FURANOSESQUITERPENES FROM *EREMOPHILA ROTUNDIFOLIA* A STRUCTURAL, STEREOCHEMICAL AND SYNTHETIC INVESTIGATION

A
Thesis
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Doctor of Philosophy

in

The University of Adelaide

by

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SUMMARY

The leaves and twigs of *E. rotundifolia* provided a number of 3-furano-sesquiterpenes. Among the known compounds isolated were dendrolasin, (*E*) and (*Z*)-dihydrophymaspermones, dehydrongaione and dehydroepingaione. Some of the sesquiterpenes isolated which had not been previously described included (*S*,*E*)-4-hydroxydendrolasin (8) and an unstable tetrahydrobenzofuran diene (46) with a novel skeleton. A major plant constituent was a stable and crystalline bicyclic acetal which contained three centres of chirality. The greater part of the thesis describes the structure, stereochemistry, reactions and utility of eremoacetal (47) as a useful chiral precursor to a number of other furanoterpenes.

A synthesis of the tetrahydro benzofuran diene (46) *via* a cationic intermediate derived from the dihydrophymaspermones, confirmed the structure of this sesquiterpene.

(*S*,*E*)-4-Hydroxydendrolasin (8) was synthesised from eremoacetal confirming the structure and stereochemistry of (8). Most importantly the synthesis confirmed the results obtained from the application of Horeau's technique to this alcohol.

While exploring the ring opening of the acetal function, some interesting reactions were observed and investigated. In particular, the acidic and basic hydrolysis, and the Birch reduction were examined with eremoacetal and certain derivatives. The results from these investigations allowed the conversion of eremoacetal into a variety of highly functionalised compounds of predictable stereochemistry. These products were utilised in the preparation of a number of furano-sesquiterpenes. In this way, in addition to 4-hydroxydendrolasin, (-)-dehydrongaione, (+)-epingaione, ipomeanine and (-)-athanagrandione were synthesized. The preparation of (-)-(S)-athanagrandione allowed the previously unknown stereochemistry to be determined.

Utilising the previously explored reactions of eremoacetal and its derivatives a synthesis of (-)-furospongin-1, a C_{21} difuranoterpene, was completed for the first time. A number of useful furospongin-1 double bond isomers and epimers was concurrently synthesised. These isomers proved useful in a study of Horeau's method particularly with respect to steric effects in the determination of absolute configuration. The epimers of each double bond isomer were obtained in an enantiomerically pure form. However, the synthetic (-)-furospongin-1 was contaminated with its inseparable epimer. This synthesis was valuable in that it demonstrated the utility of eremoacetal derivatives as useful chiral templates.

Finally, eremoacetal was used to synthesise a wide variety of enantiomerically pure secondary alcohols of known stereochemistry. These alcohols were then used in a study of effective steric size of substituents about the chiral centre bearing the secondary hydroxyl group by the application of Horeau's method. The study was carried out using the g.c. modification of Horeau's method allowing some conclusions to be made as to the effective sizes of various substituents. Some of the limitations of the g.c. modified technique were overcome and h.p.l.c. was shown to be a good alternative procedure.

The appendix includes a list of ^{13}C n.m.r. spectral data of various related bicyclic, monocyclic and acyclic compounds presented in a systematic, tabular manner to show the influence of substituents, structure and stereochemistry upon chemical shift.

STATEMENT

This thesis presents the work of the author during the period 1977 to 1979 in the Department of Organic Chemistry at the University of Adelaide. This thesis contains no material previously submitted for a degree or diploma in any university, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

(Eugene Dimitriadis)

ACKNOWLEDGEMENTS

To Dr. R.A. Massy-Westropp I wish to express my sincere gratitude for his interest, encouragement, and guidance extended to me during his supervision of this work. He has extended my appreciation of new fields of chemistry for which I am very thankful.

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In particular, I am sincerely appreciative of the tolerant and loving support of my wife Mary.

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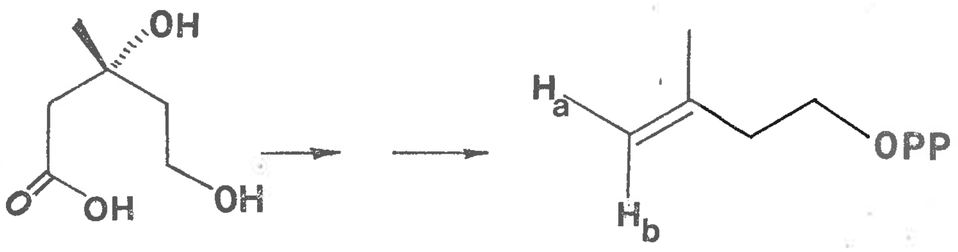
INTRODUCTION:

0.1 General

Natural products have for many years been a source of intensive research. Within this field terpenes constitute a large and important class. Interest in terpenes arose from their widespread occurrence in higher plants, microorganisms and some animals, their part in flavour and odour constituents as well as their biological effects on certain organisms. Consequently, terpenes constitute a rich field for the study of structure, stereochemistry, mechanism and especially rearrangment reactions. Much effort has been devoted to their synthesis and biosynthesis. Many books and reviews have been written about terpenes and appear frequently in the chemical literature.[1-11]

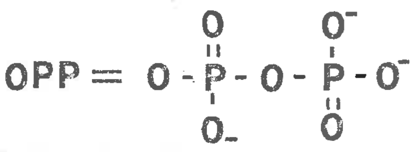
Terpenes can be considered as secondary metabolites arising from mevalonic acid (1) or mevalonolactone. Much information is now available on their mode of biosynthesis from the work of Cornforth, Arigoni and others using labelled precursors.[12-15]

It is now widely accepted that mevalonic acid[6] (1) undergoes a sequence of reactions including decarboxylation to produce isopentenyl pyrophosphate (2) which undergoes enzymatic isomerisation to give 3,3-dimethylallyl pyrophosphate (3)

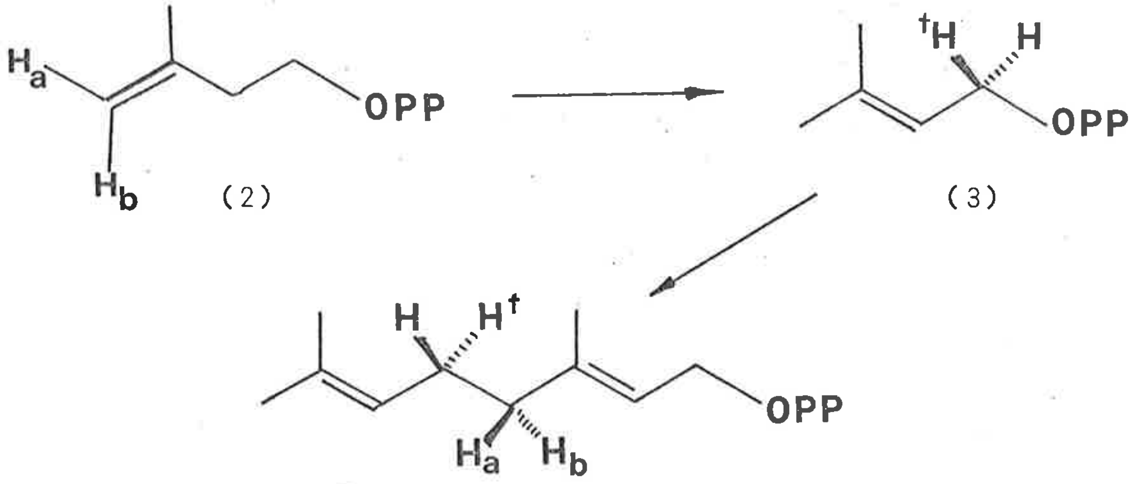


(1)

(2)



$$OPP = O-\overset{O}{\underset{O^-}{\overset{\|}{P}}}-O-\overset{O^-}{\underset{O}{\underset{\|}{P}}}-O^-$$

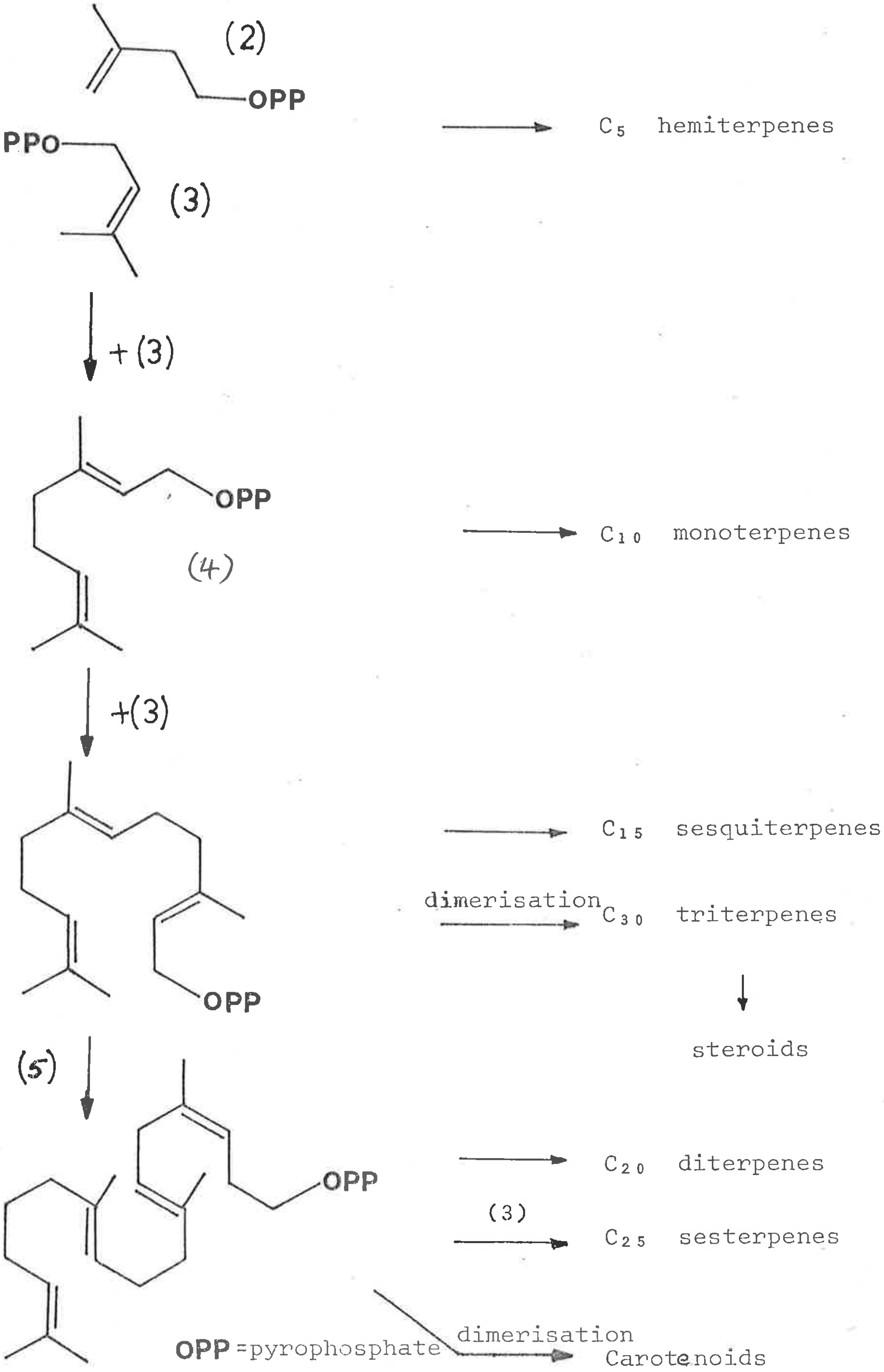


(2) (3)

(4)

Although the biosynthetic pathway has been extensively studied[12] recent work has given further information about the condensation of the two pyrophosphates (2) and (3).[16] The presently accepted view is that (2) and (3) condense in a highly stereospecific manner, probably in a carbonium ion like process, to form geranyl pyrophosphate (4). It has been shown that the further condensation of (2) with (4) then occurs with inversion at Cl, and the *pro-E* hydrogen (Ha) of (2) becomes the *pro-S* hydrogen of farnesyl pyrophosphate (C_{15}) (5). Monoterpenes (C_{10}), the volatile and odoriferous constituents of many fruits, flowers and other parts of many plants, are derived from geranyl pyrophosphate (4). Farnesyl pyrophosphate (5) is the precursor to sesquiterpenes (C_{15}). Similar such condensations lead to geranylgeranyl pyrophosphate (C_{20}) which leads to diterpenes. The intermediate pyrophosphates can undergo a series of enzyme mediated solvolyses (see Fig. 1) which gives rise to cyclised, dimerised, rearranged and further functionalised terpenes. Such a polymerisation scheme involving the parent acylic C_5 compounds resulting in the familar 'head to tail' pattern of unrearranged

Fig. 1


(2)
OPP
PPO
(3)
C5 hemiterpenes
+(3)
OPP
(4)
C10 monoterpenes
+(3)
C15 sesquiterpenes
dimerisation
C30 triterpenes
steroids
OPP
(5)
OPP
C20 diterpenes
(3)
C25 sesterpenes
OPP =pyrophosphate
dimerisation
Carotenoids

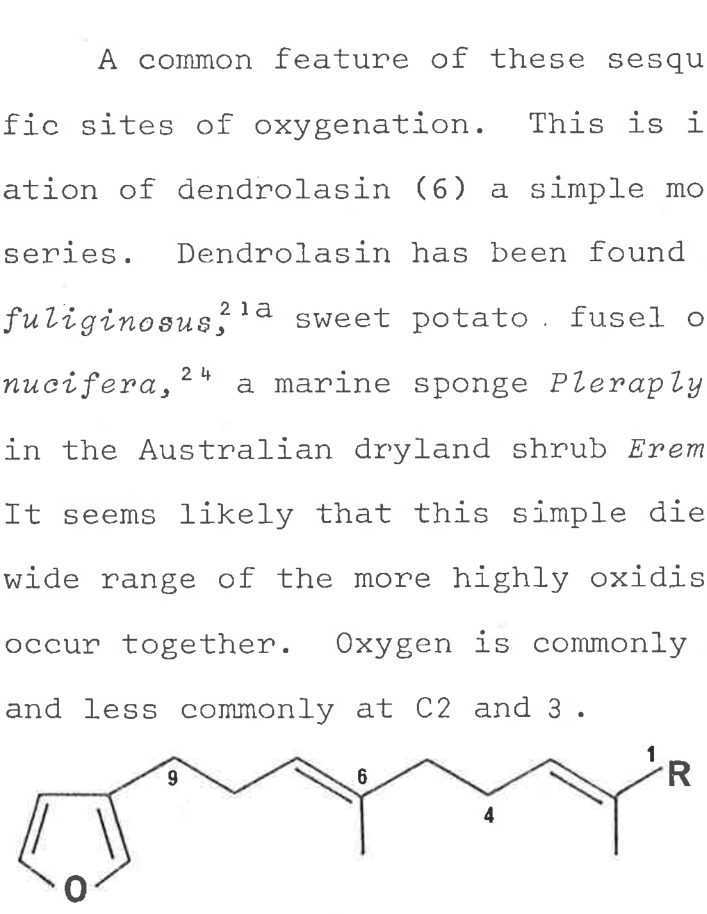
terpenes, has been called the Biogenetic Isoprene Rule.

Terpene skeletons arising from rearrangement and/or degradation are of particular interest, such as the steroids, the eremophilanes[46] and recently the C_{21} furospongin group.[53,56]

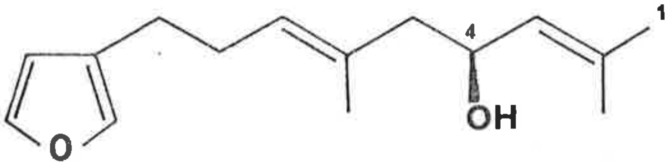
0.2 Furanosesquiterpenes

A large group of furanoterpenes has been found which contain 3-substituted furan rings and some are of interest because of their toxicity.[17-20] Such furanoterpenes occur in animals (ants,[21a] termites[22]), marine organisms,[23] tropical trees,[24] and infected tubers[19,20,25] as well as in some Australian plants.[17,18,26]

A common feature of these sesquiterpenes is their specific sites of oxygenation. This is illustrated by an examination of dendrolasin (6) a simple monoxygenated member of this series. Dendrolasin has been found in the ant *Dendrolasius fuliginosus*,[21a] sweet potato fusel oil,[29] the tree *Torreya nucifera*,[24] a marine sponge *Pleraplysilla spinifera*[28] and now in the Australian dryland shrub *Eremophila rotundifolia*.
It seems likely that this simple diene is the precursor to a wide range of the more highly oxidised members which frequently occur together. Oxygen is commonly found at C1, 4, 6 and 9 and less commonly at C2 and 3.

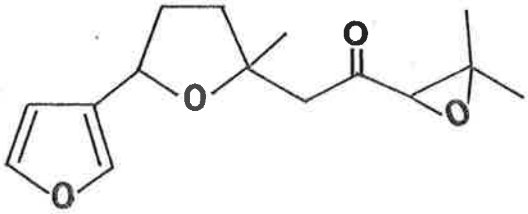


R = CH_3 (6)
R = CHO (7)



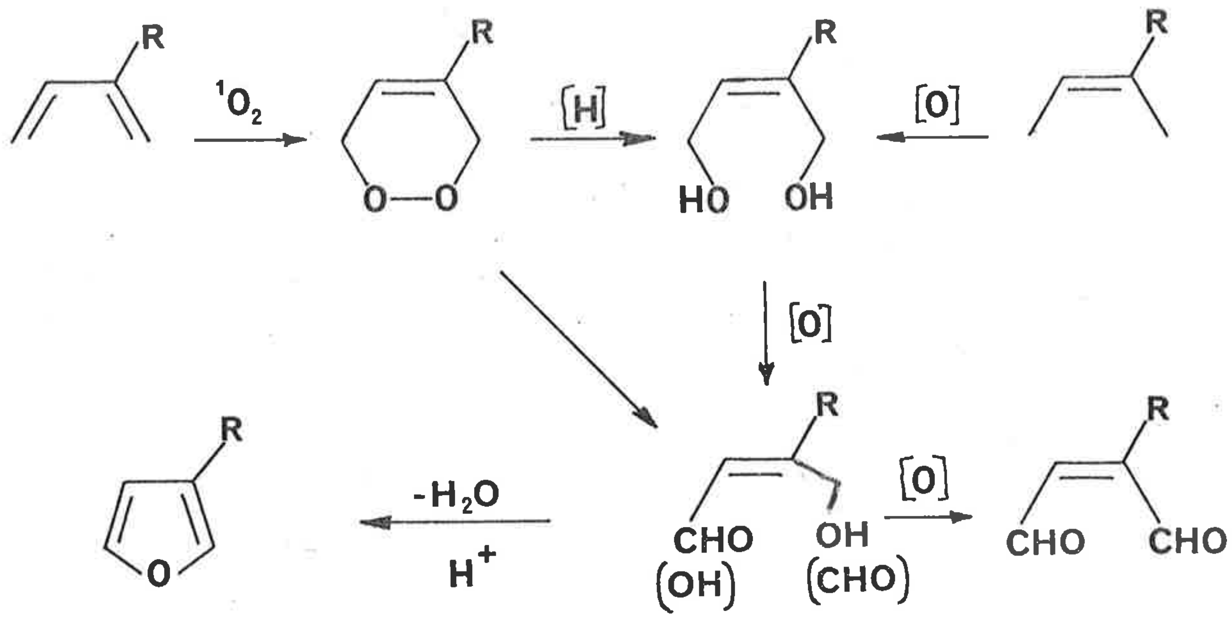
(8)

Functionality at these positions occurs as hydroxyl, carbonyl, ether and epoxide groups. Some examples include torreyal[24] (7), 4-hydroxydendrolasin (8), cycloeumorphinone[30] (9). It can be seen that the commonly oxygenated sites are activated, being allylic, or presumably oxidation has arisen from attack on the double bonds. A specific hydroxylase enzyme facilitates



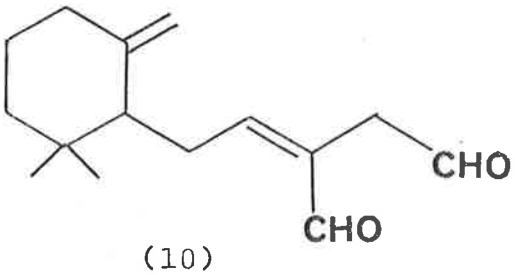
(9)

allylic oxidations and initially produces alcohols which may be further oxidised and/or cyclised.[6,33] Enzyme assisted hydration or epoxidation of double bonds[35] probably accounts for the other less frequent oxygenation or they might arise by oxygenation of the reduced compounds. Although the furan ring has been synthesised by the addition of singlet oxygen across a conjugated diene[29] followed by base and then with acid workup, it is not clear whether this pathway is also followed *in vivo* (Scheme 1).



Scheme 1

However, aldehyde (10) has been isolated[22] together with the corresponding furanoterpene (11) which suggests that (10) may be an intermediate or a by product from such a pathway.



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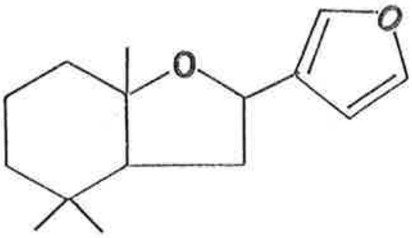
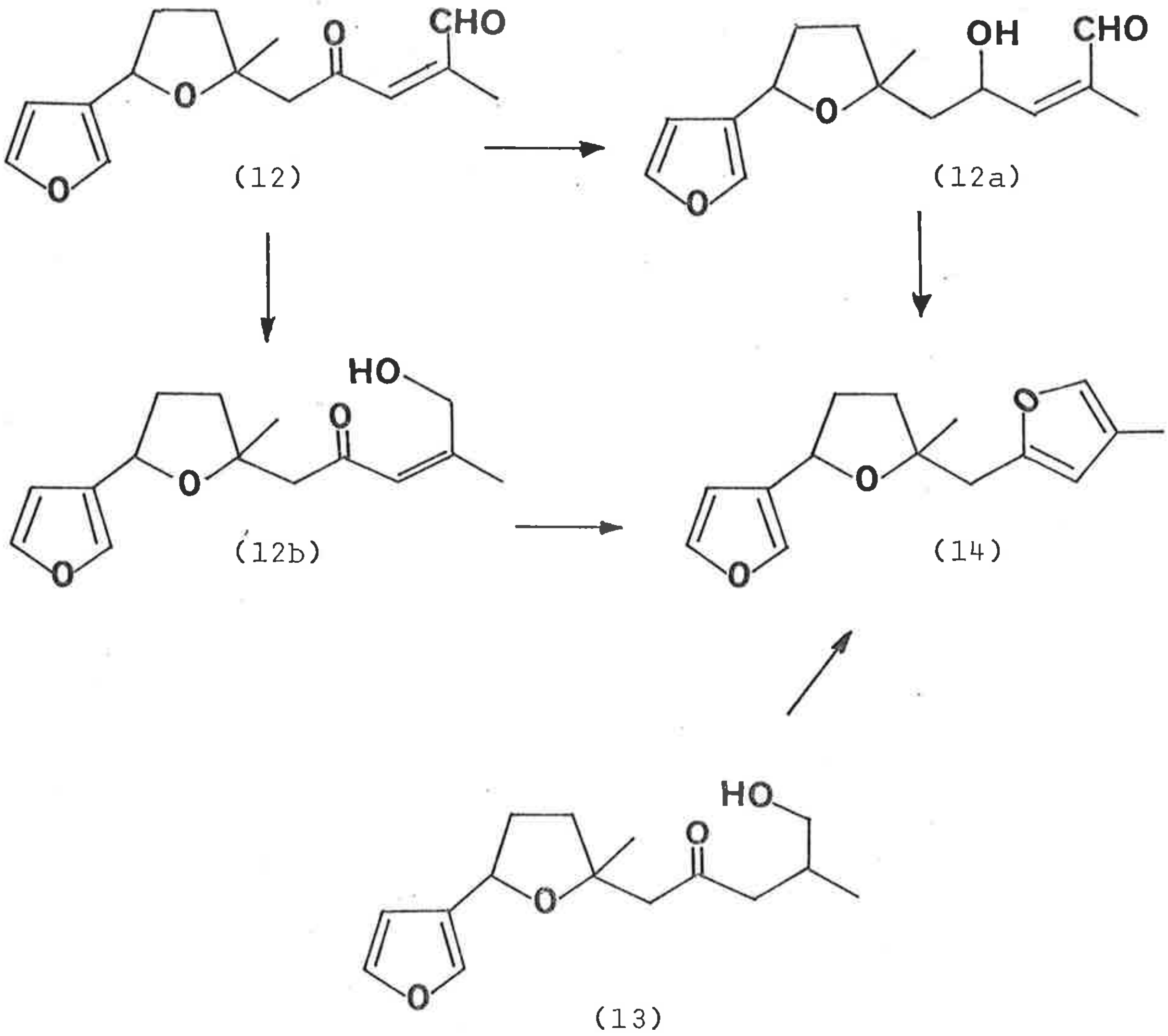


(11)

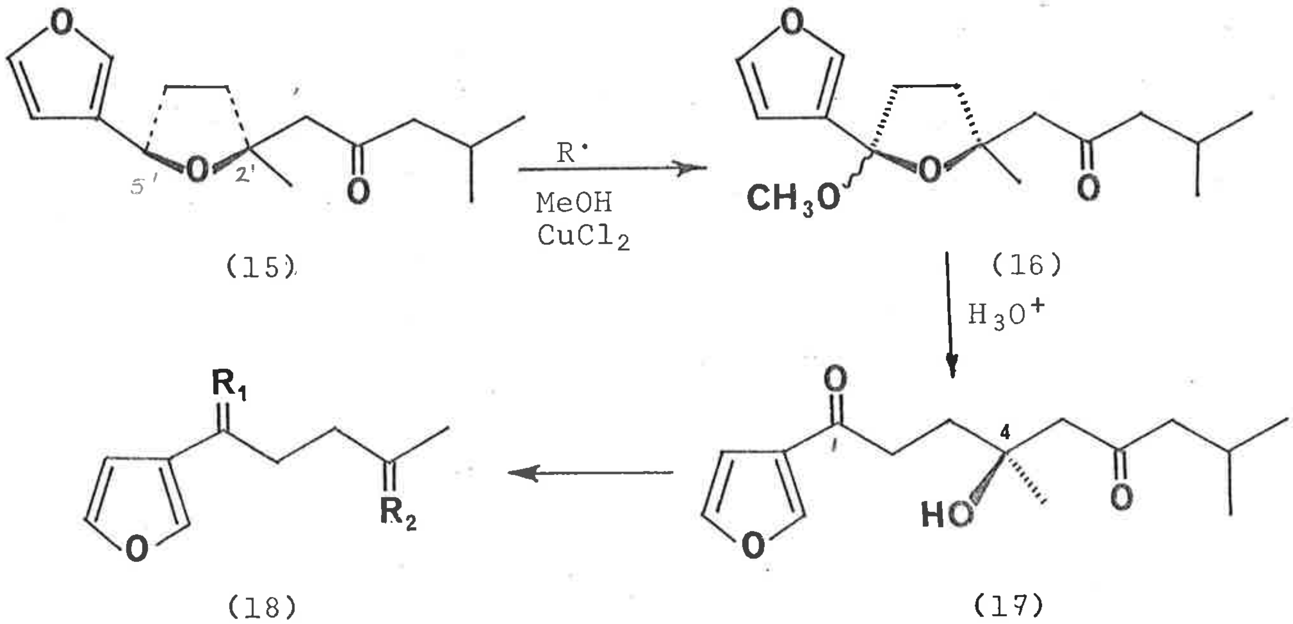
Similarly (12), related to ngaione,[32] and the alcohol (13) are found together with the difuran (14). The difuran may arise from a reductive condensation of keto aldehyde (12) resulting in cyclisation and aromatisation of the intermediates (12a) or (12b) as shown in Scheme 2.



Scheme 2

Some toxic furanosequiterpenes from infected sweet potatoes (*Ipomea batatas*) have caused concern and considerable research by American[19,36,40] and Japanese[20,25,37] workers. Burka has shown[38] that the hepatotoxic (+)-ngaione (15) (called ipomeamarone) is the precursor to 4-hydroxymyoporone (17). This is then further metabolised to a group of potent lung toxins,[19] (18) to (21) by the pathogen *Fusarium solani*. In particular, the biogenesis of the toxic metabolites has been studied[19] using labelled precursors. The importance of the sweet potato as a food source in many parts of the world has stimulated this continued research.

An important key intermediate to the lung toxins is the furanoterpene 4-hydroxymyoporone[39] (17). A suggested biomimetic pathway to (17) as demonstrated by Burka,[38] involved an allylic oxidation of (+)-ngaione (ipomeamarone) (15) to form an acetal (16).



$R_1 = R_2 = O$ (18)

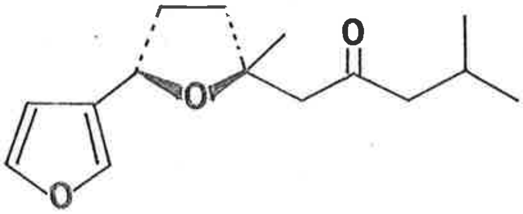
$R_1 = O$, $R_2 = H,OH$ (19)

$R_1 = H,OH$, $R_2 = O$ (20)

$R_1 = R_2 = H,OH$ (21)

Acid catalysed hydrolysis of acetal (16) then led to 4-hydroxymyoporone (17) which had the same sign and magnitude of optical rotation as the same metabolite isolated from sweet potatoes.[19] However, neither the optical rotation nor the stereochemistry of (17) are reported. The configuration shown, for (17) is based upon the known stereochemistry of (15) in which the stereochemistry at C4 in (17) has been retained during the transformation.

'4-Hydroxymyoporone' has also been isolated from the *Athanasia* species[34] and named athanagrandione by Bohlmann. Although some spectral data and an optical rotation have been reported, the configuration at the chiral centre was not determined. However, (-)-ngaione (22) (the enantiomer of ipomeamarone) has been isolated from the same species as athanagrandione (23) which, by analogy with Burka's work, is the likely precursor of (23).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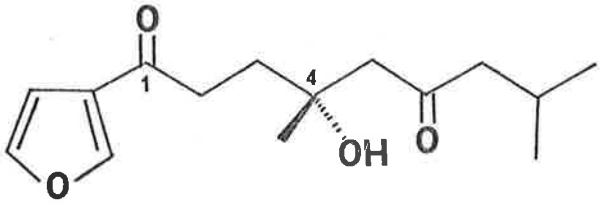
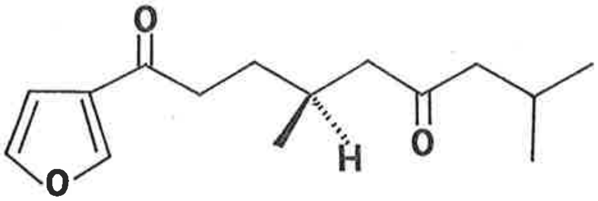


(23)

Therefore, athanagrandione (23) is probably the 4-*R* isomer of 4-hydroxymyoporone while the compound isolated from infected sweet potatoes (17) is presumably the enantiomer. A synthesis of the 4-*R* isomer (23) from eremoacetal (47) has confirmed this assumption.

Myoporum deserti, a shrub found in the drier regions of Australia, has been intensively examined by Sutherland and co-workers[17,18,31] and found to contain at least eleven toxic furanoid sesquiterpenes. Many of these compounds were demonstrated to be liver toxins which produced the same symptoms in sheep and cattle as the plant did. Myoporone[20,31] (24) was the first substance isolated together with the enone, myodesmone (25), which probably arises from an intramolecular aldol condensation of (24). Other important components of



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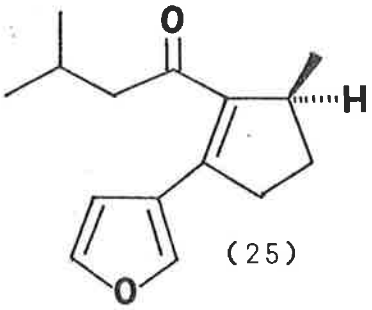
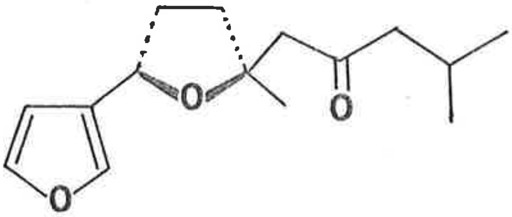


(25)

M.deserti are (-)-ngaione (22), (-)-epingaione (26) and the dehydroisomers (44) and (45).

Recent reports[19,29] have shown the incorrect absolute configuration for (+)-ngaione (15) isolated from sweet potatoes (also named ipomeamarone), the enantiomer of (-)-ngaione (22).



(26)

The publication of the incorrect configuration persists despite the thorough investigation of Sutherland et al.[20,21] Both enantiomers of ngaione, (15) and (22), are hepatotoxic but only the (+) isomer (20) is formed as a stress metabolite* (or phytoalexin**) of the sweet potato.

0.3 Terpenes in the *Eremophila* species

From the numerous species of the genus *Eremophila* (family Myoporaceae), commonly found in the arid regions of Australia, many structurally interesting terpenes have been isolated. Chemical similarities with the related *Myoporum* genus has been noted.[17],[18] The skeletal variation in terpenes derived from the *Eremophila* species is noteworthy and some main types are shown below. This thesis describes some further examples .

The cembrenes (27) and (28) are two of a group of macrocyclic diterpenes which have been isolated from *E. georgii*[41] and *E. clarkei*[42] The former species also contains the triclic sesquiterpene zizaene[43] (29). A series of related cembrenes have also been isolated from soft corals.[44]

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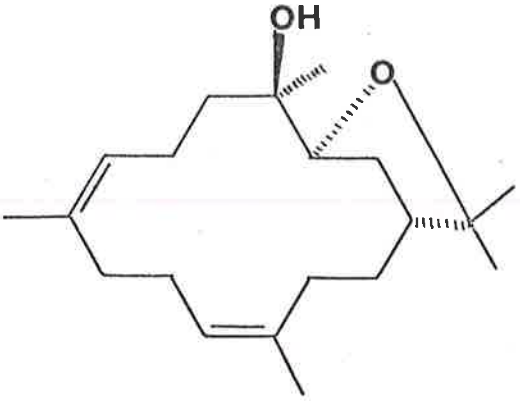
* Stress metabolites are produced when the host plant is subjected to microbial infection, or chemically induced 'stress' (e.g. with mercuric chloride).

** Phytoalexins are metabolites produced when the plant is infected with fungi, bacteria or virus.



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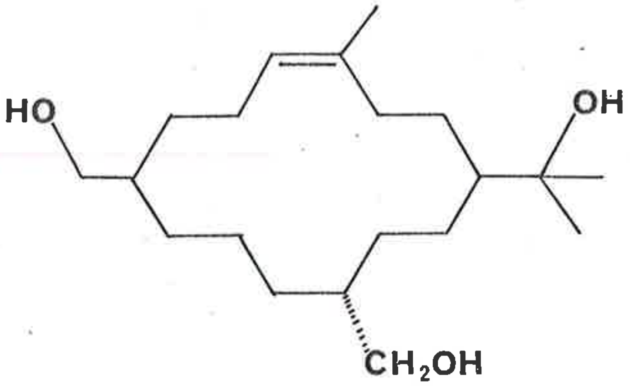
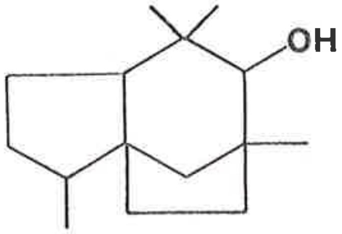


(28)

The species *E. serulata* and *E. decipiens*[45] have provided the diterpenes (30) and (31) which are clearly related to each other biogenetically.



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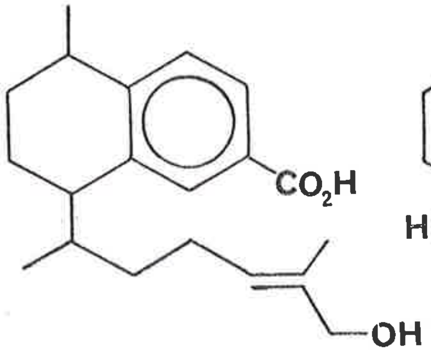

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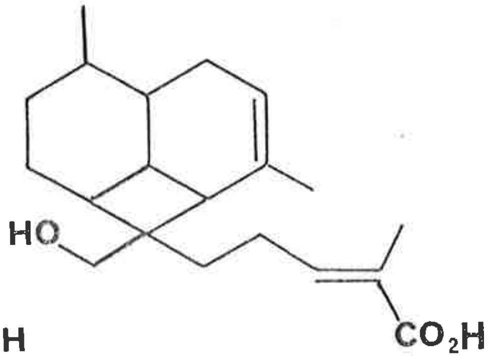
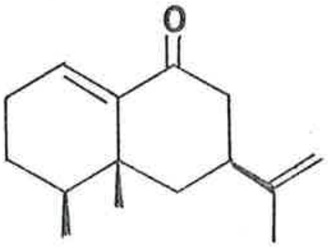


(31)

E. mitchelli contains several eremophilanes, e.g. eremophilone[46] (32) and the recently characterised sesquiterpene dimer[47] (33), both having a rearranged terpene skeleton.



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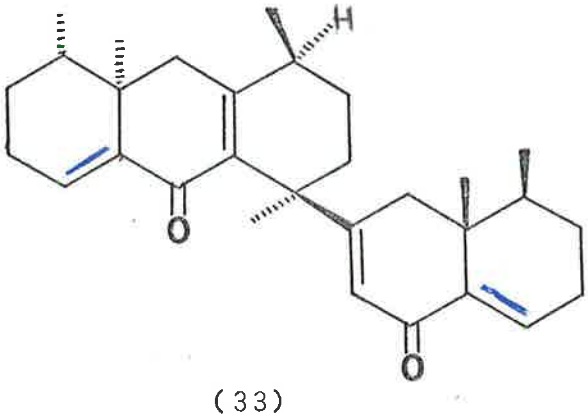
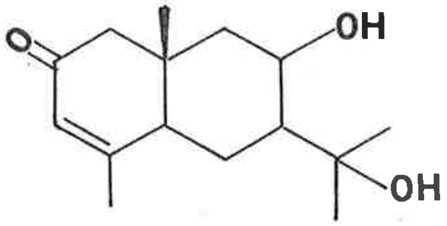


(33)

Extraction of *E. scoparia*[48] gave the diol (34) the first member of the eudesmane group to be isolated from an *Eremophila* species.



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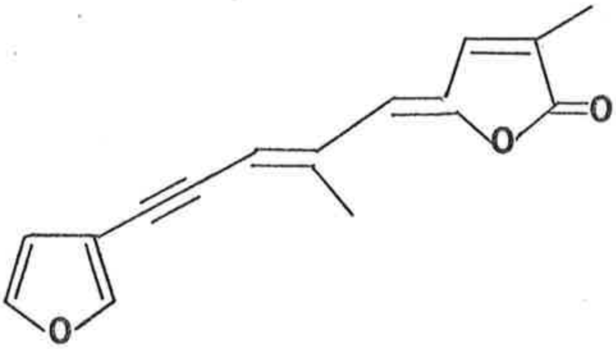
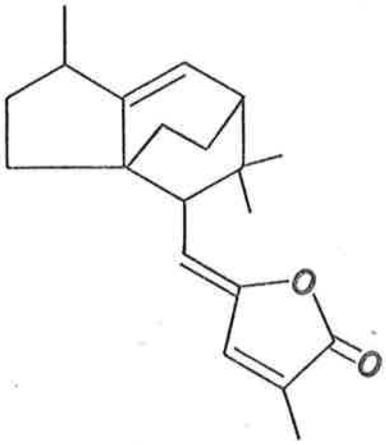


(35)

Some highly unsaturated furanoterpenes have been found in the heartwood of some *Eremophila* species. Freelingyne[49] (35) is the most unsaturated furanoterpene yet found and was the first example of an acetylenic terpene. *E. freelingii* also contains the butenolide, eremolactone[50] (36)



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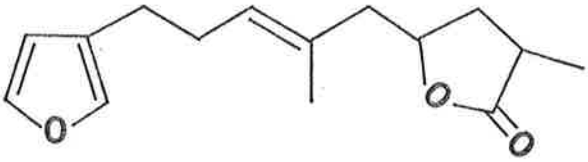

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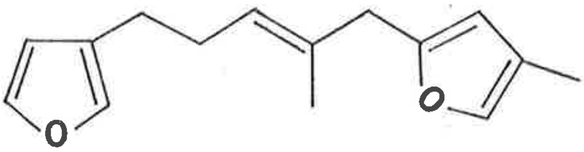
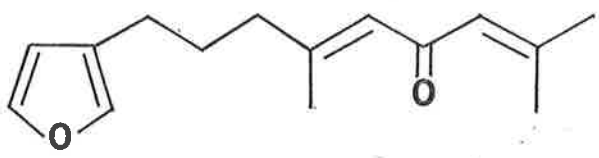


(38)

It has been suggested[51] that lactones are the biogenetic oxidation products of furans. Terpenes (37), (38), (40) and (42) co-occur in the same *Athanasia* species[51] which supports this hypothesis.



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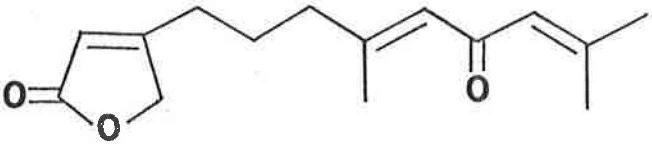
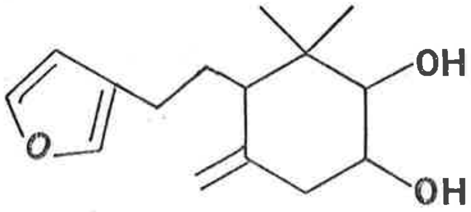


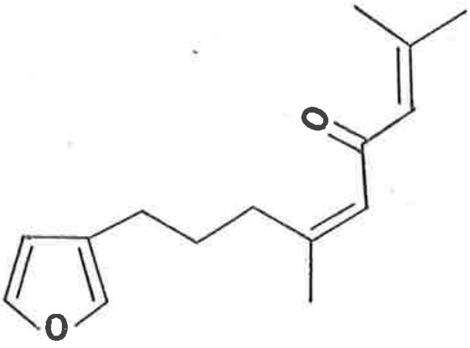
(40)

Alternifolenediol[52] (41) has recently been isolated from *E. alternifolia.* This skeleton appears to be of fairly common occurrence, particularly from marine sources.[23a]



(41)

This thesis describes the terpenes isolated from *Eremophila rotundifolia.* Extraction and separation of the leaf oil constituents gave the known terpenes dendrolasin[24] (6), *E* and *Z* dihydrophymaspermones[32] (42) and (43), (-)-dehydrongaione[18] (44) and (-)-dehydroepingaione [18] (45).



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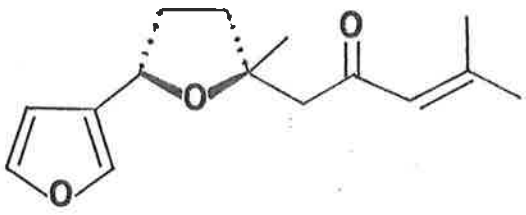
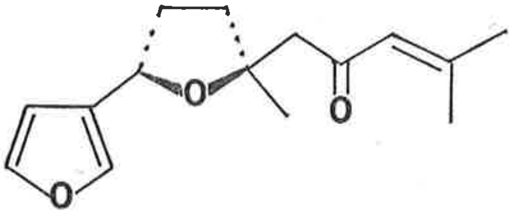


(44)



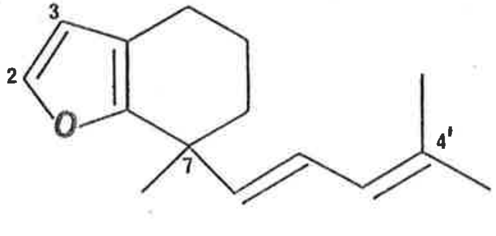
(45)

Dendrolasin (6), the simplest acyclic member in the 3-furanoterpene series, was isolated as a minor constituent of the leaves and twigs (0.1%). It was characterised by comparison of its spectral data with the literature values.[24] It has been found in a variety of different natural sources e.g. the ant *Lasius (Dendrolasius) fuliginosus*,[23a] the wood of the tree *Torreya nucifera*[24] and the marine sponge *Oligocerous hemorrhages*. It is a likely precursor to the more highly oxygenated members in the series.

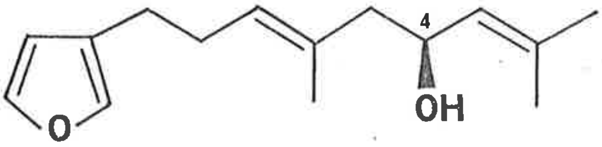
(-)-Dehydrongaione (44) and (-)-dehydroepingaione (45) were isolated from *E. rotundifolia* as a mixture (2:1). Both isomers have essentially the same proton n.m.r. spectra[18] except for twin peaks for one of the methyl groups. The spectrum was superimposable upon that of authentic (-)-dehydrongaione from *Myoporum deserti*.[18] Reduction of the mixed enones, (44) and (45), gave four allylic alcohols, two of which were identical with those obtained by reduction of authentic (-)-dehydrongaione (44). The other two alcohols were characterised as the reduction products of (-)-dehydroepingaione (45).

The dihydrophymaspermones (42) and (43) were separated using h.p.l.c. and characterised by spectral comparison with those reported by Bohlmann.[32] There were minor differences in chemical shift values of some protons in the n.m.r. spectrum.

Among the new compounds isolated was the diene (46). This furanoterpene has a novel skeleton, hitherto unknown, and was isolated in very small quantities (0.001%) as an unstable oil from enriched chromatographic fractions. It might be an artifact as it could not be detected unambiguously by g.c. in the crude extract. Also, although it has an asymmetric carbon no optical rotation was detected for (46) over a range of wavelengths. Diene (46) may arise from cyclisation of alcohol (8) or a derivative of (8). This possibility was demonstrated by cyclisation *via* a bisallylic cationic intermediate in a synthesis of (46) (see chapter 6).



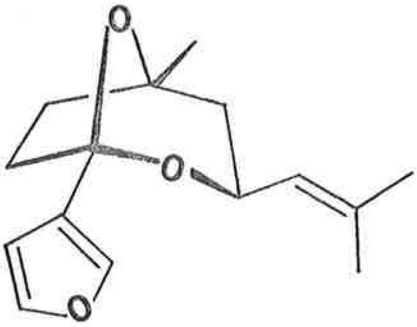
(46)



(8)

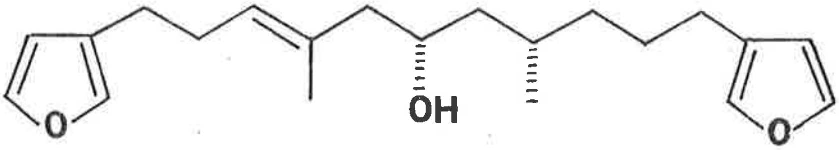
Allylic alcohol (8), 4-hydroxydendrolasin, is a minor constituent of the leaf oil. The structure and stereochemistry were established by spectroscopic evidence, chemical transformation to known compounds and finally by synthesis from (47) (see chapter 5).

The major part of this thesis is concerned with the bicyclic acetal, named eremoacetal (47). Its abundance (1.6%) in the leaves and twigs of *E. rotundifolia* allowed a study into its structure, stereochemistry, chemical properties and application as a multichiral synthon. Some unusual properties of eremoacetal have been investigated more thoroughly. In particular, opening of the acetal function has provided routes to a number of oxygenated furanosesquiterpenes. A synthesis of furospongin-1[53,56] (48) was completed for the first time using the acetal (47) as a chiral synthon. Finally the asymmetry of the acetal was used in the



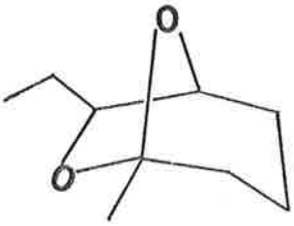
(47)

preparation of a series of chiral secondary alcohols for a stereochemical study using Horeau's method.



(48)

Acetals containing the dioxabicyclo[3.2.1]octane skeleton have been found as the pheromones[58] of the elm bark beetle e.g. brevicomin[57] (49). Other interesting and stable acetal structures are found in nature, like the iridoid sarracenin[59] (50) and the pheremones (51) and (52).[60] An acid stable bicyclic acetal has been found in a marine product[61] and also as a part of a complex alkaloid, daphniphyline.[62]



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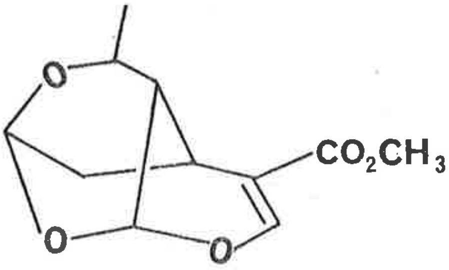

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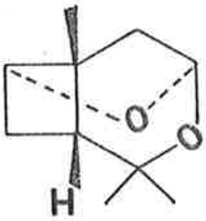
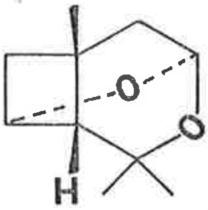
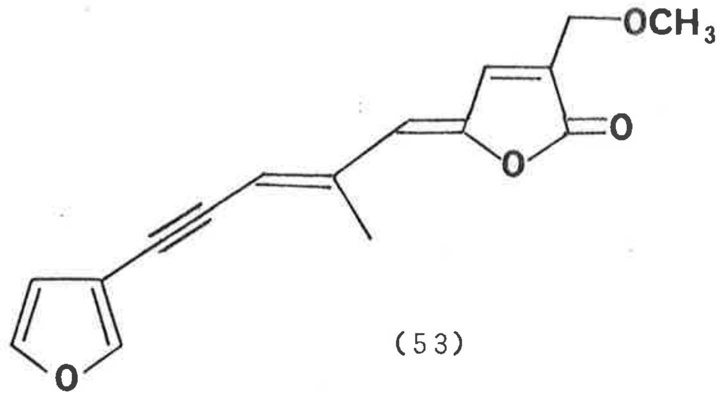


(51)



(52)

The heartwood of *E. rotundifolia* was also briefly examined. Chromatography of the wood extracts gave freelingyne[26a] (35) and a new compound, the methoxyfreelingyne (53).



(53)

Also present was a diterpene alcohol and an aldehyde but these have been only partly characterised.

It is interesting to note that the heartwood of both *E. rotundifolia* and the botanically related *E. freelingii* contain the more highly unsaturated furanoterpenes while the living tissue (leaves and twigs) contains the less oxidised terpenes. It appears that the highly oxidised and possibly phytotoxic terpenes are stored in the dead tissue, the heartwood, of these plants. What function the acetal (47) or the other furanoterpenes maintain in the life of *E. rotundifolia* is unknown although some constituents are known to be toxic to animals. Neither *E. rotundifolia* nor *E. freelingii* appears to be eaten by animals.

Chapter 1

The Structure of Eremoacetal

1.0. The leaves and twigs of *Eremophila rotundifolia* contain a number of furanoterpenes. Chromatography of the plant extract allowed the isolation of the major constituent as a colourless crystalline solid, (m.p. 63-64°), in 1.6% yield. This compound, subsequently shown to be a sesquiterpene acetal, was named eremoacetal (47)[82].

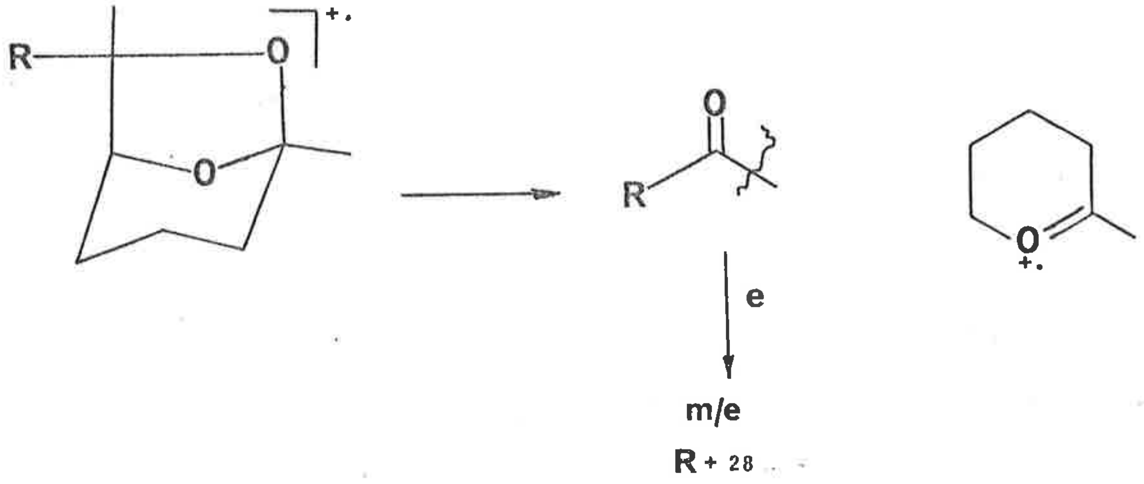
The mass spectrum and elemental analysis confirmed the molecular formula to be $C_{15}H_{20}O_3$, m/e 248. No hydroxyl or carbonyl absorptions were evident from an examination of the infrared spectrum and hence the oxygens present exist as ethers. The infrared spectrum showed absorptions at 1515, 1165, 1010 and 885 cm^{-1}, typical of a 3-substituted furan.[20,21a] Confirmation of the presence of a furan ring was obtained from the proton n.m.r. spectrum which showed resonances at δ 7.45, 7.32 and 6.39. From these chemical shifts and published coupling constants these protons were ascribed to a 3-substituted furan ring. The n.m.r. spectrum also showed an olefinic proton δ 5.24 ppm as a doublet (J 8Hz) with fine coupling (2Hz) to an allylic methyl group. A one proton multiplet (d,d,d) at δ 4.6 ppm was coupled to the olefinic proton at 5.24 ppm as well as two other neighbouring protons (J 10, 5Hz).

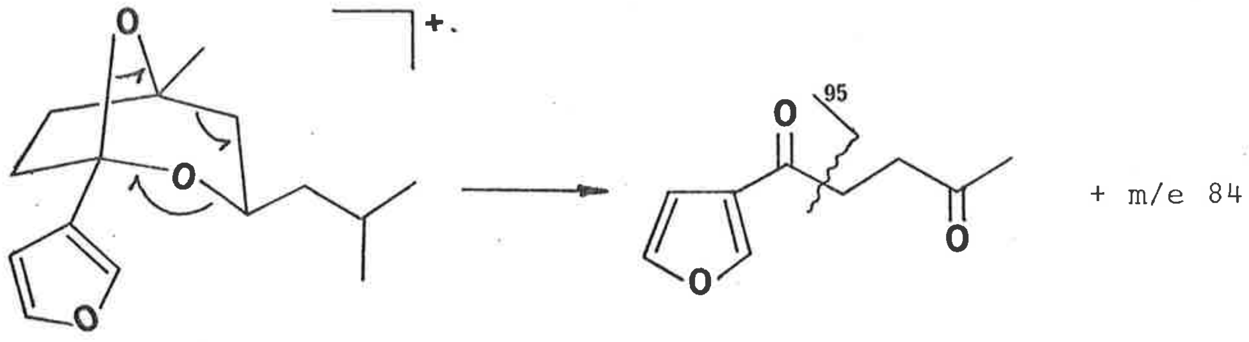
Two methyl groups on a double bond resonated as a broadened singlet at δ 1.72 ppm and another methyl group on a carbon bearing oxygen resonated as a singlet at δ 1.33. In view of the likely isoprenoid backbone and the most likely sites of oxygenation of 3-alkyl furans (e.g. dendrolasin (6)), structure (47) was tentatively proposed for eremoacetal. It was consistent with all the spectral evidence.

The U.V. spectrum showed only the furan chromophore at 220 nm (ε 8,000). The ^{13}C n.m.r. spectrum showed the four furan carbons typically at 142.7 (d), 139.6 (d), 127.2 (s) and 108.6 (d) and the olefinic carbons (1" and 2") at 125.5 (d) and 135.5 (s). An acetal carbon[70] was clearly evident at 103.5 (s) ppm. Two resonances for carbons bearing oxygen (C3 and C5) were seen in the spectrum at 67.0 (d) and 80.6 (s) ppm respectively. These data were also in accord with the structure proposed for eremoacetal (47).

A closer examination of the mass spectral fragmentation and comparison with a similar fragmentation pattern for dioxabicyclooctanes[57] gives further proof of structure for (94). The following important fragmentation is shown below as a comparison.

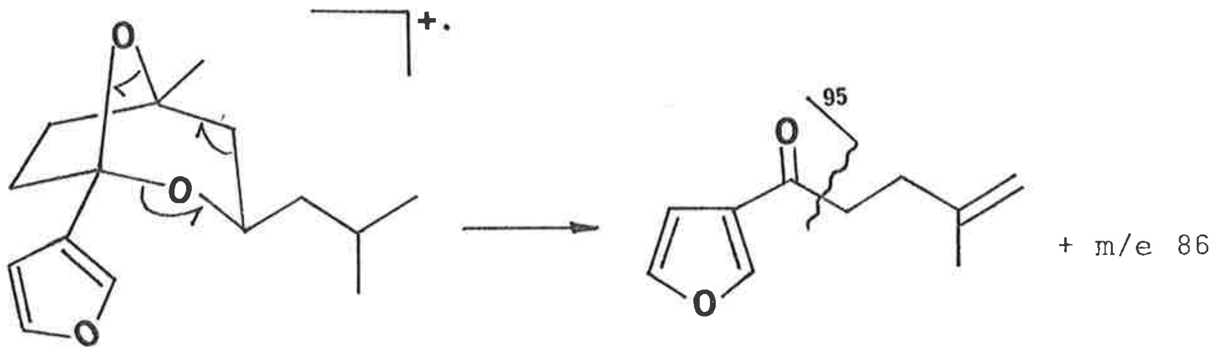
The 3-furyl ketones (m/e 166 and 164) give rise to the major mass spectral fragment at m/e 95 from fission α to the ketone.





m/e 250

m/e 166



m/e 250

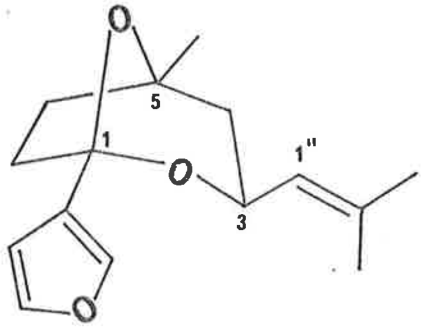
m/e 164

1.1 Therefore, most of the structural investigation was directed towards the determination of the configuration of eremoacetal. An examination of the structure reveals three asymmetric centres, C1, 3 and 5. The determination of the stereochemistry at C3 and C5 would provide that of C1, which results from the structure of the dioxabicyclooctane ring system. To achieve these aims it was initially necessary to open the acetal ring. A study of various methods to achieve this ring opening is discussed in chapter 2.

The configuration of C5 was established by correlation of eremoacetal with (-)-dehydrongaione (44), while that at C3 was found by the application of Horeau's method.[64,65]

It was envisaged that for the correlation of eremoacetal with (-)-dehydrongaione (44), the preparation of the dihydroxy ketone (54) from eremoacetal would be necessary.

Although the acid catalysed hydrolysis of eremoacetal was unsatisfactory for its preparation it was found that when (47) was heated in aqueous pyridine, a mixture (approx. 7:3) of the acetal (47) and dihydroxy ketone (54) was obtained (see Chapter 2). The acetal and dihydroxyketone (54) were readily separated by solvent extraction due to the large difference in their polarity and the slow rate of cyclisation of (54) at low temperature under basic conditions. Acetylation of the unstable diol (54) gave the monoacetate (55) together with some eremoacetal. Selective reduction of the ketoacetate (55) with zinc borohydride gave the corresponding dihydroxyacetates (56) and (57) in a ratio of 2:1, together with some diol (58). Other similar allylic substitutions have been observed in the reduction and hydrolysis of the dehydrongaiol esters.



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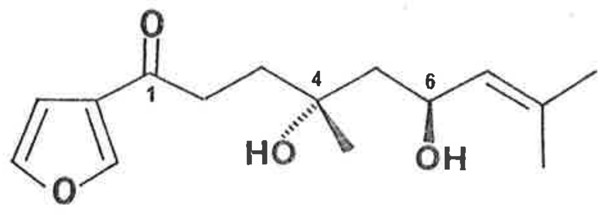

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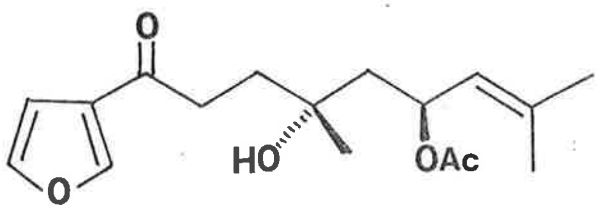
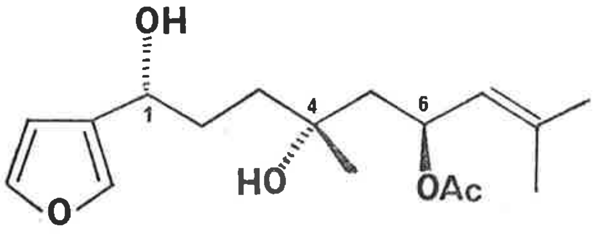
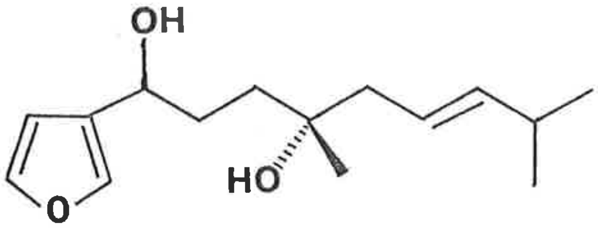


(55)



(56)



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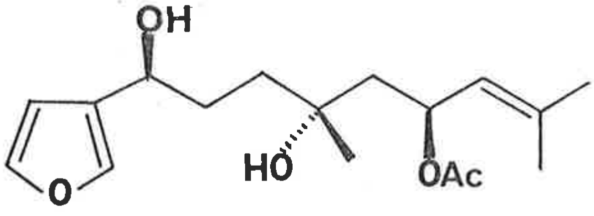
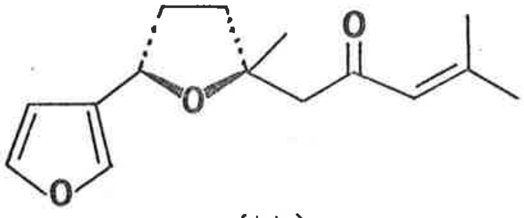


(57)

An intramolecular cyclisation of the dihydroxy acetate (56) to the tetrahydrofuran derivative (63) proceeded readily when it was treated with *p*-toluenesulphonyl chloride in pyridine. A similar cyclisation has been recently reported in the literature.[22] The epimeric diol (57) was similarly cyclised to the corresponding tetrahydrofuran (66). It was assumed that cyclisation in both cases involved inversion at C1. This fact was confirmed by determining the configuration at C1 in (56) and correlating it with that of the cyclised product of known configuration. The determination of configuration was done using Horeau's method with the reasonable assumption that the furan ring is effectively larger than the other substituent at C1.

Reduction of the acetates (63) and (66) with lithium aluminium hydride gave the corresponding alcohols (62) and (65) respectively. When (-)-dehydrongaione (44) was reduced with lithium aluminium hydride, of the two allylic alcohols isolated, (60) and (62), the latter was identical by spectral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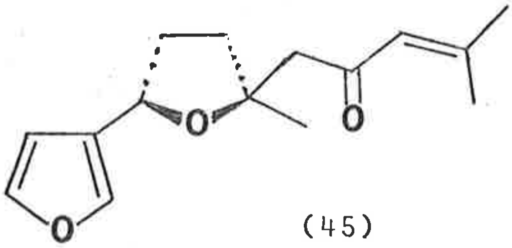
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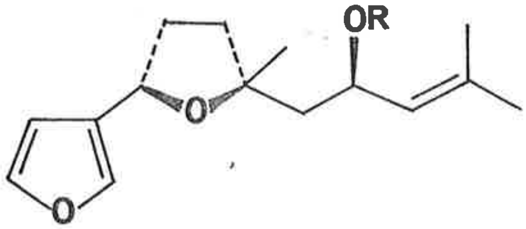
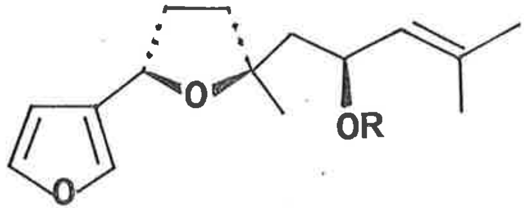
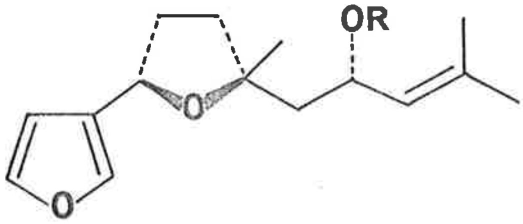

R = H (60)

R = p-PhC$_6$H$_4$CO-(61)

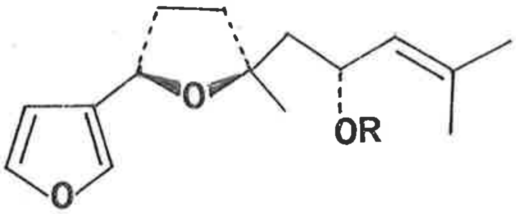

R = H (68)

R = p-PhC$_6$H$_4$CO-(69)

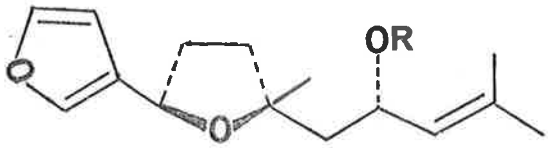

R = H (62)

R = Ac (63)

R = pPhC$_6$H$_4$CO-(64)


R = H (70)

R = pPhC$_6$H$_4$CO-(71)

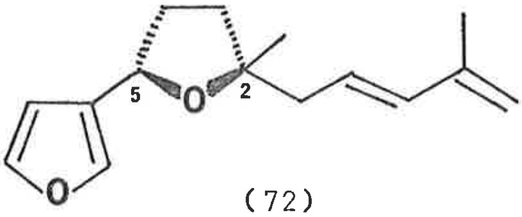

R = H (65)

R = Ac (66)

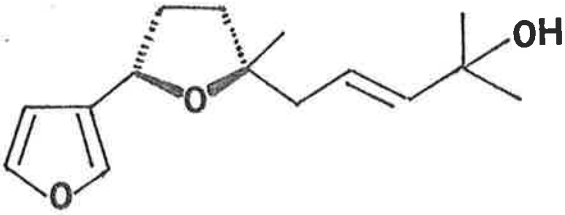
R = p-Ph-C$_6$H$_4$CO- (67)

comparison with that product from eremoacetal. The alcohols were converted to their corresponding 1,1'-diphenyl-4-carboxylates.[68] The esters (64) from both eremoacetal and (-)-dehydrongaione were identical (m.p., spectra and optical rotation). The correlation of alcohol (62) from both eremoacetal and (-)-dehydrongaione established the configuration at C5 in the former as *R*. The use of sodium borohydride in ethanol gave considerable quantities of saturated alcohols from reduction of the double bond in (44) and was slow. When lithium aluminium hydride was used to avoid basic conditions, likely to cause β-elimination, some (5%) reduction of the double bond took place to give the saturated ketone on workup. However, it was found later that an efficient and rapid reduction of enone (44) to allylic alcohols (60) and (62) could be carried out using cerium trichloride-sodium borohydride.[66] No reduction of the double bond was detectable from an examination of the products with this reagent. Similarly, sodium borohydride in methanol gave only (60) and (62) but was less rapid than in the presence of cerium trichloride. The reduction of the mixed enones, (-)-dehydrongaione (44) and (-)-dehydroepingaione (45) from *E. rotundifolia*, gave the isomeric allylic alcohols (60), (62), (68) and (70) (the enantiomer of (65)) which were isolated and characterised as their 1,1'-biphenyl-4-carboxylates. Physical data was therefore available for all the stereoisomers.

Initially, attempts to oxidise the alcohols (62) and (65) to the enones (44) and (45) were unsuccessful. Oxidation would have provided a more rapid correlation of the acetal (47) with the enones. However, difficulties were experienced with the oxidation of the allylic alcohols using Collins reagent, silver carbonate and manganese dioxide.[82] No ketone was detected but with the manganese dioxide, (62) gave the diene (72) as a result of dehydration.

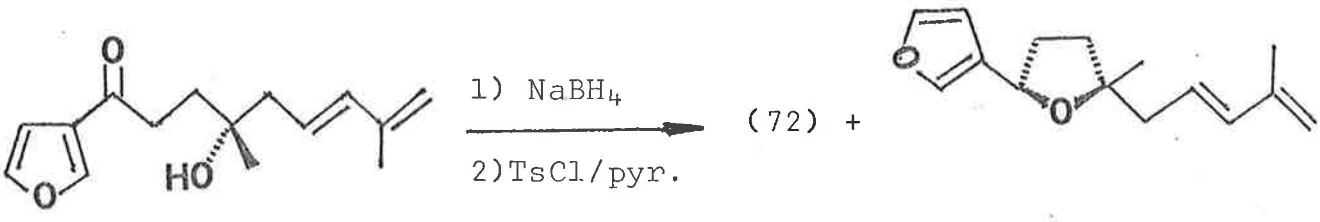


(72)



(73)

Diene (72) and its C5 epimer (75) were prepared from ketodiene (74) by reduction with sodium borohydride followed by cyclisation of the epimeric diols with *p*-toluenesulphonyl chloride in pyridine.

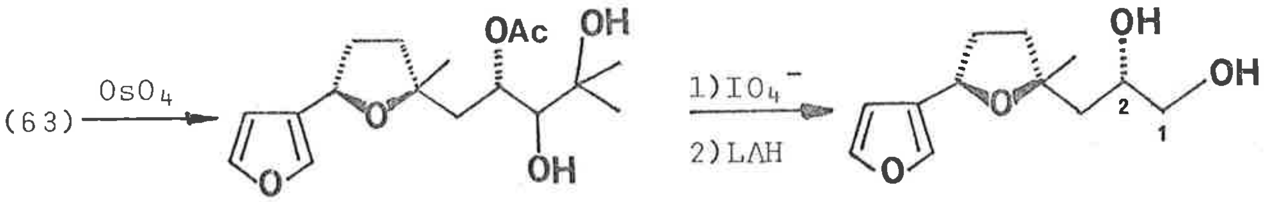


(74) (75)

An oxidation of alcohol (62) to (-)-dehydrongaione (44) was finally accomplished at -70° in modest yield (23%)

using dimethyl sulphoxide-oxalyl chloride.[67] Again, the diene (72) was the major product with smaller amounts of the rearranged allylic alcohol (73). The isolated dehydrongaione was identical to authentic (-)-dehydrongaione by infrared, n.m.r. and mass spectra and optical rotation. It is possible that a derivative of the rearranged alcohol (73) might be the intermediate leading to the diene (72). Similarly, the allylic alcohol (62), might undergo a rearrangment to (73) before undergoing dehydration when manganese dioxide was used as an oxidant.

Before Horeau's method could be applied to determine the configuration at C3 in eremoacetal it was necessary to convert it to an appropriate alcohol. However, alcohols of type (62) and (65) have not been studied and some ambiguity exists with respect to the effective size of the isobutenyl group relative to the other subtituent. Because it was necessary to remove this ambiguity, the acetate (63) was converted to diol (77). Diols of this type have been studied by Guetté[65] and the results show that it should be possible to determine unambiguously, the configuration at C2 in (77) using Horeau's technique.



(76)

(77)

Diol (77) was prepared by oxidation of acetate (63) with osmium tetroxide, fission of the diol (76) with periodic acid and reduction of the acetoxy aldehyde with lithium aluminium hydride. Epimerisation of the intermediate aldehyde was excluded by using deuterated periodic acid and using D_2O in the workup of the reduction mixture. Less than 9% deuterium was incorporated in (77) (by mass spectrometry).

The (*S*)(+)-2-phenylbutanoic acid, was recovered with 20% optical yield, when Horeau's technique was applied to (77). This result established that the configuration at C2 was (*S*) in (77) and was therefore also (*S*) at C3 in eremoacetal (47).

Because the configurations in eremoacetal (47) had been established as (*S*) at C3 and (*R*) at C5, it followed that the configuration at C1 is (*R*). Therefore, eremoacetal has the structure (47). The 1,3-dioxane ring of eremoacetal is presumed to exist preferentially in the most stable chair form by analogy with other dioxanes[72,73]. This conformation is in accord with the proton coupling between the 3H and axial 4H and equatorial 4H (*J* 10 and 5Hz respectively).

Chapter 2

Ring Opening Reactions of Eremoacetal and its Derivatives

2.0 During the initial investigation into the stereochemistry of eremoacetal (47), it was necessary to hydrolyse the acetal function to provide the keto diol (54). The application of Horeau's method to the diol (54) would allow the determination of stereochemistry at C6. However, under various conditions the formation of (54) from eremoacetal (47) was not possible due to the formation of rearranged and other products. Therefore, a closer investigation was necessary.

In order to determine some mechanistic details, the structure and stereochemistry of the products from different ring opening reactions were examined. In addition to solvolysis, a variety of methods was used for the reduction of the acetal and its derivatives, for example, the Birch reduction and hydride reduction.

The synthetic value of these investigations has been demonstrated by the preparation of a number of useful intermediates and natural products. In particular, some reactions occurred with a high degree of stereoselectivity, giving isomers which were readily separated. Many of the secondary alcohols, obtained enantiomerically pure, were useful in a study of effective steric sizes using Horeau's technique (see Chapter 8).

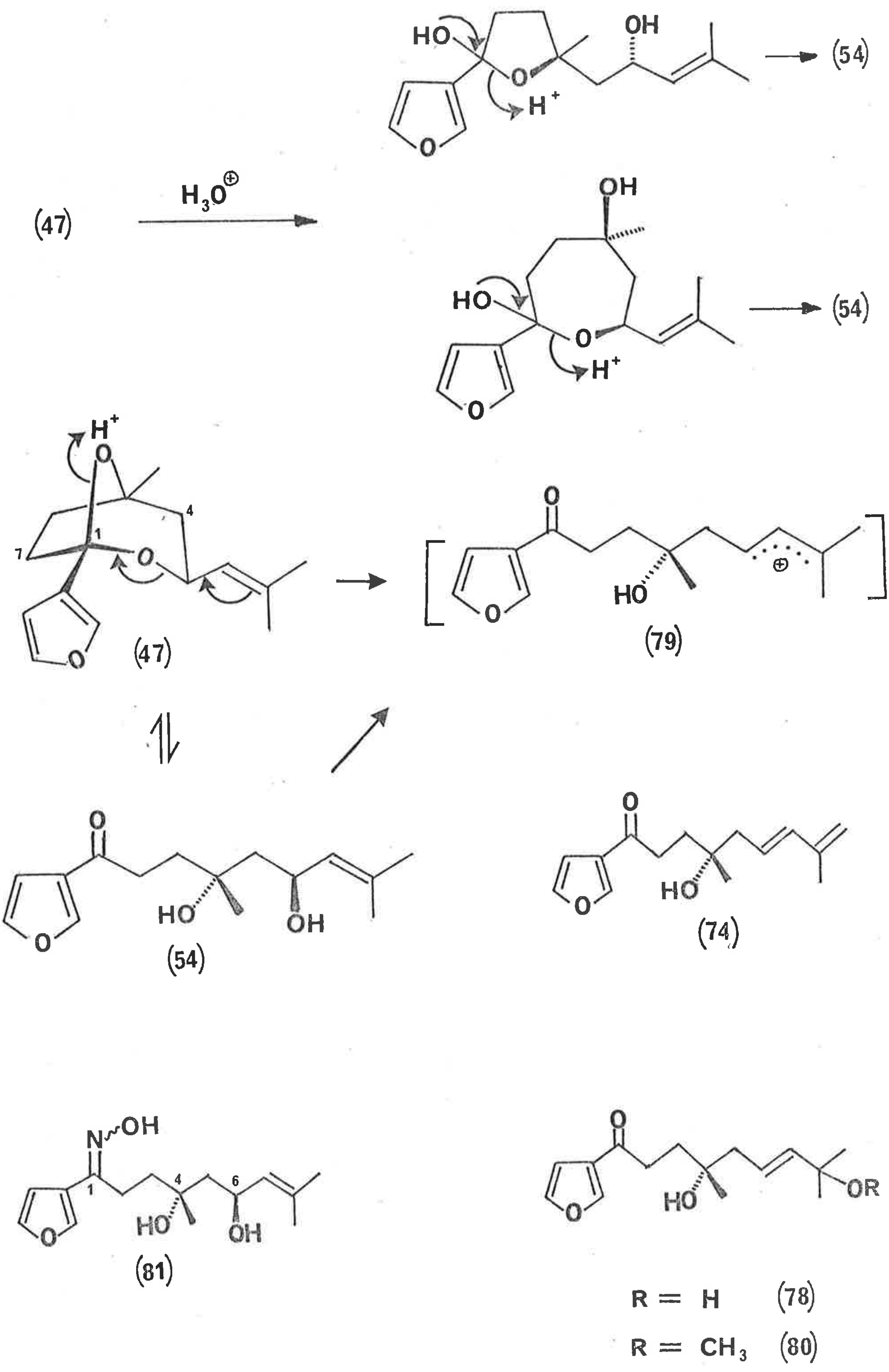
2.1 Acid Catalysed Hydrolysis

(a) Dilute, aqueous perchloric acid ($pH < 1$) in co-solvents (tetrahydrofuran, or methanol or dioxan) at room temperature, only slowly reacted with eremoacetal (47). Under these mild conditions only the rearranged allylic alcohol (78) and small quantities of diene (74) were formed after 15 h. When dilute aqueous acetic acid (10%) at reflux was used as solvent, a mixture of diene (74) and (78) was formed in varying proportions depending on the reaction time. Formation of (74) was complete in acetic acid after 1 h at reflux. As heating alcohol (78) alone in dilute acetic acid also produced diene (74), the unstable allylic alcohol (78) can be assumed to be the intermediate leading to (74), probably *via* the allylic cation (79). None of the required unrearranged alcohol (54) was obtained under any of the acid catalysed hydrolyses. This might be due to two reasons.

i) The equilibrium between the acetal (47) and diol (54) lies well in favour of the cyclic form (47) under acidic conditions.

ii) The allylic alcohol (54) is unstable under the acidic conditions and rearranges readily at low temperature to (78) which at elevated temperature dehydrates to give the diene (74): This possibility is analogous to the behaviour of prenyl alcohol under acidic conditions.[74]

The formation of products can be explained by a simple C1-O2 or O8 cleavage leading to stabilised cations, (110) or (111), followed by hemiacetal formation, ring opening to give


HO
OH
O
H⁺
(54)
(47)
$H_3O^{\oplus}$
OH
HO
O
H⁺
(54)
H⁺
O
1
4
7
O
(47)
O
HO
(79)
(54)
O
HO
OH
(54)
O
HO
(74)
N~OH
1
4
6
HO
OH
(81)
O
HO
OR
R = H (78)
R = CH₃ (80)

Scheme 2.11

(54) then rearrangment to (78) and water loss to give (74). Alternatively, concerted ring opening (see scheme 2.11) leading directly to products can be proposed.

