THE CHEMISTRY OF HUMULENE

A Thesis submitted to the
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for the degree of
Doctor of Philosophy

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This thesis is dedicated to the
memory of Mrs. Barbara Joan Camfield,
whose courage and determination should
be an example to us all.

CONTENTS

INTRODUCTION

Plants, fungi and corals have provided a rich source of naturally occurring compounds whose occurrence, structural elucidation, and biogenesis have proved of great interest to the organic chemist. Historically, it was the high proportion of terpenes, particularly the sesquiterpenes, in essential oils of plants that first commanded attention. In 1895 Chapman isolated a sesquiterpene from oil of hops which he distinguished from caryophyllene by the preparation of a number of derivatives and suggested the name humulene. The structure of humulene, however, remained a mystery for over fifty years. Later work showed it to be monocyclic and to possess three double bonds which were not in conjugation.[2-4] The position and stereochemistry of the double bonds were then deduced by degradative experiments and analysis of n.m.r. spectroscopic data, which placed them as endocyclic and all trans.[5,6] The structure of humulene was confirmed as (1) by X-ray analysis of the bis-silver nitrate adduct.[7]

The occurrence of humulene (1) (also called α-humulene and in the older literature, α-caryophyllene) is widespread in Nature, as is its isomer, γ-humulene (2).[8] One of the richest natural sources of humulene is oil of hops from which the episulphides (3) and (4) are also isolated.[9] These are thought not to be naturally occurring compounds, but to arise when the hop plant is heavily dressed with flowers of sulphur to control mildew.

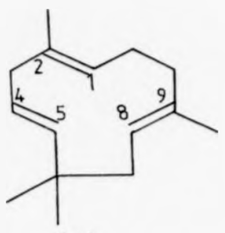
Many oxygenated derivatives of humulene exist;

humulene-1,2-epoxide (5), humulene-8,9-epoxide (6), humulene-4,5-epoxide (7), humulene-1,2-8,9-bisepoxide (8), humulene trisepoxide (9), humulenol II (10) and humulenone II (11)[10] are all well documented compounds.* In recent years, many new humulene derivatives have been isolated from various sources. The novel alcohol (12) was found in the aerial parts of Helichrysum chionsphaerum.[11] It was also isolated from Lychophora columnaris,[12] together with the acid (13) and the related compounds (13)-(18). The rearranged acid (19) isolated from the same source is thought to arise from re-arrangement of (13). The novel humulenoids (20) and (21) have been isolated from Torilis scabra.[13]

Zerumbone (22, and zerumbone epoxide (23) display plant grovth promoting activity associated with the cross-conjugated ketone grouping. As might be expected, zerumbone epoxides (24) and (25) and zerumbol (26) also display this activity but to a lesser degree.[14] The analogous γ-humulene-3-one (27) was recently isolated from Cineraria fruticulorum, together with its dihydro derivative (28).[15]

The first sesquiterpenoid lactone based on the humulane skeleton, called asterisconolide A (29), has been isolated from Asteriscus aquaticus, along with its three configurational and/or conformational isomers asterisconolides B (30), C (31) and D (32).[16] The configurational/conformational isomers are quite stable and are not interconvertible in

* The numbering system used in this thesis is according to I.U.P.A.C. rules based on humulene as a tetramethylcyclo-undecatriene. It should be noted that Shirahama et al. prefer to use a numbering system for humulene based on its derivation from farnesyl pyrophosphate.



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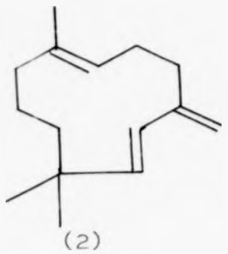

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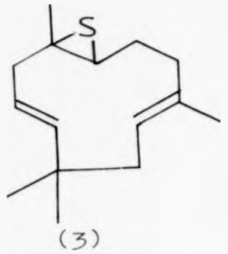

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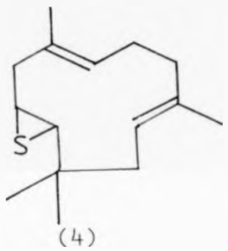

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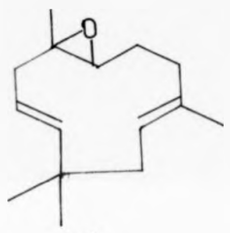

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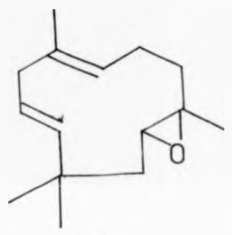

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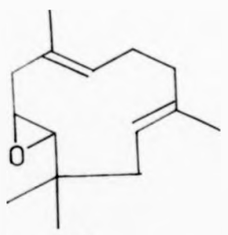

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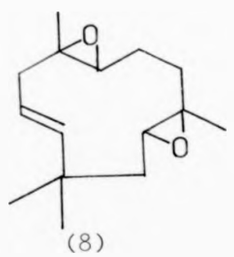

