H$ NMR spectrum that their bromodiene made by Julia's method was 85% E, 15% Z.

To confirm the presence of the two isomers the $^{13}C$ NMR spectrum of the bromodiene was recorded and this showed (figure 35) two signals for each carbon atom present, one for the *cis* and one for the *trans* product. The trans/cis ratio was more difficult to estimate but from this spectrum appeared to be approximately 3:1.

To obtain the pure *cis* bromide required for the farnesene synthesis, a separation would be necessary at this point. Before attempting this however, it was decided to try out the next stage of the synthesis, preparation of the phosphonium salt, on the mixture of isomers.

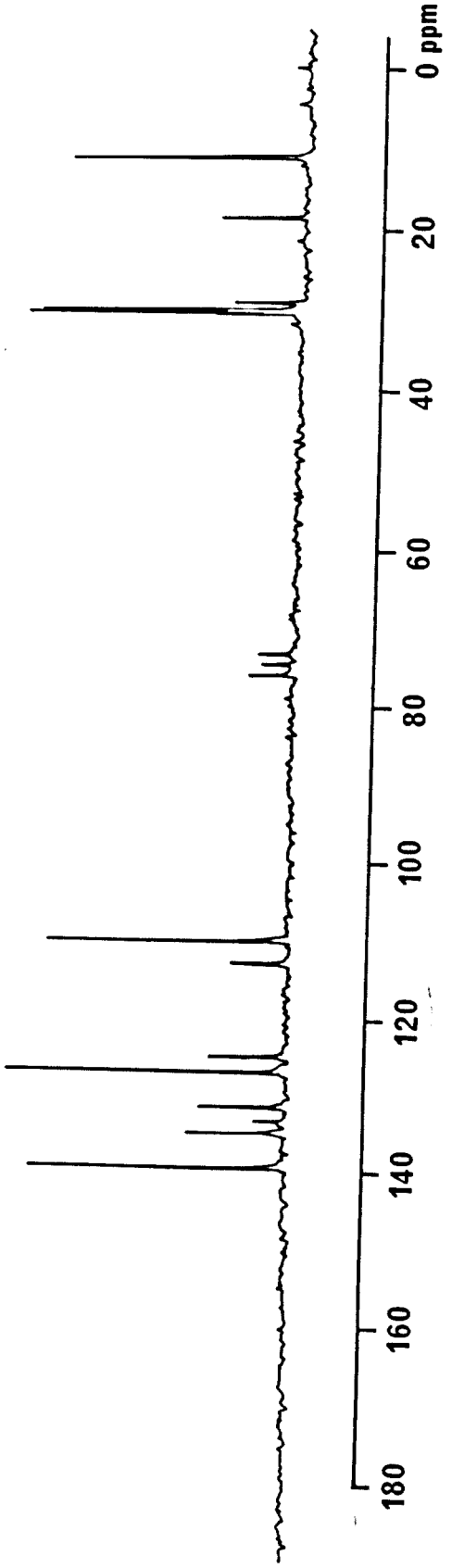



**Figure 35**

$^{13}C$ NMR spectrum of (Z)- and (E)-6-bromo-3-methylhexa-1,3-diene

Baumann et al.[90] had obtained a good yield (92%) of crystalline salt by treating the bromodiene with triphenyl phosphine in refluxing toluene for forty-eight hours. The formation of the salt was expected to be more rapid if a polar solvent were used and therefore the trial preparation of the salt was attempted in dimethylformamide. After boiling the mixture under reflux for nine hours it was allowed to cool before adding diethyl ether to precipitate the salt as an oil. Washing the oil with diethyl ether and light petroleum did not cause it to crystallize. By further washing with toluene and drying in an electrically-heated drying pistol a brittle solid was obtained which was used in a trial Wittig reaction with 6-methyl-5-hepten-2-one in dimethoxyethane with sodium bistrimethylsilylamide as base. GC of the product from this suggested that α-farnesene isomers were present.

Preparation of cis-bromodiene

Meanwhile the problem of obtaining the pure cis-bromodiene still had to be solved. The cis isomer of the corresponding alcohol had been prepared[89] by Julia's group from cyclopropylmethyl ketone by a modification of the route used to obtain the mixture of cis and trans isomers. In the modified route, outlined in figure 36, cyclopropyl methyl ketone was treated[96] with sodium acetylide (**91**) instead of vinyl magnesium bromide. Ring-opening of the resulting carbinol (**92**) and conversion of the bromide (**93**) to the alcohol (**94**) were then carried out, and finally the reduction of the triple bond to give the cis diene alcohol (**95**) was achieved by hydrogenation over Lindlar's catalyst[97].

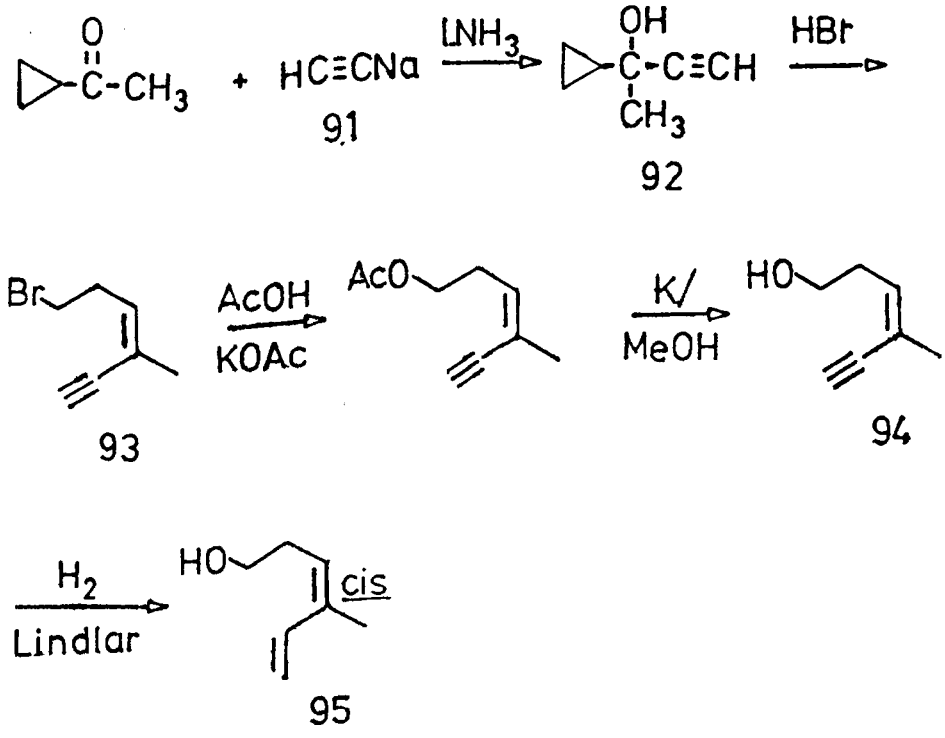



Figure 36

The rearrangement of the cyclopropylcarbinol, which gives a predominantly trans product with a vinyl substituent, gives an exclusively cis product when this is changed to an acetylene substituent. Julia explains[89] this in terms of the relative size of these two groups compared with the other substituent, the methyl group. The vinyl group is more bulky than the methyl group whereas the linear acetylene group is less bulky.

The cis-alcohol (**95**) would not itself be useful for the synthesis of farnesene but would need to be converted to the corresponding bromide (**96**) by treatment with phosphorus tribromide and then to the phosphonium salt (**97**) as shown in figure 37.

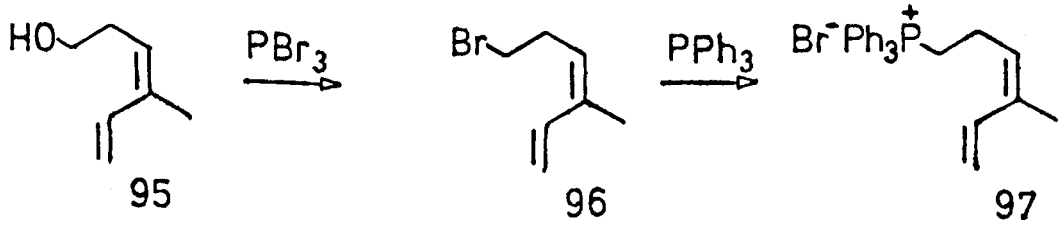
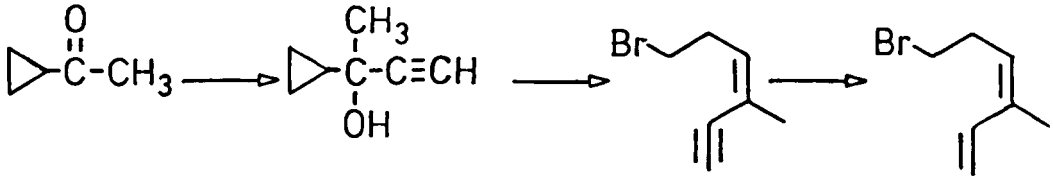



Figure 37

Synthesis of the cis-phosphonium salt by this route would involve a total of seven steps from cyclopropyl methyl ketone, whereas synthesis of the cis/trans mixture involves only three steps. The number of extra steps could be reduced to only one, if direct hydrogenation of the acetylenic bromide (**93**), to the cis-bromodiene (**96**) could be successfully achieved.




92 93 96

Figure 38

Three alternative procedures were therefore available for the preparation of the pure cis-bromodiene and the corresponding phosphonium salt; separation of the mixture of isomers already prepared, use of Julia's route to the cis alcohol and conversion of this to the bromide, or finally the route outlined in figure 38 involving direct hydrogenation of the acetylenic bromide (**93**). Separation of the isomeric mixture would give a low yield of the desired cis product since this was the minor component. Similarly the overall yield via Julia's synthesis of the cis alcohol, would probably be low due to the number of steps involved. It was therefore felt that the most favourable approach would be to prepare the acetylenic bromide (93), as described by Julia[96], and attempt to hydrogenate this directly to the cis-bromodiene (**96**).

Ethynylation of cyclopropyl methyl ketone was carried out by addition of the ketone in ether to sodium acetylide, which was prepared

by bubbling acetylene through a suspension of sodamide in liquid ammonia. This gave the expected 2-cyclopropylbut-3-yn-2-ol (**92**) which on treatment with 48% hydrobromic acid rearranged to give 6-bromo-3-methyl hex-3-ene-1-yne (**93**).

The next stage in the proposed synthesis was the partial hydrogenation of the triple bond of the bromide (**93**) to a double bond, and for this a suitable catalyst was required. Julia[89] had used the well-known Lindlar's catalyst[97] for the hydrogenation of the corresponding alcohol and this was therefore prepared using the modified procedure described[98] by Lindlar and Dubuis.

The prepared Lindlar's catalyst was used in the first attempt to reduce the acetylenic bromide to the cis-bromodiene. The reaction was attempted using toluene as solvent and with the addition of 1 ml of quinoline as described by Lindlar and Dubuis but no uptake of hydrogen was observed.

A second batch of catalyst was prepared as before and its activity was compared with that of the first batch of Lindlar's catalyst and with that of another catalyst, palladium on barium sulphate, which had been prepared previously in this department using the method of Mozingo[97]. This catalyst had been reported by Cram and Allinger[100] to be superior to the Lindlar catalyst in reproducibility and ease of preparation. The catalysts were compared by performing trial hydrogenations of phenylacetylene in light petroleum (boiling range 40-60 $^{o}$C) with added quinoline as described by Lindlar and Dubuis[98]. Uptake of hydrogen was most rapid with palladium on barium sulphate as catalyst.

A second attempt to reduce the acetylenic bromide to the cis--bromodiene was made using the more active catalyst, palladium on barium sulphate, with added quinoline and using toluene as solvent as in the previous attempt. Although the more active catalyst was used, the

reaction was still slow and seyeral days were taken for the required amount of hydrogen to be absorbed.

While this hydrogenation was taking place, a sample of the acetylenic bromide was converted to the alcohol to see if this would hydrogenate more rapidly. The first stage of the conversion to the alcohol, treatment with potassium acetate in glacial acetic acid to form the acetate, proceeded smoothly to give an 86% yield of crude acetate. The next step, treatment with sodium in methanol, however gave only a 20% yield of the alcohol (**94**, figure 34). Hydrogenation of this with palladium on barium sulphate and quinoline in methanol as described by Julia[89], was much more rapid than for the bromide, taking only 75 minutes. However, due to the low yield at the previous stage, there was insufficient diene alcohol available for conversion to the cis-bromodiene with phosphorus tribromide.

Although hydrogenation of the acetylenic bromide was slow, requiring several days for completion, the overall yield of cis-bromodiene was higher than for the longer route via the alcohol, and this was therefore abandoned. Hydrogenation of the bromide was repeated several times during the attempts to synthesise farnesene and its homologues, and the solvent and catalyst were varied to find the best reaction conditions. From these hydrogenations it was found that palladium on barium sulphate was a more active catalyst than either the samples prepared in this department, or the commercially prepared samples (Aldrich, Gillingham) of Lindlar's catalyst. The activity of palladium on barium sulphate was also found to be improved when the hydrogenation was carried out in methanol as described by Cram and Allinger[100], rather than light petroleum or toluene. The specificity of the catalyst for reduction of triple bonds only seemed to be reduced in methanol however, and care had to be taken to stop the reaction after the absorption of the

required amount of hydrogen, or over-hydrogenation could occur. Using this combination of catalyst and solvent the time necessary for the reaction to go to completion was reduced to only two or three days.

The cis-bromodiene from the hydrogenation was isolated by filtering off the catalyst, and then for the reactions performed in toluene, washing the solution with dilute acid to remove the added quinoline, drying, evaporating off the solvent and distilling the crude product to give the pure cis-6-bromo-3-methylhexa-1,3-diene. Absence of any trans isomer was shown by the $^{1}H$ NMR spectrum (figure 38a) which had only one doublet of doublets for the $C_2$ proton, centred at δ 6.6 and only one methyl signal at δ 1.8. The $^{13}C$ NMR spectrum (figure 39) also contained only one signal for each carbon atom in the molecule.

Phosphonium salt of diene

With the preparation of the pure cis-bromodiene accomplished, the next stage in the synthesis was the conversion of this to the phosphonium salt for the Wittig reaction with 6-methyl-5-hepten-2-one. Since the attempted preparation of the salt of the mixed cis- and trans-bromodienes in dimethylformamide described earlier, had not yielded a crystalline product, it was decided to try a different solvent for the reaction of the cis-bromodiene. The first choice of solvent was toluene which Baumann had used[90] to obtain a crystalline salt from the mixed bromodienes. However when a mixture of the cis bromodiene and triphenylphosphine in toluene was boiled under reflux an oil began to form almost immediately. After forty eight hours the mixture was allowed to cool and the oil was triturated with light petroleum (boiling range 40-60 °C) to give a powdery solid. This was

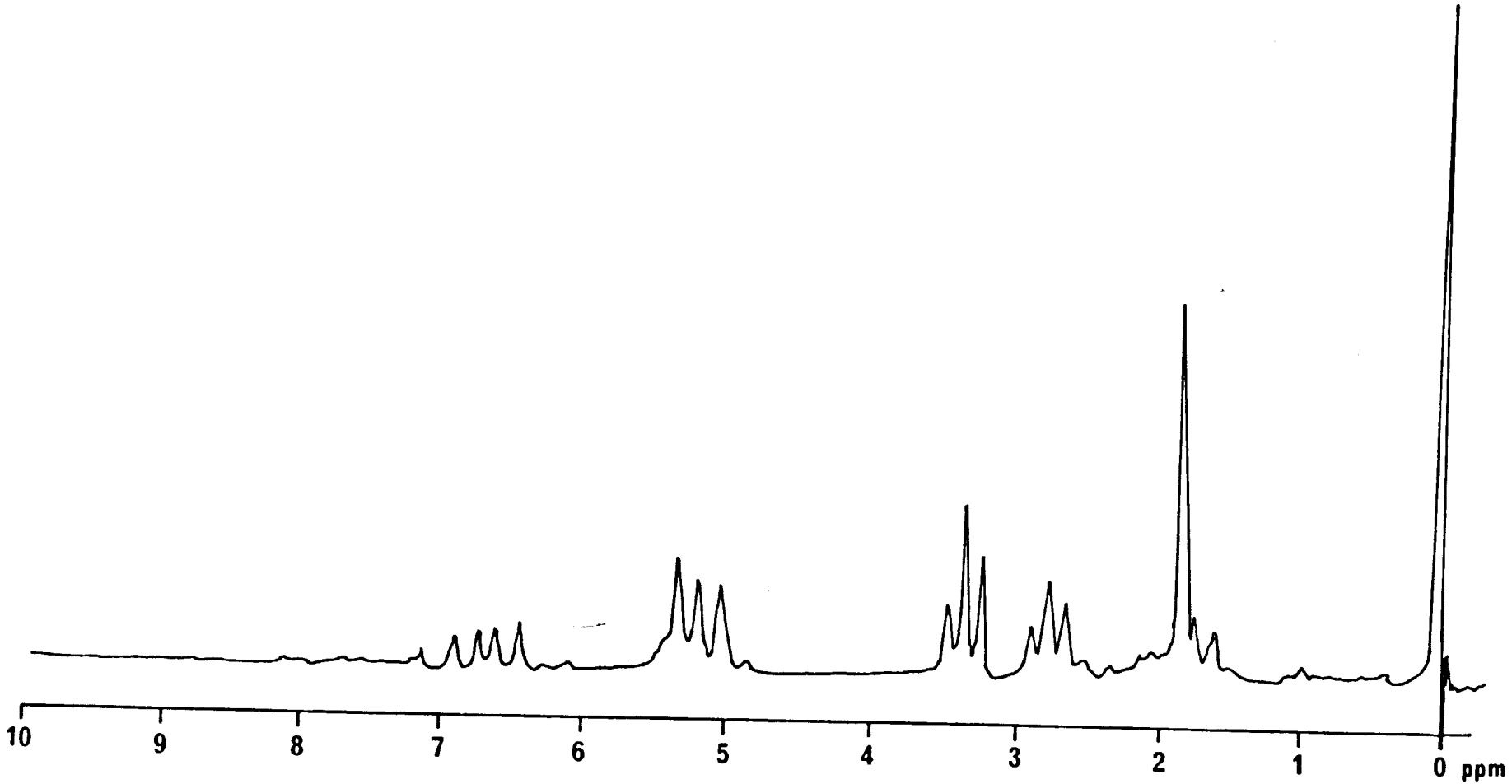



**Figure 38a**

$^{1}H$ NMR spectrum of (Z)-6-bromo-3-methylhexa-1,3-diene

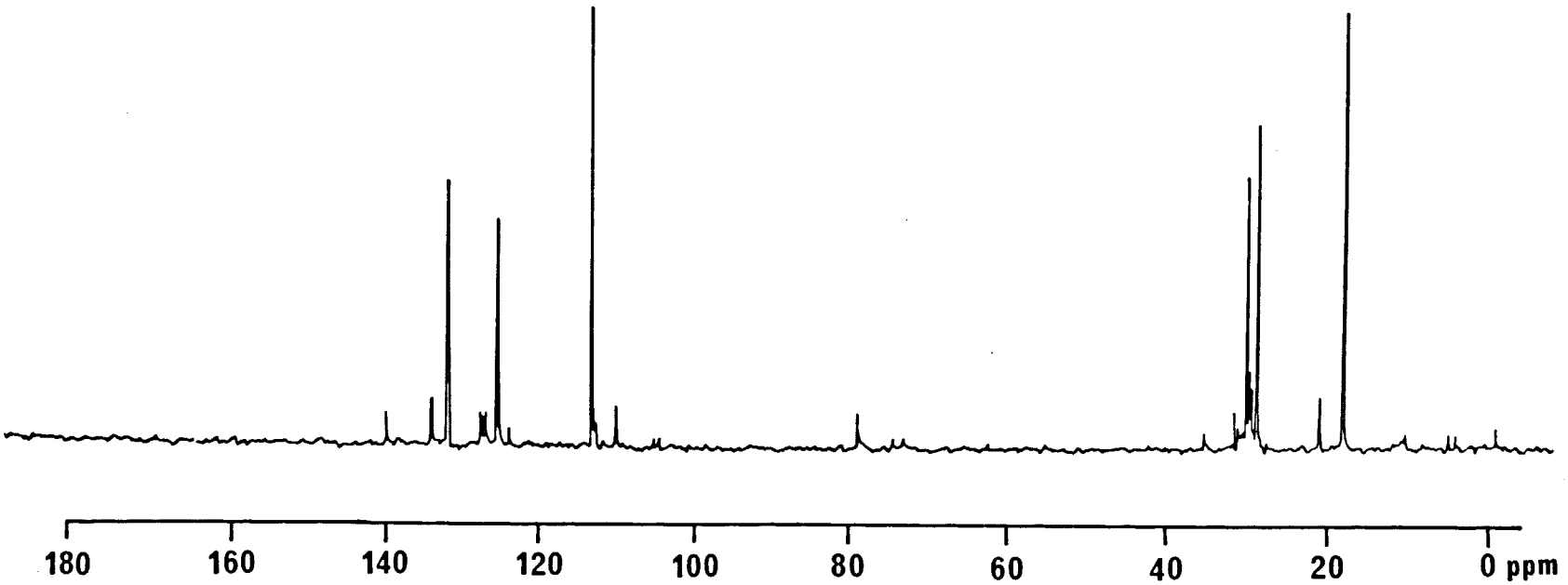
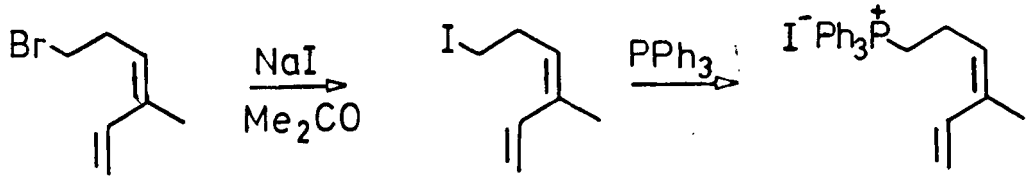



**Figure 39**

$^{13}C$ NMR spectrum of (Z)-6-bromo-3-methylhexa-1,3-diene

filtered off and dried but its low melting point (80-90 °C) suggested that it was very impure. This was also shown by the $^{1}H$ NMR spectrum which suggested contamination with unreacted triphenylphosphine. In an attempt to purify the salt it was resuspended in toluene which caused it to become oily again. Further trituration with light petroleum gave a solid again but this reverted to an oil on attempting to filter it off. Recrystallization from a tetrahydrofuran/acetone mixture gave some crystals (mp. 206-208 °C) but the yield was so low that they may have been only a side product of the reaction.