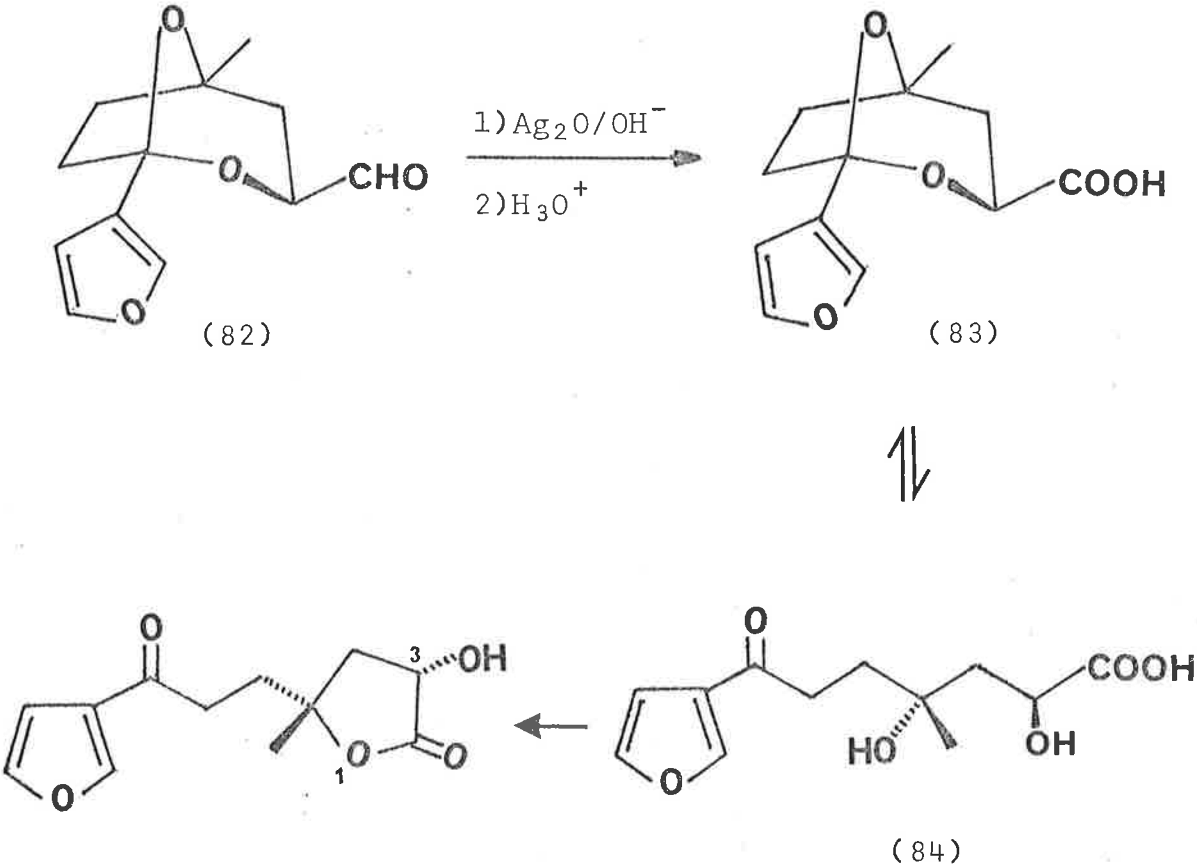
The required orbital overlap between migrating double bond of (47) and the breaking O2-C3 bond is readily achieved in the conformation shown for (47).

A similar reaction in methanol gave the methyl ether (80) in addition to diene (74). To confirm that the acetal was in equilibrium with the alcohol (54) in acidic conditions at room temperature, the ^{1}H n.m.r. spectrum of (47) was observed in d^1-chloroform containing DCl/D$_2$O (pH $<$ 1). The two C7 protons resonating at approximately δ2.4, exchanged for deuterium within 15 min. After exchange, the two protons at C6 appeared as a broadened singlet due to deuteration at C7. No evidence for any of the acyclic hydrolysis products was seen in the ^{1}H n.m.r. spectrum over 1 h.

(b) When eremoacetal (47) was treated in aqueous methanol (pH 4-5) containing hydroxylamine, two oximes of (54) were formed after 15 h. The oximes (81), formed quantitatively, were separated and their ^{1}H n.m.r. spectra confirmed they were the *E* and *Z* isomers (81). Each of the isomers underwent spontaneous isomerisation to the same equilibrium mixture of oximes (81) within 24 h. The fact that the oximes of (74) or (78) were not isolated suggests that a concerted opening of the acetal (47) under these milder conditions is unlikely.

When Horeau's technique for determining configuration (see Chapter 8) was applied to the isomeric oximes (81), it was confirmed that the stereochemistry at C6 was *S*, as it is at C3 in the natural product (47). This result therefore demonstates that no epimerisation occurred at C6 in (81) during its formation.

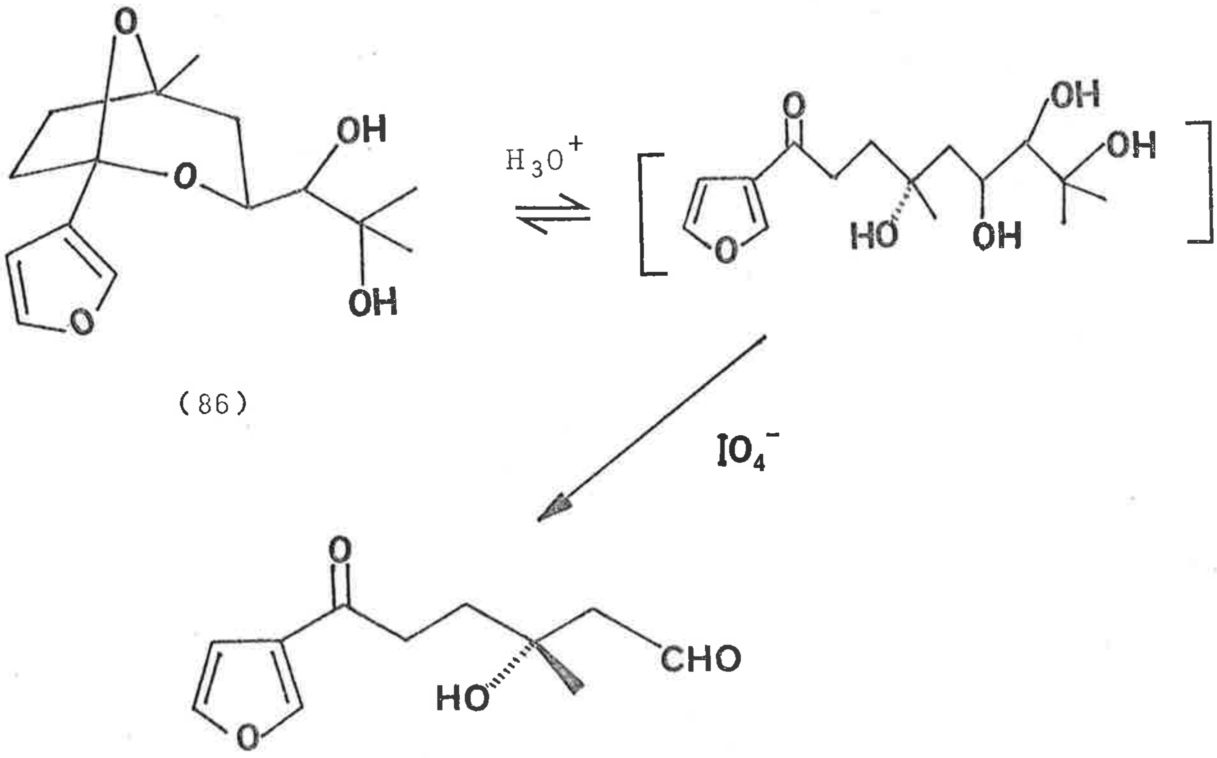
(c) In an attempt to prepare the acid (83) for another purpose from aldehyde (82) using alkaline silver oxide oxidation, workup with acid gave instead the lactone (85). Presumably, the acid (83) was hydrolysed in aqueous acid to the dihydroxyacid (84) which underwent a facile alternative



cyclisation to the thermodynamically more stable product, lactone (85).

A determination of configuration on the lactone (85) confirmed the retention of stereochemistry at C3 using the reasonable assumption that the carbonyl group has the larger effective steric requirement (see Chapter 8).

(d) During an attempt to form the aldehyde (82) by sodium periodate oxidation of diol (86) at pH 3-5, the keto aldehyde (87) was isolated instead. The formation of (87) can readily be explained by fission of the acyclic species which would be expected to be in equilibrium with the cyclic form under the reaction conditions.



(86)

(87)

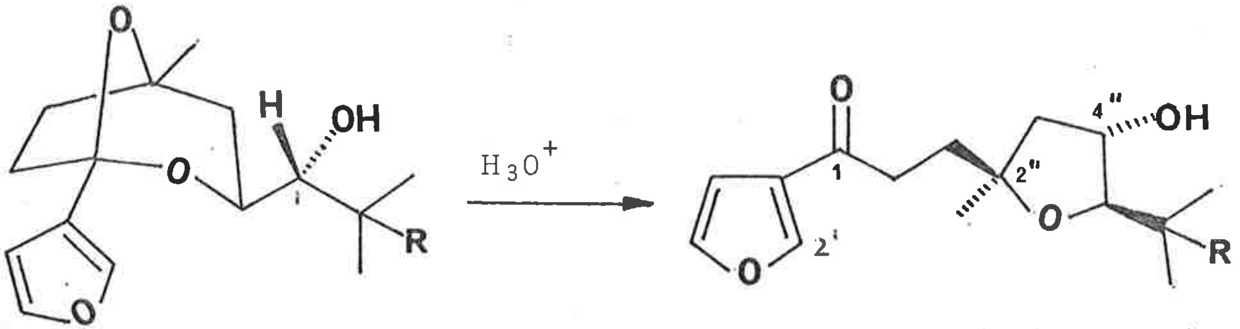
When diol (87) was treated with sodium periodate at pH > 7, no products were formed; the reaction therefore requiring acid catalysis.[75]

(e) When diol (86a), the major isomer from treatment of eremoacetal with osmium tetroxide and reductive hydrolysis (see Chapter 3.1), was warmed in aqueous methanol (1:1) containing 5% oxalic acid a single product was formed. Similarly, the epimeric diol (86b) gave an isomer, as a single product, when it was treated in the same manner. The structures of these two products, proposed as (88) and (89) respectively, were based on their ^{1}H and ^{13}C n.m.r. spectral data, infrared spectra, chemical transformations, use of Eu(fod)$_3$ shift reagent (in the ^{1}H spectra) and finally the determination of configuration at C4" in both isomers (88) and (89).

The structures shown for (88) and (89) were based on the following considerations.

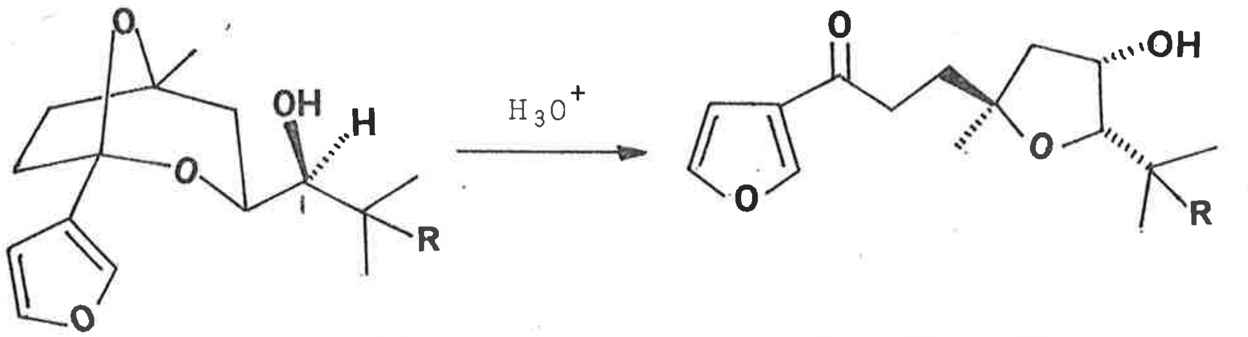
Upon examination, the infrared spectra of the two isomers showed strong absorptions at 3500 and 1680 cm^{-1} due to hydroxyl and conjugated carbonyl groups respectively. These data confirmed that ring opening had occurred.

The ^{1}H n.m.r. spectrum of each isomer showed two D_2O exchangeable protons and two protons on neighbouring carbons each bearing an oxygen function. The latter two protons were coupled, one appearing as a doublet, the other as a multiplet.



R = OH (86a)
R = H (90a)

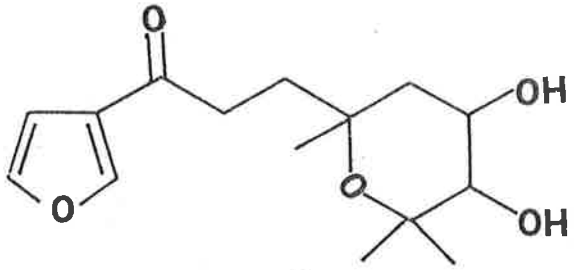
R = OH (88)
R = H (91)



R = OH (86b)
R = H (90b)

R = OH (89)
R = H (92)

Both isomers (88) and (89) formed monoacetates, each still retaining an hydroxyl absorption in the infrared spectra. The ^{1}H n.m.r. of the acetates showed the expected downfield shift for the one proton multiplet in each case. Neither (88) nor (89) gave any reaction products with periodic acid which excluded the possibility that they were vicinal diols.[75] All the facts mentioned support the structures (88) and (89) and exclude the alternative isomeric pyrans, like (93a) which would be expected to form diacetates and to react with periodic acid.



(93a)

The ^{13}C n.m.r. spectrum of each isomer (88) and (89) confirmed that each was pure and the spectra obtained (see appendix) were fully in accord with the proposed structures. The homogeneity of (88) and (89) was also evident from the t.l.c. examination and their sharp melting points. The reactions leading to the tetrahydrofurans (88) and (89) were concluded to be highly stereospecific as no other isomers were detected. Excessive heating of diols (86a) or (86b) in aqueous oxalic acid only lead to hydrolysis of the furan ring and lower yields of (88) and (89).

Information about the relative stereochemistry at C4'' and C5'' was obtained by acetonide formation. When the diols (88) and (89) were treated with acetone and 2,2-dimethoxypropane with a trace of acid only one isomer, (89), rapidly formed an acetonide. Under more forcing conditions (reflux for 24 h), isomer (88) could still not be induced to form an acetonide. These results were rationalised after an inspection of Dreiding models which indicated that the *trans* relationship of the two groups at C4'' and C5'' in (88) gave rise to the more remote hydroxyl groups and consequent inability to form an acetonide. However, the *cis* isomer, assigned to (89), from an inspection of Dreiding models would be expected to readily form an acetonide.

The assignment of relative configuration to (88) and (89) was supported by a closer examination of the ^{1}H n.m.r. spectra. The doublet for H5'' in both isomers showed a small coupling constant (5.0 and 2.6 Hz respectively) from coupling to H4'' consistent with *trans* and *cis* stereochemistry. These coupling constants are in agreement with similarly substituted dihydrobenzofurans.[76] However, assignments based on coupling constants alone can be ambiguous[76] and complex to analyse in such substituted tetrahydrofurans. A comparison of the ^{13}C n.m.r. spectra of the *cis* (89) and *trans* (88) isomers, showed that C4'' resonated at lower field in the former due to a proximity effect (hydrogen bonding) of the two hydroxyl substituents.

The determination of absolute configuration (by Horeau's method) at C4'' in (88) and (89), showed that only the *cis* isomer (89) gave a significant optical yield (20%). The configuration assigned was *S* for C4'' in (89) (see chapter 8.4), confirming that this centre has *not* been inverted. It is reasonable to assume that the more severe steric interactions occurring in the *cis* isomer lead to a higher optical yield during esterification in Horeau's procedure. This steric interaction is reduced in the *trans* isomer (88) to a point where kinetic resolution, arising from the steric interaction with the C5'' substituent, is negligible resulting in a low optical yield. However, as the pathway leading to (88) and (89) is expected to be the same, the configuration at C2'' and C4'' is assumed to be the same. Therefore, the stereochemistry for the cis isomer (89) at both C4'' and C5'' is *S* and *R* respectively. It follows that the stereochemistry at both C4" and C5" for the trans isomer (88) is *S*.

As a final confirmation of relative stereochemistry, a lanthanide shift reagent (l.s.r.) was used with (88) and (89). The europium complex, Eu(fod)$_3$, is known to complex to hydroxyl groups and other electron rich centres, resulting in deshielding of neighbouring protons in the ^{1}H n.m.r. spectrum.[77,78] The magnitude of the deshielding is related to proton-europium distance (r) as well as the angle subtended (ϕ) between the major magnetic axis of the complex and the proton-europium vector. When a linear relationship exists between the induced shift ($\Delta\delta$) and relative concentration of the reagent l.s.r. , then the slope of the plot, $\Delta\delta$ *vs* $[\text{l.s.r.}]/[\text{substrate}]$ is given by the McConnell-Robertson equation.[78d]

$$\Delta\delta = \frac{K\,(3\cos^2\phi - 1)}{r^3}$$

The results of such plots for (88) and (89) are shown in Fig. 2.11 and 2.12. A linear relationship between the induced shifts (δ) and the mole ratio of shift reagent to substrate is evident. The induced chemical shift is largely dependent on the metal-proton distance (r) in the complex.

An examination of Fig. 2.11 shows that in the *cis* isomer (89), H4" is the more rapidly deshielded multiplet in comparison to H5" (doublet). This isomer also showed a one proton doublet (J ± 13Hz), assigned to αH3", as a rapidly deshielded feature in the spectrum after incremental addition of shift reagent. This feature was not observed in the *trans* isomer (88) (Fig. 2.12) where the 4" and 5" substituents

Figure 2.11

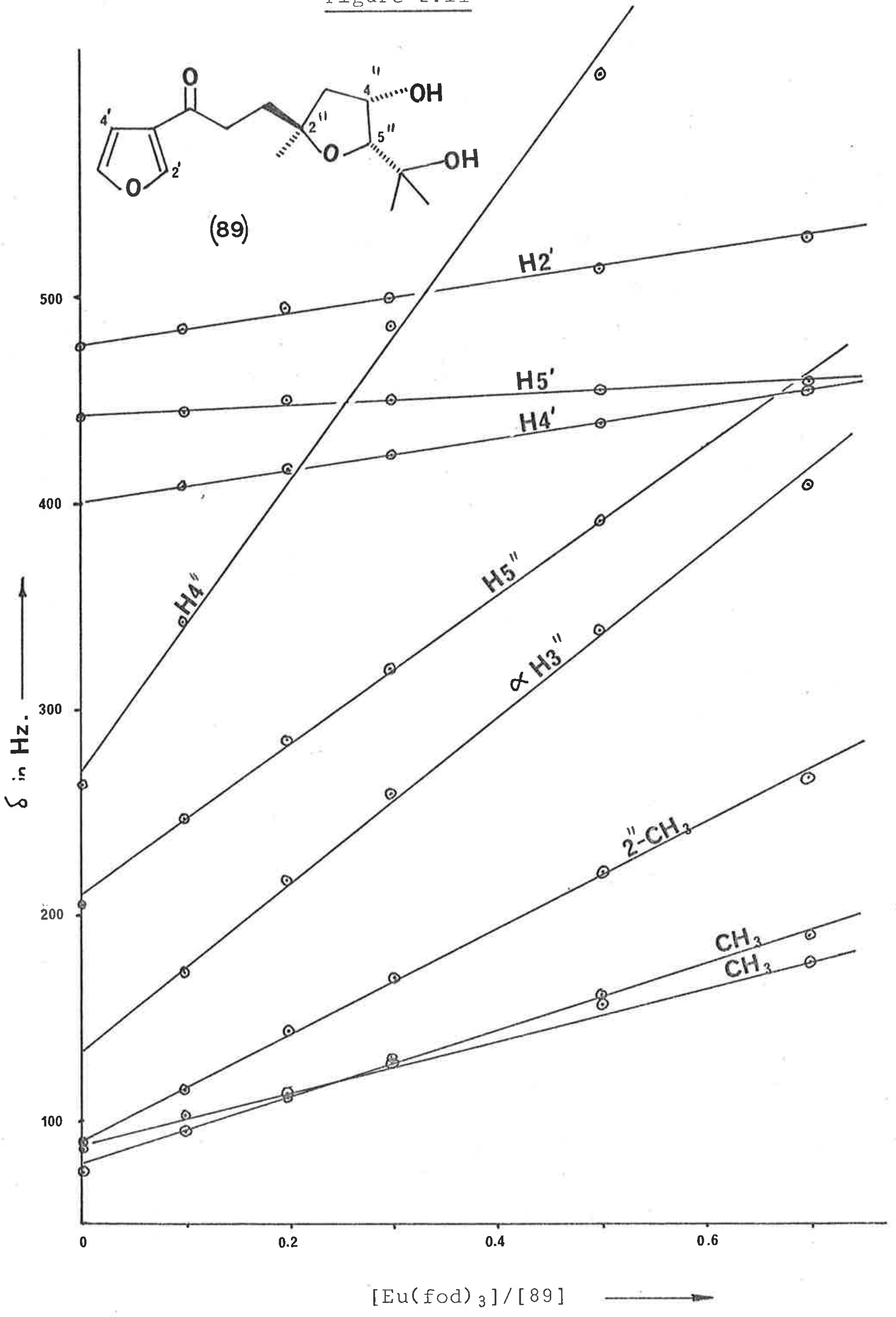
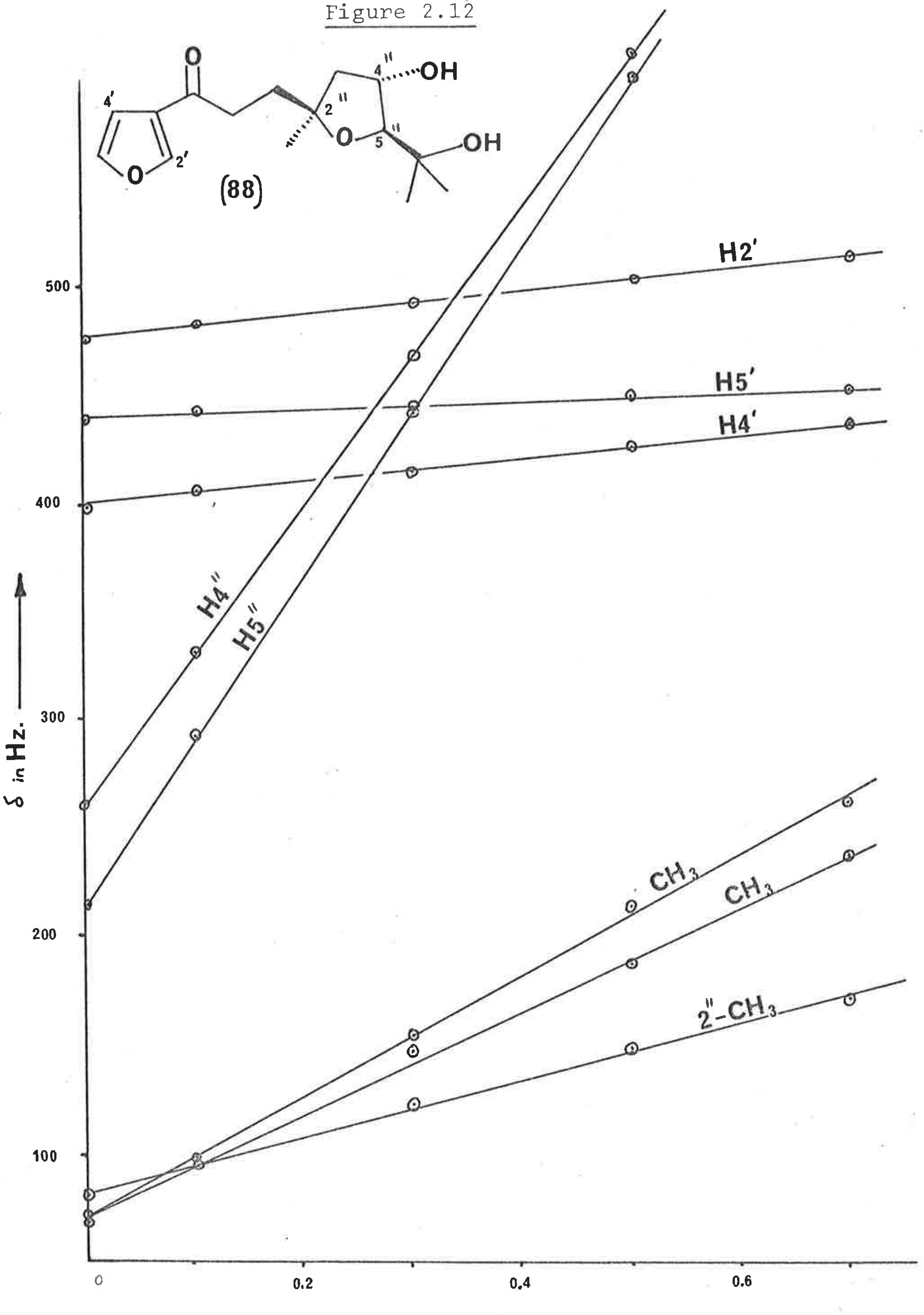

O
4'
2'
O
2''
4''
5''
OH
O
OH
(89)
H2'
H5'
H4'
H4''
H5''
α H3''
2''-CH3
CH3
CH3
500
400
300
200
100
δ in Hz.
0
0.2
0.4
0.6
[Eu(fod)3]/[89]

Figure 2.12

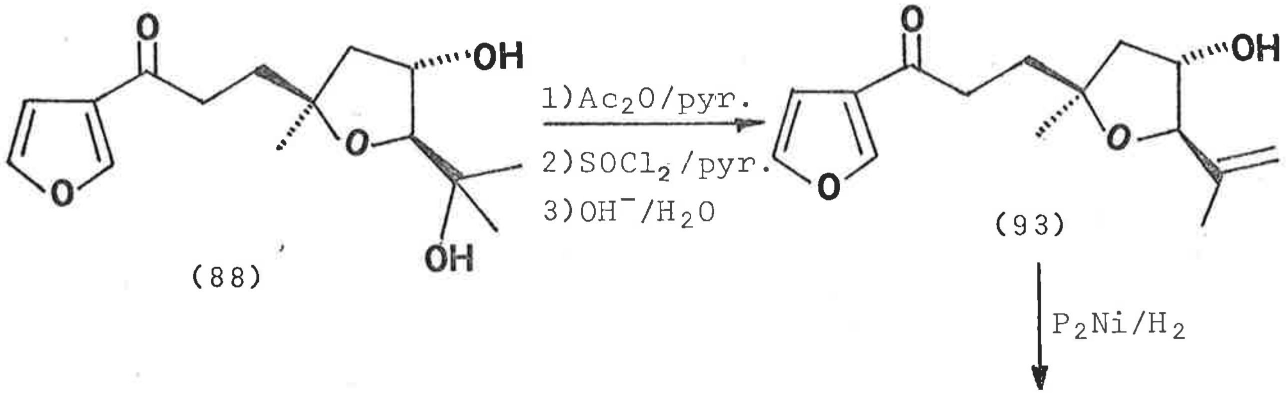


[Eu(fod)$_3$]/[88]

lead to the complexation of Europium more or less in the same plane as the tetrahydrofuran ring and therefore more remote from both of the H3$''$ protons. By comparison, the *cis* isomer forms a complex where the europium lies between the two hydroxyl groups and below the plane of the tetrahydrofuran ring. The *cis* isomer, (89) also showed a three proton singlet, assigned to 2$''$-CH$_3$, which was deshielded more rapidly than the corresponding singlet in the *trans* isomer (88). This result supports the *S* stereochemistry at C2$''$ in (89) in which the two polar groups and europium are *cis* to the 2$''$-CH$_3$. In the *trans* isomer, (88) the 2$''$-CH$_3$ is more remote from the europium and the two methyl groups, near C5$''$ undergo the more rapid deshielding. Although the stereochemistry at C2$''$ was not rigorously established, the mechanism postulated leading to (88) and (89) was expected to result in inversion at C2$''$. The data otherwise is clearly only consistent with structures of the type (88) and (89).

Two other alcohol isomers (90a) and (90b) were also examined as they were expected to behave similarly on acid hydrolysis. When alcohols (90a) and (90b) were treated separately with aqueous acidic methanol, the two keto alcohols (91) and (92) respectively, were formed. Application of Horeau's method to each of these alcohols again gave the configuration at C4$''$ only in the *cis* isomer (92). An optical yield of only 12% was obtained with (92) but the recovery of the (−)-*R*-2-phenylbutanoic acid confirmed that the *S* stereochemistry at C4$''$ had been retained. As with (88), the *trans* isomer (91) gave no detectable kinetic resolution but the configuration at $C4''$ is also assumed to be *S* as both would be expected to arise *via* the same pathway.

Further confirmation of stereochemistry was obtained by converting (88) to (91) by the following sequence of reactions.



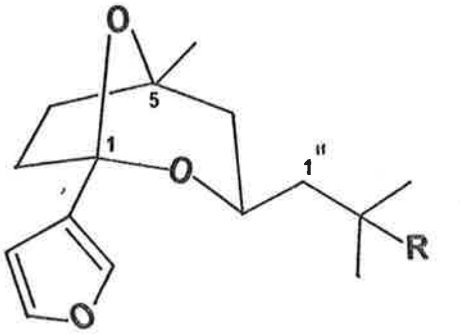
(88)

(93)

(91)

Protection of the secondary hydroxyl group as the acetate, followed by dehydration and deprotection, gave the hydroxy alkene (93) as the minor product. The enol ether also formed but decomposed during purification on silica gel to a complex mixture which was not investigated. Hydrogenation of (93) using P_2-Ni in ethanol/acetone (9:1) for 7 h gave (91), identical by m.m.p., t.l.c., n.m.r. and i.r. with the authentic sample. No other products were formed in the hydrogenation which demonstrated the synthetic utility of P_2-Ni in the reduction of alkenes in the presence of the reducible furan ring. No hydrogenolysis was observed. By this chemical interconversion of (88) to (91) the parent acetal alcohols (86a) and (90a), formed from different reactions were shown to have the same stereochemistry at C1′, *S* and *R* respectively. This was an important result as assignment of stereochemistry by the application of Horeau's method to (86a), (86b), (90a) and (90b), gave ambiguous results (see Chapter 8).

The facile formation of the tetrahydrofurans (88), (89) (91) and (92) from the corresponding bicyclic acetal alcohols is in marked contrast with the stability of dihydroeremoacetal (94), alcohol (95) and ether (96) in dilute aqueous acid. It is evident that the difference in reactivity lies in the

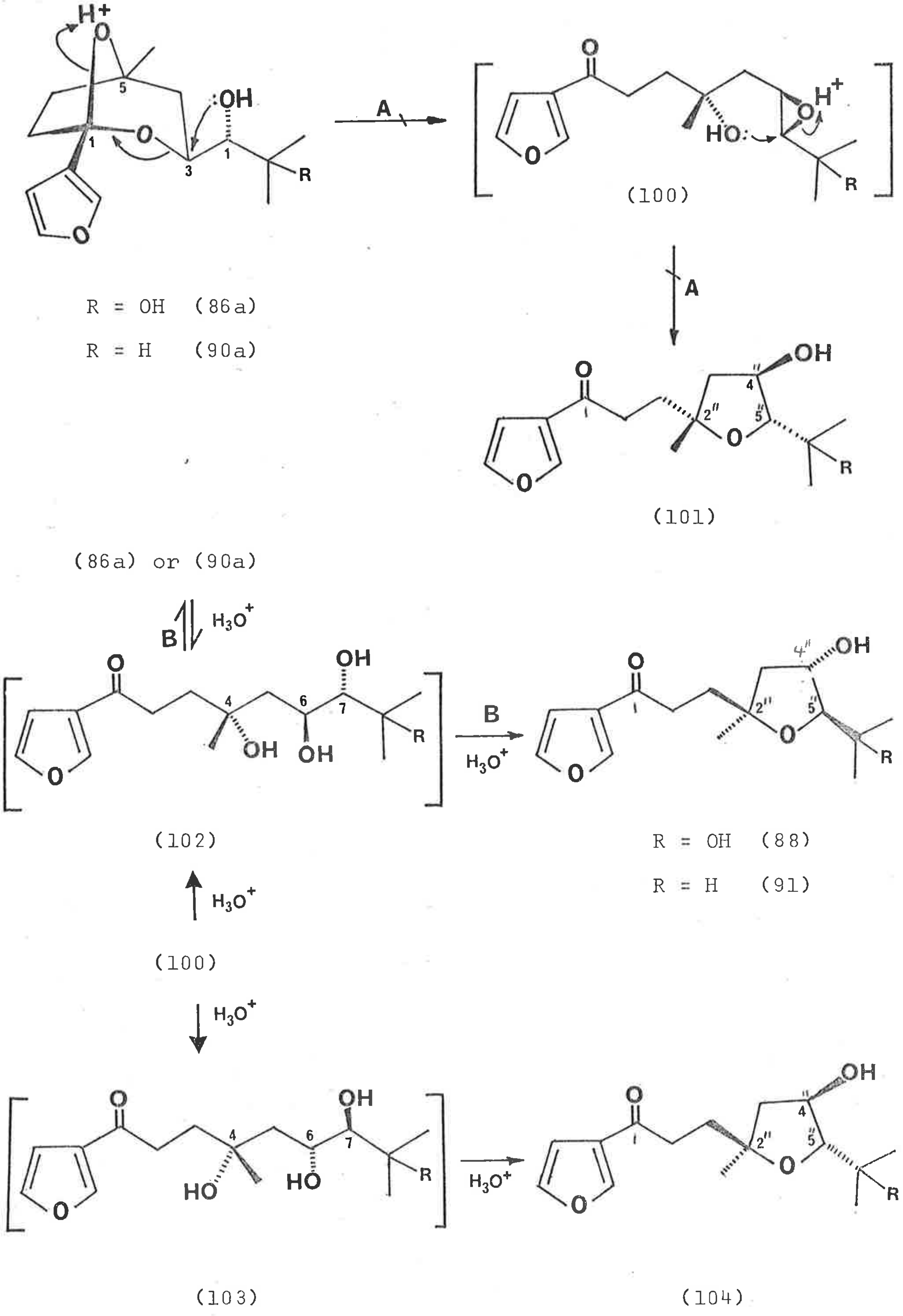


R = H (94)
R = OH (95)
R = OCH_3 (96)

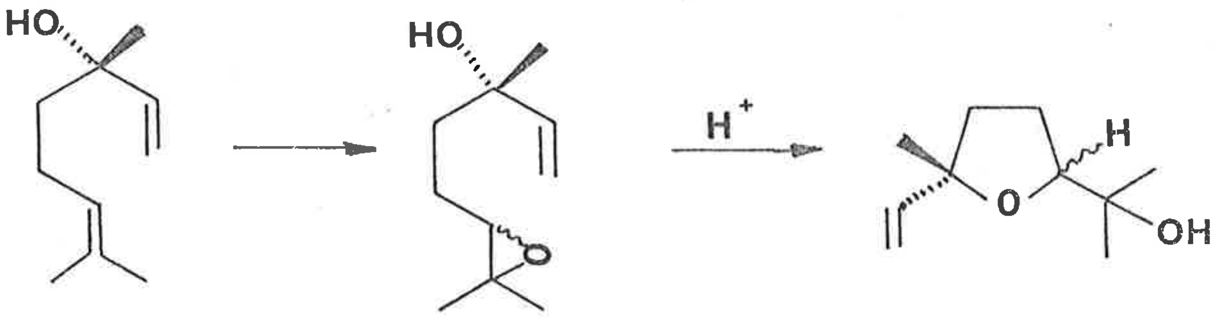
presence of the hydroxyl group at C1". A number of pathways leading to the tetrahydrofurans (88), (89), (91) and (92) can therefore be postulated (scheme 2.12).

Route 'A' involves a concerted acid catalysed opening of the acetal function (described by Baldwin[79] as a favoured '3-exo-tet/trig' process) in (86) and (90) with inversion at C3 to give a hydroxy-epoxide. However, the formation of an epoxide, under conditions in which epoxides are known to be unstable e.g. aqueous acidic conditions, seems unlikely. The formation of oxirane (100) from the relatively stable bicyclic system might be thermodynamically unlikely. If the epoxide was the intermediate formed, according to Baldwin's rules[79] the required '5-endo-trig/tet' ring closure, leading to the tetrahydrofurans, would be a disfavoured process. Alternatively, the epoxide (100) might undergo hydrolysis to the acyclic polyol intermediate before cyclisation, but this would result

Scheme 2.12


H+
A
H+
(100)
A
R = OH (86a)
R = H (90a)
(101)
(86a) or (90a)
B
H_3O^+
(102)
B
H_3O^+
R = OH (88)
R = H (91)
H_3O^+
(100)
H_3O^+
H_3O^+
(103)
(104)

in inversion at C6 or C7 to give (102) or (103). The acyclic alcohols (102) and/or (103) could cyclise to give (88), (91) and/or (104) as shown in scheme 2.12. However, a stereoselective hydrolysis by attack at C6 of the epoxide (100) to form (102) cannot be discounted yet. Pathway ('A'), results in inversion at C4'' and C5'' of (101) which is in conflict with the *S* stereochemistry obtained at C4''. In view of the above considerations based on the thermodynamic and stereochemical grounds as well as application of Baldwin's rules,[79] pathway 'A' was rejected from the possible routes. However, facile cyclisations[80] of epoxy alcohols, of a similar nature, like (98) derived from linalool (97) proceed by the allowed '5-exo-trig/tet' process.

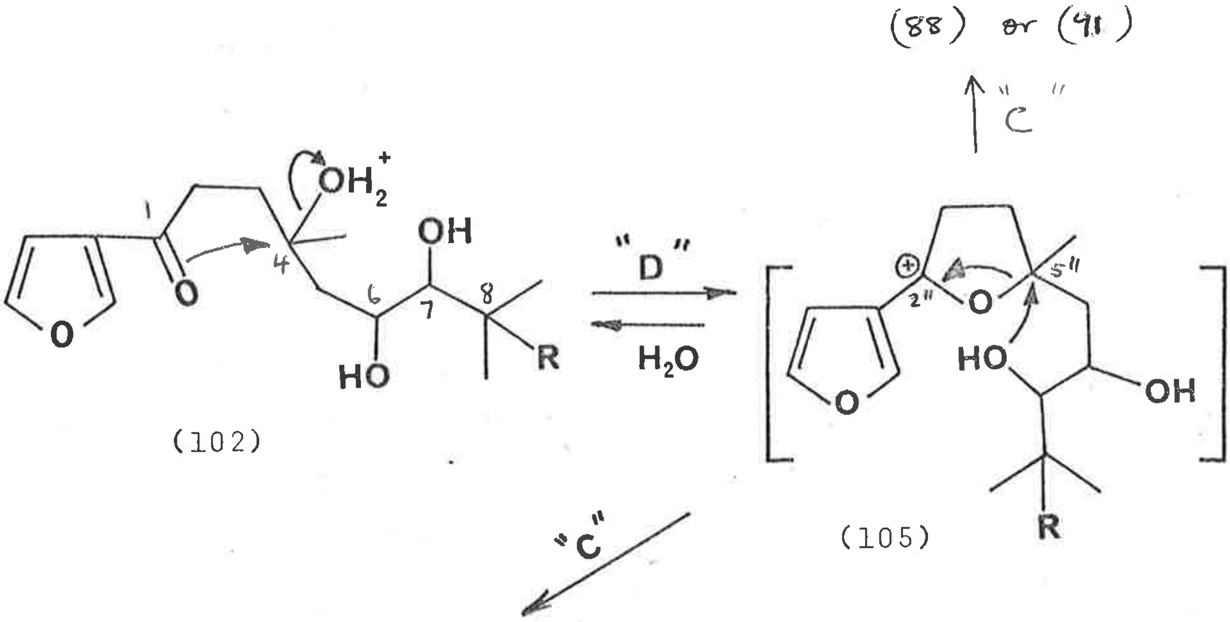


(97) (98) (99)

Epoxy alcohol (98) is difficult to isolate and rapidly cyclises to the tetrahydrofuran alcohols (99) with small quantities of the tetrahydropyran also being formed.

In pathway 'B' the keto tetraol (102), formed by hydrolysis of the acetals, could undergo an intramolecular cyclisation involving the hydroxyl groups at C4 and C7. Protonation of the tertiary hydroxyl at C4 followed by an intramolecular substitution by the C7-hydroxyl group would form (88) or (89), with resultant inversion at C4 in (102). Other mechanisms involving a carbonium ion at C4 of (102) are unlikely because no epimers or olefins were detected among the products.

Alternatively, intramolecular attack at C4 as shown in path 'D' by the carbonyl oxygen would produce a stabilised intermediate species (105) which can give (88) or (91). This pathway would however, result in a double inversion at C4 in (102) resulting in retention of stereochemistry at C2'' in (88) or (91). The reactive intermediate (105) if formed might form a hemiacetal which could lead to keto alcohols (102) except with inversion at C4. Consequently, pathway 'D' may give some or complete epimerisation at the tertiary centre if the rate of hemiacetal formation was as fast or faster than the rate of intramolecular cyclisation. No epimeric mixtures were detected among the products of these hydrolyses.



(102)

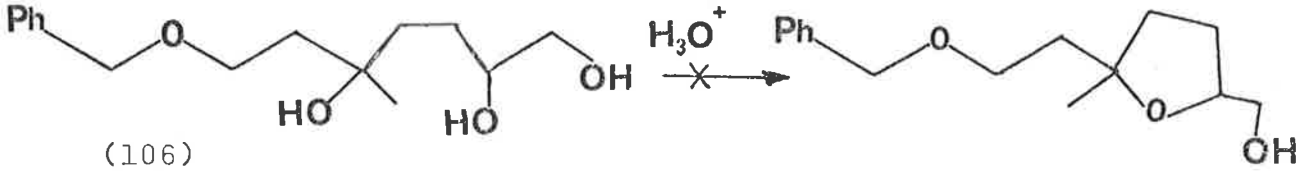
(105)

R = OH (86a)

R = H (90a)

Pathway 'C' involves the formation of a reactive intermediate like (105), by simple heterolysis of the C1-20 bond in (86a) or (90a), but without inversion at C5. Intramolecular cyclisation of (105) with inversion at C5'' would give the tetrahydrofurans (88) and (91) with inversion of stereochemistry at C2'' (i.e. *S*) and retention at C4'' and C5''. The stereochemical outcome of path 'C' is completely compatible with the stereochemistry of the products obtained. As previously discussed, the configurations at C4'' and C5'' in the tetrahydrofurans (89) and (92) show that these centres have <u>not</u> been inverted and the homogeneity of the products excludes epimerisation.

In summary, the outcome of the pathways discussed only leads to the isomers (88) and (91) in the case of pathways 'B' and 'C'. An analogy for pathway 'B' was found in the attempted cyclisation of triol (106), in hot dilute oxalic

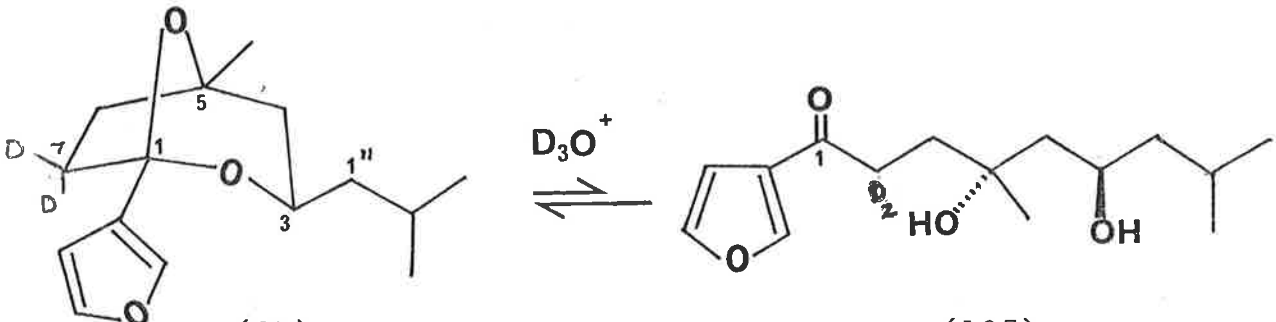


(106)

acid under the same conditions as used for (86) and (90). No cyclisation occurred showing that triols of the type (106) require more forcing conditions to cyclise.[73] The carbonyl group therefore appears to be important in the mechanism. As a result of this, the acyclic alcohols of the type (102) are unlikely intermediates leading directly to the tetrahydrofurans obtained.

From the above observations it can be concluded that the most likely pathway leading to the tetrahydrofurans (88), (89), (91) and (92) is 'C'.

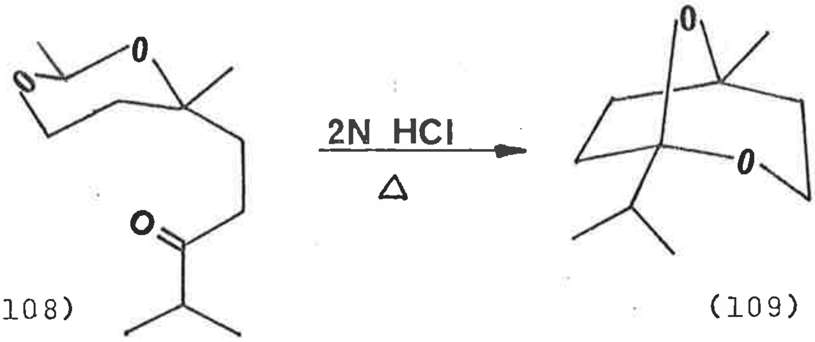
Although the acetals not having hydroxyls at the C1" carbon, (94) to (96), were resistant to tetrahydrofuran formation it could be shown with (94) that an equilibrium existed between the acyclic form (107) and the more stable dioxabicyclooctane (94) using DCl/D_2O in $CDCl_3$. After some days at 35° the two protons at C7 were exchanged *via* ketone (107)



(94) (107)

as seen in the ^1H n.m.r. spectrum of (94). This exchange was evident as a simplification in the region around δ2.4 and also by integration of this region. The equilibrium in this example is clearly in favour of the bicyclic form (94) which is the only species indicated in the n.m.r. spectrum. These results are consistent with observations obtained in some closely related dioxabicyclo[3.2.1]octanes. For example, Cornforth[81] has shown that the monocyclic acetal (108) readily forms the more stable bicyclic system (109) upon treatment with 2N hydrochloric acid at reflux.

In conclusion it appears that under acidic conditions and in the absence of competing irreversible reactions (e.g. tetrahydrofuran formation, dehydration, oxime formation), 2,8 dioxa



(108) (109)

bicyclo [3.2.1] octanes are resistant to ring opening.

2.2 Hydrolysis in Aqueous Pyridine

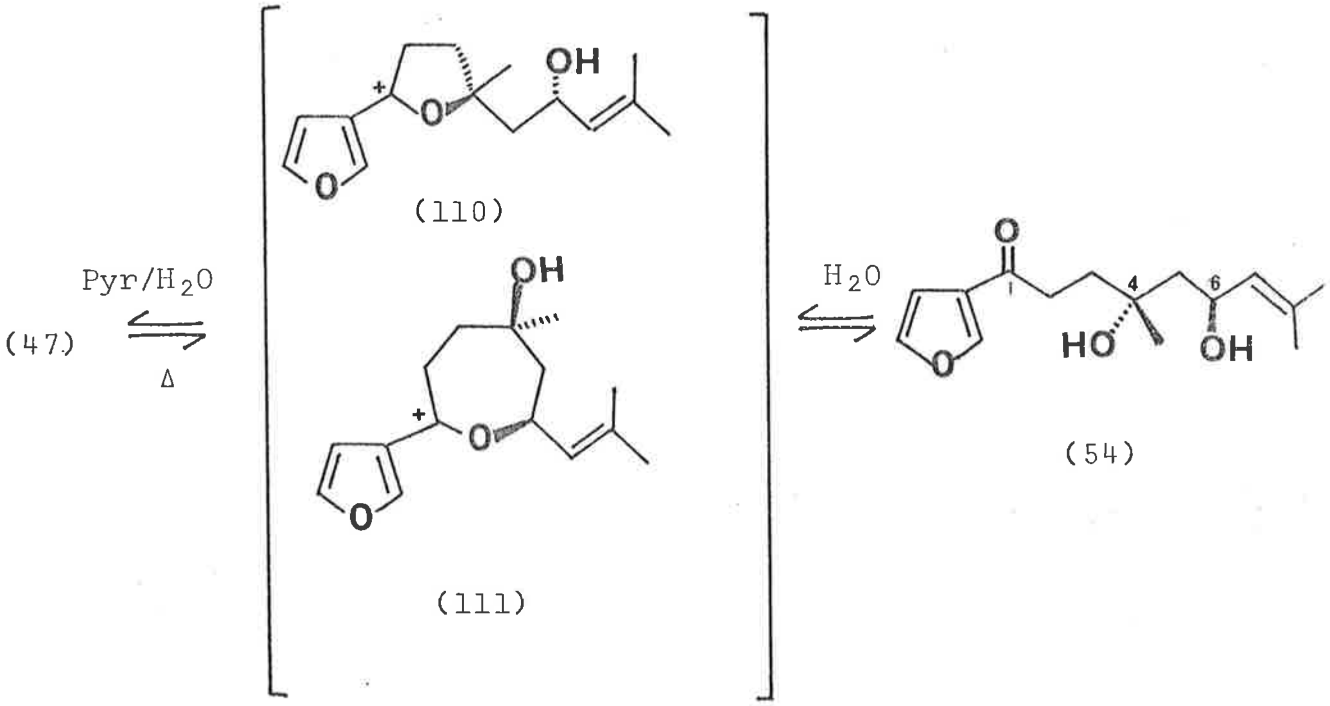
Although ring opening of eremoacetal (47) to diol (54) was unsatisfactory under acidic conditions, it was possible to obtain the diol under alkaline conditions.

When eremoacetal was heated with pyridine and water (2:1) for 3-4 days, an equilibrium mixture of eremoacetal and diol (54) was formed in a ratio of approximately 2:1. However, the use of dioxane/water or diglyme/water containing a trace of pyridine (i.e. almost neutral conditions) gave little ring opening.

This slow equilibration was observed when the acetal was heated in an n.m.r. tube with d^5-pyridine and D_2O. The characteristic H2' and H4' protons on the furan ring in ketone (54) became more intense with time and could be readily integrated. Because the forward and reverse reactions are slow at room temperature it is possible to isolate the ketone (54). Extraction of the cooled equilibrium mixture with hexane removed most of the less polar eremoacetal from the aqueous mixture which was extracted with chloroform.

Removal of the chloroform and pyridine under vacuum at room temperature allowed the isolation of the unstable ketone (54). When the keto-diol (54) was heated in D_2O/d^5-pyridine the appearance of the eremoacetal resonances was seen in the ^1H n.m.r. spectrum with increasing time, the mixture of the ketone (54) and the formed eremoacetal (47) reached the same equilibrium ratio of approximately (1:2). The ketone (54) however was unstable to traces of acid and rapidly underwent cyclisation to (47).

This solvolysis is envisaged to proceed at elevated temperatures by cleavage of either C1-20, or C1-80 bonds of eremoacetal to produce the stabilised cationic species (110) or (111). Solvation of the cations leads to the hemiacetals which undergo further ring opening to the ketone (54).



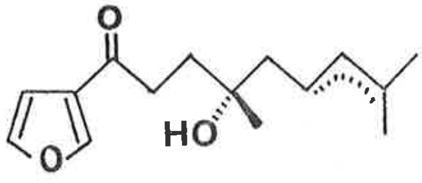
Therefore it is possible to obtain the keto diol (54) by solvolysis of (47) in aqueous pyridine without epimerisation at C4 or C6 and without the formation of rearrangement products. The conditions are in marked contrast to the usual acidic conditions used for the hydrolysis of acetals, which with eremoacetal leads to other products.

2.3 Birch Reduction

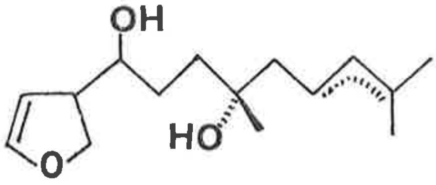
It is well established that allylic and benzylic ethers undergo reductive fission in the metal/ammonia solutions used in the Birch reduction. An examination of eremoacetal shows it has both allylic and benzylic type ethers. In order to get further confirmation of structure and produce alcohols suitable for configurational examination, eremoacetal (47) was reduced using various metals in liquid ammonia.

The metals lithium, sodium and calcium in ammonia at -33° containing a proton source (ethanol) gave complex mixtures of polar products when used to reduce eremoacetal.[82]
An examination of the ^{1}H n.m.r. spectrum of the crude products showed no furan protons and the infrared spectrum showed a strong hydroxyl absorption.

Similarly, reduction with lithium in ammonia without a proton source for 15 min gave a mixture. The n.m.r. spectrum of the crude reaction products showed no furan protons. However, preparative t.l.c. gave the furyl ketones (112) (15%) and apparently the dihydrofurans (113) (35%), both characterised by their n.m.r. spectra.[82]



(112)

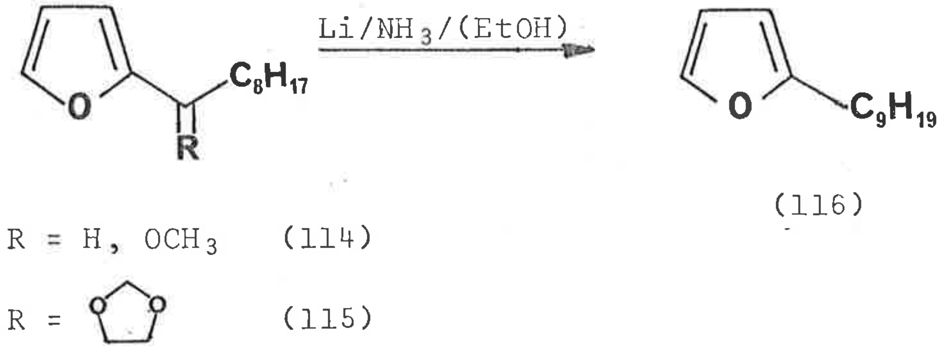


(113)

The other products were not identified but contained no furan protons by n.m.r. examination.

Because of the complexity of the products a study of various substituted furans was initiated and is still in progress. This work[83] shows some interesting variations in reduction rates and products therefore meriting a brief discussion here. All reductions were done using lithium in ammonia at -33° for 15 min before quenching with ammonium chloride.

Reductions of the ether (114) and acetal (115) both with and without a proton source, gave the 2-alkyl furan (116).



(114)

(115)

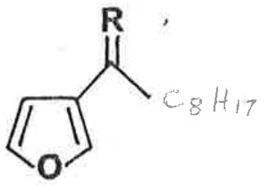
(116)

However, the 3-substituted furans behaved differently on reduction.

The methyl ether (117) on reduction in the absence of ethanol gave the 3-alkyl furan (119) (12%) and starting material after 15 min. In the presence of ethanol the reduction of (117) gave a higher yield of alkyl furan.

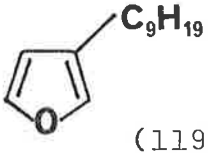
When the acetal (118) was reduced in the absence of a proton source the products consisted of starting material (18%), alkyl furan (119) (23%) and the partly reduced hydroxy ether (120) (59%). However, in the presence of a proton source, the product contained (119) (11%), the alkyl tetrahydrofuran (121) (62%), the keto tetrahydrofuran (122) (11%) and small amounts of the dihydrofurans.

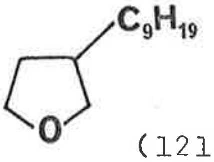
It is interesting to note the differences between the rate and products of reduction in the 2-substituted furan derivatives and the 3-substituted furan derivatives. The acetals and ethers of 2-substituted furans are readily hydrogenolysed without reduction of the aromatic ring whereas the acetals but not ethers of the 3-substituted furans give extensive ring reduction in the presence of a proton source. This work is still under investigation.[83]

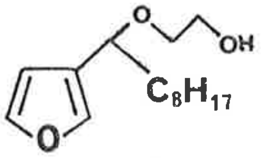


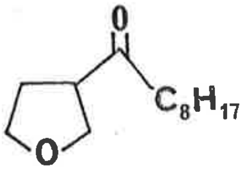
R = H, OCH_3 (117)

R =  (118)


(119)

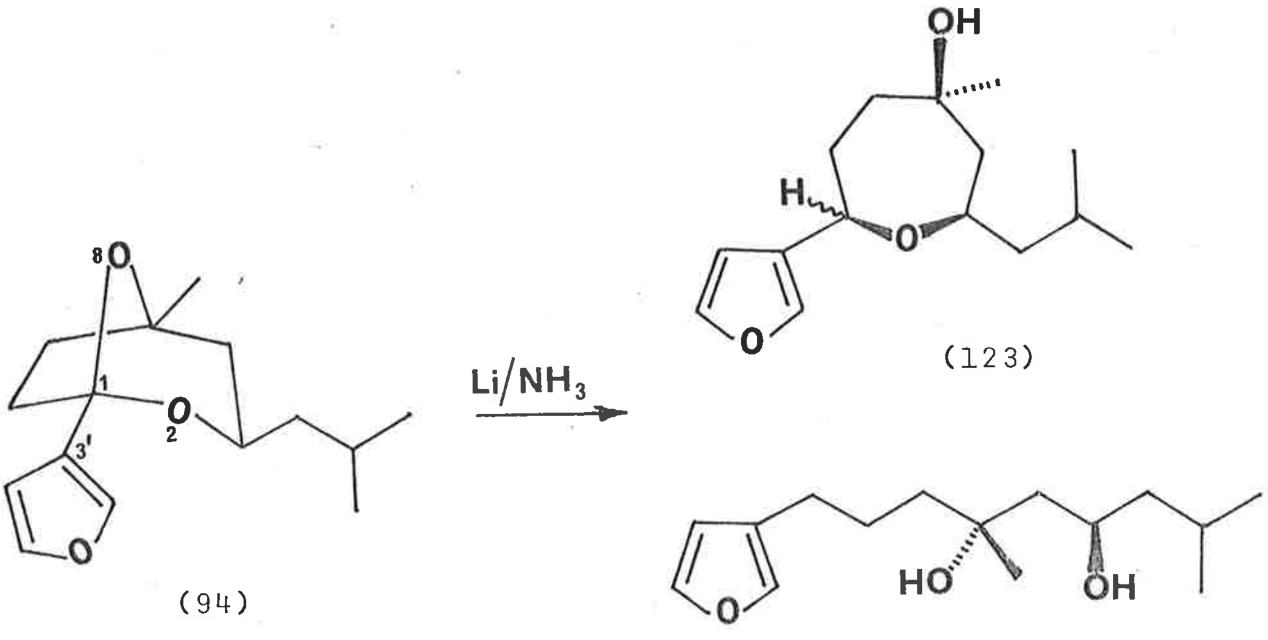

(121)


(120)


(122)

The reductive removal of the thioacetal function from a 3-substituted furan derivative has been reported by Hoppmann and Weyerstahl[84] to give the 3-alkyl furan in moderate yield (63%). No proton source was used in the above reduction and no other products were reported by the authors. In another recent report,[85] an ether derivative of 9-hydroxydendrolasin was reduced to dendrolasin in good yield.

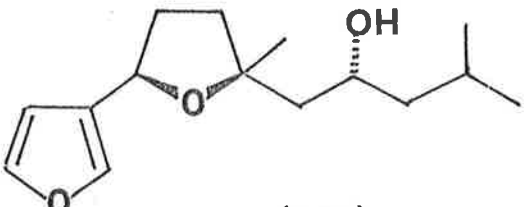
As some of the complexity in the products was due to the allylic ether in eremoacetal it was decided to explore the saturated analogue. In the eremoacetal series, the dihydroacetal (94), when reduced with a proton source, again gave products in which the furan ring had been reduced. In the absence of a proton source, however, reduction of the acetal function was very slow. Starting material (30%) was recovered (even after reduction for 7 h) in addition to oxepanes (123) (20%) and diol (124) (40%). None of the tetrahydrofuran isomers (135) was detected in the reduction products.



(94)

(123)

(124)

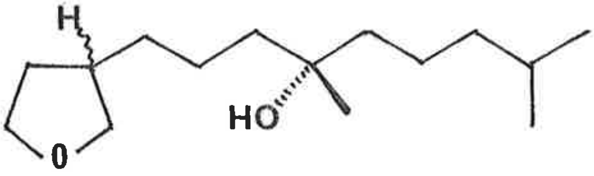


(135)

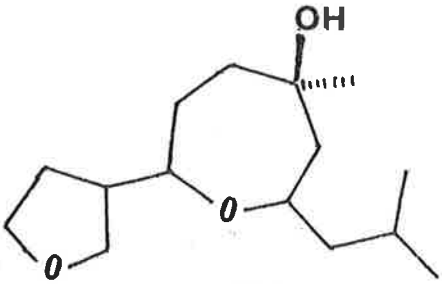
The reasons for the differences in reduction rates between acetal (118) and the bicyclic acetal (94) are not clear. The rates may reflect differences in strain energy in the two compounds, or differences in orbital overlap of the developing radical (or anion) at C3' with the breaking carbon oxygen bond. Other differences may be due to the restricted stabilisation of the radical (or anion) at C3' by p orbital overlap with the oxygen atoms in (94) leading to slower reduction rates. An examination of Dreiding models did not provide an insight into orbital overlap and explain the results obtained.

Because the tetrahydrofuran (135) (or its epimer) was not observed as a reduction product, it was not clear whether the reduction of (135), if formed, occurred rapidly relative to (123), or that preferential cleavage of the C1-80 bond had occurred. To establish the relative rates of reduction between the oxepane isomer (123a) and the tetrahydrofuran (135), a reduction was carried out for 1 h on a mixture (1:1) of the two isomers. Isolation of the reduction products showed that only a trace of the tetrahydrofuran (135) remained, whereas 90% of the oxepane (123a) was recovered in addition to diol (124) (50%). Clearly, the tetrahydrofuran (135) has been reduced to the diol (124) while the oxepane was much more slowly reduced. Therefore, if the tetrahydrofuran was formed in the original reduction of (94), it would have been rapidly reduced to the diol (124). However, it is difficult to rationalise the differences in reduction rates of the various cyclic ethers and the acyclic methyl ether (117) in 3-substituted furans. It is likely that the reduction rates may be affected by the proton source present at the hydroxyl groups in (135) and (123a).

Reduction of (94) in n-propylamine with lithium at ambient temperatures gave products containing no furan protons. A similar reaction at 0° for 15 min also gave mostly furan reduction products with approximately 20% of diol (124), by n.m.r. examination of the crude products. Perhaps when a large excess of metal was present, the addition of ammonium chloride to destroy it may allow some reduction to proceed in the presence of this proton source before all the metal is destroyed.[86] The tetrahydrofurans (125), and (126) characterised by n.m.r. and mass spectra, were the products from reduction of (94) in the presence of ethanol as a proton source or possibly arising from the use of ammonium chloride. during quenching. Higher temperatures also increase the rate of furan reduction, as shown above using propylamine as solvent. Reductions using propylamine were not explored further and subsequently, the excess of metal was removed by the addition of isoprene before ammonium chloride was added.

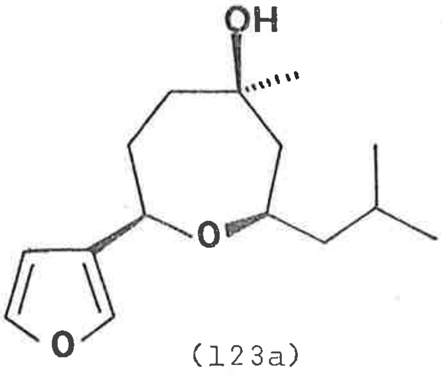


(125)

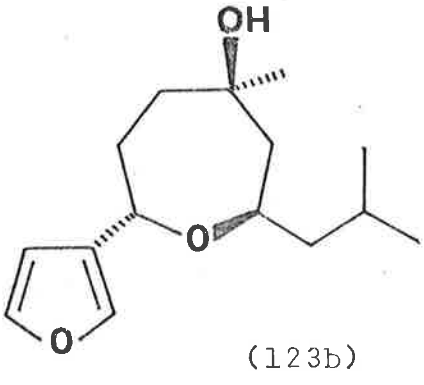


(126)

In a number of large scale reductions of (94), the oxepanes (123a) and (123b) were formed in a ratio of 15 to 20:1 after 7 h reduction. In one, atypical example, the isomeric ratio of oxepanes obtained was 4:1 in a reaction done for 1 h.

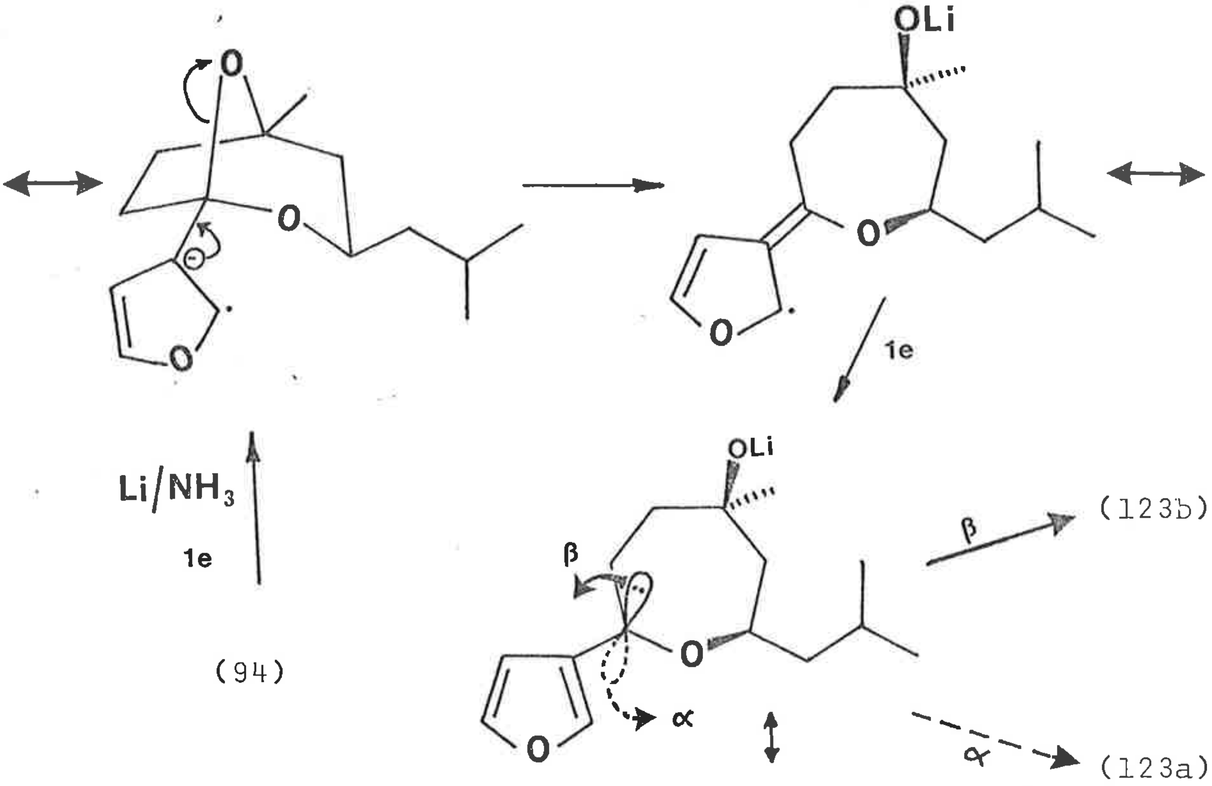


(123a)



(123b)

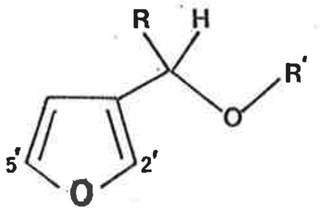
This ratio implies that either one isomer is formed more rapidly by a preferred protonation from one face of the oxepane ring (giving a kinetic product) or, that one of the oxepane isomers, after protonation in the medium, is more rapidly reduced further to the diol (124). The production of a multicharged species may account for the slow reduction and possibly for the selectivity shown for oxepane (123a). The major oxepane isomer, assigned to (123a) arose by protonation at the α face of the resonance stabilised anion.



The structures of the oxepanes (123a) and (123b) followed from their H n.m.r. spectra and some chemical tests.

i) They each showed one proton resonance (multiplet) at δ4.4 and 4.7 which is consistent with a proton on a carbon bearing oxygen and which was also allylic. This resonance was assigned to H7.

ii) The two furan protons, H2' and H5', had almost identical chemical shifts at δ7.35 in both isomers of (123). It has been observed, in several examples of the type (127) bearing one oxygen substituent as shown, that both α-protons resonate at the same chemical shift.



R, R' = alkyl

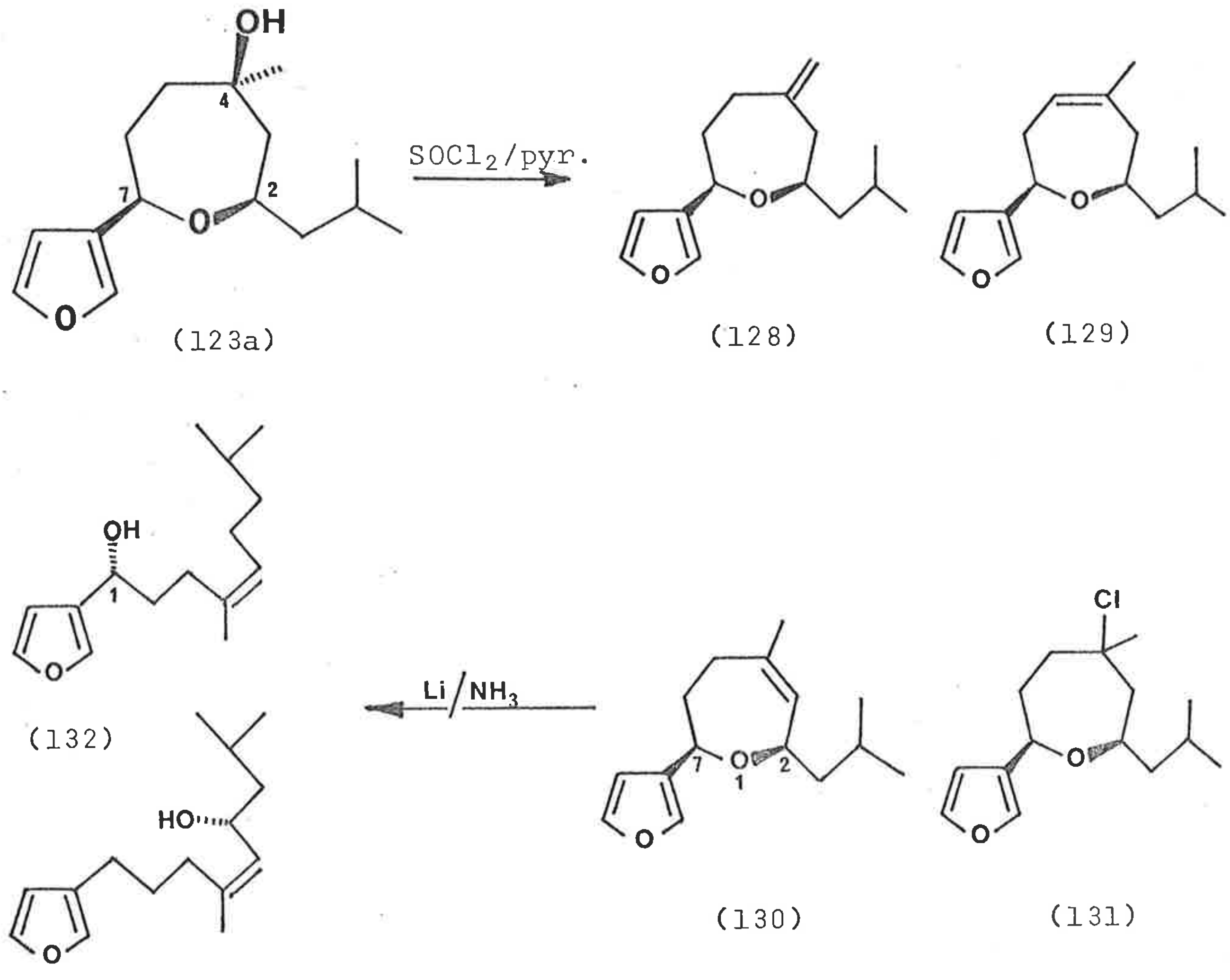
(127)

iii) The hydroxyl groups at C4, which was clearly evident in the infrared spectra of both isomers, was tertiary as neither (123a) nor (123b) readily formed an acetate. However, forcing conditions gave a tertiary acetate which showed a downfield shift of 0.3 ppm for the 4-CH_3 only but not protons resonating at δ4.3 or 4.6 and 3.6 ppm.

iv) Therefore, the other proton on a carbon bearing oxygen, H2, which resonated at δ3.6, must bear an ether oxygen and not a secondary hydroxyl group.

These observations are clearly only compatible with the oxepane structures and not with the known tetrahydrofuran (135) which was prepared unambiguously by another method.

Separation of the oxepane isomers (123a) and (123b) was readily achieved by chromatography as they showed large differences in their R_f. An attempt was made to assign their stereochemistry by determining the absolute configuration at C7. In order to do this the preparation of (132) was undertaken according to scheme 2.31.



Scheme 2.31

The dehydration of the oxepane epimer (123a) was expected to give a mixture of the alkenes (128), (129) and (130). Reduction of (130) with lithium in ammonia would be expected to give predominantly alcohol (132) as earlier reduction work based on oxepane (123a) established that the alternative cleavage (1O-C7 bond) of the oxepane to give (133) would be slow. Alcohol (132) would retain the original stereochemistry at C7 in (123a). The application of Horeau's method to (132) would then provide the configuration at C1 in (130) and therefore C7 in (123a).

When the major oxepane isomer (123a) was dehydrated in pyridine using thionyl chloride, a mixture containing at least four products was obtained. The most polar was characterised as the tertiary chloride (131) (29%). Of the olefinic products, the exocyclic alkene (128) (40%) predominated and was readily distinguished by its n.m.r. spectrum. The two vinylic protons of (128) resonated as a broadened singlet at δ4.5, the four allylic methylene protons at δ2.25, and the two methines, H2 and H7, at δ3.5 and 4.7 respectively. Of the remaining alkene mixture (16%), the alkene (129) predominated, as assessed by the n.m.r. spectrum.

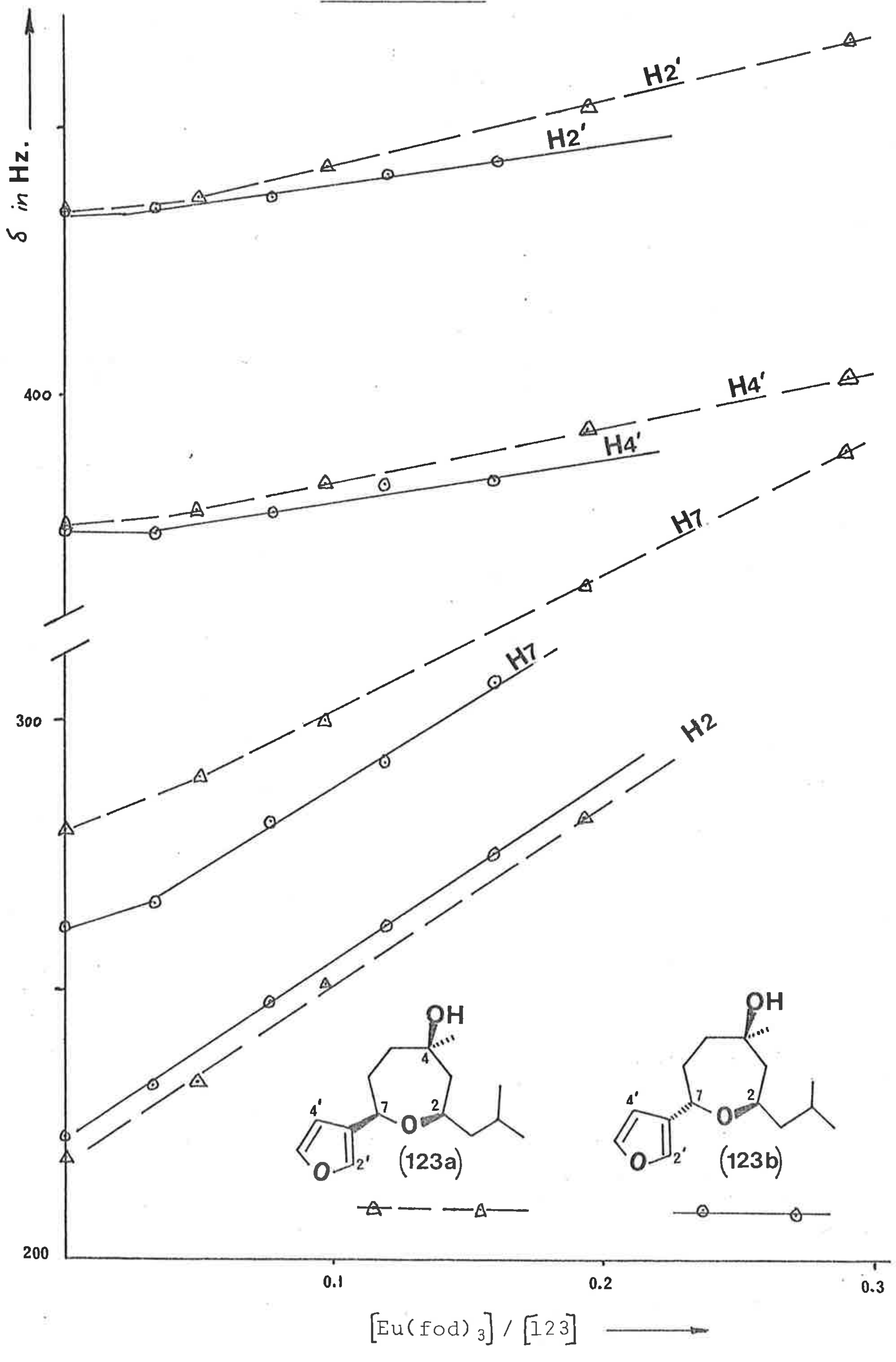
The small amount of isomer (130) present in the products was insufficient to permit isolation, but its presence in the mixture was seen as the allylic methine (H2) resonance at δ 4.8 in the n.m.r. spectrum. Attempts to isomerise the exocyclic methylene of (128) with mild Lewis acids (boron triacetate, silica gel, zinc chloride on silica) were all unsuccessful and accompanied by decomposition. Distillation of (128) from silica (120°/1.5 mm) gave a low recovery of unchanged alkene.

Because the configuration at C2 and C4 in the two oxepanes (123a) and (123b) was not changed as a result of reduction, it was thought that europium shift reagent could profitably be used to determine the relative configuration of C2, 4 and 7. An examination of models showed that for each oxepane isomer the number of stable conformations is limited due to steric interactions across the ring. Also, hydrogen bonding between the C4 hydroxy and the ether oxygen would be expected to add some rigidity to the oxepane ring. It is important to note that because the configurations at C2 and C4 are known, complexation of europium to the hydroxyl and ether oxygen would produce predictable and distinct differences in the rate of deshielding of the H7 protons and furan protons in the two oxepanes (123a) and (123b).

When the lanthanide shift experiment was done on the two oxepanes and the proton shift plotted against the quantity of added Eu(fod)$_3$, clear differences between the two isomers were evident (fig. 2.31).