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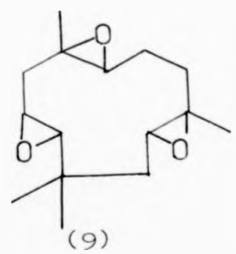

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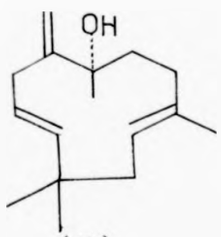

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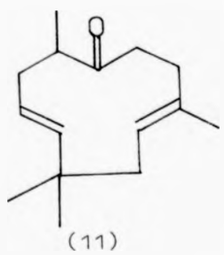

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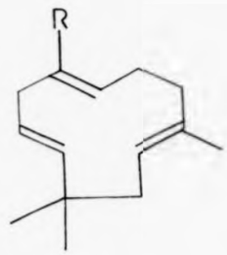
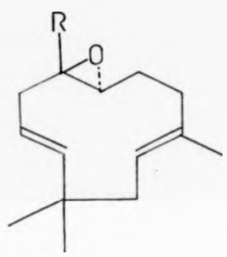
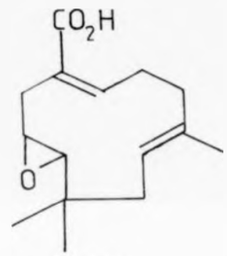


R = CH_2OH (12)
R = CO_2H (13)
R = CH_2OAc (14)
R = CHO (15)

R = CH_2OH (16)
R = CHO (17)





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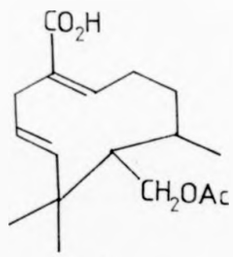

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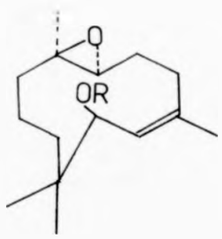
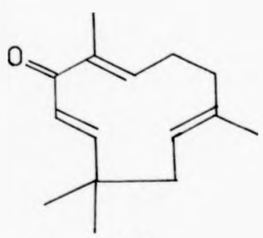


R = Ac (20)
R = H (21)



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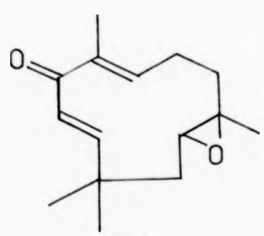

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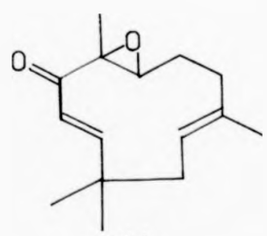

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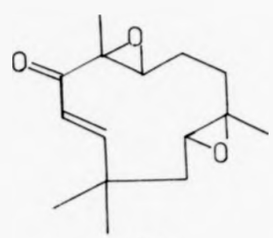

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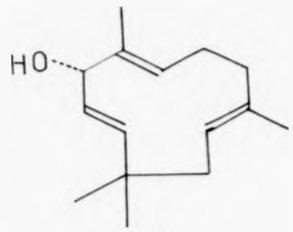

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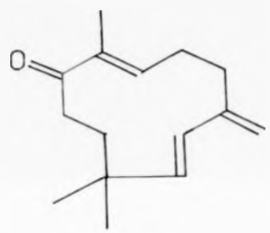

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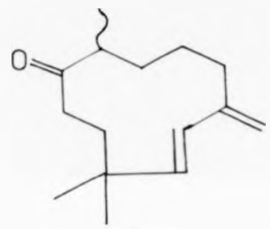

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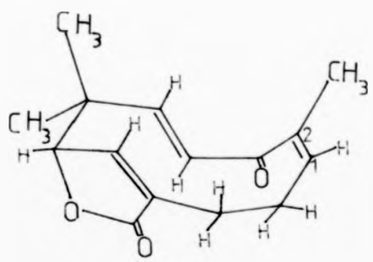
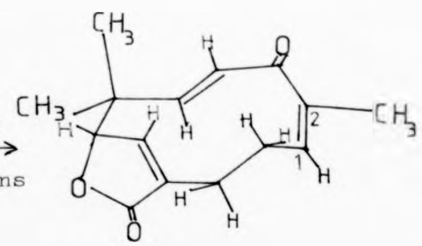


(29)

200 C

10 mins



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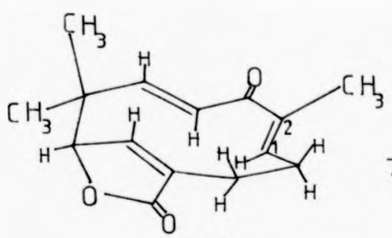

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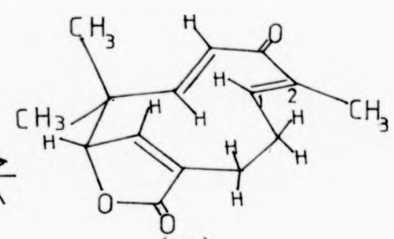
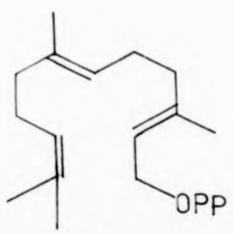


(32)

common solvents at room temperature. However asterisconolide A (29) is irreversibly converted into asterconolide C (31) on melting. An interesting feature of (29) and (31) is the cis configuration of the $\Delta^{1,2}$ double bond.