A second attempt was made to prepare the phosphonium salt of the cis bromodiene using dimethoxyethane as solvent but once again an oil was formed. Although it was not possible to crystallise the salt, the $^{31}P$ NMR spectrum showed that it was fairly pure with only slight contamination from the trans isomer and from triphenylphosphine and triphenylphosphine oxide. The major peak for the salt of the cis--bromodiene was at 23.27 ppm downfield from phosphoric acid.




96 98 99

Figure 39a

For use in a Wittig reaction a crystalline salt was considered to be preferable, and this did not seem possible for the salt of the cis--bromodiene (**96**). It was thought however, that by changing the counter-ion to iodide instead of bromide it might be possible to crystallize the salt. This could be achieved by treating the cis--bromodiene (**96**, figure 38a) with excess sodium iodide in refluxing

acetone to give the iododiene (**98**) which could then be treated with triphenyl phosphine to give the phosphonium iodide (**99**). Problems could occur in the formation of the iododiene (**98**) if any free iodine were to be formed since this can cause isomerization of double bonds.

Cis 6-bromo-3-methylhexa-1,3-diene was converted to the iodide by treatment with sodium iodide in acetone, as described above, for twelve hours. The conversion was shown to be complete by the $^1H$ NMR spectrum of the crude iododiene; the triplet at δ 3.3 for the methylene group next to bromine had disappeared and another triplet for a methylene group next to iodine had appeared at δ 3.0. The spectrum also revealed that the cis double bond of the diene was intact and no isomerization to the trans form had occurred.

The crude iododiene was therefore used for preparation of the phosphonium salt without distillation, by treatment with triphenylphosphine in dimethyl formamide at 100 °C for 1½ hours. The cooled solution was poured into excess diethyl ether and a crystalline salt was obtained by trituration of the resulting oil. The salt was purified by dissolving it in hot isopropyl alcohol and reprecipitating with diethyl ether.

Synthesis of farnesene

Only one step now remained in the synthesis of farnesene- a Wittig reaction between the ylid (**99a**) formed from this salt (**99**) and 6-methyl-5-hepten-2-one (**59**) as shown in figure 40.

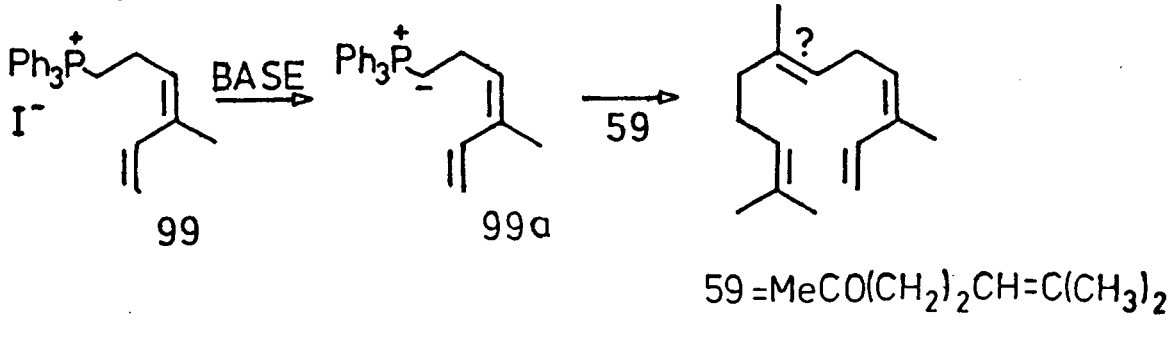



Figure 40

Preliminary reactions were carried out using two bases for the formation of the ylid, sodium bis(trimethylsilyl)amide and n-butyl--lithium. No farnesene was obtained with the silylamide but with n-butyl-lithium, GC analysis of the crude product showed peaks of comparable retention times to those of farnesenes obtained by dehydration of nerolidol. Distillation of the product however, caused rearrangement of the farnesene to give cyclized products with longer retention times on GC.

Since it had been ascertained that it was possible to prepare farnesene by a Wittig reaction between 6-methyl-5-hepten-2-one and the phosphonium salt, (99), the possibility of carrying out the reaction stereospecifically to give a trans double bond was considered. The method used by Schlosser and Christmann for trans selective olefin synthesis[101,102] appeared to be the only appropriate one available. This method was thought to be especially suitable because the base used to form the ylid was phenyl- or n-butyl-lithium which had already proved suitable for formation of an ylid from the salt (99) which was to be used here. Treatment of the ylid with carbonyl component leads to the formation of a betaine as an adduct with lithium halide. The betaine is diastereomeric, existing in threo and erythro forms and, in order to achieve trans-selective olefination, equilibration between these forms must be accelerated. This can be achieved, as outlined in figure 41, by addition of a second equivalent of phenyl- or n-butyl-lithium to form the diastereomeric betaine-ylids. The lithium halide--betaine adducts can be regenerated by addition of a proton donor such as hydrogen chloride or t-butyl chloride. Equilibrium between the betaine ylids lies far over to the side of the form which on protonation gives the threo-betaine. This on treatment with potassium t-butoxide liberates almost pure trans olefin.

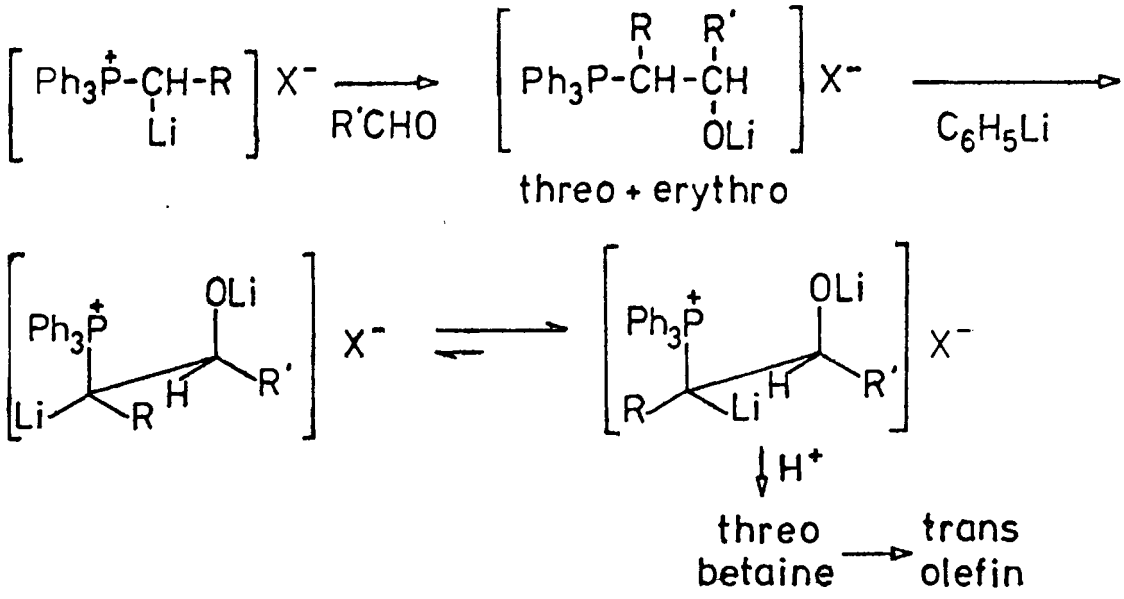



Figure 41

Although Schlosser and Christmann found that stereoselectivity was reduced in the case of a trisubstituted olefin this still seemed the best method to use. The diene salt (**99**) was therefore suspended in a mixture of tetrahydrofuran and diethyl ether and treated at room temperature with a 1.6 M solution of n-butyllithium in hexane to form the ylid. When a negative Gilman test indicated that all the base had been consumed the solution was cooled to -70 °C before addition of 6-methyl-5-hepten-2-one. Decolourization of the solution showed that conversion to the betaine was complete and more n-butyllithium in hexane was added at -30 °C. After waiting for the Gilman test to become negative again, dry HCl in ether and potassium t-butoxide were added to the reaction mixture. After working-up, the $^{1}H$ NMR spectrum of the crude product suggested that farnesene was present. Examination of the distilled product by GC however, showed two peaks in the α-farnesene region indicating that the final Wittig reaction had not been stereospecific and had given a mixture of (Z,E)- and (Z,Z)-α--farnesenes. Comparison of the retention times of the two peaks with that of the natural ant farnesene revealed that the desired isomer was the minor component of the mixture. The overall reaction scheme for

the partially stereospecific synthesis of α-farnesene from cyclopropropyl methyl ketone is shown in figure 42. The mass spectra of the two components obtained by GC-MS were compared with that of the ant material and this confirmed that the minor component was identical to ant farnesene.

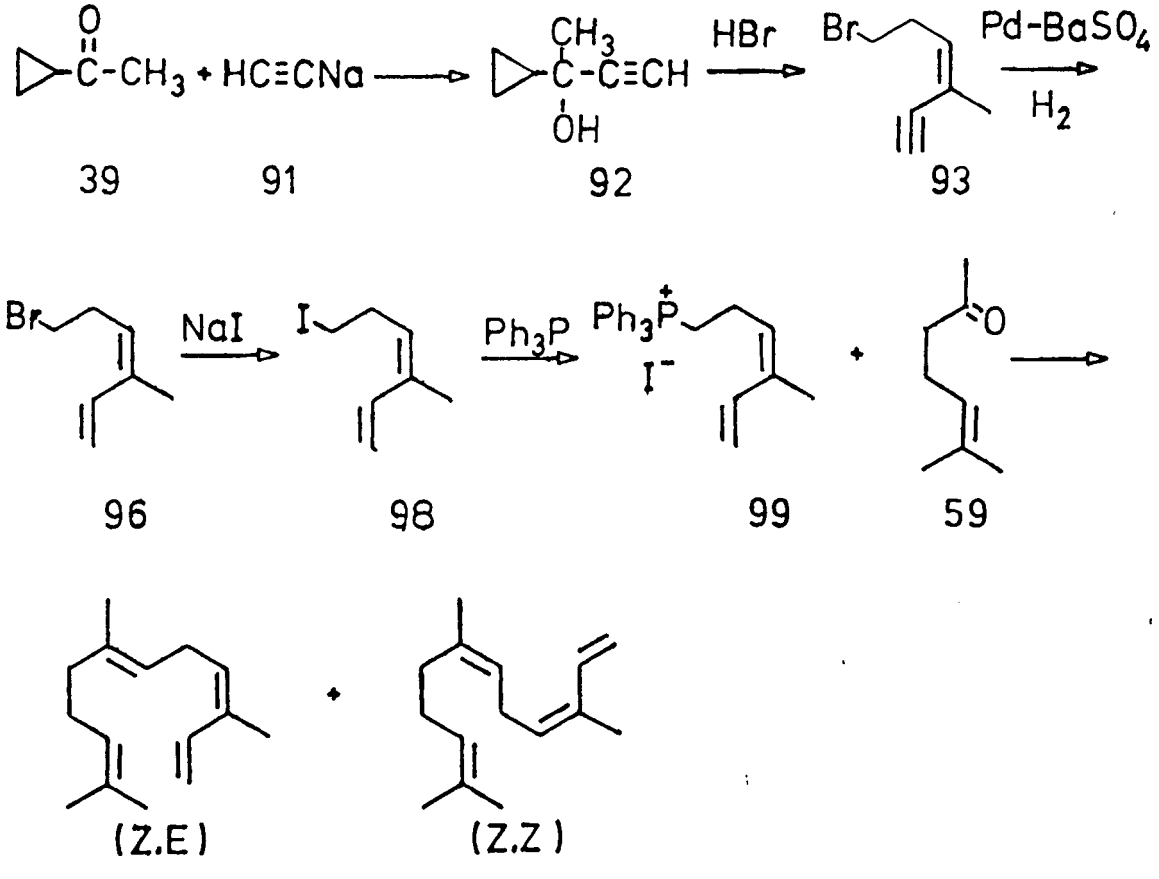



Figure 42

The overall yield of mixed farnesene isomers from the Wittig reaction was 33% and use of Christmann's conditions did not give the desired stereoselectivity. Trial reactions conducted during the synthesis of homofarnesene (see next section) showed that it was possible to obtain a comparable ratio of (Z,E)- to (Z,Z)-α-farnesene by a straightforward Wittig reaction in dimethoxy ethane at 80°, using n-butyl lithium as base. Also the total yield of farnesenes under these conditions was estimated from GC peak area to be in the region of 70%.

Separation of (Z,E) and (Z,Z)-α-farnesenes

As a pure sample of the (Z,E)-α-farnesene was required for characterization and biological testing, a method of separating this isomer from the mixture was sought. The two isomers were readily separable on GC but use of a preparative column to separate a reasonable quantity of the desired isomer would be a tedious process.

Various forms of argentation chromatography[103] have been used for the separation of mixtures of geometrical isomers, including TLC[103, 104] on silica impregnated with silver nitrate. The basis for this form of chromatography is the ability of silver ions to coordinate with double bonds. The degree of coordination is dependent on the environment around the double bond and so it is often possible to use this to separate cis and trans isomers.

Using 5 x 20 cm TLC plates impregnated with 5% silver nitrate and eluting with mixtures of light petroleum (boiling range 40-60 $^{o}$C) and diethyl ether separation of the two isomers of farnesene from the reaction was achieved. A preparative scale separation was then attempted using 40 x 20 cm plates loaded with 10% silver nitrate. The two bands containing the farnesene isomers were removed separately from the plates and extracted with an acetone-ethanol mixture. Concentration of the extracts and bulb distillation of the residues gave sufficient of the two isomers for spectra to be recorded.

Use of these preparative scale, silver nitrate loaded TLC plates was a tedious procedure since the maximum quantity of mixed farnesenes which can be separated on a single plate is only 250 mg so that several plates are needed for separation on a gram-scale. Also it is an expensive form of chromatography because it is difficult to recover the silver nitrate from the silica after the plates have been used. In

addition to this, removal of the bands of silica from the plates and extraction with solvent involves exposure to the air of the farnesene isomers, which are susceptible to autoxidation.

In view of these factors, an alternative form of chromatography was sought which could be used on a larger scale, with minimal exposure of the farnesene to the atmosphere, and which would be reusable. A number of references had been found in the literature to the use of HPLC with silver nitrate loaded columns,[105,106] and with a silver aluminosilicate[107] support in which silver ions are bound to the poly-anionic alumino silicate surface, for the separation of mixtures of cis and trans isomers. HPLC on reverse-phase columns with silver ions in the mobile phase had also been used[108] for such separations but when this was attempted here, difficulties were encountered due to deposition of metallic silver in the fine tubing of the apparatus causing a considerable reduction in flow rate through the column.

The use of a silver loaded support for HPLC was considered as a possible means of separating farnesene isomers since this would be reusable and would involve minimum exposure of the farnesenes to the atmosphere. However even when preparative columns were used, Heath and his coworkers[105] were only able to handle samples of 100 mg, so for separation of one gram of material ten runs would be necessary. There was however a medium pressure liquid chromatography (MPLC) system available and the possibility of adapting the HPLC method for use with this was considered.

An MPLC column of silica loaded with 20% silver nitrate was prepared and used to separate the farnesene isomers, eluting with an ether-light petroleum mixture. Fractions were collected and analysed by GC. This revealed that fractions 26–48 contained only (Z,Z)-α-farnesene and

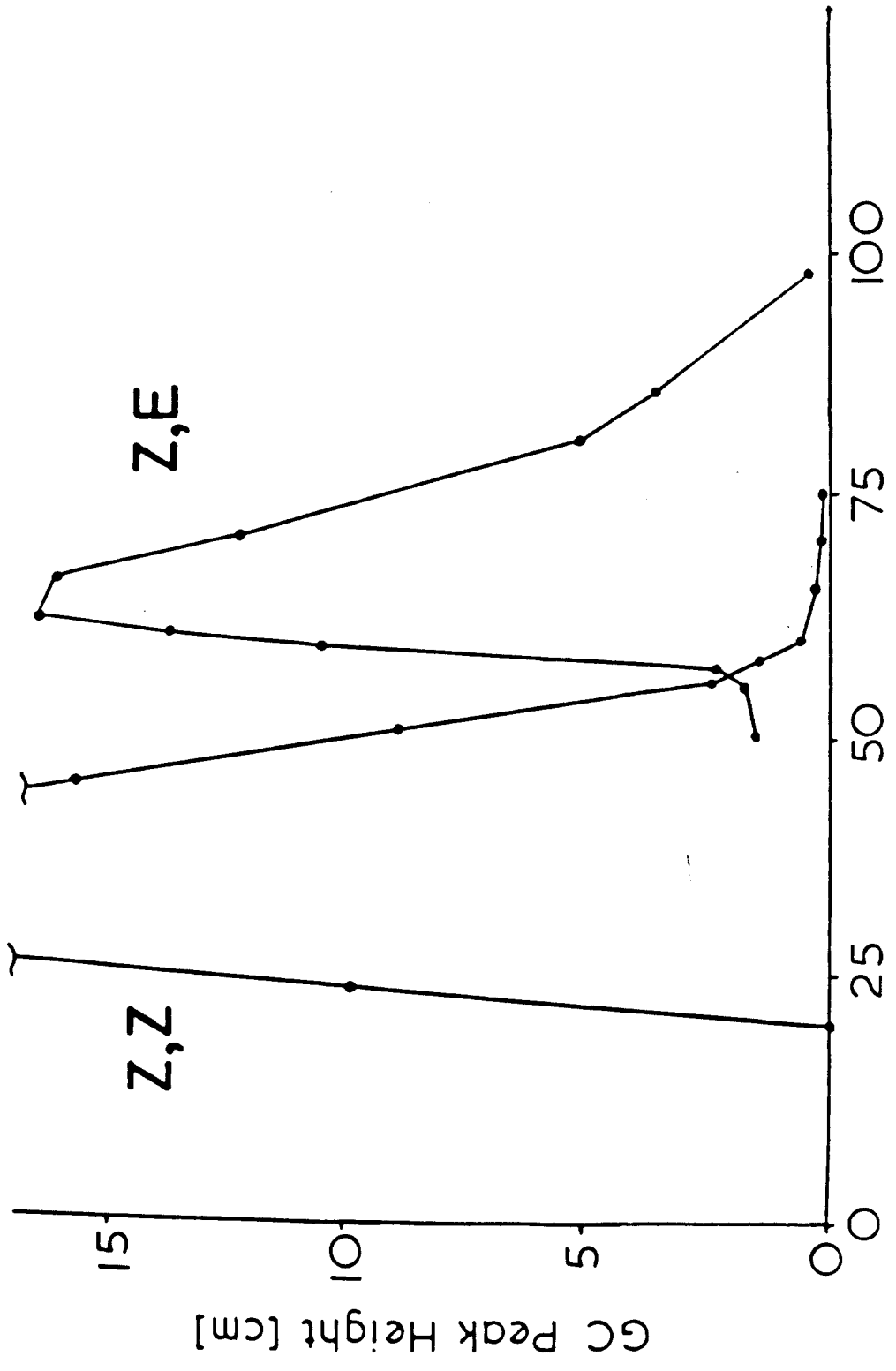



Figure 43

fractions 62-93 contained only (Z,E)-α-farnesene as shown in figure 43. Evaporation of the two groups of fractions and bulb-tube distillation gave sufficient of each isomer for spectra and biological testing.

Spectra of (Z,E) and (Z,Z)-α-farnesenes

The UV spectra of the two isomers were recorded on samples obtained from both the TLC and MPLC separations. The extinction coefficients for both isomers from the TLC separation were in the region of 10,000 which disagreed with the values given by Anet[6] of $\varepsilon$ = 22,500 for the (Z,Z) isomer and $\varepsilon$ = 11,300 for the (Z,E) isomer. When the spectra were recorded again on samples from the MPLC separation higher values, in the region of 20,000 were obtained for both isomers ((Z,Z), $\varepsilon$ = 22,350; (Z,E), $\varepsilon$ = 23,150). Since the conjugated diene system responsible for the UV absorption is essentially the same for both isomers, the extinction coefficients would be expected to be similar. It was thought therefore that the higher values obtained for the HPLC separated samples were correct and that the lower values obtained for the TLC separated samples were due to these being partially autoxidised.

$^1$H NMR spectra of the two isomers were recorded and the chemical shifts are compared with literature[6,18] values for (Z,E)- and (Z,Z)-α--farnesenes in table 1.

Table 1

$^1$H NMR spectral data for (Z,E)- and (Z,Z)-α-farnesenes

| | | | | | $-CH_2-CH_2-$(4H) | $=C-CH_2-C=$ (triplets) | $-CH=$(5H) (multiplet) | $=CH-C=$ (quartets) |
|---|---|---|---|---|---|---|---|---|
| (Z,E)-α- $\delta_{CDCl_3}$ | 1.59 | 1.62 | 1.67 | 1.80 | 2.01(s) | 2.79<br>2.85<br>2.93 | 5.0 -5.33 | 6.66<br>6.77<br>6.84<br>6.94 |
| Lit[18] (Z,E) $\delta_{CCl_4}$ | 1.60 | 1.65 | 1.69(3s,12H) | | 2.00 | 2.78 | 4.95-5.25 | 6.74 |
| (Z,Z)-α- $\delta_{CDCl_3}$ | 1.60 | 1.67(6H) | | 1.80 | 2.00(d) | 2.83 | 4.9 -5.3 | 6.7 |
| Lit[6] (Z,Z)-α- δ* | 1.62 | 1.68 | 1.69 | 1.80 | - | 2.87 | - | 6.77 |

* solvent not specified, either $CDCl_3$ or $CCl_4$

The NMR spectra of the two isomers are very similar; the main differences being in the positions of the methyl group signals. In the (Z,E)-α-farnesene spectrum (figure 44) these appear as four singlets, one for each methyl group at the positions shown in Table 1. In the (Z,Z)-α-farnesene spectrum (figure 44a) two of the methyl groups coincide at δ1.67. In going from the (Z,E) to the (Z,Z) isomer there is a downfield shift from δ1.62 to 1.67 in the position of one of the methyl signals. The methyl group concerned must be the one at C-7 which is on a trans double bond in the (Z,E) isomer and cis double bond in the (Z,Z) isomer. Such shifts have been reported by several authors,[70,89,93-95] as discussed earlier for the cis and trans bromodienes prepared during the farnesene synthesis.