The minor isomer (123b) showed a faster rate of deshielding for the H7 proton relative to the major isomer, (123a). In contrast, (123a) showed a more rapid rate of deshielding of the furan protons, H2' and H4'. These two results complement one another as in the former case H7 is in closer proximity to the europium than in the latter where the protons of the furan ring at C7 are closer. As expected, the H2 methine was deshielded at the same rate in both isomers and at the same rate as the H7 methine of the major isomer (123a). These results are in agreement with the C7 *R* configuration

Figure 2.31


δ in Hz.
400
300
200
0.1
0.2
0.3
H2'
H2'
H4'
H4'
H7
H7
H2
OH
4
7
2
O
4'
2'
O
(123a)
OH
4'
7
2
O
2'
O
(123b)
[Eu(fod)$_3$] / [123]

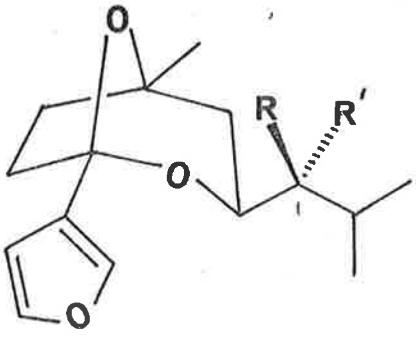
for the major isomer (123a) and the C7 *S* configuration for minor isomer (123b).

Another reductive cleavage of an acetal was carried out during the synthesis of 4-hydroxydendrolasin (see chapter 5) Reduction of alcohol (95) with lithium in ammonia over 3 h gave the triol (183) (63%), starting material (28%) and traces of unidentified polar products. In this example it is interesting to note that no monocyclic ethers were isolated. The more rapid reduction without isolation of intermediates, as with (94) must be attributable to the hydroxyl group. The hydroxyl function at C2" presumably provides a proton intramolecularly for the intermediate species allowing the reduction to proceed to the acyclic form. It is possible that complexation of lithium to the two oxygen atoms at C2" and 20 (see chpt. 5.1) allows a more facile cleavage of the C1-20 bond to give the tetrahydrofuran derivative. This tetrahydrofuran intermediate might then be rapidly cleaved to the triol (183) as shown with the ngaiol (135) in an earlier experiment.

2.4 Cleavage of Acetals with Diborane

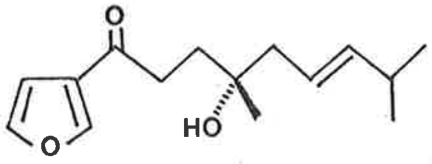
The reductive cleavage of acetals has been previously achieved using various reagents such as sodium cyanoborohydride,[87] the aluminium chlorohydrides,[88] diisobutylaluminium hydride,[89] hydrogen with rhodium on alumina.[91] The applicability of these reagents, to compounds like eremoacetal which have a furan ring, is restricted due to the susceptiblity of the furan nucleus to electrophilic reagents. In order to prepare alcohols (90a) and (90b) for another study it was necessary to examine the behaviour of eremoacetal towards diborane.

When eremoacetal **(47)** was treated with a small excess of diborane (1·1 equivalents 0°, 1 h) in tetrahydrofuran the products obtained, after oxidative workup, included the expected isomeric alcohols (90a) and (90b) (2:3) in variable yield (40-60%). Accompanying these alcohols and starting material (10-20%), was isolated the ketone **(136)** (5-10%) and triols **(137)** and **(138)** (10-20%).

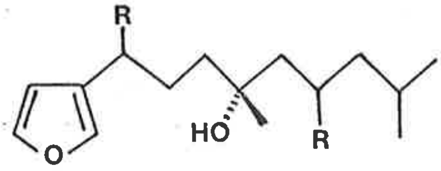


R = H, R' = OH (90 a)

R = OH, R' = H (90 b)

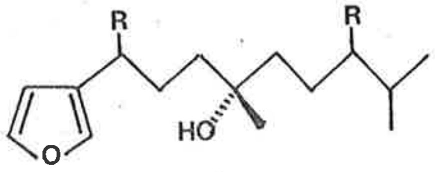


(136)



R = OH (137)

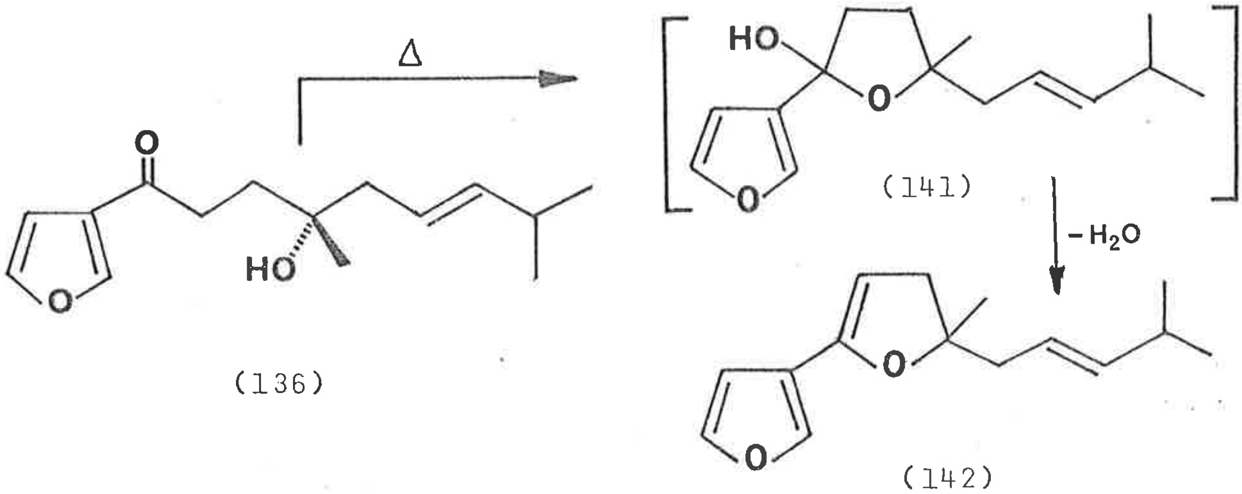
R = OAc (139)



R = OH (138)

R = OAc (140)

In an attempt to purify the ketone **(136)** by distillation it underwent a cyclic dehydration to give the labile enol ether **(142)** presumably *via* hemiacetal **(141)**.

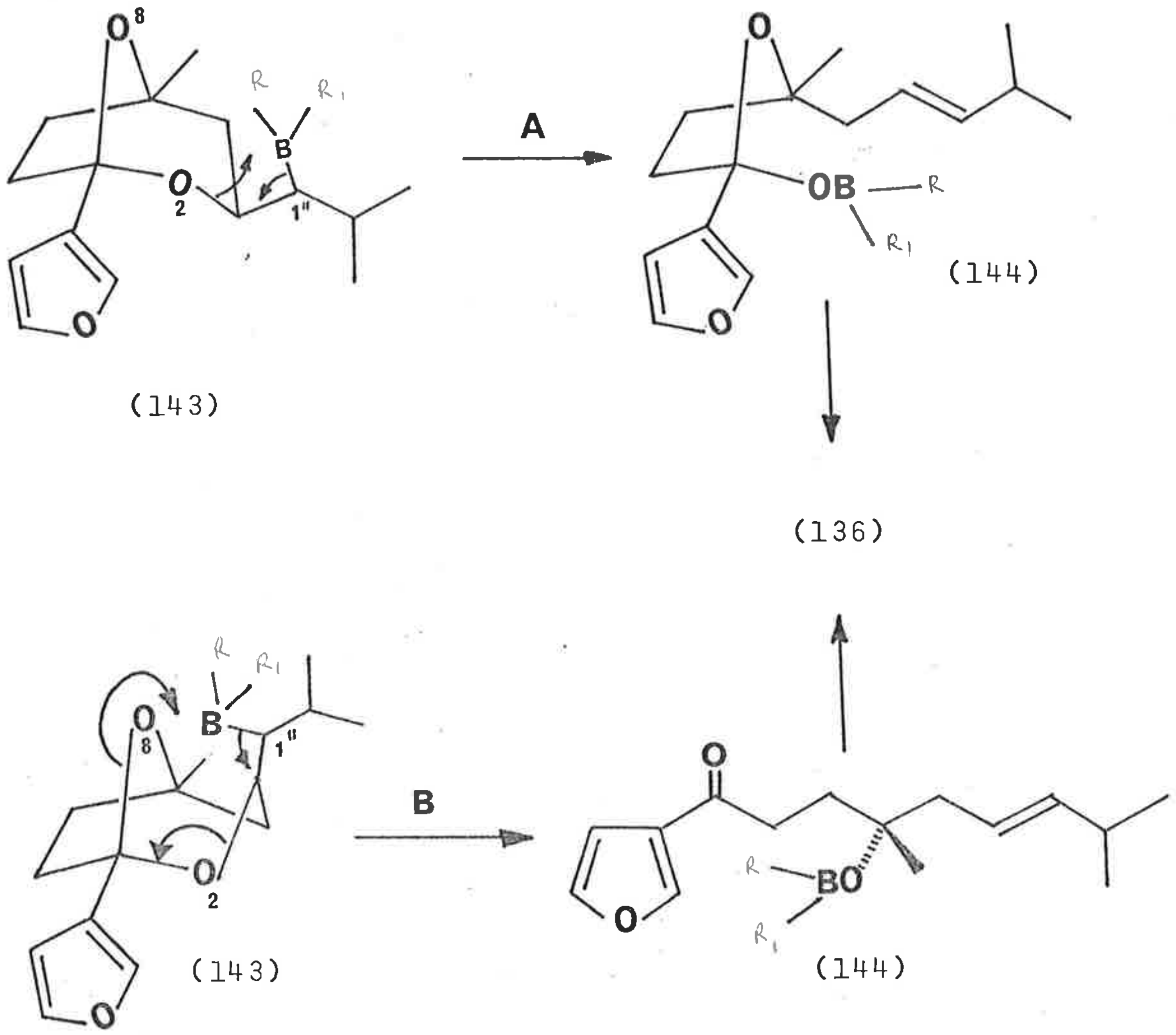


(136)

(141)

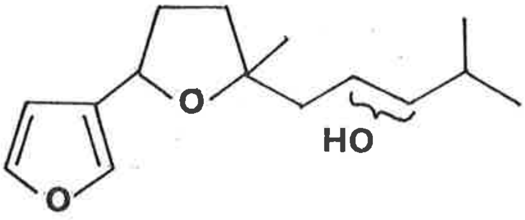
(142)

The ketone (136) from a number of different reactions consisted predominantly of the *E* isomer (85%) as shown by ^{13}C n.m.r. (see appendix). Two mechanisms (A and B) can be postulated, as depicted in scheme 2.41, to explain the formation of the ketone (136).



Scheme 2.41

Both mechanisms proceed by the established β-cleavage of the ether group[92] with migration of boron to oxygen (2O in A and 8O in B) with regeneration of the double bond. The isomeric ratio of *E* to *Z* isomers in (136) would be expected to reflect the epimeric ratio at C1" of alkyl boranes (143), initially formed, which would eliminate in a synchronous cyclic manner as shown in routes A and B. In all reactions with diborane the triols (137) and (138) (see chapter 3) were obtained by further reaction of (136) with diborane. Small quantities (5%) of other products, like the tetrahydrofurans (146), were

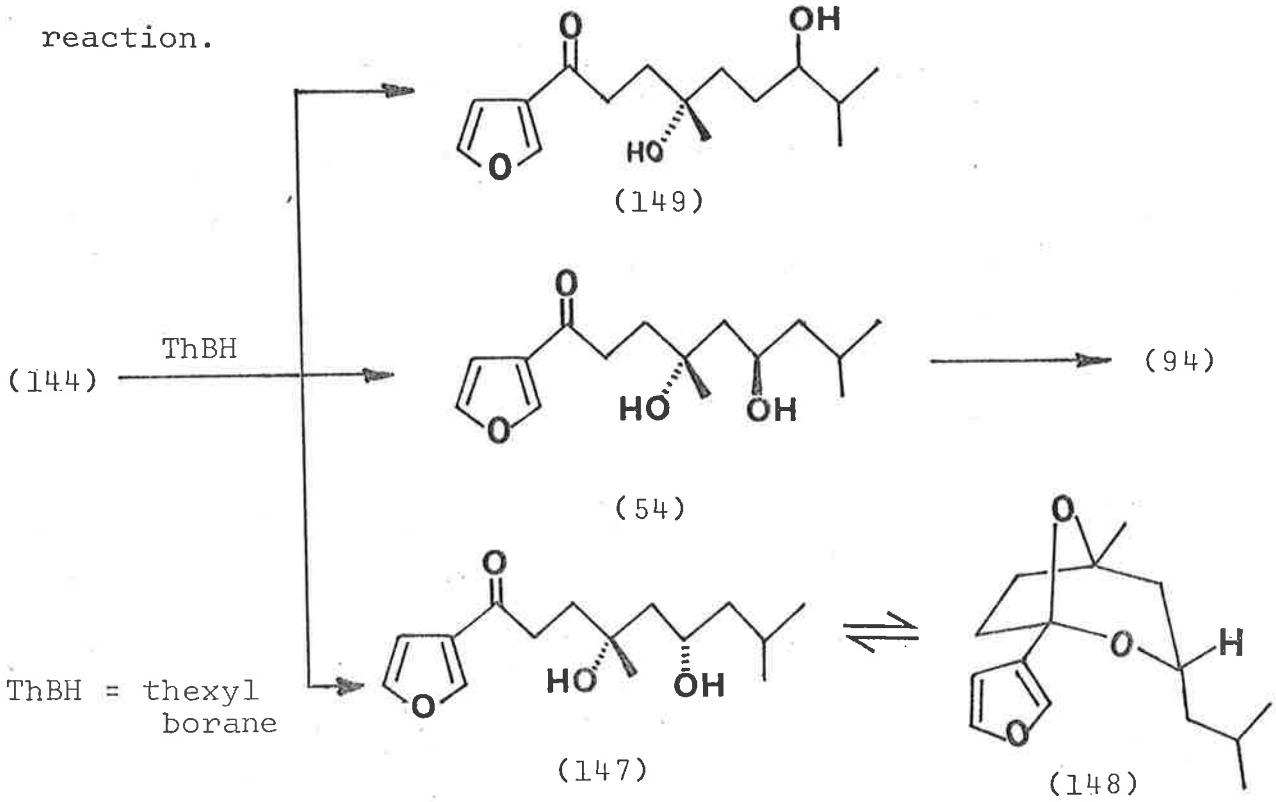


(146)

isolated but not fully characterised.

Other attempts were made to improve the stereoselectivity of this reaction by lowering the temperature during the addition of diborane, and using ether[93] in place of tetrahydrofuran as solvent, which is claimed to decrease elimination. Dimethoxyborane was prepared because this reagent would be expected to be a poorer Lewis acid, but it also gave a similar mixture of products when it reacted with (47).

Thexyl borane (2 equivalents) was also tried but it gave a mixture of products after 30 min at 0°. In this case the products included starting material (15%), and the dihydroeremoacetal epimer (148) (9%) contaminated with the keto diol (147) after chromatography. The epimeric dihydroacetals (94) and (148) could not be readily separated due to hydrolysis of (148) on silica. The dihydroacetals (94) and (148), presumably arise from the keto diols (54) and (147) which can be formed from intermediate (144) by further hydroboration of the double bond. The isomeric keto diols (149) and perhaps (147) were identified (23% yield) by n.m.r. spectroscopy among the more polar products of the thexyl borane reaction. In this reaction the triols (137) and (138) were formed in 10% yield. However, the thexyl borane stereoselectively produced only one of the acetal alcohols, (90b), in only 15% yield, although acetal cleavage products still dominated this reaction.



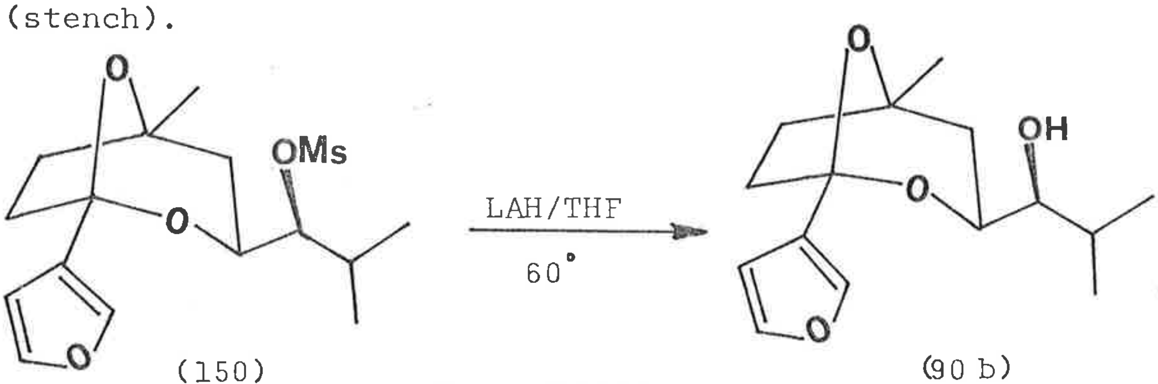
In no experiment could an efficient hydroboration be achieved without acetal opening; starting material and acyclic alcohols were always present among the products. However, the acyclic products formed were of synthetic value and mechanistically interesting.

In contrast to eremoacetal (47), neither alcohol (95) nor ether (96) showed evidence of ring opening when allowed to stand with diborane for 2 h at room temperature. This result confirms that acetal ring opening is a result of the elimination of the alkyl borane intermediate (143) as shown in scheme 2.41.

2.5 Reductive Cleavage with other Hydride Reagents

During an early study of the removal of oxygen functionality from the 1 position of (90) for synthetic purposes, it was decided to explore the reduction of the corresponding mesylates (150) and (151). Primary and secondary mesylates have been reduced to the corresponding alkanes with various hydride reagents.[94-96]

When mesylate (150) was treated with lithium aluminium hydride in tetrahydrofuran, reduction occurred to produce alcohol (90b) and possibly methane thiol or a thioketene (stench).

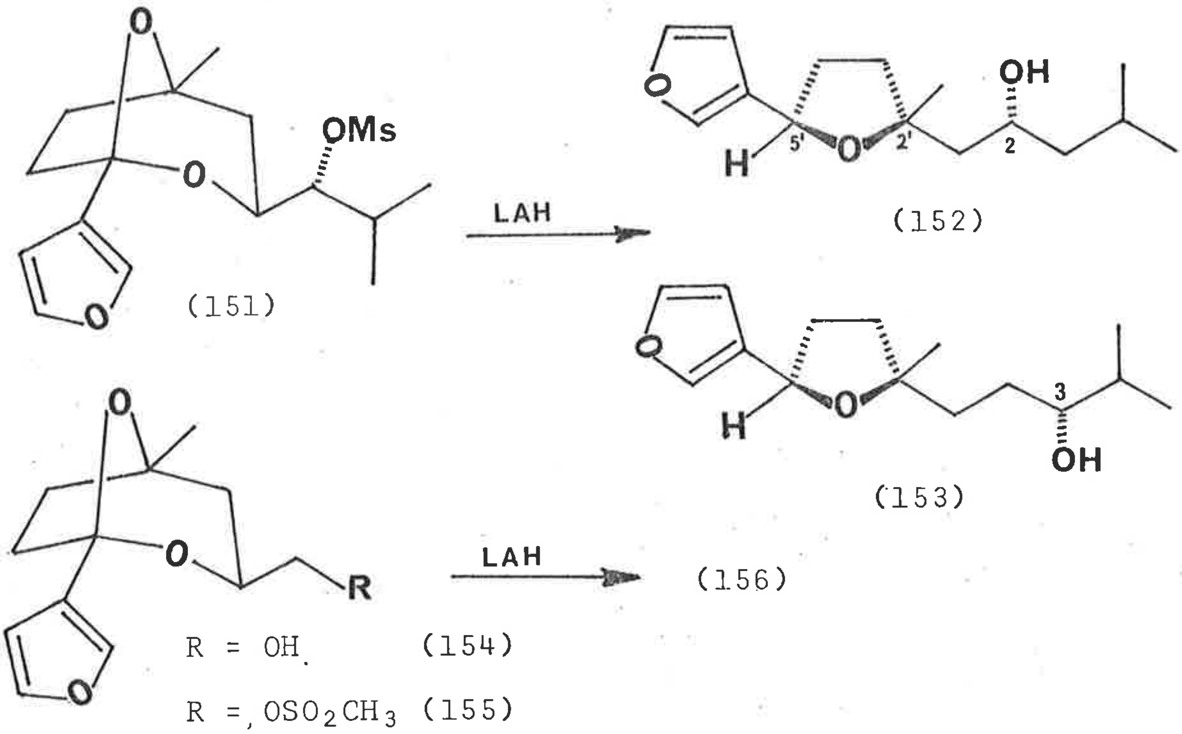


(150) (90 b)

Ms = SO_2CH_3

None of the required dihydroacetal (94) was isolated from this reduction.

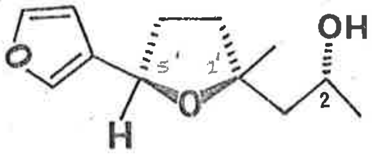
Surprisingly, when the epimeric mesylate (151) was treated in the same way, two products were formed (quantitatively) which were characterised as the tetrahydrofuran alcohols (152) and (153). The alcohols, (152) and (153) were formed in a 1:2 ratio respectively.



R = OH (154)

R = OSO_2CH_3 (155)

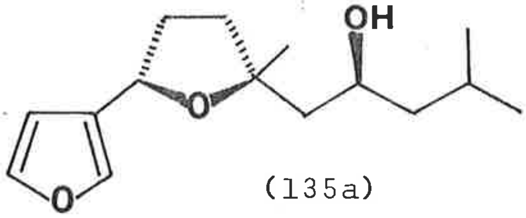
Also, when the mesylate (155) of the primary alcohol (154) was treated with lithium aluminium hydride in tetrahydrofuran an exothermic reaction occurred to give, almost quantitatively, the tetrahydrofuran derivative, alcohol (156).



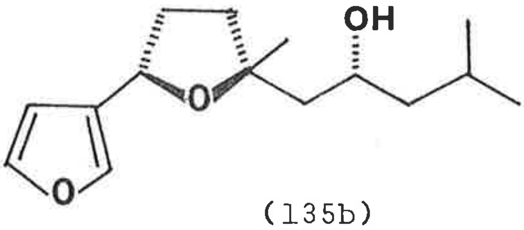
(156)

In order to obtain some mechanistic information about this highly stereocontrolled reduction, the configuration of the products was investigated.

An unambiguous confirmation of C5' stereochemistry in (152) was obtained by a spectral comparison with the known *cis* isomers (135a) and (135b). Alcohols (135a) and (135b) were the minor reduction products when (-)-dehydrongaione (44) was reduced with sodium borohydride in ethanol. Their formation is a result of reduction of the double bond, followed by reduction of the saturated ketone (ngaione) which is formed as an intermediate. Alcohol (135b) was alternatively prepared

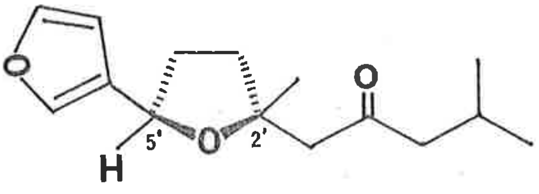


(135a)

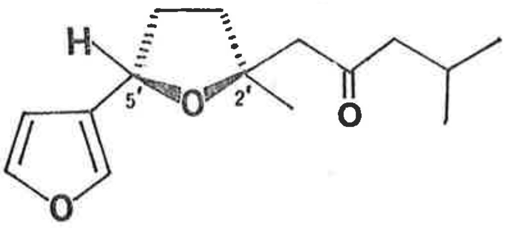


(135b)

by hydrogenation of the dehydrongaiol (62) with hydrogen and P_2-Nickel catalyst. Although (152) was similar by ^1H n.m.r. and i.r. spectra to (135a) and (135b) there were distinct differences which suggests that (152) is the *trans* isomer. Further and conclusive confirmation was obtained by oxidation of (152) to the enantiomer of the known *trans* isomer, epingaione (26). Using Swern's oxidant,[67] the ketone corresponding to (157) was obtained. It was, by comparison of spectral data (n.m.r., i.r.), identical in all respects to (26) but had an optical rotation of opposite direction and of the same magnitude. Ketone (157) was therefore the enantiomer of 2'S,5'S (-)-epingaione (26). These results confirm the 5'*R*



(157)

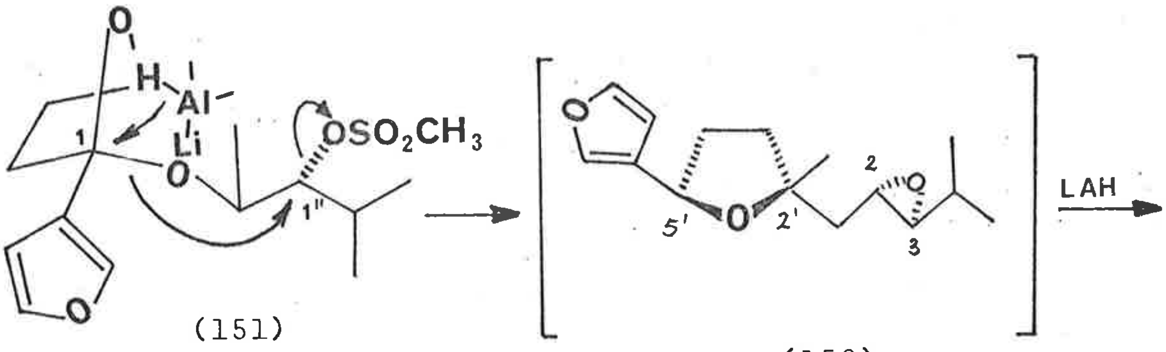


(26)

stereochemistry in (152) and by analogy allowed the assignment of the same configuration at C5' in (153) and (156).

In order to determine the configuration at C2 in (152) and (156) and C3 in (153) the Horeau's procedure was considered. However, the procedure could only be applied unambiguously to alcohol (156) where the methyl substituent at C2 is clearly the smaller of alkyl substituents. Using the modified Horeau's procedure (see chapter 8.4), the stereochemistry at C2 in (156) was determined to be *R*. By analogy, the stereochemistry at C2 in (152) is *R* and that at C3 in (153) is *R*.

The behaviour of the two mesylates, (151) and (155), with lithium aluminium hydride is clearly dependent on the configuration of the mesylate. From the results of the above stereochemical assignments of the reduction products, it is possible to rationalise their formation on the basis of the following mechanism (scheme 2.51). Complexation of the hydride reagent through lithium between the two acetal oxygen atoms, can occur. This arrangement allows the hydride ion to attack the C1 centre from the *same side* as the C1-20 bond is broken with concomitant formation of an intermediate epoxide (158). Reduction of the epoxide (158), predominantly at the less hindered site C2, produces alcohol (153). The minor alcohol (152) arises from hydride attack at the more hindered position, C3 of (158).

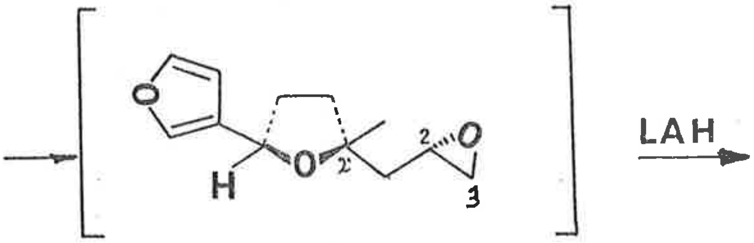


(151) (158) (152) (153)

Scheme 2.51

Overall, this mechanism would provide a product with *trans* stereochemistry about the tetrahydrofuran ring with retention of configuration at C5' (formerly C1 of (151)) in the products (152) and (153). The formation of epoxide (158), by this mechanism, would occur with inversion at the C1'' centre of (151). The subsequent hydride reduction of (158) results in the R configuration at C3 in (153) and *R* at C2 in (152). A similar mechanism presumably operates in the reduction of the primary mesylate (155) (scheme 2.52) to give an epoxide intermediate (159), which undergoes selective reduction at C3 to give the secondary alcohol (156).

(155)



(156)

(159)

Scheme 2.52

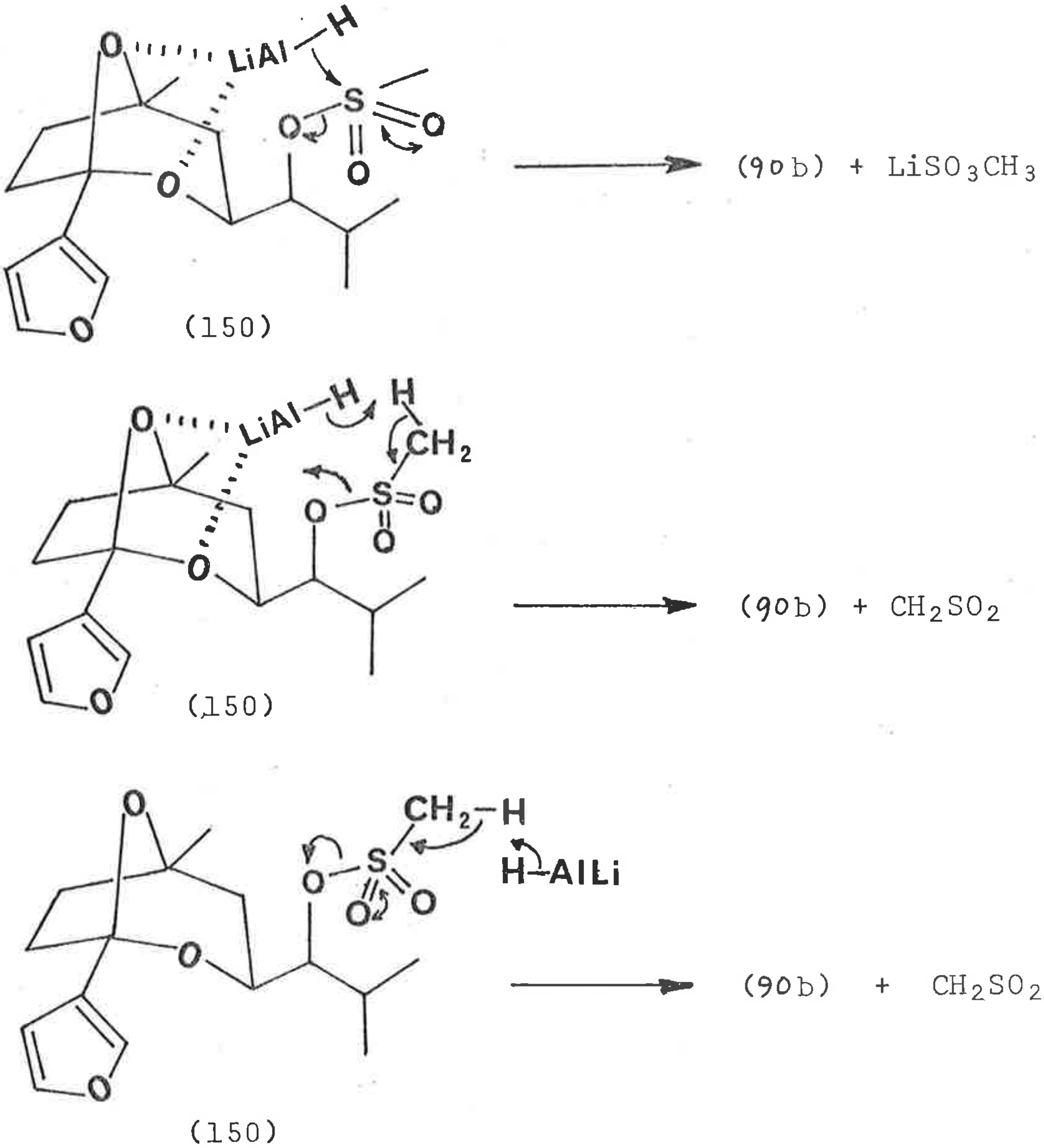
None of the isomeric primary alcohol, from hydride attack at C2 of (159), was detected. These mechanisms, involving epoxide intermediates, are completely compatible with the stereochemical information obtained from the products.

As expected, neither eremoacetal (47) nor dihydroeremoacetal (94) showed any ring opening when treated with lithium aluminium hydride.

The reduction of the mixed mesylates (150) and (151) to dihydroeremoacetal (94) was possible using the powerful hydride donor, lithium triethylborohydride, over an extended period (see chapter 7.8). However, this reduction was slow and considerable starting material was recovered together with the elimination product (47).

An examination of Dreiding models, in an attempt to explain the differences in reactivity between mesylates (150) and (151), showed that steric interactions were minimal in mesylate (151) when the mesylate substituent was *trans* antiplanar to the incoming oxygen, 2O. However, in the mesylate epimer (150), this conformation, presumably necessary for epoxide formation, could not be achieved without more severe steric interactions. Consequently, the ability of the mesylate (151) to adopt a lower energy conformation, in which the incoming oxygen and leaving group are *trans* antiplanar, appears to adequately explain the differences in the reactivities between (150) and (151) upon reduction.

Isomer (150), alternatively undergoes attack at sulphur or perhaps a base induced elimination of a ketene sulphone (which is probably reduced)(scheme 2.53). No evidence for such a reaction was found except for the stench of the sulphur containing reduction product.



Scheme 2.53

In an attempt to form tetrahydrofurans or epoxides from (150) and (151) by solvolytic means, the mesylates were treated in water (100°) containing some sodium bicarbonate, but only starting materials were recovered.

Some of the reaction pathways by which the acetal function in eremoacetal (47) and its derivatives can undergo ring cleavage have been discussed in this chapter. The reduction and solvolysis of this natural product has been a rich source of interesting mechanistic and stereochemical problems. By using such reactions it has been possible to transform eremoacetal into a variety of optically pure sesquiterpenes often with a high degree of stereoselectivity.

Chapter 3

Exploration of the Synthetic Utility of Eremoacetal

3.0 Syntheses which produce enantiomerically pure products are highly desirable and some natural products, with their inherent asymmetric carbons, are ideal precursors.

The control of absolute stereochemistry has been successfully obtained by the use of microbial transformations,[97] chiral reagents[97] or catalysts and the use of chiral templates derived from carbohydrates[99] or terpenes.[97,100]

Because of the abundance of eremoacetal (47) and the wide variety of products available from ring opening of the acetal, the chemistry of the compound was explored further. Some of the products of acetal ring opening appeared to be suitably functionalised intermediates which could be elaborated to known enantiomeric natural products. In addition, the double bond of eremoacetal was suitable for further functionalisation. Some aspects studied were;

i) the preferred direction of approach or stereoselectivity shown by some electrophiles to the double bond of eremoacetal (47),

ii) the preferred direction of approach shown by nucleophiles to the acetal aldehyde (82) (an application of Cram's rule),

iii) Asymmetric induction and the stereoselectivity shown in the formation of isomers from (i) and (ii) with the view to a synthesis of furospongin-1 (48),

iv) Exploration of the Wittig reaction using aldehyde (82) as the intermediate,

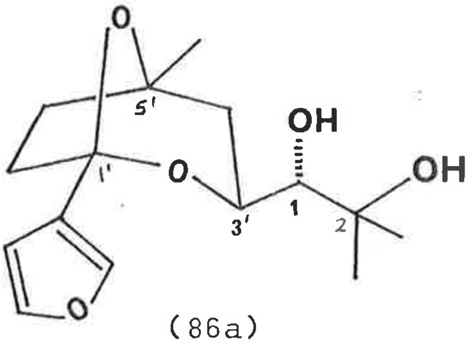
v) Preparation of a variety of enantiomeric secondary alcohols for a study of Horeau's method for the determination of stereochemistry.

Several electrophilic species, such as osmium tetroxide, *m*-chloroperbenzoic acid, boranes and mercuric salts, were reactive towards the double bond of eremoacetal. Many of these are known[111-113] to react with furan or simple alkyl substituted furans. The ability of the furan ring in eremoacetal (47), but not 4-hydroxydendrolasin (8), to show this reduced reactivity to electrophiles can be explained by the inductive effect of the oxygen substituents on the furan ring.

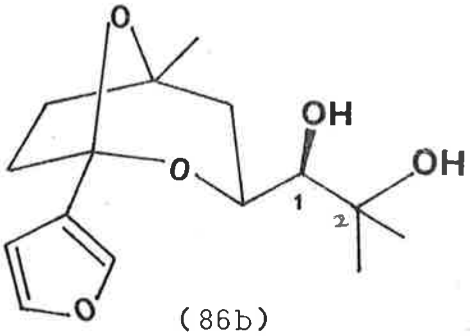
3.1 Reaction of Eremoacetal with Osmium Tetroxide

When eremoacetal (47) was treated with osmium tetroxide (catalytically) and N-methyl morpholine N-oxide as co-oxidant[114] the diol isomers (86a) and (86b) (4:1) were isolated in good yield (90%). Separation of the epimers was achieved by fractional crystallisation, chromatography or the formation and easy chromatographic separation of their corresponding acetonides (160) and (161).

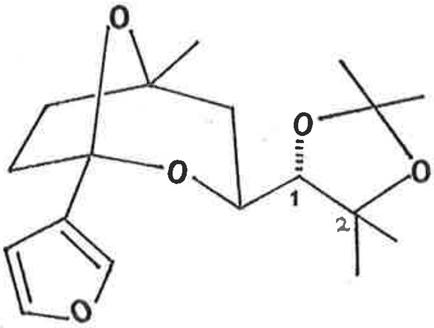
Earlier,[82] one equivalent of osmium tetroxide and pyridine gave a higher degree of stereoselectivity, diols (86a) and (86b) being isolated in a 10:1 ratio. The stereoselectivity of approach of electrophiles is difficult to rationalise due to competing steric and electronic influences in eremoacetal. In addition, the molecule can adopt different conformations in the dioxane ring and with the C3 side chain.



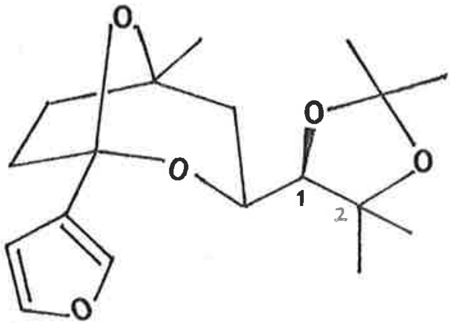
(86a)



(86b)



(160)



(161)

In order to determine the stereochemistry at C1 of diols (86a) and (86b) and therefore to establish the preferred approach of osmium tetroxide to the double bond, Horeau's procedure was used. However, the unknown relative steric influence of the two substituents at C1 on the kinetic resolution did not allow an unambiguous assignment of stereochemistry, by this method (see Chapter 8). The substituents on the more substituted carbon, 2 , may have a *lower* effective steric influence than the longer range, but potentially more severe, steric effects arising from interactions with substituents at $C1'$, and $C5'$ or hydrogens at $C4'$. The application of Horeau's method to the diols (86a) and (86b) is therefore complicated due to this ambiguity. It was, however, possible to relate stereochemically diol (86a) with epoxide (163) which in turn could be related to alcohol (169) where this ambiguity does not exist. By the application of a modified Horeau's method to (169) and (170) (see chapter 8) the stereochemistry at C1 in the major isomer (86a) was found to be *S*. This stereochemistry for the major diol isomer suggests that approach of the osmium reagent to the double bond is preferred from the α side as shown in fig. 3.1. This approach is presumably the least hindered if the molecule adopts the lower energy conformation as shown in fig. 3.11. On this assumption, and, from examination of Dreiding models, it appears that steric influences over-ride potential electronic effects from the two ether oxygens and the furan ring in the osmylation of eremoacetal.

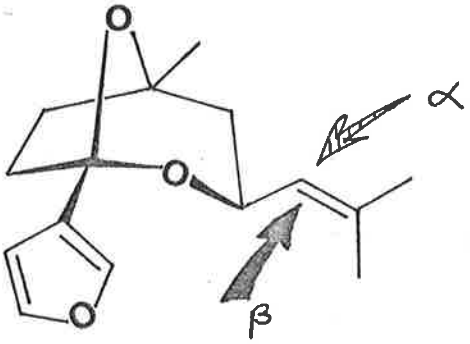
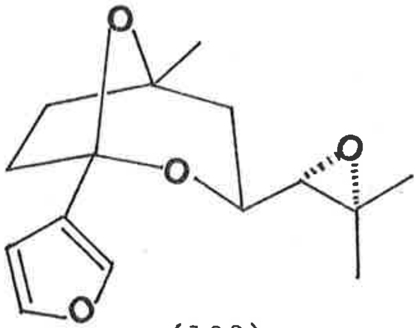


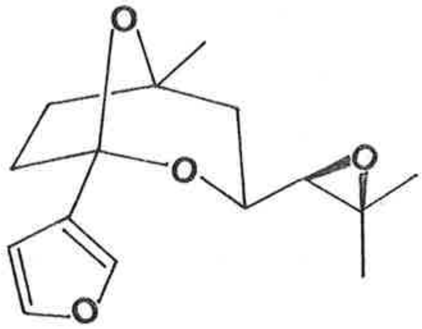
Figure 3.11

3.2 Reaction of Eremoacetal with a Peracid

When eremoacetal (47) was treated with a small excess of *m*-chloroperbenzoic at 0°, the isolated double bond was readily epoxidised. Separation of the epimeric epoxides, (162) and (163) (4:1), was readily achieved by chromatography. The minor epoxide (163) was related to the major diol epimer (86a) by interconversion.

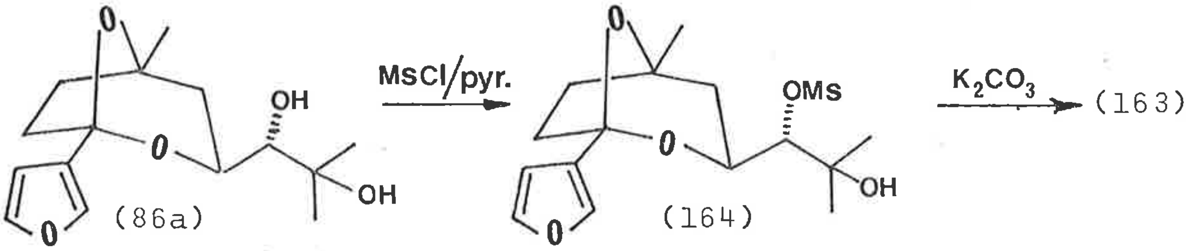


(162)



(163)

Neither (162) nor (163) could be hydrolysed cleanly to the corresponding diols (86b) or (86a) under aqueous acidic conditions, mixtures containing the expected diols and ring opened products invariably formed from such reactions. However, diol (86a) was converted to epoxide (163), *via* the intermediate mesylate (164),[*] as shown below. It would be expected that the formation of epoxide (163) would occur with inversion of configuration at C1 .



From the interconversion of diol (86a) with the minor epoxidation product (163), it is clear that approach of *m*-chloroperbenzoic acid and osmium tetroxide occurs predominantly from the same face (α) of the double bond (see fig. 3.11). This type of asymmetric induction in acyclic systems has been reviewed recently.[100]

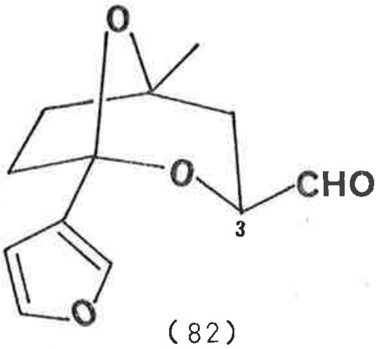
---

[*] Although diol (86a) formed a mesylate and acetate, it could not be induced to form a tosylate. The lower steric requirement of the thioketene intermediate presumably allowed the formation of mesylate (164).

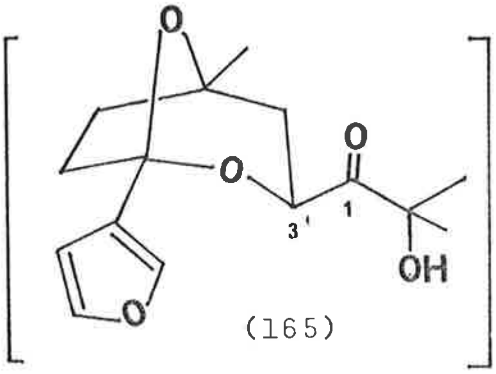
3.3 Oxidation of Diol (86a)

In order to examine the ease of epimerisation at C3' in compounds with a carbonyl function at C1, the oxidation of diol (86a) with pyridinium chlorochromate was attempted. None of the required hydroxyketone (165) was isolated but a low yield (30%) of the aldehyde (82) was obtained. Cleavage of α-hydroxyketones[116] and 1,2-diols[117] by chromium reagents perhaps *via* a concerted (periodate type) cleavage has previously been reported.

(86a) $\xrightarrow[\text{or Pb(OAc)}_4\text{(90\%)}]{\text{P.C.C.(30\%)}}$



(82)



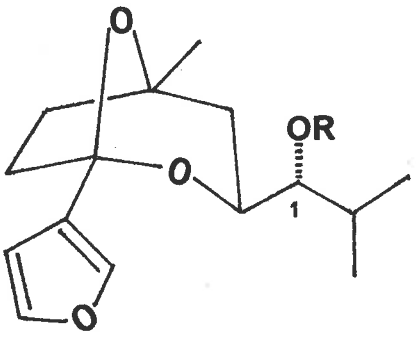
(165)

Because the aldehyde (82) was considered to be a useful synthetic intermediate which could also be used to examine the epimerisation at C3 , its preparation was explored further. Selective ozonolysis of (47) by varying conditions (differing solvents and temperature) gave poor yields (<20%) of (82) due to rapid attack of ozone on the furan ring. An attempt to lower the electron density (and therefore the degree of oxidation of the furan ring) *via* a charge transfer complex using benzoquinone and chloranil was unsuccessful. However, the aldehyde could be readily prepared in high yield by oxidation of diols (86) with lead tetracetate[118] in methylene chloride. Reactions of (86) with periodate gave ring opened products (see Chapter 2).

Attempts to epimerise the aldehyde (82) under acidic and basic conditions gave mixtures of starting material and decomposition products. However, it was possible to convert the aldehyde (82) to eremoacetal (47) *via* a Wittig reaction confirming that epimerisation at C3 in such reactions, does not readily occur. A similar epimerisation attempt using an analogous ketone is discussed latter.

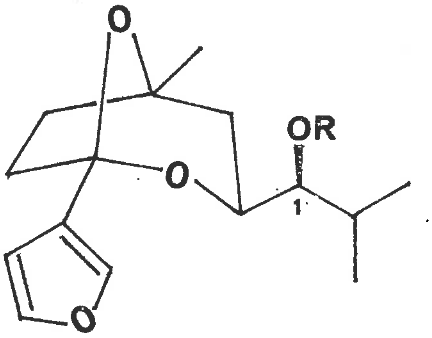
3.4 Reaction of Eremoacetal with Diborane

The treatment of eremoacetal with diborane and other alkyl boranes (discussed in Chapter 2) gave varying yields (40-60%) of the two epimeric alcohols (90a) and (90b) on workup. In order to determine the preferred direction of approach of the borane it was necessary to determine the stereochemistry at C1 in (90a) and (90b). However, when Horeau's technique was applied to the alcohols the initial results were confusing (see Chapter 8). It was possible to remove this ambiguity by correlation of (90b) with the products (170) and (90b) from the Grignard reactions (see Chapters 3.7 and 8). These results showed that the stereochemistry at C1 in (90b), the major isomer from hydroxylation using diborane, was *S*. Therefore the preferred approach of diborane, in contrast to osmium tetroxide and peracid, is from the β face of the double bond of (47) (fig.3.11), assuming the conformation shown for (47) is favoured. However, the degree of stereoselectivity with diborane was low (approximately 3:2). Only epimer (90b) was formed when thexyl borane was used, although, as with all the borane reactions, ring opened products were also formed (see Chapter 2). The higher electrophilicity of diborane



R = H (90a)

R = $COCH_3$ (90c)



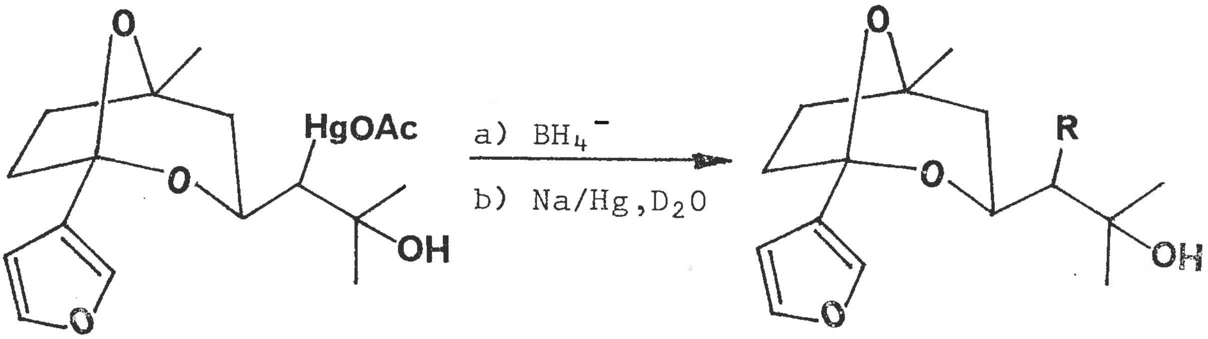
R = H (90b)

R = $COCH_3$ (90d)

relative to the other electrophiles, might allow the acetal oxygens and the furan ring to exert a greater directive influence.

3.5 Oxymercuration of Eremoacetal

It was also possible to hydroxylate the double bond of (47) by oxymercuration.[119] However, the stereoselectivity of the initial adduct formation giving the alkyl mercury derivative (166) was not investigated. The use of deuterium in the reduction of (166) using sodium amalgam/deuterium oxide, known to proceed stereospecifically,[120,21] would give the deuterated compound (95a) for such a study. The use of methanol as solvent gave the corresponding methyl ether (96).



(166)

a) R = H (95)

b) R = D (95a).

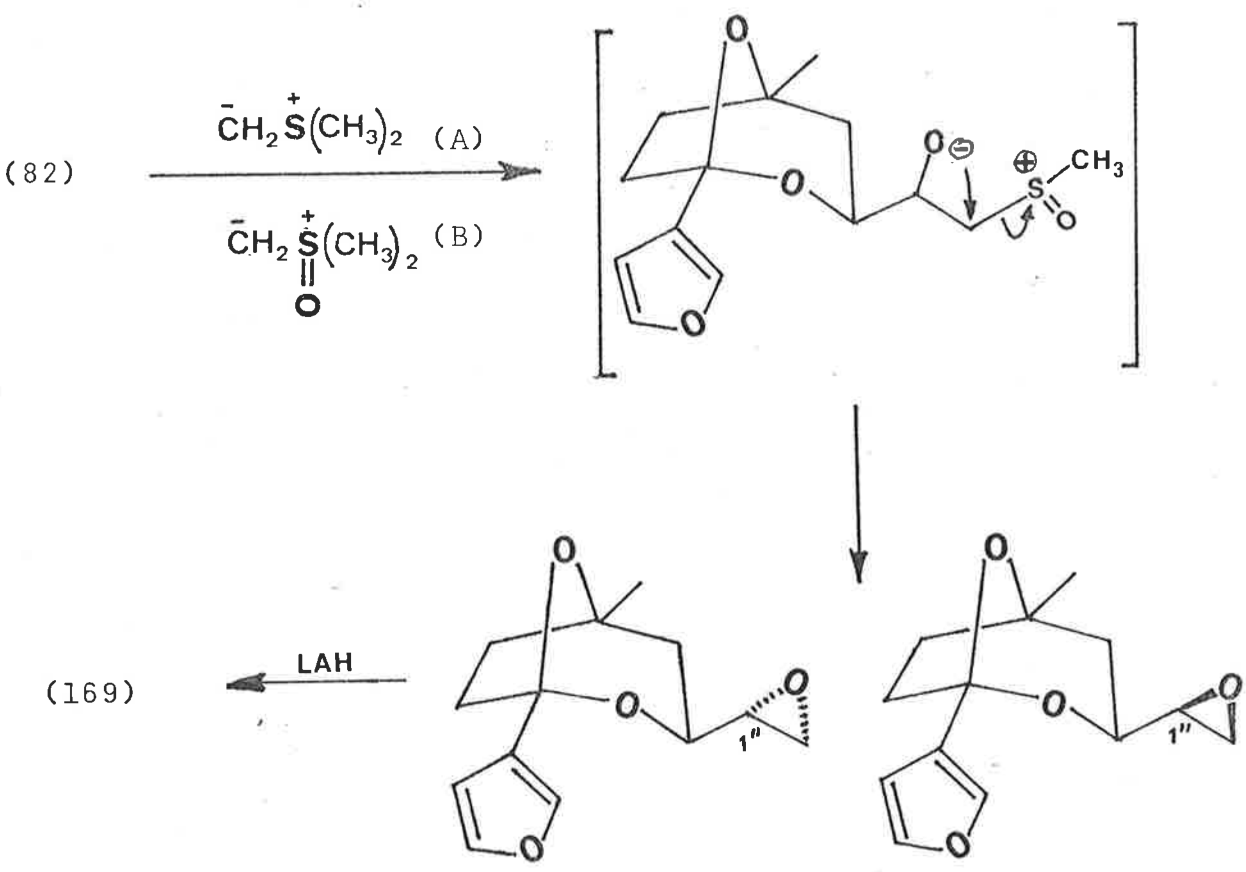
3.6 Reactions of Aldehyde (82) with Sulphur Ylides

In contrast to attack of eremoacetal by electrophiles, the aldehyde (82) was examined to determine the stereoselectivity it showed when reacted with some nucleophiles. The nucleophiles chosen were sulphur ylides and Grignard reagents.

Initially, some epoxides were prepared using sulphur ylides. Epoxides are sometimes mutagenic[122] and the synthesis provided a number of epimeric epoxides for testing[123] using the Ames test.[124]

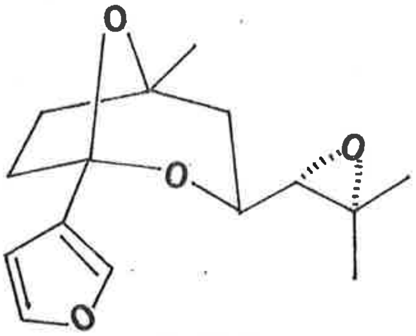
Using the dimethylsulphonium[125] ylide (A) and dimethylsulphoxonium[125a] ylides (B) the epoxides (167) and (168) were prepared from aldehyde (82). The former reagent used at room temperature gave the epoxide epimers, (167) and (168) (3:1), in 67% yield. When the dimethylsulphoxonium ylide (B) was used at a lower temperature (-10°) the epoxides (167) and (168) were formed in lower yield (52%) and with no enhancement in stereoselectivity.

It was possible to determine the stereochemistry at C1" in (167) or (168), after reduction to the corresponding alcohols, (169) and (170), with lithium aluminium hydride. Hydride reduction occurs at the less hindered C2" carbon with retention of stereochemistry at C1 in (169) and (170). Horeau's procedure when applied to alcohols (169) and (170) gave the configuration at C1 as *R* and *S* respectively (see Chapter 8).

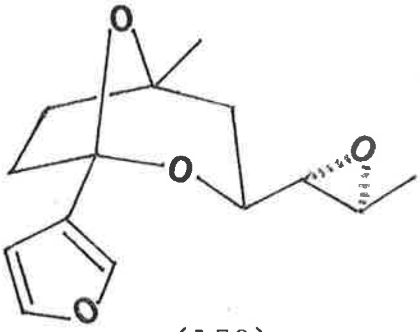


(167) (168)

Similarly, the epoxide analogue (162) was prepared from an isopropylsulphonium ylide. To prepare the unstable isopropyl ylide, it was necessary to alkylate the ethyl sulphonium ylide at low temperature, according to the method outlined by Corey and Chaykovsky.[126] Diphenylethylsulphonium tetrafluoroborate was prepared and the ylide of this was alkylated using methyl iodide. The reformed ylide was then reacted with aldehyde (82) to give the epoxide (162) (38%) stereoselectively although epoxide (172) (22%), (presumably arising from incomplete alkylation in the earlier step), was also isolated. Epoxide (162) was identical with that major epoxide isomer isolated from epoxidation of (47). From these results, it is apparent that the more bulky ylides, like that from diphenylisopropylsulphonium tetrafluoroborate, therefore can give a high degree of stereoselectivity.



(162)



(172)

The stereochemistry of the epoxides resulting from the sulphur ylides, therefore shows the preferred direction of attack at the carbonyl centre by nucleophiles (Nu). According to Cram's[126]/Cornforth's[127] proposals the *anti* orientation of the aldehyde function is such that it minimizes steric and electrostatic interactions between groups. The study of such nucleophilic attacks in chiral carbonyl compounds has been reviewed by Morrison and Mosher[98b] and continues to attract the interest of researchers.[100,128]

The accepted conformation that the aldehyde (82) adopts, shown in fig. 3.61, is based on Cram's model and Cornforth's dipolar model.

Therefore it is possible to explain the preferred direction of attack by nucleophiles (Nu) at the aldehyde carbon.

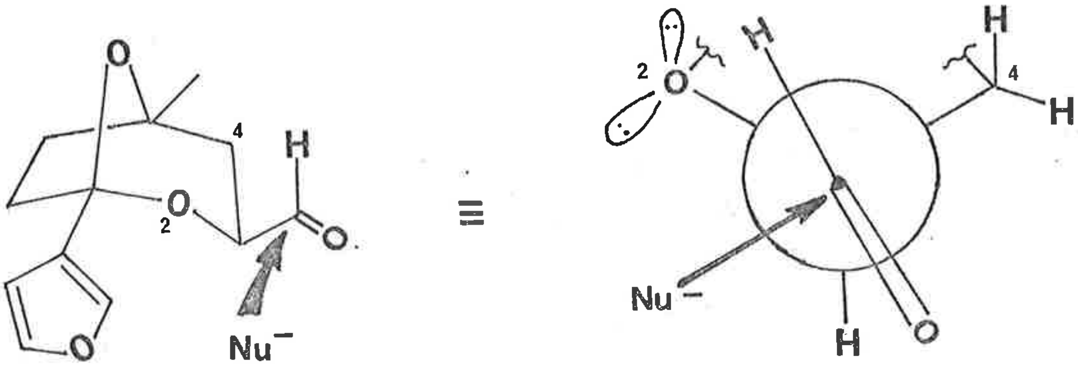
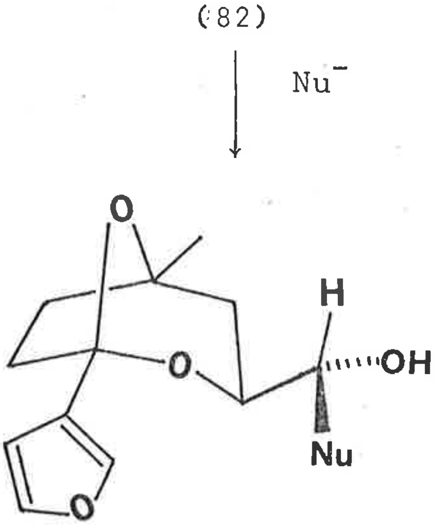
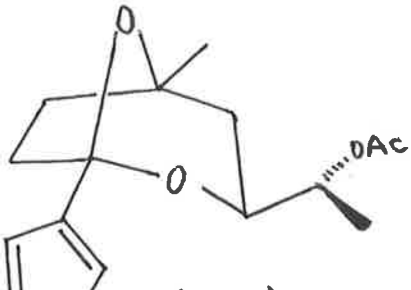


Figure 3.61

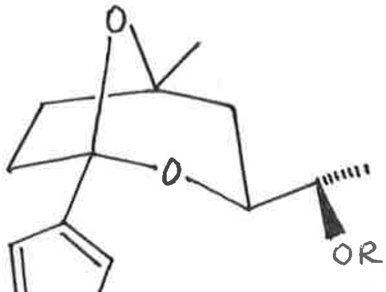


Nu = CH_3 (169)

Nu = $-CH(CH_3)_2$ (90a)



(169a)



R=H (170)
R=Ac (170a)

3.7 Reaction of Aldehyde (82) with Grignards Reagents.

Aldehyde (82) readily reacted with various Grignard reagents to give good yields of the corresponding alcohols. With methyl magnesium iodide at -70° the two epimeric alcohols, (169) and (170) (62:38), were obtained. They were more readily separated and characterised as their crystalline acetates (169a) and (170a).

Similarly, the use of 2-propyl magnesium bromide at -70° gave the two alcohols, (90a) and (90b) (3:1), also obtained by hydroboration of eremoacetal. The increased stereoselectivity is expected with the more bulky isopropyl group. Alcohols (90a) and (90b) were characterised as their crystalline acetates (90c) and (90d) respectively. The configurations of alcohols (169) and (170) were crucial to the assignment of stereochemistries, by analogy, to alcohols (90a) and (90b), which were also the products of a diborane reaction. Assignment of stereochemistry to alcohols (90a) and (90b) was possible *assuming that the preferred approach of the Grignard reagent was, in the two cases above, from the same side of the aldehyde function.* This condition was necessary to assign stereochemistry to (90a) and (90b), as the application of Horeau's method gave ambiguous results. However, no ambiguity existed when Horeau's technique was applied to alcohols (169) and (170) (see Chapter 8).

It was found, as with the sulphur ylides, that the preferred approach of the Grignard reagent* was from the furan side of the aldehyde (see fig. 3.61).

In this way it was also possible to relate the configurations of alcohols (169) and (170) with epoxides (162), (163), (167) and (168) and these with diols (86a) and (86b) which also gave confusing results using Horeau's method.

It was shown independently, by a chemical interconversion to a common derivative, that diol (86a) and alcohol (90a) have the same configuration at C1 (see Chapter 2).

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* An alternative model for the reaction of the Grignard with the aldehyde involves the chelation of the metal with 20 and the carbonyl oxygen.[100] This arrangement does not appear to dominate because it would result in reversed stereoselectivity.

Chapter 4

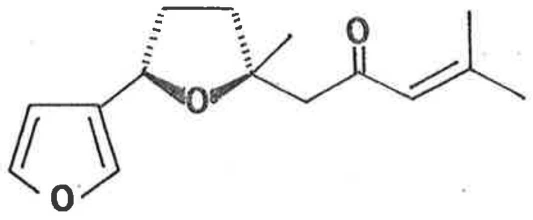
Synthesis of Some Natural Products using Eremoacetal

4.0 The synthesis of a number of sesquiterpenes was undertaken during the course of this work for various important reasons. It was necessary to verify the structures and stereochemistries of some reaction products derived from eremoacetal by conversion to known natural products. Furthermore, these syntheses provided evidence to support proposed mechanisms or pathways in the formation of some derivatives. In addition, the syntheses demonstrated the usefulness of certain transformations and reagents in the presence of the sensitive furan nucleus. Finally, the syntheses of some of the natural products from eremoacetal was expected to allow the previously unknown stereochemistry of the natural products to be assigned or confirmed.

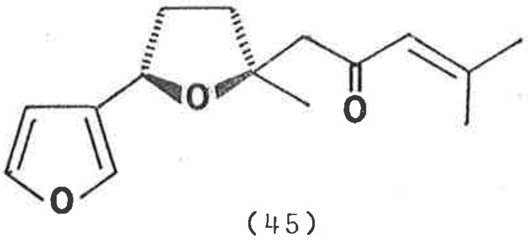
4.1 (-)-Dehydrongaione (44)

In chapter 2 the synthesis of (-)-dehydrongaione (44) from eremoacetal was discussed. (-)-Dehydrongaione occurs in *Eremophila rotundifolia* together with its epimer, dehydroepingaione (45). Both isomers have been previously isolated from both the *Athanasia*, and *Myoporum* species and characterised by Sutherland et al.

The conversion of eremoacetal (47) to (-)-dehydrongaione (44) established the *R* stereochemistry at C5 in the former, and demonstrated the feasibility of a synthesis of (44) from a suitable acyclic precursor.



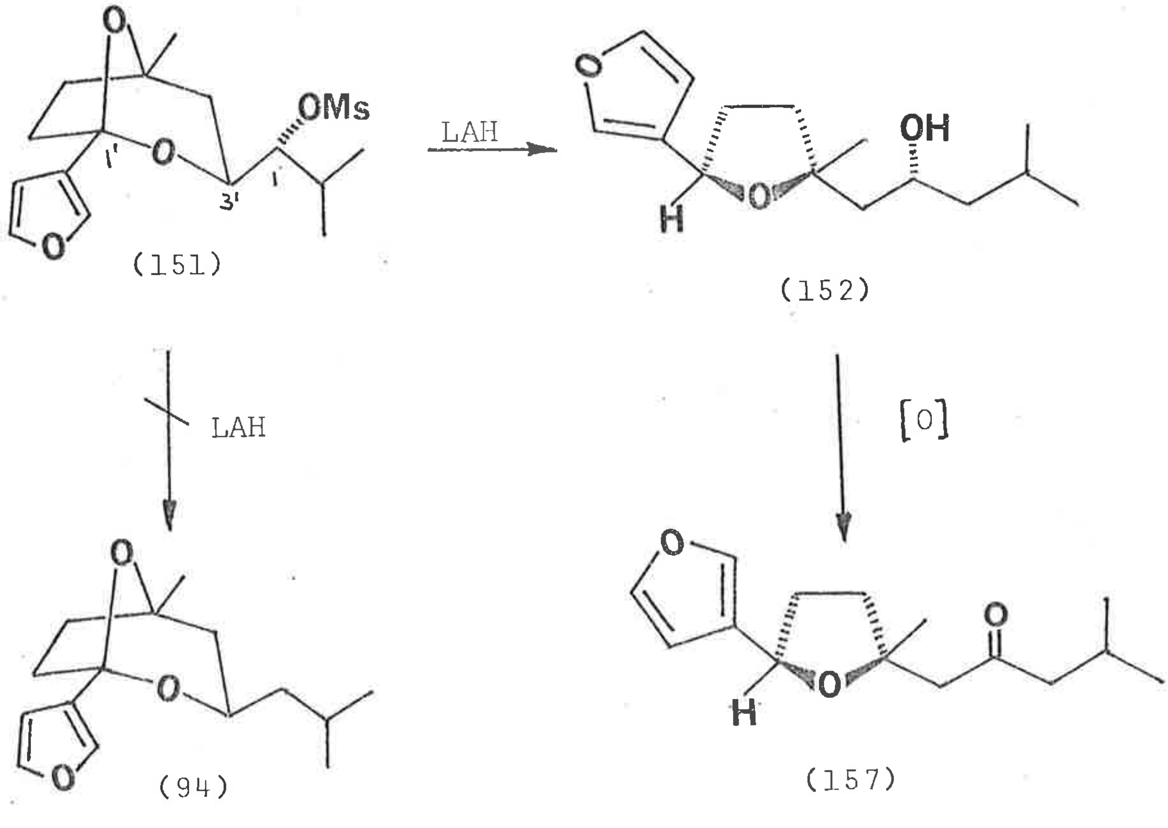
(44)



(45)

4.2 (+)-Epingaione (157)

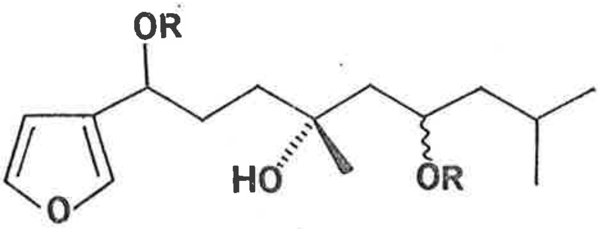
During the attempted reduction of the mesylate (151) to dihydroeremoacetal (94), two isomeric alcohols were obtained (see Chapter 2). One of them, (152), was oxidised to (+)-epingaione (157); the enantiomer (26) is known, having been characterised by Sutherland et al.$^{20\ 21}$ This interconversion established that hydride attack on (151) occurred at C1$'$ in a stereospecific manner which could be rationalised in terms of the configuration at C1 of mesylate (151).

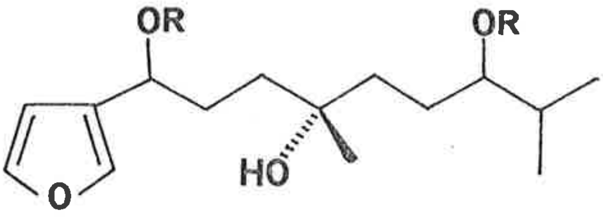


4.3 (*R*)-4-Hydroxymyoporone (Athanagrandione) (23)

Since the isolation of 4-hydroxymyoporone (stereochemistry not defined) from fungus infected sweet potatoes[19,39] it has been identified as a major metabolite[38] arising from (+)-ngaione (15) (called ipomeamarone) which leads to a variety of related potent lung toxins.[39 19] Some of these were readily prepared from eremoacetal (47).

When an excess of diborane was reacted with eremoacetal for 2-3 days, ring opening of the acetal occurred and gave a mixture of isomeric triols (137) and (138) (see Chapter 2).





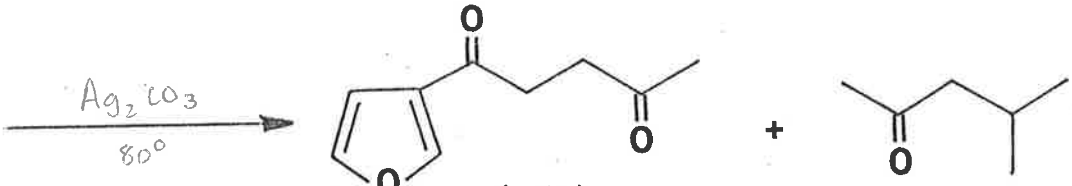
R = H (137)
R = $COCH_3$ (139)

R = H (138)
R = $COCH_3$ (140)

Triols (137) and (138) (7:3) were readily separated from each other by chromatography of their diacetates (139) and (140). The ^1H n.m.r. spectra of each of the diacetates, were very similar except for protons at C6 in (139) and C7 in (140).

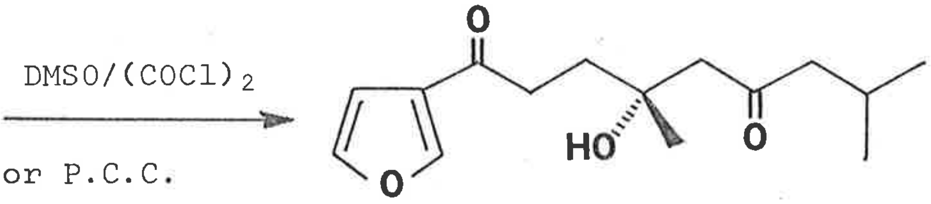
It was apparent that oxidation of the triols (137) to the diketone (23) would confirm the gross structure of (137). Also, the synthesis of (23) and subsequent determination of optical rotation would enable an assignment of stereochemistry to natural athanagrandione, (23), to be made.

(137)



(173)

(137)



(23)

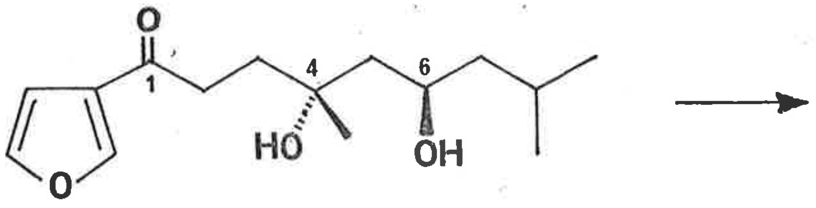
Oxidation of (137) with Fetizon's reagent[129] gave only the diketone (173) formed from (23) by a retroaldol reaction. Ketone (173) has been previously isolated from sweet potatoes and named ipomeanine by Kubota.[20] Oxidation of (137) with either Swern's oxidants or pyridinium chlorochromate gave the hydroxy ketone (23) (17-20%) in addition to other products.

The optical rotation of 4-hydroxymyoporone has not been published but a conversion of (+)-ngaione (ipomeamarone) (15) to the 4*S* epimer (the enantiomer of 23), was recently reported[38] to give a product with the same optical rotation as the 4-hydroxymyoporone from sweet potatoes.[19,39] As the stereochemistry at C2′ in (+)-ngaione (15) is known to be *S*, it is likely that the product from sweet potatoes is the enantiomer, that is, (*R*)-4-hydroxymyoporone also derived from eremoacetal.

Recently Bohlmann described[34] a product (4-hydroxymyoporone) isolated from the *Athanasia* species, and named it athanagrandione. The configuration of athanagrandione however is not given but the optical rotation of (23) ($[\alpha]_D$-1.0°) and that of athanagrandione ($[\alpha]_D$-0.7°), agree closely. The structure and configuration of athanagrandione is therefore

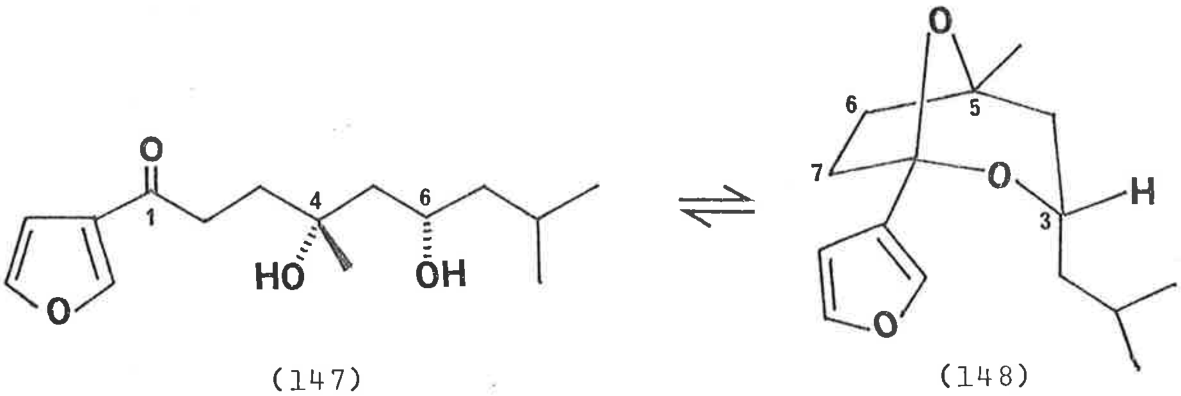
R as shown for (23). The isolation by Bohlmann of (-)-ngaione (22) from the same species, by analogy with Burka's work, adds support to the *R* configuration assigned to anthanagrandione as the stereochemistry of the same carbon in (-)-ngaione (22) is also *R*.

The oxidation of triols (137) also produced the keto diols (54) and (147) (40%) by reaction at C1.



(94)

(54)



(147)

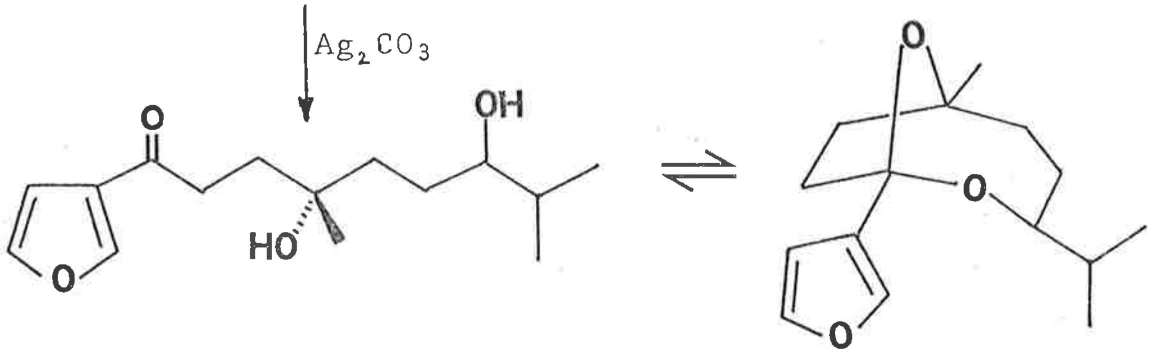
(148)

The keto diol (54) formed was not isolated; its formation was assumed by the isolation of its cyclised product dihydroeremoacetal (94), identical in all respects to authentic material.

However, the epimeric keto diol (147), was unstable on silica resulting, on isolation, in a mixture of (147) and the equally unstable *epi*-dihydroeremoacetal (148). The less polar 3*S* acetal (148), was isolated as a mixture with some of the 3*R* epimer (94). The two acetals (94) and (148), showed small differences in R_f on silica, and were very similar by spectral comparison, although C5-CH$_3$ of (148) resonated at 5Hz lower field in the ^{1}H n.m.r. spectrum than did its epimer. This difference, and possibly the instability of (148) on silica may be due to increased steric interactions with the *endo* hydrogen atoms H6 and H7. These interactions might result in conformational changes in the 1,3-dioxane ring. The formation of the two acetals confirms the presence of isomers at C6 in (137) resulting from hydroboration to both sides of the double bond of the likely intermediate, ketone (136). The ^{13}C n.m.r. spectrum (see appendix) of (139) confirmed the presence of isomers; 23 resonances were clearly discernible. The nature of the sterochemistry at C1 in (137) remains unknown.

Similar oxidation of the minor triols (138), with silver carbonate,[129] gave a mixture of keto-diol (149) and acetals (174).

(138)

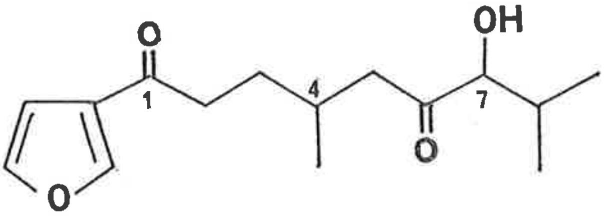


(149) (174)

The complex spectra (^{1}H n.m.r. and i.r.) even after purification on silica, can be explained by the presence of both the acyclic and cyclic forms (149) and (174) again showing the lability of both species.

The ^{13}C spectrum of (140), the diacetate of (138), showed only the expected 19 resonances, indicating that it might be only a single epimer at C1 and C7. This could be the result of an asymmetric reduction of the ketone intermediate,(136),leading to (137) and (138), perhaps through a cyclic borane intermediate involving the chiral C4 centre (see Chapter 3.4).

Recently a furanosesquiterpene, (175) hydroxylated at the uncommon C7 position, has been isolated from infected sweet potatoes and named 7-hydroxymyoporone.[36]



(175)

Triols (137), (138) or ketone (136) may be useful in a stereochemical study of (175) which has recently been synthesised in racemic form by Reich.[131]

Oxidation of the acyclic diol (124) was explored to confirm its structure and to demonstrate the use of such a transformation in the syntheis of myoporone[20,25,36] analogues and the furospongenone[54 56] like compounds. Diol (124)was derived from a Birch reduction of dihydroeremoacetal (94) (see Chapter 2.3).

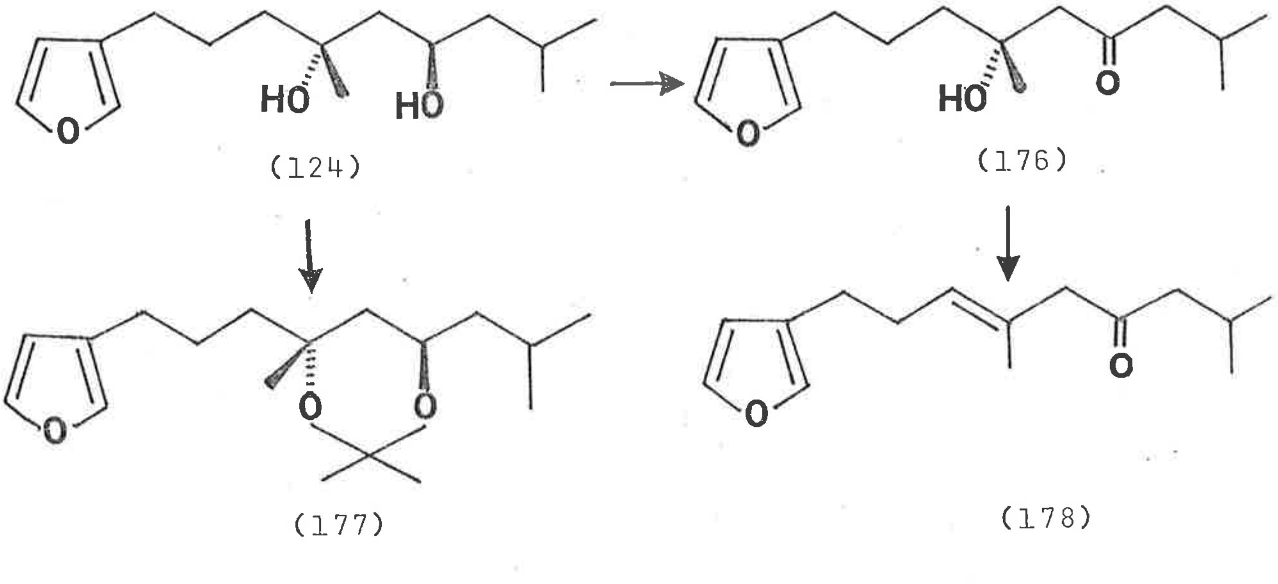
Pyridinium chlorochromate[131] oxidation of (124) gave the hydroxy ketone (176) in good yield without the formation of retroaldol or elimination products. A dehydration of (176) would be expected to give the natural product,[30] (178), with other isomers.