The biogenesis of humulene (1) was proposed initially in terms of the Biogenetic Isoprene Rule[17] and subsequent embellishments were later added.[18] Thus the derivation of humulene is viewed in terms of cyclisation of farnesyl pyrophosphate (33) and deprotonation of the intermediate cation (34). The related sesquiterpene, caryophyllene (35), can arise by further cyclisation and deprotonation and this seems reasonable in view of the fact that these two compounds normally coexist in Nature.



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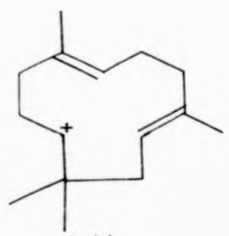

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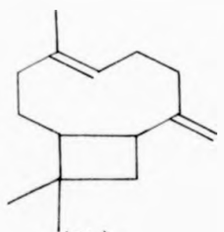
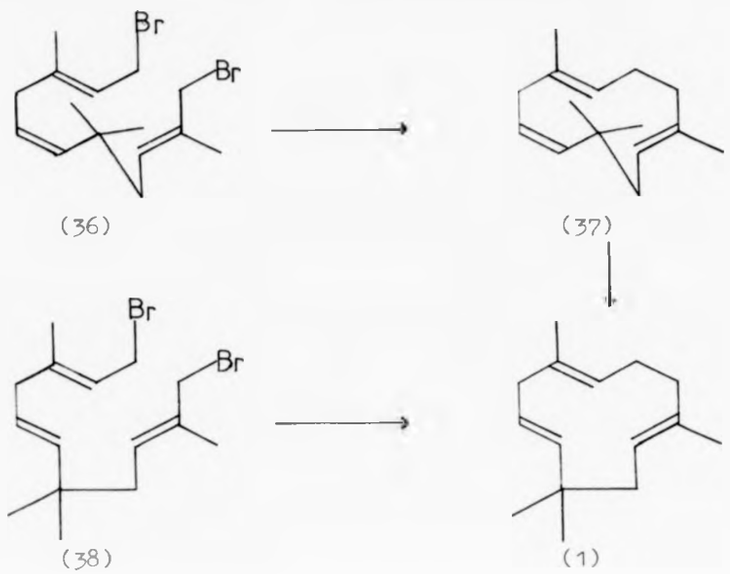


(35)

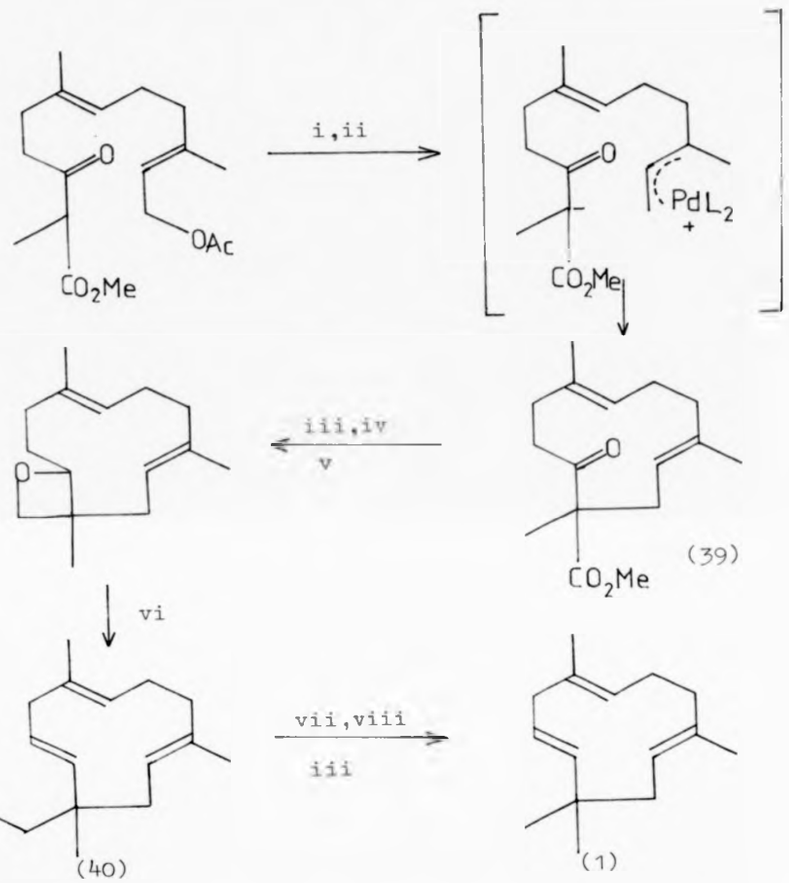
Before proceeding to consider the chemistry of humulene, it should be noted that there are now six total syntheses of the compound, reflecting a growing interest in the stereoselective synthesis of macrocyclic rings. The first synthesis of humulene was reported by Corey,[19] the key step being the intramolecular cyclisation of the 1,11-dibromo-2,5,9-undecatriene derivative (36) with nickel carbonyl to give the $\Delta^{4,5}$ cis isomer of humulene (37). Irradiation of (37) at > 350 nm in the presence of diphenyl disulphide gave all trans humulene (1).