IR spectra were obtained, both as thin films and in solution, for each isomer and positions of the more important absorptions are given with the literature values in table 2.

Table 2

IR spectral data for (Z,E)- and (Z,Z)-α-farnesenes

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| (Z,E)- | $\nu_{film}$ | 835 s,br | 900(br) | 990s, | 1805 | 1150 | 1595 | 1640 | 3100 |
| | $\nu_{CCl_4}$ | - | 905 | 985 | - | - | - | - | 3080 |
| | Lit$\nu_{film}$ | 830 | 900 | 985 | - | 1590 | | 1635 | 3085 |
| (Z,Z)- | $\nu_{film}$ | 830 | 900s | 985 | 1800br | 1135yw | 1590 | 1640 | 3090 |
| | $\nu_{CCl_4}$ | 830 | 905 | 988 | 1800br | 1130 | 1585 | 1635 | 3085 |
| | Lit$\nu$ | 830m | 906s | 990 | 1815yw | 1140yw | 1599m | 1648w | - |

As with the NMR spectra there are only slight differences between the IR spectra of the two isomers.

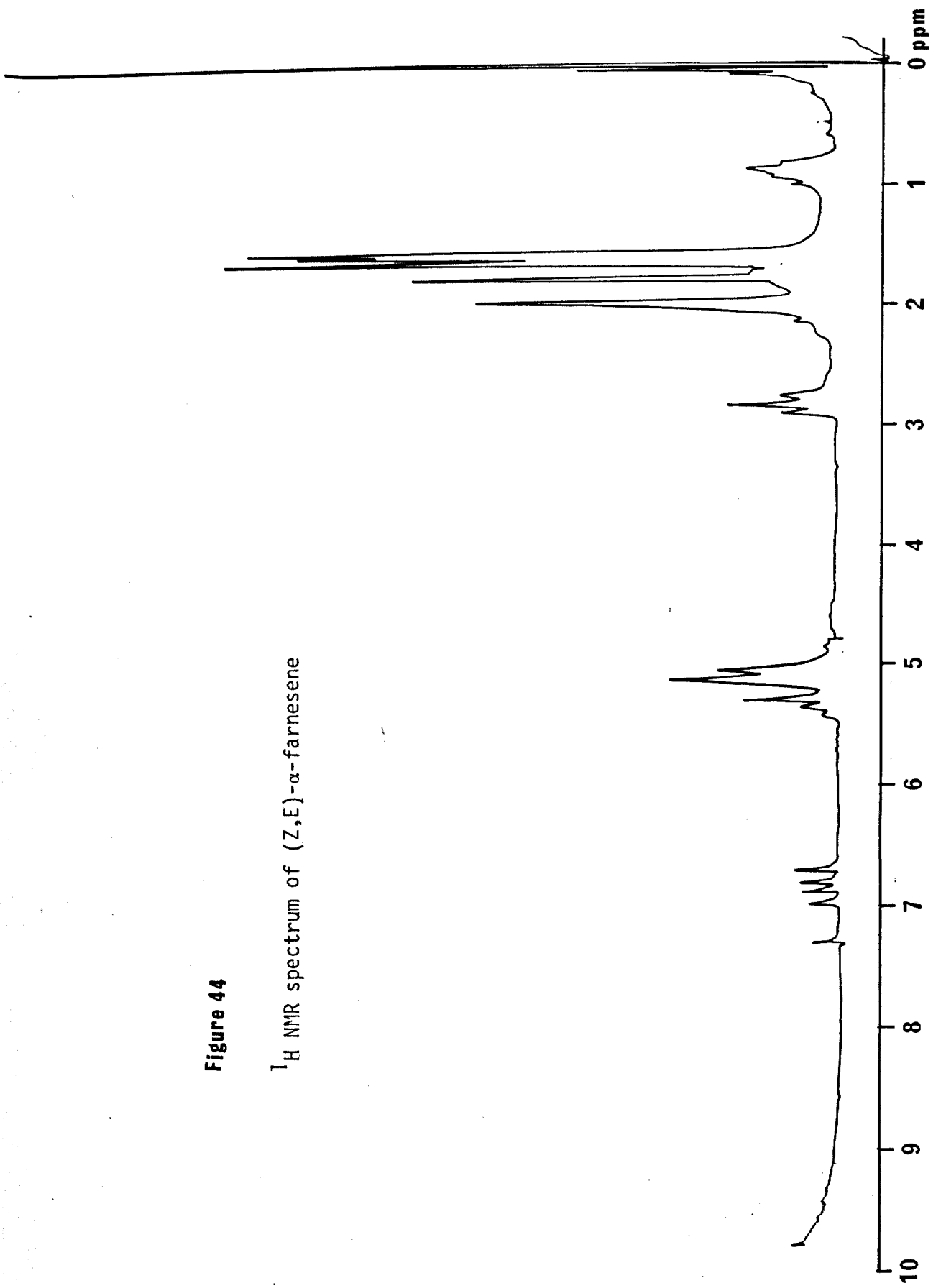



**Figure 44**

$^1$H NMR spectrum of (Z,E)-α-farnesene

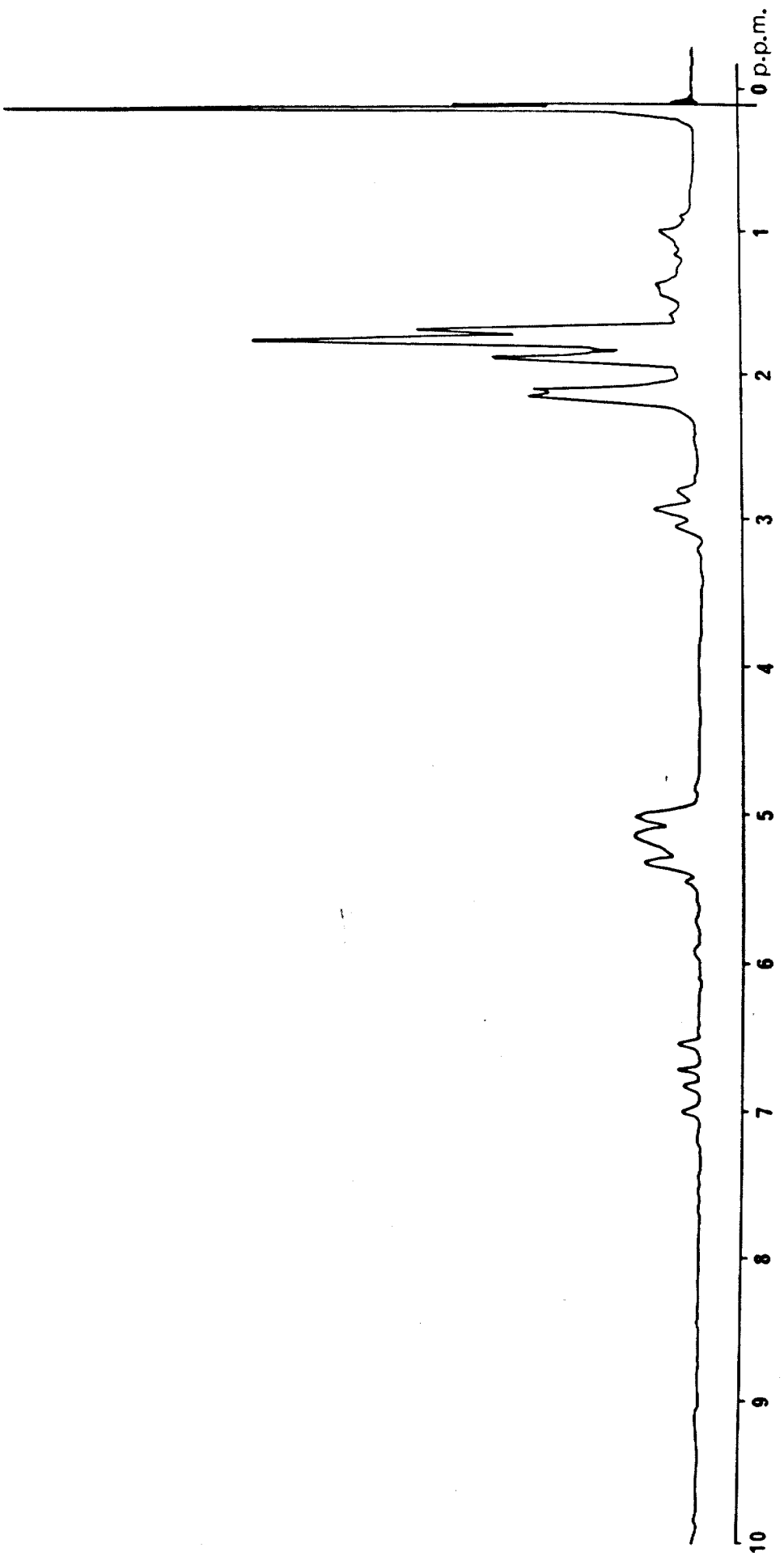



**Figure 44a**

$^1$H NMR spectrum of (Z,Z)-α-farnesene

GC-MS was used to obtain mass spectra of the two pure isomers and these were compared with the spectrum obtained from a sample of ant farnesene (see figure 45). The spectra of all three compounds are very similar, but close examination shows that those of the synthetic (Z,E)-α-farnesene and the ant material are almost identical whereas that of (Z,Z)-α-farnesene differs in the relative intensities of some of the groups of peaks. For example the peak at m/e 133 is the most prominent peak in that group for the (Z,Z) isomer but for the (Z,E) isomer and the ant farnesene the m/e 135 peak is more intense. Similarly in the spectrum of the (Z,Z) isomer the peak at m/e 81 is more prominent than either m/e 77 or 79 which are of similar intensity while the spectra of the ant farnesene and (Z,E) isomer have m/e 79 predominating with m/e 77 slightly less intense and m/e 81 even less intense.

The spectral data for the (Z,E)- and (Z,Z)-α-farnesenes, obtained from this first true synthesis of these compounds agrees with that for these isomers separated by GC from the dehydration products of nerolidol. However, what is more important, is that the mass spectrum of the (Z,E) isomer is clearly the same as that of the ant farnesene. Mass spectra of farnesene have been recorded by courtesy of colleagues elsewhere on several different instruments, and, they are consistent in the minor patterns of peaks, first observed by Anet[6]. These patterns therefore are not instrument artefacts and can be reliably used to identify farnesene isomers. Thus on the basis of GC retention time and mass spectra, the identification of the ant farnesene can be confirmed.

Acceptable microanalysis results could not be obtained for either of the synthetic farnesene isomers presumably due to oxidation. Farnesenes rapidly oxidize in air to a colourless gel which makes them difficult to handle in air in the absence of a solvent. In view

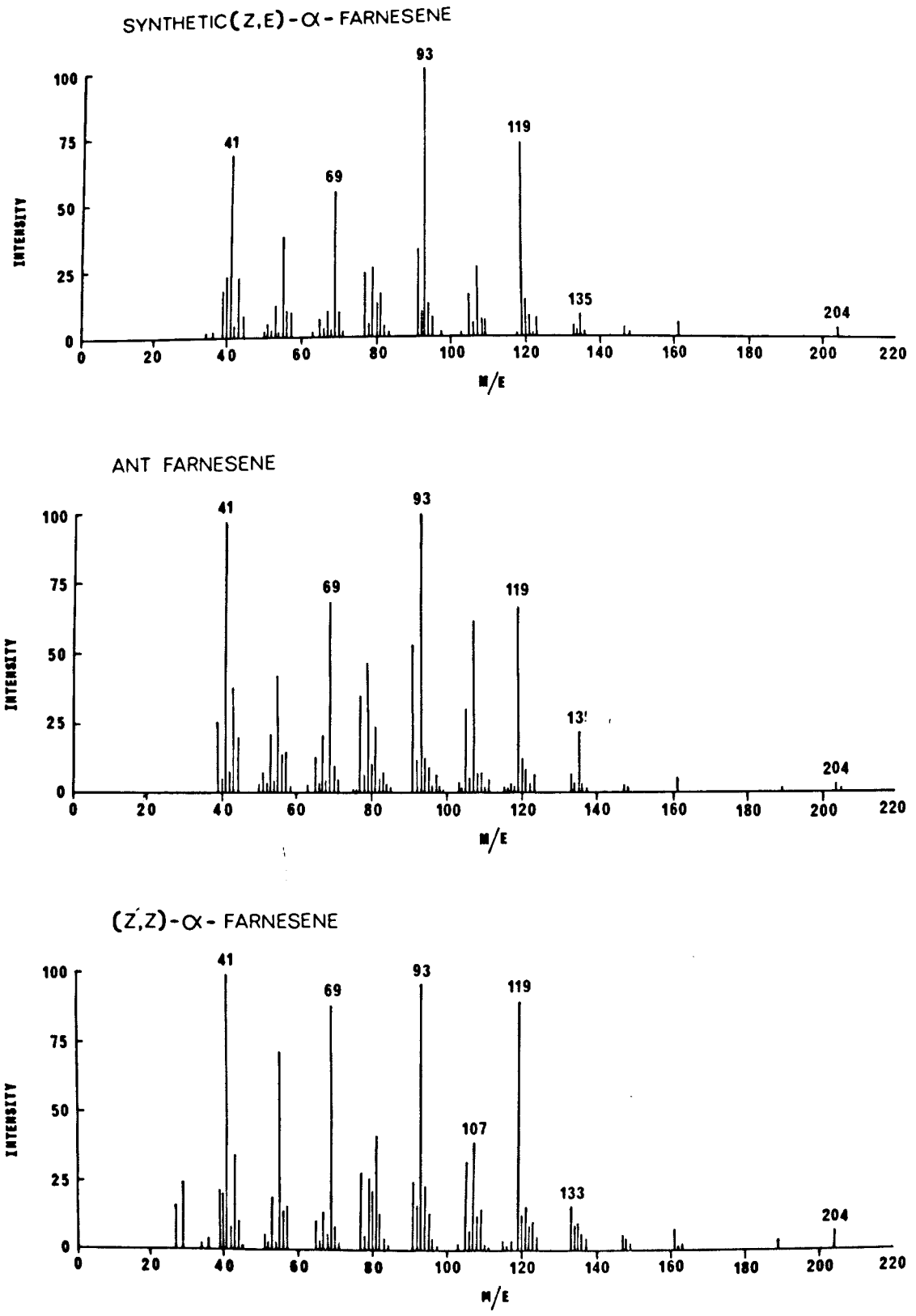

SYNTHETIC(Z,E)-α-FARNESENE
INTENSITY
M/E
41
69
93
119
135
204
ANT FARNESENE
INTENSITY
M/E
41
69
93
119
204
(Z,Z)-α-FARNESENE
INTENSITY
M/E
41
69
93
107
119
133
204

**Figure 45**

of this instability, it is difficult to understand why farnesenes should be produced and used by ants. It does not appear that they are used in a defensive way, as some unsaturated terpenoid compounds are by termites,[109] and the lifetime on a natural earth surface, of the nanogram quantities used by the ants, remains uncertain.

## ATTEMPTED SYNTHESIS OF HOMOFARNESENE

With a synthetic route to α-farnesene established, there remained the problem of adapting this to the synthesis of the higher homologues. The C-1 to C-6 fragment of both homofarnesene and bishomofarnesene, is identical to that of farnesene itself, and the same phosphonium salt could be used for their synthesis. Different ketones would be necessary however, to introduce the extra methylene groups at the C-7 and C-11 positions. The ketones required were 7-methyl-6-octen-3-one (**100**, figure 41) for homofarnesene and 7-methyl-6-nonen-3-one (**101**) for bishomofarnesene.

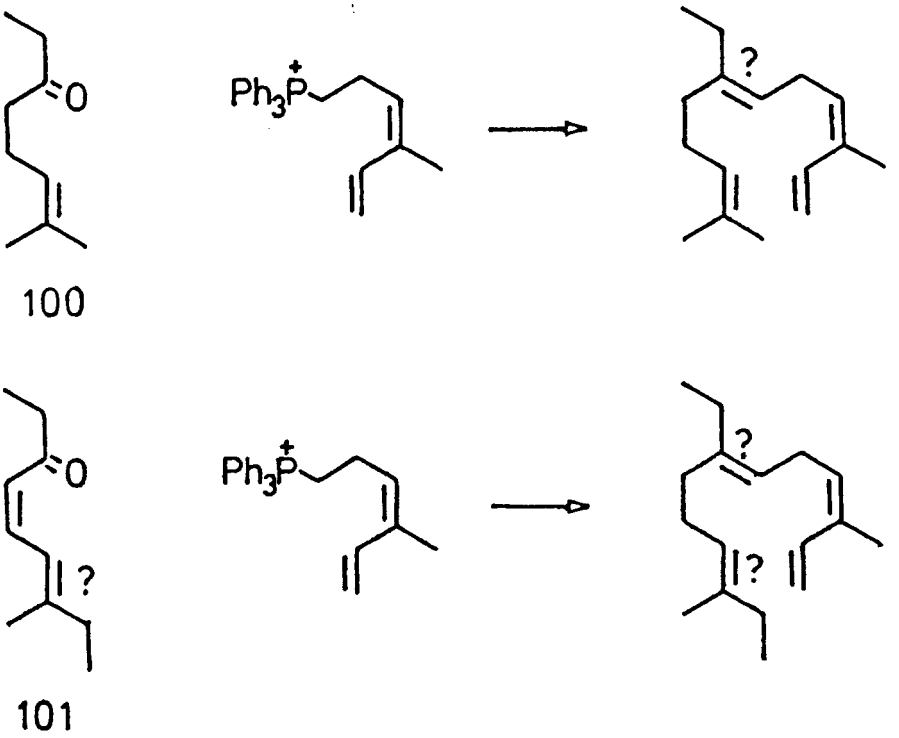



Figure 46

Synthesis of ketone homologues

Unlike the ketone used for the synthesis of farnesene, these ketones (**100** and **101**) were not available commercially and syntheses for them had to be devised. The route chosen for the synthesis was based on a scheme used by Findlay et.al. to prepare 6-methyl-5-octen--2-one (**106**) as an intermediate in a juvenile hormone synthesis.[110] Findlay's method, starting from 5-chloropentan-2-one (**102**) is outlined in figure 47. The chloroketone (**102**) was converted to the iodoketone (**103**) and then to the iodoketal (**104**) which was treated with triphenylphosphine to form its phosphonium salt (**105**). A Wittig reaction with butan-2-one and removal of the protecting group gave the ketone (**106**).

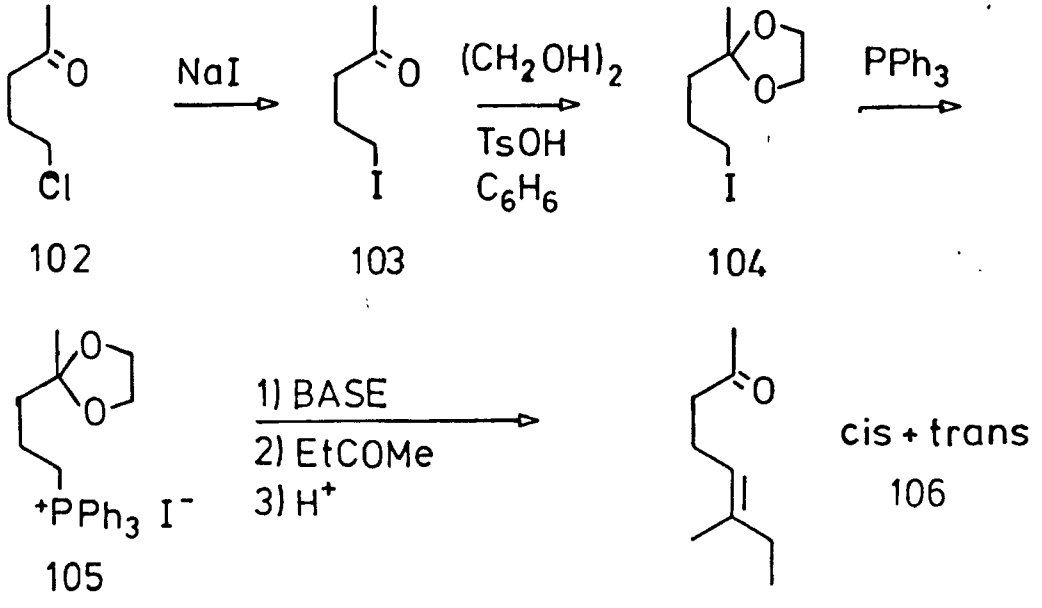



Figure 47

To prepare the ketones (**100, 101**) required for the synthesis of the farnesene homologues, by this route the starting material required would be 6-chloro-hexan-3-one (**108**, figure 48). This, unlike 5-chloro--pentan-2-one (**102**) is not available commercially but its preparation from 4-chlorobutyryl chloride (**107**) using diethyl cadmium[111-113] or

ethyl magnesium bromide in the presence of a ferric chloride[114] catalyst has been reported in the literature. The proposed scheme for the synthesis of the two ketones from 4-chlorobutyryl chloride (**107**) is outlined in figure 48.