Attempts to characterise ketone (176) as the crystalline 2,4-dinitrophenylhydrazone failed as the two products, *E* and *Z* isomers, although readily separated, could not be crystallised.

Subsequently, diol (124) was readily converted to the acetonide (177) which was purified by distillation.

The diol (124) was a useful model in studying various dehydration products and separation methods for a synthesis of 4-hydroxydendrolasin and furospongin-1.[54]

The synthesis of a new furanoterpene, (*S*)-4-hydroxydendrolasin, from eremoacetal is described in Chapter 5. From the reactions discussed it can be seen that eremoacetal (47) is a source of a variety of bicyclic, monocyclic and acylic intermediates having useful functionalities suitable for the synthesis of an array of naturally occurring furanoterpenes in optically active form. Two applications of eremoacetal in such syntheses are discussed in the synthesis of enantiomeric 4-hydroxydendrolasin (Chapter 5.4) and furospongin-1 (Chapter 7).



(124) (176) (177) (178)

Chapter 5

The Structure and Synthesis of 4-Hydroxydendrolasin (8)

4-Hydroxydendrolasin (8) is a minor consituent (0.1%) which was isolated from the polar fractions after chromatography of the leaf extract of *E. rotundifolia*. It was unstable to distillation but was readily purified as the acetate (8a) by h.p.l.c. Reduction of the acetate with lithium aluminium hydride gave pure 4-hydroxydendrolasin (8) as an optically active, colourless oil with a faint pleasant odour. The pure alcohol exhibited an $[\alpha]_D^{15}$ of $-15.8 \pm 0.6^\circ$ (C, 4.8 in $CHCl_3$). Analysis of the following data led to the assignment of the structure (8) to this natural product.

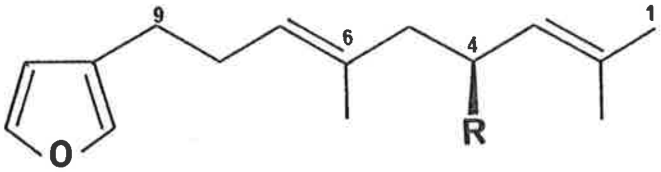
Combustion analysis and high resolution mass spectrometry confirmed the molecular formula as $C_{15}H_{22}O_2$ (m/e 232).

The infrared spectrum showed the presence of an hydroxyl group (3400 cm^{-1}) and indicated the presence of a furan ring (1500, 1155, 1020, 870 cm^{-1}).

Examination of the proton n.m.r. spectrum (see Experimental) revealed the 3-substituted furan ring by the characteristic resonances at δ 7.3, 7.2 and 6.25. Also evident in the n.m.r. spectrum was a two proton olefinic absorption at δ 5.15 (m). A one proton multiplet at δ 4.3 was ascribed to a proton (H4) which was both allylic and on a carbon bearing an oxygen atom. On acetylation H4 was shifted downfield to δ 5.6 and appeared as a doublet of triplets (J 9,7Hz). Irradiation of the multiplet, ascribed to $(H5)_2$ at δ 2.3 in the spectrum of the acetate of (8), resulted in collapse of the multiplet at δ 5.6 to a doublet (J 9Hz). In other respects the ^1H n.m.r. spectrum of

(80) was almost identical with that of dendrolasin[24] (6).

The ^{13}C n.m.r. spectrum of (8) (see appendix) was also very similar to that of dendrolasin (6). In particular, the



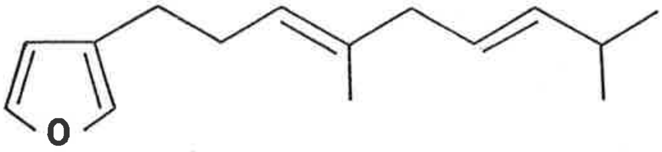
R = OH (8)
R = OAc (8a)
R = $OCOC_6H_4Ph$ (8b)
R = H (6)

^{13}C n.m.r. spectrum showed the presence of the 6-methyl substituent at δ 16.4, which confirmed the *E* configuration for the Δ6 double bond. It has been observed in the ^{13}C n.m.r. spectra of acyclic terpenes[132] and carotenoids,[133] that the methyl group on trisubstituted double bonds resonated near δ 16 for the *E* configuration and δ 24 in the *Z* configuration.

Sesquiterpenes related to dendrolasin (6) are commonly found to be oxygenated at the C1, C4, C6 or C9 positions. The proton n.m.r. evidence is clearly only compatible with C4 oxygenation. The possibility of C9 oxygenation was eliminated by the non equivalent chemical shifts for the H2' and H4' furan protons. Compounds having one oxygen on the carbon adjacent to the furan ring show identical chemical shifts for these protons in their ^1H n.m.r. spectra.

The allylic disposition of the hydroxyl group in 4-hydroxydendrolasin (8) and the stereochemistry of the double bond were confirmed by Birch reduction and also by oxidation.

5.1 Reduction of the acetate (8a) with lithium in liquid ammonia gave dendrolasin (6), of established structure and stereochemistry, as the major product (63%). Also isolated from this reduction was the double bond isomer (6a).

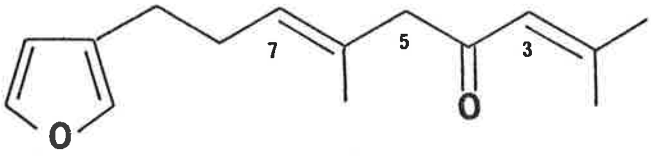


(6a)

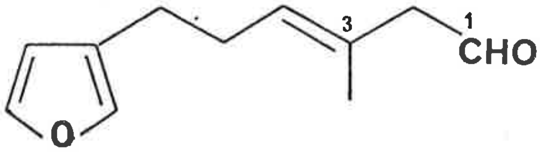
Both products, (6) and (6a), could be readily separated by preparative g.l.c. The major product, from the reduction, dendrolasin (6), was identical in all respects (^{1}H n.m.r., i.r. m.s., t.l.c. and g.l.c.) with authentic material isolated from the same plant.

Isomer (6a) was assigned the structure shown on the basis of its ^{1}H n.m.r. spectrum. This showed the geminal dimethyl groups ($2\text{-}CH_3$ and $(H1)_3$) at δ 0.95 as a doublet and three vinylic protons (H3,4 and 7) at δ 5.1-5.4 (m). The *E* stereochemistry shown for (6a) could not be confirmed by examination of its spectra.

5.2 Oxidation of the alcohol (8), followed by conjugation of the double bond, was expected to give the known dienone (42), which is also a constituent of *E. rotundifolia*. However, oxidation with activated manganese dioxide led predominantly to dehydration products. This facile loss of an allylic hydroxyl groups was also observed in the manganese dioxide oxidation of dehydrongaiol (62). The use of silver carbonate[129] as oxidant gave the desired ketone (179) in 86% yield. Oxidation with pyridinium chlorochromate[131] gave (179) in lower yield (35%) and was accompanied by a cleavage product, probably aldehyde (180), which was identified from its ^{1}H n.m.r. spectrum.



(179)

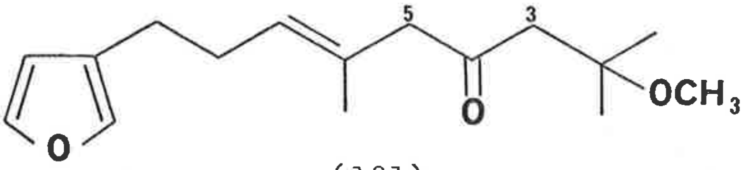


(180)

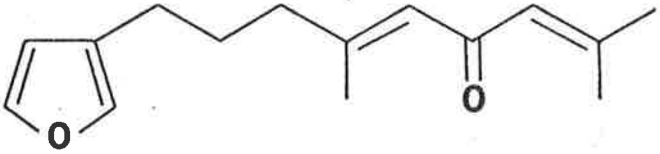
Although ketone (179) has been reported[32] as a natural product, it has been poorly characterised. From the ^{1}H n.m.r. spectrum of (179) it was evident that no double bond migration had occurred during the oxidation. In particular, H3 appeared as a broad singlet at δ 6.1, H7 as a multiplet at δ 5.3 and the C5 methylene protons as a singlet at δ 3.0.

Aldehyde (180) had a readily interpreted ^{1}H n.m.r. spectrum. The vinylic methyl protons resonated at δ 1.65 as a singlet, the C2 methylene protons as a doublet (J 2Hz) at δ 3.0, and the vinylic proton at δ 5.4 (m). The protons, (H5)$_2$ and (H6)$_2$, resonated at δ 2.6-2.2 as a multiplet. The infrared spectrum of (180) showed the aldehyde function at 3160 and 1730 cm^{-1}. Pyridinium chlorochromate oxidation can result in allylic oxidation[125] and cleavage.[134] Oxidation of furan rings with this reagent has also been reported.[111]

An attempt was made to isomerise the ketone (179) into the known dienone (42). Treatment with a dilute solution of sodium methoxide in methanol at room temperature gave the methanol addition product (181) (45%), in addition to starting material (179) (40%). Only small amounts of the isomerised products (42) and (43) were detected in the ^{1}H n.m.r. spectrum



(181)

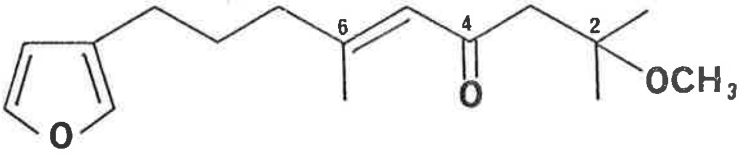


E (42)

Z (43)

(δ6.1). When d'-methanol was used the starting material (179) was extensively deuterated (d_3) at C3 and C5 and the addition product (181), was deuterated (d_4) at C3 and C5.

However, at higher temperatures (65°, 3 h) conjugation of the double bond occurred to give the isomeric dienones (42) and (43) in 70% yield. It is interesting to note that, under the same reaction conditions at room temperature, the dienone (42) gave mainly the methanol addition product (182).



(182)

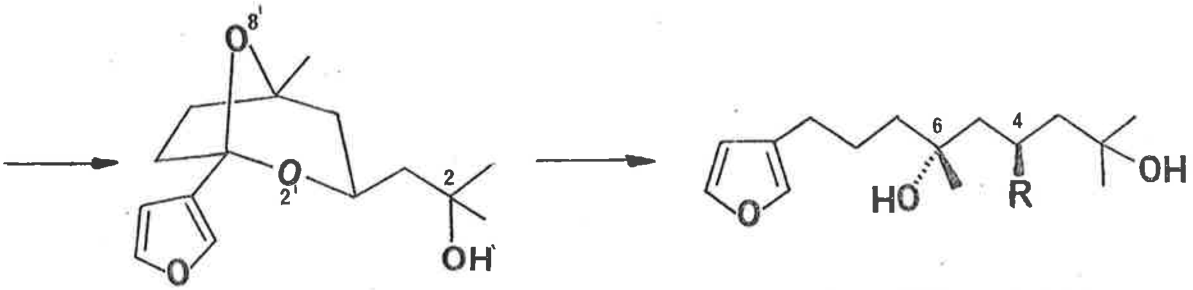
These results indicate that the facile addition of methanol, specifically at C2, is rapid at lower temperature allowing the isolation of the adducts (181) and (182). Although enolate formation was demonstrated by the deuteration experiment, protonation at C5 was the kinetically preferred process at lower temperature resulting in no significant conjugation of the Δ6 double bond. Under thermodynamic conditions (higher temperatures) the more stable conjugated dienone (42) was formed and addition products were minimal. The oxidation and reduction reactions described above confirm the structure of the natural product as 4-hydroxydendrolasin (8).

An attempt to prepare a crystalline derivative of (8), using the 1,1'-biphenyl-4-carbonyl chloride, was unsuccessful because the ester could not be crystallised.

5.3 Other reactions of (8) were briefly explored to examine the reactivity of the double bonds and prepare other derivatives for further stereochemical studies.

The oxymercuration of (8) was expected to give the triol (183) together with its C6 epimer. Triol (183) could be related to the known stereochemistry of eremoacetal via scheme 5.1.

(47)



(95)

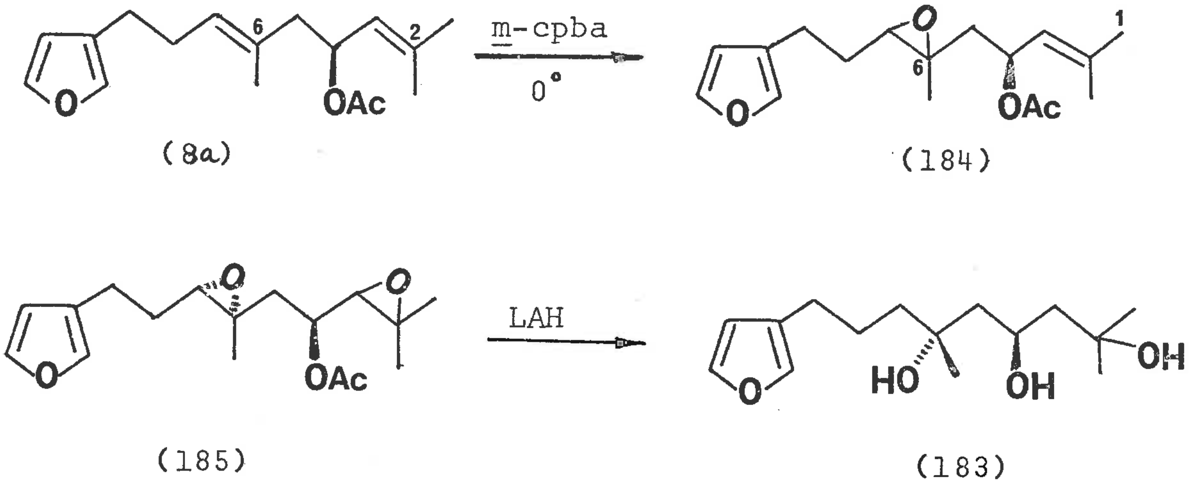
R = OH (183)

R = OAc (183a)

Scheme 5.1

The products from oxymercuration experiments of (8) and (8a) were complex polar compounds showing loss of the furan ring (n.m.r.). The electrophilic nature of the mercury cation results in attack of the furan ring[113] (see Chapter 3.5). In contrast, eremoacetal (47) produces the alcohol (95) in high yield.

An attempt to prepare the triol (183) by epoxidation of acetate (8a) with peracid followed by reduction (Scheme 5.2) was also briefly explored. Epoxidation at room temperature gave rapid oxidation of the furan ring. It was possible, however, to epoxidise (8a) at low temperature (0°) over 30 min. Isolation of the products gave a mixture (60%) of the two

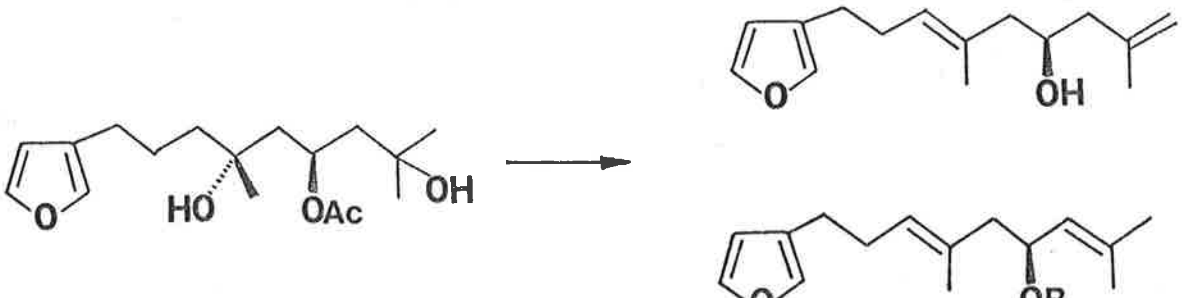


Scheme 5.2

epimeric epoxy acetates (184) which could be separated by chromotography on silica. No diepoxide (185) was isolated, nor was any improvement found on epoxidation at -20° with m-chloroperoxybenzoic acid. Attempted further epoxidation of (184) resulted in oxidation of the furan ring. The two epimeric epoxides (184) were separated and their structures confirmed by examination of their ^{1}H n.m.r. spectra. Each showed the two methyl groups on a double bond at δ 1.7, and the C6-CH$_3$ at δ 1.2, therefore confirming that selective epoxidation of the Δ6 double bond (perhaps with assistance from the homoallylic acetoxyl group at C4 had occurred. Such stereocontrol, directed towards improved asymmetric epoxidation,[100] was not explored further.

5.4 The absolute configuration at C4 was determined by two methods: firstly, by the synthesis of (-)-4-hydroxydendrolasin from eremoacetal (47), of known configuration, and secondly, by application of Horeau's procedure[64] using the g.l.c. modification of Brooks and Gilbert.[136]

The oxymercuration product of eremoacetal, alcohol (95), was reduced withlithium in liquid ammonia for 4 h to give the triol (183) (60%) and starting material (20%).



(183a)

E R = *p*-COC$_6$H$_4$Ph (8b)
Z R = *p*-COC$_6$H$_4$Ph (8c)

Acetylation of the triol (183) gave the monoacetate which was dehydrated with thionyl chloride in pyridine[136] at 0°. Reduction with lithium aluminium hydride then gave a mixture of olefinic alcohols which was chromatographed on silica gel and then silver nitrate impregnated silica gel. In this way the *E* and *Z* isomers of 4-hydroxydendrolasin were isolated as a mixture which was esterified with 1,1'-biphenyl-4-carbonyl chloride. The resulting *E* and *Z* 1,1'-biphenylcarboxylates were separated by h.p.l.c. Reduction of the pure ester (8b), with lithium aluminium hydride gave (*S*)*E*-4-hydroxydendrolasin, $[\alpha]_D$ − 15 ± 2°, identical with the natural product ($[\alpha]_D$ − 15.8 ± 0.6°). The synthetic and natural alcohol (8) were identical in all other respects (^{1}H n.m.r., i.r., m.s., and t.l.c.). The n.m.r. spectrum of the ester (8b) was also identical with that derived from the natural product.

5.5 The configuration at C4 was determined, in both the synthetic and natural 4-hydroxydendrolasin, by employing the g.c. modified Horeau's procedure.[136] Both samples have the *S* configuration on the assumption that the isobutenyl group is effectively the larger substituent. This assumption was used by Minale[53] when determining the configuration of a structurally similar compound, furospongin-1 (see Chapter 7). Because the configuration at C4 is known by interconversion of eremoacetal (47) with 4-hydroxydendrolasin (8) the experiments also give unambiguous data on the relative sizes of the two alkyl groups in (8). In this case the isobutenyl group is clearly the larger.

This synthesis and reactions of 4-hydroxydendrolasin (8) conclusively established its structure and configuration and demonstrated the use of eremoacetal as a valuable starting material.

Chapter 6

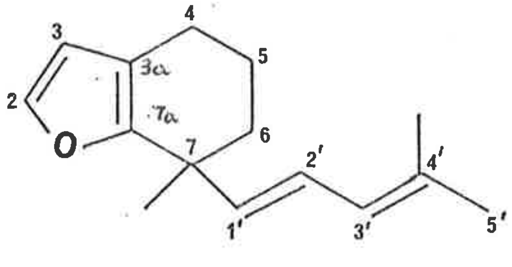
The Structure and Synthesis of 7-Methyl-7-(4'-methylpenta-1',3'-dienyl)-4,5,6,7-tetrahydrobenzofuran (46)

6.0 The diene (46) was isolated as a very minor (0.001%) component of the *E. rotundifolia* leaf and twig extract by repeated chromatography on silica gel. Examination of a small quantity of (46) on a silica t.l.c. plate showed the characteristic magenta colour[21a,138] of alkyl furans when exposed to vanillin/sulphuric acid. The structure of (46) was based on the following evidence.

The diene, isolated as a colourless oil (b.p. 95 /0.2 mm) was found to be sensitive to air and light. By examination of the mass spectrum, it was established that the formula was $C_{15}H_{20}O$ (m/e 216). Also, the major fragment ion at m/e 201 for $C_{14}H_{17}O$ ($M^{+\cdot}$-15) came from a very facile loss of a methyl radical.

Absorptions in the infrared spectrum at 1500, 1180, 1145, 1050, 870 cm^{-1} supported the presence of an alkyl substituted furan ring.

Support for the presence of a 2,3-disubstituted furan ring came from the ^1H n.m.r. spectrum which showed a pair of doublets (J 1.8Hz) at δ 7.18 and δ 6.10 for protons H2 and H3 respectively.[139]



(46)

The proton resonances due to the conjugated diene (46) appeared as a three proton AMX pattern[140] as overlapping multiplets between δ 6.0 and 5.7. This pattern was ascribed as part of a conjugated diene system, δ_A 6.0 d,d J 16,10Hz(H2'), δ_M 5.80 d, J 16Hz (H1'), δ_X 5.75 d,q J 10,1.3Hz (H3'). The large (16Hz) coupling constant was consistent with the *trans* stereochemistry. The small coupling constant (1.3Hz) was consistent with long range allylic coupling of H3' with 4'-CH_3. The 7-CH_3 group appeared as a sharp singlet at δ 1.33 and the two other methyl groups as a broadened singlet at δ1.69. The allylic methylene protons $(H4)_2$ resonated at δ 2.42 as a broadened singlet.

Table 6.1 The ^{13}C and ^1H n.m.r. spectra of diene (46)

Carbon[A]	^{13}C n.m.r.[B] at 20.1 MHz		^1H n.m.r. at 80 MHz	
2	140.6	d	7.18	1H,d,J 1.8Hz
3	110.1	d	6.10	1H,d,J 1.8Hz
4	22.7	t	2.42	2H,m
5	20.3	t	1.63	2H,br,s
6	38.7	t	1.63	2H,br,s
7	38.7	s		
7-CH_3	26.0	q	1.33	3H,s
7a	154.5	s		
3a	116.7	s		
1'	138.3	d	5.72	d,J10Hz
2'	125.0	d	6.00	d,d,J16,10Hz
3'	125.0	d	5.75	d,q,J10,1.3Hz
4'	133.7	s		
4'-CH_3	18.4	q	1.69	3H,br,s
5'	26.0	q	1.69	3H,br,s

A See structure (46) for the numbering sequence.

B The assignment of the carbon resonances is tentative.

The ^{13}C n.m.r. spectrum was in accord with structure (46) although there were overlapping resonances. Therefore, the carbon assignments are tentative and are based on chemical shift data of reported spectra and not by the use of hetereonuclear decoupling experiments. Both ^{1}H and ^{13}C n.m.r. spectral data are shown in Table (6.1).

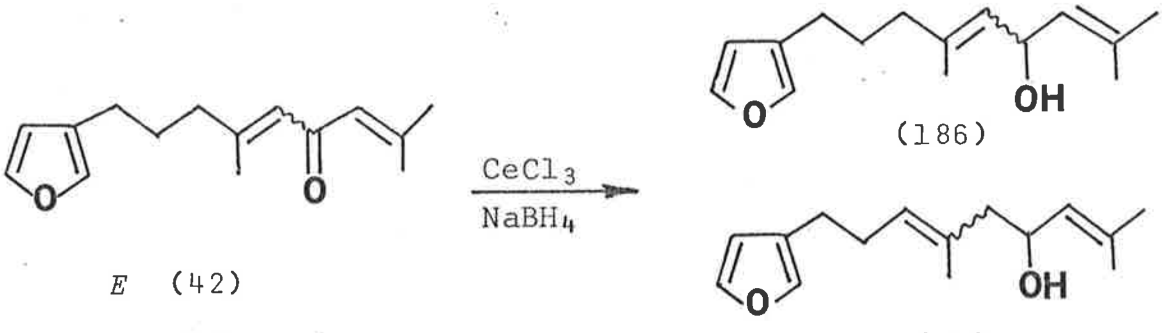
Examination of the ultraviolet absorption spectrum showed overlapping peaks at λ_{max} 225, 231 and 246 nm (log ε 4.36, 4.37 and 4.29 respectively). These absorptions are consistent[21a,142] with the presence of a furan ring isolated from a substituted, conjugated diene. On the basis of the above evidence structure (46) was assigned to the diene.

No detectable optical rotation was observed over the range 360-600 nm which suggests that (46) could be an artefact arising from a labile precursor during isolation. Because it is present in low concentration in a complex mixture, it has not been possible to detect it unambiguously until after chromatography.

6.1 A likely biosynthesis in the plant, or method of formation during its isolation, involves cyclisation of a cationic species. This approach, which was used in the following synthesis from the dihydrophymaspermones (42) and (43), confirmed the structure of the diene as (46).

Similar cationic induced cyclisations have been recently reported.[143,144]

Reduction of a mixture of the *E* and *Z* dihydrophymaspermones (42) and (43) with sodium borohydride in the presence of cerium trichloride[66] gave a mixture of the *E* and *Z* alcohols (186) together with *E* and *Z* isomers of (8e).



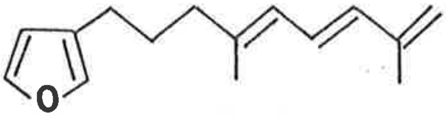
E (42)

Z (43)

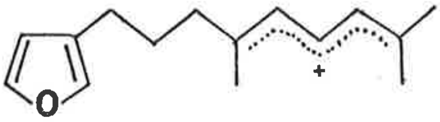
(186)

(8e)

The allylic alcohols were unstable and the mixture was not purified but treated directly with methane sulphonyl chloride in pyridine. This procedure resulted in the formation of the isomeric trienes (e.g. (187)) together with some cyclic products, (4:1) by n.m.r. examination.



(187)

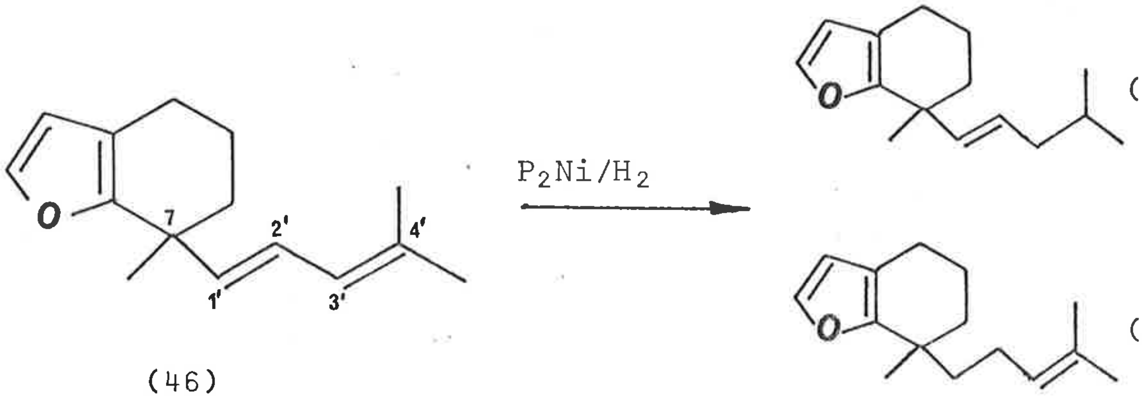


(188)

Several electrophilic reagents were used to induce cyclisation. They included iodine, boron triacetate, boron trifluoride and *p*-toluenesulphonic acid.

The last of these reagents proved to be the most efficacious. Thus, when the triene mixture in carbon tetrachoride was allowed to stand with a trace of *p*-toluenesulphonic acid (anhyd) for 2 h, up to 50% cyclisation was achieved. Cyclisation, occurring presumably *via* a cationic intermediate like (188), was accompanied by some polymer formation. The pure diene (46) was isolated in 20% overall yield and had spectral properties (^{1}H, ^{13}C, i.r. and m.s.) identical with those of the product isolated from the leaf extract.

6.2 In order to obtain further confirmation of structure an hydrogenation of the diene was carried out. Hydrogenation of (46) in the presence of P2 nickel* proceeded in a highly selective manner. After 40 hs, the diene (46) (50%) was recovered in addition to the products (190) (20%) and (191) (20%) arising from selective reduction of one of the two double bonds of the conjugated diene. Neither the tetrahydroderivative nor the Δ2' alkene was detected.



(46)

(190)

(191)

The mass spectrum of (191) showed, in addition to loss of C7 methyl (m/e 203), the loss of C_6H_{11} (m/e 135) from the molecular ion (m/e 218) which gives further confirmation of the structure proposed for diene (46). Each of the hydrogenation products (190) and (191) was readily separated by chromatography (both less polar then the diene). The structure for each was based on their characteristic ^{1}H n.m.r. spectra.

The dihydroproduct (190) showed resonances for the geminal dimethyl groups as a high field doublet (δ 0.92) as well as a

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* This catalyst has been shown to be particularly useful for the selective reduction of alkenes in the presence of a furan nucleus.

resonance for two olefinic protons at δ 5.21. This compound showed a molecular ion at m/e 218, consistent with the reduction of only one double bond, Δ3'.

The more polar of the two products, was assigned structure (191). In the n.m.r. spectrum the geminal groups on a double bond resonated at δ 1.62 and there was one olefinic proton resonance at δ 5.0. Also present was a high field triplet at δ 0.89 which could be ascribed to the $(H1')_2$ protons. This absorption is unexpectedly high field but may be due to the sterically crowded environment, resulting in the shielding observed.

Diene (46), with a unique sesquiterpene skeleton, was confirmed to have the structure (46) proposed based on spectral evidence. Structural confirmation was obtained by an cationic type cyclisation involving a furan ring.

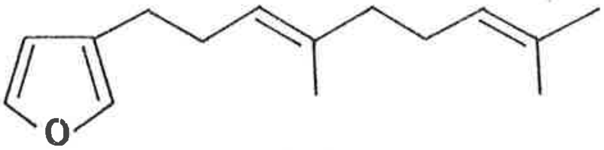
Chapter 7

The Synthesis of Furospongin-1

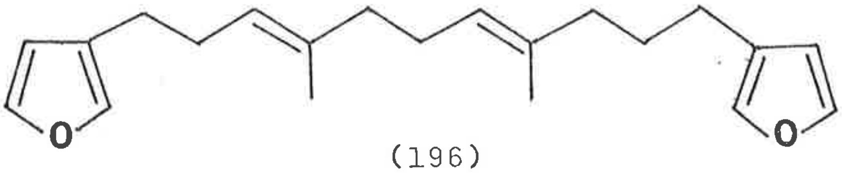
7.0 In recent years a growing interest in the examination of various marine species has resulted in the isolation of a wide variety of structurally related furanoid compounds.[23] Of particular interest has been the identification of a number of C_{21} acyclic furanoterpenes.

The characterisation of furospongin-1 (192), nitenin (193), anhydrofurospongin (196), *E*-furospongin-2 (197), ketones (198) and (199), and dihydronitenin (194) was reported by Minale *et al* in 1971-1972.[53] [55] More recently, Kazlauskas[56] *et al* have isolated furospongin-1 (192) and tetradehydrofurospongin (195) from sponges collected in Australian waters.

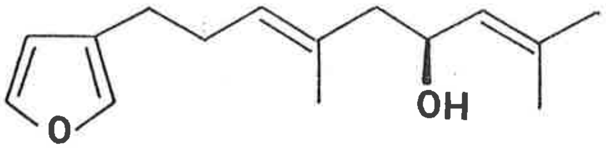
The biogenetic origin of such C_{21} difurans is not clear but they are thought to arise from the biological degradation of higher C_{25} sesterterpenes.[54] This hypothesis is supported by the isolation of C_{25} furanosesterterpenes from a related sponge.[146] Bohlmann has isolated a diterpene acid (200) from a centipede which has a similar acyclic backbone.[49] The similarity between furanoterpenes found in some terrestrial plants and in marine species is surprising.



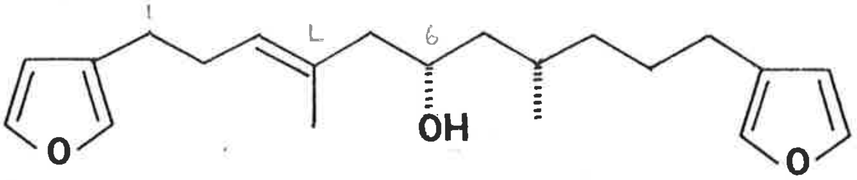
(6)



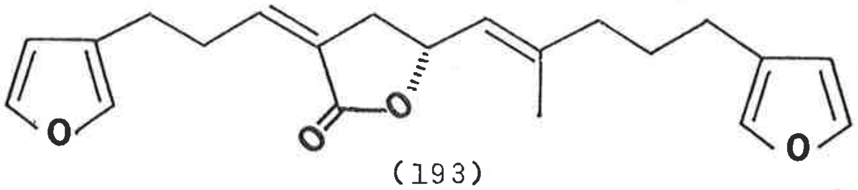
(196)



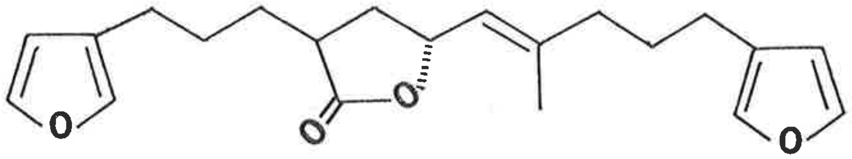
(8)



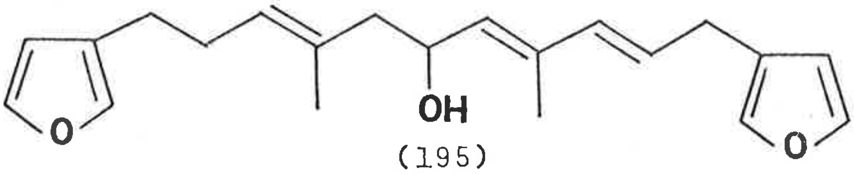
(192)



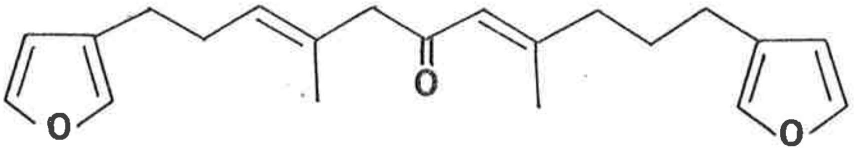
(193)



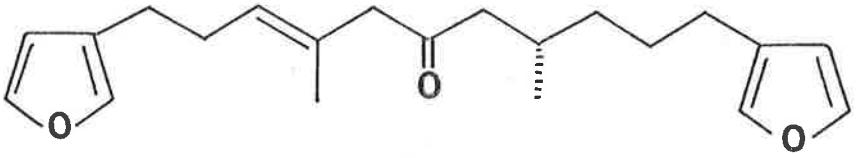
(194)



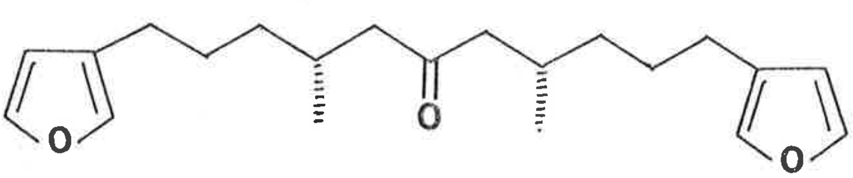
(195)



(197)



(198)

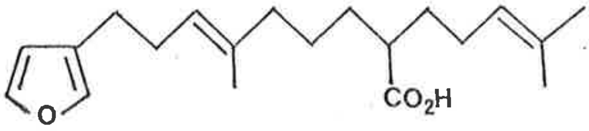


(199)

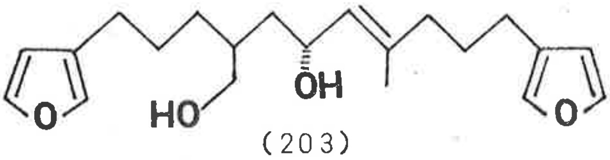
In the recently isolated C_{21} furanoterpenes,[55] alcohol (201) and ketone (202), the site of oxygenation is not in the centre of the prenyl chain as it was with the earlier examples.

The absolute stereochemistry at the chiral centres in (195) (201) or (202) was, however, not reported, although they would be expected to be related to (192), (193) and (194) biogenetically. Structural similarities between dendrolasin (6) and (196), (8) and (192) are undeniable, particularly with respect to the double bond positions and site of oxygenation. This contrast is striking as the species arise from such diverse environments. Despite similarities in the gross stucture, the stereochemistry of the secondary hydroxyl in (192) and (8) is different.

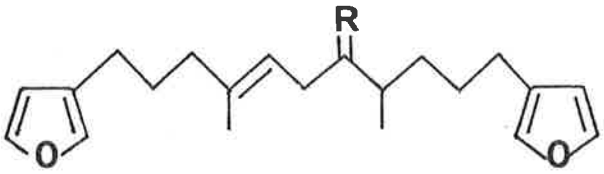
In both of the natural products, (192) and (8), Horeau's method was used to determine the configuration of the hydroxyl group (discussed in chapter 8). In the original examination of furospongin-1 (192) by Horeau's procedure, Minale assumed that the alkyl substituent containing the double bond had the larger (L) steric requirement, as shown. The configurational assignment using Horeau's technique at C6 in alcohols (192), (204) and (203), was based on this tacit assumption. Diols, (204) and (203), were derived from the natural lactones (193) and (194), by hydride reduction. The small difference in size of groups about the hydroxyl centre, is reflected in the low optical yields (9-10%) obtained by the application of Horeau's procedure to alcohols (192), (203) and (204).



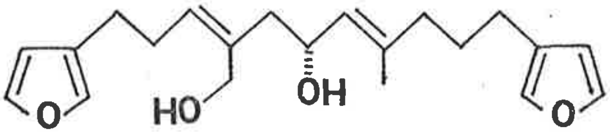
(200)



(203)



R = H,OH (201)
R = O (202)



(204)

Because of the lack of suitable models and literature precedence for the assignment of effective steric sizes, it was envisaged that a synthesis of furospongin-1 or its enantiomer would be valuable for the following reasons.

A synthesis of furospongin-1 would aim to provide a series of double bond isomers in which the stereochemistry at C6 was known. The application of Horeau's method to these models might then provide a comparison of effective steric size of the substitutents (see Chapter 8).

In addition, a synthesis of furospongin-1 would allow the application of some of the methods developed using eremoacetal derivatives as chiral synthons, as described earlier particularly in the synthesis of 4-hydroxydendrolasin (8) (see chapter 5.4).

The synthesis of 4-hydroxydendrolasin (8) from eremoacetal (47) followed by a determination of configuration, confirmed that the alkene substituent adjacent to the chiral centre had the larger (L) steric requirement.

Whether this can be assumed, as the Italian authors did, in the more symmetrical C_{21} alcohols (192), (203) and (204) is more doubtful.

An enantiomeric synthesis of furospongin-1 (192), and some double bond isomers, would test the validity of these assumptions.

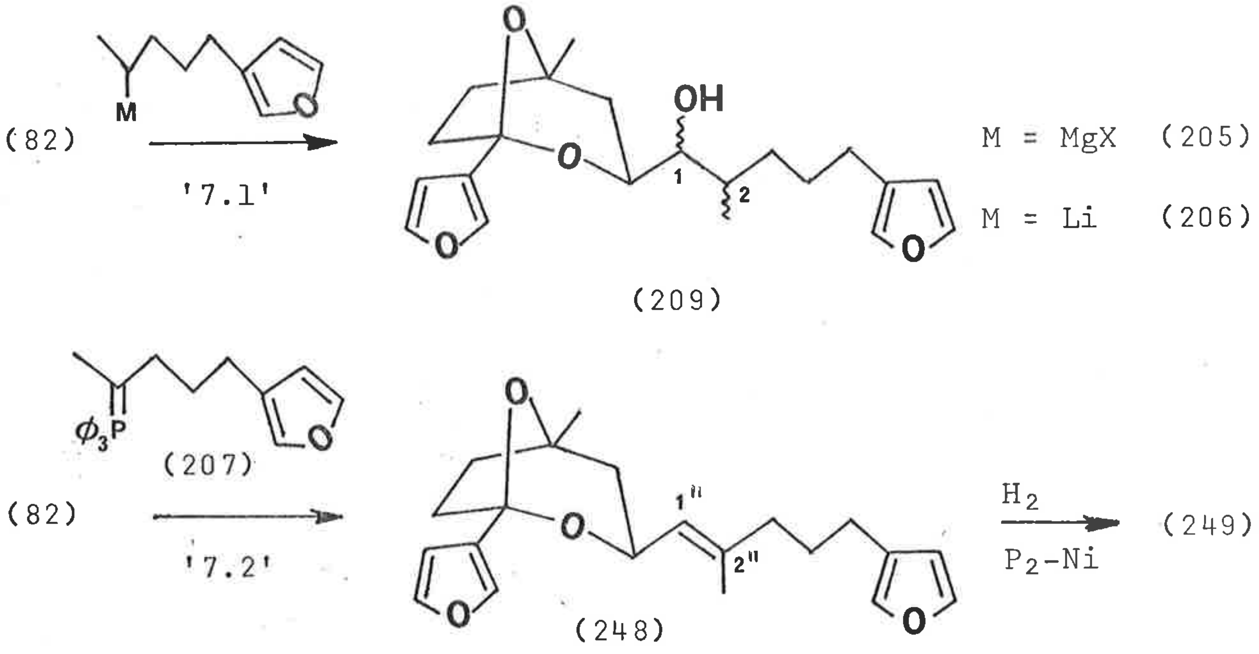
7.1 Synthetic Explorations

Earlier synthetic explorations showed that the aldehyde (82) was a versatile and usefully functionalised key synthon. It was envisaged that a nucleophilic addition of a C9 unit, containing a terminal furan ring, would give the required C_{21} backbone.

The addition of some nucleophilic reagents has been previously discussed and included the sulphur ylides, and Grignard reagents. It was demonstrated that the aldehyde (82) was not epimerised at C3 in the presence of these reagents and in addition, the isomers formed at C1 , were easily separated.

It was also shown in a Wittig reaction that aldehyde (82) gave eremoacetal smoothly and in good yield, without isomerisation at C3. That the stereochemical integrity at C3 could be maintained throughout the synthesis of furospongin-1 was demonstrated by the synthesis of 4-hydroxydendrolasin (8) (see Chapter 5).

Both schemes 7.1 and 7.2 employ previously explored chemistry for the formation of the C_{21} carbon skeleton. Scheme 7.2 requires hydrogenation of the trisubstituted double bond and separation of the resulting C2" epimers. Scheme 7.1 requires the separation of isomers at C2 and removal of oxygen at C1 .



Schemes 7.1 and 7.2

Because hydrogenation of eremoacetal (47) was previously shown to give dihydroeremoacetal in good yield, this approach to (249) was favoured.

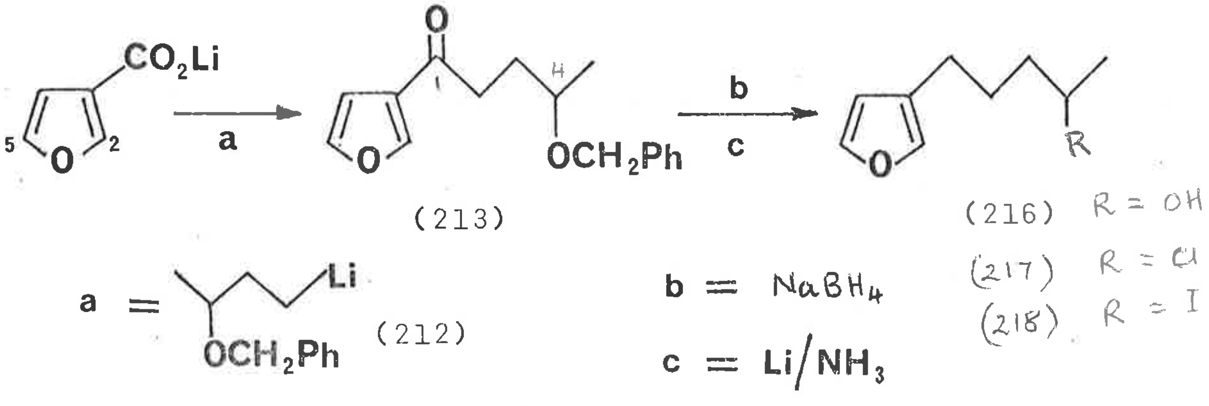
Reduction of the acetal function to the corresponding diol by the Birch reduction has been previously explored (see chapter 2.3). The resulting diol (211), (p.131) could be protected at C6 as the acetate, and the tertiary hydroxyl at C4 dehydrated to give the olefinic alcohols, including the enantiomeric furospongin-1 epimers. The dehydration and separation of the olefinic alcohols was explored in the analogous C_{15} series, and also used in a synthesis of 4-hydroxydendrolasin (8). Although the synthesis attempted was neither stereoselective nor regiospecific (dehydration step), it was considered that the various isomers, if they could be separated, would be useful models in a study utilising Horeau's method to study steric sizes (Chapter 8). Simpler systems, in general, gave no problems with separation of isomers. The potential problems in the separation of the C2" epimers of (249), or derivatives of it, was an inherent risk in the synthesis.

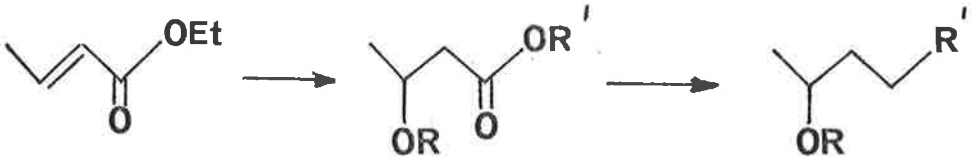
Both schemes 7.1 and 7.2 require the C9 alkyl halide for the preparation of the nucleophile and a synthesis of it was undertaken.

7.2 Synthesis of the 2-Halo-5-(furan-3'-yl)pentanes and the phosphonium salt (238)

Although the preparation of a number of 3-alkyl furans has been described,[85,21c,29,69] the synthesis proposed, in scheme 7.1, embodies removal of oxygen adjacent to the furan ring by metal/ammonia reduction, a topic of interest in this report. Similar reductions have been carried out by Clark-Still[84] and Weyerstahl[85] in the removal of heteroatoms at benzylic type positions.

3-Furyl ketones are readily prepared by reaction of alkyl lithium reagents with lithium 3-furoate. This reaction is reported[148] to proceed in good yield using methyl lithium and lithium 3-furoate to form the methyl ketone. Consequently, it was thought that the suitably protected alkyl lithium (212) would provide ketone (213). Reduction of the ketone (213) and subsequent hydrogenolysis would give the alcohol (216).





(220)

R = CH_2Ph

R' = Et, CH_2Ph

R' = OH (221)

R' = Cl (222)

R' = I (223)

R' = MgX (224)

R' = Li (212)

Alcohol (216) could then be readily converted to a halide, (217) or (218) for the preparation of the corresponding Grignard reagent, alkyl lithium or the ylide.

The Wittig approach was chosen as it obviated the need to remove oxygen at C1" in (209).

The benzyloxyhalide (222) was prepared by the following procedure. A Michael-type addition of benzyl alcohol to ethyl crotonate at 50° or 150° in the presence of base gave, in moderate yield, the mixed esters (220), due to ester exchange, Reduction of the mixed esters (220) with lithium aluminium hydride gave the protected alcohol (221). Using triphenylphosphine and carbon tetrachloride the alcohol (221) was converted to the chloride* (222) for the preparation of the alkyl lithium reagent.

The preparation of the alkyl lithium (212) from the chloride (222) was only achieved after considerable exploration.

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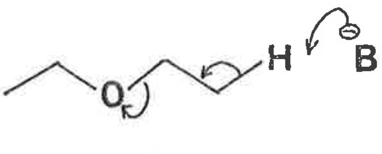
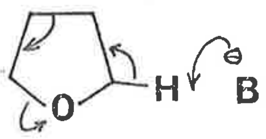
* The haloether (222) was found to be unstable to air and light over extended periods. Benzaldehyde and benzoic acid were identified among the oxidation products and are probably formed by a radical initiated oxidation.

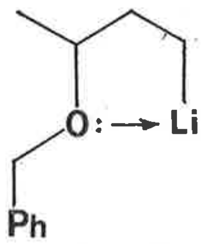
Neither the purified chloride (222) nor iodide (223) could be induced to form the alkyl lithium (212) in hexane using lithium alloy (0.2% Na) as wire or filings. In contrast, reaction of the analogous 1-chlorobutane was readily initiated by the same conditions. Metalation using n-butyl lithium gave mainly substitution products. When diethyl ether was used as solvent, the metal dissolved readily at room temperature. However, the resultant solution gave only low yields of the required ketone (213) on reaction with lithium 3-furoate. The isolated products contained mostly the ether (227) and 3-furoic acid. Workup with D_2O gave no deuterium incorporation into the ether (227) as evidenced by mass spectrometry or proton n.m.r. This result indicates that protonation of the alkyl lithium was occurring before workup, during its formation or upon addition to the lithium carboxylate. Deprotonation of H2 and H5 of furan has been shown to be very slow in ether^{149} using n-butyl lithium although the H2 proton may be more acidic in the furan-3-carboxylate.

It is also possible that the alkyl lithium (212) is basic enough to react with diethyl ether, perhaps via an E2 type mechanism, to form ethylene and lithium ethoxide. n-Butyl lithium is known^{150} to attack tetrahydrofuran in this way at the more acidic α-proton and at elevated temperatures. Deprotonation of diethyl ether however, might involve attack at the presumably less acidic β-protons of diethyl ether as shown below:

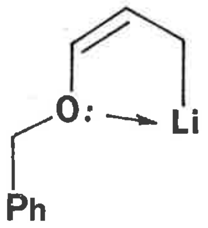




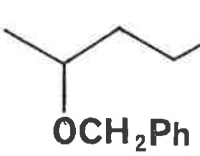
Such enhanced basicity of the alkyl lithium (212) must be due to the benzyloxy substituent. Intramolecular coordination to the lithium by the ether oxygen, as shown below, could increase the electron density on carbon. Such internal chelation by ethers is well documented[151,152] in allylic systems like (226).[151] Lowered aggregation of the alkyl lithium species due to solvation (by ethers) is known to enhance basicity.[153]



(212)



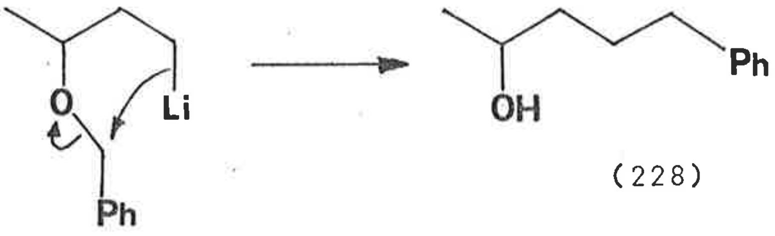
(226)



(227)

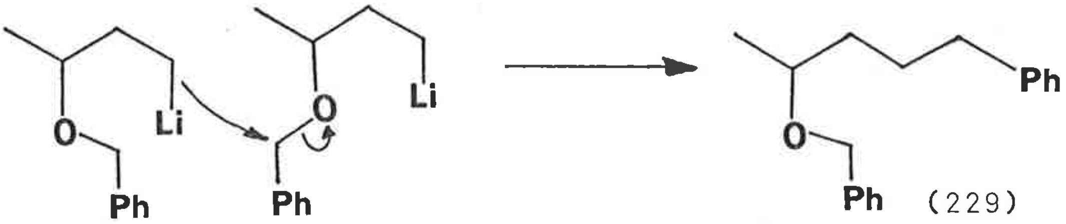
Similar products were obtained using t-butyl methyl ether as solvent.

However, when tetrahydrofuran was used as a solvent, the dissolution of metal was more rapid and the alkyl lithium formed more reactive. In this case, none of the required ketone (213) was isolated but the alkyl lithium (212) formed (227), (228) and (229) by protonation, intramolecular and intermolecular exchange of benzyl groups. Reaction of alkyl lithium, in this solvent, occurred within the time required to dissolve the metal (3-4 h at -30° to -40°). The enhanced reactivity of Grignard reagents and alkyl lithium in tetrahydrofuran has been ascribed[153] to its solvating ability which results in the more reactive monomeric species.



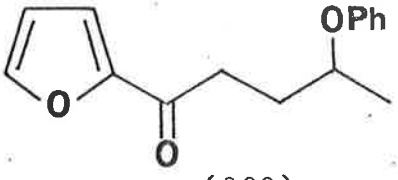
(212)

(228)



(229)

The apparent reactivity of the alkyl lithium (212) and its short life in ether solvents, suggest that it might be possible to alkylate the furan carboxylate *in situ*. A trial experiment in ether at room temperature using lithium 2-furoate gave ketone (230) in a promising 50% yield. When lithium 3-furoate was used, the yield of ketone (213) was higher (65-70%). However, with lithium 3-furoate, some of the diketone (231) (5-8%) was also isolated. This arose from metalation at C2 of the furan ring followed by further reaction with furan carboxylate. A small quantity (1-5%) of the 2 and 3-benzyl ketones (232) and (233) were also obtained from each respective reaction and were readily identified by their ^{1}H n.m.r. spectra. These ketones presumably arise from benzyl lithium formed by some disproportionation of alkyl lithium (212).



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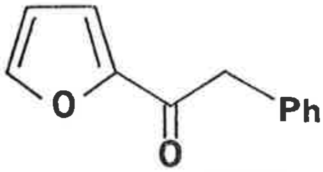
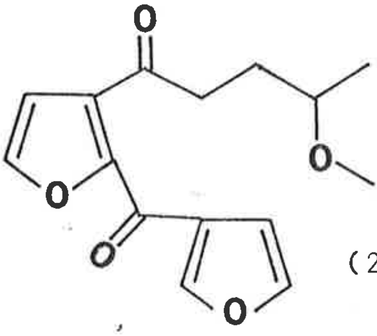
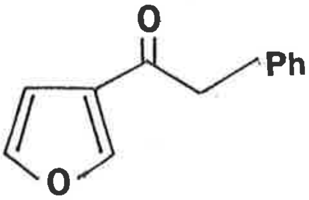


(232)



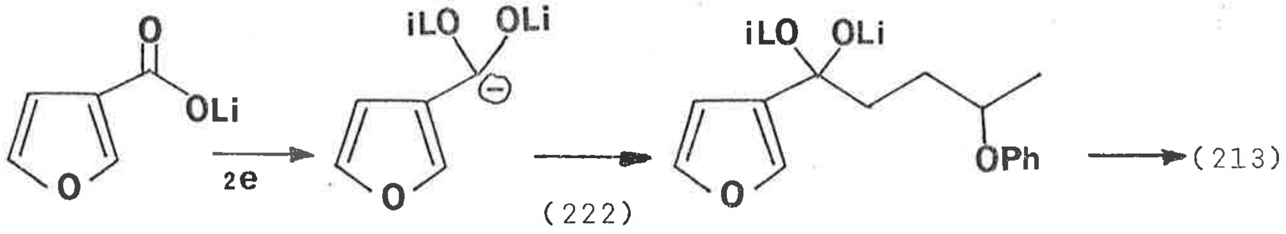
(231)



(233)

The success of the *in situ* reaction showed that reaction at the carboxylate group was faster than proton abstraction from the furan ring or solvent. Furthermore, the isolated products confirmed that metalation at C2 on the furan ring was a relatively slow process and did not account for the source of protons in earlier attempts to prepare the alkyl lithium (212).

An alternative mechanism for the formation of ketone (213) can be considered but seems less likely. The dialkoxyanion, shown below, might be the reactive species and displaces the chloro group of (222) to give the same intermediate before workup as obtained in the conventional reaction discussed earlier.

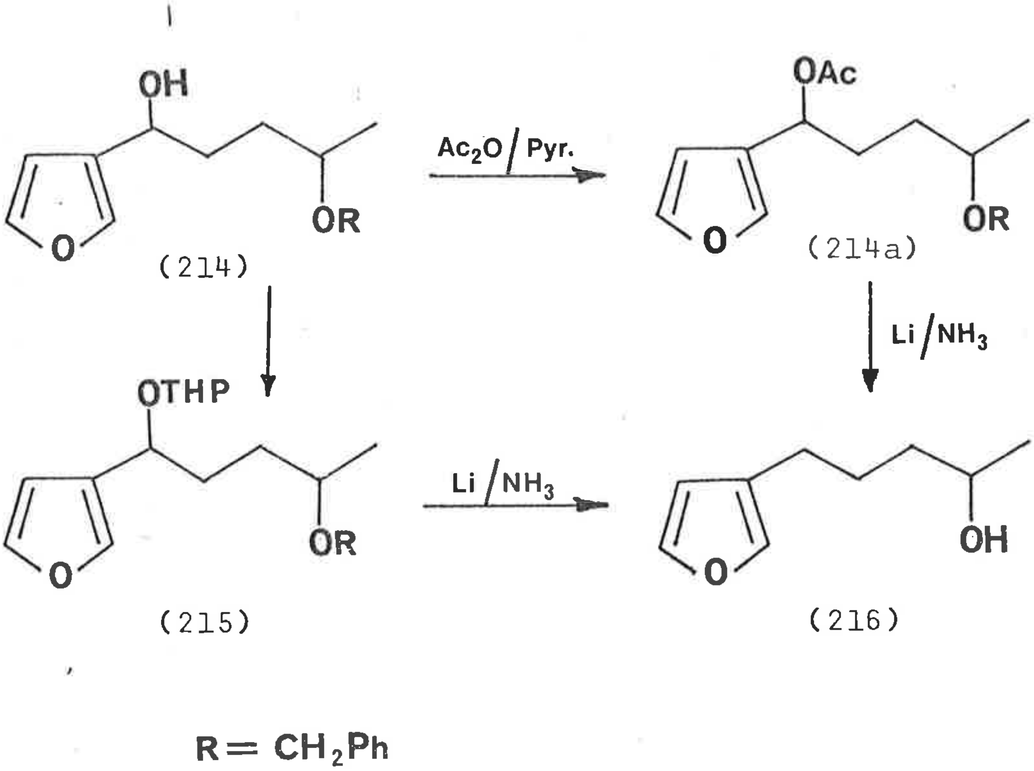


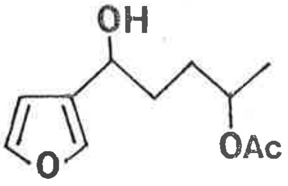
No tertiary alcohols were isolated from the reactions although highly coloured polar products were also formed (15%)

In order to remove oxygen functionality at C1 in (213) the ketone was reduced with sodium borohydride or lithium aluminium hydride to the alcohols (214). It was hoped that conversion of alcohols (214) to the benzylic-like acetates followed by reduction with lithium in ammonia would give the desired alcohols (216). However, reduction of the acetates (214a) without a proton source (over 15 min) gave on workup a mixture consisting of alcohol (216) (21%), acetates (235) and (236), and the diacetate of (237) in yields of 22-25% each. A reduction done over 2 h gave alcohol (216) (55-60%) and diol (237) (20%).

It is apparent from the above results that the benzylic group is rapidly removed which then allowed some transfer of acetate by an inter and/or intramolecular process leading to alkoxide species which could not be reduced further in the absence of a proton source. Although alcohols (235) and (237) were reacetylated and successfully reduced to (216) (74% overall yield), a more efficient one step reduction was required. This was achieved by conversion of alcohol (214) to the tetrahydropyranyl ether (215) which was cleanly and rapidly reduced to the alcohol (216) in 70-75% yield. No other reduction products were isolated.

At this point it was decided to pursue the synthesis via the Wittig route, and therefore the iodide (218) was prepared from alcohol (216) *via* a tosylate in 80% yield.





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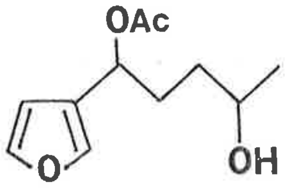

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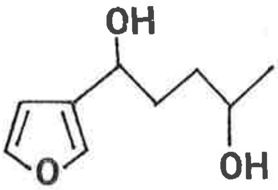

(237)

However, iodide (218) was prone to spontaneous decomposition and a larger scale preparation gave a lower yield.

The preparation of phosphonium salt (238) was investigated using triphenylphosphine and iodide (218). Reactions with and without solvents at temperatures* from 20° to 135° resulted in

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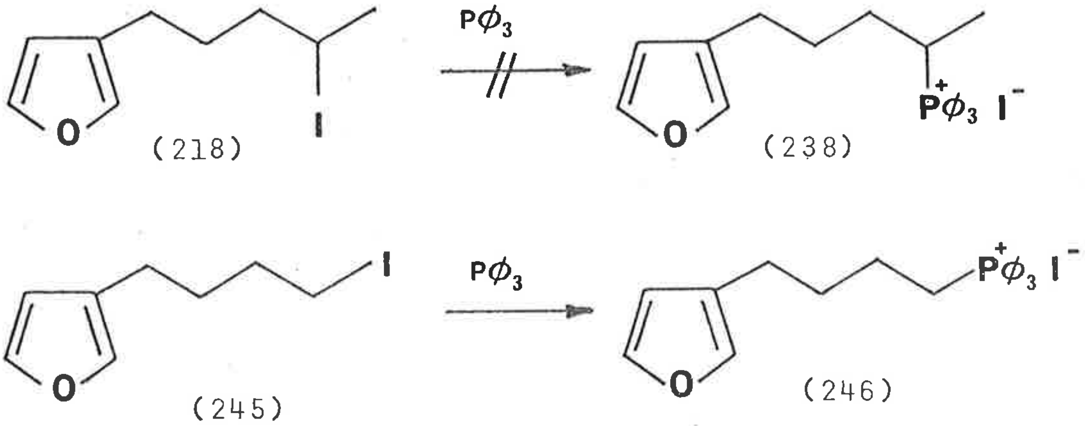
* When 2-bromo and 2-iodopentanes were used as models, the conditions for complete salt formation were 150° (15 h) for the former and 150° (6 h) for the latter. The 2-iodopentane and triphenylphosphine mixture on heating (with or without calcium carbonate) showed darkening due to the formation of iodine.

no salt formation because of decomposition of iodide (218). This was assumed to occur with the formation of hydrogen iodide and iodine which subsequently resulted in attack on the susceptible furan ring. A reaction in the presence of calcium carbonate to absorb any acid, also failed to give (238).

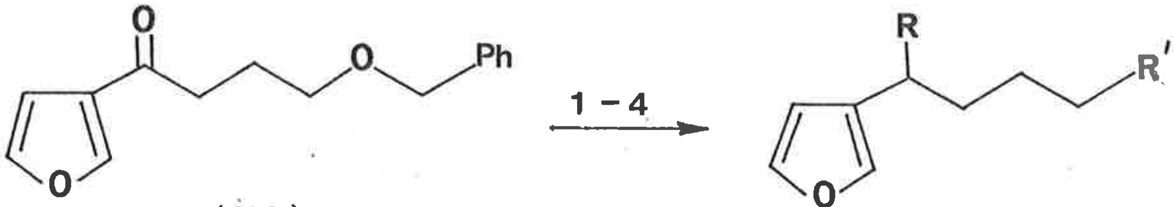
As ylides have been alkylated[166] to give phosphonium salts, it was decided that the preparation of the required salt could be achieved by alkylation of (246). However, this route required the preparation of the lower homologue, iodide (245). The formation of the phosphonium



salt from the primary iodide (245) was expected to be a more favourable process on steric grounds.

Using the benzyl ether of commercially available 3-chloro propanol, the ketone (241) was synthesised, (78-80%) under the same conditions as previously described for (213). This product was again accompanied by the diketone (247) (4%) and the benzyl ketone (233) (2%). Reduction of ketone (241), conversion to the tetrahydropyranyl ether (243) and Birch reduction gave 4-(3'-furanyl)butan-1-ol (244) (76% overall). Conversion of alcohol (244) to the mesylate and displacement with sodium iodide produced the iodide (245) (84-87%). This iodide, in contrast to the secondary iodide, readily formed a phosphonium salt (246) in boiling benzene (87% yield) without any decomposition.

The ylide (239) of the primary phosphonium salt (246) was prepared, using n-butyl lithium as base, and transferred into an excess of methyl iodide. In this way the required salt (238) was prepared in good yield (90%).



(241)

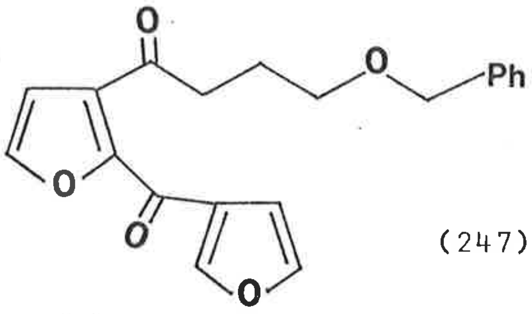
1) NaBH$_4$ $\longrightarrow$ (242) R = OH, R' = OCH$_2$Ph

2) dihydropyran $\xrightarrow{H^+}$ (243) R = OTHP, R' = OCH$_2$Ph

3) Li/NH$_3$ $\longrightarrow$ (244) R = H, R' = OH

4) MsCl/TEA, NaI $\longrightarrow$ (245) R = H, R' = I

When the base used to prepare ylide (239) was methyl lithium the n.m.r. spectrum of the products isolated showed that considerable quantities of ring alkylated products were formed. These could not be readily removed from (238). This result is unusual considering the relative basicities of the two alkyl lithiums.



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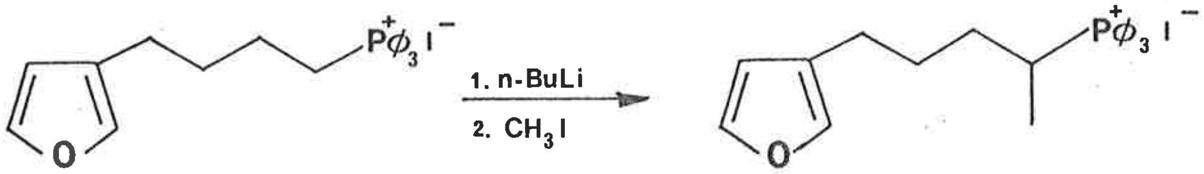


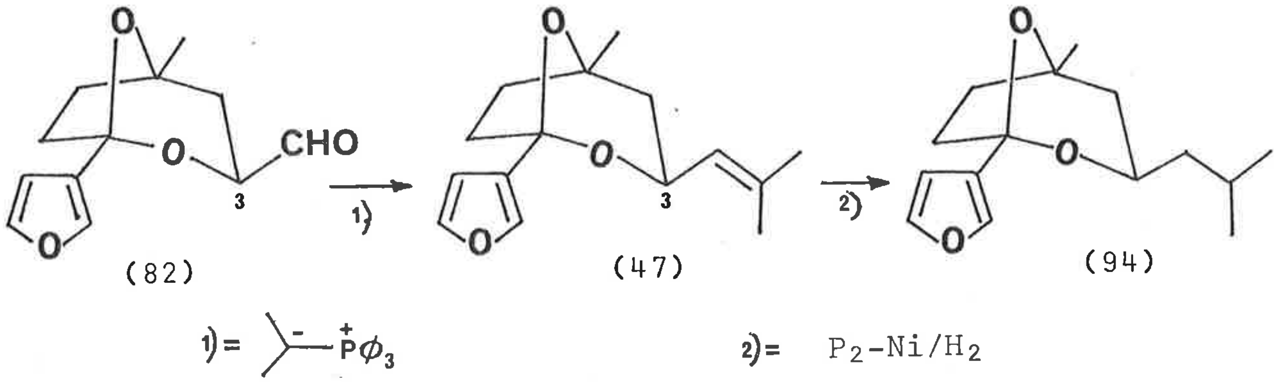
(246)

(238)

7.3 Coupling of aldehyde (82) with the C9 alkyl furan.

As alternatives to the ylide reagent the preparation of Grignard reagents and alkyl lithium from iodide (218) could not be achieved. This approach (scheme 7.1) was however only very briefly explored. Coupling products of the halide (218) were isolated together with starting material in such preparations. The chloride or bromide would probably be more suitable for the Grignard or alkyl lithium preparations.

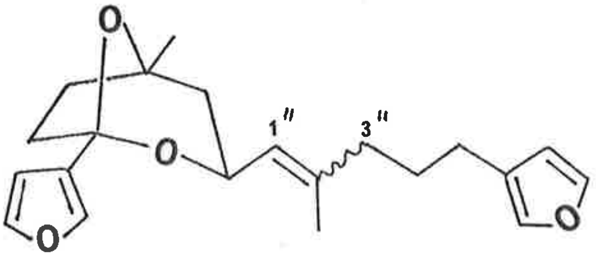
The viability of the Wittig reaction was demonstrated by the synthesis of eremoacetal (47) from aldehyde (82) in good yield without isomerisation at the vital C3 centre. Similarly,



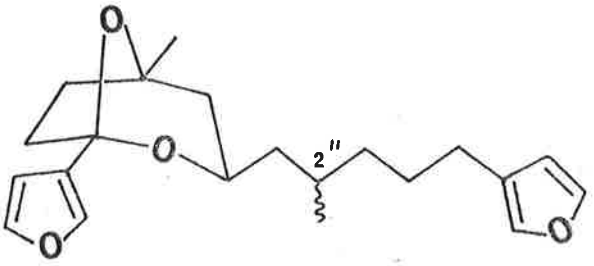
(82) (47) (94)

2)= P_2-Ni/H_2

when the phosphorane of (238) reacted with aldehyde (82), the alkenes (248) were isolated as a mixture of *E* and *Z* isomers



(248)



(249)

(3:2) (78%). The isomers could not be separated by t.l.c. but structural confirmation was obtained from the ^{1}H and ^{13}C n.m.r. spectra. In particular, the ^{13}C spectra showed the distinct C2" methyl at 16.7 and 27.3 ppm and C3" at 39.0 and 31.9 ppm for the *E* and *Z* isomers respectively.[133] Separation of the isomers of (248) was considered unnecessary as hydrogentation of each was expected to produce a similar mixture of the dihydroepimers (249).

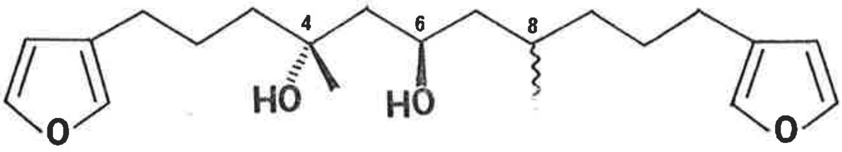
7.4 Hydrogenation of C_{21} alkene (248).

Hydrogenation of eremoacetal as previously described, proceeds well albeit slowly, using P_2-Ni and hydrogen. The reduction of the analogous trisubstituted mixed alkenes (248) was even slower but could be carried out with a high degree of selectivity.

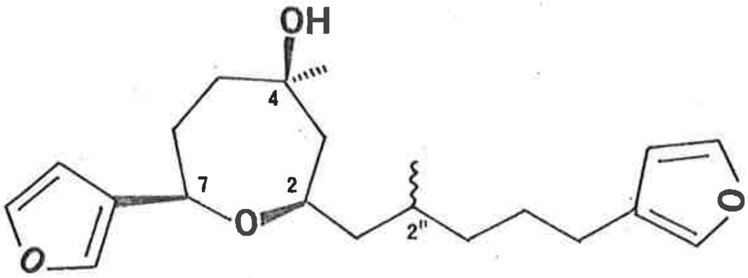
Only traces (< 5%) of furan reduction or hydrogenolysis products were detected by t.l.c. After 7 days, approximately 53% of the dihydroproducts (249) and 34% of starting material (248) were recovered. In a large scale reduction (0.13 mole ratio of catalyst to substrate) hydrogenation was 90% complete after 20 days. Faster reduction was achieved by using a higher mole ratio of catalyst (1.6 mole ratio) and after 15 h no alkene remained. The dihydrocompounds (249) were isolated (70%) and also two more polar biproducts (25%) arising from hydrogenation of the furan on the alkyl chain. From the above observations optimisation of the substrate to nickel catalyst ratio would allow a highly selective reduction in reasonable times. No separation of the two C2" isomers (249) could be achieved using t.l.c. or h.p.l.c. It was clear from the ^{13}C spectrum that both epimers were present; the chemical shift of carbons near the asymmetric centre at C2" were different in the two isomers (see appendix).

7.5 Birch Reduction of C_{21} Acetal (249)

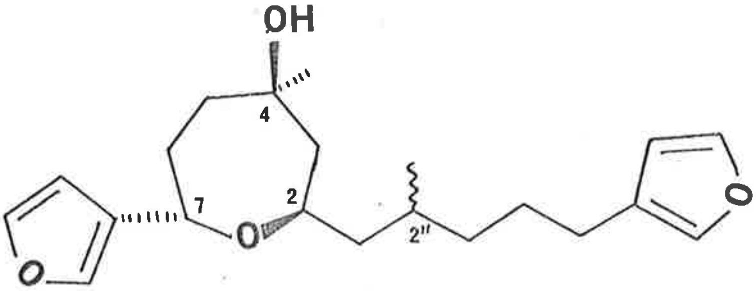
The possibility of reducing the acetal function of (249) was earlier demonstated with the reduction of the analogous dihydroeremoacetal to the corresponding diol (124) and oxepanes (see Chapter 2.3). A trial reduction of (249) using lithium in ammonia at -33° without a proton source gave (after 9 h) 30% recovered starting material, 22% of the required diols (211), 26% of the polar oxepane isomers (250) and 9% of the epimeric less polar oxepane isomers (251).



(211)



(250)



(251)

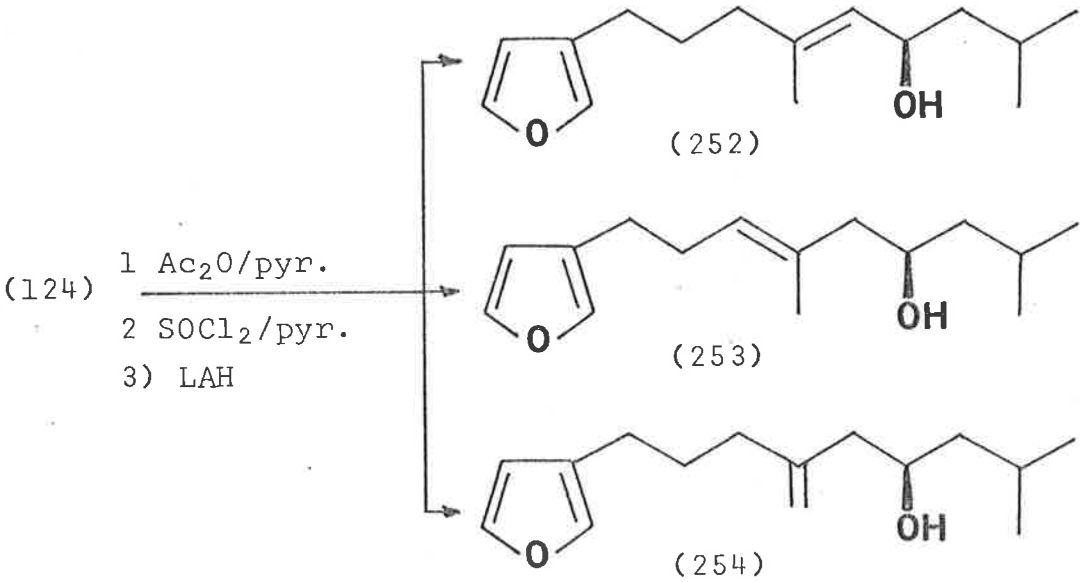
An extended reduction of acetal (249) over 20 h gave diols (211) 56%, minor high R_f oxepanol (251) (2%), major lower R_f oxepane isomers (250) (30%) together with starting material (4%). By analogy with the C_{15} oxepanols, (using their ^1H and ^{13}C n.m.r. spectra) together with the very different polarity of (250) and (251), the stereochemistries at C7 were assigned as *R* for (250) and *S* for (251). Again, no separation of the C2" epimers of the oxepanols was evident by t.l.c. on silica.

The oxepanols (250) and (251) were reduced over 22 h without purification to the required diol (211) in 38% yield, with considerable recovery of starting materials (32%).

The isomeric diols (211) could not be separated by t.l.c. or h.p.l.c. nor could their acetates or 1,1'-biphenylcarboxylates. The ^{13}C n.m.r. spectra clearly showed a diastereomeric mixture for the diols (211) and their monoacetates, the major and minor oxepanol isomers (250) and (251) respectively (see appendix).

7.6 Dehydration of the Tertiary Alcohol

A suitable model for the dehydration of the C4 hydroxyl in (211) was the readily available C_{15} diol (124). Using this model it was possible to establish conditions for dehydration and separation of the alkenes. These results were then applicable to the furospongin-1 and to the 4-hydroxydendrolasin synthesis (see Chapter 5).

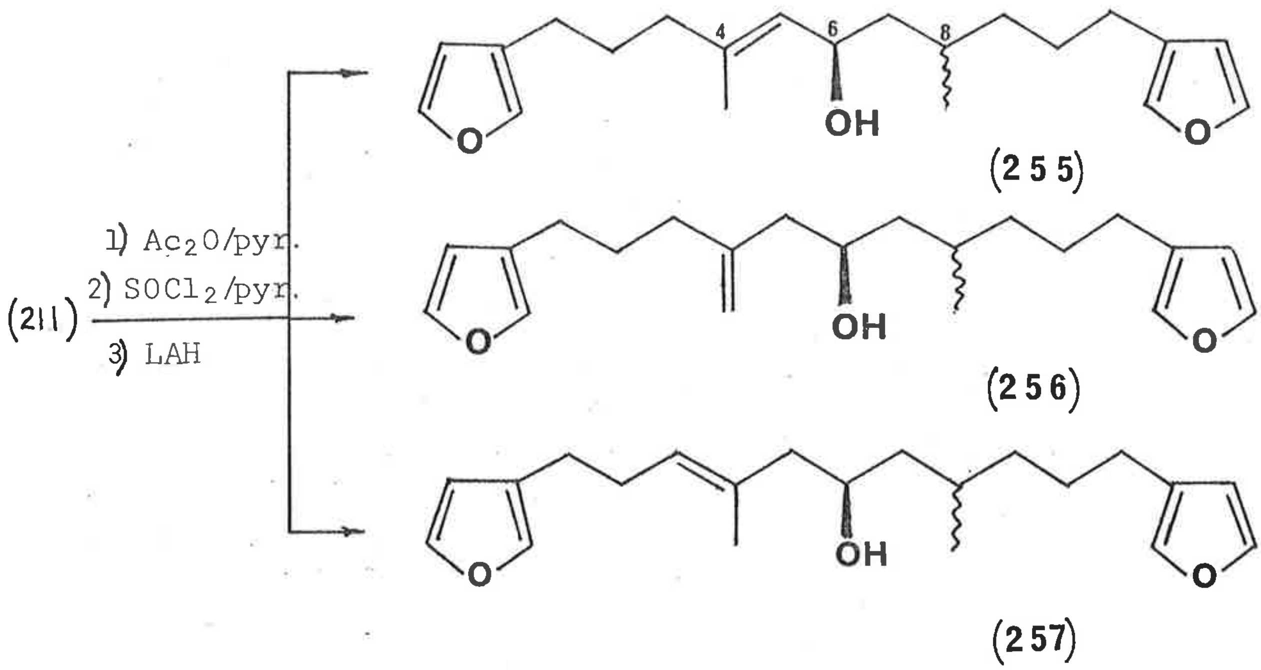


Protection of the secondary hydroxyl group of (124) as the acetate gave, after treatment with thionyl chloride/pyridine at 0°, a mixture of isomeric alkenes. These alkenes were readily separated as the alcohols, after reductive removal of the acetate, on silica gel and silver nitrate impregnated silica gel. Separation of the allylic alcohols (252) (25%) from (254) and (253) (60%) was achieved on silica. The non allylic alcohols (253) and (254) (*E* and *Z*) were separated on silver nitrate/silica in 20% and 36% yields respectively. The alkenes (252) and (253) consisted of a mixture of *E* and *Z* isomers (approx. 2:1) as shown by their ^{1}H and ^{13}C n.m.r. spectra (see appendix). It was possible to separate the *E* and *Z* isomers, as their esters, using h.p.l.c. as demonstrated with the analogous 4-hydroxydendrolasin (Chapter 5.4).