This method of nickel carbonyl-induced cyclisation was also employed by Vig et al.,[20] in which they achieved the all trans configuration in the dibromide (38) prior to cyclisation.

A more stereoselective synthesis[21] uses an electrostatically-driven cyclisation by a π-allyl palladium complex to form a functionalised eleven membered ring (39) (Scheme 1). The $\Delta^{4,5}$ double bond is introduced regiospecifically via an oxetane ring which is opened by an organo-aluminium reagent involving a cyclic syn elimination process to give the corresponding allylic alcohol (40), which can be reduced to humulene (1).

McMurry et al.[22] have reported a short and efficient synthesis of humulene. This employed the titianium-induced dicarbonyl coupling of the keto-aldehyde (41) as the key step,



Reagents : i NaH

ii tetrakis (triphenylphosphine) palladium , HMPTA , 1,3-bis (diphenylphosphino) propane

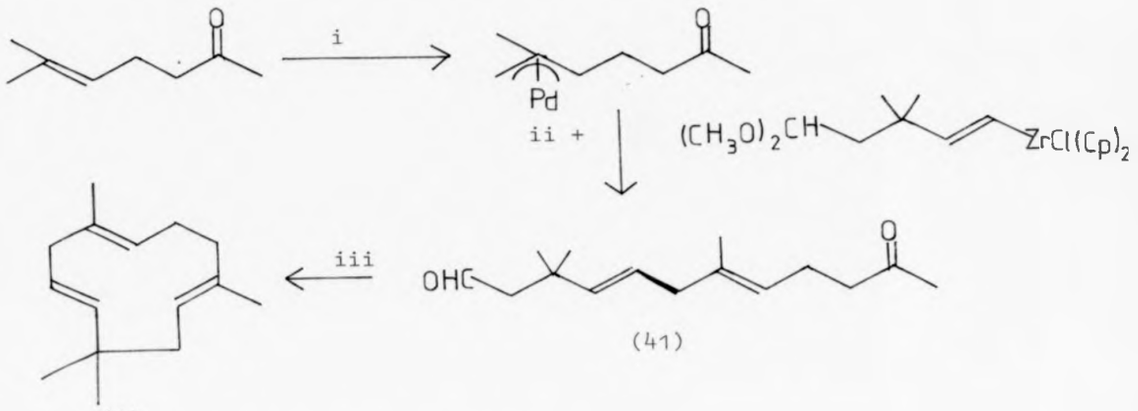
iii $LiAlH_4$ iv p-TSA , py

v K-tBuO vi $Et_2AlNMePh$

vii Me_2S-NCS-Et_3N viii tosyl hydrazine

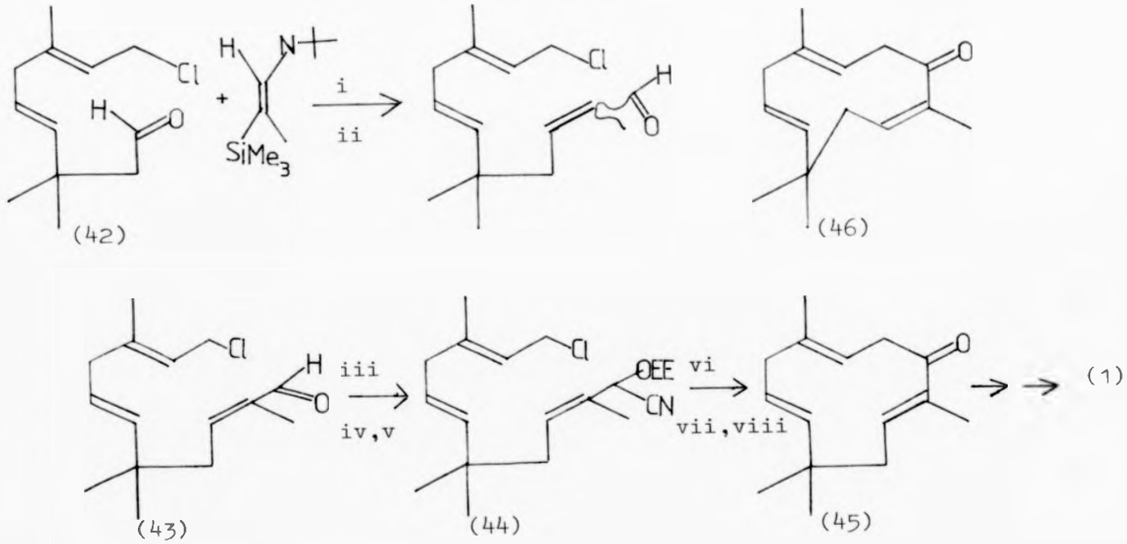
Scheme 1

to give humulene (1) in high yield (Scheme 2).