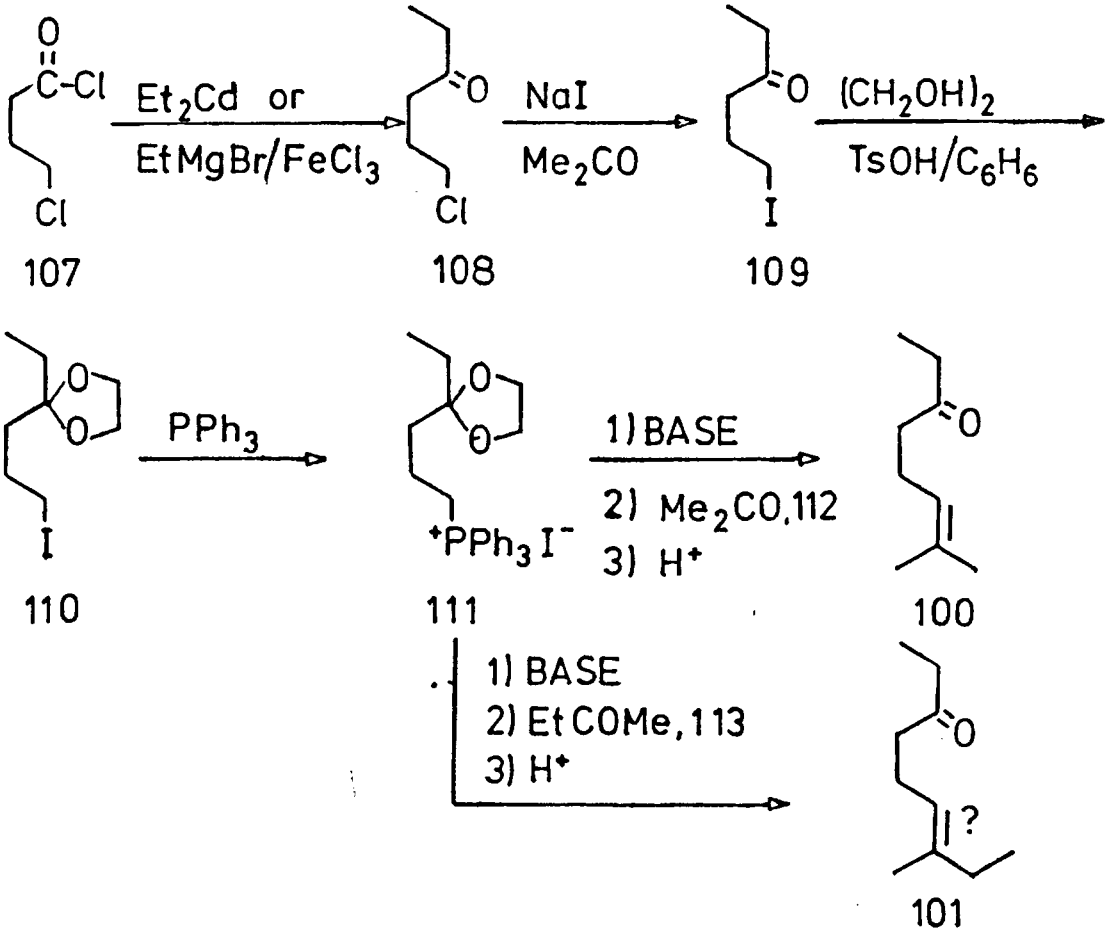



Figure 48

An alternative route which was considered was also reported by Findlay et. al. for the synthesis of 7-methyl-6-nonen-3-one (**101**) starting from 3-methylpent-1-en-3-ol and ethyl vinyl ether.[110] By starting with 3-methylbut-1-en-3-ol, this could also be used for the other desired ketone (**100**).

The first stage in the synthesis of the two ketones (**100, 101**) by the chosen route was the preparation of 6-chloro-hexan-3-one from 4-chlorobutyryl chloride. This was attempted using diethylcadmium, which was obtained by first preparing the Grignard reagent, ethyl

magnesium bromide, and treating it with cadmium chloride. 4-chlorobutyryl chloride was then added to the organo-cadmium reagent to form the desired chloro-ketone (**108**). The product from the reaction however was a mixture of 6-chlorohexan-3-one and the ethyl ester of 4-chlorobutyric acid. The ester was successfully removed by hydrolysis with sodium carbonate in aqueous methanol but after redistillation the overall yield of ketone was very poor.

The same chloroketone had been prepared from 4-chlorobutyryl chloride by Tasinken[114] using ethyl magnesium bromide with a ferric chloride catalyst in an ether/toluene mixture, as described by Cason and Kraus.[115] Ferric chloride had been found by Percival *et. al.* to be more effective than any of the other metallic halides tried, as a catalyst for Grignard reactions to form ketones from acid chlorides.[116] This method was therefore used to prepare 6-chlorohexan-3-one in 59% yield.

The next stage in the synthesis, conversion to the iodide (**109**) was carried out as described by Findlay *et. al.* using excess sodium iodide in acetone. $^{1}H$ NMR spectrum of the crude product revealed that none of the chloride remained so it was converted to the ketal without distilling. This step was also accomplished using Findlay's method to give the iodoketal (**110**), in 71% overall yield (after distillation) from the chloroketone.

Preparation of the phosphonium salt (**111**) from the iodoketal was achieved by treatment with triphenylphosphine in dimethyl formamide at reflux for 6 hrs. This salt could then be used to form either 7-methyl-6-octen-3-one (**100**) or 7-methyl-6-nonen-3-one (**101**) by Wittig reactions with acetone (**112**) or butan-2-one (**113**), since this appeared to give a very good yield (83%). The recorded yield however was based on the ketone, butan-2-one (**113**), with an excess of phosphonium

salt being used. As the salt was prepared by a multistage synthesis whereas the two ketones required were readily available commercially, an excess of the ketone was used for the work here. Yields for the two ketones, 7-methyl-6-octen-3-one (**100**) and 7-methyl-6-nonen-3-one (**101**), based on the phosphonium salt were 44% and 49% respectively, using sodium hydride in dimethylsulphoxide as base. When the base was changed to n-butyllithium, with dimethoxyethane as solvent, for the preparation of the first of these ketones (**100**), the yield was much lower.

Attempted separation of 7-methyl-6-nonen-3-one isomers

For the second of the ketones 7-methyl-6-nonen-3-one cis and trans isomers were possible about the C-6 double-bond and the product formed in the Wittig reaction was found to be a mixture of the two, which was not completely resolvable by GC. The $^{13}C$ NMR spectrum (figure 49) showed that the mixture contained 66% E and 34% Z Isomer. The stereochemistry of this double bond in the bis- and trishomofarnesenes had not been determined, so both isomers needed to be prepared, in order to ascertain which was correct. However it was considered preferable to separate the ketones if possible and use them independently in Wittig reactions to form the farnesene homologues. Attempts to separate the cis/trans mixture on the 20% silver nitrate MPLC column used for the (Z,E)- and (Z,Z)-α-farnesenes only gave partial separation. The $^{13}C$ NMR spectrum (figure 50) of the first fractions from the column showed that the E/Z ratio was now 78/22, i.e. there was an enrichment of the E isomer. Use of an MPLC column with a higher loading of silver nitrate (40%) gave no significant improvement in the separation achieved. Attempts to separate the two isomers at this stage were therefore abandoned.

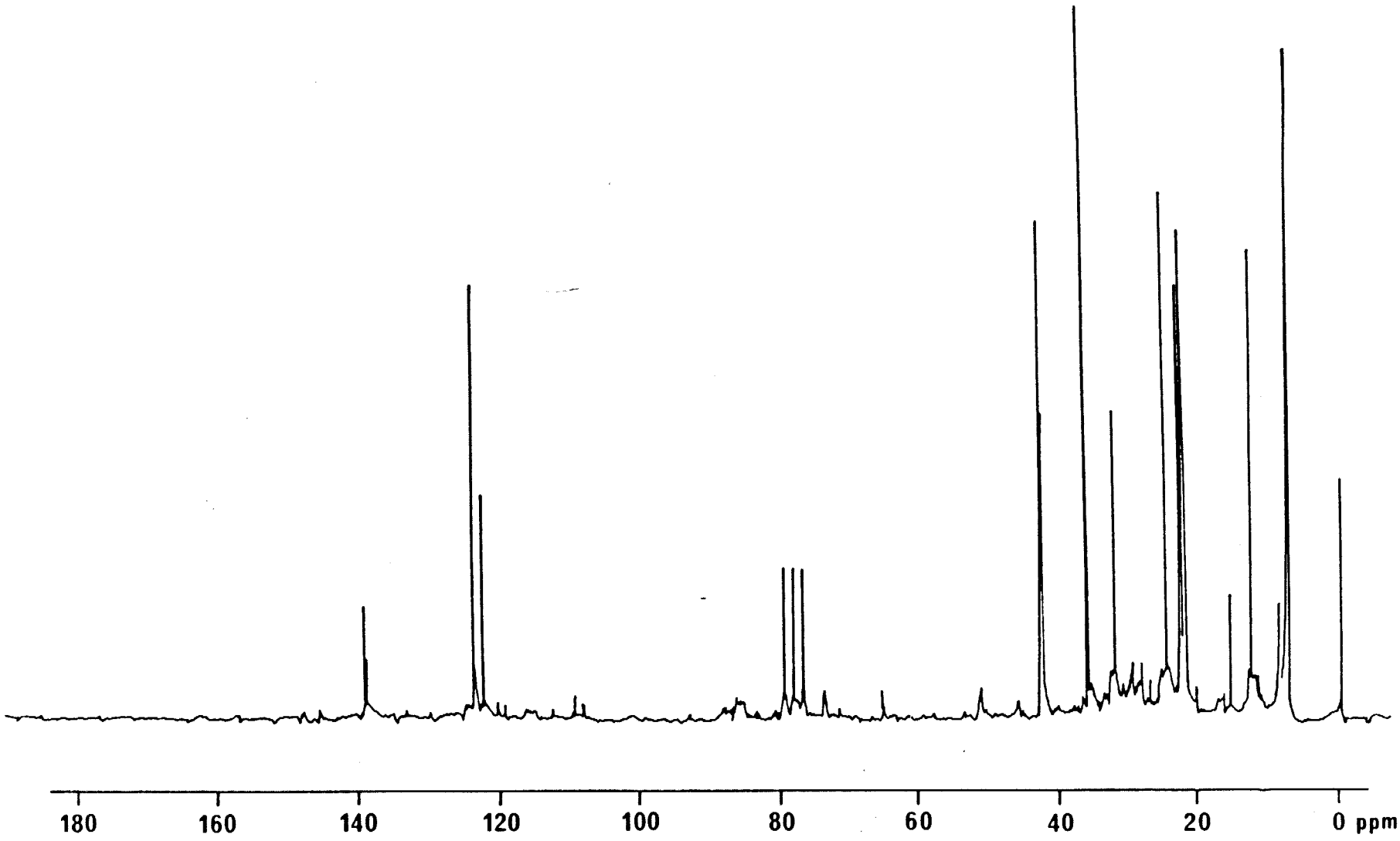



**Figure 49**

$^{13}C$ NMR spectrum of total mixture of (Z)- and (E)-7-methyl-6-nonen-3-one

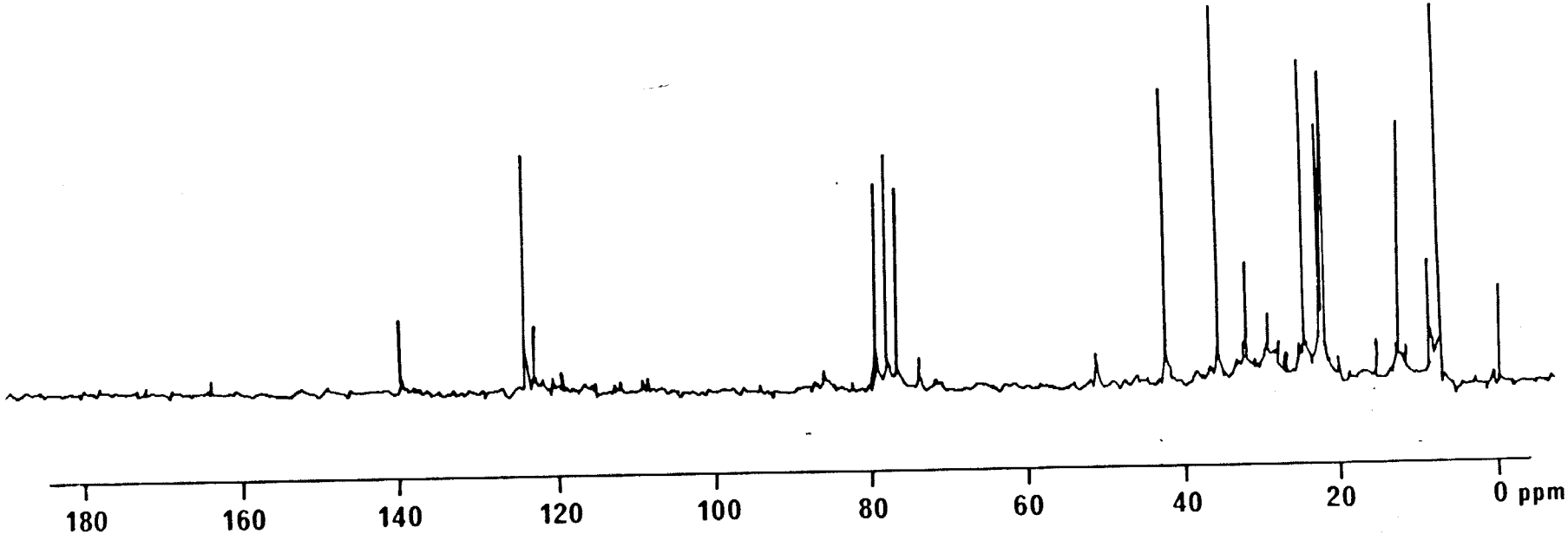



**Figure 50**

$^{13}C$ NMR spectrum of first fractions from MPLC separation of (Z)- and (E)-7-methyl-6-nonen-3-one

Attempted Wittig reaction with 6-methyl-7-octen-3-one

To complete the synthesis of homofarnesene, the condensation of the ketone, 7-methyl-6-octen-3-one, with the phosphonium salt was attempted. Sodium hydride in dimethyl sulphoxide was chosen as the base for this reaction since it had given better yields than n-butyl lithium in the preparation of the homologous ketones. Also sodium hydride being a solid could be handled more conveniently than n-butyl lithium. However when the crude product from the reaction was examined by GC this revealed the presence of a large amount of unchanged ketone and only a trace of product.

Trial reactions with 6-methyl-5-hepten-2-one

In order to find out the best conditions for this Wittig reaction, a number of small scale trials were carried out using different bases, solvents and reaction temperatures. Since the ketone required for the homofarnesene synthesis had been prepared by a multistep synthesis, preliminary tests were carried out using the commercially available 6-methyl-5-hepten-2-one, used in the farnesene synthesis and these reactions are summarized in table 3. The reactions were followed by gas chromatography.

From these reactions it was found that the best yield of farnesene (measured by GC peak area) was obtained in reaction number 4 in which the base used was n-butyl lithium. A two-fold excess of base was used for this reaction and the solvent was dimethoxyethane. After adding the ketone at 0 $^{o}$C the reaction mixture was stirred at room temperature for 1½ hrs after which time farnesene peaks were visible in the GC trace. Boiling under reflux for 50 minutes caused the farnesene peaks to increase in size to approximately five times the area of the ketone peak. Another hour at reflux temperature produced

Table 3

Trial Wittig reactions with 6-methyl-5-hepten-2-one

| Reaction No. | Solvent | Base | Equivs. base | Time/Temp before ketone added | Temp at which ketone added | Time/Temp after ketone added | GC Analysis |
|---|---|---|---|---|---|---|---|
| 1. | DMSO | NaH | 2. | 80°C/70M | 30°C | RT. 30M<br>80°C 4hrs | Possible farnesene peaks present.<br>No farnesene on work up but ketone recovered. |
| 2. | THF | BuLi | 1 | RT/30M | 0°C | 0°C 1hr<br>67°C 8.5hr | Possible F peaks<br>F peak > K peak |
| 3. | DME | BuLi | 1.5 | RT/30M | 0°C | RT 1hr<br>84° 3hrs | F peaks present<br>F peak > K peak |
| 4. | DME | BuLi | 2. | RT/30M | 0°C | RT 1.5hr<br>84° 50M<br>84° 1h50m | F peak present<br>F peak ∿ 5 x K peak<br>F peak ∿ 6.5 x K peak |
| 5. | DMSO | BuLi | 2. | RT/30M | RT | RT. 30M<br>RT. 1hr<br>60°C 1hr | No farnesene<br>No farnesene<br>No farnesene<br>Small peaks seen when crude product examined |
| 6. | DMSO | BuLi | 2. | RT/5M | RT | RT 2½ days | No evidence of product after work-up but K present. |

a further increase in the farnesene peak area, to 6.5 times the area of the ketone peak.

A second attempt was made to prepare homofarnesene using the conditions found to be best for farnesene synthesis. The reaction was carried out as for reaction 4, (table 3), except that the mixture was heated to reflux temperature immediately after additon of the ketone was complete. After two hours at reflux some small peaks were seen in the GC trace at approximately the retention time expected for homofarnesene isomers. These peaks had not increased in size significantly after a total of 15 hrs reflux when the reaction was worked up. The crude product was distilled under reduced pressure to give mostly unchanged ketone and no homofarnesene.

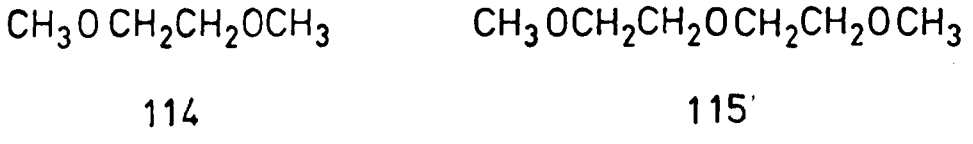
GC and GC-MS investigation of the distillation residue revealed that homofarnesene was present as a minor component while the major component had a molecular weight of 220 and appeared to be a dihydro-homofarnesene. The presence of this unexpected product must be due to some over-hydrogenation during preparation of the phosphonium salt for this reaction. The dihydrohomofarnesene would be expected to be more stable than homofarnesene itself and this would account for it being present in greater yield in the distillation residue.

Comparison of reactivity of ketones

The failure of the Wittig reaction to give homofarnesene, under conditions which had given a good yield of farnesene, was attributed to a wide difference in reactivity between the two ketones used. This was confirmed by performing two Wittig reactions simultaneously using identical reagents and solvents except for the ketones. Examination of the reaction mixtures by GC after 3 hrs at room temperature revealed a considerable difference in the size of the peaks for farnesene and

homofarnesene and on heating to reflux the farnesene peak increased but the homofarnesene peak did not.

A means of increasing the rate of reaction between the ylid and 7-methyl-5-octen-3-one was sought and one way of doing this was by raising the temperature which could be achieved in one of two ways; a solvent of higher boiling point could be used, or the reaction could be performed in a sealed tube. In selecting a higher-boiling solvent, one with similar properties to dimethoxyethane (**114**, figure 51) was preferred, and diethyleneglycol dimethyl ether or diglyme (**115**, figure 51) seemed a suitable choice with a sufficiently high boiling point (162°).



114 115

Figure 51

Homofarnesene from sealed-tube Wittig Reaction

Before trying the new solvent however, the reaction was attempted in dimethoxyethane in a sealed Carius tube. The phosphonium salt and solvent were placed in the tube which was flushed with nitrogen and fitted with a rubber septum. n-Butyllithium in hexane and the ketone were injected through the septum then the tube was sealed, placed inside the outer metal tube, and heated to 135° for 2 hrs. The cooled tube was opened and the contents worked-up as usual to give a crude product which was shown to contain two components of appropriate retention times on GC, and correct molecular weight by GC-MS for homofarnesene isomers. The two isomers could be assigned as (Z,E)- and (Z,Z)-homofarnesenes since these would be the expected products from the Wittig reaction, and by analogy with the corresponding

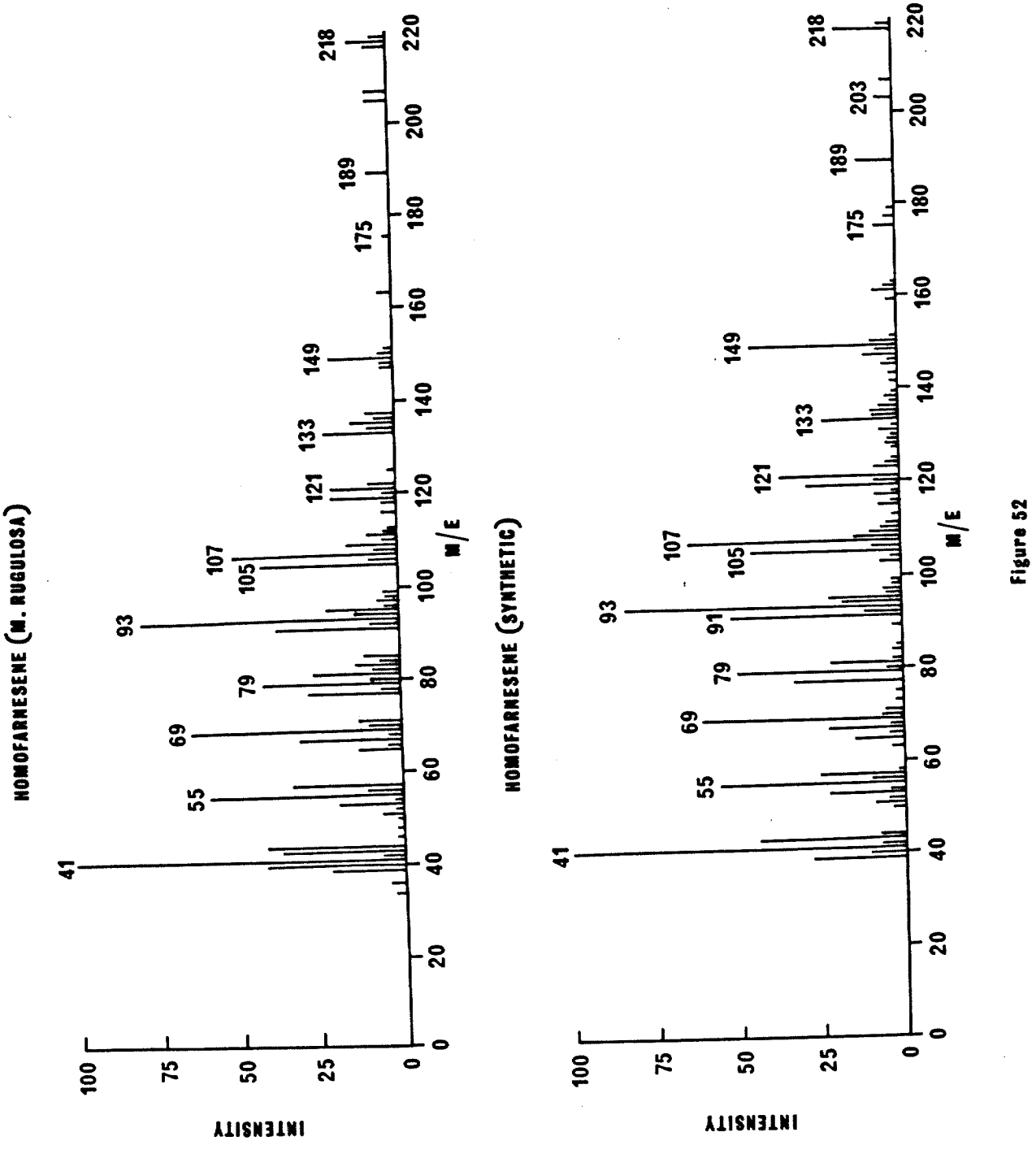

HOMOFARNESENE (M. RUGULOSA)
INTENSITY
M/E
HOMOFARNESENE (SYNTHETIC)
INTENSITY
M/E

Figure 52

farnesenes the isomer with longer GC retention time would be the (Z,E) isomer. The mass spectrum of this (Z,E)-homofarnesene obtained by GC-MS was found to be almost identical to that of ant homofarnesene as shown in figure 52. Strong ions at m/e 149 and 69 arise from primary allylic cleavage of the m/e 218 molecular ion at the C-8 to C-9 single bond. The m/e 149 ion corresponds to the m/e 135 of farnesene itself, while m/e 69 is common to farnesene and homofarnesene. The base peak of the spectrum at m/e 41 arises by loss of ethylene from the m/e 69 ion. Similarly cyclisation of the m/e 149 primary fragment followed by loss of ethylene or butene produces ions at m/e 121 and 93 respectively. In turn, loss of methane from m/e 93 would produce an m/e 77 ion. These fragmentation pathways and possible structures of the various ions are illustrated in figure 53, below.