Attempts to improve the preparation of isomer (253) using other reagents like phosphorus oxychloride, methanesulphonyl chloride, with other bases such as triethylamine or 2,6-dimethylpyridine gave poorer overall yields without significant enhancement of desired product (253). The bulky 1,1'-biphenylcarboxylate ester of diol (124) showed no significant change in alkene ratios after dehydration.

By analogy with diol (124) the protection and dehydration sequence was applied to the C_{21} diol (211).

Conversion of diol (211) to the acetate and reaction with thionyl chloride and pyridine gave a mixture of alkenes.



Reductive cleavage of the acetate group and chromatography on silica, as with the C_{15} analogues, gave the more polar allylic alcohols (255) (20%). The two C8 epimers of (255) (stereochemistry unassigned at C8) were separated after repeated chromatography on silica and each consisted almost exclusively of the *E* isomer (>95% estimated from the ^{13}C and ^{1}H n.m.r. specta). The increased stereoselectivity for the *E* isomer in the C_{21} series can be explained in terms of the increased steric interactions in the transition state.

Separation of isomers (256) (16%) from (257) (32%) was possible by chromatography on silver nitrate impregnated silica. Again, the epimers of (256) (unassigned) were separated by repeated chromatography. As with the two C8 epimers of (255), those of (256) showed small but distinct differences in the ^{1}H and ^{13}C spectra (see appendix), especially near the epimeric centre.

The major alkene (257) (32%) consisted of a mixture of *E* and *Z* isomers as well as the C8 epimers. The *E* and *Z* isomers (3:2) were separated as their 1,1'-biphenylcarboxylates using h.p.l.c. The minor *Z* isomers showed the vinylic methyl substituent at δ 1.77 and 23.8 ppm in the ^{1}H and ^{13}C n.m.r. spectra. In contrast, the spectra of the isolated *E* isomers showed the same methyl substituent at δ 1.67 and 16.3 ppm (see appendix).

Although it was possible to separate all the alkene regioisomers; the *E* and *Z* isomers and the C8 epimers in (255) and (256), it was not possible to separate the C8 epimers in *E* (257) to provide pure enantiomeric furospongin-1.

Attempts to separate the C8 epimers of *E* (257) included h.p.l.c. and t.l.c. (silica, silver nitrate on silica, alumina) on both the alcohols of *E* (257) and its biphenylcarboxylate ester as well as g.c. of its silyl ether using a variety of stationary phases. No separation was achieved in any of the above cases. It was evident from the ^{13}C n.m.r. spectra that both the *E* and *Z* isomers of (257) each consisted of an epimeric mixture; the chemical shift of carbons near C8 were different for each epimer and were similar to the separated epimers of (255) and (256).

The specific rotation of the synthetic furospongin-1 mixture was +10.5 ± 1.5°. This result together with the unexpected result for the Horeau's stereochemical determination, suggests that the influence of one C8 epimer in the mixture dominates in both determinations. The enantiomeric furospongin-1

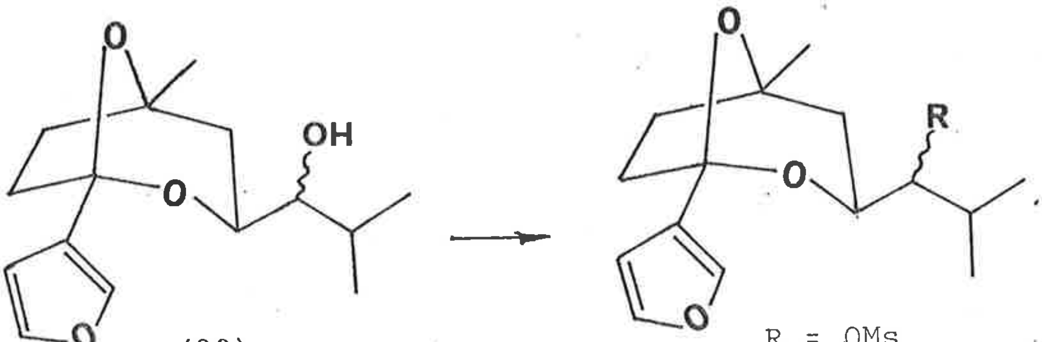
Footnote: Recent attempts to obtain ^{13}C spectral data for Furospongin-1 from Dr. Wells^{56} or Prof. Minale^{53} were unsuccessful.

would be expected to have a specific rotation of approximately -9°, based on Minale's measurements.[53] The dextrorotation obtained for the mixture (257) (approx. 1:1) indicates that the C8 epimer of enantiomeric furospongin-1 is dextrorotatory to a larger extent ($[\alpha]_D^{20}$ approx $+20^\circ$). Similarly, the furospongin-1 epimer presumably exerts a larger than expected effect in the determination of configuration (see Chapter 8.4).

Although the furospongin-1 synthesis was successful in providing a variety of related double isomers for Horeau's determination the synthesis did not provide pure enantiomeric furospongin-1. Therefore, any alternative synthesis would require a stereoselective approach or separation of epimers earlier in the synthetic sequence: the other route, *via* alcohols (260) and (261), was briefly explored using the C_{15} alcohols (90) as models.

7.7 The alternative scheme, resulting in (260) and (261) (p.139) by using Grignard, alkyl lithium or hydroboration reagents, would require separation of isomers at C1 and C2 and removal of the C1 oxygen substituent. The C1 epimers of alcohol (90) have been separated and the separation of the C1 isomers in the C_{21} analogues would also be expected to be possible. Furthermore, the separation of C2 epimers would be expected to be more facile because of the adjacent asymmetric centre at C1 . The formation of the alcohols (90) *via* Grignard reagents and by hydroboration has been discussed (Chapter 3) and consequently the removal of oxygen from C1 was explored.

Initally, a proposal for the removal of the oxygen from C1 in the model alcohols (90), involved conversion to a halide (263) followed by a radical reduction with tributyltin hydride. However, the mesylates (150 and 151) prepared from alcohols (90) were inert towards substitution by halides in a number of aprotic solvents (DMF,[156] DMSO,[155,157] HMPTA). The chloride could not be prepared from alcohols (90) using triphenylphosphine and carbon tetrachloride, nor thionyl chloride. Neither starting material nor decomposition products was isolated in these reactions. Consequently halide formation was abandoned. The difficulty in forming halides (263) was presumed to be due to steric reasons.



(90)

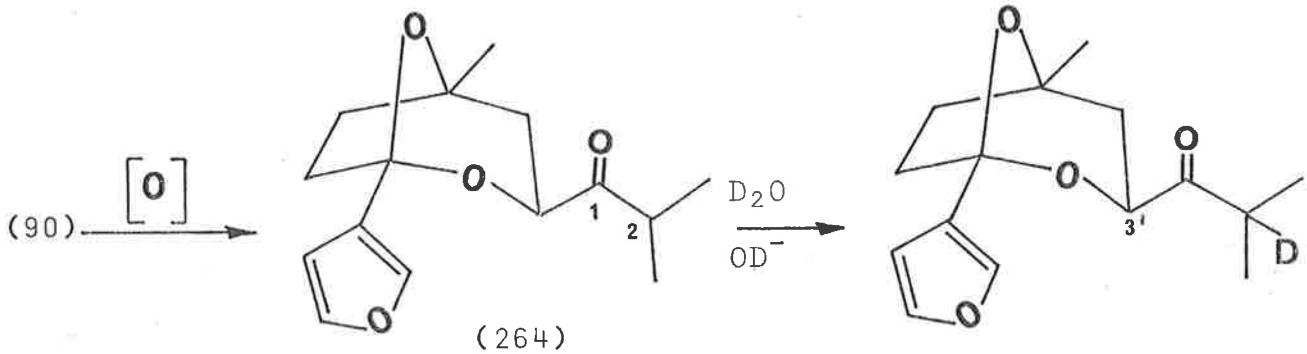
R = OMs (150/151)

R = Cl,Br,I (263)

R = H (94)

It was possible, however to reduce the mesylates (150 and 151) to the dihydroacetal (94) by using an excess of lithium triethylborohydride[95] in boiling tetrahydrofuran. After 2 days, the isolated products consisted of the required dihydroacetal (94) (35%), some elimination product (47) (10%) and starting material (30%). With optimisation, this reduction might provide an alternative to the hydrogenation of the double bond. The use of sodium borohydride in DMSO[94] to reduce the mesylates (150/151) gave a complex mixture of polar products at 100° and no reaction occurred at 20°. The reductive removal of the C1 oxygen requires further investigation before it can be synthetically useful.

Some preliminary oxidation and deuteration experiments to see whether the C3′ and C2 carbon centres of (90) could be epimerised were carried out. This might allow the conversion of one C2 epimer to another in the earlier stages of a synthesis. Oxidation at C1 was possible by the use of Swern's reagent[67] to give the C_{15} ketone (264) (85%). In contrast, chromium based oxidants (e.g. pyridinium chlorochromate, Collins reagent), gave lower yields (15-20%) of ketone (264). Furans have been oxidised to butenolides [111,112] and this reaction together with ring opened products may explain the low yield. Difficult oxidations of furan containing alcohols were generally successful if Swern's procedure[67] was used.



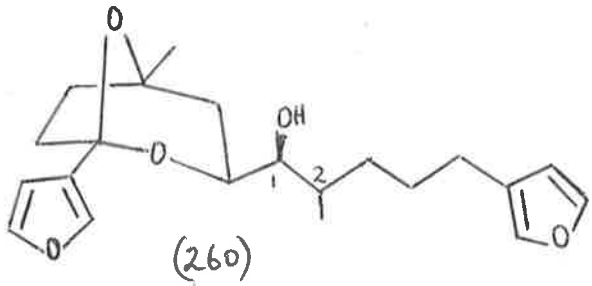
(264)

The possibility of epimerisation at C2 was demonstrated by the treatment of ketone (264) with base in D_2O (15 h, 20°);

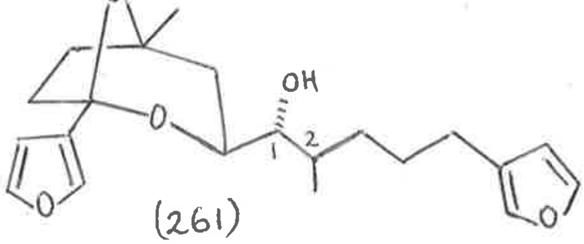
deuterium being incorporated at C2 (3H (s) at 1.1 ppm in the ^{1}H n.m.r. spectrum). Some exchange without epimerisation (t.l.c., n.m.r.) at C3$'$ (40-50%) was also observed. Therefore it seems likely that oxidation of (260) or (261), followed by epimerisation and/or reduction would allow interconversion of one epimer at C2 of (260) or (261) with another.

The previously discussed reductions of mesylate C_{15} (see Chapter 2.5) might provide a useful and novel alternative to the metal/ammonia reduction of the acetal. Hydroboration of pure *E* or *Z* isomers of (248) would occur in a *cis* manner to produce alcohols (260) and (261) where the stereochemistry at C1 and C2 are clearly related. Ring opened products of hydroboration are also potential precursors to furospongin related compounds.

It is evident from the above discussion that much of the known chemistry, of eremoacetal can be utilised to provide useful chiral intermediates in the synthesis of compounds related to furospongin-1.



(260)



(261)

Chapter 8

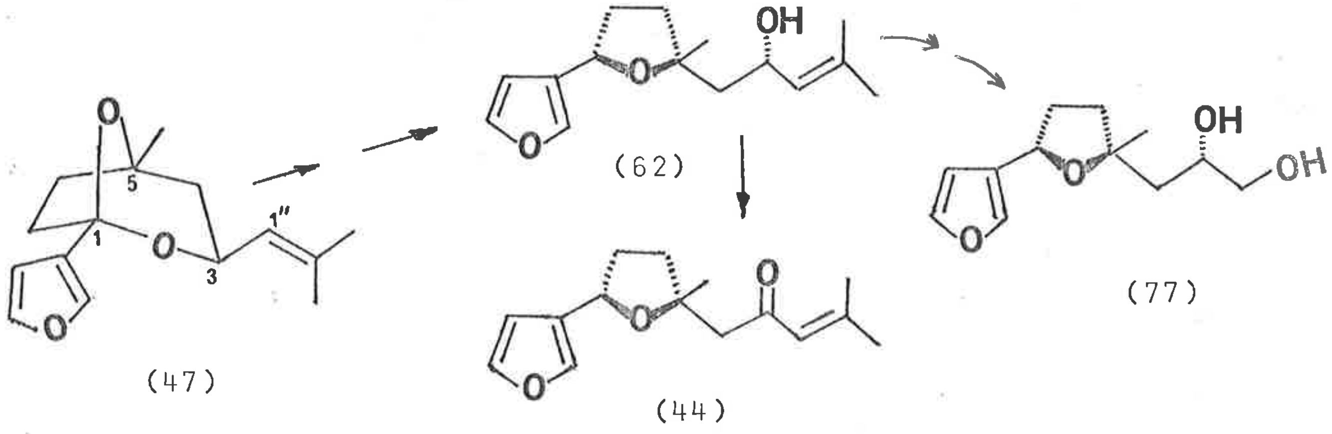
Steric Effects in Horeau's Method of Determining Absolute Configuration.

8.0 Necessary for a complete structural description of a compound, one must consider any stereochemical features inherent in it. In chapter 2 the structure and stereochemistry of eremoacetal were described. In this natural product the determination of configuration of two asymmetric centres involved the application of two different methods.

A number of methods are available for the determination of absolute stereochemistry. Chemical degradation or interconversion to a compound of previously defined stereochemistry has been frequently applied. This method was used to determine the stereochemistry at C5 in eremoacetal (47) by conversion to dehydrongaione (44) and dehydrongaiol (62). Both X-ray analysis and chiroptical methods,[158 159] can provide useful stereochemical information. Recently a ^{13}C n.m.r. method has appeared[160] whereby the configuration of secondary alcohols is obtained from the spectra of their glycosides. A method frequently used for the determination of absolute configuration of secondary alcohols, is Horeau's method[64 65] of partial kinetic resolution. This method was used to determine the configuration at C3 in eremoacetal after modification of the molecule. The need for this modification, as applied to eremoacetal, emphasises an important limitation of Horeau's method, namely the assessment of the effective steric sizes of the two groups about the chiral secondary alcohol. This particular aspect has been studied using eremoacetal as a chiral precursor to a number of chiral secondary alcohols with varying substituents.

8.1 Although many alcohols have been subjected to Horeau's method the steric ambiguity in many others has precluded its wider application. Indeed, this problem arose in the determination of the stereochemistry of dehydrongaiol (62) derived from eremoacetal. In order to remove this ambiguity regarding the steric requirements of groups, it was necessary to remove the geminal dimethyl groups to give diol (77). Diols of this type give unambiguous results, according to the studies by Guetté.[65]

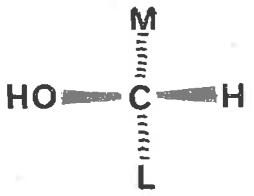
During the chemical investigation of eremoacetal (see Chapters 2,3), because of its availability and the variety of secondary alcohols which could be prepared from it, it was clear that the natural product would be a useful material for a study of steric effects. A series of alcohols have been made with the known stereochemistry of (47) at C3 retained. Also, the alkene group of (47) allowed the formation of a new chiral



centre at Cl" by various means. Early investigations showed that epimers at Cl" could be readily separated and used in such stereochemical studies. Other alcohols derived from the synthetic investigations were also studied and the results obtained allowed the determination of stereochemistry of a natural product, 4-hydroxydendrolasin (see Chapter 5).

In general, the g.l.c. modification of Horeau's technique was used with as many chiral secondary alcohols derived from eremoacetal as were available. Some determinations were necessarily repeated using the unmodified method.

8.2 Horeau's method involves the partial kinetic resolution of (±)-2-phenylbutanoic anhydride and is, in general, highly reliable.[64] An empirical correlation between configuration based on known effective steric sizes, as shown below, and the more reactive enantiomeric anhydride species, has been established and successfully used. Accordingly, alcohols of configurational type show below, preferentially react with the (R)-2-phenylbutanoyl species, resulting in a depletion of these forms in the remaining excess of anhydride.



M = medium size group

L = larger size group.

In practice the unreacted anhydride is hydrolysed, the acids isolated and their optical rotation measured and related to the configuration of the alcohol. This method requires relatively large samples of alcohols, (typically 50-150 mg), although the optical yields are often high and may approach 50-60%.

A recent modification has been described[136] in which the enantiomerically enriched anhydrides are converted to diasteriomeric amides for quantitation using gas chromatography. This convenient procedure permits the application of Horeau's method to small quantities (10 mg or less) of chiral secondary alcohols. After esterification of the unknown alcohol, addition of (+)-*R*-2-phenylethylamine rapidly forms the *RS* and *RR* diastereomeric amides, without any appreciable kinetic resolution of the anhydride. The resulting mixture is then analysed for the relative proportions of the two amides by g.l.c.

This investigation utilised the Brooks and Gilbert modification in order to test its general applicability and limitations. In addition to the steric and mechanistic information resulting from this investigation, the determination of the configuration of several compounds enabled the preferred approach of electrophilic reagents to the double bond of (47) or nucleophiles to the aldehyde (82) to be determined.

8.3 Application of Horeau's method

The Brooks and Gilbert modification was used for almost all the alcohols in order to confirm Brooks' findings, to obtain some estimate of relative amide response ratios and/or to determine if *any* resolution of anhydride occurs during their formation. These investigations were carried out because the symmetry of some of the alcohols was expected to result in low optical yields. Therefore, it was necessary to determine the limitations of the method and, if possible, to improve its sensitivity and/or applicability. Minor modifications to the method were accordingly made where necessary. Where some doubt existed in the stereochemical results, the unmodified Horeau's method was used or a h.p.l.c. modification of Brooks' method used for further confirmation.

Resolution of (±)-2-phenylbutanoic acid was carried out with cinchonidine[161] and the acids converted to the sodium salts. Treatment of each of the sodium salts with oxalyl chloride gave the enantiomeric anhydrides in high yield and greater than 85% optical purity.[64b] The respective amides were prepared from each anhydride using (+)-*R*-2-phenylethylamine. Each amide was purified by recrystallisation. Purity checks, by g.l.c., showed the *RR* isomer (m.p. 76-78°) to be 97.0 ± 0.05% pure and the *RS* amide (m.p. 118-119°) to be 98.3 ± 0.07%. Each isomer was only contaminated by its epimeric amide and the composition of the synthetic mixtures was corrected for purity.

Several stationary phases have been used by other workers, including OV-17,[162] OV-101,[163] OV-225[162] and FFAP.[163] From the published results[162] of relative retention times the OV-225 was chosen as it resolved the two amides best without the need for temperature programming.

It was confirmed that the *RR* amide isomer was eluted first. The use of Helium as carrier gas rather than N_2 gave better resolution of the two amides although this was not employed in practice. Resolution to baseline was achieved with good peak symmetry using OV-225 as stationary phase and Nitrogen as carrier gas.

In all cases the most appropriate racemic or achiral reference alcohols (cyclopentanol, isopropanol, or hexan-3-ol) were run concurrently with the alcohols under test.

Standard mixtures of the two *RS* and *RR* amides of known composition were prepared and analysed (see Table 8.31) by g.c. using a computerised integrator. Reproducibility and accuracy from analysis of these standards were shown to be within ±0.3%, (excepting std. No. 7).

TABLE 8.31

Standard Mixtures of *RR* and *RS* amides - Composition by G.l.c.

Mixture No.	Calculated %* Composition (weighing error)	Found Composition % (reproducibility) **	Δfound-calc. % *RR* amide
1	53 (±1)	53.1 (±0.1)	0
2	53.8 (±0.3)	53.5 (±0.1)	-0.3
3	49.6 (±0.5)	49.7 (±0.1)	0.1
4	48.6 (±0.3)	48.2 (±0.1)	-0.4
5	46.3 (±0.7)	46.4 (±0.1)	0.1
6	44.7 (±0.4)	44.5 (±0.1)	0.3
7	43.0 (±0.4)	43.6 (±0.1)	0.6
8	31.0 (±0.5)	31.1 (±0.1)	0.1

* Only the *RR* isomer is listed, the *RS* isomer consitutes the remainder.

** Based on the average of 2-3 determinations

The racemic or achiral alcohols typically gave 50.9 ± 0.8% of the *RR* amide isomer using an excess of pyridine and two equivalents of racemic anhydride.

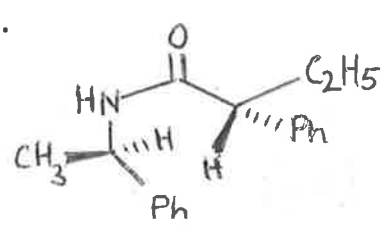
The response of the detector was shown to be invariant to the two amides, therefore the predominant *RR* amide formed in the reference sample must reflect a small but significant kinetic resolution of the anhydride by the amine.

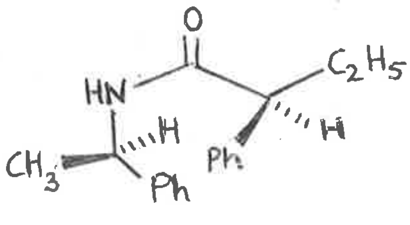
Initially, esterification was carried out over 1.5 h at 40° as recommended by Brooks and Gilbert. However, it was found that increasing the esterification time to 15 – 20 h at 20° improved enantiomeric anhydride yields. Presumably this was due to more complete esterification, especially with hindered and less reactive alcohols. Racemisation of the resulting enantiomerically enriched anhydride with extended esterification time, must therefore be of lesser significance than the gain made from more complete esterification.

The percentage area representing the *RR* amide (265) (derived from the (-) *R* acid) in the reference was substracted from the corresponding *RR* amide in the sample containing the alcohol under investigation. Each reaction mixture was injected and analysed in duplicate or triplicate (or until the agreement was < ±0.3%).

Where sufficient alcohol was available and the results were indefinite, the conventional Horeau's method was used. The cause of ambiguous results can be due to low optical yields, insufficient esterification or interference by other components (alcohol, esters, impurities etc.) in the mixture. Most of these problems were encountered. Routinely, if the stability of the alcohol to esterification conditions was good, an extention of reaction time overcame incomplete esterification problems.

(265)





(266)

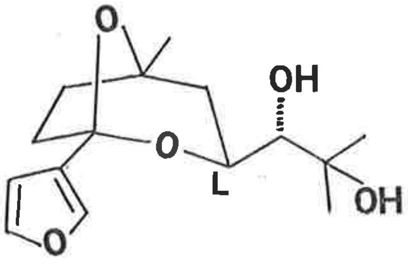
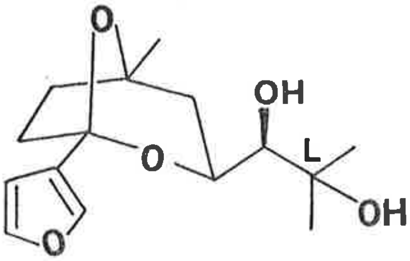
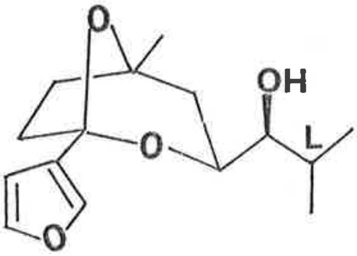
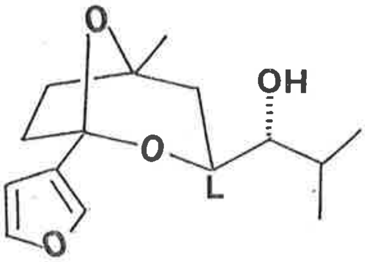
As the two *RR* and *RS* amides showed good separation on silica t.l.c. plates, it was considered useful to use h.p.l.c. for the analysis. This was found, in some cases to eliminate interference problems arising from the coincidence of retention times of the amides with alcohols, esters or other products. Therefore, it appears that h.p.l.c. is a good alternative to g.c. but in this technique the *RS* amide is eluted first, and calculations are based on this isomer. Both amides had the same response ratios when the U.V. detector was used at 254 n.m. in conjuction with h.p.l.c.

8.4 Results and Discussion:

The application of the Horeau's procedure to the listed secondary alcohols gave results which are summarised in Tables 1-4. In most cases an unambiguous conclusion can be made about the relative sizes of groups in those alcohols of known stereochemistry. Where the stereochemistry is unknown, but where effective steric priorities could be assigned, the technique usually allowed the assignment of stereochemistry.

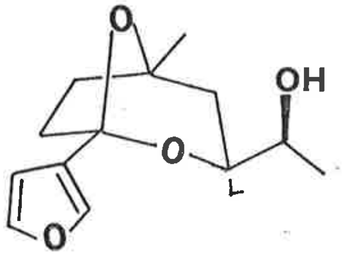
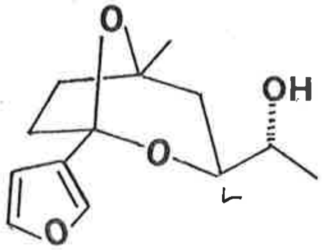
As the aim of the investigation was in part to explore the modified g.c. method , that technique was applied whenever possible; sometimes with modification. To confirm the g.c. results, the original Horeau method was used for some alcohols. The results obtained from g.c. are expressed as a percent decrease (-), or increase (+) in the *RR* amide isomer (265), derived from the corresponding *R*-2-phenylbutanoyl group after kinetic resolution. It was necessary to check some results by the original Horeau method when the optical yields were low or interference suspected in the determination.

Table 8.41

Compound	Average ΔRR% (2h,40°)	Average Δ RR% (16h,25°)	Recovered Acid ** (Opt. Yield)	Configuration
(-)-menthol	-6.0	-6.9	(+)S	R
 (86a)	-2.1	-4.0	(+)S(50%)	S *
 (86b)	-	<1	(+)S(8%)	R *
 (90b)	<1	-1.4	(+)S(17%)	S *
 (90a)	<1	-2.0	(+)S(25%)	R

L = larger substituent

Table 8.41 continued

Compound	Average Δ RR% (2h,40°)	Average Δ RR% (16h,25°)	Recovered Acid ** (optical yield)	Configuration
 (170)	-	+6.0	-	S
 (169)	-	-6.8	-	R

* See discussion for assignments

** Results from the unmodified Horeau's method[64]

When using the g.c. method, the results were considered inconclusive when kinetic resolution by the alcohol resulted in less than a 1% excess of one of the amides relative to the same amide in the reference.

Before the application of the modified Horeau's method to the acetal alcohols shown in Table 8.41, the method was applied to (-)-menthol. The result obtained, after a 2 h esterification period at 40° (Brooks and Gilbert conditions), compares well with the published decrease in the *RR* amide. This reflects, according to Brooks, half the uncorrected enantiomeric yield. It is also related to the degree of esterification which may well be incomplete.

However, when the esterification time was increased to 16 h (at 25°), the % decrease in the *RR* amide isomer was improved from an average -6.0% to -6.9%. This improvement in the decrease of recovered isomeric amide was particularly evident in the other cases examined where the esterification time was increased.

When the method was applied to the epimeric diols (86a) and (86b) from osmylation of eremoacetal, no stereochemical conclusion could be reached. The major diol isomer (86a), gave a large decrease in the recovered *RR* amide (average -4% after 16 h esterification) but the epimeric diol (86b), showed no significant change in % *RR* amide. When diols (86a) and (86b) were examined by the original Horeau method, they *both gave the same recovered acid,* although in different optical yields; 50% and 8% respectively. It was possible however to determine the configuration of the diols by correlation with other compounds of known stereochemistry as described earlier. The *S*, and major diol isomer (86a) gave the higher optical yield with the dioxabicycloctyl groups having the larger (L) steric influence during the esterification. Surprisingly, the *R* (minor) isomer (86b) gave the same recovered acid (+ *S*) although in low optical yield. The low optical yield would explain the insensitivity of the g.c. method in this isomer. In this case, the hydroxyisopropyl group has the slightly larger steric influence. This observation might be rationalised in terms of preferred conformations resulting from strong intramolecular hydrogen bonding. It is important to note the potential importance of nearby polar substituents[64] and of long distance effects in determining the course of kinetic resolution.

The stereochemistry of alcohols (90a) and (90b) were determined by correlation with alcohols (169) and (170) formed by the addition of Grignard reagents to aldehyde (82). Again both (90a) and (90b) gave the same acid from esterification as analysed using both the g.c. method and the original method. Optical yields of 17% and 25% were obtained from (90b) and (90a) with recovery of the *S* acid in both cases. From the known *S* stereochemistry at C1 in (90b) the results show that the isopropyl group is clearly the *larger* substituent (L), whereas in the epimer (90b) the dioxabicyclooctyl substituent is effectively the larger (L) substituent. The decreased optical yield in the esterification of (90a), by comparison with (86a), must result from the absence of the tertiary hydroxyl group at C2 in (90a). It is possible that the tertiary hydroxyl of diol (86a) is involved in hydrogen bonding to the O2 atom increasing the effective relative size of the dioxabicyclooctane ring. However, the *S* alcohol (90b) unexpectedly gave a higher optical yield (17%) than the corresponding diol (86b) (8%). Again, removal of the tertiary hydroxyl, from C2 in (86b) effectively *increases* the size of the isopropyl group. This result is difficult to explain without assuming a change in conformation or hydrogen bonding affecting the degree of kinetic resolution.

When alcohols (169) and (170), derived from Grignard reactions on aldehyde (82), were subjected to Horeau's procedure there was a clear and predictable result. The methyl group in (169) and (170) is clearly the smaller of the two groups and this is evident from the high enantiomeric yields obtained in both cases. One alcohol, (169) assigned the *R* configuration, gave the *S* 2-phenylbutanoic acid in excess after esterification. The other isomer (170), assigned the *S* configuration, gave the *R* acid in excess.

Table 8.42 shows the tetrahydrofuranyl derivatives which were examined by the Horeau's procedure to determine their stereochemistry. The determination of the steric effects with the two dehydrongaiols (60) and (62) was considered an important part of investigating the Horeau procedure. Related allylic alcohols occur in terpenoids. Initially the stereochemistry at C2 was obtained from the degradation product, the 1,2-diol (77) and from other correlation studies. Diols of this type have been studied by Guetté.[65] He has shown that the hydroxymethyl group was the smaller of the two groups.

Table 8.42

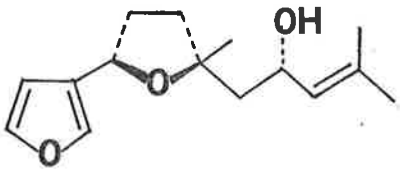
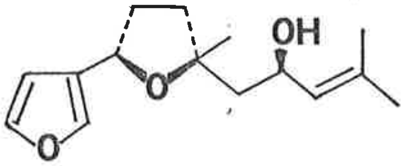
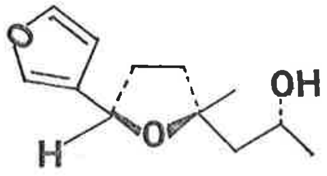
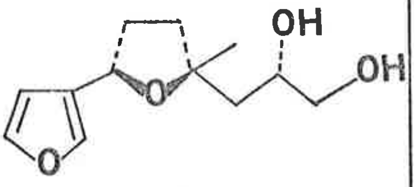
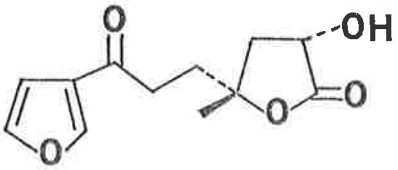
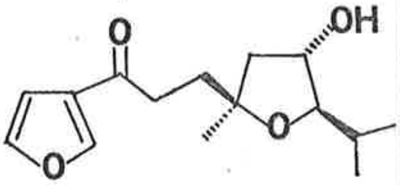
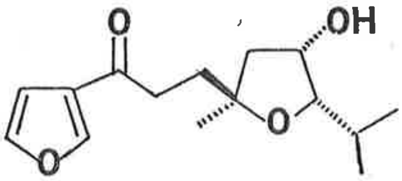
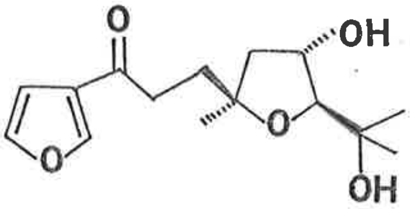
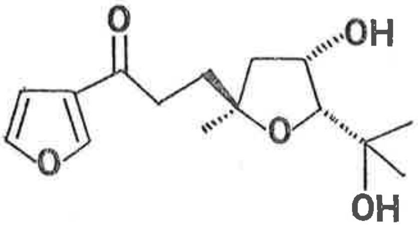
Compound	Average ΔRR% (2h,40°)	Average ΔRR% (16h, 25°)	Recovered Acid (Optical Yield)	Assigned Configuration
 (62)	-	+2.7	-	S
 (60)	-	-1.1	-	R
 (156)	-1.7	-	–	R
 (77)	1%	-	(+)S(20%)	S
 (85)	+7.5	-	-	S

Table 8.42 continued

Compound (No.)	Average ΔRR% (2h, 40°)	Average ΔRR% (16h, 25°)	Recovered Acid (optical yield)	Assigned Configuration
 (91)	<1%	-	-	*S*
 (92)	+1.0	+1.8	(-)R(12%)	*S*
 (88)	<1%	+1.4*	(±) (<5%)	*S*
 (89)	1%**	-	(-)R(20%)	*S*

* interference by g.c.
** determined by h.p.l.c.

Knowing that the stereochemistry at C2 in (62) and (60) is *S* and *R* respectively, the results obtained confirm that the isobutenyl group can unambiguously be assigned as the larger group.

Alcohol (156), when subjected to Horeau's method, gave the *RS* amide in excess, confirming the *R* stereochemistry at C2. This result gave support to the mechanism proposed for the formation of (156) (see Chapter 2.5).

Lactone (85), gave the *RR* amide in large excess, indicating a high enantiomeric yield from effective kinetic resolution. This result suggests that the neighbouring carbonyl group (π bond) is effectively the larger group as was also found with other allylic alcohols examined.

When Horeau's determination was applied to the substituted tetrahydrofurans (88) and (91), no excess of amide could be detected using the g.c. method. A repeat determination on (88), using the conventional Horeau's method, confirmed that the optical yield was below 5%. These results were not unexpected after an examination of models. The reagent approaching the α face encounters little steric interaction with the remote C2″ substituents. The hydroxypropyl substituent at C5″ of (88) does little to increase the effective steric size relative to the isopropyl group at C5″ in (91), as the substituents at C4″ and C5″ are *trans* to each other.

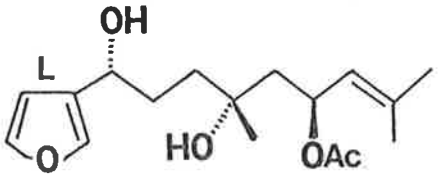
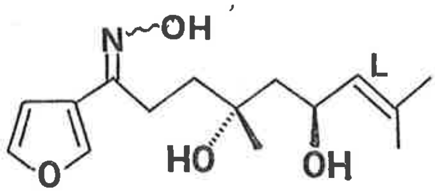
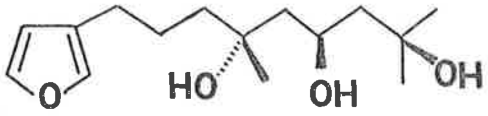
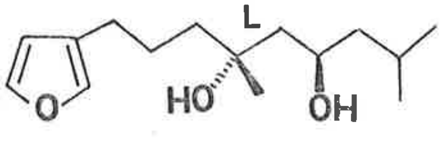
However, in the corresponding 4″,5″-*cis* isomers (89) and (92), the steric interaction between reagent approaching the C4″ hydroxyl and the substituents at C5″, is significant. Alcohol (92) gave predominantly the *RR* amide and the *R* acid was isolated in 12% optical yield when repeated using the conventional procedure. The corresponding *cis* compound, the diol (89), gave the *R* acid with an increased optical yield. The result confirms the *S* stereochemistry at C4'' on the reasonable assumption that the C5'' substituent is the larger in the case of (89) and (92).

Table 8.43 shows the results of a series of Horeau's determinations on a number of C_{15} sesquiterpene derived acyclic alcohols. When the g.c. modified technique was applied to diol (56), an abnormally high depletion in the *RR* amide (-11% average) was obtained after esterification. A determination using the original Horeau's method, gave predominantly the *S* acid, recovered in 35% optical yield. When the composition of the same mixture used for the g.c. determination was checked using h.p.l.c., the *RR* amide was depleted by only 3.2%. These differences in the *RR* amide suggest that the g.c. determination was in error due to an interfering impurity. As with the phenyl analogues,[64] the 3-furanyl substituent had the larger (L) steric requirement. The stereochemistry at C1 in (56) was confirmed independently by chemical correlation with (62).

As with the dehydrongaiols (60) and (62), the isobutenyl groups in (81) and (8) were confirmed to have the larger steric influence upon the resolution.

Interference was again encountered with the alkenols (252), (253) and with triol (183) using the g.c. method. The problem was overcome in the case of (252), (253) and (183) by

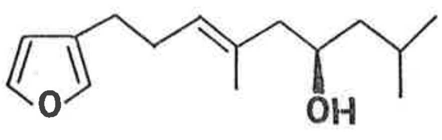
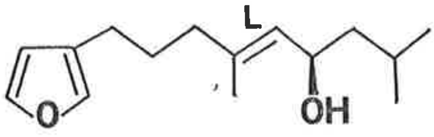
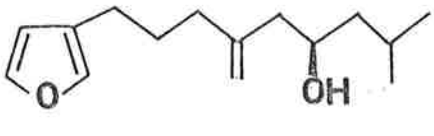
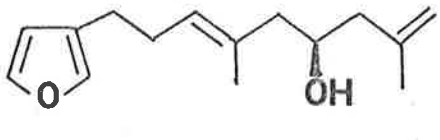
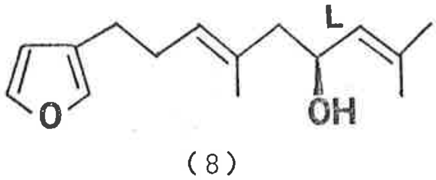
Table 8.43

Compound (No.)	ΔRR% (2h,40°)	ΔRR% (15h,25°)	Recovered Acid (Opt. Yield)	Configuration
 (56)	-3.2 *†	-	(+)S(35%)	R
 (81)	+2.5	-	-	S
 (183)	<1.0 *†	-	-	R
 (124)	<1%	-1.9	-	R

* interference by g.l.c.

† by h.p.l.c.

Table 8.43 continued

Compound	ΔRR% (2h, 40°)	ΔRR% (15h, 25°)	Recovered Acid (Optical yield)	Configuraation
 (253)	-	<1% *†	-	R
 (252)	*	-1.7†	-	R
 (254)	*	-	-	R
 (254 a)	**		-	R
 (8)	+2.1	-	-	S

* interference by g.c.
** interference by g.c. and h.p.l.c.
† by h.p.l.c.

using the h.p.l.c. for analysis. Triol (183), because of the symmetry about C4, showed insufficient enantiomeric enrichment during esterification to be detected as the *RR* amide by h.p.l.c.

Diol (124) however, did show a small excess of the *RS* amide by g.c. (+ 1.9%), confirming that substitution at the β and γ position (C6,7), remote from the reactive C4 centre, is sufficient to give a detectable enantiomeric excess.

In the case of a remote double bond, as in alcohol (253), no detectable enantiomeric excess was observed by h.p.l.c. This model for the analogous furospongin-1 isomers (257), is less symmetrical about the alcohol centre than (257E). Where the double bond is nearer the chiral C4 centre, as in (252), a small excess of the *RS* amide was detected by h.p.l.c. showing that the alkene containing group to be the larger.

In the C_{21} acyclic alcohols shown in Table 8.44, the high degree of symmetry results in similar effective steric sizes about the reactive centres, C6, and consequently low enantiomeric yields. Diol (211), like (124) gave no significant amide excess in the g.c. analysis. However the allylic alcohols (255h) and (255ℓ), like the C15 model (252), gave a significant excess of the *RS* amide using the Horeau's/Brooks' method.

The stereochemistry at C6 in (255h) and (255ℓ) is known to be *R* in both cases. These results again confirm that the alkene containing substituent exerts the larger effective size during the resolution.

Table 8.44

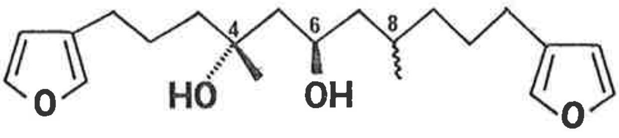
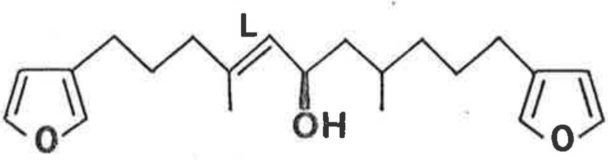
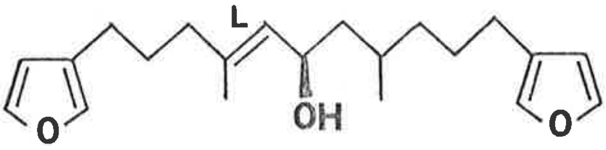
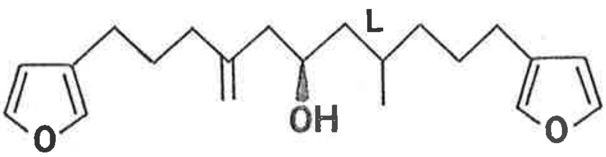
Compound (No.)	ΔRR% (2h,40°)	ΔRR% (15h,25°)	Configuration
 (211)	<1.0	-	R
 (255h) (high R_f isomer)	-2.1	-	R
 (255ℓ) (low R_f isomer)	-2.2	-	R
 (256h) (high R_f isomer)	+2.4	-	R

Table 8.44 continued

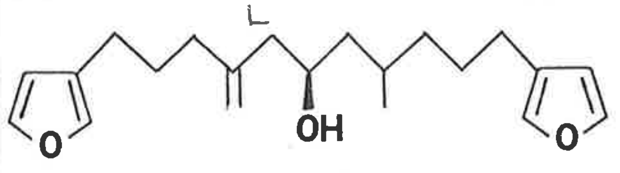
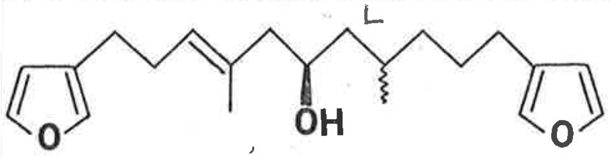
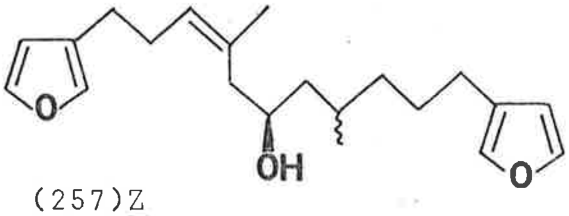
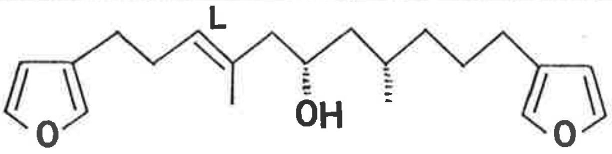
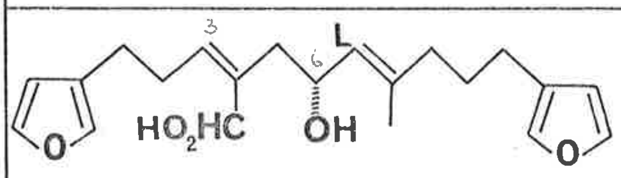
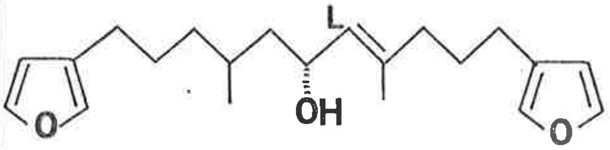
Compound (No.)	ΔRR% (2h,40°)	ΔRR% (15h, 25°)	Configura-tion
 (256ℓ) (low R_f isomer)	-2.2	-	R
 (257)E	-	+1.5	R
 (257)Z	-	<1%	R

Table 8.45*

	Recovered Acid	Optical Yield	Assigned Configuratio
 (192)	(-) R	(9.8%)	S
 (204)	(-) S	(9.6%)	R
 (203)	(+) S	(9.7%)	R

* These results were obtained by Minale et.al. using the Horeau method without modification.

However, in epimeric alcohols (256h) and (256l) the more remote double bond, gave inexplicable but significant and contrasting results. One alcohol (256h), (the higher R_f isomer) gave an unexpected result in showing a *depletion* in the *RS* amide. From these results it can be implied that at least in examples (256h) and (256ℓ) the effective steric size is determined by the stereochemistry at C8. Again, as with examples in Table 8.41, the conformation of the two isomers may influence the outcome of the kinetic resolution during esterification.

The synthetic furospongin-1 isomers (257E), which could not be separated, gave a barely significant result in which the *RR* amide just predominated (+ 1.5%), indicating, that the saturated substituent might have the larger steric influence during esterification. The *Z* C8 epimers of synthetic furospongin-1 (257Z) also inseparable, gave no significant amide excess by g.c. indicating a higher degree of symmetry about the chiral C6 centre than in the *E* isomers. No evidence of interference by impurities was seen in the g.c. trace.

The results obtained for alcohols (255) to (257) are in contrast to Minale's results, shown in Table 8.45, and other models (e.g. (252), (8), (255h) and (255ℓ). It is interesting to note that the Δ7 double bond in (204) reversed the effective steric size of the two alkyl groups, even though hydroxyl substitution at the 4-CH_3 would be expected to oppose this reversal. Removal of the more remote Δ3 double bond of (204) did not change the optical yield obtained by Minale et.al. confirming the inconsequential effect of Δ3 double bond on this kinetic resolution.

It is possible to account for the results obtained for the synthetic alcohol mixture, if the 6*R*,7*S* epimer in (257E) gave a significantly higher enantiomeric excess than the 6*R*,7*R* isomer ((-)-furospongin-1) (257E). This is a real possibility from the unusual results obtained with the epimeric alcohols (256h) and (256ℓ). Thus, an optical yield of approximately 20% for the 6*R*,7*S* isomer of (257E) (i.e. 10% higher than that determined for furospongin-1 by Minale) would account for the overall formation of an excess of *R*-2-phenylbutanoic acid instead of the *S* acid as expected.

8.5 Conclusion:

In general the Horeau's technique was successfully applied to a variety of alcohols. The results gave insights into and supported the mechanisms leading to their formation, stereochemistry and the relative effect of different substituents at the asymmetric centre. Some interesting anomalies were encountered which may serve as a caution when a stereochemical assignment is sought using the Horeau method. As a result of this study, the method is of more general applicability to chiral secondary alcohols because of the variety of model compounds studied. The work with furospongin-1 isomers showed that subtle variations may lead to ambiguities if the Horeau's technique is applied without caution.

Some general comments and conclusions can be made from this comparison of the two Horeau methods. Some have been outlined by Gilbert and Brooks.[136]

(i) The g.c. modification of the Horeau's technique can allow a stereochemical determination to be carried out on less than 10 μ mol of alcohol.

(ii) The g.c. method is limited to alcohols giving adequate optical yields (greater than 10 to 15%), so that one isomeric amide exceeds the other by more than 1%. Lower amide excesses may lead to errors in assignment.

(iii) The use of helium as a carrier gas was superior to nitrogen in combination with the OV-225 stationary phase. The amide isomers (*RR* and *RS*) showed excellent peak shape and baseline separation which allows more accurate electronic integration.

(iv) With many of the sesquiterpenes, interference by esters and/or unreacted alcohols was a serious problem by g.c. In those instances the h.p.l.c. method can be applied using an analytical silica column and U.V. detector. However, in contrast to the g.c. method, the *RS* amide was eluted first.

(v) It was found that amide excesses, which are related to enantiomeric yields, could be usefully increased by extending the esterification time to 15-18 h at 20°. This is particularly useful with hindered alcohols which react slowly. The rate of racemisation during esterification, appears to be a much slower process and slightly lowers the enantiomeric excess with extended times.[64]

(vi) The original Horeau technique is recommended in instances where adequate quantities of alcohol are available because of its greater sensitivity in cases of low optical yields.

EXPERIMENTAL

Melting points were determined using a Reichert hot stage apparatus and are uncorrected. Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

Infrared spectra were recorded on either a Jasco IRA-1 or a Unicam SP 200 spectrophotometer. Where relevant the characteristics of the infrared bands are expressed as follows: s, strong; m, medium; w, weak.

Ultraviolet spectra were recorded on a Pye Unicam SP 800 instrument.

Mass spectra were measured on a Hitachi Perkin-Elmer RMU-7D or AE1 MS 30 operating at 70 eV.

^1H n.m.r. spectra were obtained on a Varian T-60 or Jeol PMX 60 instrument. ^{13}C n.m.r. spectra were obtained on a Bruker WP 80 Fourier Transform spectrometer using deuterochloroform solutions. Chemical shifts (δ) are in ppm downfield from the internal standard, tetramethylsilane; multiplicities were abbreviated to: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; m = multiplet; br = broad; exch. implies that the signal exchanges on the addition of D_2O to the sample.

Separation by Gas Chromatography was done using Perkin Elmer 990 or Pye Unicam 104 instruments coupled to a Perkin Elmer M-2 Integrator.

High Pressure Liquid chromatography was carried out on a Spectra Physics Chromatronix Model 3500.

The optical rotations were determined using a Hilger-Watts Polarimeter.

Sorbsil silica gel was used for column chromatography and Merck KielselgelG and HF_{254} (1:1) for thin layer chromatography.

Light petroleum refers to the fraction of b.p. 60-70°.

Sodium sulphate (anhydrous) was used as the drying agent for non aqueous solutions unless otherwise specified.

Isolation of (+)-(1R,3S,5R)-1-(furan-3'-yl)-5-methyl-3-(2"-methylprop-1"-enyl)-2,8-dioxabicyclo[3.2.1.]octane (Eremoacetal) (47) and other Sesquiterpenes.

The finely ground leaves and twigs (10 kg) of *Eremophila rotundifolia* were extracted with ethyl acetate/light petroleum (1:4) until the extracts showed only a slight colouration. The solution was concentrated under reduced pressure at 30-40 to leave a green semi-solid residue (800 g). A substantial quantity of a waxy material in this extract made chromatography difficult and therefore most of it was removed by the following procedure prior to chromatography.

After warming to liquefy the solid, the green oil was poured with vigorous stirring into methanol (4 l). On cooling the methanol solution in ice, a solid waxy material separated.

Celite (100 g) was added and the solids collected on a bed of Celite and washed with cold methanol. Extraction of the Celite-wax mixture with hot light petroleum gave a yellow solid (70 g) m.p. 60-70°.

The filtrate (after removal of the wax) was concentrated under reduced pressure at 30-40° to give a green viscous oil (600 g).

Chromatography of the dewaxed oil on silica gel (8 kg) using increasing percentages of ether in light petroleum gave a colourless sweet smelling oil (10 g) in the early fractions. Purification of a portion of this fraction by preparative t.l.c. (activated at 100°, light petroleum) and evaporative distillation (90°/0.5 mm) gave (E)-1-(furan-3'-yl)-4,8-dimethylnona-3,7-diene (6) (dendrolasin) (Found: C, 82.8; H, 9.9. $C_{15}H_{22}O$ requires C, 82.5; H, 10.1%). ν_{max} (film) 1510, 1030, 875, 780 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.3 (1H, m, H5'), 7.2 (1H, m, H2'), 6.2 (1H, m, H4'), 5.1 (2H, m, H3 and H7), 2.3-2.0 (8H, m, $(H1)_2$, $(H2)_2$, $(H5)_2$ and $(H6)_2$), 1.65 (3H, brs, $(H9)_3$), 1.60 (6H, 2 brs, 4-CH_3 and 8-CH_3). M/e 218 ($M^{\dagger}$), 217, 81, 69.

The above spectral data agree closely with the published values.[24]

Subsequent fractions contained mixtures of the isomeric dienones (42) and (43). A portion was separated by h.p.l.c. Lichrosorb S1-60, 10μ; ethyl acetate/hexane (1:20) . The (*E*)-isomer (42) and the (*Z*)-isomer (43) were obtained in approximately equal amounts.

(*E*)-9-(furan-3'-yl)-2,6-dimethylnona-2,5-dien-4-one (42) was isolated as a pale yellow oil and showed the following spectral data. ν_{max} (film) 785, 880, 1030, 1110, 1630, 1680 cm^{-1}. λ_{max} (EtOH) 255 nm (ε 9800). ^{1}H n.m.r. (CCl_4): δ 7.4, 7.2 (each 1H, m, H5' and H2'); 6.3 (1H, brs, H4'); 6.0 (2H, m, H3 and H5); 2.2 (6H, s, 6-CH_3 and 2-CH_3); 1.9 (3H, s, $(H1)_3$), 2.5-1.6 (6H, m, $(H7)_2$, $(H8)_2$ and $(H9)_2$). M/e 232 ($M^{\dagger}$), 217, 138, 123, 109, 95, 83, 81.

(*Z*)-9-(Furan-3'-yl)-2,6-dimethylnona-2,5-dien-4-one (43) a pale yellow oil, exhibited the following spectral data. ν_{max} (film) 770, 870, 1110, 1630, 1680 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.3 (2H, m, H5' and H3'); 6.3 (1H, m, H4'); 6.0 (2H, m, H3 and H5); 2.7 and 2.5 (each 2H, t, J 8Hz, $(H7)_2$ and $(H9)_2$); 2.2 (3H, s, 2-CH_3); 1.9 (6H, s, $(H1)_3$ and 6-CH_3).

These spectral values are in close agreement with the published values.[32]

Later fractions contained mixtures of the dienones and the major constituent, eremoacetal. On standing at 0° these fractions gave large colourless prisms. Recrystallisation from petroleum ether gave colourless prisms of (+)-(1*R*,3*S*,5*R*)-1-(furan-3'-yl)-5-methyl-3-(2"-methylprop-1"-enyl)-2,8-dioxabicyclo[3.2.1.] octane (47) (eremoacetal) (160 g) after rechromatography of various fractions), m.p. 63-63.5°, $[\alpha]_D^{20}$ + 10.3° (30% $CHCl_3$) (Found: C, 72.8; H, 8.3. $C_{15}H_{20}O_3$ requires C, 72.5; H, 8.1%). ν_{max} (Nujol) 810, 885, 940, 1010, 1080, 1120, 1165, 1515, 1615 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.45 (1H, m, H2'), 7.32 (1H, m, H5') 6.39 (1H, m, H4'); 5.24 (1H, d, J 8Hz, H1"); 4.6 (1H, d,d,d, J 5,8,10Hz, H3); 1.3-2.5 (6H, m, methylene); 1.72 (6H, brs, 2"-CH_3 and $(H3")_3$); 1.33 (3H, s, 5-CH_3). ^{13}C n.m.r. see appendix. M/e 248 ($M^{\dot{+}}$), 231, 230, 164, 148, 136, 121, 105, 95, 83, 67.

Further elution gave a mixture of (2'R, 5'S) and (2'S, 5'S)-1-[5'-(furan-3"-yl)-2'-methyltetrahydrofuran-2'-yl]-4-methylpent-3-en-2-one (44) (dehydrongaione)[18] and dehydroepingaione[18] (45). Chromatography on alumina, followed by distillation (94-96°/0.1 mm), gave a sample with $[\alpha]_D^{20}$ -19.5°. This value corresponds approximately to a 2:1 mixture of (44) and (45). ^1H n.m.r. (CCl_4): δ 7.34 (2H, app s, H2" and H5"), 6.32 (1H, m, H4"), 6.14 (1H, m, H3), 4.84 (1H, m, H5'), 2.64 (2H, s, H1), 2.12 (3H, s, 4-CH_3), 1.6-2.3 (methylene), 1.88 and 1.86 (3H, 2s, H5, indicative of both isomers[18]), 1.30 (3H, s, 2'-CH_3).

Continued elution gave a colourless oil of (6*E*)-9-(furan-3'-yl)-2,6-dimethylnona-2,6-dien-4-ol (4-hydroxydendrolasin) (8), b.p. 115-120°/0.5 mm (decomp.). Purification was achieved via the acetate. Acetylation of (8) with acetic anhydride and pyridine gave the acetate (8a) which was purified by h.p.l.c. on Lichrosorb 10μ (25 x 1 cm) using ethyl acetate/hexane (3:97). ^1H n.m.r. (CCl_4): δ 7.30 (1H, m, H5') 7.18 (1H, m, H2'); 6.58 (1H, m, H4'), 5.63 (1H, d, t J 6,7Hz, H4), 5.15 (2H, m, H3 and H7), 2.5-2.0 (6H, methylene); 1.93, (3H, s, CH_3CO); 1.75 (6H, s, $(H1)_3$ and 6-CH_3); 1.65 (3H, s, 2-CH_3).

Reduction of the acetate with lithium aluminium hydride then gave the pure alcohol (8) (Found: C, 76.9; H, 9.7. $C_{15}H_{22}O_2$ requires C, 76.9; H, 9.5%). $[\alpha]_D^{20}$ -15.8° ± 0.6 (c, 4.8 in $CHCl_3$). ν_{max} (film) 3400, 1500, 1155, 1020, 870, 780 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.34 (1H, m, H5'); 7.22 (1H, m, H2'); 6.25 (1H, m, H4'); 5.2 (2H, m, H3 and H7); 4.35 (1H, dt, J 6,8Hz); 2.5-2.0 (6H, m, $(H5)_2$, $(H8)_2$ and $(H9)_2$); 1.7 (9H, m, $(H1)_3$; 2-CH_3 and 6-CH_3. ^{13}C n.m.r. see appendix. M/e 234 ($M^{\dagger}$) 216, 179, 151, 150, 135, 94, 93, 91, 85 (100%), 82, 91, 69, 55, 53.

The early fractions from chromatography were rechromatographed repeatedly on silica (activated at 100°) using hexane to give 7-methyl-7-(4'-methylpenta-1',3'-dienyl)-4,5,6,7-tetrahydrobenzofuran (46) isolated as a colourless, unstable oil, b.p. 95°/0.2 mm (block) (Found *m/e* 216.1514. $C_{15}H_{20}O$ requires 216.1509). $[\alpha]_{365-600} < 1°$ (c, 5.0 in $CHCl_3$). ν_{max} (film) 1500, 1180, 1145, 1090, 1050, 1025, 980, 955, 890, 870, 725 cm^{-1}. λ_{max} (EtOH) 225 (log ε 4.36), 231 (4.37), 246 nm (4.29). ^1H n.m.r. (CCl_4): δ 7.18 (1H, d, J 1.8Hz, H2), 6.10 (1H, d, J 1.8Hz, H3), 6.0 (1H, dd, J 16,10Hz, H2'), 5.8 (1H, d, J 16Hz, H1'); 5.75 (1H, d2, J 10,1.3Hz, H3'); 2.42 (2H, m, $(H4)_2$), 1.69, (6H, brs, (H5') and 4'-CH_3); 1.63 (4H, brs, $(H5)_2$ and $(H6)_2$); 1.33 (3H, s, 7-CH_3). ^{13}C n.m.r. ($CDCl_3$): δ 154.5 (s); 140.6 (d), 138.3 (d), 133.7 (s), 125.0 (d), 116.7 (s), 110.1 (d), 38.7 (s,t), 26.0 (q), 22.7 (5), 20.3 (t), 18.4 (q). M/e 216 ($M^{\dagger}$), 201 (100%), 173, 147, 145, 135, 121, 93, 91, 69, 67.

Action of Aqueous Acid on Eremoacetal (47)

i) A mixture of eremoacetal (47) (200 mg), acetic acid (2 ml) and water (20 ml) was heated under reflux for 30 min. (After 15 min the colourless solution became turbid and t.l.c.

indicated the presence of some eremoacetal together with two or more polar products). Solid sodium carbonate was added slowly to the cooled mixture to neutralise the acid. After extraction with methylene chloride (5 x 10 ml) the extract was dried over potassium carbonate. Removal of the solvent gave an almost colourless oil (196 mg) which gave two compounds after preparative t.l.c. (ether).

The less polar product, (*R*,*E*)-1-(furan-3'-yl)-4-hydroxy-4,8-dimethylnona-6,8-dien-1-one (74) was isolated as a colourless oil (125 mg, 63%). A satisfactory analytical sample could not be obtained due to instability but the 2,4-dinitrophenylhydrazone was prepared under mildly acid conditions, as orange needles, m.p. 125-125.5° (Found: C, 59.1; H, 5.7; N 13.0. $C_{21}H_{24}N_4O_6$ requires C, 58.9; H, 5.7; N 13.1%). The following data were obtained for the keto diene (74) immediately after chromatography. λ_{max} (EtOH) 230 (ε 19,000); 240 (sh) nm (ε 12,000). ν_{max} (film) 880, 1160, 1520, 1570, 1670, 3450 cm^{-1}. ^{1}H n.m.r. ($CDCl_3$): δ 8.2 (1H, m, H2'), 7.5 (1H, dd, H5'), 6.8 (1H, m, H4'), 6.3 (1H, d, J 16Hz H7), 5.7 (1H, dt, J 7,16Hz, H6), 5.0 (2H, brs, $(H9)_2$), 2.95 (2H, t, J8Hz, $(H2)_2$), 2.35 (2H, d, J 7Hz, $(H5)_2$), 2.0 (1H, brs, D_2O exch., OH), 1.9 (2H, t, J 8Hz, $(H3)_2$), 1.9 (3H, brs, 8-CH_3), 1.2 (3H, s, 4-CH_3). M/e 248 ($M^{\dagger}$), 230, 149, 95, 93.

The more polar consistuent (*R*,*E*)-1-(furan-3'-yl)-4,8-dihydroxy-4,8-dimethylnon-6-en-1-one (78) was isolated as a colourless oil (45 mg, 23%) (Found: C, 68.0; H, 8.6. $C_{15}H_{22}O_4$ requires C, 67.6; H, 8.3%). λ_{max} (EtOH) 248 (ε 2300).

ν_{max} (film) 880, 1160, 1520, 1570, 1670, 3400 cm^{-1}. ^1H n.m.r ($CDCl_3$): δ 8.2 (1H, m, H2'), 7.5 (1H, dd, H5'), 6.8 (1H, m, H4'), 5.8 (2H, brs, H6 and H7), 2.95 (2H, t, J 8Hz, $(H2)_2$), 2.25 (2H, m, $(H5)_2$), 1.85 (2H, t, J 8Hz $(H2)_2$), 1.35 (6H, s, 8-CH_3 and $(H9)_3$), 1.2 (3H, s, 4-CH_3). M/e 248 ($M^{+\cdot}$-M_2O), 230, 189, 149, 95.

ii) When a mixture of eremoacetal (47) (90 mg), acetic acid (0.5 ml), methanol (5 ml) and water (3 ml) was heated under reflux for 1 h, the product mixture consisted of (74), (78) and 1-(furan-3'-yl)-4-hydroxy-8-methoxy-4,8-dimethylnon-6-en-1-one (80) (25%). ^1H n.m.r. ($CDCl_3$): δ 8.2 (1H, m, H2'), 7.55 (1H, m, H5'), 6.8 (1H, m, H4'), 5.65 (2H, brs, H6 and H7), 3.2 (3H, s, OCH_3), 3.0 (2H, t, $(H2)_2$), 2.25 (2H, m, $(H5)_2$), 1.9 (1H, exch. D_2O, OH), 1.9 (2H, t, $(H3)_2$), 1.3 (6H, s, 8-CH_3 and $(H9)_3$), 1.2 (3H, s, 4-CH_3).

iii) Eremoacetal was converted to the extent of 50% into the allylic alcohol (78) when it was allowed to stand in aqueous perchloric acid/tetrahydrofuran (pH 1-2) at room temperature for 5 h. The allylic alcohol (78) when heated with the aqueous perchloric acid in tetrahydrofuran gave the diene (74) exclusively.

iv) When eremoacetal was allowed to stand in $CDCl_3$/DCl/D_2O solution in an n.m.r. tube, with occasional shaking, the exchange of the H7 protons was evident by examination of the proton n.m.r. spectrum. Exchange was complete after 30 min at 30° and the multiplet at δ2.3-1.8 due to $(H6)_2$ and $(H7)_2$ collapsed to a 2 proton singlet at approximately δ2.0 due to $(H6)_2$.

Hydrolysis of Eremoacetal to (4*R*,6*S*)-1-(furan-3'-yl)-4,6-dihydroxy-4,8-dimethylnon-7-en-1-one (54)

i) The acetal (47) (4 g) was dissolved in pyridine (30 ml) and water was added until the solution became turbid (approx. 25 ml). The mixture was heated under reflux for 27 h, cooled and extracted with light petroleum (4 x 25 ml). The petroleum extracts were backed-washed with water (2 x 10 ml) and the aqueous washings were added to the pyridine water solutions. Evaporation of the dried petroleum extracts gave eremoacetal (2.9 g, 72%).

The aqueous pyridine solution was extracted with chloroform (4 x 20 ml) and the extracts dried over sodium sulphate. Removal of the solvents at room temperature under vacuum gave (4*R*,6*S*)-1-(furan-3'-yl)-4,6-dihydroxy-4,8-dimethylnon-7-en-1-one (54) as an unstable viscous violet oil (1.0 g). ν_{max} (film) 880, 1160, 1520, 1565, 1675, 3400 cm^{-1}. ^{1}H n.m.r. ($CDCl_3$): δ 8.2 (1H, m, H2'), 7.5 (1H, dd, H5'), 6.5 (1H, m, H4'), 5.3 (1H, d, J 8Hz, H7), 4.8 (1H, dt, J 4,8Hz, H6), 3.8-4.4 (2H, m, exch. D_2O, 2OH); 3.0 (2H, m, $(H2)_2$), 1.6-2.1 (4H, m, $(H3)_2$ and $(H5)_2$), 1.7 (6H, brs, 8-CH_3 and $(H9)_3$), 1.2 (3H, s, 4-CH_3). Traces of acid in the chloroform resulted in rapid cyclisation of (54) reforming (47) and water. M/e 248 (M-H_2O). This compound, and also its acetate, decomposed slowly and microanalyses were not obtained.

ii) When a pyridine/water solution of the dihydroxy ketone (54) was heated under reflux, equilibration occurred to give a mixture of (54) and eremoacetal (47). After 24 h the mixture was 1:1 and reached a final ratio of 2:3 (by n.m.r. after 48 h.

iii) When eremoacetal (47) was warmed in d_5-pyridine/ D_2O (1:1, 37°), examination by n.m.r. after 3 days showed the ratio of (54) to acetal was 1:4. After heating the mixture to 87° for 6 h the ratio changed to 3:7 and further heating at 100° for 7 h gave a ratio of 2:3 which remained unchanged with further heating.

Reaction of Eremoacetal with Hydroxylamine

Eremoacetal (47) (100 mg) in methanol (5 ml) was added to a solution of hydroxylamine hydrochloride (70 mg) in water (5 ml) containing sodium acetate (100 mg) (pH 4-5). After standing at room temperature for 16 h, t.l.c. showed the absence of eremoacetal and two more polar products. After removal of the methanol under reducted pressure at 40°, the residue was extracted with chloroform (3 x 5 ml) and the dried extracts evaporated to give the *oximes* (81) (90 mg) of (4*R*,6*S*)-1-(furan-3'-yl)-4,6-dihydroxy-4,8-dimethylnon-7-en-1-one (54) as a viscous oil which analysed for a dihydrate (Found: C, 57.0, H, 7.3; N, 4.2. $C_{15}H_{23}O_4N$, $2H_2O$ requires C, 56.8; H, 7.3; N, 4.4%). ν_{max} (film) 740, 800, 880, 1160, 1510, 3300 (br) cm^{-1}. M/e 263 ($M^{+\cdot}-H_2O$), 248, 208, 182, 164, 121, 95.

The isomeric oximes were separated by preparative t.l.c. (ethyl acetate/benzene, 1:1) and gave the following n.m.r. data before equilibration occurred.

The higher R_f oxime was isolated as a colourless oil (45 mg). ^{1}H n.m.r. ($CDCl_3$): δ 7.8 (1H, m, H2'); 7.45 (1H, dd, H5'); 6.75 (1H, m, H4'); 5.3 (1H, d, J 8Hz, H7); 4.85, (1H, dt, J 4,8Hz, H6); 2.74 (2H, m, $(H2)_2$); 2.0-1.7 (4H, m, $(H3)_2$ and $(H5)_2$); 1.7 (6H, brs, 8-CH_3 and $(H9)_3$); 1.25 (3H, s, 4-CH_3).

The lower R_f oxime isomer was a colourless oil (40 mg). ^{1}H n.m.r. ($CDCl_3$): δ 8.45 (1H, m, H2'); 7.5 (1H, dd, H5'); 6.8, (1H, m, H4'), 5.3 (1H, d, J 8Hz, H7), 4.85 (1H, dt, 4,8Hz, H6); 2.75 (2H, m, $(H2)_2$), 2.0-1.7 (4H, m, $(H3)_2$ and $(H5)_2$); 1.7 (6H, brs, 8-CH_3 and $(H9)_3$); 1.25 (3H, s, 4-CH_3).

Both n.m.r. samples isomerised to a mixture (approx. 1:1) of oximes (81) within 24 h.

Acetylation of (4*R*,6*S*)-1-(furan-3'-yl)-4,6-dihydroxy-4,8-dimethylnon-7-en-1-one (54).

The crude dihydroxy ketone (54) (2 g) in dry pyridine (10 ml) was acetylated with acetic anhydride (2 ml) at room (24 h). Ice water (20 ml) was added and the solution was made slightly acidic with dilute hydrochloric acid. Extraction with chloroform (3 x 10 ml) and evaporation of the combined and dried extracts under reduced pressure gave a colourless oil. The product (1.9 g) was a mixture of eremoacetal (47) and (4*R*,6*S*)-6-acetoxy-1-(furan-**3**'-yl)-4-hydroxy-4,8-dimethylnon-7-en-1-one (55) in a ratio of 3:7. Preparative t.l.c. (ethyl acetate/benzene, 1:10) of the mixture (350 mg) gave the pure acetate (55) (200 mg) as an unstable oil.

ν_{max} (film) 880, 1155, 1520, 1570, 1675, 1720, 3450 cm^{-1}. ^1H n.m.r. (CCl_4): δ 8.2 (1H, m, H2'); 7.45 (1H, dd, H5'); 6.8 (1H, m, H4'); 5.7 (1H, m, H6); 5.1 (1H, d, J 10Hz, H7); 3.2 (1H, brs, exch. D_2O, OH); 2.9 (2H, t, J 8Hz, $(H2)_2$); 2.0 3H, s, CH_2CO); 1.75 (6H, brs, 8-CH_3 and $(H9)_3$); 2.1-1.5 (4H, m, $(H3)_3$ and $(H5)_3$); 1.2 (3H, s, 4-CH_3).

Reduction of Acetoxy ketone (55) with Zinc Borohydride

The crude ketone (55) (containing 30% pf eremoacetal by n.m.r.) (3.1 g) was dissolved in dry ether (20 ml) and a solution of zinc borohydride[167] in ether (0.1 M, 80 ml) was added slowly with stirring at room temperature. A yellow oil separated and the ketone was not detected, after 1 h, by t.l.c. Water (5 ml) was added cautiously and the mixture was filtered after the addition of celite (2-3 g).

The salts were washed with chloroform (20 ml) and the combined solvents were dried and evaporated to give a yellow oil (3.17 g, 100%) which partly crystallised on standing. A product (1.2 g, 52%) m.p. 86-89 was obtained by tituration of the product in chloroform with light petroleum. Recrystallisation gave (1*R*,4*R*,6*S*)-6-acetoxy-1-(furan-3'-yl)-4,8-dimethylnon-7-ene-1,4-diol (56) as colourless needles, m.p. 98-99° (Found: C, 66.0; H, 8.4. $C_{17}H_{26}O_5$ requires C, 65.8; H, 8.4%). ν_{max} (Nujol) 815, 880, 900, 1020, 1060, 1245, 1720, 2300 cm^{-1}. ^1H n.m.r. ($CDCl_3$): δ 7.4 (2H, m, H2' and H5'), 6.45 (1H, m, H4'); 5.5 (1H, d,d,d, J 6,7,10Hz, H6); 5.2 (1H, d, J 10Hz, H7); 4.7 (1H, 6, J 6Hz, H1); 2.8 (2H, brs, exch. D_2O, 2X OH); 2.0 (3H, s, CH_3CO); 1.75 (6H, brs, 8-CH_3 and

$(H9)_3$); 1.8-1.6 (6H, m, $(H2)_2$, $(H3)_2$ and $(H5)_2$); 1.2 (3H, s, 4-CH_3). M/e 232 ($M^{+\cdot}$-HOAC, H_2O), 217, 151.

Application of Horeau's method[64,65] gave (+)-2-phenyl butanoic acid with an optical yield of 35%. This result leads to the configuration at C1 shown in (56).

Evaporation of the mother liquors from the crystallisation of the major isomer, followed by extraction with petroleum ether to remove eremoacetal and chromatography of the residue on t.l.c. (benzene/ethyl acetate 4:6), gave the minor isomer, **(1*S*,4*R*,6*S*)-6-acetoxy-1-(furan-3'-yl)-4,8-dimethylnon-7-ene-1,4-diol** (57) (0.62 g, 25%) as a colourless oil. ^1H n.m.r. ($CDCl_3$): δ 7.4 (2H, m, H2' and H5'); 6.45 (1H, m, H4'); 5.7 (1H, m, H6); 5.2 (1H, d, J 10Hz, H7); 4.7 (1H, 5, J 6Hz, H1);2.9 2.9 (2H, brs, 2X OH); 2.0 (3H, s, CH_3CO); 1.7 (6H, s, 8-CH_3 and $(H9)_3$); 1.2 (3H, s, 4-CH_3).

This compound was not obtained homogeneous but a pure derivative is reported below the tetrahydrofuran (65) .

When purification was done by using h.p.l.c. a by-product (7%) was isolated. The n.m.r. spectrum was consistent with that expected for **1-(furan-3'-yl)-4,8-dimethylnon-6-ene-1,4-diol**. ^1H n.m.r. (CCl_4): δ 7.3 (2H, brs, H2' and H5'); 6.4 (1H, brs H4'); 5.4 (2H, m, H6 and H7); 4.6 (1H, 5, J 5Hz); 4.0 (2H, brs, 2OH); 1.25 (3H, s, 4-CH_3); 0.95 (6H, d, J 6Hz, 8-CH_3 and $(H9)_3$).

Preparation of tetrahydrofurans (62) and (65) (dehydrongaiols and dehydroepingaiols), their acetates and biphenylcarboxylates.

i) A solution of p-toluenesulphonyl chloride (2.5 g) in dry pyridine (5 ml) was added to a solution of the diol (56) or a mixture of the C1 epimers (1.0 g) in dry pyridine (10 ml). The mixture was allowed to stand overnight and was then poured into ice-water (50 ml). Cold hydrochloric acid (1M) was added with stirring until the pH was 3 and then the solution extracted with light petroleum (3 x 50 ml). The combined extracts were washed successively with hydrochloric acid (1M, 10 ml) and water (20 ml). After drying, removal of the solvent gave the tetrahydrofuran derivatives as a mobile oil (0.9 g, 96%).

The mixture of isomers (approx. 2:1) was separated by h.p.l.c. (ether/light petroleum 1:10).

The minor isomer, (2*S*,2'*R*,5'*R*)-1-[5'-(furan-3"-yl)-2'-methyltetrahydrofuran-2'-ylmethyl]-3-methyl-but-2-enyl acetate (66) was eluted first as a colourless oil. ν_{max} (film) 790, 875, 920, 940, 1025, 1090, 1155, 1240, 1505, 1725 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.3 (2H, m, H2" and H5"); 6.3 (1H, m, H4"); 5.7 (1H, m, H1); 5.1 (1H, d, J 9Hz, H2); 4.85 (1H, m, H5'); 1.9 (3H, s, CH_3CO); 1.75 (6H, brs, 3-CH_3 and $(H4)_3$); 1.2 (3H, s, 2'-CH_3).

The major isomer, (2*S*,2'*R*,5'*S*)-1-[5'-(furan-3"-yl)-2'-methyltetrahydrofuran-2'-ylmethyl]-3-methylbut-2-enyl acetate (63), was isolated as a colourless oil. ν_{max} (film) 720, 795, 875, 925, 935, 1025, 1090, 1155, 1240, 1505, 1725 cm^{-1}. ^1H

n.m.r. (CCl_4): δ 7.3 (2H, m, H2" and H5"); 6.3 (1H, m, H4"); 5.7 (1H, m, H1); 5.1 (1H, d, J 11Hz, H2); 4.9 (1H, t, J 6Hz, H5'); 1.9 (3H, s, CH_3CO); 1.7 (6H, brs, 3-CH_3 and $(H4)_3$); 1.2 (3H, s, 2'-CH_3).

ii) Lithium aluminium hydride (0.17 g) was added to the (1*S*,2'*R*,5'*S*) acetate (63) (1.70 g) in dry ether (50 ml). After stirring at room temperature for 1 h, wet ether (30 ml) was cautiously added followed by sodium sulphate. The mixture was filtered and the salts were washed with ether (2 x 20 ml). After removal of the ether the crude alcohol was purified by h.p.l.c. (Lichrosorb, ethyl acetate/hexane 1:6) to yield (2*S*,2'*R*,5'*S*)-1-[5'-(furan-3"-yl)-2'-methyltetrahydrofuran-2'-yl]-4-methyl-pent-3-en-2-ol (62) (970 mg, 67%), $[\alpha]_D^{15}$ + 28.6° (C, 4.6 in $CHCl_3$). ν_{max} 710, 785, 870, 910, 1020, 1085, 1150, 1500, 3400 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.4 (2H, m, H2" and H5"); 6.4 (1H, m, H4"); 5.2 (1H, d, J 8Hz, H3); 4.9 (1H, m, H5'); 4.55 (1H, dt, J 4,8Hz, H2); 3.2 (1H, brs, D_2O exch., OH); 1.7 (6H, brs, 4-CH_3 and $(H5)_3$): 1.3 (3H, s, 2'-CH_3). M/e 250 ($M^{\ddagger}$), 232, 217, 151.