Reagents : i $PdCl_2$, acetone
ii maleic anhydride , CH_2Cl
iii $TiCl_3$, Zn-Cu , DME

Scheme 2



Reagents : i t-BuLi
ii oxalic acid
iii Me_3SiCN
iv 18-crown 6 , $PhCH_2N^+Me_3F^-$
v ethyl vinyl ether , H^+
vi $NaN(SiMe_3)_2$
vii p-TsOH ,MeOH
viii NaOH

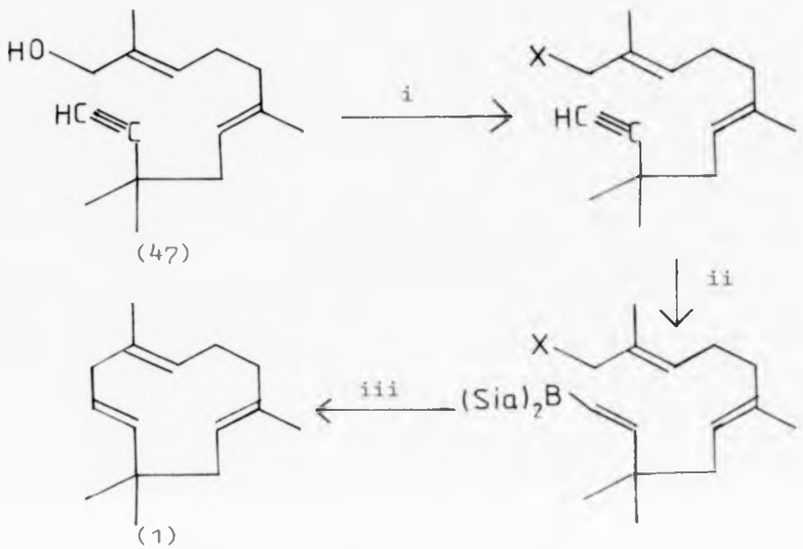
Scheme 3

Another synthesis has been reported which permits the synthesis of humulene and its derivatives[23] (Scheme 3). Addition of the aldehyde (42) to a metalised imine produced a mixture of E- and Z-enals which were separated. The pure E-enal (43) was converted to the protected cyanohydrin (44) which could then be cyclised and hydrolised to the ketone (45) and thence to humulene through a number of conventional steps. Treatment of the Z-enal in the same manner proceeded smoothly but, base treatment of the cyclised Z-cyanohydrin produced a mixture of the Z,E,E-trieneone (46) and the E,E,E-trieneone (45).

The most recent synthesis of humulene utilises geranyl acetate or the corresponding bromide as the starting materials.[24] These were converted by different means to the key acetylenic alcohol (47). Halogenation of (47) gave the corresponding halides (48) which were hydroborated and cyclised with tetrakis (triphenylphosphine) palladium (O) to give humulene (1) (Scheme 4).

Early interest in humulene centred on structural elucidation studies and on the formation of novel cyclisation products. Although the latter were more chemical curiosities in their time, they would later have an important bearing on the mechanistic studies of humulene.

The major product of the reaction of humulene with sulphuric acid proved to be a compound of significant interest.[25,26] Known as α-caryophyllene alcohol, it possesses the symmetrical structure (49), and was subsequently discovered to be a naturally occurring compound.[27] The proposed mechanism for

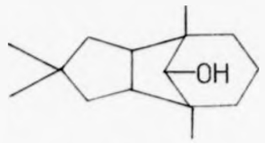


Reagents : i collidene , LiCl , MsCl or PBr_3
ii disamyl borane
iii Pd $(PPh_3)_4$, NaOH , PhH

Scheme 4

its formation is outlined in Scheme 5.[28] Deuterium labelling experiments coupled with ^{13}C n.m.r. spectroscopy gave definitive evidence in favour of this mechanism.