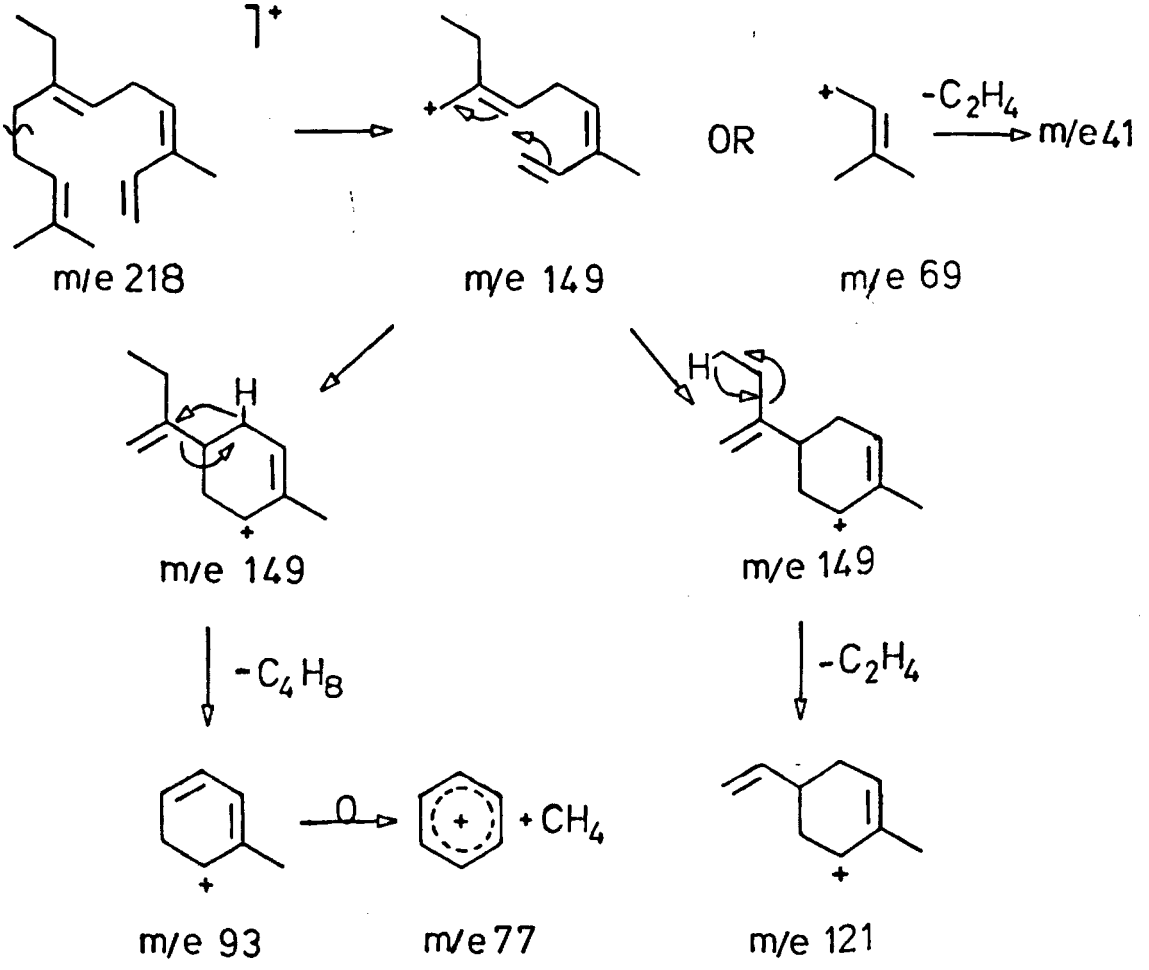



Figure 53

Other strong ions at m/e 133, 119, 105 and 91 are suggested by Parry[7] to be various substituted tropylium ions generated during fragmentation and slightly weaker ions at m/e 203 and 189 are obviously due to loss of methyl and ethyl groups respectively from the molecular ion.

The original structural assignment of homofarnesene with its extra methylene on C-7, has been shown to be correct by the synthesis carried out here and the demonstration that the synthetic and natural compounds have the same mass spectrum. Further confirmation of its correctness has been provided by some recent work in this department by A.B. Attygalle who performed microozonolysis on a sample of ant homofarnesene and analysed the products by GC-MS[117]. He found that homofarnesene (**117**, figure 54) gave 4-oxohexanal (**119**) as an ozonolysis product whereas farnesene (**116**) gave 4-oxopentanal (**118**).

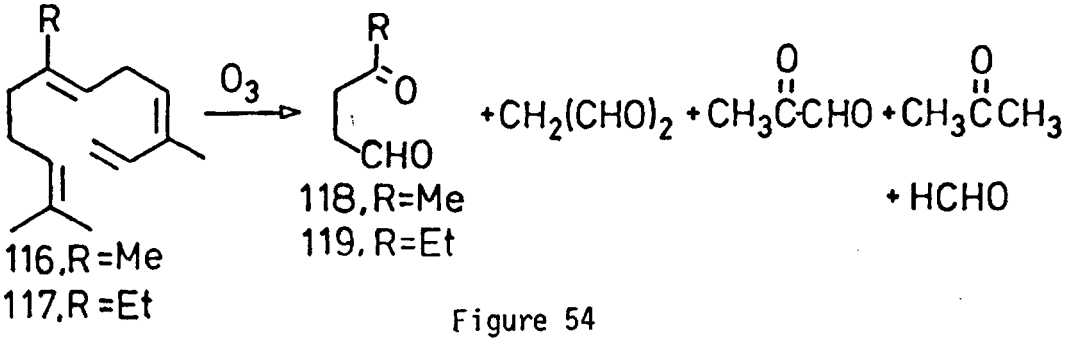



Figure 54

The sealed tube Wittig reaction was only carried out on a small scale (< 2m moles) and therefore it was not possible to isolate the homofarnesene isomers for complete characterization although the mass spectrum had confirmed the structure assigned to the natural compound.

As it was impractical to scale-up the sealed tube reaction sufficiently further reactions were attempted in the higher boiling solvent, diglyme. A series of small scale reactions were performed under various temperature conditions using n-butyllithium as base

Table 4

Trial Wittig reactions with 7-methyl-6-octen-3-one

| Reaction No. | Solvent | Base/ No. of moles | Time/Temp before ketone added | Temp at which ketone added | Time/Temp after ketone added | GC/Comments |
|---|---|---|---|---|---|---|
| 1. | Diglyme | BuLi/2 | 35mins/RT | RT | 130° 3hrs<br>150° | Possible homofarnesene peaks (7-14% yield). No change on increasing temperature or on adding more BuLi. |
| 2. | Diglyme | BuLi/2 | 30M/RT | 0°C | 0° 1hr<br>→ 140° | No product. T. raised slowly, no product seen until 140° All 4 isomers formed. |
| 3. | Diglyme | BuLi/2 | 30M/RT | RT | 140° 15M<br>135° 2.5hrs | 4 peaks formed. E,E and E,Z decreasing. Continued to decrease when more BuLi and ketone added. No increase in Z,E, Z,Z. |
| 4. | Diglyme | BuLi/2 | 30M/RT | RT | 125°C 0M<br>125°C 15 mins<br>125°C 3 hrs | E,E and E,Z peaks formed immediately. Z,E and Z,Z peaks appeared. Z,E and Z,Z no longer increasing. E,Z and E,E, decreased with excess BuLi. |
| 5. | Diglyme | BuLi/2 | 30M/RT | RT | Raised slowly to 70°C<br>" " " to 134°<br>134°/30M<br>134° 1hr | 4 peaks forming.<br>Peaks increased<br>No overall increase but peak ratio changing.<br>No change. |
| 6. | DME | BuLi/2 | 30M/RT | RT | RT<br>84°C 5hrs | Two homofarnesene peaks formed immediately which increased with stirring at RT and further increased on heating. GC of crude product shows ~10% yield |

and these are summarized in table 4. In these reactions isomerization occurred to give all four homofarnesene isomers; the two unexpected isomers (E,Z) and (E,E) being formed more rapidly than the (Z,E) and (Z,Z), but also decomposing more rapidly on prolonged heating. Finally a further reaction in dimethoxyethane was attempted (Reaction 6, table 4) which gave homofarnesene in 10% yield (estimated from GC peak area) after heating the reaction mixture under reflux for 5hrs. The reaction was only carried out on a small scale and it was not possible to isolate the product.

These trial reactions indicated that it would be difficult to obtain sufficient homofarnesene for complete characterization, by this method. Maximum yields of the order of 10% were estimated from GC peak areas but the isolated yield would be lower than this. A suitable alternative to the Wittig reaction was therefore sought, with preference being given to methods which would allow the already prepared ketones to be used.

Possible alternatives to Wittig reaction

Various reagents similar to the Wittig reagents, with sulphur, silicon or selenium in place of phosphorus, are known in recent literature, and the uses of many of them are summarized by Krief in a review entitled, "Synthetic methods using α-heterosubstituted organometallics".[118] Both sulphur and selenium reagents have been used for the conversion of carbonyl compounds to alkenes, but the sulphur reagents were considered more suitable as a first choice, as they are simpler and less expensive to prepare, and of lower toxicity than selenium compounds.

Four types of sulphur-containing reagent were considered; sulphide (120, figure 55), sulphoximine (121), sulphoxide (122) and sulphone (123).

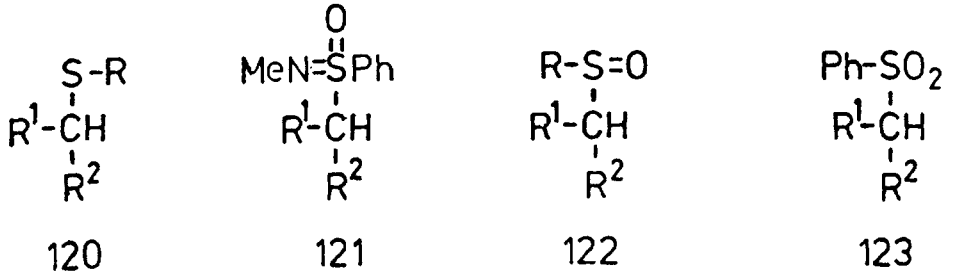



Figure 55

On treatment with organolithium reagents these compounds form α-lithio derivatives (**124-127**) which react with carbonyl compounds to form β-hydroxy-sulphides (**128**), -sulphoximines (**129**), -sulphoxides (**130**) and -sulphones (**131**), respectively. These in turn can be made to undergo elimination, directly or indirectly, to give olefins (figure 56).

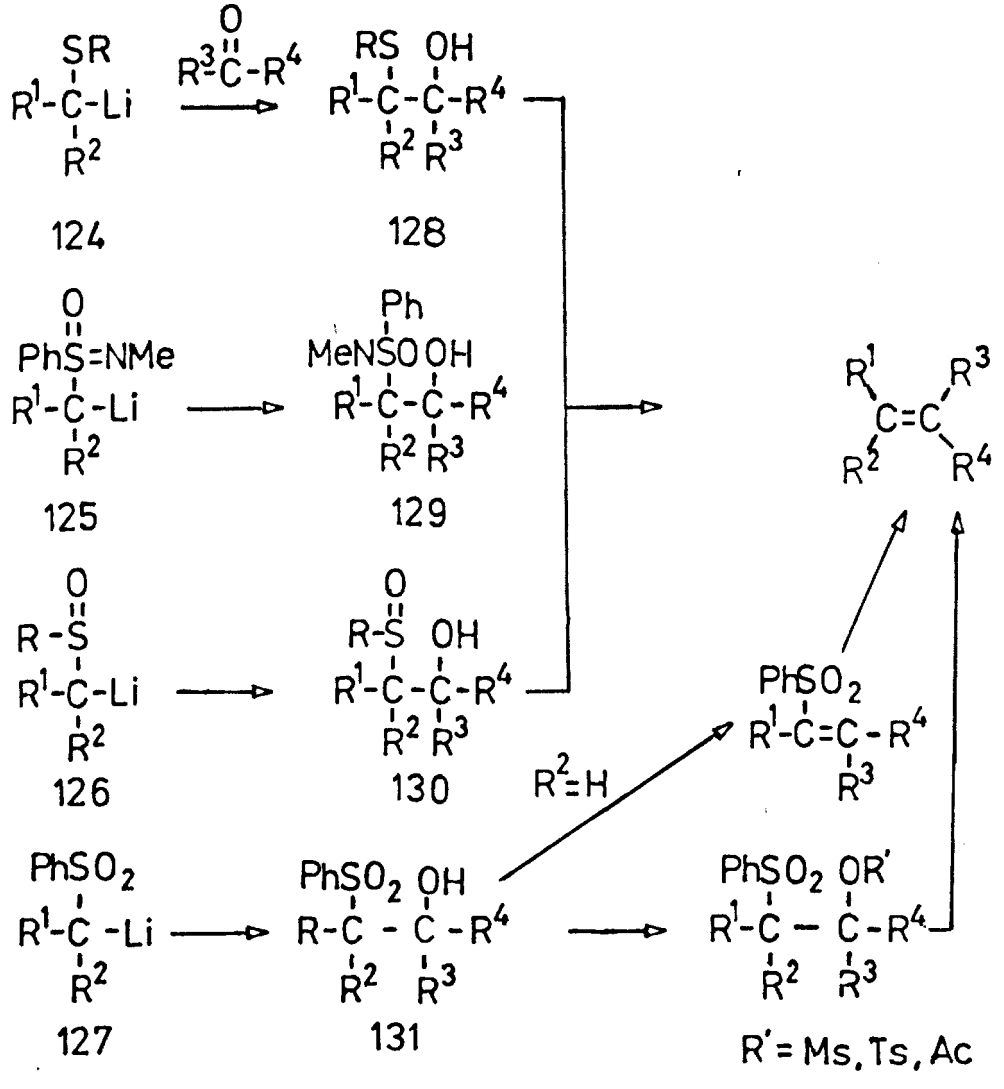
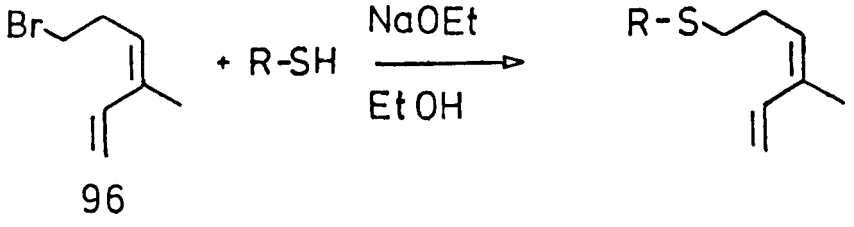



Figure 56

Sulphides

The sulphide method seemed attractive in that the starting sulphide could be prepared in one step from the appropriate thiol and the cis-bromodiene (**96**), which was one of the intermediates in the farnesene synthesis, as outlined in figure 57.




96

Figure 57

This method however had not been used for the synthesis of a trisubstituted double bond. Krief and his coworkers[119] had prepared a disubstituted double bond using an aldehyde as the carbonyl compound and although Coates and Sowerby had used a ketone, it was a cyclic ketone and they had only added a methylene group[120].

Sulphoximines

The sulphoximine method, although it had been used for the formation of trisubstituted double bonds[121], had disadvantages in the conditions used to form the starting sulphoximine (**121**, figure 55). This was prepared by a two-step process from the corresponding sulphoxide, as outlined in figure 58.

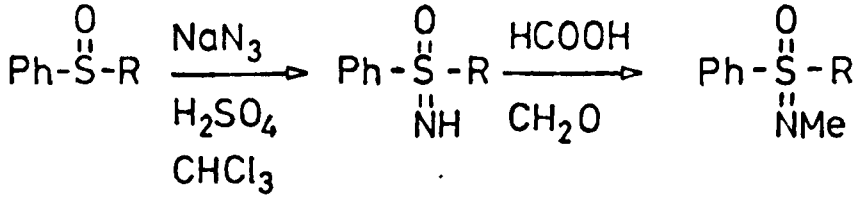



Figure 58

Both steps of this process involve use of acidic conditions and in the second step the mixture is heated for four days on a water bath. In the preparation of the necessary sulphoximine reagent for homofarnesene synthesis the diene system present at this stage would be damaged by this lengthy heating under strongly acidic conditions.

Sulphoxides

The sulphoxide method had been used by Jung et al.[122] to form trisubstituted olefins via β-hydroxysulphoxides. With octan-2-one as the carbonyl component (**133**, figure 59) and an n-butyl group on the sulphoxide (**132**) they had obtained a 51% yield for the formation of the β-hydroxysulphoxide (**134**) and a 74% yield for the conversion of this to the olefin (**135**).

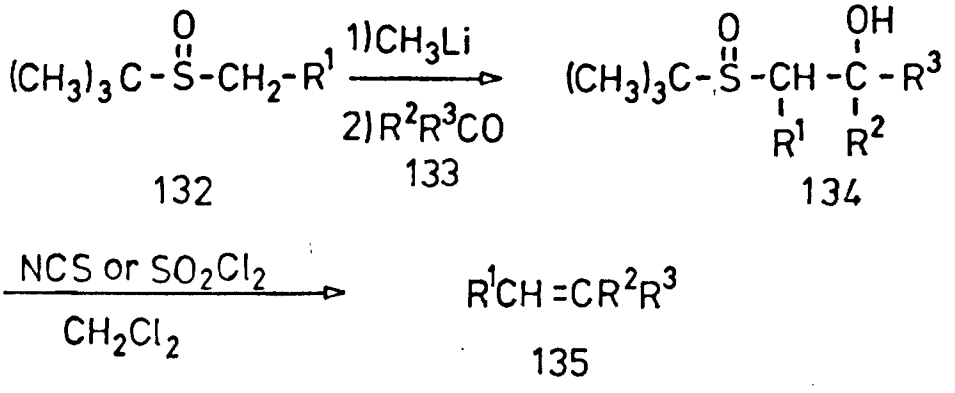



Figure 59

The main problem with this method was the use of a positive halogen species such as sulphuryl chloride or N-chlorosuccinimide in the conversion of the β-hydroxysulphoxide to the olefin. This again might attack the diene system, if homofarnesene were to be prepared by this route.

Kuwajima and Uchida also used a sulphoxide method to prepare terminal olefins.[123] Their method involved addition of o-phenylene phosphochloridite to the adduct (**138**) formed by reaction of lithio

methylsulphinyl carbanion (**136**) with benzophenone (**137**) as outlined in figure 60.

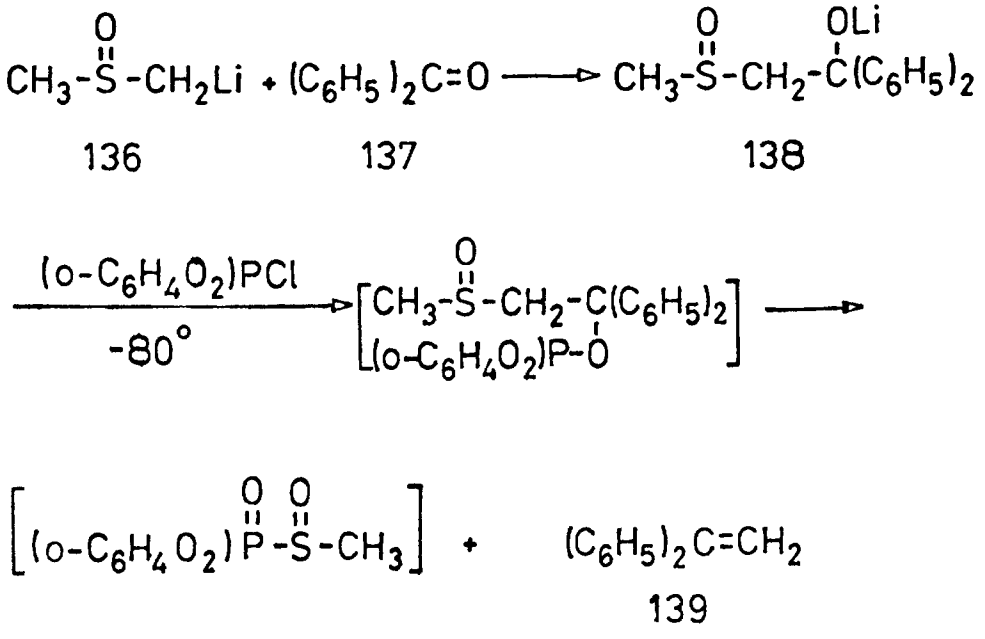
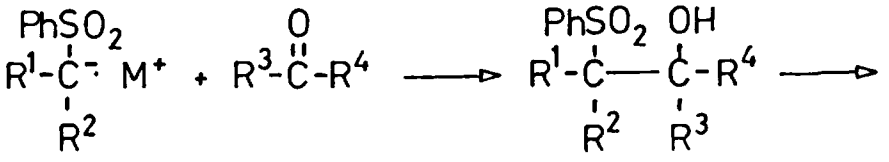


Figure 60

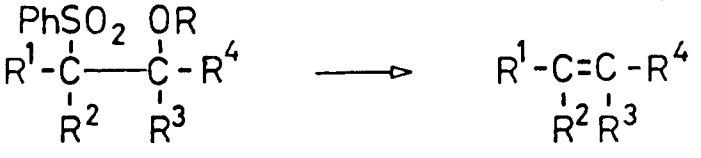
This gave a good yield (91%), of 1,1-diphenylethylene (**139**) and the method also worked well with benzaldehyde and cinnamaldehyde, giving 73 and 71% yields respectively. However, unsatisfactory results were obtained when an enolizable carbonyl compound was used and this was attributed to difficulty in the initial formation of the β-hydroxy-sulphoxide.