The alcohol (62) (0.62 g) was added to a solution of 1,1'-biphenyl-4-carbonyl chloride (0.65 g) in dry pyridine (15 ml) and the mixture allowed to stand for 15 h. Water (50 ml) was added to the red solution and the solution was extracted with methylene chloride (3 x 20 ml). The extracts were washed with dilute hydrochloric acid (1M, 3 x 20 ml), water (20 ml), sodium hydrogen carbonate solution (5%, 10 ml) and water (10 ml). After removal of solvent the product was purified by preparative t.l.c. (ether/hexane 1:4). Crystallisation from benzene/

light petroleum gave (1*S*,2'*R*,5'*S*)-1-[5'-(furan-3"-yl)-2'-methyltetrahydrofuran-2'-ylmethyl]-3-methylbut-2-enyl 1,1'-biphenyl-4-carboxylate (64) as colourless needles (800 mg, 73%), m.p. 114-115°, $[\alpha]_D^{15}$ + 78.7 ($CHCl_3$). This compound was identical (m.m.p., $[\alpha]_D^{15}$, i.r. and n.m.r.) with one of the isomers prepared from the reduction of authentic (–)-dehydrongaione (44); see below.

iii) The minor isomer from the cyclisation, the (1*S*, 2'*R*,5'*R*) acetate (66) (0.76 g) was reduced with lithium aluminium hydride and the product purified by h.p.l.c., as described above. The corresponding alcohol, (1*S*,2'*R*,5'*R*)-1-[5'-(furan-3"-yl)-2'-methyltetrahydrofuran-2'-yl]-4-methylpent-3-en-2-ol (65) (400 mg, 60%), was obtained as a colourless oil, $[\alpha]_D^{15}$ + 60° (C, 3.7 $CHCl_3$). ν_{max} (film) 715, 735, 785, 870, 905, 1020, 1085, 1150, 1500, 3450 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.3 (2H, m, H2" and H5"); 6.3 (1H, m, H4"); 5.2 (1H, d, J 8Hz, H3); 4.9 (1H, m, H5'); 4.5 (1H, d, t, J 4,8Hz, H2); 3.1 (1H, brs, D_2O exch., OH); 1.7 (6H, brs, 4-CH_3 and $(H5)_3$); 1.3 (3H, s, 2'-CH_3).

This alcohol (65) (350 mg) when esterified and purified as described above, gave (1*S*,2'*R*,5'*R*)-1-[5'-(furan-3"-yl)-2'-methyltetrahydrofuran-2'-ylmethyl]-3-methylbut-2-enyl 1,1'-biphenyl-4-carboxylate (67) (0.49 g, 77%) as an oil, $[\alpha]_D^{15}$ + 65.7° (C, 5.1 in $CHCl_3$). This compound has spectral properties identical to those of (71) (isolated from the reduction of a mixture of dehydrongaione and dehydroepingaione - see later) but had an equal but opposite rotation. It is therefore the enantiomer of (71).

Reduction of (-)-dehydrongaione*(44), from *Myoporum deserti* with hydride reagents

i) A solution of (-)-dehydrongaione (44) (90% pure 250 mg) in dry tetrahydrofuran (5 ml) was added to a stirred mixture of lithium aluminium hydride (19 mg) in dry tetrahydrofuran (10 ml). After 10 min, wet ether was added followed by sodium sulphate (0.5 g) and celite (0.2 g). The mixture was filtered and the salts washed with ether (20 ml). After removal of the solvent, the residue was purified by h.p.l.c. (lichrosorb, S1-60, 10μ, ethyl acetate/light petroleum, 1:10) to give the first eluted product, (2*R*,2'*R*,5'*S*)-1-[5'-(furan-3"-yl)-2'-methyltetrahydrofuran-2'-yl]-4-methylpent-3-en-2-ol (60) (98 mg, 44%) as an oil. ^{1}H n.m.r. ($CDCl_3$): δ 7.4 (2H, m, H2" and H5"); 6.4 (1H, m, H4"); 5.2 (1H, d, J 9Hz, H3); 5.0 (1H, t, J 6Hz, H5'); 4.6 (1H, d, t, J 4,8Hz, H2); 3.3 (1H, brs, D_2O exch., OH); 1.y (6H, brs, 4-CH_3 and $(H5)_3$); 1.35 (3H, s, 2'-CH_3). M/e 250 ($M^{\dot{+}}$), 232, 217, 151.

Further elution gave (2*S*,2'*R*,5'*S*)-1-[5'-(furan-3"-yl)-2'-methyltetrahydrofuran-2'-yl]-4-methylpent-3-en-2-ol (62)(50 mg, 22%). ^{1}H n.m.r.; i.r. and m/e spectra were identical to those described for this isomer (62) from eremoacetal (see earlier).

Esterification of (60) with 1,1'-biphenyl-4-carbonyl chloride, as described earlier, gave after separation on preparative t.l.c. (ethyl acetate/benzene 1:9) and recrystallisation from light petroleum, colourless needles of

* Kindly donated by Professor M.D. Sutherland

(1*R*,2'*R*,5'*S*)-1-[5'-(furan-3"-yl)-2"-methyltetrahydrofuran-2'-yl methyl]-3-methylbut-2-enyl 1,1'-biphenyl-4-carboxylate (61) (216 mg, 69%), m.p. 100-101° (Found: C, 78.3; H, 7.3. $C_{28}H_{30}O_4$ requires C, 78.1; H, 7.0%). $[\alpha]_D^{15}$ - 84° (C, 1.33 in $CHCl_3$). ν_{max} (Nujol) 685, 745, 870, 975, 1100, 1270, 1600, 1700 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 8.1 (2H, d, J 8Hz, aromatic) 7.7-7.2 (9H, aromatic and H2" and H5"); 6.45 (1H, m, H4"); 6.1 (1H, m, H1), 5.25 (1H, d, J 9Hz, H2); 4.85 (1H, m, H5'); 1.8 and 1.6 (each 3H, s, 3'-CH_3 and $(H4)_3$); 1.3 (3H, s, 2'-CH_3).

Esterification of alcohol (62) (180 mg) followed by purification on t.l.c. and recrystallisation as above gave colourless needles of (1*S*,2'*R*,5'*S*)-1-[5'-(furan-3"-yl)-2'-methyltetrahydrofuran-2'-ylmethyl]-3-methylbut-2 -enyl 1,1'-biphenyl-4-carboxylate (64) (150 mg, 48%), m.p. 115-116° (Found: C, 78.0; H, 7.2. $C_{28}H_{30}O_4$ requires C, 78.1; H, 7.0%). $[\alpha]_D^{15}$+ 77° (C, 4.4 in $CHCl_3$). ν_{max} (Nujol) 740, 785, 925, 1020, 1115, 1600, 1715 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 8.1 (2H, d, 8Hz, aromatic); 7.7-7.3 (9H, aromatic and H2", H5"); 6.3 (1H, m, H4"); 6.0 (1H, m, H1); 5.2 (1H, d, J 9Hz, H2); 4.8 (1H, t, J 6Hz, H5') 1.8 and 1.6 (each 3H, s, 3'-CH_3 and $(H4)_3$); 1.3 (3H, s, 2'-CH_3).

ii) When (-)-dehydrongaione (600 mg) was reduced with sodium borohydride (200 mg) in ethanol (10 ml) for 15 h, the ratio of isomeric allylic alcohols to isomeric saturated alcohols was 5:2 (92% isolated yield).

iii) Reduction of (-)-dehydrongaione (120 mg) in methanol (1 ml) and cerium trichloride[66] (1.25 ml; 0.4M $CeCl_3$. $7H_2O$ in methanol) with sodium borohydride (0.1 g) gave after 4 min a 95% yield of allylic alcohols (60) and (62) in the same ratio as from the reduction using lithium aluminium hydride.

iv) Reduction of dehydrongaione (44) with sodium borohydride in methanol gave a similar result to (iii) after 2 h.

Reduction of dehydrongaione (44) and dehydroepingaione (45) from *E. rotundifolia*

The mixture of (44) and (45), $[\alpha]_D^{20}$ - 19.5° (C, 7.9 in $CHCl_3$) purified by chromatography and distillation - homogeneous by t.l.c. and n.m.r. (the spectra[18] of the two epimers are almost identical with only a slight difference in the chemical shifts of one of the vinylic methyl groups); the optical rotation corresponds to a 2:1 mixture of (44) and (45) (3.5 g), was stirred in ether (50 ml) while lithium aluminium hydride (0.35 g) was added over 20 min. After stirring for 1 h wet ether was added cautiously and the mixture was dried and filtered through celite. The solids were washed with ether and the combined solvent was evaporated to leave a colourless oil (3.4 g, 96%). Although the four allylic alcohols were present only two spots were evident from t.l.c. examination of the mixture (ether/light petroleum, 1:4).

Chromatography of the mixed alcohols on silica (ether/light petroleum gave the (2*R*,2'*R*,5'*S*) and (2*S*,2'*S*,5'*S*) isomers, (60) and (68), as one fraction (0.98 g, 28%). The more polar fractions contained the (2*S*,2'*R*,5'*S*) and (2*R*,2'*S*,5'*S*) isomers, (62) and (70), as a mixture (1.58 g, 45%).

Alcohols (60) and (68) were esterified with 1,1'-biphenyl-4-carbonyl chloride (1:1 equivalents) in an excess of pyridine, at room temperature overnight. Workup as described above gave the isomeric biphenylcarboxylates. Some of the (1*R*,2'*R*,5'*S*) isomer, (61) crystallised from light petroleum and the mixture in the mother liquor was separated by h.p.l.c. (Lichrosorb Si-60, 10µ, ethyl acetate/light petroleum, 1:10).

The isomer with the shorter retention time, (1*S*,2'*S*,5'*S*)-1-[5'-(furan-3"-yl)-2'-methyltetrahydrofuran-2'-ylmethyl]-3-methylbut-2-enyl 1,1'-biphenyl-4-carboxylate (69) (720 mg) was obtained as an oil (Found: C, 78.1; H, 7.4. $C_{28}H_{30}O_4$ requires C, 78.1; H 7.0). $[\alpha]_D^{23}$ + 44°(C, 4.4 in $CHCl_4$). ν_{max} (film) 680, 740, 870, 1100, 1270, 1610, 1710 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 8.1 (2H, d, J 8Hz, aromatic); 7.7-7.3 (9H, aromatic and H2" and H5"); 6.3 (1H, m, H4"); 6.0 (1H, m, H1); 5.3 (1H, d, J 9Hz, H2); 4.9 (1H, m, H5'); 1.9 and 1.8 (each 3H, s, 3-CH_3 and $(H4)_3$); 1.3 (3H, s, 2'-CH_3).

The more polar (1*R*,2'*R*,5'*S*) isomer (61) (520 mg), m.p. 100-102 , was identical (m.m.p., i.r., n.m.r., and $[\alpha]_D$) with (61) from the reduction of (-)-dehydrongaione from *M. derserti* (above).

Similarly, the mixed allylic alcohols (62) and (70) were esterified and the esters separated by h.p.l.c. The less polar isomer, (1*R*,2'*S*,5'*S*)-1-[5'(furan-3"-yl)-2'-methyltetrahydrofuran-2'-ylmethyl]-3'-methylbut-2-enyl 1,1'-biphenyl-4-carboxylate (71) (0.52 g) was obtained as an oil (Found: m/e 430.214. Calc. for $C_{28}H_{30}O_4$: m/e 430.213).

ν_{max} (film) 680, 740, 870, 1270, 1605, 1710 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 8.1 (2H, d, J 8Hz, aromatic), 7.7-7.3 (9H, aromatic, H2" and H5"); 6.3 (1H, m, H4"); 6.0 (1H, m, H1); 5.3 (1H, d, J 9Hz, H2); 4.9 (1H, m, H5'); 1.8 and 1.7 (each 3H, s, 3-CH_3 and $(H4)_3$); 1.3 (3H, s, 2'-CH_3).

The more polar (1*S*,2'*R*,5'*S*) isomer (64) (0.86 g) was obtained as colourless needles, m.p. 114-116°. This sample was identical (m.m.p., i.r., n.m.r. and $[\alpha]_D$) with (71) produced from the reduction of (-)-dehydrongaione from *M. deserti* (above).

Preparation of (2*R*,5*S*) and (2*R*,5*R*)-5-(furan-3"-yl)-2-methyl-2-(4'-methylpenta-2',4'-dienyl)tetrahydrofuran, (72) and (75).

i) Lithium aluminium hydride (0.35 g) was added over 10 min to a stirred solution of hydroxyketone (74) (3.3 g) in dry ether (100 ml). After stirring the mixture for 1.5 h, workup gave a mixture of the corresponding diols (3.25 g, 95%). These unstable dienols were not purified but immediately cyclised as described below.

ii) p-Toluenesulphonyl chloride (5 g) in dry pyridine (25 ml) was added to the diol mixture in dry pyridine (10 ml) After 6 h at 35-40°, ice water (150 ml) was added and the solution extracted with light petroleum (4 x 100 ml). The extracts were washed successively with dilute hydrochloric acid and water, dried and evaporation gave a mobile oil of the epimeric dienes (72) and (75). The two epimers (approx 1:1) were separated using h.p.l.c. (ether/light petroleum, 1:10, Merck silica gel 60).

The more polar isomer (lower R_f on t.l.c. and eluting second) was (2*R*,5*S*)-5-(furan-3"-yl)-2-methyl-2-(4'-methylpenta-2',4'-dienyl)tetrahydrofuran (72) obtained as a colourless, unstable oil (Found: C, 77.9; H, 8.7. $C_{15}H_{20}O_2$ requires C, 77.6; H, 8.7%). ν_{max} (film) 780, 870, 915, 965, 1150, 1365, 1445, 1500, 1605 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.2 (2H, m, H2" and H5"); 6.2 (1H, m, H4"); 6.0 (1H, d, J 14Hz, H3'); 5.55 (1H, dt, J 6,14Hz, H2'); 4.8 (2H, brs, $(H5')_2$); 4.8 (1H, m, H5); 2.3 (2H, d, J 6Hz, $(H1')_2$); 1.8 (3H, s, 4'-CH_3); 1.2 (3H, s, 2-CH_3). M/e 232 ($M^{\dot{+}}$), 215,151, 109, 107, 81.

The less polar (2*R*,5*R*) isomer (higher R_f) (75) was also isolated as a colourless unstable oil (Found: C, 77.5; H, 8.4. $C_{15}H_{20}O_2$ requires C, 77.6; H, 8.7%). The ^1H n.m.r. spectrum was identical with that of the (2*R*,5*S*) epimer and the infra-red spectra were almost identical.

Attempted Manganese Dioxide Oxidation of Allylic Alcohol (62)

The allylic alcohol (62) (200 mg) was stirred with freshly prepared, activated manganese dioxide (3 g) in dry light petroleum (15 ml) at room temperature for 50 h. T.l.c. of the mixture indicated little reaction had occurred, so the mixture was heated under reflux for 20 h. The mixture was filtered through celite and the solids washed with chloroform (20 ml). Removal of the solvents gave a yellow oil (190 mg) which was devoid of carbonyl absorption in the infrared spectrum. Preparative t.l.c. (ether/benzene, 1:1) gave, as a colourless oil, (100 mg, 54%) the (2*R*,5*S*) diene epimer (72), identical with the lower R_f isomer prepared from the cyclisation reaction described above.

Oxidation of Allylic Alcohol (62) to (-)-dehydrongaione (44) with Dimethyl Sulphoxide-Oxalyl chloride.[67]

Oxalyl chloride (73µl, 83 mmole) was added to dry methylene chloride (5 ml) at -60° to -70°. After 5 min, dry dimethyl sulphoxide (120 µl, 172 mmole) was added with stirring at -60° followed by the alcohol (62) (180 mg, 73 mmole) in methylene chloride (2 ml). After 20 min, triethylamine (420 µl) was added at -60°, and after the mixture had warmed to room temperature, water (5 ml) was added. The organic layer was separated and the aqueous extracted with methylene chloride (3 x 10 ml). The combined organic extracts were dried and evaporation under reduced pressure gave a colourless oil (190 mg). T.l.c. showed three products. Separation of the mixture by preparative t.l.c. (ether/hexane, 4:6) gave:

i) The diene (72) (71 mg, 42%).

ii) (-) Dehydrongaione (44) (42 mg, 23%). $[\alpha]_D^{20}$ - 9° (C, 1.5 CHCl$_3$) lit.[18] -12.5° (CHCl$_3$) .

ν_{max} (film) 790, 870, 920, 1020, 1150, 1375, 1445, 1500, 1615, 1680, 2860, 2900, 3160(w) cm^{-1}. ^{1}H n.m.r. (CDCl$_3$): δ 7.3 (2H, m, H2" and H5"); 6.3 (1H, m, H4"); 6.05 (1H, m, H3); 4.8 (1H, m, H5'); 2.6 (2H, s, (H1)$_2$); 2.1 (3H, brs, 4-CH$_3$); 1.8 (3H brs, (H5)$_3$); 1.25 (3H, s, 2'-CH$_3$). m/e 248 ($M^{\dot{+}}$), 233, 215, 190, 151, 108, 95, 83, 79, 55.

These spectral data were identical with those recorded on an authentic sample of (-)-dehydrongaione kindly provided by Professor Sutherland.[18]

iii) 5-[5'-(furan-3"-yl)-2'-methyltetrahydrofuran-2'-yl]-

2-methylpent-3-en-ol (73) (22 mg, 12%). ^{1}H n.m.r. (CCl_4): δ 7.3 (2H, m, H2" and H5"); 6.3 (1H, m, H4"); 5.6 (2H, m, H3 and H4); 4.9 (1H, 5, J 6Hz, H5'); 2.2 (2H, m, $(H5)_2$); 1.2 (9H, s, 2-CH_3, 2'-CH_3 and $(H1)_3$). Confirmation of the structure of this alcohol was obtained from the observation that its n.m.r. spectrum was superimposable on that of a sample (mixed with the C5' epimer) prepared from the keto-allylic alcohol (78) by hydride reduction followed by intramolecular cyclisation as described above for diene (72).

Preparation of the Tetrahydrofuran Diol (77) from Acetate (63)

i) A solution of osmium tetroxide (1.00 g) in pyridine (5 ml) was added to the acetate (63) (1.06 g) in pyridine (5 ml). The dark coloured mixture was left for 20 h at room temperature, a solution of sodium bisulphite (1.8 g) in water (30 ml) was added and the mixture stirred for 7 h. Extraction with methylene chloride (6 x 10 ml) followed by removal of solvents under reduced pressure gave the crude isomeric dihydroxy acetates (76) (1.05 g, 88%). ν_{max} (film) 870, 1025, 1240, 1500, 1740, 3450 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.4 (2H, m, H2" and H5"); 6.4 (1H, m, H4"); 5.2-4.5 (2H, m, H1 and H5'); 3.4 and 4.2 (each 1H, br, 2OH); 3.4 (1H, m, H2); 2.0 (3H, s, CH_3CO); 1.3 (3H, s, 2'-CH_3); 1.2 (6H, s, 3-CH_3 and $(H4)_3$). The crude diols were used without further purification.

ii) Deuterated methanol (CH_3OD, 2 x 0.5 ml) was added to the dihydroxy acetates (110 mg) and the solvent removed under vacuum. Deuterated periodic acid, prepared by dissolving periodic acid (100 mg) in D_2O (2 x 1 ml), followed by removal of solvent under vacuum; used as a saturated solution in anhydrous ether (16 mg/ml), (5 ml) was added to the dihydroxy acetates (76) in dry ether (1 ml). After 10 min the mixture was rapidly filtered through celite, and the product in ether reduced directly with lithium aluminium hydride (100 mg) for 1 h. After the addition of ether saturated with D_2O, the mixture was dried and filtered. The solids were washed with methylene chloride (10 ml) and the combined filtrates evaporated to give the crude diol (77) as a colourless oil (55 mg, 77%). Preparative t.l.c. (ether) gave (2*S*,2'*R*,5'*S*)-3-[5'-(furan-3"-yl)-2'-methyl-tetrahydrofuran-2'-yl]-propane-1,2-diol (77) (45 mg, 58%), b.p. 90°/0.1 mm (block) (Found: C, 64.0; H, 8.2. $C_{12}H_{18}O_4$ requires C, 63.7; H, 8.0%). $[\alpha]_D^{20}$ + 7° (C, 1.1 in $CHCl_3$). ν_{max} 870, 1020, 1150, 3450 cm^{-1}. ^1H n.m.r. (CCl_4/D_2O): δ 7.4 (2H, m, H2" and H5"); 6.4 (1H, m, H4"); 4.9 (1H, t, J 6Hz, H5'); 3.8 (1H, m, H2); 3.5 (2H, m, $H1)_2$); 1.3 (3H, s, 2'-CH_3). m/e 226 ($M^{+\cdot}$, 90.7%), 227 (D_1 $M^{+\cdot}$; 9.3%), 211, 208, 195, 177, 151.

Horeau's procedure[64] was used for the determination of absolute configuration. The 2-phenylbutanoic acid recovered had a positive rotation corresponding to an optical yield of 20%. The isolation of the (+)-(*S*)-acid leads[65] to the configuration at C2 shown in (77).

Hydrogenation of Eremoacetal (47)

Eremoacetal (5.0 g) was hydrogenated in ethanol in the presence of P2 nickel catalyst prepared according to the method of Brown and Ahuja.[145]

After 4 days at room temperature only a trace of eremoacetal could be detected by t.l.c. After 5 days of hydrogenation, the mixture was passed through a column of alumina to remove the colloidal catalyst and the column was washed with ethanol. Removal of the alcohol under reduced pressure gave a colourless oil (4.96 g, 96%). The product was homogeneous by t.l.c. and n.m.r., indicating the absence of hydrogenolysis products or compounds arising from the reduction of the furan ring. Distillation gave a colourless oil of pure (1*R*,3*R*,5*R*)-1-(furan-3'-yl)-5-methyl-3-(2"-methylpropyl)-2,8-dioxabicyclo[3.2.1]octane (94) (dihydroeremoacetal) b.p. 120° / 0.1 mm (Found: C, 72.2; H, 8.9. $C_{15}H_{22}O_3$ requires C, 72.0; H, 8.9%). ν_{max} (film) 785, 870, 930, 1025, 1070, 1105, 1145, 1200, 1260, 1500, 1600 (w) cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.45 (1H, m, H2'), 7.37 (1H, m, H5'), 6.33 (1H, m, H4'); 3.97 (1H, m, H3); 2.3-1.3 (9H, m, methylene), 1.37 (3H, s, 5-CH_3); 0.90 (6H, d, J 6Hz, 2"-CH_3 and $(H3")_3$). m/e 250, 207, 95.

Treatment of Dihydroeremoacetal (94) with Aqueous Acids

(i) Dihydroeremoacetal (94) was recovered after standing in aqueous perchloric acid (1M)-tetrahydrofuran (pH1) at 20° for 24 h. No products were detected by t.l.c. examination of the solution.

(ii) When dihydroeremoacetal was shaken periodically in carbon tetrachloride containing D_2O/DCl (1M) at 35°, slow exchange of two protons $(H7)_2$ was observed in the methylene region (δ 2.1) of the n.m.r. spectrum. After 1 week, integration confirmed the total exchange of both H7 protons and only dihydroeremoacetal could be detected throughout the experiment.

Oxidation of Aldehyde with Silver Oxide

Aldehyde (82) (330 mg) was stirred in methanol (20 ml) containing an excess of silver oxide (approx 1 g) (freshly prepared from silver nitrate solution by precipitation with sodium hydroxide, filtration and washing with water (5 x 20 ml) and methanol (3 x 10 ml)). After 1 h no change was observed by t.l.c. Aqueous sodium hydroxide (10 ml, 5% solution) was added. The brown suspension turned black over 15-30 min indicating oxidation (by reduction of silver oxide to silver). The solution was filtered through celite and after 15 h, most of the methanol was removed under reduced pressure and the alkaline solution extracted with methylene chloride. The methylene chloride solution contained some unreacted aldehyde (50 mg, 15%). Acidification of the aqueous solution (to pH 2) and extraction with methylene chloride (3 x 20 ml) gave an oil consisting of acyclic acid (84) and the cyclic acid (83) (ratio 45:55) by ^1H n.m.r. and i.r. spectra. After a further 24 h one product only was detected by t.l.c. and was isolated by preparative t.l.c. (ether) to give the *lactone* (85) (80 mg, 29%) m.p. 101-102.5° (Found: C, 58.32; H, 6.01. $C_{12}H_{14}O_5 \cdot \frac{1}{2}H_2O$ requires C, 58.38; H, 6.11%). ν_{max} (Nujol): 875, 1150, 1235, 1515, 1565, 1670, 1770, 3000 (w)

3040, 3160 (w) 3500 cm^{-1}. ^1H n.m.r. (CCl_4): δ 8.0 (1H, m, H2'); 7.35 (1H, m, H5'); 6.7 (1H, m, H4'); 4.67 (1H, dt, J 4,10Hz, H6); 3.83 (1H, d, J 4Hz, OH); 2.95 (2H, t, $(H2)_2$), 1.40 (3H, s, 5-CH_3). ^{13}C n.m.r. see appendix. M/e 239 ($M^{+\cdot}$ +1) 238 ($M^{+\cdot}$), 223, 195, 194, 179, 151, 150, 124, 123, 111, 110 (b.p.), 96, 95, 84.

Treatment of Diol (86a) with Sodium Periodate

(i) The diol (86) (m.p. 113-115°, 400 mg, 1.42 mmol) in ethanol (10 ml) was stirred while a solution of sodium periodate (175 mg, 2.9 mmol) in water (10 ml) was added. No starting material was detected after 30 min. After 15 h filtration and extraction of the aqueous with methylene chloride gave the crude product. Preparative t.l.c. (ether) gave a high R_f (dehydrated) product as a mixture of *E* and *Z* keto-enols (37 mg, approx 12%) together with an aldol product ^1H n.m.r. (CCl_4) δ 5.8 (olefin), 9.9 and 9.8 (CHO) 1.8 and 1.3 (vinylic CH_3) also 4.67 (t) and 3.6 (allylic methylene) of the aldol product.

The mid-R_f and major product was the unstable colourless oil of (3*R*)-6-(furan-3'-yl)-3-hydroxy-3-methyl-6-oxohexanal (87) (155 mg, 55%) (Found: m/e 210.0898. $C_{11}H_{14}O_4$ requires m/e 310.0892). ν_{max} (film) 875, 1150, 1515, 1565, 1680, 1725, 3150, 3450 cm^{-1}. ^1H n.m.r. ($CDCl_3$): δ 9.72 (1H, t, J 2Hz, H1); 7.97 (1H, m, H2'); 7.34 (1H, m, H5'); 6.65 (1H, m, H4'); 3.3 (1H, brs, D_2O exch., OH); 2.90 (2H, t, J 7Hz, $(H5)_2$); 2.59 (2H, d, J 2Hz, $(H2)_2$); 1.93 (2H, t, J 7Hz, $(H4)_2$); 1.35 (3H, s, 3-CH_3). ^{13}C n.m.r. see appendix. M/e 210 ($M^{+\cdot}$); 195, 193, 192, 167, 166 164, 151, 148, 124, 123, 99, 96, 95 (b.p.), 81, 67, 55.

(ii) When the reaction was worked up after 30 min the diol could not be detected by t.l.c. and an almost quantitive yield (95%) of aldehyde (87) was obtained without aldol or dehydration products.

Acidic Hydrolysis of Diols (86a) and (86b) to the Tetrahydrofuryl Ketones (88) and (89)

(i) The acetonide of the diol (86b) (m.p. 70-72) was stirred in ether and dilute oxalic acid (5% aqueous) (1:1) at room temperature overnight. No products were evident from the t.l.c. of the ethereal solution. The ether was removed, replaced with methanol and the mixture warmed at 50-60° until starting material could not be detected (approx 1 h). T.l.c. showed one major product. Preparative chromatography (ether) gave (2"*S*,4"*S*,5"*R*)-1-(furan-3'-yl)-3-[5"-(1-hydroxy-1-methylethyl)-4"-hydroxy-2"-methyl-tetrahydrofuran-2"-yl]-propan-1-one (89) (90%) m.p. 94-95° (Found: C, 63.77; H, 7.92. $C_{15}H_{22}O_5$ requires C, 63.81; H, 7.85%). ν_{max} (Nujol) 875, 1065, 1145, 1515, 1570, 1670, 3160 (sh), 3240 cm^{-1}. ^{1}H n.m.r.($CDCl_3$): δ 7.92 (1H, m, H2'); 7.30 (1H, m, H5'); 6.64 (1H, m, H4'); 4.37 (1H, q, J 2.6 Hz, H4"); 3.7 (2H, brs, exch., D_2O, 2OH); 3.42 (1H, d, J 2.6Hz, H5"); 2.8 (2H, m, $(H2)_2$); 1.93 (4H, m and d, J_d 2.6Hz, $(H3")_2$ and $(H3)_2$); 1.39 (3H, s, 2"-CH_3); 1.33 and 1.23 (each 3H, 2s, $(H2)_3$ and 1-CH_3). ^{13}C n.m.r. see appendix. M/e 282 ($M^{+\cdot}$), 269, 264, 246, 224, 223, 206, 193, 178, 175, 165, 159, 150, 149, 147, 141, 123, 111, 110, 95 (b.p.), 83.

(ii) The keto-diol (89) was obtained in the same yield when the diol (86b) was used instead of the acetonide (161) using the same conditions.

(iii) When the acetonide epimer (160) (m.p. 75-76°) was treated as in (i) with dilute oxalic acid, the epimeric ketone was obtained. Preparative t.l.c. (ether) gave (2"*S*,4"*S*,5"*S*)-1-(furan-3'-yl)-3-[5"-(1-hydroxy-1-methylethyl)-4"-hydroxy-2" methyl-tetrahydrofuran-2"-yl] propan-1-one (88) (85%) m.p. 74-75° (Found: c, 64.15; H, 7.50. $C_{15}H_{22}O_5$ requires C, 63.81; H, 7.85%). ν_{max} (Nujol) 745, 845, 875, 1075, 1100, 1145, 1175, 1515, 1565, 1680, 3100, 3140, 3350 cm^{-1}. ^1H n.m.r. ($CDCl_3$): δ 7.95 (1H, m, H2'); 7.32 (1H, m, H5'); 6.67 (1H, m, H4'); 4.33 (1H, d, t, J 7.0,5.0Hz, H4"); 3.59 (1H, d, J 5.0 Hz, H5"); 2.84 (2H, m, $(H2)_2$); 2.57 (2H, brs, D_2O exch., 2OH); 1.37 (3H, s, 2"-CH_3); 1.23 and 1.18 (each 3H, 2s, 1-CH_3 and $(H2)_3$). ^{13}C n.m.r. see appendix.

Acetylation of Keto-Diol (89)

The keto-diol (89) (m.p. 94-95°, 50 mg) was acetylated with pyridine and acetic anhydride for 15 h at 30°. Preparative chromatography (ether) gave the monoacetate of (89), m.p. 95-97°. ν_{max} (Nujol) 1740, 1680, 3300 cm^{-1}. ^1H n.m.r. ($CDCl_3$) δ 7.90, 7.30, 6.62 (each 1H, 3m, H2', H5' and H4'); 5.27 (1H, m, H4"); 3.64 (1H, d, J 2.8Hz, H5"); 3.0 (1H, brs, OH); 2.8 (2H, m, $(H2)_2$); 2.04 (3H, s, $COCH_3$); 1.33 (3H, s, 2"-CH_3); 1.22 and 1.20 (each 3H, 2s, 2-CH_3 and $(H3)_3$).

Attempted Oxidative Cleavage of Diol with Periodate

When the keto-diols (88) or (89) in ethanol were treated with aqueous sodium periodate at pH 2-3 for 15 h, each was recovered unchanged.

Similarly when the keto-diols (88) and (89) were treated with periodic acid in ether they were recovered unchanged after workup.

Acetonide Formation from Diols (88) and (89)

(i) The keto-diol (88) (50 mg) was warmed in a mixture of 2,2'-dimethoxypropane (1 ml), acetone (0.2 ml) and a trace of p-toluenesulphonic acid. After 20 h at 45-50° the starting material was recovered (80%) on workup.

(ii) The keto-diol (89) (m.p. 94-95°) (50 mg) when treated with the same mixture showed complete reaction (by t.l.c.) after 10 min at room temperature. Workup gave the acetonide of (89) m.p. 75-77°. ^{1}H n.m.r. (CCl_4): δ 7.88, 7.28 and 6.60 (each 1H, m, H2', H5' and H4'); 4.43 (1H, d, t, J 5.0,6.8Hz, H4"); 3.50 (1H, d, J 5.0Hz, H5"); 2.66 (2H, m, $(H2)_2$); 1.30, 1.18 and 1.13 (15H, 3s).

Treatment of Hydroxyeremoacetal (95) and Dihydroeremoacetal (94) with Aqueous Oxalic Acid

When the acetals (94) and (95) were heated separately in methanol/aqueous oxalic acid (5%) for 2 h at 50-60° no change was observed by t.l.c. in the mixture. Workup gave unchanged starting material in each case.

Treatment of Hydroxyeremoacetal (90a) and (90b) with Aqueous Oxalic Acid.

(i) When the alcohol (90b) was warmed in aqueous oxalic acid (5%) containing methanol (20-30%) an oil was obtained Preparative t.l.c. (ether/hexane, 3:1) gave a pale yellow oil (2"*S*,4"*S*,5"*S*)-1-(furan-3'-yl)-3-[4"-hydroxy-5"-(1-methylethyl)-2"-methyltetrahydrofuran-2"-yl] propan-1-one (92)(90%) b.p. 125° /0.1 mm (Found: C, 67.77; H, 8.25. $C_{15}H_{22}O_4$ requires C, 67.65; H, 8.33%). ν_{max} (film) 875, 1045, 1150, 1515, 1565, 1680 3160, 3500 cm^{-1}. ^{1}H n.m.r. ($CDCl_3$): δ 7.95 (1H, m, H2'); 7.32 (1H, m, H5'); 6.67 (1H, m, H4'); 4.17 (1H, m, H4"); 3.22 (1H, dd, J 2.4,9.2Hz, H5"); 2.80 (2H, m, $(H2)_2$); 1.31 (3H, s, 2"-CH_3); 0.98 and 0.88 (each 3H, 2d, J 6Hz, $(H1)_3$ and 2-CH_3). ^{13}C n.m.r. see appendix. M/e 268 ($M^{+\cdot}$ +2), 267 (M+1), 266 ($M^{+\cdot}$), 248, 224, 223, 194, 167-165, 152, 151, 144, 143, 125, 123, 111, 110, 95 (b.p.) 85, 84, 57.

(ii) Similarly, the alcohol (90a) was warmed with aqueous oxalic acid (5%) containing methanol (20-30%) until the starting material was hydroylsed (t.l.c.). Workup gave a pale yellow oil which crystallised. Recrystallisation from hexane gave (2"*S*,4"*S*,5"R)-1-(furan-3'-yl)-3-[4"-hydroxy-5"-(1-methylethyl)-2"-methyl-tetrahydrofuran-2"-yl] propan-1-one (91)(85%) m.p. 60° (Found: C, 67.32; H, 8.31. $C_{15}H_{22}O_4$ requires C, 67.65; H, 8.33%, m/e 266.1514 $C_{15}H_{22}O_4$ requires 266.1518). ν_{max} (film) 870, 1150, 1515, 1565, 1680, 3160, 3450 cm^{-1}. ^{1}H n.m.r. (CCl_4) δ 7.95 (1H, m, H2'); 7.34 (1H, m, H5'); 6.68, (1H, m, H4'); 4.08 (1H, dt, J 7,5Hz, H4"); 3.47 (1H, t, J 7Hz, H5"); 3.5 (1H, brs, D_2O exch., OH); 2.75 (2H, m, $(H2)_2$); 1.28 (3H, s, 2"-CH_3);

0.94 (6H, d, J 7Hz, $(H2)_3$ and 1-CH_3). M/e 266 ($M^{\dagger}$), 248, 223, 194, 165, 151, 150, 143, 125, 123, 111, 110, 95 (b.p.) 83.

Conversion of Keto-Diol (88) to Keto-Alcohol (91)

(i) The diol (88) (m.p. 74-75°, 260 mg, 0.92 mmol) was acetylated in pyridine (2 ml) and acetic anhydride (1 ml) for 6 h at room temperature to give the monoacetate of (88). (300 mg, quantitative). ^{1}H n.m.r. (CCl_4): δ 7.98 (1H, m, H2'); 7.30 (1H, m, H5'); 6.60 (1H, m, H4'); 5.14 (1H, m, H4"); 3.65 (1H, d, J 4Hz, H5"); 2.9 (3H, m, $(H2)_2$ and OH); 1.97 (3H, s, $COCH_3$); 1.27 (3H, s, 2"-CH_3); 1.10 (6H, s, $(H1)_3$ and 2-CH_3).

(ii) The acetate from (i) was dehydrated using thionyl chloride (0.3 ml) and pyridine at 0° as previously described. After 10 min workup gave the crude alkene acetate (200 mg) which was hydrolysed without purification.

The acetate was allowed to stand in methanol (20 ml) and potassium hydroxide (0.2 g in 2 ml water). Hydrolysis was complete in 2 h and two products were seen from t.l.c. examination of the mixture (SiO_2). Better separation was possible using silver nitrate on silica gel. However, separation on a short silver nitrate (10%) impregnated silica gel column gave mixtures arising from decomposition on the absorbent of the major product, the enol ether formed. The minor alkene isomer, isolated as a colourless oil, was (2*S*,4"*S*,5"*R*)-1-(furan-3'-yl)-3-(4"-hydroxy-5"-isopropenyl-2"-methyl-tetrahydrofuran-2"-yl)-propan-1-one (93)(60 mg, 24% based on diol) b.p. 130°/0.05 mm (block) (Found: C, 67.99; H, 7.86. $C_{15}H_{20}O_4$ requires C, 68.16; H, 7.63%, m/e 264.1354 $C_{15}H_{20}O_4$ requires 264.1381). ν_{max} (film) 870, 1050, 1150, 1510, 1560, 1680, 3160, 3440 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.91 (1H, m, H2'); 7.29 (1H, m, H5'); 6.65 (1H, m, H4'); 4.92 and 4.72 (each 1H, brs, $=CH_2$); 4.02 (2H, m, H4" and H5"); 2.7 (3H, m, $(H2)_3$ and OH); 1.72 (3H, brs, $=CH_3$); 1.31 (3H, s, 2"-CH_3). M/e 265 (M^++1), 264 ($M^{\dot{+}}$), 246, 231, 218, 194, 193, 167-163, 151, 150, 141, 123, 121, 111, 110 (b.p.), 95, 84, 83, 61.

(iii) The keto alkene (93) (50 mg) was hydrogenated using P_2-Ni (from 1 mmol nickel acetate) in ethanol (15 ml) for 7 h when hydrogen absorption stopped. The product was isolated by passage through a column of alumina, washing the column with ethanol (20 ml) and evaporation to give a yellow oil (50 mg) which crystallised. Recrystallisation from ether/hexane gave colourless needles m.p. 58-60° identical to the keto alcohol (91) (by n.m.r., i.r. and m.m.p.) previously described.

Reductive cleavage of Dihydroeremoacetal (94) with Lithium in Ammonia - (7*R* and 7*S*,2*R*,4*R*)-7-(furan-3'-yl)-4-methyl-2-(2"-methylpropyl)-oxepan-4-ol (123a) and (123b) and (4*R*, 6*R*)-9-(furan-3'-yl)-2,6-dimethylnonane-4,6-diol (124).

Dihydroeremoacetal (94) (1.7 g, 6.8 mmol) in dry tetrahydrofuran (10 ml) was added to a solution of liquid ammonia (approx. 100 ml) containing tetrahydrofuran (10 ml) and lithium (0.28 g, 40 mmole) at -33°. After stirring for 3 h isoprene was added until the blue colour was discharged (approx. 4-5 ml) followed (cautiously) by ammonium chloride (1-2 g). The ammonia was allowed to evaporate overnight and water (10-15 ml) was added to dissolve the salts. Extraction with ether (5 x 40 ml), drying the extracts and removal of the solvent gave an almost colourless oil (1.9 g) consisting of starting material and three more polar products by t.l.c. (ether/hexane 1:2). Chromatography gave recovered dihydroeremoacetal (94) (1.1 g, 65%).

The higher R_f product isolated was the (2R,4R,7S) oxepanol (123b).
(116 mg, 6.8% or 19% of the products) m.p. 67-68° (Found: C, 71.7; H, 9.8. $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.6%). ν_{max} (nujol) 720, 780, 800, 870, 900, 940, 1010, 1040, 1070, 1120, 1140, 1500, 3300 cm^{-1}. (90 MHz) ^1H n.m.r. ($CDCl_3$): δ 7.35 (2H, m, H2" and H5"); 6.34 (1H, m, H4"); 4.26 (1H, dd, J 9.0,4.5Hz, H2); 3.66 (1H, m, H7); 1.26 (3H, s, 5-CH_3); 0.90 (6H, d, J 6.5 Hz, 2"-CH_3 and $(H3")_3$). (60MHz) ^1H n.m.r. (CCl_4): δ 7.35 (2H, m, H2" and H5"); 6.3 (1H, m, H4"); 4.4 (1H, m, H2); 3.7 (1H, m, H7); 1.23 (3H, s, 5-CH_3); 0.95 (6H, d, J 7Hz, 2"-CH_3 and $(H3")_3$). ^{13}C n.m.r. see appendix. M/e 252 ($M^{+\cdot}$), 234, 206, 193 155, 151, 145, 133, 124, 110, 108, 97 (b.p.); 95, 82, 81, 79, 71, 69, 55.

The product of R_f between the two oxepanes was the *diol* (124) (120 mg, 7% overall or 20% of the products) (characterised as the acetonide - see later). ν_{max} (film) 770, 870, 1020, 1500, 3400 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.37 (1H, m, H2'); 7.3 (1H, m, H5'); 6.28 (1H, m, H4'); 4.4 (2H, brs, D_2O exch., 2OH); 4.0 (1H, m, H4); 2.44 (2H, m, $(H9)_2$); 1.16 (3H, s, 4-CH_3); 0.93 (6H, d, J 7Hz, 2-CH_3 and $(H1)_3$). ^{13}C n.m.r. see appendix. M/e 254 ($M^{+\cdot}$), 236, 221, 219, 218, 179, 153, 152, 145, 137, 136, 135, 134, 127, 109, 95, 94 (b.p.), 82, 81, 71, 69.

The most polar product, of lowest R_f, was (2R,4R,7R)-7-(furan-3'-yl)-4-methyl-2-(2"-methylpropyl)oxepan-4-ol (123a) (160 mg, 9.4% overall or 27% of the products) m.p. 46-47° (Found: C, 71.1; H, 9.8. $C_{15}H_{24}O_3$ requires C 71.4; H, 9.6%). ν_{max} (nujol) 730, 874, 910, 1020, 1030, 1050, 1075, 1090, 1120, 1500, 3140 (sharp), 3370 (broad) cm^{-1}. (90MHz) ^1H n.m.r. ($CDCl_3$): δ 7.37 (1H, m, H2' or H5'); 7.35 (1H, m, H2' or H5'); 6.38 (1H, m, H4'); 4.7 (1H, dd, J 3.5,9.4Hz, H2); 3.67 (1H, m, H7); 1.37 (3H, s, 5-CH_3); 0.83 and 0.75 (each 3H, 2d, J 6.5Hz, 2"-CH_3 and $(H3")_3$). (60MHz) ^1H n.m.r. (CCl_4): δ 7.34 (2H, m, H2' and H5'); 6.34 (1H, m, H4') 4.65 (1H, m, H2); 3.63 (1H, m, H7); 3.0 (1H, brs, D_2O exch., OH); 1.33 (3H, s, 5-CH_3); 0.84 and 0.77 (each 3H, 2d, J 7Hz, 2"-CH_3 and $(H3")_3$). ^{13}C n.m.r. see appendix. M/e 252 ($M^{+\cdot}$), 234, 206, 197, 191, 177, 151, 133, 127, 125, 124 (b.p.), 110, 108, 97, 95, 81, 71, 69.

(ii) A similar reduction to that described above was carried out on dihydroeremoacetal (94) (7.3 g) over 7 h. Workup gave recovered starting material (2.3 g, 30%) oxepane (123a) (1.3 g, 18%), diol (124) (2.9 g, sl.impure, 40%) and oxepane (123b) (0.07 g, 1%).

Reduction of Dihydroeremoacetal with Lithium in Propylamine

(i) To a blue solution of lithium (200 mg, 29 mmol) in n-propylamine (dry, 30-40 ml) at room temperature was added a solution of dihydroeremoacetal (94) (1.0 g, 4 mmol) in tetrahydrofuran (dry, 10 ml) over 10 min. After 90 min stirring at room temperature solid ammonium chloride (approx. 1 g) was cautiously added and the solution warmed to remove most of the amine. Brine (50 ml) was added to the residue and the mixture extracted with ether (4 x 50 ml). Evaporation of the solvent gave a colourless oil (0.95 g) containing only a trace of furan compounds by n.m.r. examination.

(ii) A similar reaction was carried out at 0° and followed by t.l.c. No starting material was detected after 15 min. Workup after 20 min gave a colourless oil which contained diol (124) (approx. 20% by n.m.r.) and a mixture of more polar furan reduction products which were not identified. None of the oxepanes (123a) or (123b) were detected.

Reduction of Eremoacetal with Metals in Ammonia

(i) The reduction of eremoacetal using various metals (lithium, sodium and calcium) in liquid ammonia containing alcohols has been reported earlier.[82]

The products of all these reductions showed complete reduction of the furan ring and complex polar products.

(ii) Eremoacetal (47) (300 mg, 1.2 mmol) in tetrahydrofuran (3 ml) was added to liquid ammonia (15 ml, dry; distilled from sodium amide) containing dissolved lithium (50 mg, 7 mmol). The blue solution was stirred for 15 min at -33° before workup with ammonium chloride (0.2 g). After evaporation of the ammonia, water (2 ml) was added and the mixture extracted with ether (4 x 20 ml). Evaporation of the combined extracts gave a colourless oil (250 mg) which yellowed on standing. Preparative t.l.c. (ether/hexane 1:1) showed four major bands.

The highest R_f band (25 mg) contained no furan protons by n.m.r. and was not examined further.

The next highest R_f band contained what is probably the 2,3-dihydrofuran diol (113) (85 mg, 29%) by n.m.r. ^{1}H n.m.r. (CCl_4): δ 6.35 (1H, m, H5'); 5.2-5.0 (3H, H4', H6 and H7); 1.0 (6H, d, $(H9)_3$ and 8-CH_3).

The next highest R_f product was consistent with the keto-alkene (112) (45 mg, 15%) formed also by treatment of eremoacetal with diborane. ν_{max} (film) 870, 1150, 1510, 1560, 1680, 3450 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.95, 7.2, 6.6, (each 1H), 5.3 (2H, m), 2.25 (2H, t), 1.1 (3H, s,), 1.o (6H, d).

The most polar products (50 mg, 17%) contained no furan protons by n.m.r. and showed a strong hydroxyl absorption at 3500 cm^{-1} in the i.r.

Treatment of mesylate (151) with Lithium in Ammonia

(i) The mesylate (151) (150 mg, 0.44 mmol) in tetrahydrofuran (5 ml) was reduced in ammonia (40 ml), and tetrahydrofuran (5 ml) containing dissolved lithium (20 mg). After 2½ h, workup gave a colourless oil (250 mg). Preparative t.l.c. (ether/hexane 4:1) gave two major products. The higher R_f product was the acetal alcohol (90a) (41 mg, 33%) identified by n.m.r., i.r. and t.l.c. comparison with authentic alcohol.

The lower R_f product (66 mg, 53%) appeared to be an acyclic furan diol or triol. ^{1}H n.m.r. (CCl_4): δ 7.17 (1H, m); 7.05, (1H, m); 6.11 (1H, m); 4.0 (brs, D_2O exch., OH); 3.7 (1H, m) 3.2 (1H, m); 2.3 (2H, m); 1.17 (3H, s); 1.0 and 0.9 (each 3H, d).

(ii) The epimeric mesylate (150) gave a similar mixture of acetal alcohol and acyclic alcohol under the same reduction conditions.

Acetylation of Oxepanes (123)

When the oxepanes (123a) and (123b) (30 mg) were allowed to stand in a mixture of acetic anhydride (0.2 ml) and pyridine (0.5 ml) no new products were detected by t.l.c. after 15 h at room temperature. Heating oxepane (123a) in the same mixture to 80° for 4 h gave one less polar product. Workup gave a colourless oil of the oxepane acetate. ν_{max} (film) 870, 1020, 1500, 1730 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.17 (2H, m, H2' and H5'); 6.2 (1H, m, H4'); 4.57 (1H, t, J 6Hz, H2); 3.6 (1H, m, H7); 1.87 (3H, s, CH_3CO); 1.57 (3H, s, 5-CH_3); 0.9-0.8 (6H, 2d, J 6Hz, C2"-CH_3 and $(H3")_3$). M/e 294 ($M^{+\cdot}$), 235, 234, 207, 206 (b.p.), 197, 177, 151, 149, 138, 133, 124, 123, 110, 109, 95, 94, 82, 81, 69.

Oxidation of Diol (124) to (6*R*)-9-(furan-3'-yl)-6-hydroxy-2,6-dimethylnonan-4-one (176)

A suspension of pyridinium chlorochromate (0.60 g, 2.8 mmole) in dry methylene chloride (30 ml) containing sodium acetate (anhydrous, 0.1 g) was vigorously stirred while a solution of diol (124) (120 mg, 0.47 mmol) in methylene chloride (2 ml) was added at once. Conversion to ketone was complete after 3 h (t.l.c. and workup according to the standard procedure and preparative chromatography (ether/hexane, 4:6) gave a colourless oil of (6*R*)-9-(furan-3'-yl)-6-hydroxy-2,6-dimethylnonan-4-one (176) (96 mg, 82%) (Found: C, 71.2; H, 9.3. $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.6). $[\alpha]_D^{15} < \pm 0.3°$ (C, 9 in $CHCl_3$). ν_{max} (film) 770, 870, 1020, 1060, 1500, 1700, 3520 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.2 (1H, m, H5'); 7.0 (1H, m, H2'); 6.1 (1H, m, H4'); 3.4 (1H, brs, D_2O exch., OH); 2.4 (2H, s, $(H5)_2$); 1.12 (3H, s, 6-CH_3); 0.90

(6H, d, J 6Hz, 2-CH_3 and $(H1)_3$). ^{13}C n.m.r. see appendix. M/e 252 (M^{+}), 234, 219, 211, 197, 183, 153, 152, 149, 143, 134, 133, 113, 109, 99, 95, 94, 85 (b.p.), 81, 71, 67, 57, 43.

2,4-Dinitrophenylhydrazones of Ketone (176)

The ketone (176) (55 mg) in pure ethanol (1 ml) was added to a solution of 2,4-dinitrophenylhydrazine (70 mg) in hot ethanol (10 ml) containing sulphuric acid (3 drops). Examination of the solution by t.l.c. showed three products. The higher R_f band, after preparative chromatography, was an orange oil, (10 mg) the 2,4-dinitrophenylhydrazone of the dehydrated ketone.

The major products were the E and Z isomers of the ketone (176) but each was a red oil which failed to crystallise. Each was characterised by its proton n.m.r. and i.r. spectra.

The higher R_f isomer, an orange oil, was assigned to (*E*)-2,4-dinitrophenylhydrazone of ketone (176) (48 mg, 45%). ν_{max} (film) 710, 735, 785, 825, 870, 920, 1020, 1060, 1130, 1500, 1515, 1590, 1620, 3120, 3240, 3580 cm^{-1}. ^1H n.m.r. (CCl_4): δ 8.78 (1H, d, J 2Hz, aromatic); 8.02 (1H, dd, J 10,2Hz aromatic); 7.59 (1H, d, J 10Hz, aromatic); 7.19 (1H, m, H5'); 7.09 (1H, m, H2'); 6.15 (1H, m, H4'); 1.31 (3H, s, 6-CH_3); 1.0 (6H, d, J 6Hz, 2-CH_3 and $(H1)_3$).

The lowest R_f isomer, an orange oil, was assigned to the (Z)-2,4-dinitrophenylhydrazone of ketone (176) (40 mg, 40%). ν_{max} (film) 720, 740, 785, 825, 870, 920, 1020, 1215, 1515, 1590, 1620, 3120, 3340, 3480, 3560 cm^{-1}. ^1H n.m.r. (CCl_4): δ 8.88 (1H, d, J 2Hz, aromatic); 8.17 (1H, dd, J 2,10Hz, aromatic);

7.65 (1H, dd, J 10Hz, aromatic); 7.18 (1H, m, H5'); 7.05 (1H, m, H2'); 6.12 (1H, m, H4'); 1.21 (3H, s, 6-CH); 1.05 (6H, d, J 6Hz, 2-CH_3 and $(H1)_3$).

Conversion of Diol (124) to Acetonide (177)

The diol (124) (150 mg) was dissolved in acetone (10 ml) and 2,2-dimethoxypropane (10 ml) and a small crystal of p-toluene-sulphonic acid was added. After 20 min, t.l.c. showed a non polar product and no diol. The mixture was passed rapidly through a short column of alumina, the alumina was washed with ether and the solvent removed to give a colourless oil (170 mg, quantitative). Distillation gave a colourless liquid of the *acetonide* (177) (b.p. 100° /0.05) (Found: C, 73.33; H, 10.03. $C_{18}H_{30}O_3$ requires C, 73.43; H, 10.27). ν_{max} (film) 780, 875, 960, 1020, 1500 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.1 (1H, m, H5'); 7.0 (1H, m, H2'); 6.1 (1H, m, H4'); 3.8 (1H, m, H4), 2.3 (2H, m, $(H9)_3$); 1.3 (6H, brs, $O_2C(CH)_3$); 1.1 (3H, s, 6-CH_3), 0.9 (6H, d, J 6Hz, 2-CH_3 and $(H1)_3$). M/e 294 ($M^{\ddagger}$), 279, 254, 236, 219, 211, 203, 201, 197, 185, 179, 175 171, 163, 162, 161, 157-149, 137-135, 127, 121, 112, 109, 99, 95, 94, 85, 82, 81, 71, 69, 59.

Dehydration of Oxepane (123a)

The oxepane (123a) (m.p. 46-47°, 0.90 g, 3.5 mmol), dissolved in hexane (15 ml) and pyridine (3 ml), was stirred at 0° while thionyl chloride (0.5 ml) was added dropwise. After 15 min at 0 the reaction mixture was quenched with water (10 ml) and extracted with hexane (3 x 20 ml). The combined extracts were washed with dilute acid (5% HCl, 2 x 10 ml), water (10 ml), dried and evaporated to give a mixture of less polar products (0.85g). Purification by preparative t.l.c. (2x ether/hexane, 1:19) gave the most polar product, (2R,7R) 4-chloro-7-(furan-3'-yl)-2-(2''-methylpropyl)-oxepane (131) (241 mg, 29% of products) m.p. 43° (hexane) (Found: C,67.9; H, 8.6 Cl 12.9. $C_{15}H_{23}O_2Cl$ C, 66.5; H, 8.6;Cl, 13.1%). ν_{max} (nujol) 720, 740, 780, 830, 870, 1005, 1015, 1030, 1080, 1120, 1135, 1500, 3140 cm^{-1}. ^1H n.m.r. δ (CCl_4) 7.20 (2H, m, H2′ and H5′); 6.25 (1H, m, H4′); 4.60 (1H, dd, J 2.0, 5.2Hz, H2); 3.70 (1H, m, J 3.4, 0.7 Hz), 1.60 (3H, s, H-CH_3); 0.80 and 0.60 (each 3H, 2d, J 6Hz, 2" -Ch_3 and $(H_3'')_3$). ^{13}C n.m.r. see appendix. M/e 270 ($M^{+\cdot}$, ^{35}Cl), 235, 234, 219, 213, 206, 186, 184. 177, 169, 159, 151, 149, 148, 135-3, 123, 119, 95 (b.p.), 83-1, 69.

The higher R_f products (587 mg, 94% of dehydrated alcohol) were a mixture of three compounds by t.l.c. and all attempts to isolate the components pure failed but the major product (approx. 330 mg) isolated in moderate purity was the exocyclic alkene, (2R,7R) 7-(furan-3'-yl)-4-methylene-2-(2''-methylpropyl)-oxepane (128) (b.p. 120°/15 (block)) (Found: C, 76.16; H, 9.55. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46). ν_{max} (film) 780, 800, 880, 1035, 1095, 1160, 1510, 1650, 3100 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.17 (2H, m, H2' and H5'); 6.2 (1H, m, H4'); 4.7 (1H, m, H1); 4.5 (2H, brs, Δ5-CH); 3.5 (1H, m, H7); 2.25 (4H, m, $(H4)_2$ and $(H6)_2$); 0.8 and 0.9 (each 3H, 2d). M/e 234 ($M^{+\cdot}$), 219, 206, 205, 191, 177, 148 (b.p.), 133, 119, 105, 95, 94, 91, 81, 80, 69, 67.

The other alkenes formed were isolated as a mixture (140 mg) containing mostly the Δ4 oxepin (129) and only a trace of the Δ3 oxepin (130) by n.m.r.

(ii) Attempts to isomerise the double bond of the exocyclic methylene oxepane (128) using boron triacetate (r.t.), heating on SiO_2 , gave recovered starting material.

Competitive Reduction of Oxepanol (123a) and Tetrahydrofuran (135b) in Liquid Ammonia with Lithium

A mixture of the tetrahydrofuranyl alcohol (135b) (52 mg) and oxepanol (123a) (52 mg) in tetrahydrofuran (2 ml) was added with stirring to a blue solution of ammonia (70 ml), tetrahydrofuran (8 ml) and lithium metal (20 mg). After 1 h at -33° The blue colour was discharged by the dropwise addition of isoprene. The mixture was worked up as previously described and the crude products purified by preparative t.l.c. (ether/hexane 4:1) to give a trace of the tetrahydrofuranyl alcohol (135b) (approx 3 mg, 6%), diol (124) (50 mg, 95% based on unrecovered tetrahydrofuran (135b), and oxepanol (123a) (50 mg, 96% recovery).

Preparation of (1'*R*,3'*S*,5'*R*,1*R*)-1-[(furan-3"-yl)-5'-methyl-2',8'-dioxabicyclo[3.2.1]oct-3'-yl]-2-methylprop-1-yl methanesulphonate (151)

The (1R) alcohol, isomer (90a) (143 mg) was added in pyridine (1 ml) to mixture of pyridine (2-3 ml) containing methanesulphonyl chloride (0.2-0.3 ml) at 0-10 . Conversion was complete within 1 h and the addition of ice water gave the crude mesylate as a solid. Recrystallisation from ether/hexane gave colourless needles of the pure *mesylate* (151) (180 mg, 97%) m.p. 96-97° (Found: C, 55.72; H, 6.87. $C_{16}H_{24}O_6S$ requires C, 55.80; H, 7.03%). ν_{max} (nujol) 720, 755, 805, 815, 860, 875, 920, 940, 970, 1010, 1070, 1145, 1165, 1505(w), 1600(w), 3150(w), 3180 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.4 (1H, m, H2"); 7.3 (1H, m, H4"); 4.4 (1H, dd, J 8,3Hz, H1'); 4.2 (1H, d,t, 3Hz, H3); 2.8 (3H, s, OSO_2CH_3), 1.4 (3H, s, 5-CH_3); 1.05 (6H, 2d, J 6Hz, 2'-CH_3 and $(H3')_3$). M/e 344 ($M^{\dagger}$), 249, 193, 165, 148, 137, 124, 121, 109, 107, 95 (b.p.), 85-79, 57, 55.

Preparation of (1'*R*,3'*S*,5'*R*,1*S*)-1-[(furan-3"-yl)-5'-methyl-2',8'-dioxabicyclo[3.2.1]oct-3'-yl]-2-methylprop-1-yl-methanesulphonate (150)

The (1S) alcohol (90b) was converted to the mesylate as described above for the epimer. Recrystallisation gave colourless needles of the *mesylate* (150) (95%) m.p. 136-137° (Found: C, 56.14; H, 6.99; S, 9.1. $C_{16}H_{24}O_6S$ requires C, 55.80; H, 7.03; S, 9.3%). ν_{max} (nujol) 760, 820, 915, 945, 1000, 1030, 1060, 1140, 1160, 1510, 1615, 3150, 3180 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.5 (1H, m, H2"); 7.3 (1H, m, H5"); 6.4 (1H, m, H4"); 4.5 (1H, dd, J 8,3Hz, H1'); 4.1 (1H, m, H3); 2.9 (3H, s, OSO_2CH_3); 1.4 (3H, s, 5-CH_3); 1.0, 0.9 (each 3H, 2d, J 6Hz, 2'-CH_3 and $(H3')_3$). M/e 334 ($M^{\ddagger}$), 249, 193, 165, 148, 137, 124, 121, 111, 109, 107, 95 (b.p.), 85-79, 57, 55.

Reduction of Mesylates (150) and (151) with Lithium Triethylborohydride

The mesylates (150) and (151) (150 mg) were reduced with triethylborohydride (3 mM) in boiling tetrahydrofuran according to the method of Holder and Matturro.[95]

After heating for 48 h workup gave a colourless oil (107 mg). Preparative chromatography (ether/hexane, 1:2) gave recovered mesylate (30%). The highest R_f product was identified as dihydroeremoacetal (94) (30 mg, 41% based on non recovered mesylate). This was identical by n.m.r., i.r., mass spectra and t.l.c. to authentic dihydroeremoacetal (94). A mixture containing two minor products (10 mg, 14%), which were not separated, appeared to consist, predominantly of eremoacetal (47) (n.m.r., i.r., t.l.c.) was also isolated.

Reductive Opening of Acetal Mesylate (151) to the Tetrahydrofuranyl Alcohols (152) and (153)

The pure mesylate (151) (240 mg, m.p. 96-97°) in dry tetrahydrofuran (5 ml) was added to a suspension of lithium aluminium hydride (200 mg) in the same solvent (30 ml). The mixture was heated under reflux for 3 h and stirred overnight at 20°. Reaction appeared almost complete after 2 h by t.l.c. examination. Workup with aqueous tetrahydrofuran and sodium hydroxide (1 ml, 15% in water), filtration and removal of solvent gave a colourless oil (187 mg). Preparative t.l.c. (ether/hexane, 1:1) gave two products.

The high R_f product was a colourless oil of (2*R*,2'*R*,5'*R*)-1-[5'-(furan-3"-yl)-2'-methyltetrahydrofuran-2'-yl]-4-methylpentan-2-ol (152) (65 mg, 35%), b.p. 120°/1 mm (block), $[\alpha]_D^{20}$ + 36° (C, 3.2 in $CHCl_3$) (Found: m/e 252.1723. Calculated for $C_{15}H_{24}O_3$: m/e 252.1725). ν_{max} (film) 780, 870, 905, 1020, 1090, 1130, 1150, 3480 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.3 (2H, m, H2" and H5"); 6.3 (1H, m, H4"); 4.9 (1H, m, H5'); 3.2 (1H, m, H2); 1.2 (3H, s, 2'-CH_3); 0.9 (6H, d, J 7Hz, 4-CH_3 and $(H5)_3$). ^{13}C n.m.r.: see appendix.

The lower R_f product, a colourless oil was (3*R*,2'*R*,5'*R*)-5-[5'-(furan-3"-yl)-2'-methyltetrahydrofuran-2'-yl]-2-methylpentan-3-ol (153) (120 mg, 64%) b.p. 100-110°/1 mm (block), $[\alpha]_D^{20}$ + 20° (C, 5.7 in $CHCl_3$) (Found: m/e 252.1723. Calculated for $C_{15}H_{24}O_2$: m/e 252.1725). ν_{max} (film) 780, 870, 910, 1020, 1130, 1150, 1500, 3400 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.3 (2H, m, H2" and H5"); 6.3 (1H, m, H4"); 4.9 (1H, m, H2'); 3.8 (1H, m, H3); 3.3 (1H, s, D_2O exch., OH); 1.2 (3H, s, 2'-CH_3); 0.9 (6H, d, J 6Hz, 2-CH_3 and $(H1)_3$). ^{13}C n.m.r see appendix. M/e 252 ($M^{+\cdot}$), 235, 234, 207, 191, 173, 167, 151 (b.p.), 145, 127, 123, 110-107, 95, 94, 81, 79, 69, 55.

Preparation of (1*R*,3*S*,5*R*)- 1-(furan-3'-yl)-5-methyl-2,8-dioxabicyclo[3.2.1] oct -3-yl -methanol (154) and mesylate (155)

(i) A solution of aldehyde (82) (220 mg) was reduced using lithium aluminium hydride (0.2 g) in ether (50 ml). Workup with wet ether and removal of the solvent gave a colourless oil of crude product (220 mg). Distillation gave the pure *alcohol* (154) (206 mg, 94%) b.p. 110-120°/0.3 mm (block) (Found: C, 64.48, H, 7.27. $C_{12}H_{16}O_4$ requires C, 64.27, H, 7.19%). ν_{max} (film) 790, 870, 930, 945, 1000, 1050, 1120, 1140 1150, 1500, 1600, 3160, 3450 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.45 (1H, m, H2'); 7.3 (1H, m, H5'); 6.4 (1H, m, H4'); 3.9 (1H, m, H3); 3.4 (3H, m, CH_2-OH, 1H, D_2O exch., OH), 1.4 (3H, s, 5-CH_3).

(ii) Using the procedure outlined previously for the preparation of mesylates, the reaction product after purification by preparative chromatography gave a colourless oil of the *mesylate* (155) (80%) which was used without further purification. ν_{max} (film) 800, 870, 890, 920, 940, 1030, 1050, 1170, 1500, 3160 cm^{-1}. ^{1}H n.m.r. (CCl$_4$): δ 7.45 (1H, m, H2'); 7.3 (1H, m, H5'); 6.4 (1H, m, H4'); 4.2 (3H, m, H3 and CH$_2$-OMS); 2.9 (3H, s, SO$_2$CH$_3$); 1.4 (3H, s, 5-CH$_3$).

A minor (9%) product was isolated but not characterised although some resonances in the ^{1}H n.m.r. spectra and i.r. spectra suggest a ring opened product. ν_{max} (film) 875, 1150, 1170, 1500, 1560, 1680, 3160, 3420 cm^{-1}. ^{1}H n.m.r. (CCl$_4$): δ 8.1 (1H, m); 7.4 (1H, m); 6.8 (1H, m); 2.8 (2H).

Reductive Hydride Fission of Mesylate (155) to (2*R*,2'*R*,5'*S*)-1-[5'-(furan-3"-yl)-2'-methyltetrahydrofuran-2'-yl]-propan-2-ol (156)

A solution of mesylate (155) (220-230 mg) in dry tetrahydrofuran (2 ml) was added to lithium aluminium hydride (200 mg) in tetrahydrofuran (20 ml). A vigorous reaction ensued and the mixture was worked up after 1 h reflux by the cautious addition of wet ether (50 ml) and filtration. Evaporation of solvents gave a colourless oil (190 mg). Preparative chromatography (ether/hexane, 1:1) gave a colourless oil of the *alcohol* (156) (160 mg, quant.) b.p. 90°/0.6 mm (block) (Found: C, 68.79; H, 8.64. $C_{12}H_{18}O_3$ requires C, 68.54; H, 8.63%). ν_{max} (film) 780, 870, 900, 910, 1020, 1130, 1150, 1500, 3450 cm^{-1}. ^{1}H n.m.r. (CCl$_4$): δ 7.3 (2H, m, H2" and H5"); 6.25 (1H, m, H4"); 4.95 (1H, m, H5'); 4.0 (1H, m, H2); 1.25 (3H, s, 2'-CH$_3$); 1.1 (3H, d, J 6Hz, 2-CH$_3$). M/e 210 ($M^{+\cdot}$), 192, 177, 166, 151, 134, 110 (b.p), 107, 97, 95, 81, 79, 77, 70, 69-65, 55, 53.

Oxidation of (+) Epingaiol (152) to (+)-Epingaione (157)

(i) The alcohol (152) (16 mg) in dry methylene chloride (1 ml) was added to a suspension of pyridinium chlorochromate (50 mg) and sodium acetate (anhydrous, 10 mg) in methylene chloride (5 ml). Oxidation of the alcohol was very slow even after the addition of more oxidant (2 x 10 mg) after 5 h and 8 h. After 20 h t.l.c. showed the alcohol was still present together with the required ketone. The proton n.m.r. and i.r. spectra of the oxidation products (12 mg) confirmed that it contained the ketone and alcohol (approx. 1:1 by n.m.r.).

(ii) The alcohol (152) (distilled, 50 mg) was oxidised using oxalyl chloride (100 µl) and dimethyl sulphoxide (170 µl) in methylene chloride at -70°, as previously described. After 45 min the mixture was worked up to give a yellow oil.

Preparative chromatography (ether/hexane, 2:3) gave recovered starting material (4 mg, 8%). A higher R_f product was identified as the ketone (157) ((+)-epingaione) (34 mg, 70%) b.p. 110°/0.5 mm (block) (lit.[20] b.p. 95°/0.01), $[\alpha]_D^{17}$ + 18° (C, 1.5 in benzene) (Lit.[18] $[\alpha]_D^{27}$ - 14.8° (C, 1.0 in benzene) ν_{max} (film) 790, 875, 915, 1020, 1155, 1365, 1500, 1710, 2890, 2970, 3160 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.21 (2H, m, H2" and H5"); 6.19 (1H, m, H4"); 4.78 (1H, m, H2); 2.53 (2H, s, $(H1)_2$; 1.25 (3H, s, 5-CH_3); 0.90 (6H, d, J 6Hz, 4-CH_3 and $(H5)_3$). M/s 250 ($M^{+\cdot}$), 234, 191, 177, 167, 165, 151 (b.p), 150, 140, 110, 125, 123, 11-107, 97, 95, 85, 83, 81, 79, 57, 69.

Oxidation of Alcohol (153) to (2'*S*,5'*R*)-1-[5'-(furan-3"-yl)-2'-methyltetrahydrofuran-2'-yl]-4'methylpentan-3-one (153b)

(i) The alcohol (153) (23 mg) was added in methylene chloride (1 ml) to a stirred suspension of pyridinium chlorochromate (80 mg) and sodium acetate (10 mg) in methylene chloride (10 ml). After 3 h more oxidant was added (30 — 40 mg) as considerable alcohol was detected by t.l.c. The mixture was worked up after 5 h to give a yellow oil (15 mg) containing alcohol (153) (30-40%) and the required ketone (153b) (approx. 20%).

(ii) An oxidation of alcohol (153) (75 mg) was carried out using an excess (3.5 equivalents) of Swern's reagent[67] (oxalyl chloride/dimethyl sulphoxide, -70°) as previously described. After oxidation for 20 min at -70° workup and preparative chromatography (ether/hexane 1:2) gave recovered alcohol (14 mg, 19%) and the *ketone* (153b) (14 mg, 23%) (Found: m/e 250.1569. Calculated for $C_{15}H_{22}O_3$; 250.1569). ν_{max} (film) 785, 875, 915, 1020, 1150, 1500, 1715, 3150 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.14 (2H, m, H2" and H5"); 6.14 (1H, m, H4"); 4.68 (1H, apparent, J 6Hz, H2); 1.17 (3H, s, 5-CH_3); 1.03 (6H, d, J 6Hz, 2-CH_3 and $(H1)_3$). M/e 251 ($M^{\dagger}$ + 1); 250 ($M^{\dagger}$), 207, 165, 161, 151, 110-107, 95 (b.p), 94, 86, 81, 79, 77, 71, 69, 67, 65, 61, 55, 53.

Treatment of Eremoacetal and Dihydroeremoacetal with Lithium Aluminium Hydride

When either eremoacetal (47) or dihydroeremoacetal (94) was heated in tetrahydrofuran (10-15 ml) containing lithium aluminium hydride for 18 h, workup gave only unchanged starting materials.

Attempted Solvolysis of Mesylate (151)

The mesylate (151) (20 mg) was allowed to stand in a solution of tetrahydrofuran (0.5 ml) and water (0.5 ml) containing sodium bicarbonate (10-20 mg). After 18 h only starting material was visible by the t.l.c. examination of the mixture. The solution was heated under reflux for 3 h and workup gave unchanged mesylate (151).

Hydrogenation of (2*S*,2'*R*,5'*S*) Dehydrognaiol (62)

The alcohol (62) (90 mg) was reduced with P$_2$-Ni[145] (prepared from 1 mmol nickel acetate) in ethanol for 3 days. Workup and purification by preparative chromatography (ether/hexane, 1:3) gave starting material (62) (15 mg, 17%) and (2*R*,2'*R*,5'*S*)-1-[5'-(furan-3"-yl)-2'-methyltetrahydrofuran-2'-yl]-4-methylpentan-2-ol (135b) (70 mg, 93% based on unrecovered starting material) as a colourless oil. (Found: C, 71.25; H, 9.14. $C_{15}H_{24}O_3$ requires C, 71.39; H, 9.59%. M/e 252.1729. $C_{15}H_{24}O_3$ requires m/e 252.1725) b.p. 110° /0.05 mm (block). ν_{max} (film) 785, 880, 920, 1025, 1160, 1505, 1600(w), 3150(w), 3500 cm^{-1}. ^{1}H n.m.r. (CCl$_4$): δ 7.22 (2H, m, H2" and H5"); 6.25 (1H, m, H4"); 4.80 (1H, t, J 6.8Hz, H5;); 3.84 (1H, pentuplet, J 4Hz, H2); 3.3 (1H, brs, OH); 1.23 (3H, s, 2'-CH$_3$); 0.88 (6H, d, J 6Hz, 4-CH$_3$ and (H5)$_3$). M/e 252 ($M^{+\cdot}$), 234, 219, 177, 152, 151 (b.p), 133, 134, 135, 107, 110, 97, 95, 94, 81, 79, 77, 69.

Catalytic Preparation of (1*S*,1'*R*,3'*S*,5'*R*) and (1*R*,1'*R*,3'*S*,5'*R*) 1-{1'-(furan-3"-yl)-5'-methyl-2',8'-dioxabicyclo[3.2.1]oct-3'-yl}-2-methyl-propane-1,2-diols (86a) and (86b)

This procedure is based on modification of the method of Van Reenan, Kelly and Cha.[114]

To a solution of eremoacetal (47) (5.0 g, 20 mmole) in t-butanol (20 ml), was added as solution of osmium tetroxide (20-30 mg) in ether followed by N-methyl morpholine N-oxide dihydrate (3.5 g, 21 mmoles) in aqueous acetone (30 ml water, 60 ml acetone). A purple-brown colour of the osmate ester rapidly formed.

After 2 days the yellow solution contained no starting material by t.l.c. examination (ether). Addition of sodium sulphite (1 g) and stirring for 30 min gave a dark solution which was filtered through a bed of florisil to remove the osmium dioxide. Concentration of the filtrate under reduced pressure to a small volume (20-30 ml) followed by extraction with methylene chloride (5 x 30 ml) gave a solution of the diols together with some N-methyl morpholine.

The amine was removed from the methylene chloride by extraction with acidified brine (3 x 20 ml). Drying and removal of the solvent gave an oil (5.34 g, 94%) which partly solidified.

Crystallisation from methylene chloride/hexane gave the major (1*S*,1'*R*,3'*S*,5'*R*) *diol* (86a) (3.69 g, 65%). m.p. 117-118°

(Found: C, 63.8; H, 7.8. $C_{15}H_{22}O_5$ requires C, 63.8; H, 7.9%). ν_{max} (nujol) 810, 940, 1070, 1170, 3350 cm^{-1}. ^1H n.m.r. ($CDCl_3$): δ 7.6 (1H, m, H2"); 7.4 (1H, m, H5"); 6.5 (1H, m, H4"); 4.15 (1H, ddd, J 6,9,6Hz, H3'); 3.45 (1H, d, J 6Hz, H1); 2.9 (2H, brs, exch. D_2O, 2OH); 1.4 (3H, s, 5'-CH_3); 1.3,1.2 (each 3H, 2s, 2-CH_3 and $(H3)_3$). ^{13}C n.m.r. see appendix. M/e 264 ($M^{+\cdot}$ - H_2O).

The mother liquor from the crystallisation was a mixture of (86a) and (86b) which could be separated by repeated chromatography (chloroform/methanol, 20:1) and then characterised as the acetonides (see later). Crystallisation gave a colourless needles of the minor (1*R*,1'*R*,3'*S*,5'*R*) isomer, *diol* (86b) (1.61 g) m.p. 110-112°. ν_{max} (nujol) 800, 950, 1080, 1150, 3450 cm^{-1}. ^1H n.m.r. ($CDCl_3$): δ 7.6 (1H, m, H2"); 7.4 (1H, m, H5"); 6.5 (1H, m, H4"); 4.4 (1H, ddd, J 2,12,4Hz, H3'); 3.1 (1H, d, J 2Hz, H1); 2.8 (2H, brs, exch. D_2O, 2OH); 1.4 (3H, s, 5'-CH_3); 1.3,1.2 (each 3H, 2s, 2-CH_3 and $(H3)_3$). ^{13}C n.m.r. see appendix. M/e 264 ($M^{+\cdot}$ - H_2O).

Acetonides (160) and (161).

(i) The (1*S*,1'*R*,3'S,5'*R*) diol (86a) (282 mg, 1 mmole) was dissolved in dry acetone (2 ml) and 2,2-dimethoxypropane (5 ml) a small crystal of p-toluenesulphonic acid was added and the mixture stirred. After 10 min no diol could be detected.

Solid potassium carbonate was added, the solution was filtered and the solvents removed under reduced pressure. Recrystallisation of the residue gave colourless needles of the (1*S*,1'*R*, 3'*S*,5'*R*) *acetonide* (160) (320 mg, quantit.) m.p. 75-76° (Found: C, 67.1; H, 8.2. $C_{18}H_{26}O_5$ requires C, 67.0; H, 8.1%). ν_{max} (nujol) 800, 940, 1010, 1060, 1080, 1130, 1510 cm^{-1}. ^1H n.m.r. (CCl_3): δ 7.4 (2H, 2m, C2" and C5"); 6.4 (1H, m, H4"); 3.9 (1H, ddd, J 9,9,4Hz, H3'); 3.6 (1H, d, J 9Hz, H1), 1.4-1.2 (15H, 5 x s, methyls).

(ii) The (1*R*,1'*R*,3'*S*,5'*R*) diol (86b) was similarly converted to its *acetonide* (161), m.p. 70-72° (Found: C, 67.2; H, 8.1. $C_{18}H_{26}O_5$ requres C, 67.0; H, 8.1%). ν_{max} (nujol) 800, 940, 1010, 1060, 1080, 1150, 1200, 1510 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.5 (1H, m, H2"); 7.35 (1H, m, H5"); 6.45 (1H, m, H4"); 3.95 (1H, ddd, J 7,12,4Hz, H3'); 3.6 (1H, d, J 7Hz, H1); 1.4-1.15 (15H, 5 x s, methyls).

Conversion of Diol (86a) to Epoxide (163)

(i) The diol (86a) (100 mg, 0.36 mm) was dissolved in cold dry pyridine (2 ml) and methane sulphonyl chloride added (5 drops). The solution assumed a pink colour and no diol was detected by t.l.c. after 3 h. After 4 h, brine (20 ml) was added and the solution extracted with ether (4 x 10 ml). The combined ether extracts were washed with acidified brine and dried. Evaporation of the solvent gave a colourless oil of the crude hydroxy mesylate (130 mg) which was used without further purification.

(ii) The hydroxy mesylate (130 mg) was stirred with potassium carbonate (50 mg) in methanol (5 ml). After a short time the solution was filled with a crystalline suspension, presumably potassium methane sulphonate. No starting material was detected after 30 min and ether (20 ml) was added. Filtration of the solution through celite and evaporation under reduced pressure gave the crude epoxide. Purification by chromatography gave diol (86a) (15 mg) and colourless needles of epoxide (163) (67 mg, 85% overall) m.p. 101-102.5° (recrystalised from hexane) identical in all respects (m.m.p., i.r., n.m.r.) to the minor product of epoxidation of eremoacetal with peracid.

Reaction of Eremoacetal with Diborane

(i) To a solution of eremoacetal (47) (2.50 g, 10 mmole) in dry tetrahydrofuran (20 ml) under nitrogen at 0 , was added a solution of diborane (10 ml, 0.9M BH_3 in THF). After stirring for 30 min at 0°, t.l.c. showed only a trace of starting material. Wet tetrahydrofuran was cautiously added after 40 min, followed by sodium hydroxide (15 ml, 10% solution), hydrogen peroxide (10 ml, 30%) and the mixture stirred for 1 h. The aqueous layer was separated and extracted with ether (3 x 15 ml). The combined organic solvents were washed with brine (2 x 10 ml), dried and the solvents removed under reduced pressure.

T.l.c. showed a variety of products. Separation by chromatography (ethyl acetate/hexane) gave recovered starting material (10%).