Further to this work three groups independently carried out a detailed study of the treatment of humulene with various acids.[29-31] They showed that humulol (50) was the initial product, which then rearranged to the bicyclic compounds (51)-(54). The proposed mechanism is summarised



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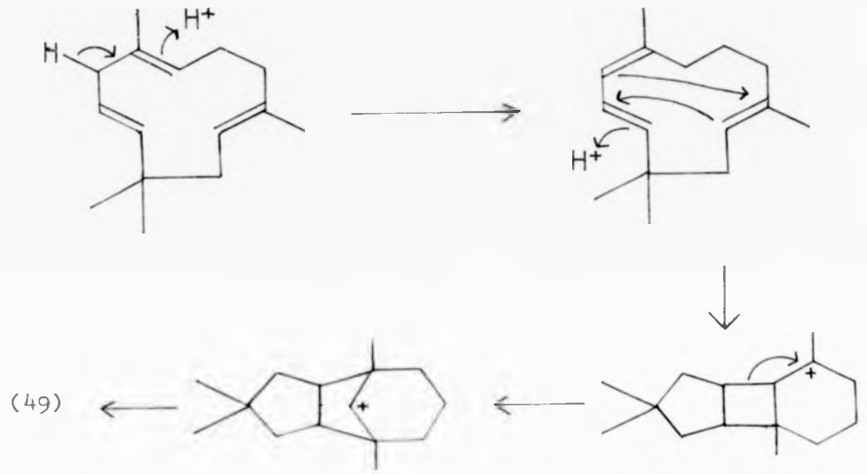
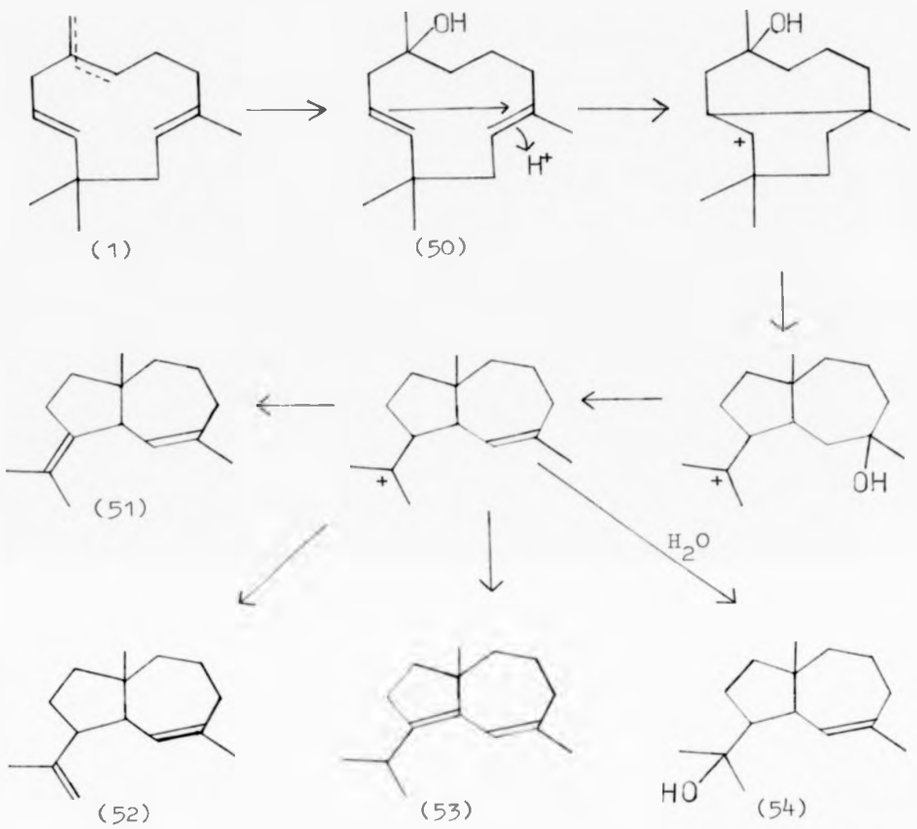


Scheme 5

in Scheme 6. As might have been expected α-caryophyllene alcohol (49) was also found as a component of the reaction mixtures.

Interestingly the tin (IV) chloride treatment of humulene-8,9-epoxide (6) produced one major alcohol (55) which was converted to the hydrocarbon (53).[32] The proposed mechanism for this reaction parallels the one previously suggested for the formation of (51)-(54) from acid treatment of humulene (Scheme 7). The carbon skeleton of (51)-(55) is