Sulphones

Finally the sulphone method was considered. This differs from the other methods in that the olefin cannot be obtained by direct elimination from the β-hydroxysulphone. Julia and Paris[124] reported that the elimination to give the olefin can be achieved indirectly by first converting the hydroxyl group to an acetate tosylate, or mesylate and then treating the product (**140**) with sodium amalgam in alcohol as shown in figure 61.



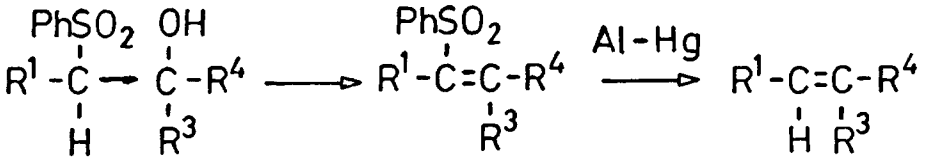
131



140, R=Ms,Ac,Ts 141

Figure 61

This method was not used to make a trisubstituted olefin but one tetra-substituted olefin, 2,3-dimethylbut-2-ene (**141**, $R^1R^2R^3R^4 = CH_3$-) was prepared. The yield in this case was much lower than for the disubstituted or terminal olefins. Alternatively in cases where the group $R^2$ = H (**142**, figure 62), dehydration of the β-hydroxysulphone can be achieved directly by treatment with hot phosphoric acid[125], or indirectly by halogenation and dehydrohalogenation[126], to give αβ-unsaturated phenyl sulphones (**143**, figure 62).



142 143 144

Figure 62

Pascali et al. also formed αβ-unsaturated phenylsulphones by reaction of the dianion of benzylphenylsulphone with carbonyl compounds.[127] Conversion of the αβ-unsaturated phenylsulphone (**143**) to the olefin (**144**) was then carried out by reduction with aluminium amalgam.[128] This method however, had not been used for the synthesis of trisubstituted olefins in which the substituents ($R^1R^3R^4$, 144) were alkyl groups as would be required in the case of homofarnesene.

Use of sulphoxide method

The most favourable of the methods for olefin synthesis using sulphur reagents, seemed to be that reported by Jung et al.[122] using β-hydroxysulphoxides formed by reaction of t-butyl alkyl sulphoxides with aldehydes or ketones. This method had been used to form trisubstituted olefins with alkyl substituents, and an additional point in its favour was that by separating the diastereomeric β-hydroxysulphoxides and decomposing them separately pure cis or trans olefins could be obtained. Decomposition of the β-hydroxysulphoxides (**145**) was achieved using sulphuryl chloride or N-bromosuccinimide, and the proposed mechanism involves formation of a cyclic-intermediate, a β-sultine (**146**) which readily loses sulphur dioxide to give the olefin (**147**) as outlined in figure 63.

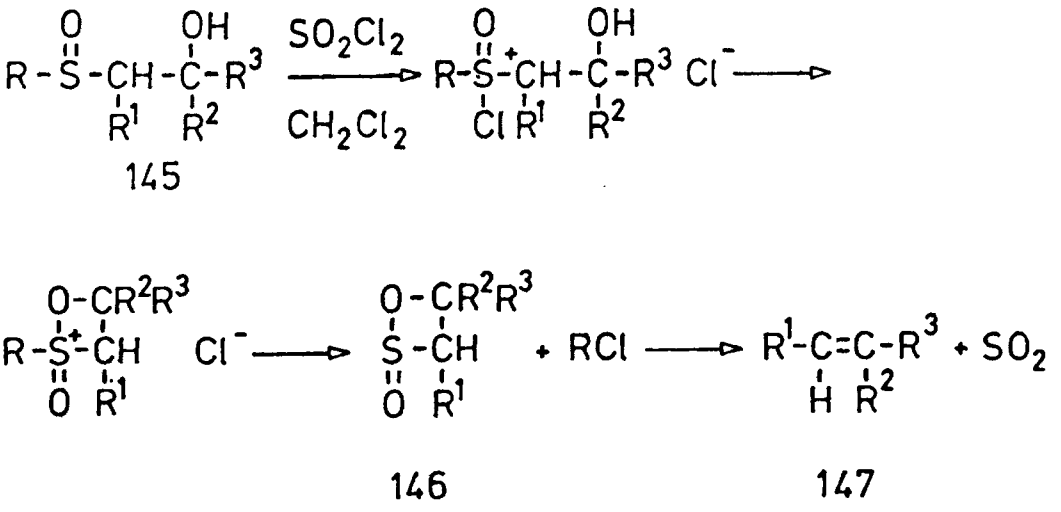


Figure 63

Preparation of a t-butyl sulphide

In order to synthesise homofarnesene by this method the tertiary butyl sulphoxide (**150**, figure 64) was required. Sulphoxides are generally prepared by oxidation of the corresponding sulphide and a variety of oxidising agents have been used.[129,130] The sulphides themselves are prepared[130] by reaction of the sodium salt of a thiol with an alkyl halide. Here the alkyl halide required is cis 6-bromo--3-methylhexa-1,3-diene (**96**), which was an intermediate in the synthesis of farnesene.

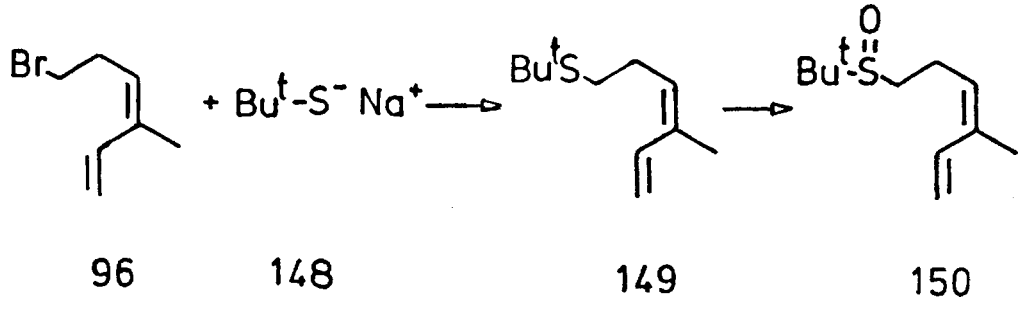


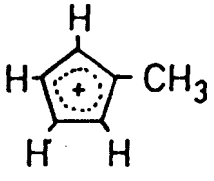
Figure 64

The tertiary butyl sulphide (**150**) was prepared following the procedure described by Barnard et al.[127] for methyl-2-methyl allyl sulphide.[131] The sodium salt (**148**) was first prepared by addition of t-butyl mercaptan to sodium ethoxide solution, and was then treated with the bromodiene (**96**). The reaction was followed by GC which showed that all of the bromodiene had reacted after thirty minutes. $^1$H NMR of the distilled product showed it to be the desired sulphide (**150**).

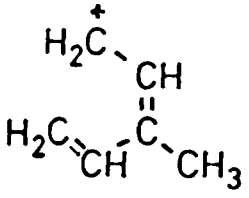
Oxidation to the sulphoxide

Oxidation of the sulphide was first attempted using hydrogen peroxide in acetone at 0°, again following the procedure of Barnard et al.. After thirty minutes GC showed no decrease in the sulphide peak and the absence of any product peak. The reaction mixture was then allowed to warm up to room temperature and examined by GC at intervals. After being left overnight at room temperature there was still no sign of any sulphoxide in the GC trace and the sulphide peak was still present. Price and Hydock[132] had used acetic acid at reflux temperature for the oxidation of phenyl methyl sulphide with hydrogen peroxide so glacial acetic acid was added to the reaction mixture and some of the acetone was removed by distillation. Examination by GC after approximately 10% of the acetone had been distilled out showed that the sulphide peak had disappeared although no product peak could be seen. This was probably due to the much higher boiling point of the sulphoxide and its greater polarity causing it to have a very much longer retention time than the sulphide. The $^1$H NMR spectrum of the crude product was identical to that of the sulphide. The IR spectrum howeyer showed a strong peak at 1,045 $cm^{-1}$, characteristic of a sulphoxide group.

In a second preparation of the sulphoxide, a 1:1 mixture of acetic acid and acetone was used as solvent and the reaction was found to be virtually complete after 1½ hrs at 0°. Successful microanalysis results were not obtained for the sulphoxide possibly due to the absorption of water by the sample. The mass spectrum of the sulphoxide did not show a molecular ion peak, the ion of highest mass was at m/e 146 corresponding to a loss of $C_4H_6$, which is difficult to interpret. However there was also a peak at m/e 144 corresponding to loss of the tertiary butyl group as isobutene which is a common feature of the mass spectra of dialkyl sulphoxides according to Budzikievicz et al.[132] Other prominent peaks at m/e 81 and 79 can be attributed to a $C_6H_9^+$ ion (**151**, figure 15) and a $C_6H_7^+$, methyl cyclopentenium (**152**) ion respectively, both arising from the diene portion of the molecule.



152



151

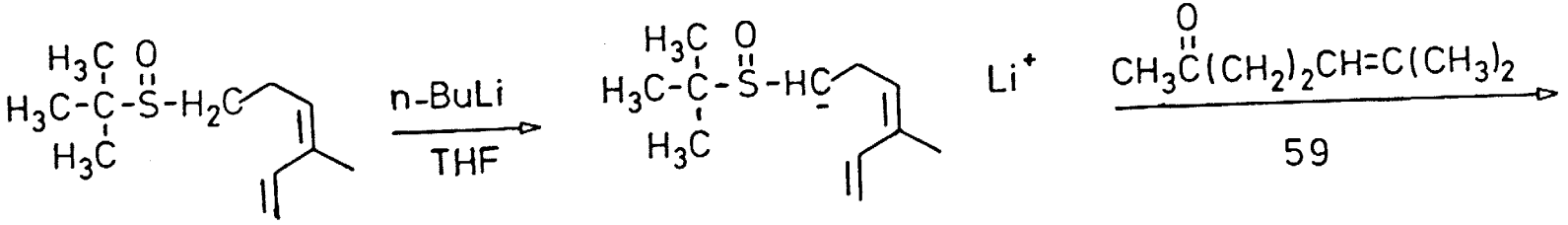
Figure 65

Preparation of a β-hydroxysulphoxide

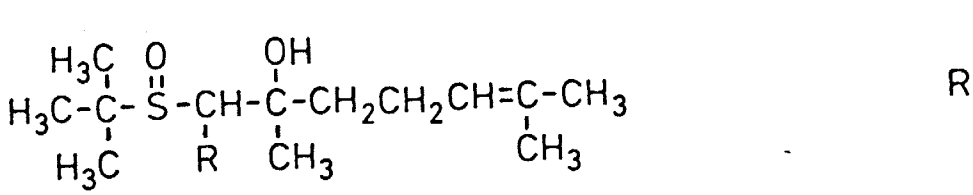
Although the sulphoxide was not completely characterized, the $^1H$ NMR and IR spectra were consistent with the structure and condensation with a ketone to form a β-hydroxysulphoxide, was attempted. For initial trials the commercially available, 6-methyl-5-hepten-2-one was used rather than its higher homologue to form the β-hydroxysulphoxide (**153**, figure 66).

In the first attempt at preparing the β-hydroxysulphoxide, n-butyl lithium was added to the sulphoxide in tetrahydrofuran at $-80^{o}$ producing a dark-green solution. After stirring the mixture for 20 minutes at $-80^{o}$ the ketone was added causing the colour to disappear immediately. The mixture was allowed to warm up slowly to $0^{o}$ and examined by GC at intervals. This showed that ketone was still present even after being left overnight. The crude product was examined by $^{1}H$ NMR and this suggested that the β-hydroxysulphoxide was present and also some ketone.

Three further attempts were made to prepare the β-hydroxysulphoxide. Once at room temperature and twice at $-60^{o}$. The room temperature reaction gave none of the desired product and none of the starting sulphoxide was recovered. The $^{1}H$ NMR spectrum of the crude product revealed that the t-butyl group was absent and the IR spectrum showed no sulphoxide band. In the first of the reactions at $-60^{o}$, the mixture was kept at $-60^{o}$ for 1½ hrs after addition of the ketone then allowed to warm up to room temperature. Although the β-hydroxysulphoxide was formed, it was contaminated with both the ketone and the starting sulphoxide. In the final reaction the mixture was kept at $-60^{o}$ for 1 hr after addition of the ketone then allowed to warm up to $0^{o}$ overnight. This time no sulphoxide remained but there was still ketone present. By chromatography on alumina, a sample of β-hydroxysulphoxide free from ketone was obtained. The $^{1}H$ NMR spectrum has the doublet of doublets centred at δ6.6 for the central proton of the cis diene system, a complex pattern at δ4.9-5.3 for the other four alkene protons, a one proton singlet at δ5.7 for the hydroxyl group, a one proton triplet at δ3.0 for the CH- next to the sulphoxide group, a nine proton singlet at δ1.3 for the tertiary butyl group, and a doublet at δ1.6 for the




150



153

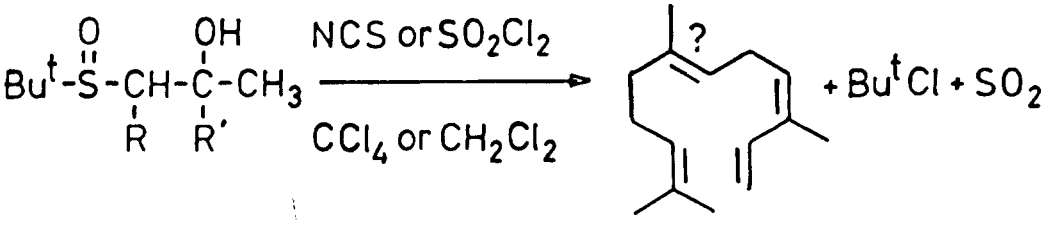
R = $-CH_2-C(H)=C(CH_3)-C(H)=CH_2$

Figure 66

terminal methyl groups from the ketone, all suggesting that the product was the desired β-hydroxysulphoxide. Similarly the IR spectrum has a strong band at 1005 $cm^{-1}$ for the sulphoxide group and a broad -OH absorption centred at 3340 $cm^{-1}$; the sulphoxide band being shifted slightly from its position in the spectrum of the starting sulphoxide.

Attempted decomposition of β-hydroxysulphoxide

There now remained only one stage in the synthesis, decomposition of the β-hydroxysulphoxide (**153**) using a positive halogen species to give farnesene. A choice of two reagents was available (Figure 67), N-chlorosuccinimide and sulphuryl chloride and two solvents, methylene chloride and carbon tetrachloride had been used in similar reactions.[121]




153. R = $-CH_2CH=C(CH_3)CH=CH_2$

R' = $-(CH_2)_2CH=C(CH_3)_2$

Figure 67

The reaction was attempted with each of the solvents and chlorine reagents and under a variety of temperature conditions. In each case small peaks of the correct retention times for farnesene isomers were seen in the GC trace immediately, both at room temperature and lower temperatures. Yields of up to ten percent were estimated by GC but no improvement could be achieved either by prolonging the reaction at room temperature, or allowing the low temperature reactions to warm up.

Alternative method for decomposition of β-hydroxysulphoxide

Work on the project had to be concluded at this point without having successfully achieved a synthesis of homofarnesene better than the 10% (unisolated) yield obtained by the Wittig reaction but one possible alternative method for obtaining farnesene from the β-hydroxysulphoxide (**153**) was considered. This was the method discussed earlier, involving addition of o-phenylenephosphochloridine to the lithio compound (**138**, Figure 60) formed by reaction of a ketone with lithio methylsulphinyl carbanion (**136**). The method had also been used to convert β-hydroxyundecylsulphoxide, isolated by TLC, to 1-undecene by addition of methyl lithium and then the o-phenylenephosphochloridite.[122]

Other possible routes to synthesis of farnesne homologues

Another approach which could be used in future attempts to prepare the farnesene homologues is based on a juvenile hormone synthesis by Corey and Yamamoto.[134] The method involves stereospecific formation of trisubstituted olefins from β-oxido phosphonium ylids.[135,136] The proposed scheme for synthesis of homofarnesene by this route is shown in figure 68.

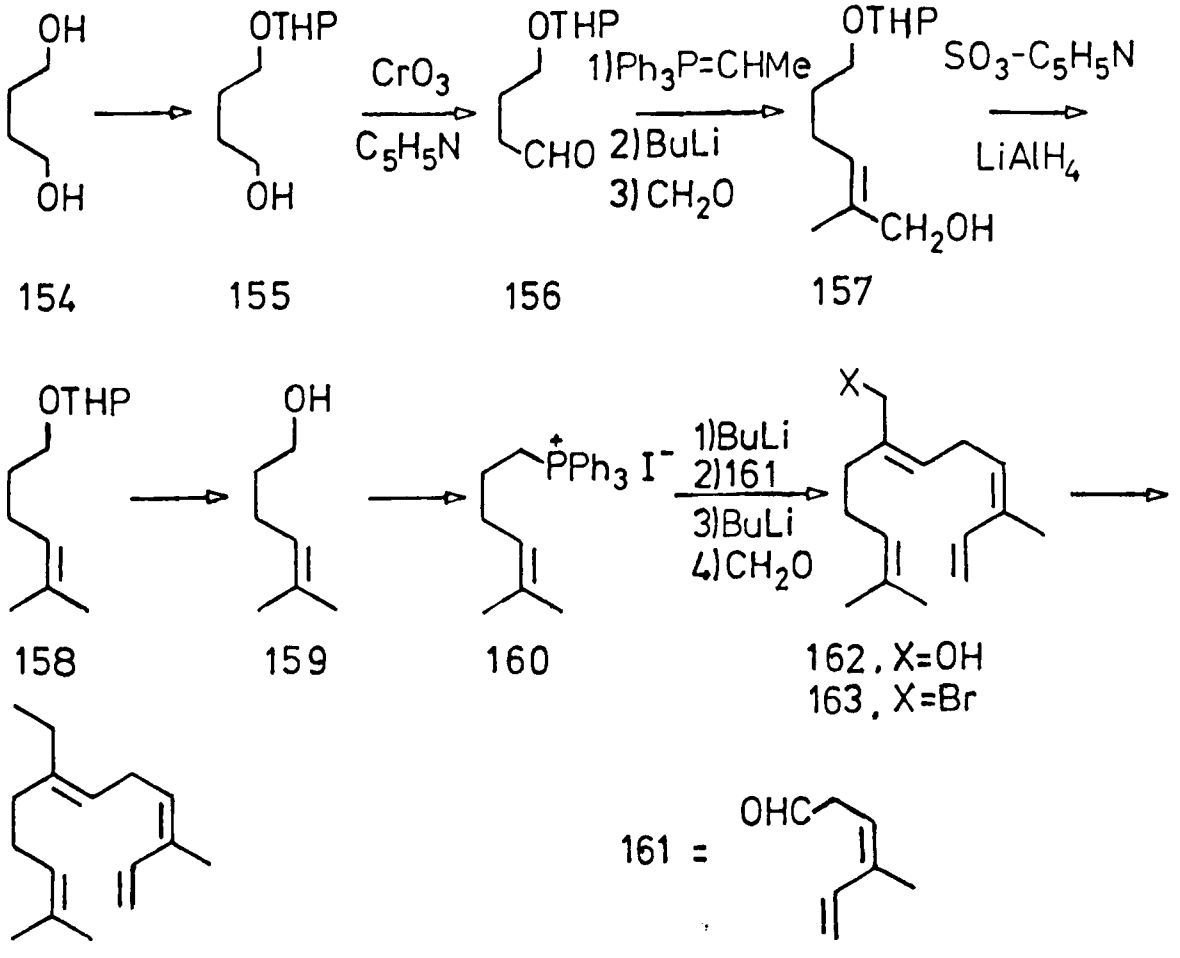



Figure 68

Preparation of the tetrahydropyranyl alcohol (**157**) by treatment of the aldehyde (**156**) with ethylidenetriphenylphosphorane, followed by addition of n-butyllithium to form the β-oxido-ylid and treatment with paraformaldehyde is as described by Corey et al.[139] The aldehyde (**156**) is prepared from the monotetrahydropyranyl ether (**155**) of 1,4-butanediol (**154**). Conversion of the tetrahydropyranyl alcohol (**157**) to the unsaturated alcohol (**159**) could be achieved using sulphur trioxide-pyridine complex in tetrahydrofuran followed by lithium aluminium hydride [138] to form the protected alcohol (**158**) and then removal of the protecting group. The unsaturated alcohol (**159**) could then be converted to the phosphonium salt (**160**) as described by Corey and Yamamoto.[134]

The diene aldehyde (**161**) required for reaction with the phosphonium salt (**160**) could be obtained by oxidation of the corresponding alcohol prepared by the method of Julia *et al.*[89] Reaction of the diene aldehyde (**161**) and the ylid from the phosphonium salt (**154**) followed by treatment with n-butyllithium and paraformaldehyde should then give the hydroxytetraene (**162**). Conversion of this to the bromide (**163**) and treatment with trimethyliron lithium[137,139] should then give homofarnesene.