Continued elution gave the two epimeric alcohols. The higher R_f and major product was identified as <u>(1*S*,1'*R*,3'*S*,5'*R*)-1-</u>

{1'-(furan-3"-yl)-5'-methyl-2',8'-dioxabicyclo[3.2.1]octa -3'-yl}-2-methylpropan-1-ol (90b) (640 mg, 28%). ν_{max} (film) 790, 870, 930, 1140, 1150, 1500, 1600, 3180(w), 3500 cm^{-1}. ^{1}H n.m.r. (CCl$_4$): δ 7.3 (1H, m, H2"); 7.2 (1H, m, H5"); 6.3 (1H, m, H4"); 3.9 (1H, dt, J 4.6,11.2Hz, H3'); 3.0 (1H, apparent t, J 4.6Hz, H1); 1.33 (3H, s, 5'-CH$_3$); 0.93 and 0.90 (3H, each, 2d, J 6Hz each, 2 -CH$_3$ and (H3)$_3$).

This alcohol (90b) was characterised as its *acetate* (90d) m.p. 78-79° (Found: C, 66.3; H, 8.0. $C_{17}H_{24}O_4$ requires C, 66.2; H, 7.9%). ν_{max} (film) 785, 870, 910, 930, 950, 1030, 1070, 1140, 1150, 1240, 1340, 1500, 1730 cm^{-1}. ^{1}H n.m.r. (CCl$_4$) δ 7.45 (1H, m, , H2"); 7.37 (1H, m, H5"); 6.4 (1H, m, H4"); 4.87 (1H, m, H1); 3.97 (1H, m, H3'); 2.05 (3H, s, CH$_2$CO); 1.40 (3H, s, 5'-CH$_3$); 0.93 (6H, d, J 8Hz, 2-CH$_3$ and (H3)$_3$).

The lower R$_f$ minor isomer, was alcohol (1*R*,1'*R*,3'*S*,5'*R*)-1-{1'-(furan-3"-yl)-5'-methyl-2',8'-dioxabicyclo[3.2.1]oct -3'-yl}-2-methylpropan-1-ol (90a) (560 mg, 24%). ν_{max} (film) 790, 870, 900, 930, 1000, 1060, 1135, 1460, 1500, 1600, 3500 cm^{-1}. ^{1}H n.m.r. (CCl$_4$): δ 7.4 (1H, m, C2"-H); 7.3 (1H, m, C5"-H); 6.35 (1H, m, H4"); 3.95 (1H, d, t, J 11,4Hz, H3'); 3.3 (1H, dd, J 7.4Hz, H1); 1.4 (3H, s, 5'-CH$_3$); 1.0 and 0.9 (each, 3H, 2d, J 5Hz, 2-CH$_3$ and (H3)$_3$).

This alcohol (90a) was characterised as its *acetate* (90c) m.p. 90-91° (Found: C, 66.3; H, 8.0. $C_{17}H_{24}O_5$ requires C, 66.2; H, 7.9%). ν_{max} 785, 870, 930, 950, 1035, 1055, 1150, 1225, 1240, 1500, 1730 cm^{-1}. ^{1}H n.m.r. (CCl$_4$): δ 7.45 (1H, m, H2"); 7.37, (1H, m, H5"); 6.4 (1H, m, H4"); 4.70 (1H, m, H1); 4.07 (1H, m, H3'); 2.09 (3H, s, CH_3CO); 1.39 (3H, s, 5'-CH_3); 0.97 and 0.89 (each 3H, 2d, J 7Hz, 2-CH_3 and $(H3)_3$).

A minor lower R_f product isolated during chromatography was the *ketone* (*R*; *E* and *Z*)-1-(furan-3'-yl)-4-hydroxy-4,8-dimethyl-non-6-en-1-one (136) (200 mg,~10%) (Found: C, 71.4, H8.7. $C_{15}H_{22}O_3$ requires C, 71.9; H, 8.9%). ν_{max} (film) 975, 1150, 1505, 1565, 1675, 3160(w), 3500 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.93 (1H, m, H2"); 7.25 (1H, m, H5"); 6.60 (1H, m, H4"); 5.23 (2H, m, H6, H7); 2.80 (2H, apparent t, J 7Hz, $(H2)_3$); 2.17 (2H, d, J 6Hz, $(H5)_3$); 1.07 (3H, s, 4-CH_3); 0.93 and 0.88 (each 3H, 2d, J 6Hz, 8-CH_3 and $(H9)_3$). ^{13}C n.m.r. see appendix. M/e 232 ($M^{\dot{+}}$ - H_2O), 189, 168, 167, 150, 149 (b.p), 148, 122, 121, 107, 99, 95.

Attempted purification by distillation gave (5'*R*)-3-5'-methyl-5'-(4"-methylpent-2"-enyl)-4',5'-dihydrofuran-2'-yl furan (142) b.p. 80-90°/0.05 (block) (Found: C, 75.5; H, 8.6. $C_{15}H_{20}O_2$ requires, C, 77.5; H, 8.7%). ν_{max} (film) 730, 790, 870, 965, 1055, 1100, 1150, 1510, 1565, 1685, 1730 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.37 (1H, m, H2'); 7.20 (1H, m, H5"); 6.28 (1H, m, H4'); 5.3 (2H, m, H2", H3"); 4.74 (1H, t, J 2.4Hz, H3'); 2.5-2.2 (5H, m, $(H4")_3$, $(H1")_3$, H4"); 1.33 (3H, s, 5'-CH_3); 0.97 (6H, d, J 6Hz, 4"-CH_3, $(H5")_3$).

Further elution gave the triols (137) and (138) (10%) which were separated by h.p.l.c. (ethyl acetate/hexane, 1:4) as the diacetates (139) and (140) (described later).

Hydroboration of Eremoacetal - Other Experiments

(i) Disiamylborane was prepared according to the method of Brown.[93]

The borane was treated with eremoacetal (0.75 equivalents) at 0° for 90 min and room temperature for 2 h. T.l.c. showed considerable starting material was still present after 5 days. Workup and chromatography gave eremoacetal (50%) and a mixture of products which could not be separated.

(ii) 3-Methylbut-2-yl borane was similarly prepared from diborane (1 eq.) and 2-methylbut-2-ene (1 eq.).

Eremoacetal (47) (0.9 eq.) was added to the borane in tetrahydrofuran at -10° and after 20 min the mixture allowed to stand at room temperature for 1 h. Workup with basic peroxide and extraction gave a mixture which was separated by preparative t.l.c. (ether/hexane, 4:1) to give eremoacetal (47)(22%) the alcohol acetal epimers (90a) and (90b) (31%), the ketone (136) (5%), higher R_f triols (137) (22%) and triols (138) (7%).

(iii) When the disiamyborane was added to the eremoacetal (reverse addition) at 0° over 30 min gave an identical mixture to (ii) but with less of the polar products (by t.l.c.).

(iv) Thexylborane was prepared according to the method of Brown.[93]

The alkylborane was added slowly to eremoacetal (47) (0.9 eq.) in tetrahydrofuran at 0°. After 30 min at 0° and 30 min at room temperature workup gave a colourless oil. Preparative t.l.c.

gave a mixture of eremoacetal (15%) and the *epi*-dihydroeremoacetal (**148**) in equilibrium with the keto-diol (**147**) (10%).

The monohydroxylated (1*S*) alcohol (90b) (15%) was the only isomer isolated. None of the 1*R* isomer (90a) was detected by t.l.c.

The ketoalkene (**136**) was also isolated (23%).

A lower R_f ketone was identified as the keto-diols (**149**) (23%) probably epimeric at C6. The triols (**137**) and (**138**) were isolated in small yields (2% and 5% respectively).

(v) Methoxy borane was prepared by the addition of methanol (1 eq.) to diborane (1 eq.) in tetrahydrofuran containing a trace (0.05 eq.) of sodium borohydride.

The borane was added to eremoacetal (0.9 eq.) in tetrahydrofuran at 0°. The mixture was worked up after 40 min and separation showed an almost identical mixture to that from reaction with diborane.

(vi) Dimethoxyborane was similarly prepared and reacted for 1 h with eremoacetal at room temperature. Workup showed a similar mixture to that from (v).

Reductive Opening of Eremoacetal with Diborane

Eremoacetal (47) (2.48 g, 10 mmol) in tetrahydrofuran (30 ml) under nitrogen was treated with diborane (14 mmol) at 0° for 1 h and room temperature for 2 days. The mixture after workup with basic peroxide and extraction gave a viscous oil (3 g) which was largely two polar compounds by t.l.c. (ethyl acetate/

ether 1:1) and traces of less polar compounds.

The mixture was acetylated to give the crude acetates (3.5 g). The mixture was separated by chromatography to give a complex mixture of non-polar products (1.15 g, 28%).

The less polar products contained the epimeric acetal acetates (90c) (15%) and what appeared to be the partially cleaved epimeric tetrahydrofuranyl acetates (146) (5%). ^{1}H n.m.r. (CCl_4): δ 7.35 (2H, m, H2' and H5'); 6.34 (1H, m, H4'); 5.3-4.7 (2H, m, H2 and H3"), 2.04, 1.95, 1.98 (each 3H, s, $COCH_3$); 1.27 (3H, s, 5-CH_3); 0.93 (6H, d, $(H5")_3$ and 4"-CH_3).

A less polar product was identified as the *E* and *Z* 1-acetoxy-1-(furan-3'-yl)-4,8-dimethyl-non-6-en-4-ol (9%) (Found: C, 69.4; H, 8.85. $C_{15}H_{26}O_4$ requires C, 70.0; H, 8.8%). ν_{max} (film) 800, 880, 1030, 1245, 1380, 1740, 3500 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.3 (2H, m, H2' and H5'), 6.3 (1H, m, H4'), 5.6 (1H, t, 7Hz, H1); 5.4 (2H, m, H6 and H7); 2.0 (3H, s, $COCH_3$); 1.1-0.9 (9H, m, 4-CH_3, 8-CH_3, $(H9)_3$).

Of the two polar major products obtained, the higher R_f was viscous oil of 1,6-diacetoxy-1-(furan-3'-yl)-4,8-dimethyl-nonan-4-ol (139) as mixed isomers (1.44 g, 40%) (Found: m/e 294.184. $C_{19}H_{30}O_6$ -HOAc requires 294.183). A satisfactory elemental analysis could not be obtained. ν_{max} (film) 870, 940, 1020, 1130, 1150, 1240, 1500, 1730, 3500 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.4 (2H, m, H2' and H5'); 6.44 (1H, m, H4'); 5.75 (1H, t, J 6Hz, H1); 5.18 (1H, m, H6); 2.5 (1H, brs, D_2O exch. D_2O); 2.04 and 2.00 (each 3H, 2s, 2 x $COCH_3$); 1.12 (3H, s, 4-CH_3); 0.93 (6H, d, J 6Hz, $(H9)_3$ and 8-CH_3). ^{13}C n.m.r. see appendix. M/e

354 ($M^{\dot{+}}$), 294, 234, 219, 152, 151, 150, 127, 110, 108, 71, 69.

The lowest R_f product isolated as a viscous oil was 1,7-diacetoxy-1-(furan-3'-yl)-4,8-dimethylnonan-4-ol (140) (0.60 g, 17%) (Found: M/e 294.184. $C_{79}H_{30}O_6$-HOAc requires 294.183). A satisfactory elemental analysis could not be obtained. ν_{max} (film) 860, 940, 1020, 1150, 1240, 1500, 1735, 3500 cm^{-1}. ^{1}H n.m.r. (CCl): 7.45 (2H, m, H2' and H5'); 6.47 (1H, m, H4'); 5.77 (1H, t, J 6Hz, H1); 4.67 (1H, m, H7); 2.5 (1H, brs, OH); 2.04 (6H, s, 2 x $COCH_3$); 1.12 (3H, s, 4-CH_3); 0.91 (6H, d, J 7Hz, $(H9)_3$ and 8-CH_3). ^{13}C n.m.r. see appendix. M/e 354 ($M^{\dot{+}}$), 310, 294, 279, 234, 219, 217, 191, 152, 151, 150, 127, 110, 108, 97, 94, 81, 79, 69.

Treatment of Dihydroeremoacetal (94) and Methoxyeremoacetal (96) with Diborane.

(i) Dihydroeremoacetal (94) (50 mg) in tetrahydrofuran (5 ml) was allowed to stand with diborane (2 ml, 1M soln. in THF) for 48 h. After workup, t.l.c. showed only dihydroeremoacetal with traces of polar products. A proton n.m.r. spectrum of the isolated product showed only dihydroeremoacetal.

(ii) The methoxyeremoacetal (96), similarly, was recovered after treatment with diborane in THF for 48 h.

Epoxidation of Eremoacetal-(1'*S*,1*R*,3*S*,5*R*) and (1'*R*,1*R*,3*S*,5*R*)-3-(1',2'-epoxy-2'-methyl-propyl)-1-(furan-3"-yl)-5-methyl-2,8-dioxabicyclo-[3.2.1] octane (162) and (163)

Eremoacetal (0.90 g, 36 mmole) was dissolved in dry methylene chloride (50 ml) and a solution of m-chloroperbenzoic acid (1.1

g, approx. 80% pure, approx. 50 mmole) was added in dry methylene chloride, at 0° with stirring. Reaction was complete and eremoacetal was not detected by t.l.c. after 2 h. A solution of sodium bisulphite (10 ml, 10% in water was stirred with the methylene chloride until all the peracid was reduced (potassium iodide/starch paper). Washing with potassium carbonate solution (10% in water, 2 x 30 ml) removed the acids. Removal of the solvent and preparative chromatography (ethylacetate/hexane 1:20) gave the two epoxides. The higher R_f and major isomer was isolated as colourless needles of *epoxide* (162) (0.66 g, 75%) m.p. 79-80° (Found: C, 68.3; H, 7.7. $C_{15}H_{20}O_4$ requires C, 68.2; H, 7.6%). ν_{max} (nujol) 745, 805, 860, 920, 995, 1015, 1055, 1100, 1125, 1145, 1495 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.48 (1H, m, H2"); 7.38 (1H, m, H5"); 6.44 (1H, m, H4"); 3.67 (1H, m, H3); 2.64 (1H, d, J 8Hz, H1'); 1.40 (3H, s, 5-CH_3); 1.33 (6H, s, 2'-CH_3, $(H3')_3$).

The lower R_f product was the minor *epoxide* (163) (0.18 g, 20%) m.p. 101.5-102.5° (Found: C, 68.4; H, 7.9. $C_{15}H_{20}O_4$ requires C, 68.2; H, 7.6%). ν_{max} (nujol) 710, 780, 825, 860, 875, 890, 920, 930, 990, 1020, 1040, 1055 cm^{-1}. ^{1}H n.m.r. (CCl_4) 7.54 (1H, m, H2"); 7.35 (1H, m, H5"); 6.48 (1H, m, H4"); 3.74 (1H, m, H3); 2.73 (1H, d, J 8Hz, H1'); 1.40 (3H, s, 5-CH_3); 1.30 (6H, s, 2'-CH_3 and $(H3')_3$).

Preparation of (1*R*,3*S*,5*R*)-1-(furan-3'-yl)-5-methyl-2,8-dioxabicyclo[3.2.1]-octane-3-carbaldehyde (82)

To a stirred mixture of dry diols (86) (4.9 g, 17.3 mmoles) dissolved in methylene chloride (dry, 150 ml) and containing calcium carbonate (dry, 10 g) was added a solution of lead tetraacetate (recryst. 8.4 g) in methylene chloride (approx. 100 ml) over 15 min. After 30 min, ether (100 ml) was added and the solution passed through a column of florisil which was washed with ether (100 ml). The combined eluates on evaporation gave an almost colourless oil of the aldehyde (82) (3.9 g, quantit.) which was pure enough for most purposes. The product could be purified with some loss by distillation to give a colourless viscous oil of pure *aldehyde* (82) (2.95 g, 77%), b.p. 110°/0.1 mm. (Found: $M^{+\cdot}$ 222.0894, $C_{12}H_{14}O_4$ requires $M^{+\cdot}$ 222.0892). ν_{max} (film) 800, 880, 905, 930, 1510, 1610, 1740, 3190 cm^{-1}. ^1H n.m.r. (CCl_4): δ 9.7 (1H, d, J 1Hz, CHO); 7.5 (1H, m, H2'); 7.4 (1H, m, H5'); 6.45 (1H, m, H4'); 4.2 (1H, dd, J, 10,6Hz, H3); 1.43 (3H, s, 5-CH_3). M/e 222 ($M^{+\cdot}$), 205, 204, 193, 186, 165, 164, 148, 139, 119, 110, 95 (b.p.), 86, 84, 51, 49.

Preparation of Eremoacetal (47) from aldehyde (82).

(i) This procedure is an adaption of that described in 'Organic Reactions' (John Wiley) Vol. 14, p. 295.

Methansulphanyl sodium (0.55 mmole) in dimethyl sulphoxide was added to a solution of i-propyl phosphonium iodide (225 mg, o.5 mmole) in dry DMSO (2 ml). After 10 min, the aldehyde (82) (110 mg, 0.5 mmole) was added in dry ether (2 ml) to the red ylide solution and stirred for a further 10 min. Brine (80 ml) was added and the solution extracted with petroleum ether (5 x 20 ml). The extracts were concentrated and the residue purified by preparative chromatography (petroleum ether/ether 4:1) to give eremoacetal (40 mg, 32%) m.p. 63-63.5°, identical (m.m.p., i.r., n.m.r. and t.l.c.) to authentic material.

(ii) To a suspension of i-propyl phosphonium iodide (225 mg, 0.5 mmole) in dry tetrahydrofuran (10 ml) at -20° was added n-butyl lithium (0.5 mmole). After 5 min at -20° the aldehyde (82) (110 mg, 0.5 mmole) in tetrahydrofuran (2 ml) was added and the solution allowed to reach room temperature. Water (50 ml) was added and the solution extracted with petroleum ether (5 x 20 ml). Evaporation of the dried solvent and preparative chromatography of the residue gave eremoacetal (47) (100 mg, 80%) identical in all respects to authentic material.

Preparation of Silver Tetrafluoroborate

To a solution of tetrafluoroboric acid (approx. 40%, 10 ml) was added portions of silver carbonate, slowly and with stirring until no further effervesence occurred. Filtration through celite followed by washing the solids with water (2 x 1 ml) gave a colourless solution of the silver salt. Most of the water was removed azeotropically using benzene in a Dean and Stark apparatus. The benzene was vigorously stirred while light was excluded. On cooling the benzene the salt crystallised. Rapid filtration followed by drying over phosphorus pentoxide under vacuum with occasional breaking up of the lumps gave the salt as an off-white solid (almost quantitative). The hygroscopic silver salt, when kept in the dark and well stoppered, was stable indefinitely.

Ethyldiphenylsulphonium Fluoroborate

This was prepared using the procedure described by Trost and Melvin[125b] using ethyl iodide, diphenylsulphide and silver tetrafluoroborate. Colourless prisms of Ethyldiphenylsulphonium fluoroborate were obtained, m.p. 70-72° (lit.[125a] 70-72°).

Sulphur Ylide Reaction - Synthesis of Epoxides (162) and (172).

The procedure outlined by Corey and Chaykovsky[125b] was used without modification to prepare the isopropylidene ylide and react it with aldehyde (82).

Separation of the crude product by preparative t.l.c. gave recovered aldehyde (50%) and two epoxides. The higher R_f epoxide (162) was identical in all respects (m.m.p., i.r., n.m.r. and t.l.c.) to the major epoxide isomer from peroxidation of eremoacetal. None of the epimeric epoxide was detected.

A minor epoxide product (22%) was the 3-(1'-2'-epoxypropyl)-1-(furan-3"-yl)-5-methyl-2,8-dioxabicyclo[3.2.1]octane (172) resulting from incomplete alkylation of the intermediate ylide. ^{1}H n.m.r. (CCl$_4$): δ 7.4 (1H, m, H2"); 7.3 (1H, m, H5"); 6.3 (1H, m, H4"); 3.6 (1H, ddd, J 10,6,5Hz, H3); 2.8 (1H, dq, J 2,6Hz, H2'); 2.55 (1H, dd, J 2,6Hz, H1'); 1.35 (3H, s, 5-CH$_3$), 1.25 (3H, d, J 6Hz, 2'-CH$_3$). M/e 251 ($M^{+\cdot}$ + 1), 250 ($M^{+\cdot}$), 249 ($M^{+\cdot}$ - 1), 235, 236, 221, 207, 194, 193, 179, 175, 165, 164, 155, 147, 124, 123, 97, 96, 95 (b.p.), 83, 81, 79, 69, 68, 56.

Sulphur Ylide Reaction - Synthesis of (1'*R*,1*R*,3*S*,5*R*) and (1'*S*,1*R*,3*S*,5*R*) 3-(1',2'-epoxyethyl)-1-(furan-3"-yl)-5-methyl-2,8-dioxabicyclo[3.2.1]octane (167) and (168).

The ylide was prepared according to the method described by Corey and Chaykovsky[125b] using trimethyloxosulphonium iodide (0.85 g, 3.8 mmoles), aldehyde (82) (0.65 g, 2.9 mmole) and 'dimsyl sodium' (8 ml, 0.5 M). After 40 min the reaction showed no aldehyde by t.l.c. After 1 h workup as described by Corey, gave a yellow oil (480 mg). Preparative chromatography (ether/hexane 1:1) gave a high R_f product, *epoxide (167)* (269 mg, 39%) m.p. 67-68° (hexane), (Found: C, 66.2; H, 6.8. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8). ν_{max} (nujol) 735, 810, 880, 905, 940, 950, 1005, 1120, 1140, 1510, cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.5 (1H, m, H2"); 7.4 (1H, m, H5"); 6.4 (1H, m, H4"), 3.6 (H, quintet, J 5Hz, H3); 2.9-2.5 (3H, m, H1" and $(H2")_2$); 1.4 (3H, s, 5-CH_3). M/e 237 ($M^{+\cdot}$ + 1), 236 ($M^{+\cdot}$), 235 ($M^{+\cdot}$ - 1), 219, 207, 193, 175, 165, 164, 124, 109, 95 (b.p.), 81, 79, 69, 68, 67, 54.

A low R_f isomer was isolated, *epoxide (168)* (86 mg, 19%) m.p. 84-86°, b.p. 120-130°/0.5 mm (block) (Found: C, 66.4; H, 7.0. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8). ν_{max} (nujol) 800, 860, 870, 900, 930, 1000, 1030, 1070, 1110, 1140, 1150, 1500 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.45 (1H, m, H2"); 7.3 (1H, m, H5"); 6.4 (1H, m, H4"); 3.7 (1H, dt, J 12,10Hz, H3); 2.9 (1H, m, H1'); 2.6 (2H, m, $(H2")_2$); 1.4 (3H, s, 5-CH_3). M/e 237 ($M^{+\cdot}$ + 1), 236 ($M^{+\cdot}$), 235 ($M^{+\cdot}$ - 1), 193, 164, 124, 109, 95 (b.p.), 81, 80, 54 cm^{-1}.

Oxymercuration of Eremoacetal -(1'R,3'R,5'R)-1-(1'-{furan-3"-yl}-5'methyl-2',8'-dioxabicyclo[3.2.1]oct. .-3'-yl)-2-methylpropan-2-ol (95)

Eremoacetal (47) (0.25 g, 1 mmole) was added to a yellow suspension prepared by the addition of mercuric acetate (0.32 g 1 mmole) to a solution of water (5 ml) and tetrahydrofuran (5 ml). The mixture became colourless after stirring for 2 min.

After 10 min, sodium borohydride (0.1 g in sodium hydroxide 3M, 5 ml) was added and the mixture stirred for 2 h. The clear solution was extracted with methylene chloride (4 x 10 ml), the extracts dried and the solvent removed to give a colourless oil of *alcohol* (95) (0.26 g, quantitative). b.p. 135°/0.05 mm (block) (Found: C, 67.84; H, 8.30. $C_{15}H_{22}O_4$ requires C, 67.64; H, 8.33%). ν_{max} (film) 795, 880, 935, 1160, 1510, 1610, 3500 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.46 (1H, m, H2"); 7.37 (1H, m, H5"); 6.43 (1H, m, H4"); 4.27 (1H, m, H3'); 2.8 (1H, brs, exch. D_2O, OH); 1.33 (3H, s, 5'-CH_3); 1.22 and 1.17 (each 3H, s, 2-CH_3 and (H3')$_3$). M/e 266 ($M^{+\cdot}$), 207, 193, 95 (b.p.), 70, 59.

Methoxymercuration of Eremoacetal-(1*R*,3*R*,5*R*)-1-(furan-3"-yl)-3-(2'-methoxy-2'-methylpropyl)-5-methyl-2,8-dioxabicyclo[3.2.1] octane (96)

The procedure outlined above for the oxymercuration was used with methanol as solvent in place of water/tetrahydrofuran. Reaction time was extended to 3 h before the addition of borohydride (5 equivalents), and then the mixture diluted with water before extraction. Purification by chromatography gave a colourless oil of the *methoxy-acetal* (96) (92%) b.p. 138°/0.7 mm (Found: C, 68.83; H, 8.53. $C_{18}H_{24}O_4$ requires C, 68.54; H, 8.63%). ν_{max} (film) 795, 875, 935, 1010, 1030, 1070, 1155, 1500, 2860 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.39 (1H, m, H2"); 7.34 (1H, m, H5"); 6.40 (1H, m, H4"); 4.17 (1H, m, H3); 3.17 (3H, s, OCH_3); 1.35 (3H, s, 5-CH_3); 1.20 and 1.15 (each 3H, s, 2'-CH_3 and (H3')$_3$).

Reduction of Epoxide (167) to (1S,1'R,3'S,5'R) [1'-(furan-3"-yl)-5'-methyl-2',8'-dioxabicyclo[3.2.1]-oct-3'-yl] -ethan-1-ol(169)

The (1'*R*,1*R*,3*S*,5*R*) epoxide (167) (8 mg) was reduced with lithium aluminium hydride (2-3 mg) in dry ether (2 ml). Work-up with wet ether after 30 min gave the alcohol (169a) (7 mg) as a colourless oil.

Acetylation with acetic anhydride and pyridine gave a crystalline acetate which was identical (m.m.p., i.r., n.m.r., and t.l.c.) to the (1'*R*,3*S*,5*R*) acetate (169a) formed as a major product, after acetylation, from a grignard reaction (see below).

Grignard Reactions with Aldehyde (82) - Synthesis of (1'*R*,1*R*,3*S*,5*R*) and (1'*S*,1*R*,3*S*,5*R*)-3-(1'acetoxy ethyl)-1-(furan-3''-yl)-5-methyl-2,8-dioxabicyclo[3.2.1]octane (169a) and (170a).

(i) To a solution of methyl magnesium iodide (prepared from 2 mmol methyl iodide, 2.1 mmol magnesium) in ether (10 ml) was added the aldehyde (82) (300 mg, 1.35 mmoles) in dry ether at 0°. After stirring for 15 min at 0°, the mixture was stirred at room temperature for 15 min followed by addition of ammonium chloride (saturated, 10 ml). Ether extraction (4 x 20 ml) and evaporation gave a colourless oil (385 mg). The alcohol isomers were difficult to separate but the acetates, prepared by reaction with acetic anhydride and pyridine (15 h), (346 mg, 92%) were separated by preparative t.l.c. (2x, ether/hexane, 1:2). The high R_f and major product was (1'*R*,1*R*,3*S*,5*R*) *acetate* (169a) (196 mg, 52%) m.p. 58-59° (Found: C, 64.67; H, 7.35. $C_{15}H_{20}O_5$ requires C, 64.27, H, 7.19%). ν_{max} (nujol) 790, 870, 900, 930, 950, 1050, 1070, 1150, 1140, 1240, 1500, 1600, 1740, 3180(w) cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.45 (1H, m, H2"); 7.35 (1H, m, H5"); 6.35 (1H, m, H4"); 4.8 (1H, apparent quintet, J 6Hz, H1'); 3.85 (1H, dt, J 10,6Hz, H3); 2.0 (3H, s, $COCH_3$); 1.35 (3H, s, 5-CH_3); 1.2

(3H, d, J 6Hz, 1'-CH_3).

The lower R_f and minor isomer was the (1'*S*,1R 3*S*,5*R*) *acetate* **(170a)** isolated as colourless needles (113 mg, 30%) m.p. 87-89° (Found: C, 64.56; H, 7.4. $C_{15}H_{20}O_4$ requires C, 64.27; H, 7.79%). ν_{max} (nujol) 790, 870, 900, 930, 940, 1050, 1070, 1140, 1150, 1230, 1500, 1600, 1740, 3180(w). ^1H n.m.r. (CCl_4): δ 7.4 (1H, m, H2"); 7.3 (1H, m, H5"); 6.35 (1H, m, H4"); 4.9 (1H, apparent quintet, J 6Hz, H1'); 3.9 (1H, dt, J 11,6Hz, H3); 2.0 (3H, s, $COCH_3$); 1.35 (3H, s, 5-CH_3); 1.2 (3H, d, J 6Hz, 1'-CH_3).

(ii) When the addition of aldehyde was done at -70° the proportion of recovered acetates (62:38) remained unchanged.

Grignard Reaction with Aldehyde - Synthesis of (1*S*,1'R 3'*S*,5'*R*) and (1*R*,1'R 3'*S*,5'*R*) Alcohols (90b) and (90a)

(i) Using the Grignard reagent from 2-propyl magnesium bromide (1.5 eq.) in ether at 0°, the aldehyde (82) gave the two alcohols (90a) and (90b) (90%).

Acetylation followed by preparative chromatography gave the minor high R_f acetate (90c) (31%) m.p. 88-89°, identical (m.m.p., n.m.r., i.r. and t.l.c.) to the acetate from hydroboration/acetylation of eremoacetal (see earlier). The lower R_f major acetate (90d) (50%) m.p. 76-78° was identical (m.m.p., n.m.r., i.r. and t.l.c.) to one of the products obtained by hydroboration/acetylation of eremoacetal.

(ii) A similar reaction, except that it was done at -70° (2.5 h), gave the alcohols (90a) and (90b) in the ratio of 1:3.

Oxidation of Triol (137)

(i) A mixture of silver carbonate (200 mg) and triol (137) (45 mg) in benzene (20 ml) was heated under reflux. After 3 h no starting material was detected using t.l.c. but two less polar products were formed. Filtration through celite and evaporation of the solvent gave a yellow oil of the known diketone (ipomeanine) (173) (20 mg, 72%) b.p. 90° /0.05 mm (block) (lit.^{20} 74-79° /10^{-3} mm). ν_{max} (film) 870, 1145, 1510, 1560, 1680, 1720, 3160 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 8.1 (1H, m, H2'); 7.45 (1H, m, H5'); 6.8 (1H, m, H4'); 3.0-2.7 (4H, m, $(H2)_2$ and $(H3)_2$); 2.2 (3H, s, 4-CH_3).

(ii) A suspension of pyridinium chlorochromate (1.4 g, 6.7 mmol), sodium acetate (dry, 0.3 g) in anhydrous methylene chloride (60 ml) was vigorously stirred while the triol (137) (250 mg, 0.94 mmol) in methylene chloride (5 ml) was added at once. After stirring for 2 h a t.l.c. check of the mixture showed no starting material and four less polar products. After workup the crude products were purified by preparative t.l.c. (ether/petroleum ether, 6:4).

The highest R_f, U.V. visualised compound, was the hydroxy diketone (4*R*-hydroxymyoporone) (23) (40 mg, 17%) a yellow oil which darkened on standing. $[\alpha]^{20}_{700}$ + 2.7°, $[\alpha]^{20}_{600}$ - 0.8°, $[\alpha]^{20}_{D}$ - 1.0°, $[\alpha]^{20}_{577}$ - 0.8°, $[\alpha]^{20}_{546}$ - 1.7°, $[\alpha]^{20}_{436}$ > + 85° (C, 2.0 in $CHCl_3$) (lit.^{34} $[\alpha]_D$ - o.7°). ν_{max} (film) 875, 1150, 1510, 1565, 1680, 1700(sh), 3160, 3500 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 8.0 (1H, m, H2'); 7.3 (1H, m, H5'); 6.65 (1H, m, H4'); 3.5 (1H, brs, D_2O exch. OH); 2.8 (2H, apparent t, J 8Hz, $(H2)_2$); 2.5 (2H, s, $(H5)_2$); 2.3 (2H, d, J 2Hz, $(H7)_2$); 2.2-2.1 (1H, obscured m, H8); 1.8 (2H, apparent t, J 8Hz $(H3)_2$); 1.17 (3H, s, 4-CH$_3$); 0.93 (6H, d, J 6Hz, 8-CH$_3$ and $(H9)_3$). M/e 266 ($M^{+\cdot}$), 167, 166, 143, 123, 99, 95 (b.p.), 85, 67, 57, 40.

The above spectra and specific rotation agree well with those given for athanagrandione[34] (4*R* isomer) and the spectra for 4-hydroxymyoporone from sweet potatoes[39] (presumably the 4*S* isomer).

The more polar products, the unstable keto diols (54) and (147), (22 mg, 10%) gave complex spectra due to cyclisation to dihydroeremoacetal (94) and its epimer (148). This was confirmed by t.l.c. and close examination of the proton n.m.r. spectrum. Some of the peaks assigned to the ketones (54) and (147) were: ^{1}H n.m.r. (CCl$_4$): δ 8.0 (1H, m); 7.2 (1H, m); 6.7 (1H, m); 2.9 (2H, t) and resonances at δ7.2, 6.2 and 1.3 which increased on standing were due to the acetals (94) and (148).

The two highest R$_f$ products acetals (94) and (148) (80 mg, 35%) which could not be completely separated, on re-examination by t.l.c. showed the presence of the polar dihydroxyketone (147) due to hydrolysis on the silica. Rechromatography gave the pure lower R$_f$ dihydroeremoacetal (94) free of its epimer (148). The pure and stable acetal (94) was identical by t.l.c., i.r., n.m.r. and mass spectra to authentic dihydroeremoacetal. The unstable epimer (148) was not isolated free of (94) but showed a ^{1}H n.m.r. spectrum almost identical with that of dihydroeremoacetal (94), except that the 5-CH$_3$ was 5Hz further downfield in (148).

(ii) When dimethyl sulphoxide/oxalyl chloride (2 eq., -60° 20 min) was used to oxidise triol (137) as previously described, the products obtained were the same as in (ii) and isolated in almost identical yields. A new non polar product (12%) also isolated appeared to be similar to the tetrahydrofuran (135) (stereochemistry unknown) formed by a cyclisation process. ν_{max} (film) 785, 870, 905, 1020, 1130, 1150, 1500, 3500 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.3 (2H, m, H2" and H5"); 6.3 (1H, m, H4"); 4.9 (1H, m, H5'); 3.8 (1H, m, H2); 1.25 (3H, s, 2'-CH_3); 0.9 (6H, d, J 6Hz, 4-CH_3 and $(H5)_3$).

Oxidation of Triols (138)

(i) A mixture of triol (138) (100 mg), silver carbonate 200-300 mg), celite (1 g) and benzene was heated under reflux. After 15 h, filtration and solvent removal gave a residual yellow oil (95 mg). Purification by preparative t.l.c. (ether) gave starting material (10 mg, 10%) and a higher R_f yellow oil (50 mg, 55%) which showed a complex n.m.r. spectrum presumably of ketodiol (149) in equilibrium with acetals and hemiacetals (perhaps epimeric at C6). ν_{max} (film) 1680, 3500 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 8.0 (m, H2'); 7.3 (m, H5'); 6.7 (m, H4' 6.1 (m, H4'); 2.8 (m, H2); 1.15 (s, 4-CH_3); 1.25 (s, CH_3). M/e 250 ($M^{+\cdot}$ - H_2O), 207, 127, 110, 109, 95. A minor high R_f product (10 mg, 11%) showed a similar complex n.m.r. spectra.

(ii) A similar mixture of products was obtained in similar yields using pyridinium chlorochromate as oxidant.

Conversion of 4-Hydroxydendrolasin (8) to Dendrolasin (6)

A solution of the acetate (8a) (230 mg) in tetrahydrofuran (4 ml) and ethanol (2 ml) was added slowly (5 min) to liquid ammonia (approx. 20 ml) containing dissolved lithium (100 mg). The blue solution was stirred at -33° for 30 min, ammonium chloride (0.5 g) was cautiously added and the ammonia allowed to evaporate over 2 h. After the addition of water (30 ml) the mixture was extracted with ether (3 x 20 ml). The ether extract was washed with brine and evaporated to give a colourless oil (180 mg, 93%). Separation of the components was achieved by preparative g.l.c. using 3% OV-17 on gas chrom.Q (100-120#) in a 2.2 m x 3 mm glass column at 150°.

Four very minor components (total 10%) were not examined. The first of the two major products to be eluted was 9-(furan-3'-yl)-2,6-dimethylnona-3,6-diene (6a) (26%). ν_{max} (film) 780, 870, 970, 1020, 1060, 1160, 1500, 1570(w) cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.3 (1H, m, H5'); 7.2 (1H, m, H2'); 6.2 (1H, m, H4'); 5.4-5.1 (3H, m, H3, H4 and H7); 2.6 (2H, m, $(H5)_2$); 2.5-2.0 (5H, m, H2, $(H8)_2$ and $(H9)_2$); 1.6 (3H, brs, 6-CH_3); 0.95 (6H, d, J 7Hz, 2-CH_3 and $(H1)_3$). M/e 218 ($M^{+\cdot}$), 203, 185, 175, 161, 136, 121, 95, 81 (b.p.), 69, 67, 55. The second major product was dendrolasin (6) (63%) with ^{1}H n.m.r., i.r., m.s., and t.l.c. data identical to those of authentic dendrolasin.[21]

(4*R*,6*S*)-9-(furan-3'-yl)-2,6-dimethylnonane-2,4,6-triol (183)

A solution of alcohol (95) (1.1 g, 4.1 mmol) in dry tetrahydrofuran (10 ml) was added slowly (5 min) to a solution of lithium (0.28 g, 40 mmol) in ammonia (approx. 100 ml). The mixture was stirred for 3 h at -33° after which time isoprene was added dropwise to discharge the blue colour. Ammonium chloride (1 g) was cautiously added and the ammonia allowed to evaporate overnight. After addition of water (20 ml) the mixture was extracted with methylene chloride to give the crude product (1.05 g, 95%). Chromatography on silica gel (ether/hexane, 4:1) gave starting material (300 mg, 27%) followed by *triol* (183), as a colourless viscous oil (660 mg, 63%) (Found: C, 66.36; H, 9.57. $C_{15}H_{26}O_4$ requires C, 66.63; H, 9.69). ν_{max} (film) 785, 865, 875, 1025, 1160, 1510, 3400 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.3 (1H, m, H5'); 7.2 (1H, m, H2'); 6.2 (1H, m, H4'); 4.7-4.3 (4H, brm, D_2O exch. in part; 3OH and H4); 2.4 (2H, m, $(H9)_2$); 1.3, 1.2 and 1.1 (each 3H, 3s, 2-CH_3, $(H1)_3$ and 6-CH_3). M/e 270 ($M^{+\cdot}$), 268, 252, 237, 234, 219, 216, 179, 178, 161, 153, 135, 134, 125, 95, 94 (b.p.), 87, 85, 83, 82, 81, 79, 59.

Synthesis of (-)-4-Hydroxydendrolasin from the Triol (183)

(i) The triol (183) (1.2 g) was acetylated with acetic anhydride in pyridine at room temperature for 15 h. The monoacetate, 6-(furan-3'-yl)-3-hydroxy-1-(2'-hydroxy-2'-methylprop-1'-yl)-3-methylhexanyl acetate (1.4 g) was obtained as an almost colourless oil. ^1H n.m.r. (CCl_4): δ 7.14 (1H, m, H5'); 7.03 (1H, m, H2'); 5.94 (1H, m, H4'); 5.17 (1H, m, H1); 4.1 (2H, brs, D_2O exch., 2 OH); 2.34 (2H, m, $(H6)_2$); 1.92 (3H, s, CH_3CO 1.18 (9H, s, 3-CH_3, 2'-CH_3 and $(H3')_3$). The acetoxydiol was dehydrated without further purification.

(ii) Thionyl chloride (1 ml) was added dropwise with vigorous stirring to a solution of acetoxydiol from (i) in pyridine (10 ml) and dry ether (20 ml) at 0 . After 10 min, water was added, the layers separated, and the ether layer washed with acidified brine. Evaporation of the solvent gave an oil (1.2 g) which on reduction with lithium aluminium hydride (0.2 g) in dry ether (50 ml), gave a mixture of olefinic alcohols (0.97 g, 80% from triol).

Chromatogrpahy of the mixture on silica gel (ether/hexane 1:2) gave trienes (2%), chlorides (6%), non-allylic alcohols (14%), allylic alcohols (21%) and a mixture of diols and triols (36%).

The least polar product isolated pure, was the dienol (4*R*, *E* and *Z*) 9-(furan-3'-yl)-2-methylene-6-methylnon-6-en-4-ol (30 mg) (Found: m/e 234.1623, $C_{15}H_{22}O_4$ requires 234.1620) ν_{max} (film) 780, 880, 890, 1025, 1060, 1160, 1505, 1620, 3100(w) 3570 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.17 (1H, m, H5'); 7.05 (1H, m, H2'); 6.10 (1H, m, H4'); 5.17 (1H, m, H7); 4.69 (2H, brs, $=CH_2$); 3.73 (1H, brm, H4); 2.35-2.0 (9H, methylene, OH); 1.68, 1.58 (6H, brs, *Z* and *E* isomer for 6-CH_3 and $(H1)_3$). M/e 234 ($M^{+\cdot}$), 219, 216, 201, 179, 150, 35, 94, 85, 82, 81 (b.p.), 69, 57, 55.

The fraction containing the allylic alcohols was rechromatographed on silver nitrate (10%) impregnated silica gel (ether/hexane, 1:1) to give a mixture of *E* and *Z* isomers of 4-hydroxydendrolasin (8). Latter fractions contained what was probably the 6-methylene derivative, 9-(furan-3'-yl)-2-methyl-6-methylenenon-2-en-4-ol. ^{1}H n.m.r. (CCl_4): δ 7.17, 7.05 (each 1H, m, H5' and H2'); 6.0 (1H, m, H4'); 5.05 (1H, d, J 7Hz, H3); 4.70 (2H, brs, $=CH_2$); 4.32 (1H, m, H4); 2.6 (1H, brs, D_2O exch., OH); 1.66 (5H, brs, 2-CH_3 and $(H1)_3$).

The mixture of *E* and *Z* isomers of (8) was esterified with 1,1'-biphenylcarbonyl chloride in pyridine and the esters separated by h.p.l.c. (silica, 10μ), using ethyl acetate/hexane (6:500). The *Z* isomer (8c) eluted first. ^{1}H n.m.r. (CCl_4): δ 7.95 (2H, d, aromatic); 7.5-7.0 (9H, H2', H5' and aromatic); 6.11 (1H, m, H4'); 5.77 (1H, dt, J 8,6Hz, H4); 5.17 (2H, m, H3 and H7); 1.75 (9H, brs, 2-CH_3, 6-CH_3 and $(H1)_3$).

The ^{1}H n.m.r. spectrum of the *E* isomer (8b) was identical with that of the 1,1'-diphenylcarboxylate ester of 4-hydroxydendrolasin, isolated from the plant, (CCl_4): δ 7.96 (2H, d, aromatic); 7.5-7.0 (9H, H2', H5' and aromatic); 6.04 (1H, m, H4') 5.77 (1H, dt, J 8,7Hz, H4); 5.13 (2H, m, H3 and H7); 1.74 (5H, brs, 2-CH_3 and $(H1)_3$); 1.67 (3H, s, 6-CH_3).

Reduction of the *E* isomer, ester (8b), with lithium aluminum hydride, followed by chromatography on silica gel gave, 4-hydroxydendrolasin (8), $[\alpha]_D^{17}$ - 15° ± 2° (c, 1.6 in $CHCl_3$) natural (8), $[\alpha]_D^{17}$ - 15.8° . Both the synthetic and natural samples of (8) had identical spectral data (n.m.r., i.r. and ms) and chromatographic properties (silica and silver nitrate impregnated silica gel).

Oxidation of 4-Hydroxydendrolasin (8) to (*E*)-9-(furan-3'-yl)-2,6-dimethylnona-2,6-dien-4-one (179)

(i) 4-Hydroxydendrolasin (8) (100 mg) was heated under reflux in benzene (15 ml) with silver carbonate on celite (0.5 g).[129] After 6 h, examination of the mixture by t.l.c. showed no starting material and the presence of one major product. Filtration of the solution, evaporation of the solvent and purification of the residue by preparative t.l.c. (ether/hexane, 1:9) gave (*E*)-9-(furan-3'-yl)-2,6-dimethylnona-2,6-diene-4-one (179) (85 mg, 86%), b.p. 120°/0.1 mm (block) (Found: C, 77.7; H, 8.85). $C_{15}H_{20}O_2$ requries C, 77.6; H, 8.7). ν_{max} (film) 780, 870, 1020, 1160, 1380, 1500, 1620, 1690, 3160 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.4 (1H, m, H5'); 7.3 (1H, m, H2'); 6.3 (1H, m, H4'); 6.1 (1H, brs, H3); 5.3 (1H, m, H7); 3.0 (2H, s, $(H5)_2$); 2.1 (3H, s, 2-CH_3); 1.9 (3H, s, $(H1)_3$); 1.6 (3H, s, 6-CH_3).

(ii) An oxidation of (8) using manganese dioxide in light petroleum gave mainly trienes resulting from dehydration.

(iii) A solution of alcohol (8) (100 mg) in dry methylene chloride (2 ml) was added to a stirred suspension of pyridinium chlorochromate (300 mg) in dry methylene chloride (10 ml). After 2 h, t.l.c. showed the absence of starting material and the presence of two products. Workup followed by preparative t.l.c. (ether/hexane, 1:9) gave the dienone (179) (35 mg, 35%) and a minor product (12 mg, 12%) of lower R_f. The ^1H n.m.r. spectrum was consistent with (180), , 6-(furan-3'-yl)-3-methylhex-3-enal ^1H n.m.r. δ (CCl_4): 9.7 (1H, t, J 2Hz, H1); 7.35 (1H, m, H5'); 7.25 (1H, m, H2'); 6.25 (1H, m, H4'); 5.4 (1H, m, H4); 3.0 (2H, d, J 2Hz, $(H2)_2$); 2.6-2.2 (4H, m, $(H5)_2$ and $(H6)_2$); 1.65 (3H, s, 3-CH_3). ν_{max} (film) 780, 870, 1020, 1060, 1150, 1500, 1730, 2750, 3160(w) cm^{-1}.

Isomerisation of Dienone (179) to *E* and *Z* Dihydrophymaspermones (42/43)

(i) The dienone (179) (50 mg) was warmed in a mixture of methanol (5 ml) and aqueous sodium hydroxide (1M, 2 ml) at 60° for 3 h. The methanol was removed under reduced pressure and the aqueous solution was extracted with methylene chloride (2 x 5 ml). Evaporation of the solvent and preparative t.l.c, (ether/hexane, 1:3) of the residue gave a mixture of *E* and *Z* dihydrophymaspermones (42) and (43) (25 mg, 50%), identified by spectral comparison with authentic material.

(ii) The dienone (179) (90 mg) was allowed to stand in methanol (3 ml) containing sodium methoxide (40 mg) at room temperature for 15 h. Isolation as described above and preparative t.l.c. (ethyl acetate/hexane, 1:3) gave starting material (40 mg, 45%) and the methanol addition product, 9-(furan-3'-yl)-2-methoxy-2,6-dimethylnon-6-en-4-one (181) (50 mg, 45%) ν_{max} (film) 780, 870, 1020, 1065, 1160, 1500, 1715 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.4 (1H, m, H5'); 7.3 (1H, m, H2'); 6.3 (1H, m, H4'); 5.3 (1H, m, H7); 3.2 (3H, s, OCH_3); 3.05 (2H, s, $(H5)_2$); 2.5 (2H, s, $(H3)_2$); 2.5-2.3 (4H, m, $(H8)_2$ and $(H9)_2$); 1.6 (3H, brs, 6-CH_3); 1.2 (6H, s, 2-CH_3 and $(H1)_3$). M/e 264 ($M^{+\cdot}$), 249, 232, 135, 123, 119, 117, 95, 85 (b.p.), 81, 73, 55. The product was not characterised further but was treated with sodium methoxide in deuterated methanol (MeOD) under the same conditions. D_2O (2 ml) was added before extraction. N.m.r. analysis showed the product was an approximately 1:1 mixture of starting material (181) and dienone (179). Integration of the p.m.r. spectrum revealed that deuterium incorporation was essentially complete α to the carbonyl group (C3 and 5) in both compounds, but little exchange had occurred at C7 or at the methyl groups.

Attempted Equilibration of Dihydrophymaspermones (42/43) with Sodium Methoxide

A mixture of the *E* and *Z* dienones (42/43) (200 mg), methanol (5 ml) and sodium methoxide (50 mg) was allowed to stand at room temperature for 15 h. Most of the methanol was removed under vacuum, water (10 ml) added and the mixture extracted with methylene chloride (2 x 10 ml) to yield a yellow oil. Purification by preparative t.l.c. (ethyl acetate/hexane, 1:4) gave mainly starting material together with the methanol addition product, 9-(furan-3'-yl)-2-methoxy-2,6-dimethylnon-5-en-4-one (182) (50 mg, 22%). ^{1}H n.m.r. (CCl_4) δ 7.3, 7.2 (each 1H, m, H5' and H2'); 6.2 (1H, m, H4'); 6.1 (1H, brs, H5); 3.2 (3H, s, OCH_3); 2.4 (2H, s, $(H3)_2$); 2.1 (3H, brs, 6-CH_3); 1.2 (5H, s, 2-CH_3 and $(H1)_3$). ν_{max} (film) 780, 870, 1020, 1070, 1160, 1500, 1610, 1680 cm^{-1}. A weak absorption at 1720 cm^{-1} indicated the presence of a small quantity of non-conjugated ketone.

Attempted Oxymercuration of 4-Hydroxy-Dendrolasin and 4-Acetoxy-Dendrolasin

(i) The alcohol (8) (220 mg, 0.94 mmol) in tetrahydrofuran (1 ml) was added to a solution of mercuric acetate (0.62 g, 2 eq) in water/tetrahydrofuran (1:1, 10 ml). A colourless solution was formed after stirring for 2-3 min and a white precipitate formed. After 5 min a solution of sodium borohydride (0.25 g) in sodium hydroxide (12% aqueous, 10 ml) was added slowly with external cooling. The solution was stirred for a further 30 min, saturated with sodium sulphate and extracted with ether (5 x 20 ml). The combined dried extracts were evaporated to give a pale yellow oil (260 mg).

The t.l.c. of this product showed it to be a complex mixture including starting material. The procedure was repeated with the mixture obtained to give an oil (200 mg) which contained no starting material and was a complex mixture by t.l.c. The ^{1}H n.m.r. spectrum showed that the furan content in the mixture was low.

(ii) The above procedure was applied to the acetate (8a) (110 mg, 0.4 mmol) and mercuric acetate (320 mg, 1 mmol) in aqueous tetrahydrofuran. A complex mixture of starting material and other products was again obtained (by t.l.c.) and the ^{1}H n.m.r. spectrum showed the mixture was low in furans.

Epoxidation of 4-Acetoxy-Dendrolasin (8a)

To a stirred solution of the acetate (8a) (50 mg, 0.18 mmol) in methylene chloride (2 ml) cooled to 0° was added a solution of *m*-chloroperoxybenzoic acid (85% pure, 100 mg) in methylene chloride (2 ml) dropwise over 5 min. After 15-20 min no starting material was detected by t.l.c. A solution of sodium hydroxide (3%, 2 ml) containing sodium sulphite (100 mg) was added and the mixture stirred at room temperature for 2 h. Separation of the organic layer, further extraction of the aqueous (2 x 2 ml, methylene chloride) and removal of the solvents gave an oil (32 mg). The t.l.c. of the product showed two products and some polar products near the origin.

When the reaction was carried out at -20°, the epoxidation required 3 h before starting material could no longer be detected by t.l.c. The recovered yield of crude product was the same.

H.p.l.c. (Lichrosorb, ether/hexane, 1:2) gave the high R_f C6,7 epimer, (4*S*)-3'-(4-acetoxy-6,7-epoxy-2,6-dimethylnon-2-enyl)furan (184) (30%) ^{1}H n.m.r. (CCl_4): δ 7.3 (1H, H5'); 7.24 (1H, m, H2'); 6.25 (1H, m, H4'); 5.6 (1H, dt, J 5,9Hz, H4); 5.05 (1H, brd, J 9Hz, H3); 2.7-2.4 (3H, m, H7 and $(H9)_2$); 1.95 (3H, s, $COCH_3$); 1.7 (6H, s, 2-CH_3 and $(H1)_3$); 1.25 (3H, s, 6-CH_3).

The lower R_f isomer was the C6,7 epimer of *epoxide* (184) (30%). ^{1}H n.m.r. (CCl_4): δ 7.3 (1H, m, H5'); 7.25 (1H, m, H2'); 6.25 (1H, m, H4'); 5.55 (1H, d,t, J 7,10Hz, H4); 5.05 (1H, brd, J 10Hz, H3); 2.7-2.4 (3H, m, H7 and $(H9)_2$); 1.98 (3H, s, $COCH_3$); 1.7 (6H, s, 2-CH_3 and $(H1)_3$); 1.2 (3H, s, 6-CH_3).

Attempted Further Epoxidation of Epoxide (184)

The epoxy-acetates (184) (30 mg) in methylene chloride (3 ml) and m-chloroperoxybenzoic acid (60 mg) were stirred at room temperature. After 1 h no starting materials were detected. Workup, as before, gave an oil (9 mg) which contained no furan protons in the n.m.r. spectrum.

Conversion of Dihydrophymaspermones (42) and (43) to Diene (46)

A mixture of *E* and *Z* dihydrophymaspermones (42) and (43) (300 mg) in methanol was reduced with sodium borohydride in the presence of cerium trichloride.[66] Workup gave a colourless oil (380 mg) which, after rapid chromatography on a short column of alumina, gave a mixture of allylic alcohols (8e and 186) (230 mg). The unstable alcohols were not separated, but instead, some of the mixture (200 mg) was treated with methanesulphonyl chloride (150 mg) in pyridine (2 ml) for 1 h at room temperature. The mainly non-polar product (150 mg), after chromatography through a short column of alumina to remove polar impurities, consisted of the unstable isomeric trienes (187) and cyclic material in a ratio of 4:1 (n.m.r.).

Treatment of the mixture (150 mg) with a few crystals of p-toluenesulphonic acid in carbon tetrachloride solution for 2 h at room temperature, gave a mixture which included about 50% of cyclised products by n.m.r. Chromatography on silica gel and silver nitrate (10%) impregnated silica gel gave (46) (65 mg).

The product was identical in all respects (^{1}H, ^{13}C, i.r., m/s spectra and t.l.c. comparison) with the product (46) isolated from the plant extract.

Partial Hydrogenation of Diene (46)

The diene (46) (100 mg) was hydrogenated in ethanol using P_2 nickel as catalyst[145] for 2 days at room temperature. After filtration through alumina the solvent was removed under reduced pressure to give a colourless oil (85 mg). Purification by preparative t.l.c. (hexane) gave starting material (46 mg, 48%) and two higher R_f products. The higher R_f product was 7-methyl-7-(4'-methylpent-1'-enyl)-4,5,6,7-tetrahydrobenzofuran (190) (20 mg) (Found: m/e 218.1669. $C_{15}H_{22}O$ requires m/e 218.1670). ν_{max} (film) 730, 900, 985(s), 1100, 1150, 1510 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.02 (1H, d, J 2Hz, H2); 5.94 (1H, d, J 2Hz, H3); 5.2 (2H, m, H1' and H2'); 2.25 (4H, m, $(H4)_2$ and $(H3)_2$); 1.13 (3H, s, 7-CH_3); 0.92 (6H, d, J 6Hz, 4'-CH_3 and $(H5')_3$). M/e 218 ($M^{\dot{+}}$), 203, 161, 147, 135, 116, 104, 91, 79, 55.

The more polar product from chromatography was 7-methyl-7-(4'-methylpent-3'-enyl)-4,5,6,7-tetrahydrobenzofuran (191) (20 mg) (Found: M/e 218.1671. $C_{15}H_{22}O$ reuqires m/e 218.1670). ν_{max} (film) 685, 720, 890, 1100, 1145, 1365, 1500 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.0 (1H, d, J 2Hz, H2); 5.92 (1H, d, J 2Hz, H3); 5.1 (1H, m, H3'); 2.37 (2H, m, $(H4)_2$); 1.62 (12H, m, 4'-CH_3 $(H5')_3$ and methylene); 1.2 (3H, s, 7-CH_3); 0.89 (2H, t, J 6Hz, $(H1')_3$). M/e 218 ($M^{\dot{+}}$), 203, 161, 149, 147, 135 (b.p.), 117, 105, 91, 79, 71, 69, 55.

Synthesis of 3-Benzyloxybutan-1-ol (221)

Ethyl crotonate (114 g, 1 mmol) containing 2,6-di*tert*-*p*-cresol (0.1 g) as a radical inhibitor, was heated at 120° with benzyl alcohol containing predissolved sodium hydride (0.5 g). After 20 h the mixture showed very little of the product by examination of the p.m.r. spectrum. Solid potassium hydroxide (2 g) was added and the heating continued at 150°.

After 55 h no further change was observed in the mixture by n.m.r. Ether (150 ml) was added and the mixture washed with acetic acid (20%, 2 x 20 ml) then water (2 x 10 ml). Drying and removal of solvent gave the crude products. Distillation gave ethyl crotonate, ethanol and benzyl alcohol followed by benzyl crotonate (85-100°/0.3 mm) from ester exchange.

The distillation residue was predominantly the mixed ethyl and benzyl esters of the addition product (220).

The crude mixed esters (220) (105 g) were added in ether (100 ml) over 1 h to a stirred suspension of lithium aluminium hydride (10 g) in ether (500 ml) with an efficient condenser After stirring overnight workup and distillation gave the 3-benzyloxybutan-1-ol (221) (52 g, 29% overall) b.p. 104°/0.6 mm. ^{1}H n.m.r. (CCl_4): δ 7.3 (5H, s, aromatic); 4.6 (1H, d, J 12Hz, -OCH-arom.); 4.4 (1H, d, J 12Hz, -O-CH arom.); 3.7-3.2 (4H, m, $(H1)_2$, H3, OH); 1.65 (2H, dt, J 6,5Hz, $(H2)_2$); 1.15 (3H, d, J 7Hz, 3-CH_3).

Synthesis of 3-Benzyloxy-1-chlorobutane (222)

The alcohol (221) (52 g, 0.29 mmol) was converted to the chloride (using the method described in 'Organic Synthesis, 54, 63') with carbon tetrachloride (200 ml) and triphenylphosphine (97 g, 0.37 mmol).

Purification by distillation gave a colourless oil of the chloride (222) (50 g, 88%) b.p. 72°/0.3 mm. ^{1}H n.m.r. (CCl_4): δ 7.3 (5H, s, aromatic); 4.5 (1H, d, J 12Hz, O-C$\underline{H}$-arom.) 4.4 (1H, d, J 12Hz, O-CH-arom.); 3.8-3.5 (3H, m, $(H1)_2$ and H3); 2.0-1.7 (2H, m, $(H2)_2$); 1.2 (3H, d, J 6Hz, 3-CH_3).

Synthesis of 3-Benzyloxy-1-iodobutane (223)

Chloride (222) (24 g, 0.121 mmol), sodium iodide (anhydrous, 20 g, 0.133 mmol) and acetone (100 ml) were heated, under reflux. After 20 h, the n.m.r. spectrum of the mixture showed that approximately 70% exchange had occurred. Further sodium iodide (5 g) was added and the mixture heated for 30 h. Most of the acetone was removed by distillation and dilute sodium thiosulphate (1% aqueous, 100 ml) added to the residue. The mixture was extracted with hexane (3 x 50 ml), the extracts washed with water, dried and the solvent removed to give a colourless oil of the pure iodide (223) (35 g, 97%). ^{1}H n.m.r. (CCl_4): δ 7.3 (5H, brs, aromatic); 4.6 (1H, d, J 12Hz, O-C$\underline{H}$Ph); 4.4 (1H, d, J 12Hz, O-C$\underline{H}$-Ph), 3.6 (1H, apparent q, J 6Hz, H3); 3.25 (2H, t, J 6Hz, $(H1)_2$); 2.0 (2H, m, $(H2)_2$); 1.2 (3H, d, J 6Hz, 3-CH_3).

Preparation of 1-(furan-3'-yl)-4-benzyloxypentan-1-one (213) from Iodide (223).

(i) Lithium pieces (containing 1% alloyed sodium, 800 mg, 114 mmol) were stirred in dry ether (50 ml) under nitrogen at

-30° while a solution of iodide (223) (16.0 g, 55 mmol) in ether (20 ml) was added slowly over 2 h. The solution assumed a yellow colour while most of the metal dissolved. After 6 h at -20 to -30° the yellow solution was transferred (via a double ended needle) into a suspension of lithium 3-furoate in ether (20 ml). (The lithium carboxylate was prepared by the slow addition of methyl lithium (1 equivalent) to 3-furoic acid (3 g, 26.8 mmol) in dry ether at -30 to -20° with stirring.)

The suspension was stirred for 2 h at 0°, overnight at room temperature and transferred slowly with vigorous stirring into a saturated solution of ammonium chloride (100 ml). Separation of the organic layer and extraction of the aqueous (2 x 50 ml) followed by drying and evaporation of the combined solvents gave the crude products as an orange oil (10.5 g).

Chromatography on neutral alumina (ether/hexane, 1:4) gave 2-benzyloxybutane (227) (5.0 g, 50%) ν_{max} (film) 685, 730, 1030, 1060, 1090, 110, 1130, 1500 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.3 (5H, brs, aromatic); 4.5 (2H, apparent s, O-CH_2-Ph); 3.4 (1H, m, H1); 1.5 (2H, m, $(H3)_2$); 1.1 (3H, d, J 6Hz, 2-CH_3); 0.9 (2H, t, J 6Hz, $(H3)_2$). M/e 164 (M^+), 163, 135, 107, 99, 92, 91 (b.p.), 77.

Further elution gave the coupled product 2,7-dibenzyloxyoctane (2.0 g, 20%). ν_{max} (film) 680, 720, 1020, 1060, 1080, 1490 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.3 (10H, apparent s, aromatic); 4.45 (4H, 2d, J 12Hz, $\underline{OCH_2}$-arom.); 3.4 (2H, m, H2 and H7); 1.4 (8H, brs, $(H3)_2$, $(H4)_2$, $(H5)_2$ and $(H6)_2$); 1.1 (3H, d, J 6Hz, 2-CH_3); 0.9 (2H, t, J 6Hz, $(H3)_2$). M/e 326 (M^+), 271, 236, 235, 219, 181, 135, 129, 127, 111, 107, 92, 91 (b.p.) 69, 65.

Continued elution with neat ether gave a yellow oil of the required ketone, 1-(furan-3'-yl)-4-benzyoxy-pentan-1-one (213) (1.7 g, 25% based on the acid) b.p. 130°/0.1 mm (Found: C, 74.3; H, 6.7. $C_{16}H_{18}O_3$ requires C, 74.4; H, 7.0%). ν_{max} (film) 730, 870, 1150, 1515, 1565, 1680, 3180 cm^{-1}. ^{1}H n.m.r. (CCl$_4$): δ 7.95 (1H, m, H2'); 7.4 (1H, m, H5'), 7.3 (5H, s, aromatic); 6.7 (1H, m, H4'); 4.6 (1H, d, J 11Hz, OCH-arom.); 4.3 (1H, d, J 11Hz, OCH-arom.); 3.5 (1H, n, H4); 2.7 (2H, t, J 6Hz, (H2)$_2$); 1.9 (2H, m, (H3)$_2$); 1.1 (3H, d, J 6Hz, (H5)$_3$). ^{13}C n.m.r. see appendix.

Continued elution gave a yellow oil identified as the diketone (231) 4-benzyloxy-1-[2'-(furan-3"-oyl)furan-3'-yl] pentan-1-one (0.4 g, 7%) (Found: C, 71.5; H, 6.0. $C_{21}H_{20}O_5$ requires C, 71.6; H, 5.7%). ν_{max} (film) 680, 740, 780, 840, 1150, 1480, 1510, 1570, 1635, 1700-1680 (br), 3180 cm^{-1}. ^{1}H n.m.r. (CCl$_4$): δ 8.4 (1H, dd, J 0.8,1.6Hz H2"); 7.45 (1H, d, J 1.6Hz, H5'); 7.40 (1H, dd partly obscurred, H5"); 7.30 (5H, s, aromatic); 6.95 (1H, dd, J 0.8,1.6Hz, H4"); 6.65 (1H, d, J 1.6Hz, H4'); 3.1 (2H, t, J 7Hz, (H2)$_2$); 1.9 (2H, m, (H3)$_2$); 1.2 (3H, d, J 6Hz, (H5)$_3$). ^{13}C n.m.r. see appendix. M/e 352 (M$^{+\cdot}$), 334, 319, 261, 247, 246, 243, 217, 204, 189, 176, 95, 91 (b.p.), 77, 65.

(ii) When the chloride (222) was substituted for the iodide (223) in the above procedure and metal dissolution allowed to proceed for 4 h before transfer to the lithium carboxylate, isolation of products gave the ketone (213) (36%), diketone (231) (7%) and (227) (50%).

Attempted Grignards Preparations using Chloride (222) and Iodide (223)

(i) Using standard conditions for Grignard initiation, the chloride (222) could not be induced to form a Grignard reagent in ether.

(ii) The use of the iodide (223), however resulted in the dissolution of most of the magnesium after 2 h at 34°. Workup of a portion with D_2O gave only the protonated product (227) and coupled product with no significant deuterium incorperation (by n.m.r. or m/s).

Preparation of Methyl t-Butyl Ether

This ether was prepared by the procedure of Norris and Rigby[165] in 90% yield, b.p. 55° (lit.[165] b.p. 55°).

The ether was dried by refluxing with sodium and benzophenone until blue, followed by distillation.

Attempted Preparation of Ketone (213) in Methyl t-Butyl Ether

The same procedure as previously described was followed using chloride (222) in methyl t-butyl ether at -20 to -10° for 2 h before transfer to the lithium carboxylate. Workup gave only the benzyl ether (227) and starting material (222).

Attempted preparation of Ketone (213) in Tetrahydrofuran

Essentially the same procedure as previously described for preparation in diethyl ether was followed.

Tetrahydrofuran (distilled from lithium aluminium hydride) was used as solvent and the temperature kept at -40 to -30° for 3 h during dissolution of the metal. After transfer to the lithium carboxylate the mixture was stirred at -30° for 1 h, 0° for 1 h and room temperature overnight. Workup gave no furan containing products. Chromatography of the products (ether/hexane, 1:9) gave **2-benzyloxy-5-phenylpentane** (229) (54%). ν_{max} (film) 680, 720, 760, 1020, 1060, 1090, 1125, 1500, 1600, 3040, 3060, 3100 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.25 (5H, s, arom.); 7.15 (5H, s, arom.); 4.4 (2H, 2d, J 12Hz, $-OC\underline{H_2}Ph$); 3.4 (1H, m, H2); 2.6 (2H, m, $(H5)_2$); 1.8-1.4 (4H, m, $(H3)_2$ and $(H4)_2$); 1.1 (3H, d, J 6Hz, $(H1)_3$). M/s 254 ($M^{\dot{+}}$), 162, 145, 104, 91 (b.p.), 77, 65.

The more polar product isolated as a sweet smelling colourless oil was **5-phenylpentan-2-ol** (228) (36%). ν_{max} (film) 685, 740, 1080, 1120, 1500, 1600, 3040, 3400 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.2 (5H, s, arom.); 3.6 (2H, m, H2, OH); 2.6 (2H, m, $(H5)_2$); 1.9-1.3 (4H, m, $(H3)_2$ and $(H4)_2$); 1.1 (3H, d, J 6Hz, $(H1)_3$). M/s 163 ($M^{\dot{+}}$ - 1), 145 ($M^{\dot{+}}$ - H_2O), 131, 117, 104 (b.p.), 91, 65, 45.

A minor non polar product isolated was probably dibenzyl (5%). ^1H n.m.r. (CCl_4): δ 7.1 (10H, s, arom.); 2.9 (4H, s, methylene).

In Situ Preparation of 4-Benzyloxy-1-(furan-2'-yl)pentan-1-one (230)

2-Furoic acid (440 mg, 4 mmol) in dry ether (20 ml) was converted to the lithium salt by the slow addition of methyl lithium (4 mmole) with stirring at -40° under nitrogen. Lithium (containing 0.2% alloyed sodium 70 mg, 10 mmoles) and the chloride (222) (1.0 g, 5 mmol) were added and the mixture stirred at -30°. After 2 h no reaction was evident so the mixture was stirred overnight at room temperature. The solution was transferred slowly with vigorous stirring into a concentrated aqueous solution of ammonium chloride. Extraction of the aqueous solution with ether (2 x 50 ml) gave a yellow oil. Preparative t.l.c. (ether/hexane, 1:9) gave the ether (227) (12%), starting material (222) (35%) and benzyl-2-furanyl ketone (232), (5%). ^{1}H n.m.r. (CCl_4): δ 7.6 (1H, m, H5); 7.2 (1H, m, H3); 7.25 (5H, s, phenyl H); 6.5 (1H, m, H4); 4.05 (2H, s, CH_2-Ph).

The lower R_f product was the **2-furyl ketone** (230) (44%) ν_{max} (film) 685, 725, 760, 880, 1130, 1465, 1495, 1570, 1680, 3150-3120 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.5 (1H, m, H5'); 7.25 (5H, s, aromatic); 7.1 (1H, m, H3'); 6.4 (1H, m, H4'); 4.4 (2H, 2d, J 14Hz, O-$\underline{CH}_2$-Ph); 3.6 (1H, m, H4); 2.9 (2H, t, J 6Hz, $(H2)_2$); 1.9 (2H, m, $(H3)_2$); 1.2 (3H, d, J 6Hz, $(H5)_3$). M/s 259 ($M^{+\cdot}$ + 1), 241, 216, 186, 167, 151, 152, 135, 124, 123, 121, 110, 107, 99, 95, 91 (b.p.), 77, 65.

An 'in situ' Preparation of Ketone (213) in Diethyl Ether.

3-Furoic acid (6.7 g, 60 mm01) in dry ether (100 ml) was deprotonated by the slow addition of methyl lithium (1 eq.) with stirring at -30 to -40°. The dry and freshly distilled chloroether (222) (15 g, 75 mmol) was added followed by lithium alloy (containing 0.2% sodium, 1.4 g, 200 mmol). The mixture was stirred under nitrogen at -50 to -40° until most of the lithium had dissolved (approx. 2 h). After

3 h the mixture was slowly transferred into a vigorously stirred solution of ammonium chloride (saturated aqueous soln., 200 ml). The aqueous solution was extracted with ether (3 x 100 ml), the ether extracts dried and evaporated under reduced pressure to give an orange oil (18 g). Chromatography of the crude product on neutral alumina gave the ketone (213) (63%), diketone (231) (5%) and ether (227) (20%).

Reduction of Ketone (213) to 4-Benzyloxy-1-(furan-3'-yl)-pentan-1-ol (214).

To a suspension of lithium aluminium hydride (0.8 g, 21 mmol) in dry ether (150 ml) was added the ketone (213) (18 g, 70 mmol) in ether (50 ml) over 30 min. After stirring for 30 min, water (1 ml) was cautiously added followed by sodium hydroxide (3 ml, 15% aqueous solution) and water (1 ml), stirring for 20 min after each addition. Sodium sulphate (anhydrous, 10 g) and celite (2 g) were added, the solution stirred for 15 min, filtered and the solids washed with ether (50 ml). Evaporation of the solvent gave a colourless oil of the *alcohol* (214) (18.5 g, quantitative) b.p. $140^{\circ}/0.1$ mm (Found: C, 73.5; H, 7.4 . $C_{16}H_{20}O_3$ requires C, 73.8; H, 7.7%). ν_{max} (film) 680, 730, 870, 1020, 1130, 1150, 1500, 3400 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.3 (7H, s, arom., H2' and H5'); 6.2 (1H, m, H4'); 4.4 (3H, m, -O$\underline{CH}_2$Ph and H1); 3.45 (1H, m, H4); 2.8 (1H, brs, D_2O exch., OH); 1.6 (4H, brm, $(H2)_2$ and $(H3)_2$); 1.1 (3H, d, J 6Hz, $(H5)_3$). M/s 260 ($M^{+\cdot}$), 243, 224, 168, 152, 151, 135, 110, 107, 104, 97, 95, 91 (b.p.), 85, 79, 77, 69, 65.

Reductive Fission of Acetoxyether (214a) to 5-(furan-3'-yl)-pentan-2-ol (216)

(i) Alcohol (214) (1.4 g) was acetylated in pyridine (10 ml) and acetic anhydride (3 ml) over 15 h at room temperature. Workup gave a colourless oil of the crude acetate (214a) (1.6 g) which was used without further purification. ν_{max} (film) 680, 720, 790, 870, 1020, 1230, 1500, 1735 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.3 (7H, m, arom., H2' and H5'); 6.4 (1H, m, H4'); 5.7 (1H, t, J 6Hz, H1); 4.5 (2H, 2d, J 12Hz, $-OCH_2Ph$): 3.5 (1H, m, H4); 2.0 (3H, s, $COCH_3$), 1.15 (3H, d, J 6Hz, $(H5)_3$).

(ii) To a stirred solution of liquid ammonia (approx. 70 ml) at -33° containing dissolved lithium (400 mg, 57 mmol) was added a solution of the crude acetoxyether (214a) (1.75 g) in dry tetrahydrofuran (10 ml) over 10 min. After stirring for 90 min, isoprene was added dropwise until the blue colour was discharged, then ammonium chloride (1 g) was cautiously added. The ammonia was allowed to evaporate and ammonium chloride solution (20 ml, saturated) was added and the mixture extracted with ether (5 x 30 ml). The combined dried extract was evaporated and chromatographed (ether/hexane, 4:6) to give the *alcohol* (216) (0.50 g, 60%) b.p. 80°/0.2 mm (block) 56-58°/0.1 mm (Found: C, 70.1; H, 9.2. $C_9H_{14}O_2$ requires C, 70.1; H, 9.2%). ν_{max} (film) 790, 870, 1020, 1150, 1500, 3400 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.3 (1H, m, H5'); 7.2 (1H, m, H2') 6.2 (1H, m, H4'); 3.7 (1H, m, H2); 3.2 (1H, brs, D_2O exch., OH); 2.4 (2H, m, $(H5)_2$); 1.1 (3H, d, J 6Hz, $(H1)_3$).

A polar product was identified as diol (237), 1-(furan-3'-yl)pentan-1,4-diol (0.16 g, 20%) ν_{max} (film) 790, 870, 1020, 1150, 1500, 3400 cm^{-1}. ^1H n.m.r. ($CCl_4/CDCl_3$): δ 7.3 (2H, m, H2' and H5'); 6.3 (1H, m, H4'); 4.6 (1H, m, H1); 4.2 (2H, brs, D_2O exch., 2OH); 3.7 (1H, m, H4); 1.1 (3H, d, J 6Hz, $(H5)_3$).

When this diol was acetylated, as in (i), and the crude diacetate reduced as described above a further quantity of the alcohol (216) was obtained (total yield, 70-75%).

(iii) Under different reduction conditions when lithium (5 eq.) was added to the acetate (214a) in liquid ammonia (50-70 ml) and tetrahdrofuran (10 ml) at -33° until the blue colouration persisted for 15 min, workup gave different products. In addition to alcohol (216) (20%) the 1-hydroxy-4-acetoxy analogue (235) (22%), the 1-acetoxy-4-hydroxy analogue (216) (33%) and diol (237) (25%) were isolated and identified by their n.m.r. spectra.

Conversion of Alcohol (216) to 1-(furan-3'-yl)-4-iodopentane (218)

(i) A mixture of alcohol (216) (0.23 g), pyridine and p-toluenesulphonyl chloride (2 eq.) was allowed to stand at room temperature for 20 h. Workup with ice-water and hexane extraction gave the crude tosylate as a pale yellow oil (0.43 g, 94%).

(ii) The crude tosylate of (216), sodium iodide (0.7 g) and acetone (dry, 15 ml) was heated under reflux for 5 hours. Water (50 ml) was added and the product extracted with light petroleum. Removal of the solvent gave the almost colourless *iodide* (218) (302 mg, 87%). (Found m/e 264.0016. $C_9H_{13}IO$ requires 264.0013, C, 41.52; H, 5.04. $C_9H_{13}IO$ requires C, 40.93; H, 4.96%). ν_{max} (film) 715, 870, 1020, 1370, 1500 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.3 (1H, m, H5'); 7.2 (1H, m, H2'); 6.4 (1H, m, H4'); 4.1 (1H, m, H4); 2.4 (2H, m, $(H1)_2$); 1.9 (3H, d, J 7Hz, $(H5)_3$). M/s 264 ($M^{\dot{+}}$), 253, 137, 81.

2-Pentyltriphenylphosphonium Bromide

2-Bromopentane (0.32 g, 2.1 mmol) and triphenylphosphine (0.53 g, 2.1 mmol) were sealed under nitrogen and heated in an oil bath. After 7 h at 100° no change was visible in the solution. When heated to 150° for 15 h two layers separated, the lower (50% by volume) solidified to a glass and then a crystalline solid on cooling. This was identified as the salt and the upper layer consisted of a mixture of the starting materials (n.m.r.).

2-Pentyltriphenylphosphonium Iodide

(i) 2-Bromopentane (10 g, 66 mmol), calcium carbonate (1 g), sodium iodide (12 g, 80 mmol) were heated and stirred in dry acetone under reflux for 18 h. After filtration most of the acetone was removed under reduced pressure and water (100 ml) was added. Extraction with hexane and removal of the solvent gave a colourless oil of 2-iodopentane (12 g, 92%).

(ii) The iodide was heated at 150° in a sealed tube under nitrogen with triphenylphosphine as described above. Salt formation was evident after 15 min and the solution became dark brown. After 5 h the conversion was complete judged by the lower layer filling the solution. Workup gave the salt as a colourless viscous oil which slowly solidified. ^{1}H n.m.r. ($CDCl_3$): δ 8.2-7.5 (15H, m, arom.), 4.6 (1H, m, H2); 2.2-1.5 (4H, m, $(H3)_2$ and $(H4)_2$; 1.2 (3H, d, J 7Hz, $(H1)_3$); 0.9 (3H, t, $(H5)_3$).

Attempted Preparation of the Phosphonium Iodide (238)

(i) The iodide (218) (300 mg, 1.2 mmol) and triphenylphosphine (520 mg, 1.3 mmol) were heated successively under reflux in benzene and toluene for 24 h each time. Evaporation of the solvent and an n.m.r. spectrum run on the darkened residue confirmed that no significant salt had formed in either solvent. The spectrum showed unchanged starting materials.

(ii) A reaction at 140° under nitrogen gave rapid darkening and a brown viscous residue after 1 h due to extensive decomposition and polymerisation.

(iii) A reaction of the neat iodide (218), triphenylphosphine and calcium carbonate (1 mmole of each) under nitrogen in a sealed tube at 140° for 2 h gave no furan containing products as evidenced by the n.m.r. spectra of the dark viscous product.

Preparation of 1-Benzyloxy-3-chloropropane

(i) To 1,3-Propane diol (40 g, 0.5 mmol) in dry tetrahydrofuran (100 ml) was added sodium hydride (50% in oil, 10 g, 0.2 mol) with stirring and external cooling. After stirring for 2 h the evolution of hydrogen ceased and a solution of benzyl bromide (34 g, 0.2 mol) in dimethylformamide (20 ml) was added over 1 h. After a few minutes an exothermic reaction began and sodium bromide precipitated. The mixture was stirred at 50-60° overnight and water 200 ml was added. The aqueous solution was extracted with ether (3 x 50 ml) and methylene chloride (3 x 50 ml). The combined extracts were dried, evaporated and chromatographed on silica (hexane/ether 2:1). Distillation gave 1-benzyloxypropan-3-ol (19 g, 58%) b.p. 95-97°/0.1 mm.