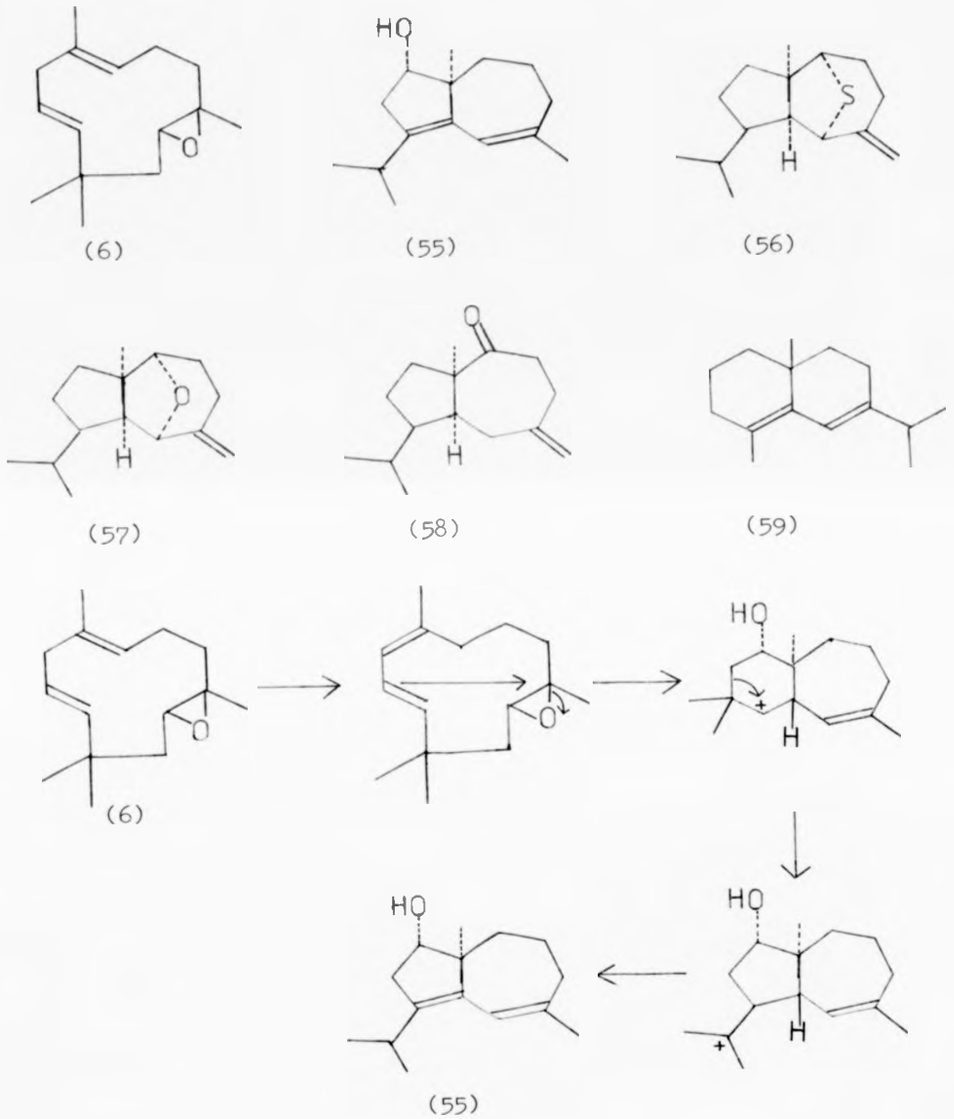


Scheme 6

identical to that of the salvialanes, which are typified by mintsulphide (56), (1R,5R)-1,5-epoxysalvial-4)(14)-ene (57), and salvial-4(14)-en-1one (58).[33,34]

Mehta and Singh reported that treatment of humulene with concentrated sulphuric acid yielded δ-selinene (59), but could not suggest any viable mechanism for its formation.[35]

Relevant to the chemistry of humulene is the work of Sutherland[36] who examined the regio- and stereospecificity of the cyclisation of cyclic 1,5 dienes. Humulene can be



(6) (55) (56)

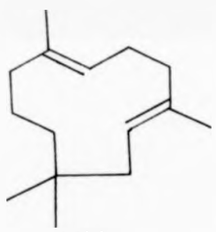
(57) (58) (59)

(6) (55)

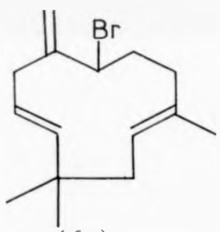
Scheme 7

considered to exist in the Chair Twist boat conformation (60) from the X-ray analysis of the bis-silver nitrate adduct.[7] The CT conformation can be visualised by considering humulene as two 1,5 diene units, the first from C-3 - C-8 in a chair cyclohexane (C) form, whilst the second from C-4 - C-10 in a twist boat (T) ring configuration.

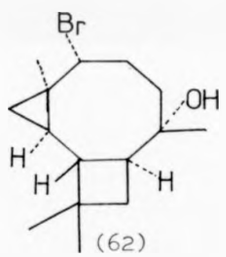
The cyclisation of humulene with N-bromosuccinimide gives the bromide (61) and the tricyclic bromohydrin (62) in equal proportions.[37] It was noted that the bromohydrin (63) had maintained the starting CT conformation of humulene (60).



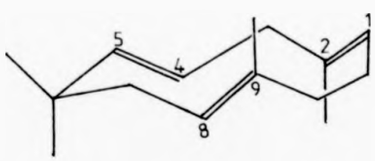
(64)



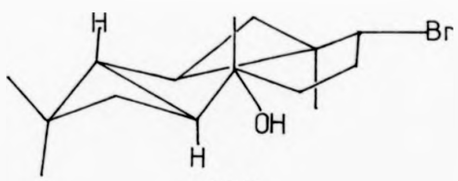
(61)



(62)