Finally, during the preparation of this thesis, a new stereoselective synthesis of faranal (**16**, figure 6) which could be adapted for the synthesis of farnesene and its homologues was reported by Baker *et al.*[140] This involved preparation of a substituted vinyl iodide (**166**, $R^1$ = Et, $R^2$ = Me) by reactions of alkyl copper reagents with terminal acetylenes as outlined in figure 69. The vinyl iodide was then converted to its lithium derivative (**167**, $R^1$ = Et, $R^2$ = Me) and alkylated with another iodide (**168**).

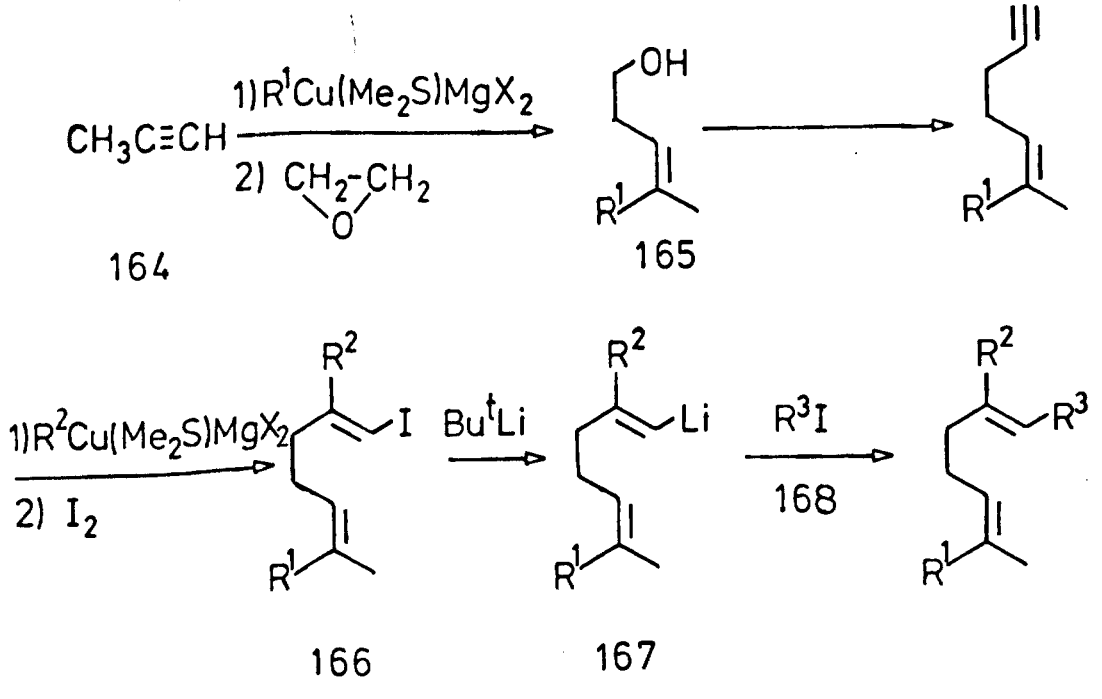
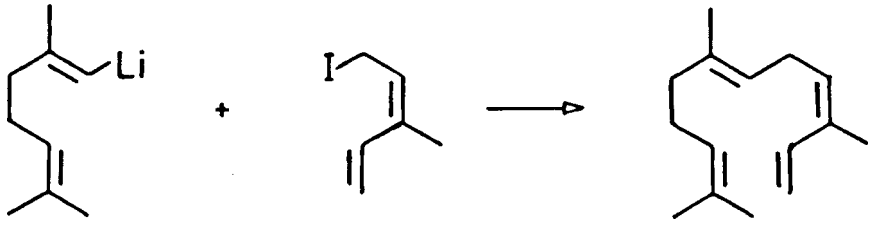



Figure 69

In order to adapt this method for the synthesis of farnesene, a different substituted vinyl iodide (**167**, $R^1 = R^2 = Me$) would be required but this could be prepared by the same route by using the copper bromide derivative of methyl magnesium iodide rather than ethyl magnesium bromide in the first step. Similarly, the vinyl iodides (**167**, $R^1 = Me$, $R^2 = Et$ and $R^1 = R^2 = Et$) required for the higher homologues of farnesene could also be obtained by this route.




167 169

Figure 70

To prepare farnesene from the lithium derivative (**167**), the cis vinyl iodide (**169**, figure 70) would be required. A literature survey revealed that this had not been prepared before, but the trans isomer of the corresponding bromide had been used in a synthesis of sinensal (**90**, figure 32) by Buchi and Wuest.[141] The trans bromide was prepared by action of phosphorus tribromide on (E)-3-methyl-2,4-pentadien-1-ol, obtained by semihydrogenation of the corresponding acetylene as described by Oroshnik.[142] The acetylene (**171**) itself was prepared as a mixture of isomers by rearrangement of methylvinyl-ethynyl carbinol (**170**) and separated by distillation. The predominant isomer, which was previously thought to be trans[143], was shown by Oroshnik to be cis. It should therefore be possible to form the

pure cis alcohol (**172**) and hence the bromide (**173**) and convert this to the desired iodide (**169**) as outlined in figure 71.

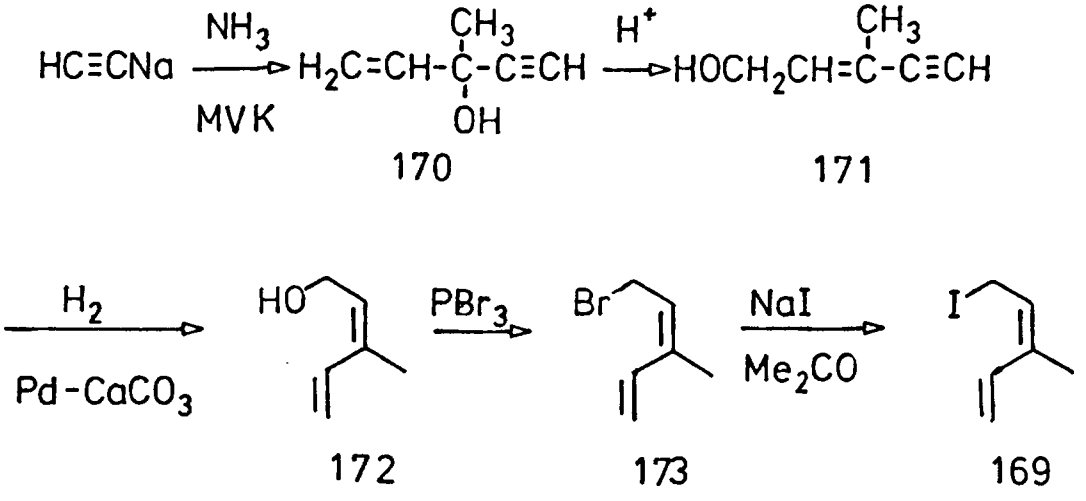



Figure 71

The starting carbinol (**170**) was prepared by Cymerman et al.[144] by addition of sodium acetylide to methyl vinyl ketone, and was heated with 10% sulphuric acid at 20° for 42 hrs to form the rearranged alcohol (**171**) in 79% yield. Cheeseman et al.[143] then obtained a 60% yield of the diene alcohol (**172**) by hydrogenation of the rearranged alcohol (**171**). The hydrogenation and rearrangement steps were also attempted in reverse order by Cheeseman et al.[143] The hydrogenation again gave a 60% yield but the rearrangement step gave only a 25% yield. This however may have been due to the use of only 1% sulphuric acid rather than 10%, and the much shorter reaction time of 4 hrs.

Of the two possible alternative routes to farnesene synthesis discussed here the latter would have an advantage in that it should give the desired stereochemistry at each of the double bonds.

# EXPERIMENTAL

NMR spectra were recorded on Hitachi-Perkin Elmer R24 60 MHz and Jeol JMN FX100 Fourier Transform instruments.

Mass spectra were recorded on an updated AEI MS12 single focusing mass spectrometer.

GC analyses were performed on a Pye model 104 gas chromatograph with flame ionization detector.

The pump used for solvent delivery on the MPLC system was an MPL series II micropump (Metering Pumps, London) with a PTFE diaphragm pumphead (maximum pressure ≈ 100 p.s.i.). Samples were injected onto the column through a 4-way Tefzel slider valve using a 10ml Hamilton 1010 gas-tight syringe.

## Purification of solvents and reagents

Tetrahydrofuran (THF) was dried by distillation from sodium--benzophenone.

Dimethyl sulphoxide was distilled under reduced pressure.
Dimethoxyethane was dried over sodium and decanted.
Diglyme was distilled from sodium.

Solvents for MPLC were dried over 4Å molecular sieves.

Ethanol was dried by refluxing over and distillation from magnesium.

Acetone for Wittig reactions was distilled from $P_2O_5$.

Sulphuryl chloride was distilled before use.

N-chlorosuccinimide was recrystallized from carbon tetrachloride and dried in an evacuated desiccator.

Butan-2-one was distilled from anhydrous potassium carbonate.

Use of glove-bag

A glove-bag which was flushed with nitrogen and sealed, with the necessary apparatus and materials inside, was used for the weighing- or measuring-out of air- and moisture-sensitive reagents.

For large-scale reactions, the crown caps from bottles of n-butyllithium in hexane solution were removed inside the glove-bag and the required volume measured out and transferred to a dropping funnel.

Samples (∿ 50mls) of n-butyllithium solution were transferred in a similar manner to small septum-capped bottles for later use in small-scale reactions. This minimised deterioration of the reagent by continued removal of small volumes from the large bottle.

Sodium bis(trimethylsilyl)amide and potassium t-butoxide were weighed out inside the glove bag.

Standardisation of n-butyllithium solutions

The titration method described by Winkle et al.[145] was used to check the concentration of n-butyllithium in hexane solutions (Aldrich, Gillingham). 100-200mg of 2,5-dimethoxybenzyl alcohol was weighed into a small flask fitted with a magnetic stirrer and sealed with a septum. After flushing the flask with nitrogen, 1-4mls of THF was added to dissolve the alcohol and n-butyllithium in hexane added dropwise with a syringe until the solution became pink.

Using this method the concentration of n-butyllithium was found to be close to the value quoted on the bottle (1.6M). For later reactions, therefore the concentration was assumed to be 1.6M.

Gilman Test[146]

Approximately 0.5ml of ethereal solution is removed from the reaction mixture and treated with an equal volume of a 1% solution of Michler's ketone in dry benzene, then slowly with water (1ml). Addition of several drops of 0.2% iodine in acetic acid solution produces a characteristic greenish-blue colour if Grignard reagent was present.

Lindlar's catalyst[97,98]

Palladium chloride (1.48g) was dissolved in 37% hydrochloric acid (3.6mls) with shaking at 30°. The solution was transferred with water (45mls) to a 150ml beaker, equipped with magnetic stirrer and pH meter. 2N NaOH was added dropwise until the pH was between 4.0 and 4.5 then the solution was diluted to 100mls and transferred to a 250ml three necked flask, fitted with a mechanical stirrer and thermometer. Precipitated calcium carbonate (18g) was added and the suspension was stirred and heated to 75-80° on a water bath. The mixture was kept at this temperature until all the palladium was precipitated and the solution became colourless (15 mins). 0.7N sodium formate solution (6mls) was added to the suspension with stirring causing the catalyst to change from brown to grey. More sodium formate (4.5mls) was added and the mixture heated for 40 mins at 75-80° to complete the reduction. The catalyst was filtered off on a buchner funnel, washed with water (8 x 65mls) and transferred to another 250ml three-necked flask. Water (60ml) and lead acetate solution (18mls) were added and the slurry stirred at 75-80° for 45 mins. The catalyst was again filtered off, washed with water (4 x 50mls), dried on the filter and finally in a drying pistol at 60-70° for 3 hrs.

Trial hydrogenation

The activity of the catalyst was tested by placing phenyl acetylene (2.04g, 0.02 moles), quinoline (1ml) and the catalyst (0.1g) in a low pressure, hydrogenation apparatus with hexane (15mls). After 3.5 hrs, 280mls of hydrogen had been absorbed.

A second batch of catalyst was prepared and tested in the same way. This was found to be slightly more active with 300mls of hydrogen being taken up in less than 3.5 hrs, in the trail with phenyl acetylene.

Palladium on barium sulphate catalyst[99]

A solution of palladium chloride (0.82g) in conc. HCl (2ml) and water (5ml) was prepared with warming on a waterbath.

To a stirred, hot (80°) solution of barium hydroxide (12.62g) in water (120ml), 6M $H_2SO_4$ (12ml) was added all at once and more $H_2SO_4$ was added until the suspension became just acidic. The prepared solution of palladium chloride and 37% formaldehyde solution (0.8ml) were then added and the suspension rendered just alkaline by addition of 30% aqueous NaOH. The mixture was stirred for 30 mins then boiled to coagulate the precipitate. The catalyst was washed with water several times by decantation, collected on a sintered funnel, washed with water several times on the filter and finally dried at 70-80° in a vacuum oven for four days.

A trial hydrogenation of phenyl acetylene as described for Lindlar's catalyst, was used to test the activity of the palladium on barium sulphate. With hexane as solvent only 110mls of hydrogen were absorbed in 3.5 hrs. When the solvent was changed to methanol however, the full theoretical amount of hydrogen was taken up in less than 1.5 hrs.

Attempted synthesis of 1-methyl-2-propenyltriphenylphosphonium bromide

A solution of triphenylphosphine (26g, 0.1 mol) and 3 chloro-1--butene (9g, 0.1 mol) in dimethylformamide (20mls) was boiled under reflux for 6 hrs. Addition of diethyl ether to the cooled solution gave 21.2g (61%) of salt. (m.p. 214-217°, $\delta_{CDCl_3}$ 1.6 (3H, m J 7Hz $-CH_3$), 4.6 (2H, dd, J 7 and 15Hz, $-CH_2-$), 5.0-6.1 (2H broad m, -CH=CH-), 7.6 (15H, broad m, Ph.) $\delta_{TFA}$ 1.25 (3H, m, J 7Hz, $-CH_3$), 3.45, dd, J 7 and 15Hz, $-CH_2-$), 4.6-5.7 (2H, br m -CH=CH-), 7.25 (15H, m, -Ph).

2-Butenyltriphenylphosphonium bromide

A solution of triphenylphospine (26g, 0.1 mol) and crotyl bromide (13.5g, 0.1 mol) in xylene (30ml) was heated to reflux causing immediate crystalization of the salt. The crystals were filtered off to give 36.4g, of 2-butenyltriphenylphosphonium bromide, m.p.232-6°. (Literature[147] gives m.p. 245°). $\delta_{TFA}$ 1.2 (3H, t, J 7Hz, $-CH_3$), 3.45 (2H, d.d. J 7 and 15Hz, $-CH_2-$), 4.6-5.6 (2H, br.m., -CH=CH-), 7.2 (15H, m, Ph-).

The NMR spectrum is identical to that of the salt prepared above from 3-chloro-1-butene.

1,3-Trimethylenebis(triphenylphosphonium)dibromide

A solution of 1,3-dibromopropane (10.1g, 0.05 mol) and triphenylphosphine (26.2g, 0.1 mol) in dimethylformamide was boiled under reflux for 30 mins. The solid, which began to precipitate out after a few minutes heating, was filtered off from the cooled solution, to give 32.5g (89.5%) of 1,3-trimethylenebis(triphenylphosphonium)dibromide, m.p.338-40°. (Literature[76] gives m.p. 335-6°). $\delta_{CDCl_3}$ 1.55-2.2 (2H, br.m, $-CH_2-$), 4.3-4.9 (4H, br.m, $-CH_2$-Ph), 7.4-8.0 (15H, br.m, -Ph).

Attempted condensation of disalt with 6-methyl-5-hepten-2-one

Sodium bis(trimethylsilyl)amide (5.2g, 0.029 mol) was weighed inside a glove-bag, placed in a dropping funnel and dissolved in dry THF. 1,3-trimethylenebis(triphenylphosphonium)dibromide (20.8g, 0.029 mol) was suspended in dry THF in a three-necked flask fitted with magnetic stirrer, reflux condenser, dropping funnel and nitrogen inlet and outlet. The base solution was added dropwise to the salt suspension with stirring. Stirring was continued for 30 minutes after the addition was complete, then the mixture was boiled under reflux for 1 hr and finally cooled to $-78^{\circ}$ in a dry ice-methylene chloride bath before adding the ketone 6-methyl-5-hepten--2-one (3.6g, 0.029 mol) was added to the reaction mixture dropwise with stirring. The mixture was stirred at $-78^{\circ}$ for 1 hr then allowed to warm-up to room temperature overnight. Aqueous ethanol and methylene chloride were added and the two phases were separated. Concentration of the organic phase and washing the residue with benzene gave a white solid (m.p. 336-$7^{\circ}$) which was shown by the $^{1}H$ NMR spectrum to be the starting disalt. The aqueous phase was extracted (3x) with methylene chloride and concentration of the combined extracts and washing with benzene gave more disalt (m.p. 333-$6^{\circ}$). Evaporation of the benzene washings gave an oil which was found by $^{1}H$ NMR to contain unchanged ketone and some triphenyl phosphine oxide. No trace of the desired product could be detected in either the aqueous or the organic phase. A white solid obtained by concentration of the aqueous phase was assumed to be inorganic since it gave no signals in the $^{1}H$ NMR spectrum.

2-Cyclopropylbut-3-yn-2-ol

Liquid ammonia (500ml) was stirred mechanically in a 2h 3 necked flask with cooling in a bath of liquid nitrogen-ethyl acetate. Ferric nitrate (0.2g) and a few small pieces of sodium were added causing the mixture to turn blue and then black. The remainder of the sodium (9.7g, 0.42 g. atom) was added in portions, waiting each time for the mixture to turn black. Stirring was continued for 30 mins after the addition of the sodium was complete before bubbling in acetylene (from calcium carbide and water, dried by passing through conc. $H_2SO_4$). The mixture became grey in colour then slowly darkened to black. The flow of acetylene was reduced and cyclopropylmethyl ketone (33.6g, 0.4 mol) in an equal volume of diethyl ether, was added dropwise. The mixture was then allowed to warm up overnight for the ammonia to evaporate. Diethyl ether was added and the mixture triturated with a solution of tartaric acid (16g) in water (40ml) with cooling in ice. The organic layer was decanted and the aqueous layer extracted with 3 portions of diethyl ether. The combined organic phases were washed with 5% tartaric acid solution then water, dried ($K_2CO_3$) and evaporated. The residue was distilled under reduced pressure to giv e 2-cyclopropylbut-3-yn-2-ol (33.9g, 77%) b.p. 48-50 °/ 15mm Hg, $n_D^{20}$ 1.4572, (Literature[96] gives b.p. 72-73 °/40mm Hg, $n_D^{21}$ 1.4565), $\delta(CDCl_3)$ 0.45 (4H, d, J 7Hz, cyclopropyl $-CH_2$ gps), 1.1 (1H, m, J 7Hz, cyclopropyl -CH-), 1.55 (3H, s, $-CH_3$), 2.3 (1H, s, $\equiv CH$), 2.4 (1H, broad s, -OH). $\nu_{max}$ 3,400 (broad, -OH), 3,300 ($\equiv C-H$), 2,100 $cm^{-1}$ (weak $-C\equiv CH$).

(Z)-6-Bromo-3-methylhex-3-ene-1-yne

2-Cyclopropylbut-3-yn-2-ol (39.8g, 0.36 mol) was stirred for 15 minutes with 48% HBr (145mls) with cooling in ice-water. The organic layer was separated and the aqueous layer extracted (2x) with light petroleum (b.p. 40-60°. The combined organic phases were washed with water, 5% $NaHCO_3$ solution and again with water, dried ($K_2CO_3$) and evaporated. The residue was distilled under reduced pressure, under nitrogen to give three fractions b.p. 62-64, 64-65 and 65-70°/ 12mm Hg which were identical by NMR. The fractions were combined to give 55.8g (89%) of (Z)-6-bromo-3-methylhex-3-ene-1-yne. $\delta(CDCl_3)$ 1.35 (3H, d, J 1Hz, $-CH_3$), 2.8 (2H, t, J 6Hz, $-CH_2-C=$), 3.1 (1H, s, $-CH\equiv CH$), 3.35 (2H, t, J 6Hz, $CH_2-Br$), 5.7 (1H, t, J 6Hz, $-CH=$) (literature[96] gives b.p. 64°/10mm Hg).

(Z)-6-Bromo-3-methylhexa-1,3-diene

A solution of 6-bromo-3-methylhex-3-ene-1-yne (55.8g, 0.32 mol) in methanol (200mls) was stirred with palladium on barium sulphate (2g) and quinoline (2mls) under an atmosphere of hydrogen for 39 hours until the required amount of hydrogen had been absorbed. The catalyst was filtered off and the methanol evaporated and replaced with light petroleum (60-80 boiling range). The resulting solution was washed with dil. HCl then water, dried ($K_2CO_3$) and evaporated. The residue was distilled under reduced pressure, under nitrogen to give 46g (86%) of (Z)-6-Bromo-3-methylhexa-1,3-diene b.p. 69-72° /13mm Hg. (Literature[90] gives b.p. 72° /12mm Hg for a mixture of (E)-and (Z)-isomers.) Found C, 48.00; H, 6.26. $C_7H_{11}Br$ required C, 48.02; H, 6.33%, m/e 174 ($M^+$). $\delta(CDCl_3)$ 1.8 (3H, d, J 1Hz, $CH_3C=$), 2.7 (2H, t, J 7Hz, $-CH_2-C=$), 3.25 (2H, t, J 7Hz, $-CH_2-Br$), 4.9-5.5 (3H, m, $CH_2=$ and $-CH=$), 6.4-6.9

(1H, dd, J 10Hz and 16Hz, =CH-C=), $\nu_{max}$ 3,090, 3,010, 2,960, 1,640, 1,600, 1,440 (br), 1,380, 1,270, 1,240, 1,205, 1,080, 985 and 910 $cm^{-1}$. $\lambda_{max}$ (EtOH) 233nm ($\varepsilon$ 18,200).