The alcohol from (i) (19 g) was converted to the chloride using triphenylphosphine (40 g) and carbon tetrachloride (100 ml). Chromatography on alumina (hexane) and distillation gave 1-benzyloxy-3-chloropropane (20.5 g, 98%) b.p. 78-80°/ 0.2 mm.

(ii) 3-Chloropropan-1-ol (commercially available, 9.5 g, 0.1 mol) in ether (10 ml) was added to a suspension of sodium hydride (2.5 g, 0.105 mol washed free of oil with hexane, 3 x 10 ml) in dry ether (50 ml) at 0 and the suspension stirred for 20 min. Benzyl bromide (17 g, 0.1 mol) in ether 20 ml was added over 10 min. After 30 min no reaction was evident and dimethylformamide (10 ml) was added. Sodium bromide precipitated within a few minutes. The mixture was stirred overnight, diluted with water (50 ml) and the aqueous layer extracted with ether (2 x 50 ml). The ether extracts were washed with water dried and evaporation gave a colourless oil (20.5 g). Distillation gave the pure chloroether (17 g, 93%).

Preparation of 4-Benzyloxy-1-(furan-3'-yl)-Butan-1-one (241)

(i) 3-Furoic acid (8.96 g, 80 mmol) in dry ether (100 ml) was deprotonated at -20 to -30° with methyl lithium (80 mmol) as previously described. To this suspension was added 1-benzyloxy-3-chloropropane (18.5 g, 100 mmol), the lithium alloy (2% sodium, 1.5 g, 215 mmol) and the mixture was vigorously stirred at -40 to -30° under nitrogen for 2 h. After 30 min at 0° and 30 min at room temperature the solution was slowly transferred into a solution of ammonium chloride (20%, 200 ml) with vigorous stirring. Extraction of the aqueous with ether (2 x 100 ml) and removal of the solvent from the combined extracts gave an orange oil (24 g). Chromatography on alumina (ether/hexane 1:1 to 1.0) gave non polar products containing no furan protons (9 g) followed by a trace of the benzyl 3-furyl ketone (233) (0.3 g, 2%). Further elution gave a pale yellow oil of the ketone, 4-benzyloxy-1-(furan-3'-yl)-butan-1-one (241) (13.2 g, 68%) b.p. 130°/0.4 mm (block) (Found: C, 73.70; H, 6.59. $C_{15}H_{16}O_3$ requires C, 73.75; H, 6.60%). ν_{max} (film): 700, 740, 820, 880, 1100, 1150, 1500 (sh), 1520, 1570, 1675, 1690 (sh), 3120 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 8.0 (1H, m, H2'); 7.4 (1H, m, H5'); 7.25 (5H, s, aromatic); 6.7 (1H, m, H4'), 4.4 (2H, s, $O\underline{CH_2}$-Ph); 3.45 (2H, t, J 6Hz, $(H4)_2$); 2.8 (2H, t, J 6Hz, $(H2)_2$); 2.0 (2H, m, $(H3)_2$). M/s 245 ($M^{\overset{+}{\cdot}}$ + 1), 244 ($M^{\overset{+}{\cdot}}$), 153, 139-137, 123, 111, 110 (b.p.), 107, 95, 91, 85, 79, 77, 65.

Continued elution gave 4-benzyloxy-1-[2'-(furan-3"-oyl) furan-3'-yl] butan-1-one (247)(0.6 g, 4.5% based on the acid) ν_{max} (film) 690, 740, 780, 845, 875, 1155, 1485, 1515, 1570, 1640, 1680, 1690, 3120 cm^{-1}. ^1H n.m.r. (CCl_4): δ 8.3 (1H, m, H2"); 7.4 (2H, m, H5" and H5'); 7.2 (5H, s, aromatic); 6.9 (1H, m, H4'); 6.69 (1H, m, H4"); 4.4 (2H, s, O-CH_2-Ph); 3.5 (2H, t, J 6Hz, $(H4)_2$); 3.0 (2H, t, J 6Hz, $(H2)_2$); 1.9 (2H, m, $(H3)_2$). M/s 338 ($M^{+\cdot}$), 280, 247, 243, 233-229, 217, 205-203, 189, 176, 175, 161, 147, 137, 123, 95, 91 (b.p.), 77, 65.

(ii) In another experiment the yield of ketone (241) was 78% and some 3-furoic acid was recovered from the aqueous solution.

Reduction of Ketone (241) to 4-benzyloxy-1-(furan-3'-yl) butan-1-ol (242)

The ketone (241) (13.0 g, 53 mmol) was reduced with lithium aluminium hydride (1.0 g, 25 mmol) in ether (200 ml) as previously described. Workup gave a colourless oil of the *alcohol* (242) (13.2 g, quantitative) b.p. 150°/0.2 mm (block) (Found: C, 71.35; H, 7.44. $C_{15}H_{18}O_3$ requires C, 73.14; H, 7.37%). ν_{max} (film) 700, 800, 880, 1025, 1100, 1155, 1460, 1510, 1600, 3400 cm^{-1}. ^1H n.m.r. (CCl_4): 7.25 (7H, s, aromatic H2' and H5'); 6.25 (1H, m, H4'); 4.5 (1H, partly obscured t, H1); 4.4 (2H, s, O-$\underline{CH_2}$-Ph); 3.4 (2H, n, $(H4)_2$); 3.0 (1H, brs, OH); 1.7 (4H, m, $(H2)_2$ and $(H3)_2$). M/s 246 ($M^{+\cdot}$), 228, 159, 155, 140, 139, 138, 137, 110, 107, 104, 97, 95, 91 (b.p.), 82, 81, 79, 77, 71, 69, 65.

Preparation of the Tetrahydropyranyl ether of Alcohol (242)

The alcohol (242) (11.5 g) was dissolved in an excess of dihydropyran (30 g) and stirred with external cooling while a dilute solution of p-toluenesulphonic acid (20 mg) in methylene chloride (1 ml) was added. The solution became hot and assumed a red-brown colour. After 1 h no alcohol could be detected by t.l.c. and sodium carbonate (0.5 g) was added and the mixture stirred for 15 min, filtered and excess dihydropyran removed under reduced pressure. Chromatography of the residue on alumina gave a colourless oil of the tetrahydropyranyl ether (243) (16 g, quantitative) which was used without further purification ν_{max} (film) 680, 725, 780, 870, 905, 1145, 1185, 1500 1590 (w), 3040, 3060, 3100 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.3 (7H, s, aromatic, H2' and H5'); 6.35 (1H, m, H4'); 4.8-4.5 (2H, m, H1 and H2"); 4.5 (2H, s, OCH_2-Ph); 4.0-3.2 (4H, m, $(H4)_2$ and $(H6")_2$); 2.0-1.3 (10H, brm, methylene).

Reduction of Ether (243) to 4-(furan-3'-yl)-butan-1-ol (244)

The general procedure previously described was followed. The tetrahydropyranyl ether (243) (16 g, 48.5 mmol) was reduced using lithium (1.75 g, 250 mmol) in a solution of liquid ammonia (150 ml) containing tetrahydrofuran (25 ml). The reduction was stopped after 20 min at -33° by the addition of isoprene followed by ammonium chloride. Workup and distillation gave a colourless oil of the *alcohol* (244) (4.5 g, 76%) b.p. 72-74°/0.5 mm (Found: C, 68.34; H, 8.37. $C_8H_{12}O_2$ requires C, 68.54; H, 8.63%). ν_{max} (film) 780, 880, 1020, 1060, 1160, 1500, 3400 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.25 (1H, m, H5'); 7.15

(1H, m, H2'); 6.2 (1H, m, H4'); 3.5 (3H, t, 6Hz, $(H1)_2$ and OH, exch. D_2O); 2.4 (2H, m, $(H4)_2$); 1.6 (4H, brm, $(H2)_2$ and $(H3)_2$). M/s 140 ($M^{\dot{+}}$), 123, 122, 121, 95, 94, 82, 81, 69, 53.

Conversion of Alcohol (244) to 4-(furan-3'-yl)-1-iodobutane (245)

(i) The alcohol (244) (1.4 g, 10 mmol) in dry methylene chloride (30 ml) and triethylamine (10 ml) was stirred at 0° while methanesulphonyl chloride (2 ml) was added dropwise. After 10 min ice water was added and the aqueous layer extracted with methylene chloride (2 x 20 ml). The solvents were removed under reduced pressure at 20° and the residue passed through a short column of silica, overlayed with magnesium sulphate (anhydrous), using ether. Removal of the ether gave a colourless oil of the mesylate of (244) (2.2 g, 95%).

(ii) The mesylate from (i) (2.15 g) was stirred in a solution containing sodium iodide (dry, 5 g) in dry acetone (50 ml) under nitrogen and protected from light. Sodium methanesulphonate was formed as a precipitate after 24 h. After 30 h water was added (200 ml) and the mixture extracted with hexane (3 x 50 ml). Removal of the hexane gave the *iodide* (245) (2.15 g, 87%) b.p. 70°/0.05 mm (block) (Found: C, 38.82; H, 4.42. $C_8H_{11}OI$ requires C, 38.42; H, 4.43%). ν_{max} (film) 770, 870, 1020, 1060, 1155, 1200, 1500, 1570 (w), 3160 (w) cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.17 (1H, m, H5'); 7.11 (1H, m, H2'); 6.13 (1H, m, H4'); 3.10 (2H, t, J 6Hz, $(H1)_2$); 2.42 (2H, t, J 6Hz, $(H4)_2$); 2.0-1.7 (4H, m, $(H2)_2$ and $(H3)_2$). M/s 250 ($M^{\dot{+}}$), 123, 81, 67, 55, 53.

(ii) The iodide (245) was also prepared from the tosylate of alcohol (244) by a similar procedure in 95-97% overall yield.

Preparation of 4-(furan-3'-yl)-1-butyltriphenylphosphonium iodide (246)

The iodide (245) (2.05 g, 8.15 mmol), triphenylphosphine (2.7 g, 10 mmol) was heated under reflux in benzene under nitrogen and protected from light. After 3 days the salt was filtered off and washed with benzene and hexane. Recrystallisation of a small portion from methylene chloride/hexane gave colourless needles (3.65 g, 87%) m.p. 167-168° (Found: C, 60.97; H, 5.12. $C_{26}H_{26}OPI$ requires C, 60.89; H, 5.11%). ν_{max} (nujol) 690, 715, 740, 750, 780, 805, 880, 1000, 1025, 1110, 1115, 1445 cm^{-1}. ^1H n.m.r. ($CDCl_3$): δ 7.8-7.6 (15H, m, $(Ph)_3$); 7.16 (2H, m, H2' and H5'); 6.2 (1H, m, H4'); 3.63 (2H, m, $(H1)_2$); 2.5 (2H, m, $(H4)_2$); 2.1-1.6 (4H, m, $(H2)_2$ and $(H3)_2$). M/s 385 ($M^{\dagger} - I^-$), 289, 263, 262 (b.p.), 185-183, 152, 128, 123, 108, 107, 94, 81.

Alkylation of Phosphonium Salt (246)

(i) The primary phosphonium iodide (246) (512 mg, 1 mmol) was suspended in dry tetrahydrofuran (10 ml) at 0° while *n*-butyl lithium (1.1 eq.) was added slowly with stirring to give a dark orange solution of the ylide. After 30 min the ylide was slowly transferred into a cooled solution of methyl iodide (2 ml) in tetrahydrofuran (5 ml) with efficient stirring. Removal of the solvents gave the crude product (520 mg). Recrystallisation from methylene chloride/hexane gave colourless needles of the salt , 5-(furan-3'-yl)-2-pentyltriphenylphosphonium iodide (238) (460 mg, 87%) m.p. 188-189°.

ν_{max} (nujol) 685, 715, 725, 740, 750, 780, 820, 875, 995, 1010, 1100, 1130, 1460, 3080, 3100 cm^{-1}. ^{1}H n.m.r. (CDCl$_3$): δ 8.0-7.5 (15H, m, (Ph)$_3$); 7.18 (2H, m, H2' and H5'); 6.25 (1H, m, H4'); 4.9 (1H, m, H2); 2.5 (2H, m, (H5)$_2$); 1.5 (3H, dd, J 6,19Hz, (H1)$_2$). M/s 399 ($M^{+\cdot}$ - I^-), 368, 262, 232, 215 183, 157, 135, 121, 108, 95 (b.p.), 81.

(ii) The use of methyl lithium as base gave an inseparable mixture from alkylation on the furan ring (C2') and also some dialkylation at C1 of (246).

Wittig Reaction - Synthesis of Acetal (248)

The dry phosphonium salt (238) (1.85 g, 3.5 mmol) was suspended in dry tetrahydrofuran (20 ml) while n-butyl lithium was added dropwise until a faint yellow colour of the ylide was noticed, followed by a further quantity of n-butyl lithium (3.7 mmole) to give an orange-red solution of the ylide. to the ylide was added a freshly distilled solution of the aldehyde (82) (820 mg, 3.7 mmole) in dry tetrahydrofuran (5 ml) and the mixture stirred for 1 h. Water (100 ml) was added and the solution extracted with hexane (4 x 60 ml). After evaporation of the hexane the residue was purified by rapid passage through a short column of alumina (ether/hexane, 6:4) to give a colourless oil of (*E* and *Z*) 1-(furan-3'-yl)-5-methyl-3-[5"-(furan-3'"-yl)-2"-methylpent-1"-en-1"-yl]-2,8 dioxabicyclo[3.2.1]octane (248) (943 mg, 78%) (Found: C, 73.81: h, 7.48. $C_{21}H_{26}O_4$ requires C, 73.66; H, 7.66%). ν_{max} (film) 790, 875, 900, 930, 945, 995, 1025, 1060, 1105, 1130, 1150, 1205, 1230, 1240, 1500, 3180 (w) cm^{-1}, ^{1}H n.m.r. (CCl$_4$): δ 7.3-7.0 (4H, 3m, H2', H5' H2'" and H5'"); 6.27 (1H, m, H4'); 6.13 (1H, m, H4'"); 5.13 (1H, dd, J 8,2Hz, H1"); 4.5 (1H, m, H3); 1.67 (3H, d, J 2Hz, 2"-CH_3); 1.30 (3H, s, 5-CH_3). ^{13}C n.m.r. see appendix. M/s 342 ($M^{+\cdot}$), 248, 246, 233, 232, 215, 177, 167, 164, 161, 149, 148, 135, 121, 108, 96, 95 (b.p.), 94, 82, 81, 67, 55, 53.

Hydrogenation of Acetal (248) with P_2-Nickel

P_2-Nickel was prepared by the method of Brown and Ahuja.[145]

(i) To a stirred solution of P_2-Nickel (from 1 mmol of nickel acetate) in ethanol was added a solution of the acetal alkene (248) (2.5 g, 7.3 mmol) in ethanol (5 ml) under hydrogen. The mixture was stirred for 20 days and t.l.c. showed a trace of starting material. The mixture was purified by preparative t.l.c. (ether/hexane, 1:4) to give an oil of (1*R*,3*R*,5*R*,2"*R*/*S*)-1-(furan-3'-yl)-5-methyl-3-[5"-(furan-3'''-yl)-2"-methyl pent-1"-yl]-2,8-dioxabicyclo[3.2.1]octane (249) (2.2 g, 88%) (Found: C, 73.37; H, 8.24. $C_{21}H_{28}O_4$ C, 73.22; H, 8.19%). ν_{max} (film) 785, 795, 875, 935, 1025, 1055, 1070, 1115, 1140, 1155, 1210, 1235, 1250, 1510, 1610, 3180 (w) cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.3-7.0 (4H, 3m, H2', H5', H2''' and H5'''); 6.24 (1H, m, H4'); 6.10 (1H, m, H4'''); 3.9 (1H, m, H3); 1.47 (3H, s, 5-CH_3); 0.90 (3H, d, J 6Hz, 2-CH_3). ^{13}C n.m.r. see appendix. M/s 344 ($M^{+\cdot}$) (b.p.), 327, 315, 249m 235, 232, 217, 203, 193, 179, 165, 147, 135, 95, 82, 81, 69, 67, 55, 53. Starting material (0.2 g, 8%) was also recovered.

(ii) In another experiment the ratio of catalyst to substrate was increased to (3:2) and the reduction allowed to proceed for 15 h. Preparative t.l.c. (ether/hexane 1:4) gave the dihydroacetal (249) (77%) and two more polar products isolated together (23%) which were the epimeric tetrahydrofuranyl acetals characterised by their n.m.r. spectrum. ^{1}H n.m.r. (CCl_4): δ 7.24 (1H, m, H2'); 7.17 (1H, m, H5'); 6.23 (1H, m, H4'); 4.1-3.5 (4H, m, $(H2''')_2$ and $(H5''')_2$); 3.17 (1H, dd, J 8,6Hz, H3); 1.3 (3H, s, 5-CH_3); 0.90 (3H, d J 6Hz, 2"-CH_3).

Reduction of Difuryl Acetal (249) with Lithium/Ammonia

(i) The acetal (249) (350 mg, 1 mmol) was added in tetrahydrofuran (5 ml) to a solution of lithium (50 mg, 7 mmole) in ammonia (90 ml) containing tetrahydrofuran (10 ml). Workup after 9 h with isoprene then ammonium chloride, as previously described, gave the crude products (340 mg). Preparative t.l.c. (ether/hexane, 1:1) gave starting material (104 mg, 30%). The highest R_f product was a mixture of the minor oxepanol isomers, (2*R*,4*R*,7*S*,2"*R*/*S*)-7-(furan-3'-yl)-2-[5"-(furan-3'''-yl)-2"-methylpent-1"-yl]-4-methyloxepan-4-ol (251) (32 mg, 9%) (Found m/e 346.2140. $C_{21}H_{30}O_4$ requires m/e 346.2144). ν_{max} (film) 790, 880, 1025, 1160, 1330, 1510, 1580, (w), 3450 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.10 (3H, m, H2', H5' and H5'''); 7.00 (1H, m, H2'''); 6.13 (1H, m, H4'); 6.03 (1H, m, H4'''); 4.23 (1H, n, H7); 3.63 (1H, m, H2); 2.35 (2H, m, $(H5")_2$); 1.14 (3H, s, 4-CH_3); 0.90 (3H, d, J 5Hz, 2"-CH_3). ^{13}C n.m.r. see appendix. M/s 346 ($M^{+\cdot}$), 328, 179, 151, 149, 135-133, 124, 121, 111-108, 97, 95, 94, 82, 81 (b.p.), 71, 69, 67, 57, 53.

The major product of intermediate R_f was identified as (4*R*,6*R*,8*R*/*S*)-1,11-di(furan-3'-yl)-4,8-dimethylundecan-4,6-diol (211) (78 mg, 22%) (Found: m/e 348.2297. $C_{21}H_{32}O_4$ requires m/e 348.2300. C, 72.67; H, 9.13. $C_{21}H_{32}O_4$ requires C, 72.38; H, 9.26%). ν_{max} (film) 780, 790, 880, 1025, 1160, 1380, 1505, 3360 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.13 (2H, m, $(H5')_2$); 7.0 (2H, m, $(H2')_2$); 6.07 (2H, m, $(H4')_2$); 3.8 (3H, brs, 2H, D_2O exch., 2OH and H6); 2.33 (4H, m, $(H1)_2$ and $(H11)_2$); 1.10 (3H, s, 4-CH_3); 0.87 (3H, d, J 5Hz, 8-CH_3). ^{13}C n.m.r. see appendix. M/e 348 ($M^{\dot{+}}$), 330, 312, 239, 236, 221, 203, 181, 180, 179, 163-161, 153-149, 137-134, 122, 110, 108, 95 (b.p.), 94, 82, 81.

The lowest R_f products isolated were the oxepanols, (2*R*,4*R*,7*R*,2"*R/S*)-7-(furan-3'-yl)-2-[5"-(furan-3'''-yl)-2"-methylpent-1"-yl]-4-methyloxepan-4-ol (250) (92 mg, 26%) (Found: C, 72.99; H, 9.01. $C_{21}H_{30}O_4$ requires C, 72.80; H, 8.73%). ν_{max} (film) 790, 880, 910, 1030, 1160, 1510, 3420 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.2-7.0 (4H, m, H2', H5', H2''' and H5'''); 6.17 (1H, m, H4'); 6.03 (1H, m, H4'''); 4.57 (1H, m, H7); 3.5 (1H, m, H2); 3.0 (1H, brs, D_2O exch., OH); 2.20 (2H, m, $(H5")_2$); 1.28 (3H, s, 4-CH_3); 0.77 (3H, 2d, 2'-CH_3). ^{13}C n.m.r. see appendix.

(ii) A larger scale reduction using the acetal (249) (1.3 g, 2.7 mmol) and lithium (350 mg, 50 mmole) in ammonia (120 ml) and tetrahydrofuran (25 ml) was allowed to proceed for 20 h before workup. Separation by chromatography gave starting material (53 mg, 4%); high R_f oxepanols (251) (15-20 mg, 1-2%); diol (211) (740 mg, 56%) and lower R_f oxepanols (250) (382 mg, 30%).

Reduction of Oxepanols (250) to Diol (211)

The crude oxepanols (250) (340 mg, 1 mmole) were reduced in ammonia/tetrahydrofuran (10:1) and lithium (35 mg, 5 mmole) Workup after 22 h gave the crude products (380 mg) which after preparative t.l.c. (ether/hexane 1:4) gave the diol (211) (130 mg, 38%) and recovered oxepanol (250) (126 mg, 37%) contaminated with some furan reduction products.

Preparation of (4*R*,6*R*,8*R*/*S*)-6-Acetoxy-1,11-di(furan-3'-yl)-4, 8-dimethylundecan-4-ol (211a)

The diol (211) was acetylated using pyridine and acetic anhydride for 15 h at room temperature as previously described.

Isolation by chromatography gave the *acetate* (211a) (95%). ν_{max} (film) 775, 870, 880, 1025, 1155, 1240, 1515, 1730, 3160 (w) 3500 cm^{-1}. ^{1}H n.m.r. (CCl$_4$): δ 7.17 (2H, m, (H5')$_2$); 7.04 (2H, m, (H2')$_2$); 6.09 (2H, (H4')$_2$); 5.02 (1H, m, H6); 2.33 (4H, m, (H1)$_2$ and (H11)$_2$); 2.0 (1H, brs, OH); 1.90 (3H, s, COCH$_3$); 1.08 (3H, s, 4-CH$_3$); 0.9 (3H, 2d, 8-CH$_3$). ^{13}C n.m.r. see appendix.

Dehydration of Hydroxy-Acetate (211a)

The hydroxy-acetate (211a) (910 mg) in pyridine was treated with thionyl chloride at 0° as previously described to give the crude alkene acetates (750 mg).
Reduction with lithium aluminium hydride gave the crude mixed alkenols (660 mg, 86%). Preparative t.l.c. gave two major products and a low R$_f$ product consistent with the C4 or C6 epimerised diols (211) (62 mg, 9%). ν_{max} (film) 725, 780, 880,

1030, 1070, 1160, 1510, 3380 cm^{-1}. ^{1}H n.m.r. (CCl$_4$): δ 7.13 (2H, m, (H5')$_2$); 7.0 (2H, m, (H2')$_2$); 6.07 (2H, m, (H4')$_2$); 4.2 (2H, brs, OH, H6); 2.33 (4H, m, (H1)$_2$ and (H11)$_2$); 1.18 ($^3/_2$H, s, 4-CH$_3$); 1.10 ($^3/_2$H, s, 4-CH$_3$); 0.88 (3H, d, J 6Hz, 8-CH$_3$). M/e 348 (M$^{+\cdot}$) 330, 239, 236, 221, 203, 181, 179, 163-161, 153-149, 137-134, 122, 110, 95 b.p. 82, 81.

The lower R$_f$ of the alkenol products (130 mg, 20%) was resolved by preparative chromatography (ethyl acetate/benzene, 1:4) into two isomers (approx. 1:1). The higher R$_f$ isomer was (*E*,6*R*,8*R* or 8*S*)-1,11-di(furan-3'-yl)-4,8-dimethylundec-4-en-6-ol (255) (Found: m/e 330.2190. C$_{21}$H$_{30}$O$_3$ requires 330.2195). ν_{max} (film) 705, 780, 875, 1020, 1060, 1155, 1500, 1560 (w), 3400, 3600 (w) cm^{-1}. ^{1}H n.m.r. (CCl$_4$): δ 7.17 (2H, m, (H5')$_2$); 7.05 (2H, m, (H2')$_2$); 6.10, (2H, m, (H4')$_2$); 5.09 (1H, brd, J 8.5Hz, H5); 4.29 (1H, dt, J 8.5,4.4Hz, H6); 2.36 (4H, t, J 7Hz, (H1)$_2$ and (H11)$_2$); 1.63 (3H, brs, 4-CH$_3$); 0.90 (3H, brd, J 5Hz, 8-CH$_3$). ^{13}C n.m.r. see appendix. M/e 330 (M$^{+\cdot}$), 312, 297, 203, 179, 161, 151-149, 137-133, 121, 109, 107, 105, 97-94, 82, 81 (b.p.), 71, 69, 67, 55, 53.

The lower R$_f$ allylic alcohol was (*E*,6*R*,8*R* or 8*S*)-1,11-di(furan-3'-yl)-4,8-dimethylundec-4-en-6-ol (255) (Found: m/e 330.2187. C$_{21}$H$_{30}$O$_3$ requires 330.2195). ν_{max} (film) 705, 780, 870, 1020, 1060, 1155, 1505, 1570 (w), 3400, 3500 (w) cm^{-1}. ^{1}H n.m.r. (CCl$_4$): δ 7.19 (2H, m, (H5')$_2$); 7.05 (2H, m, (H2')$_2$); 6.10 (2H, m, (H4')$_2$); 5.05 (1H, brd, J 8.5Hz, H5); 4.27 (1H, dt, J 8.5,5.6Hz, H6); 2.35 (4H, t, J 7Hz, (H1)$_2$ and (H11)$_2$); 1.63 (3H, brs, 4-CH$_3$); 0.90 (3H, d, J 5Hz, 8-CH$_3$). ^{13}C n.m.r. see appendix. M/e 330 (M$^{+\cdot}$), 312, 297, 203, 179, 161, 151-149, 137-133, 121, 109, 107, 105, 97, 95, 82, 81, 71, 69, 67, 55, 53.

The higher R_f non allylic alkenols (343 mg, 52%) were separated by preparative chromatography on silver nitrate coated (10%) silica (ethyl acetate/benzene, 1:9). The lower R_f pair of isomers, (103 mg, 15%) were the epimeric methylene alcohols. The highest R_f epimer was (6*R*,8*R* or 8*S*)-1,11-di(furan-3'-yl)-8-methyl-4-methyleneundecan-6-ol (256) (30 mg) (Found: m/e 330.2196. $C_{21}H_{30}O_3$ requires 330.2195). ν_{max} (film) 715, 770, 875, 1025, 1065, 1110, 1155, 1505, 1560 (br.w), 1640, 3450 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.20 (2H, m, $(H5')_2$); 7.07 (2H, m, $(H2')_2$); 6.12 (2H, m, $(H4')_2$); 4.80 (2H, brs, 4-CH_2); 3.67 (1H, brm, H6); 2.40 (4H, t, J 6Hz, $(H1)_2$ and $(H11)_2$); 2.04 (4H, m, $(H3)_2$ and $(H5)_2$); 0.88 (3H, d, J 6Hz, 8-CH_3). ^{13}C n.m.r. see appendix. M/e 330 ($M^{\dot{+}}$), 312, 181, 150, 131, 136-134, 121, 109, 107, 95, 94, 82 (b.p.), 81, 69, 67, 55, 53.

The lower R_f epimer was (6*R*,8*R* or 8*S*)-1,11-di(furan-3'-yl)-8-methyl-4-methyleneundecan-6-ol (256)(25 mg) (Found: m/e 330.2199 $C_{21}H_{30}O_3$ requires 330.2195). ν_{max} (film) 710, 770, 870, 1020, 1060, 1150, 1500, 1560 (w), 1640, 3405 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.18 (2H, m, $(H5')_2$); 7.05 (2H, m, $(H2')_2$); 6.10 (2H, m, $(H4')_2$); 4.77 (2H, brs, 4-CH_2); 3.60 (1H, brm, H6); 2.38 (4H, t, J 6Hz, $(H1)_2$ and $(H11)_2$); 2.04 (4H, m, $(H3)_2$ and $(H5)_2$), 0.90 (3H, d, J 6Hz, 8-CH_3). ^{13}C n.m.r. see appendix. M/e 330 ($M^{\dot{+}}$), 312, 181, 150, 137-134, 121, 109, 107, 95, 94, 82, 81, 71, 69, 67, 65, 57, 55.

The higher R_f products (one spot by t.l.c.) were the *E* and *Z* epimeric Δ^3 alkenols (207 mg). The mixture was esterified with 1,1'-biphenyl-4-carbonyl chloride in pyridine and the *E* and *Z* esters of the C8 epimers separated by h.p.l.c. (lichrosorb 10μ, ethyl acetate/hexane, 1.5:98.5).

The isomers eluted first were identified as *Z* (6*R*,8*R* and 8*S*)-1,1'-biphenyl-4-carboxylate of (257) (47 mg, 40% of the mixture) (>95% pure by h.p.l.c.). ^{1}H n.m.r. (CCl_4): δ 7.95 (2H, aromatic); 7.6-7.0 (11H, aromatic and $(H2')_2$ and $(H5')_2$), 6.08 (2H, m, $(H4')_2$); 5.20 (2H, brm, H3 and H6); 2.30 (8H, m, $(H1)_2$, $(H2)_2$, $(H5)_2$ and $(H11)_2$); 1.77 (3H, brs, 4-CH_3); 0.95 (3H, apparent doublet, 8-CH_3).

The isomer eluted later was identified as *E* (6*R*,8*S* and 8*R*)-1,1'-biphenyl-4-carboxylate of (257) (76 mg, 60% of the mixture, >95% pure by h.p.l.c.). ^{1}H n.m.r. (CCl_4): δ 7.92 (2H, d, aromatic); 7.5-6.9 (11H, aromatic, $(H2')_2$ and $(H5')_2$); 6.05 (2H, brs, $(H4')_2$); 5.20 (2H, brm, H3 and H6); 2.25 (8H, m, $(H1)_2$, $(H2)_2$, $(H5)_2$ and $(H11)_2$); 1.67 (3H, brs, 4-CH_3); 0.95 (3H, apparent d, 8-CH_3).

Reduction of *E*/*Z* 1,1'-biphenyl-4-carboxylates of (257) to *E* and *Z* Furospongin-1 isomers (257*E*) and (257*Z*).

(i) The *Z* (6R,8S and 8R)-1,1'-biphenyl-4-carboxylate of (257) was reduced with lithium aluminium hydride (2 eq.) in ether. Preparative chromatography gave the pure Z (6*R*,8*S* and 8*R*)-1,11-di(furan-3'-yl)-4,8-dimethylundec-3-en-6-ol (257*Z*) (47 mg, overall) $[\alpha]_D$ + 14° ± 2° (C, 1.3 $CHCl_3$) (Found: m/e 330.228.

$C_{21}H_{30}O_3$ requires 330.220). ν_{max} (film) 780, 875, 1025, 1060, 1380, 1460, 1505, 1570 (w), 3500 cm^{-1}. ^{1}H n.m.r. (CDCl$_3$): δ 7.23 (2H, m, (H5')$_2$); 7.13 (2H, m, (H2')$_2$); 6.20 (2H, m, (H4')$_2$); 5.33 (1H, m, H3); 3.78 (1H, m, H6); 2.38 (6H, m, (H1)$_2$, (H2)$_2$ and (H11)$_2$); 2.08 (2H, m, (H5)$_2$); 1.70 (3H, s, 4-CH$_3$); 0.92 (3H, d, J 6Hz, 8-CH$_3$). ^{13}C n.m.r. see appendix. M/e 330 (M$^{+\cdot}$), 312, 256, 230, 181, 150, 149, 135, 105, 95, 94, 82, 81 (b.p.), 69.

The *E*(6*R*,8*S* and 8*R*) 1,1'-biphenyl-4-carboxylate of (257) was similarly reduced to give a colourless oil of *E*(6*R*,8*S* and 8*R*)-1,11-di(furan-3'-yl)-4,8 dimethylundec-3-en-6-ol (257*E*) (furospongin-1 and its epimer) (76 mg overall) $[\alpha]_D$ + 10.5° ± 1.5° (C, 4.3 in CHCl$_3$) (Found: m/e 330.227. $C_{21}H_{30}O_3$ requires m/e 330.220). ν_{max} (film) 780, 880, 1030, 1070, 1165, 1390, 1450, 1470, 1510, 1580 (w), 3500 cm^{-1}. ^{1}H n.m.r. (CDCl$_3$): δ 7.22 (2H, m, (H5')$_2$, 7.12 (2H, m, (H2')$_2$); 6.20 (2H, m, H4'); 5.22 (1H, brt, H3); 3.70 (1H, m, H6); 2.38 (6H, m, (H1)$_2$, (H2)$_2$ and (H11)$_2$); 2.1 (2H, m, (H5)$_2$), 1.57 (3H, s, 4-CH$_3$); 0.88 (3H, d, J 6Hz, 8-CH$_3$). ^{13}C n.m.r. see appendix. M/e 330 (M$^{+\cdot}$), 312, 230, 181, 150, 135, 109, 107, 105, 95, 94, 82 (b.p.) 81, 69.

The alcohols (257*E*) showed no separation using h.p.l.c. (SiO$_2$ or AgNO$_3$/SiO$_2$) and a variety of solvents.

The 8R epimers of (257*E*), were converted to the trimethylsilyl ethers using trimethylsilyl chloride and hexamethyldisilazane in pyridine. The silyl ethers showed no separation by g.c. using the OV-17, SE-30, FFAP or Carbowax 20M stationary phases.

Attempted Substitution Reaction of Mesylates (150/151) with Lithium and sodium Halides

(i) The mesylates (150/151) (140 mg, 0.42 mmole) in dry dimethylformamide (3 ml) containing lithium chloride (dry 150 mg, 3.5 mmole). After 2 h at room temperature the homogeneous solution showed only mesylate by t.l.c. The mesylate remained unreactive after 1 h at 100° but gave decomposition products after 15 h at 100° . Workup with water and petroleum ether extraction gave a yellow oil (50 mg) which was shown by n.m.r. to be largely ring opened compounds with little or no elimination or required substitution products.

(ii) The use of lithium bromide in dimethyl formamide gave a similar result.

(iii) The use of lithium bromide in either dimethyl sulphoxide or hexamethylphosphorictriamide after 5 days at 40° gave unchanged starting material on workup.

(iv) The mesylate (150) (30 mg) was heated under reflux with sodium iodide (dry, 50 mg) in acetone (dry, 5 ml) and showed no products by t.l.c. after 5 days.

Attempted Preparation of the Acetal Chloride (263)

(i) The alcohol (86b) (200 mg, 0.75 mmole) was heated under reflux with triphenylphosphine (dry, 240 mg, 0.9 mmole) in carbon tetrachloride (dry, 10 ml). After heating for 18 h workup gave recovered starting material and traces (by t.l.c.) of higher R_f products.

(ii) The alcohol (108 mg) in hexane (10 ml) and pyridine (2 ml) was stirred at 0° while thionyl chloride (0.3 ml) was slowly added. After 1 h the solution contained mostly starting material with traces of other products (t.l.c. examination). After a further 30 min at r.t. workup including hexane extraction gave a yellow oil (55 mg) which contained mostly starting material and traces of at least five other products (t.l.c.)

Attempted Reduction of Mesylates (150) with Sodium Borohydride in Dimethyl Sulphoxide

The mesylate (150) (90 mg) was stirred in dimethyl sulphoxide (3 ml) containing sodium borohydride (100 mg) as described by Hutchins, Hoke, Klogh and Koharski.[94]

After 18 h at room temperature only starting material was detected by t.l.c. Heating the mixture to 100° caused the formation of a complex mixture which was not examined.

Dehydration of Diol (124) to (*R*) 9-(furan-3'-yl)-2,6-dimethylnon-6-en-4-ol (253), (*R*) 9-(furan-3'-yl)-2,6-dimethylnon-5-en-4-ol (252) and (*R*), 9-(furan-3'-yl)-2-methyl-6-methylenenonan-4-ol (254).

(i) The diol (124) (300 mg, 1.20 mmol) was acetylated (pyridine/acetic anhydride, 70 , 2 h) and workup gave the hydroxy-acetate (124a) (320 mg, 91%). This was used without further purification. ^{1}H n.m.r. (CCl_4): δ 7.3,7.2 (each 1H, m, H5' and H2'); 6.2 (1H, m, H4'); 5.15 (1H, m, H4); 2.4 (2H, m, $(H9)_2$); 2.0 (3H, s, CH_3CO); 1.1 (3H, s, 6-CH_3); 0.9 (6H, d, J 6Hz, 2-CH_3 and $(H1)_3$).

(ii) The hydroxy acetate (124a) (300 mg, 1.01 mmole) in dry pyridine (1 ml) and ether (4 ml) was stirred at -10° while thionyl chloride (4 drops) was added. The white suspension was stirred for a further 5 min at 0° and 5 min at room temperature. After quenching with brine (3 ml) separation of the organic layer, extraction of the aqueous with hexane (3 x 10 ml) and washing the combined extracts (dilute hydrochloric acid (5 ml), water, sodium bicarbonate, water) gave on evaporation a colourless oil (235 mg).

Preparative chromatography gave recovered acetate (124a) (80 mg, 27%) and the alkene acetate mixture (155 mg, 80%).

(iii) Reduction of the mixed alkene acetates with lithium aluminium hydride (0.1 g) in dry ether (20 ml), as previously described, gave the mixed alkenols (120 mg). Preparative chromatography (ether/hexane, 1:3) gave a high R_f product identified by ^{1}H n.m.r. as a mixture of (253) and (254), which were separated as described below. The low R_f product was a colourless oil of alkenol (*R*, *E/Z*) 9-(furan-3′-yl)-2,6-dimethylnon-5-en-4-ol (252) (41 mg, 31% of the products) b.p. 100°/0.01 (block) (Found: C, 76.35; H, 9.92. $C_{15}H_{24}O_2$ requires C, 76.22; H, 10.24%, m/e 236.1776. $C_{15}H_{24}O_2$ requires m/e 236.1774). ν_{max} (film) 790, 885, 1035, 1175, 1375, 1390, 1505, 3400 cm^{-1}, ^{1}H n.m.r. (CCl_4): δ 7.2 (1H, m, H5′); 7.09 (1H, m, H2′); 6.12 (1H, m, H4′); 5.09 (1H, d, q, J 8.8, 1Hz H5); 4.3 (1H, m, H4); 2.37 (2H, apparent t, J 6Hz, $(H9)_2$); 1.65 (3H, brs, 6-CH_3); 0.89 (6H, d, J 6Hz, 2-CH_3 and $(H1)_3$). ^{13}C n.m.r. see appendix. M/e 236 ($M^{+\cdot}$), 218, 203, 179, 161, 151-149, 137-135, 133, 127, 97, 95, 94, 82, 81 (b.p.), 71, 69-65, 57, 55, 53.

The mixture of alkenols of higher R_f were separated on silica impregnated with silver nitrate (10%) (ether/hexane 4:6). The higher R_f product isolated as a colourless oil, was (*R*,*E* and *Z*), 9-(furan-3'-yl)-2,6-dimethylnon-6-en-4-ol (253) (56 mg, 48% of isolated products) b.p. 100°/0.01 mm (block) (Found: C, 76.36; H, 10.41. $C_{15}H_{24}O_2$ requires C, 76.22; H, 10.24%). ν_{max} (film) 780, 880, 1030, 1065, 1140, 1165, 1510, 3450 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.18 (1H, m, H5'); 7.05 (1H, m, H2'); 6.10 (1H, m, H4'); 5.16 (1H, m, H7); 3.60 (1H, m, 4-H); 1.57 (3H, brs, 6-CH_3, E isomer); 1.75 (3H, brs, 6-CH_3 Z isomer); 0.88 (6H, d, J 6Hz, 2-CH_3 and $(H1)_3$). ^{13}C n.m.r. see appendix. M/e 236 ($M^{\ddagger}$), 218, 203, 179, 175, 167, 161, 151, 150, 149, 138-134, 121, 107, 95, 94, 82 (b.p.), 81, 69, 57, 55, 53.

The lower R_f product, isolated as a colourless oil, was (*R*)-9-(furan-3'-yl)-2-methyl-6-methylenenonan-4-ol (254) (20 mg, 17%) b.p. 100°/0.01 mm (block) (Found: C, 76.40; H, 10.27. $C_{15}H_{24}O_2$ requires C, 76.22; H, 10.24%). ν_{max} (film) 780, 880, 900, 1030, 1065, 1165, 1510, 1645, 3400 cm^{-1}. ^1H n.m.r. (CCl_4): δ 7.18 (1H, m, H5'); 7.05 (1H, m, H2'); 6.08 (1H, m, H4'); 4.78 (2H, brs, 6-CH_2); 3.60 (1H, m, H4); 2.37 (2H, t, J 6Hz, $(H9)_2$); 0.90 (6H, d, J 6Hz, 2-CH_3 and $(H1)_3$). ^{13}C n.m.r. see appendix. M/e 236 ($M^{\ddagger}$), 218, 203, 179, 175, 167, 161, 150, 149, 95, 94, 82 (b.p.), 81, 69.

(ii) When the 1,1'-biphenyl-4-carboxylate was similarly prepared and dehydrated at 0° with thionyl chloride, the esters hydrolysed, the recovered yields of alkenols (252), (253) and (254) were 30%, 43% and 16% respectively.

(iii) Reaction of the hydroxy acetate (124a) with methane-sulphonyl chloride in hexane containing triethylamine at 0° (30 min), followed by reduction of the ester with lithium aluminium hydride gave the mixed alkenols (32%), in approx. the same ratio as (ii), together with polar products.

(iv) The use of phosphorus oxychloride and pyridine at 0 with the hydroxy acetate (124a) gave no change in the isomeric ratio of alkenols (80%).

Attempted isomerisation of (253) and (254)

To a mixture of *E* and *Z* isomers of alkenols (253) and (254) (approx. ratio 7:3, 100 mg) in d_1-chloroform (0.5 ml) in an n.m.r. tube, was added two drops of trifluoroacetic acid. The mixture was shaken and the n.m.r. spectrum taken after 10 min, 45 min, and 15 h. No change was observed in the isomeric ratio from examination and integration of the n.m.r. spectrum.

Oxidation of alcohol (90) to (1'R,3'*S*,5'*R*) 1'-{(furan-3''-yl)-5'-methyl-2',8'-dioxabicyclo[3.2.1]oct-3'-yl}-2-methylpropan-1-one (264)

Method A: The alcohol (90) (mixed isomers, 132 mg, 0.5 mmole) in dry methylene chloride (2 ml) was added to a suspension of pyridinium chlorochromate (200 mg) in methylene chloride (20 ml) with stirring. After 4 h considerable starting material was still present (evident by t.l.c.) and although alcohol was detected after 15 h the mixture was worked up. Ether (50 ml) was added and the suspension filtered through Florisil which was washed with ether (50 ml). Evaporation of the ether gave a pale yellow oil (50 mg) which was purified by preparative chromatography (ether/hexane, 1:1). Recovered alcohol (90) (33 mg, 25%)

and the required *ketone* (264) (15 mg, 12%) was isolated.

Method B: An improved method using an adaption of the procedure outlined by Swern[67] is described below.

To dry methylene chloride (10 ml) at -60° was added oxalyl chloride (280 µl, 3.3 mmole) followed, after 5 min, by dimethyl sulphoxide (530 µl, 7.5 mmole) in a little dry methylene chloride (100 µl) to prevent freezing. After a further 5 min, the alcohol (90) (310 mg, 1.1 mmole) in methylene chloride (2 ml) was added dropwise and the solution stirred at -60° for 20 min. Triethylamine (1.3 ml) was added slowly at -60° and the solution allowed to reach room temperature. Water (5 ml) was added, the mixture stirred and the organic layer separated. The aqueous layer was extracted with methylene chloride, the combined organic extracts dried and the solvent removed under reduced pressure. Preparative chromatography (ether/hexane 1:1) gave alcohol (90) (77 mg, 25%) and also the *ketone* (264) (196 mg, 64% or 84% based on unrecovered alcohol) b.p. 130° / 0.1 mm (decomp.) (Found: C, 68.0; H, 7.6. $C_{15}H_{20}O_4$ requires C, 68.2; H, 7.6%). ν_{max} (film) 785, 879, 900, 925, 1020, 1065, 1240, 1500, 1600, 1720 cm^{-1}. ^{1}H n.m.r. (CCl_4): δ 7.50 (1H, m, H2"), 7.40 (1H, m, H5"); 6.47 (1H, m, H4"); 4.36 (1H, t, J 8Hz, H3'); 3.18 (1H, m, H2); 1.43 (3H, s, 5'-CH_3); 1.11 (6H, d, J 7Hz, 2-CH_3 and $(H3)_3$). M/e 265 ($M^{+\cdot}$ + 1), 264 ($M^{+\cdot}$), 247, 235, 221, 194, 193, 165, 147, 96, 95 (b.p.), 71.

Attempted Equilibration of Ketone (264)

(a) A mixture of the ketone (264) (approx. 15 mg) in methanol (2 ml) containing sodium methoxide (approx. 15 mg) was allowed to stand at room temperature for 15 h. The methanol was removed under reduced pressure, water (2 ml) added. After 1 h the solution was extracted with methylene chloride (4 x 1 ml). The methylene chloride was dried and the solvent removed under reduced pressure. The ^{1}H n.m.r. of the residue showed no change to starting material. The product was also identical to starting material by t.l.c.

(b) Similarly, d^1-methanol was used with D_2O workup. The n.m.r. spectrum of isolated products showed complete exchange of H2 (6H, singlet at δ 1.1 ppm) and partial exchange (40-50%) of H3' by integration (0.4-0.5H at δ 4.4 ppm).

Attempted conversion of alcohol (90a) to alcohol (90b)

The method of Mitsunobu[164] was followed using alcohol (90a) (188 mg, 0.71 mmole), triphenylphosphine (186 mg, 0.71 mmole), benzoic acid (86 mg, 0.71 mmole) and diethyl azodicarboxylate (124 mg, 0.71 mmole) in tetrahydrofuran. No new products were detected after 5 h at room temperature. The solution was heated under nitrogen to 50-60° for 14 h. Workup gave unchanged alcohol (90a) (90% recovery) without any ester products.

Resolution of Racemic 2-Phenylbutanoic acid

The racemic 2-phenylbutanoic acid was resolved using cinchonidine according to Delepine and Lareze.[161]

The (+) acid was obtained with $[\alpha]_D^{22}$ + 80.8° (C, 3.8 in benzene) indicating an optical purity of 83.5%.

The (-) acid was obtained with $[\alpha]_D^{22}$ - 74.4° (C, 4.5 in benzene) indicating an optical purity of 77%.

Synthesis of Enantiomeric 2-Phenylbutanoic anhydrides

(i) The acids were converted to the sodium salts by the neutralisation of the enantiomeric acids in a minimal volume of methanol with sodium hydroxide (50% aqueous solution) using a trace of phenolphthalein as indicator. The solvents were removed and the solid sodium salts dried under vacuum (50°/0.01 mm for 5 h).

(ii) The sodium salts were converted to the anhydrides by treatment with a limited quantity of oxalyl chloride in ether as described by Horeau[64].

The sodium salt of (+) or (-) 2-phenylbutanoic acid (6.55 g) was suspended in dry ether (60 ml) at 0° while oxalyl chloride (3.0 ml) was added dropwise. After stirring overnight the mixture was filtered, the salt washed with ether (20 ml) and the solvent removed from the filtrate. The anhydrides were obtained as almost colourless viscous oils (>95% yields in each case).

Preparation of (*RR*) and (*RS*)-amides (265) and (266)

The amides were prepared by reaction of the (*R*) and (*S*) anhydrides with *R*(+)-2-phenylethylamine (>99%) in the presence of pyridine over 30 min, to give the corresponding *RR* and *RS* amides in quantitative yields. Each was recrystallised from ether/hexane.

The *RR* amide (265) was obtained as colourless crystals, m.p. 76-78° (97.0 ± 0.05% pure by g.c.). This isomer had the lower R_f by t.l.c. (ethyl acetate/hexane or ether/hexane mixtures) but was eluted first using g.c.

The *RS* amide (266) was obtained as colourless crystals, m.p. 118-119° (98.3 ± 0.07% pure by g.c.). This isomer had the higher R_f by t.l.c. but was eluted after the *RR* amide on g.c.

The g.c. analyses of the amides used in the Horeau's determinations (see Chapter 8), were carried out using a glass column (2.2 m x 3 mm) packed with 5% OV-225 on Varaport 30 (80-100#) at 225° using nitrogen as carrier gas. These conditions gave baseline separation of the *RR* and *RS* amides with good peak symmetry. Peak areas were calculated using an electronic integrator. Standard mixtures of the *RR* and *RS* amides were prepared and analysed (see Table 8.31).

Horeau's Determination of Absolute Configuration

The majority of the alcohols tested (see Chapter 8) were analysed using the Brooks and Gilbert[136] modification with some changes.

The alcohol (5-15 µmol) was dissolved in dry pyridine (50 µl) and the treated with racemic 2-phenylbutyric anhydride (1 molar excess). Reactions were allowed to proceed for either 1.5-2 h at 40°, as recommended by Gilbert and Brooks,[136] or for 15-18 h at room temperature. Unreacted anhydride in the mixture was reacted (*R*)-2-phenylethylamine (2 equivalents) with thorough agitation and after 15 min diluted with ethyl acetate (200 µl).

In each case a parallel reaction was run using pure cyclopentanol, isopropanol or hexan-3-ol. Using these alcohols, assuming that the detector response to each amide was the same, the degree of kinetic resolution resulting in the formation of the amides was found to be small and variable (generally 1-2% in favour of the *RR* amide).

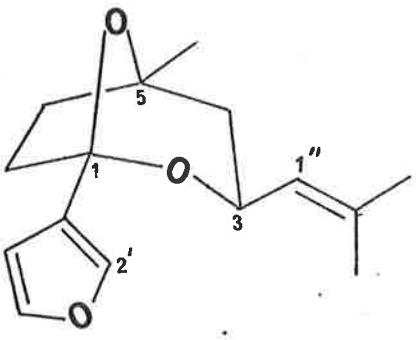
Reproducibility between injections was generally < ± 0.3%, with each mixture being analysed in duplicate or until the reproducibility was within ± 0.3%.

Typically, each g.c. analysis required 20-25 min with interfering peaks of long retention times sometimes being encountered and allowed to elute at 250° before another injection was made.

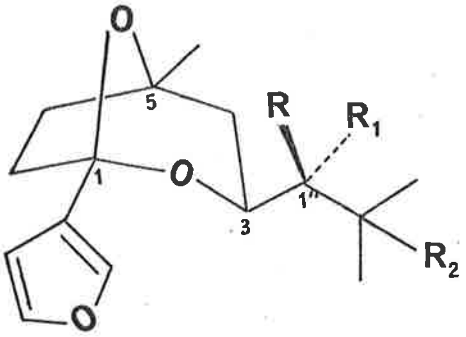
H.p.l.c. was used to analyse the amide mixtures where interference was suspected from the g.c. trace. A column (250 mm x 3 mm) packed with Lichrosorb Sl-60 (10 μ) was used with a U.V. detector (254 n.m) and integrator. In contrast to g.c. the *RS* amide was eluted first.

APPENDIX A

^{13}C N.M.R. DATA



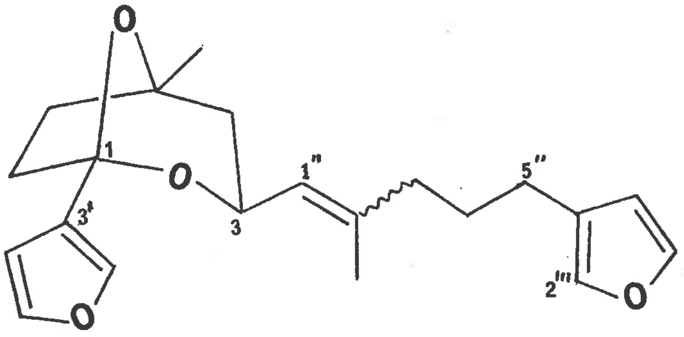
(47)



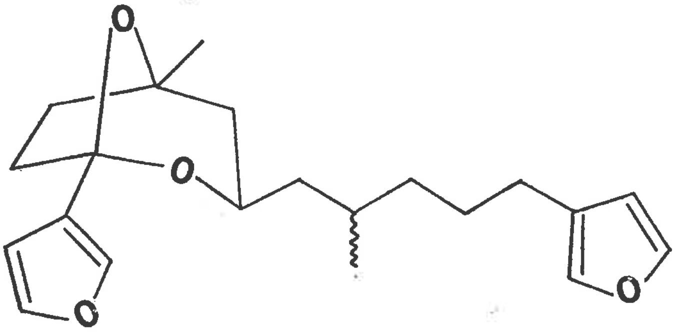
R = H R' = H R^2 = H (94)
R = OH R' = H R^2 = H (90b)
R = OH R' = H R^2 = OH (86b)
R = H R' = OH R^2 = OH (86a)

Chemical Shift in ppm (multiplicity)

compound / carbon	(47)	(94)	(90b)	(86b)	(86a)
2'	139.6 d	139.9 d	139.8	139.4	139.4 d
3'	127.2 s	127.8 s	127.3	126.8	126.8 s
4'	108.5 d	108.8 d	108.7	108.3	108.3 d
5'	142.6 d	142.9 d	143.2	143.1	143.0 d
1	103.5 s	103.6 s	104.0	103.7	103.5 s
3	67.2 d	67.8 d	70.7	69.6	70.8 d
4	42.7 d	45.4 t	38.7	38.3	38.8 t
5	80.9 s	80.7 s	81.0	81.3	81.1 s
6	37.2 t	37.7 t	37.5	37.3	38.8 t
7	34.9 t	35.2 t	35.0	34.5	32.0 t
1"	125.5 d	43.3 t	78.5	77.2	72.3 d
2"	135.2 s	24.4 d	30.0	72.9	78.4 s
3"	25.7 q	23.3 2	19.9	26.7	26.1 q
2"-CH_3	18.3 q	22.7 q	17.1	25.9	26.7 q
5-CH_3	26.0 q	26.3 q	26.2	25.9	26.7 q



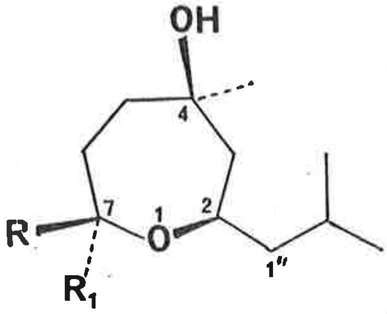
E/Z (248)

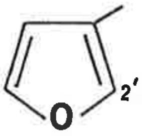


(249)

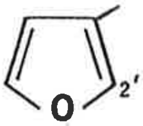
Chemical Shift in ppm

compound carbon	E/Z (248)		(249)	
2'	139.4	140.0	140.0	
3'	127.6	126.7	127.7	
4'	108.8		108.8	
5'	143.0		143.0	
2'''	139.2	139.1	139.1	
3'''	125.0		125.3	
4'''	111.1		111.3	
5'''	143.0		143.0	
1	103.8		103.7	
3	63.3	66.8	68.0	67.5
4	42.7	43.1	43.6	
5	81.0		81.1	
6	37.3		37.5	
7	35.0		35.8	
1"	125.2	125.9	43.2	
2"	139.5		27.4	25.0
3"	39.0(E)	31.8 (Z)	36.6	35.2
4"	28.0	24.5	29.1	
5"	28.4	24.4	28.7	
2"-CH_3	16.3(E)	27.3(Z)	19.7	20.2
5-CH_3	26.1		26.2	

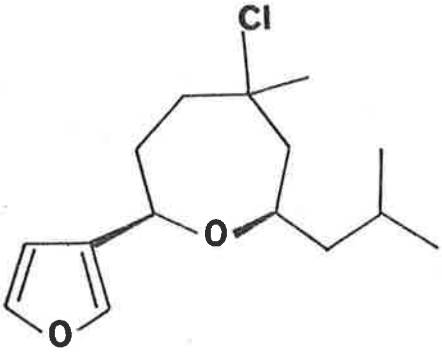


R = H R_1 = 

(123b)

R = 

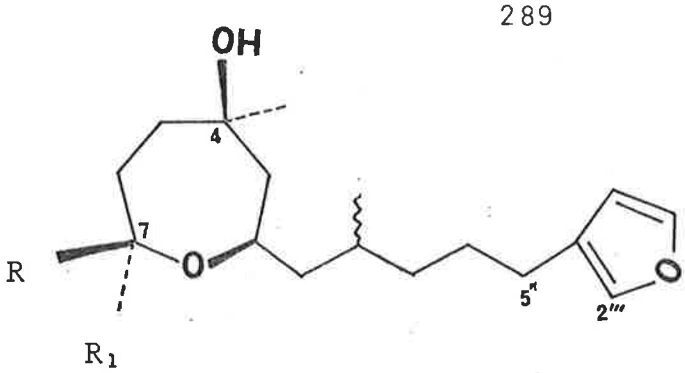
R_1 = H (123a)

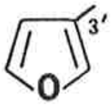


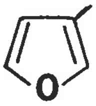
(131)

Chemical Shift in ppm (multiplicity)

compound / carbon	(123b) (high Rf, mp 68°)	(123a) (low R_f, mp 42°)	(131)
2'	138.8 d	139.2 d	139.8 d
3'	128.3 s	128.3 s	129.2 s
4'	109.2 d	109.2 d	110.5 d
5'	143.3 d	143.3 d	143.4 d
2	77.9 d	68.5 d	66.5 d
3	50.0 t	49.9 t	53.6 t
4	72.3 s	72.8 s	74.4 s
5	39.0 t	41.2 t	40.5 t
6	31.5 t	30.1 t	46.4 t
7	78.2 d	69.2 d	71.4 d
1"	47.5 t	45.7 t	28.8 t
2"	31.3 -	26.5 d	24.5 d
3"	23.4 -	23.1 -	23.2 q
2"-CH_3	21.9 q	22.1 q	22.2 q
4-CH_3	24.6 q	24.4 q	35.3 q

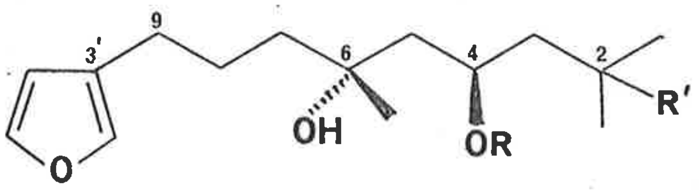


R =  R_1 = H (**251**)

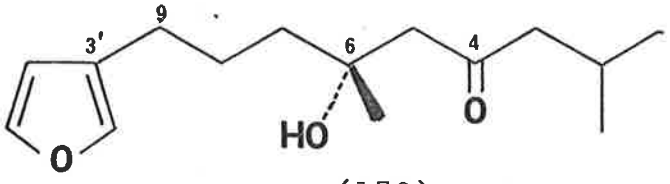
R = H R_1 =  (**250**)

Chemical Shift in ppm (multiplicity)

compound / carbon	(250)	(251)
2'	138.8 d	139.3
3'	128.4 s	128.4
4'	109.2 d	109.9
5'	143.2 d	143.3 d
2	77.7 d	69.5 69.2 d
3	50.3 49.9	50.3 49.8
4	72.3 s	72.9 s
5	39.0	41.2
6	31.6	30.1
7	79.2	68.4 d
1"	45.7	44.2 44.0
2"	27.2	28.9 26.6
3"	37.4 36.0	37.0 36.4
4"	29.5	29.4
5"	27.5	27.2
2'''	139.1 d	139.3
3'''	125.5 s	125.5
4'''	111.3 d	111.1
5'''	142.8 d	142.8
2"-CH_3	20.3 19.3	20.0 19.3
4-CH_3	25.1	25.1



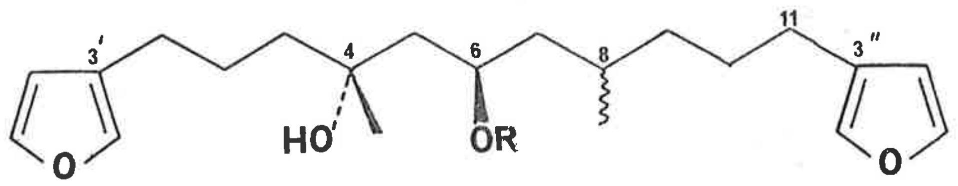
R = H R$_1$ = H (124)
R = COCH$_3$ R$_1$ = H (124a)
R = H R$_1$ = OH (183)



(176)

Chemical Shift in ppm (multiplicity)

compound / carbon	(124)	(124a)	(183)	(176)
2'	138.9 d	139.1 d	139.1 d	139.1 d
3'	124.8 s	125.1 s	125.2 s	125.2 s
4'	110.9 d	111.1 d	111.1 d	111.2 d
5'	142.8 d	142.8 d	143.0 d	143.0 d
1	23.2 q	23.0 q	31.9 q	24.6 q
2	28.8 d	24.4 d	71.8 q	26.9 d
3	46.8 t	45.3 t	47.2 t	52.2 t
4	67.4 d	70.2 d	67.3 d	213.5 s
5	47.8 t	46.3 t	48.8 t	53.7 t
6	73.6 s	71.5 s	73.6 s	71.8 s
7	40.0 t	42.4 t	40.2 t	42.0 t
8	25.2 t	24.7 t	25.2 t	26.9 t
9	25.2 t	25.3 t	25.2 t	24.6 t
2-CH$_3$	22.3 q	22.3 q	29.6 q	22.7 q
6-CH$_3$	24.4 q	21.4 q	28.6 q	24.6 q
$\underline{\text{C}}\text{OCH}_3$	-	171.3 s	-	-
$\text{CO}\underline{\text{C}}\text{H}_3$	-	27.1	-	-

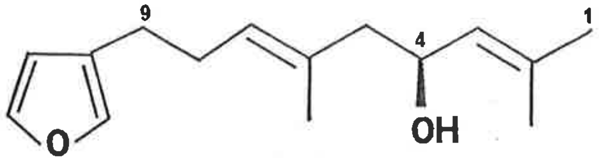


R = H (211)

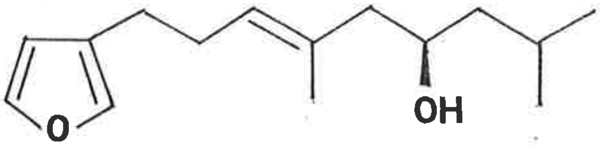
R = $COCH_3$ (211a)

Chemical Shift in ppm (multiplicity)

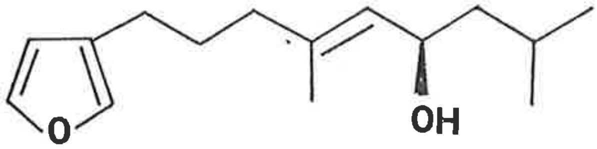
compound carbon	(211)	(211a)
2'	139.0 d	139.1
3'	125.1 s	125.3
4'	111.2 d	111.1
5'	143.0 d	143.0
1	25.3 t	25.3
2	25.0	25.0
3	40.1 t	45.9
4	73.6 s	71.7
5	47.1 t	46.6
6	67.4 67.0 d	70.3 70.0
7	46.4 46.1 t	43.5 42.4
8	27.3 d	24.5
9	37.2 36.6 t	36.9 36.4
10	28.7 t	27.1
11	27.3 t	27.3
2"	139.1 d	139.1
3"	125.4 s	124.3
4"	111.1 d	111.1
5"	143.5 d	143.0
4-CH_3	25.3 q	24.5
8-CH_3	20.3 19.5	19.9 19.6
$\underline{C}OCH_3$	–	171.4 171.1
$CO\underline{CH}_3$	–	29.5 29.3



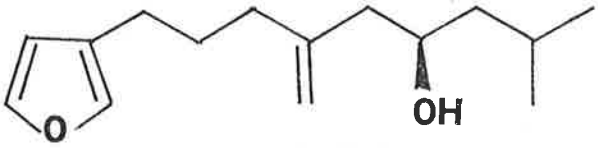
(8)



(253)



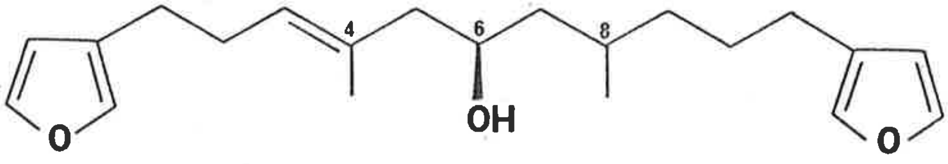
(252)



(254)

Chemical Shift

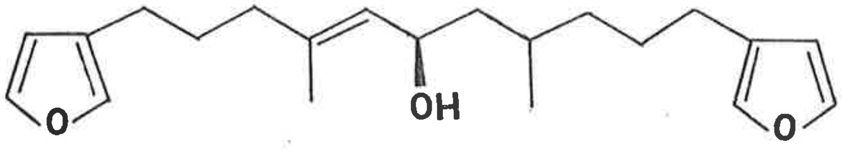
compound carbon	(8)	(252) (E/Z mixture)	(253) (E/Z mixture)	(254)
2'	139.1 d	139.1	139.1	139.2
3'	124.9 s	125.1	124.9	125.0
4'	111.1 d	111.1	111.1	111.1
5'	142.9 d	143.0	142.9	143.0
1	25.75q	22.7	23.4	23.4
2	134.7 s	26.1 25.3	24.8	24.9
3	128.1 d	47.1	46.6 46.4	46.6
4	66.3 d	66.6 67.1	66.8 67.9	67.2
5	48.2 t	129.7 129.0	48.7(E)40.8(Z)	45.2
6	132.6 s	138.1 138.5	133.1 132.9	146.7
7	127.8 d	39.1(E)32.0(Z)	129.1 127.9	35.6
8	24.9 t	24.8 24.4	24.8	24.4
9	28.5 t	28.7 28.1	28.5	28.2
2-CH$_3$	18.2 q	20.5	22.2	22.2
6-CH$_3$	16.3 q	16.5(E)23.1(Z)	16.1(E)23.8(Z)	112.7(6=CH$_2$



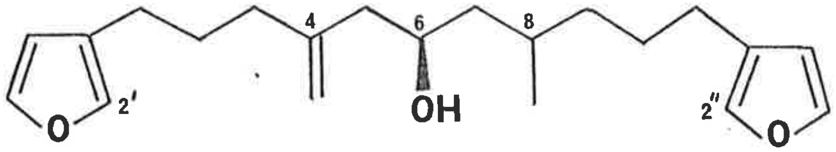
(257)

Chemical shift

Compound / carbon	(257) *E* isomers (C8 epimers)		(257) *Z* isomers (C8 epimers)	
2'	139.14		139.20	
3'	124.92		124.86	
4'	111.14		111.20	
5'	142.90		142.90	
1	28.54		28.60	
2	25.08		25.08	
3	128.08	127.96	128.39	128.29
4	133.12		132.88	
5	49.01	48.52	41.05	40.63
6	66.74	66.38	67.72	67.41
7	44.70		44.94	44.82
8	29.64	29.33	29.64	29.33
9	37.53	36.38	37.53	36.32
10	24.96		25.20	
11	27.39		27.39	
4-CH_3	16.29		23.81	
8-CH_3	20.35	19.43	20.39	19.31
2"	139.01		139.01	
3"	125.53		125.47	
4"	111.14		111.20	
5"	143.02		142.90	



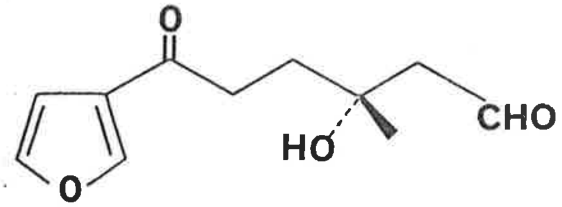
(255)



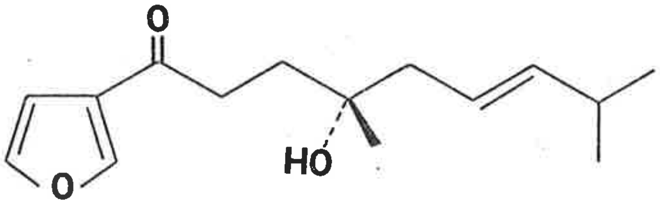
(256)

Chemical Shift in ppm

compound / carbon	(255) high R_f epimer	(255) low R_f epimer	(256) high R_f epimer	(256) low R_f epimer
2'	139.2	139.1	139.2	139.1
3'	125.6	125.5	125.4	125.5
4'	111.3	111.1	111.1	111.1
5'	143.0	143.0	142.9	143.0
1	28.2	28.2	28.2	28.2
2	25.2	25.0	25.1	25.1
3	39.2	39.2	35.6	35.5
4	138.0	138.5	146.7	146.7
5	128.2	128.9	44.8	44.8
6	66.8	67.0	66.8	67.2
7	45.4	45.3	45.5	45.1
8	29.4	29.5	29.3	29.6
9	37.3	36.8	37.5	26.3
10	24.5	24.4	24.4	24.4
11	27.6	27.5	27.4	27.5
4-CH_3	16.6	16.5	112.7	112.7
8-CH_3	19.8	20.2	19.4	20.4
2"	139.2	139.1	139.2	139.2
3"	125.6	125.5	125.4	125.4
4"	111.3	111.1	111.1	111.1
5"	143.0	143.0	142.9	142.9



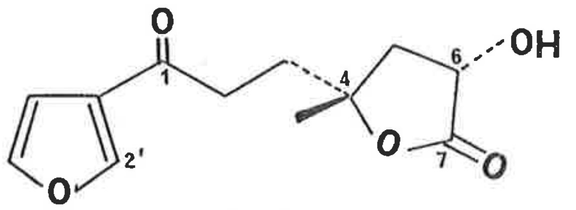
(87)



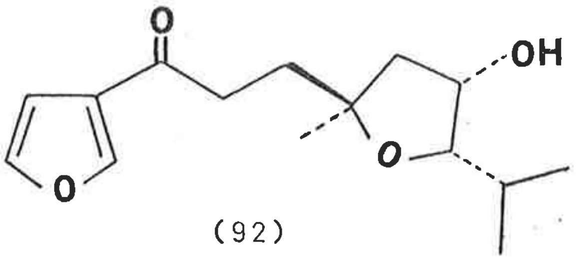
(136)

Chemical Shift in ppm (multiplicity)

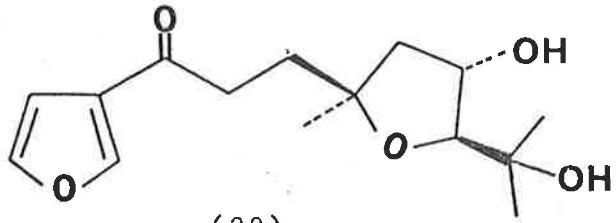
compound carbon	(87)	(136) (mixed *E*/*Z* isomers)
2'	147.7 d	147.5
3'	127.7 s	127.9
4'	108.7 d	108.8
5'	144.5 d	144.3
1	195.7 s	195.9
2	34.7 t	40.1
3	36.0 t	45.5
4	71.2 s	71.9
5	54.5 t	35.1(*E*) 31.2(*Z*)
6	203.2 d	121.8 121.6
7	-	141.4 142.8
8	-	31.2
9	-	23.0
4-CH_3	27.2 q	26.6
8-CH_3	-	22.6



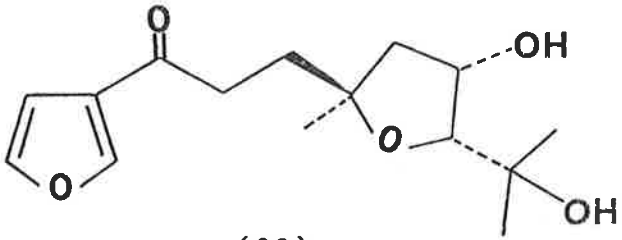
(85)



(92)



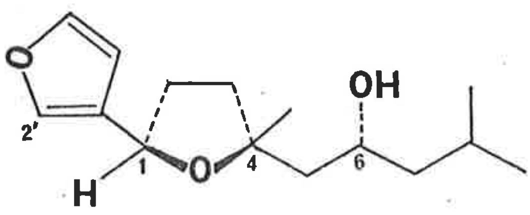
(88)



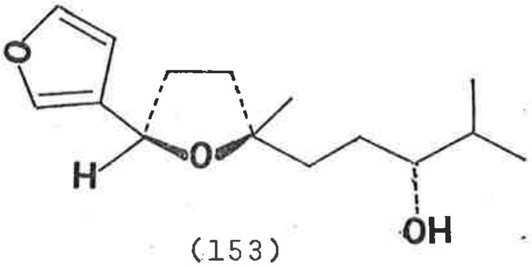
(89)

Chemical Shift in ppm (multiplicity)

compound carbon	(85)	(88)	(89)	(92)
2'	147.4 d	147.5 d	147.3 d	147.4 d
3'	127.5 s	128.0 s	128.0 s	128.0 s
4'	108.6 d	108.9 d	108.9 d	109.0 d
5'	144.4 d	144.5 d	144.4 d	144.4 d
1	193.5 s	195.6 s	195.1 s	195.4 s
2	34.5 t	35.6 t	35.8 t	35.4
3	35.1 t	36.1 t	36.1 t	35.8
4	83.5 s	81.9 s	82.0 s	80.5 s
5	41,4 t	47.2 t	47.9 t	48.5 t
6	68.6 d	72.7 d	74.3 d	73.4 d
7	177.0 s	90.0 d	85.4 d	88.2 d
8	-	71.1 s	72.2 s	27.9
9	-	25.8 q	29.0 q	20.5
4-CH_3	26.1 q	26.5 q	27.1 q	27.6
8-CH_3	-	25.7 q	24.8 q	18.8



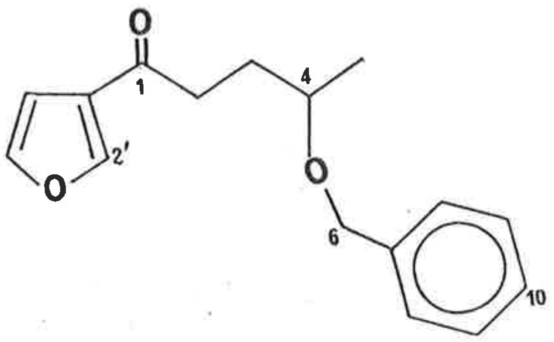
(152)



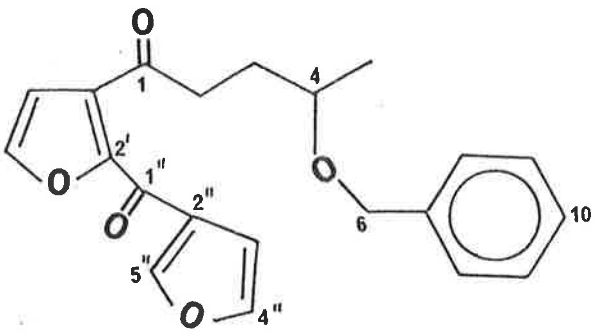
(153)

Chemical Shift in ppm (multiplicity)

compound carbon	(152)	(153)
2'	139.2 d	139.1 d
3'	127.4 s	127.5 s
4'	108.6 d	108.6 d
5'	143.3 d	143.1 d
1	74.4 d	76.8 d
2	33.4 t	33.5 t
3	36.3 t	37.5 t
4	84.4 s	83.2 s
5	47.2 t	37.8 t
6	66.6 d	33.5 t
7	47.2 t	73.5 d
8	29.8 d	28.9 d
9	23.4 q	18.9 q
4-CH_3	24.6 q	26.9 q
8-CH_3	22.5 q	17.3 q



(213)

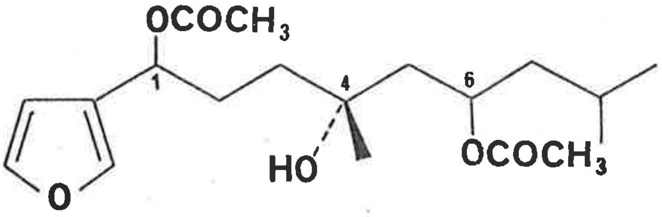


(231)

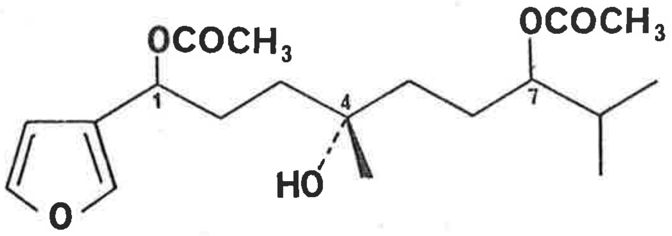
Chemical Shift in ppm (multiplicity)

compound carbon	(213)	(231)
2'	147.1 d	149.7 s
3'	127.6 s	139.3 s
4'	108.5 d	113.3 d
5'	143.9 d	144.5 d
1	194.5 s	199.7 s
2	36.1 t	39.2 t
3	30.9 t	30.7 t
4	73.8 d	74.2 d
6	70.3 t	70.5 t
7	128.2 s *	128.4 *
8	128.2	128.4 d
9	128.9	127.9 d
10	127.5	127.5 d
4-CH_3	19.6	19.6 q
1"		175.7 s
2"		132.9 s
3"		109.9 d
4"		143.9 d
5"		149.5 d

* obscurred



(139)

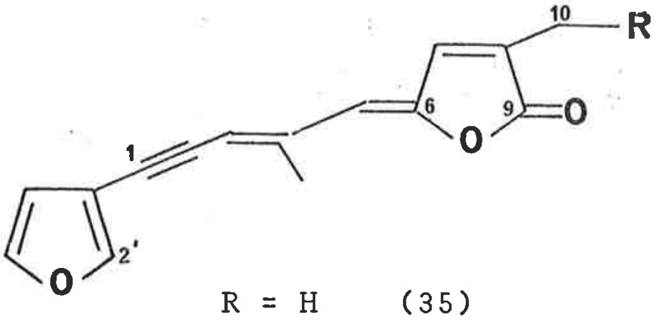


(140)

Chemical Shift in ppm (multiplicity)

compound carbon	(139)	(140)
2'	140.18 d	140.50 d
3'	124.75 s	124.85 s
4'	108.67 d	108.77 d
5'	142.98 d	143.30 d
1	68.74 d	98.95 d
2	37.56 t	37.4 t
3	37.99 t	37,4 t
4	70.90 s	71.76 s
5	46.08 t	37.12 t
6	69.82 d	29.13 t
7	45.11 t	78.88 d
8	24.17 d	31.40 d
9	22.17	25.47 q
4-CH_3	26.44 26.98	26.65
8-CH_3	22.12 29.03	21.04
$CO\underline{CH}_3$	24.39,21.04,20.83	18.56 17.56
$\underline{CO}CH_3$	170.07, 170.82	171.14 170.49

APPENDIX B



R = H (35)

R = OCH_3 (53)

Chemical Shift in ppm (multiplicity)

compound carbon	(35)	(53)
2'	139.1 d	140.1
3'	108.1 s	108.1
4'	112.6 d	112.6
5'	143.4 d	143.3
1	90.9 s	90.0
2	90.1 s	91.5
3	114.5 d	116.4
4	144.2 s	143.9
5	115.3 d	116.4
6	147.8 s	147.7
7	145.8 d	140.1
8	129.2 s	130.1
9	171.1 s	179.6
10	10.6 q	66.1
4-CH_3	18.3 q	18.2
OCH_3	-	59.2

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