(Z)-6-Iodo-3-methylhexa-1,3-diene

A solution of (Z)-6-bromo-3-methylhexa-1,3-diene (49.5g, 0.28 mol) in acetone (600ml) was treated with sodium iodide (85g, 0.56mol) at reflux for 8 hours. After evaporation of the acetone, the residue was dissolved in water and extracted (3x) with ether. The combined extracts were washed with 0.1N $Na_2S_2O_3$ solution, dried ($MgSO_4$) and evaporated to give 57.5g (92.5%) of crude (Z)-6-iodo-3-methylhexa-1,3-diene. $\delta_{CDCl_3}$ 1.8 (3H, d, J 1Hz, $CH_3$-C=), 2.7 (2H, t, J 7Hz, $-CH_2$-C=), 3.0 (2H, t, J 7Hz, $-CH_2$-I), 4.9-5.4 (3H, m, $-CH_2$= and -CH=) 6.3-6.8 (1H, dd, J 16Hz and 10Hz, =CH-C=). This was converted to the phosphonium salt without further purification.

(Z)-4-Methyl-3,5-hexadienyltriphenylphosphonium iodide

A solution of 6-iodo-3-methylhexa-1,3-diene (23.8g, 0.107 mol) and triphenylphosphine (29g, 0.11 mol) in dimethylformamide (50ml) was heated on a boiling water bath for 4 hours. The solution was then concentrated and on cooling crystallization occurred to give 12.3g of salt (m.p. 131-6°) which was filtered off and washed with ether. Addition of ether to the filtrate produced further crystals (33.3g, m.p. 130-5°) to give a total of 45.6g (88%) of (Z)-4-methyl-3,5-hexadienyltriphenylphosphonium iodide. (Found: C, 62.03; H, 5.30. $C_{25}H_{26}IP$ required C, 61.99; H, 5.41%) $\delta_{CDCl_3}$ 1.6 (3H, s, $-CH_3$), 2.2-2.9 (2H, broad m, $-CH_2$-C=), 3.4-3.9 (2H, broad m, $-CH_2$-P-), 4.9-5.5 (3H, m, $CH_2$= and -CH=) 6.0-6.5 (1H d.d, J 16Hz and 10Hz, =CH-C=), 7.6-7.8 (15H, m, phenyl) m/e 357 $(C_6H_5)_3PC_7H_{11}$).

(Z,E)- and (Z,Z)-α-Farnesenes

To a stirred suspension of 4-methyl-3,5-hexadienyltriphenyl-phosphonium iodide (48.8g, 0.1 mol) in dry ether (90ml) and dry tetrahydrofuran (100ml) under a nitrogen atmosphere, a solution of n-butyllithium in hexane (1.6M; 62.5mls, 0.1 mol) was added dropwise and stirring was continued until the Gilman test was negative (10 minutes). The mixture was then cooled to -70°C before adding 6-methyl-5-hepten-2-one (12.6g, 01 mol) and stirring was continued for 2 hours at -70°C to -20°C until decolourization was complete. A further 62.5mls of n-BuLi solution was then added at -30C and the mixture stirred until the Gilman test was again negative (20 minutes). Dry HCl (0.11 mol) in ether (25mls) and potassium t-butoxide (16.2g, 0.15 mol) were then added. Stirring was continued for one hour and the mixture allowed to stand overnight. The insoluble solid was filtered off and the filtrate washed with water to neutrality, dried ($MgSO_4$) and evaporated. The residue was distilled under reduced pressure to give 6.7g (33%) of a mixture of (Z,E)- and (Z,Z)-α-farnesenes. b.p. 71-85°/0.15 mm Hg. (Literature[66] gives b.p. 98-102°/4 mm Hg). GLC of the mixture on a 5% OV101 column gave at 162°C and with a carrier gas flow rate of 60mls $min^{-1}$ showed two peaks at retention times of 3.2 and 3.5 mins.

Medium pressure chromatography of farnesene isomers

A 1g sample of the farnesene mixture was chromatographed on a 1m x 15mm column packed with 20% $AgNO_3$ on Kieselgel 60(230-400 mesh ASTM) eluting with 10% diethyl ether/light petroleum (40-60° boiling range). 15ml fractions were collected with a LKB 2112 Redirac fraction collector and analysed by GC on a 5ft 3% OV101 on chromosorb W column (oven temperature 120°, $N_2$ flow rate 60mls $min^{-1}$).

(Z,E)-α-Farnesene

Fractions 62-93 from the medium pressure column were combined and evaporated. The residue was purified by bulb-tube distillation at reduced pressure to give (Z,E)-α-farnesene, m/e 204 ($M^+$), $\delta_{CDCl_3}$ 1.80, 1.67, 1.62, 1.59 (12H, 4s, $CH_3$ gps), 2.01 (4H, s, $-CH_2-CH_2$), 2.85 (2H, t, J = Hz, $=-CH_2-C=$), 5.0-5.33 (5H, complex m, alkene), 6.66-6.94 (1H, q, J10 and 16Hz, =CH-C=), $\nu_{max}$ 3100, 1805, 1640, 1595, 1150, 990, 900, 835 $cm^{-1}$, $\lambda_{max}$ (hexane) 233nm ($\varepsilon$ = 23,150). ($^1H$ NMR spectrum see figure 43

Mass spectrum see figure 45.)

(Z,Z)-α-Farnesene

Fractions 26-48 were combined and evaporated. Bulb-tube distillation under reduced pressure gave (Z,Z)-α-farnesene, m/e 204 ($M^+$), $\delta_{CDCl_3}$ 1.60, 1.67, 1.80 (12H, 3s, $CH_3$ gps), 2.0 (4H, d, $-CH_2-CH_2-$), 2.83 (2H, 6, J Hz, $=C-CH_2-C=$), 4.9-5.3 (5H complex m, alkene), 6.7 (1H, q, J10 and 16 Hz, =CH-C=), $\nu_{max}$ 3090, 1800, 1640, 1590, 1135, 985, 900, 830 $cm^{-1}$, $\lambda_{max}$ (hexane) 237nm ($\varepsilon$ = 22,350).
($^1H$ NMR spectrum see figure 44, mass spectrum figure 45).

6-Chlorohexan-3-one

A solution of ethyl magnesium bromide was prepared from ethyl bromide (84.5g, 0.78 mol) and magnesium (18.8g, 0.77 mol) in 300mls of diethyl ether under nitrogen in a 3-necked round bottomed flask. The solution was transferred under nitrogen by means of a ground-glass jointed, bent tube inserted into one of the side necks of the flask, into a dropping funnel. A plug of glass wool in the tube was used to filter the solution which was then added dropwise, under nitrogen

to a stirred solution of 4-chlorobutyryl chloride (99g, 0.70 mol) and anhydrous ferric chloride (3g) in dry ether with cooling in a bath of liquid nitrogen-ethyl acetate. The mixture was stirred for 5 minutes after the addition was complete before pouring onto ice. The organic layer was separated and the aqueous layer extracted (2x) with diethyl ether. The combined organic phases were washed with 10% $Na_2CO_3$ solution (2x) then water (2x), dried ($MgSO_4$) and evaporated. Distillation of the residue under reduced pressure gave 6-chlorohexan--3-one (64.6g, 68%) b.p. 70-76°/12mm Hg (Literature[110,111] gives b.p. 67-70°/12mm Hg and 85°/25mm Hg), $\delta_{CDCl_3}$ 1.05 (3H, t, J 7Hz, $CH_3$), 2.05 (2H, m, J 7Hz, $-CH_2-C-Cl$), 2.50 (2H, t, J 7Hz, $CH_2C$-Et), 2.55 (2H, q, J 7Hz, $CH_2$ of ethyl), 3.5 (2H, t, J 7Hz, $-CH_2-Cl$).

6-Iodohexan-3-one

A solution of 6-chlorohexan-3-one (68g, 0.51 mol) in acetone (1h) was treated with sodium iodide (225g, 1.5 mol) at reflux for 12 hours. The acetone was evaporated and the residue dissolved in water and extracted (3x) with diethyl ether. The combined extracts were washed with 0.1N aqueous $Na_2S_2O_3$, then water, dried ($MgSO_4$) and evaporated to give 110g (96%) of 6-iodohexan-3-one. $\delta_{CDCl_3}$ 1.0 (3H, t, J 6Hz, $CH_3$), 1.9-2.3 (2H, complex pattern, $CH_2-C-I$), 2-4-2.7 (4H, complex pattern, 2x $-CH_2C=O$), 3.2 (2H, t, J 6Hz, $-CH_2-I$). This was converted to the ketal without further purification.

2-Ethyl-2-(3-iodopropyl)-1,3-dioxolane

6-Iodohexan-3-one (110g, 0.49 mol) was treated with freshly distilled ethylene glycol (82ml, 1.5 mol) and p-toluene sulphonic acid (∿ 200mg) in refluxing benzene (1.2L) in a Dean-Stark apparatus

until no more water was collected; (13 hours). The mixture was allowed to cool before neutralizing with anhydrous $K_2CO_3$ and washing with 5% aqueous $NaHCO_3$ (3x) water, 0.1N aqueous $Na_2S_2O_3$ and finally with water, drying ($MgSO_4$) and evaporating. The residue was distilled under reduced pressure to give, after a small fore-run, two fractions b.p. 78-89° and 89-92° /0.25mm Hg which were identical by NMR. The fractions were combined to give a total of 97.6g (74%) of 2-ethyl-2--(3-iodopropyl)-1,3-dioxolane. (Found C, 35.65; H, 5.83. $C_8H_{15}IO_2$ requires C, 35.57; H, 5.61%) m/e 270 ($M^+$), δ($CDCl_3$) 0.9 (3H, t, J 7Hz, $-CH_3$), 1.4-2.0 (6H, complex pattern, 2x $CH_2$-C-O- and $CH_2$-C-I), 3.15 (2H, t, J 7Hz, $-CH_2I$), 3.85 (4H, s, 2x $CH_2$-O).

3-(2-Ethyl-1,3-dioxolan-2-yl)propyltriphenylphosphonium iodide

A solution of 2-ethyl-2-(3-iodopropyl)-1,3-dioxolane (53.8g, 0.20 mol) and triphenylphosphine (52.2g, 0.20 mol) in dimethylformamide (50mls) was boiled under reflux for 6hrs. On cooling crystalization occurred to give 76.1g of the phosphonium salt (m.p. 199-202°) which was filtered, washed with diethyl ether and dried under vacuum. Further crystals (12g, m.p. 168-188°) were obtained by adding diethyl ether to the filtrate to give a total of 88.1g (83%) of 3-(2-Ethyl-1,3--dioxolan-2-yl)propyltriphenylphosphonium iodide. (Found C, 58.76; H, 5.68. $C_{26}H_{30}IO_2P$ requires C, 58.65; H, 5.69% m/e 405 ($M^+$), δ($CDCl_3$) 0.8 (3H, t, J 7Hz, $-CH_3$), 1.5 (2H, q, J 7Hz, ethyl $-CH_2-$), 1.2-2.2 (4H, broad m, 2 x $-CH_2-$), 3.3-3.9 (2H, broad m, $-CH_2-P-$), 3.$\frac{7}{8}$ (4H, s, 2x O-$CH_2-$), 7.6-7.8 (15H, m, phenyl). $\nu_{max}$ (nujol) 1580, 1430, 1110, 1060, 1030, 995 and 905 $cm^{-1}$.

7-Methyl-6-octen-3-one

In a dry 1 litre, 3 necked flask fitted with reflux condenser, dropping funnel and $N_2$ inlet and outlet, sodium hydride (50% dispersion;

10g, 0.208 mol) was washed with light petroleum (30-40C boiling range) and then covered with dimethyl sulphoxide (200mls, dried by distillation under reduced pressure and stirring over molecular sieves). The suspension was stirred magnetically for 30 mins at 80C then cooled to 30°C before adding 3-(2-ethyl-1,3-dioxolan-2-yl)-propyltriphenylphosphonium iodide (100g, 0.19 mol) in dimethyl sulphoxide (300mls). Stirring was continued for 1½hrs at 30°C before adding acetone (14mls, 0.193 mol) in D.M.S.O. (40mls). The mixture was stirred overnight under nitrogen before adding water and extracting with light petroleum (30-40° boiling range) (2x). The combined extracts were washed with water (2x), dried ($MgSO_4$) and evaporated to give 2-ethyl-2-(4-methyl-3-pentenyl)-1,3-dioxolane (18.7g).

The crude ketal was dissolved in tetrahydrofuran (180mls) and stirred overnight with 3% aqueous HCl (180mls). The organic layer was separated and the aqueous layer extracted with light petroleum (40-60C boiling range). The combined organic phases were washed (2x) with water, dried ($MgSO_4$) and evaporated. The residue was distilled under reduced pressure to give 11.8g (44%) of 7-methyl-6-octen-3-one, b.p. 77-84° /15mm Hg. (Found C, 76.74; H, 11.53%. $C_9H_{16}O$ requires C, 77.09 ; H, 11.50%), $\delta_{CDCl_3}$ 1.0 (3H, t, J 7Hz, ethyl $-CH_3$), 1.65 (6H, J 4Hz, $2C(CH_3)_2$), 2.2-2.6 (6H, complex pattern, 3x $-CH_2-$), 5.0 (1H, broad m, CH=), $\nu_{max}$ 2970, 2930, 1710, 1670, 1445, 1410, 1380, 1115 and 1020 $cm^{-1}$.

7-Methyl-6-nonen-3-one

This was prepared using the method described for 7-methyl-6-octen-3-one using sodium hydride (50% dispersion; 6g, 0.125 mol) in 100mls

dimethylsulphoxide and the phosphonium salt (66g, 0.116 mol) in a further 150mls DMSO. Butan-2-one (10.4mls, 0.116 mol) in 20mls DMSO was added after the mixture had been stirred for 70mins at 30°. After a further 2hrs stirring an excess of butan-2-one was added and stirring was continued overnight at room temperature. Water was added and the mixture extracted (3x) with light petroleum (30-40°). The combined extracts were washed (2x) with water, dried ($MgSO_4$) and evaporated. The aqueous phase was filtered to remove the insoluble solid and extracted again (2x) with light petroleum. The combined extracts were washed, dired and evaporated as above to give a further 2g of crude product. The total crude ketal (14.9g) was dissolved in tetrahydrofuran (140mls) and treated with an equal volume of 3% aqueous HCl. Work-up as described above and distillation of the residue under reduced pressure gave 8.8g (49%) of 7-methyl-6-nonen--3-one b.p. 92-96°/15mm Hg. $\delta_{CDCl_3}$ 0.9 (3H, t, J 7Hz, ethyl $-CH_3$), 1.0 (3H, t, J 7Hz, ethyl $-CH_3$), 1.6 (3H, d, J 2Hz, $CH_3C=$), 2.0 (2H, q, J 7Hz, ethyl $-CH_2-$), 2.3 (4H, m, $-CH_2-CH_2-$), 2.35 (2H, q, J 7Hz, ethyl $-CH_2-$), 4.95 (1H, br m, $-CH=$).

The $^{13}C$ NMR spectrum of the product (see figure 49) showed that it was a mixture of 66% E and 34% Z isomer.

Homofarnesene

In a dry nitrogen-flushed Carius tube, (Z)-4-methyl-3,5-hexadienyltriphenylphosphonium iodide (0.96g, 1.98 mmol) was suspended in dimethoxyethane. The tube was fitted with a rubber septum and n-butyllithium in hexane (1.6M; 3mls, 4.8 mmol) and 7-methyl-6-octen--3-one (0.3mls, 1.98 mmol) were introduced into the tube via a syringe. The tube was sealed, placed inside the outer metal tube and heated in a muffle furnace at 135° for 2 hrs. The cooled tube was opened and

the contents dissolved in aqueous methanol and extracted (2x) with light petroleum (40-60° boiling range). The combined extracts were washed with aqueous methanol (2x) then water, dried ($MgSO_4$) and evaporated. The crude product was examined by GC which showed that there were two components of appropriate retention times for homofarnesene isomers.

The mass spectrum obtained by GC-MS of the component with longer retention time was identical to that of ant homofarnesene (see figure 52).

1-[(1,1-Dimethylethyl)thio]-4-methylhexa-3,5-diene

To a stirred, warm solution of sodium (1.97g, 0.086g atom) in dry ethanol (50mls), t-butylmercaptan was added dropwise causing the solution to become pale yellow in colour and hot (Z)-6-bromo-3-methylhexa-1,3--diene (15g, 0.086 mol) was added to the stirred solution at a rate sufficient to maintain a gentle reflux. The mixture was stirred for 30 mins then allowed to cool, filtered and poured into water (∿ 300mls). Diethyl ether was added, the organic layer was separated and the aqueous layer was extracted twice more with diethyl ether. The combined extracts were dried ($MgSO_4$) and evaporated to give 14.8g of crude product. Distillation under reduced pressure under nitrogen gave 12.53g (79%) of 4-methyl-3,5-hexadienyl-t-butylsulphide, b.p. 107-114° /14mm Hg. Found: C, 71.24; H, 10.81. $C_{11}H_{20}S$ requires C, 71.67; H, 10.94%, m/e 184 ($M^+$); $\delta_{CDCl_3}$ 1.3 (9H, s, $-C(CH_3)_3$), 1.8 (3H, br s, $-CH_3$), 2.5 (4H, br s, $CH_2-CH_2$), 5.0-5.4 (3H, complex m, -CH=), 6.7 (1H, dd, J 11 and 17Hz, =C-CH=) $\nu_{max}$ 3090, 2960, 2900, 2860, 1650, 1465, 1365, 1165, 1090, 990, 905 $cm^{-1}$.

1-[(1,1-Dimethylethyl)sulphinyl]-4-methylhexa-3,5-diene

To a stirred solution of 4-methyl-3,5-hexadienyl-t-butyl sulphide (10.67g, 0.058 mol) in acetone (30mls) and glacial acetic acid (30mls), hydrogen peroxide (27.5%; 7.2mls) was added with cooling in ice. The mixture was stirred for 1½hrs at ice temperature before allowing it to warm up to room temperature and pouring into water. The aqueous mixture was extracted (3x) with dichloromethane and the combined extracts were washed with water, dried ($K_2CO_3$) and evaporated. The residue was distilled under reduced pressure to give 9.7g (84%) of 4-methyl-3,5-hexadienyl-t-butylsulphoxide, b.p. 110-118° /0.2mm Hg. m/e 144 ($M^+ - C_4H_8$). $\delta_{CDCl_3}$ 1.22 (9H, s, $-C(CH_3)_3$), 1.83 (3H, br s, $-CH_3$), 2.52 (4H, br s, $-CH_2CH_2-$), 5.0-5.4 (3H, complex m. -CH=, and $CH_2$=), 6.75 (1H, d.d. J 11 and 15Hz =C=CH=), $\nu_{max}$ 3090, 234nm ($\varepsilon$ = 17,414).

2,6,10-Trimethyl-7-[(1,1-dimethylethyl)sulphinyl]-dodeca-2,9,11-trien-6-ol

To a cooled solution of 1-[(1,1-dimethylethyl)sulphinyl]-4-methyl-hexa-3,5-diene (1.39g, 6.9 mmol) in tetrahydrofuran, n-butyllithium in hexane (1.6M; 5mls, 8 mmol) was added under nitrogen at -60°. After 1½ hrs at -60°, 6-methyl-5-hepten-2-one (1.1mls, 7 mmol) was added and the mixture kept at -60° for a further 1hr before being allowed to warm up to 0° overnight. Water was added and the mixture extracted (3x) with dichloromethane. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated. The residue was chromatographed on alumina (100g, grade III), eluting with light petroleum with increasing proportions of acetone to give 0.8g (36%) of 2,6,10-trimethyl-7-[(1,1-dimethylethyl)-sulphinyl]dodeca-2,9,11-trien-6-ol. $\delta_{CDCl_3}$ 1.3 (9H, s, $(CH_3)_3$-C-),

1.5 (3H, s, $CH_3$-C-O-), 1.65 (6H, d, J 4.5Hz, $(CH_3)_3C$=), 1.8 (3H, brs, $CH_3$-C=), 1.9-2.3 (4H, br m, $-CH_2-CH_2-$), 2.4 (2H, br d, J 5Hz, $CH_2$-C-S=O) 3.0 (1H, t, J 5Hz, -CH-S=O), 4.8-5.5 (4H, complex m, alkene), 5.7 (1H, br s, OH), 6.4-6.9 (1H, q, J 10 and 16Hz, =CH-C=); $\nu_{max}$ 3340, br, (OH), 3090, 2970, 2925, 2870, 1465, 1380, 1003 $cm^{-1}$.

Attempted decomposition of β-hydroxysulphoxide with sulphuryl chloride

The β-hydroxysulphoxide (0.5g, $1.5x10^{-3}$ mol) was dissolved in dry dichloromethane. A solution of sulphuryl chloride (0.14ml, $1.6x10^{-3}$ mol) in dichloromethane (1ml) was added dropwise to the stirred solution under nitrogen. Samples withdrawn from the reaction mixture at intervals and examined by TLC showed that the β-hydroxysulphoxide was disappearing. Examination of the reaction mixture by GC after 1.5hrs revealed two small peaks at appropriate retention times for farnesene isomers. Comparison of the peak area with that of a hydrocarbon standard suggested a yield of about 10%.

Attempted decomposition of β-hydroxysulphoxide with N-chlorosuccinimide

A solution of β-hydroxysulphoxide (2.8g, 0.0086 mol) in dichloromethane was cooled to $-18^{\circ}$ under nitrogen and N-chlorosuccinimide (1.15g, 0.0086 mol) was added. The mixture was sampled immediately and examined by GC, which showed two peaks of appropriate retention times for farnesene. The temperature was allowed to rise slowly and after 30 minutes when the temperature had reached $-12^{\circ}$ another sample was taken. This showed no increase in the size of the GC peaks. The temperature was allowed to increase to $25^{\circ}$ but no increase in the size of peaks in the GC trace was observed although the mixture had darkened considerably.

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