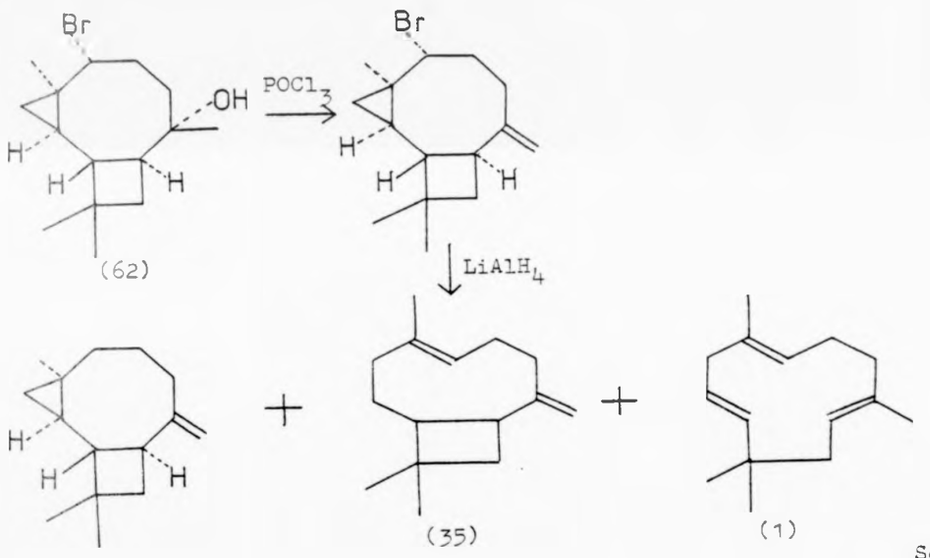
(60)



(63)

The cyclisation is initiated by electrophilic attack at C-1 with the carbonium ion thus formed at C-2 attacked by the $\Delta^{4,5}$ double bond. The $\Delta^{1,2}$ double bond has been calculated to be the most reactive based on strain calculations from the

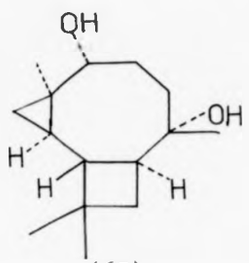
X-ray study.[38] The order of reactivity of the double bonds in humulene (1) towards electrophilic attack is $\Delta^{1,2} > \Delta^{8,9} > \Delta^{4,5}$. However, it has recently been found that diimide reduces exclusively the $\Delta^{4,5}$ double bond of humulene to give 4,5-dihydro-humulene (64),[39] steric factors appear to predominate in this case. The bromohydrin (62) was converted to caryophyllene (35) and humulene (1) by dehydration and hydride reduction (Scheme 8).



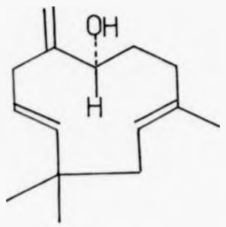
Scheme 8

Relevant to the work of Sutherland is the acid-catalysed cyclisation of humulene-1,2-epoxide (5),[40-42] which gives the tricyclic diol (65) analogous to the bromohydrin (62). Prolonged treatment with acid yields the decyclisation and rearrangement products of (65), namely humulol II (10) and the diols (66) and (67). Shirahama *et al*.[43,44] have since converted humulene-1,2-epoxide to (68) as the major product

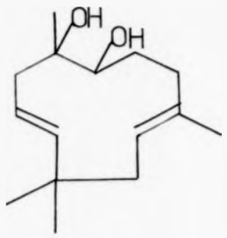
with trimethylsilyl trifluoromethanesulphonate. This tricyclic alcohol (68) was later used in a synthesis of $\Delta^{9,(12)}$ capnellene (69).



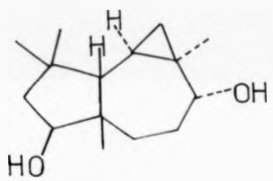
(65)



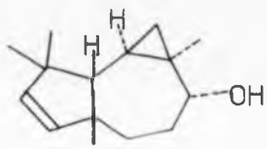
(10)



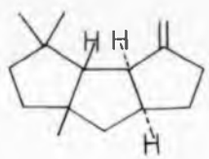
(66)



(67)

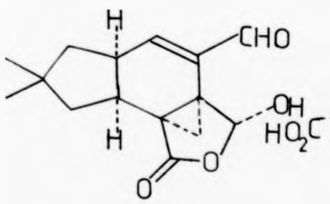


(68)

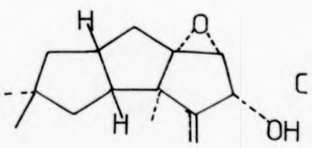


(69)

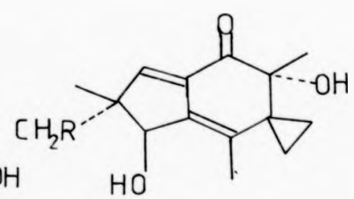
By 1965, the structures of four sesquiterpenoid metabolites, marasmic acid (70)[45], hirsutic acid (71)[46] and illudins S (72) and M (73)[47], had been identified.



(70)



(71)



R = H (72)
R = OH (73)

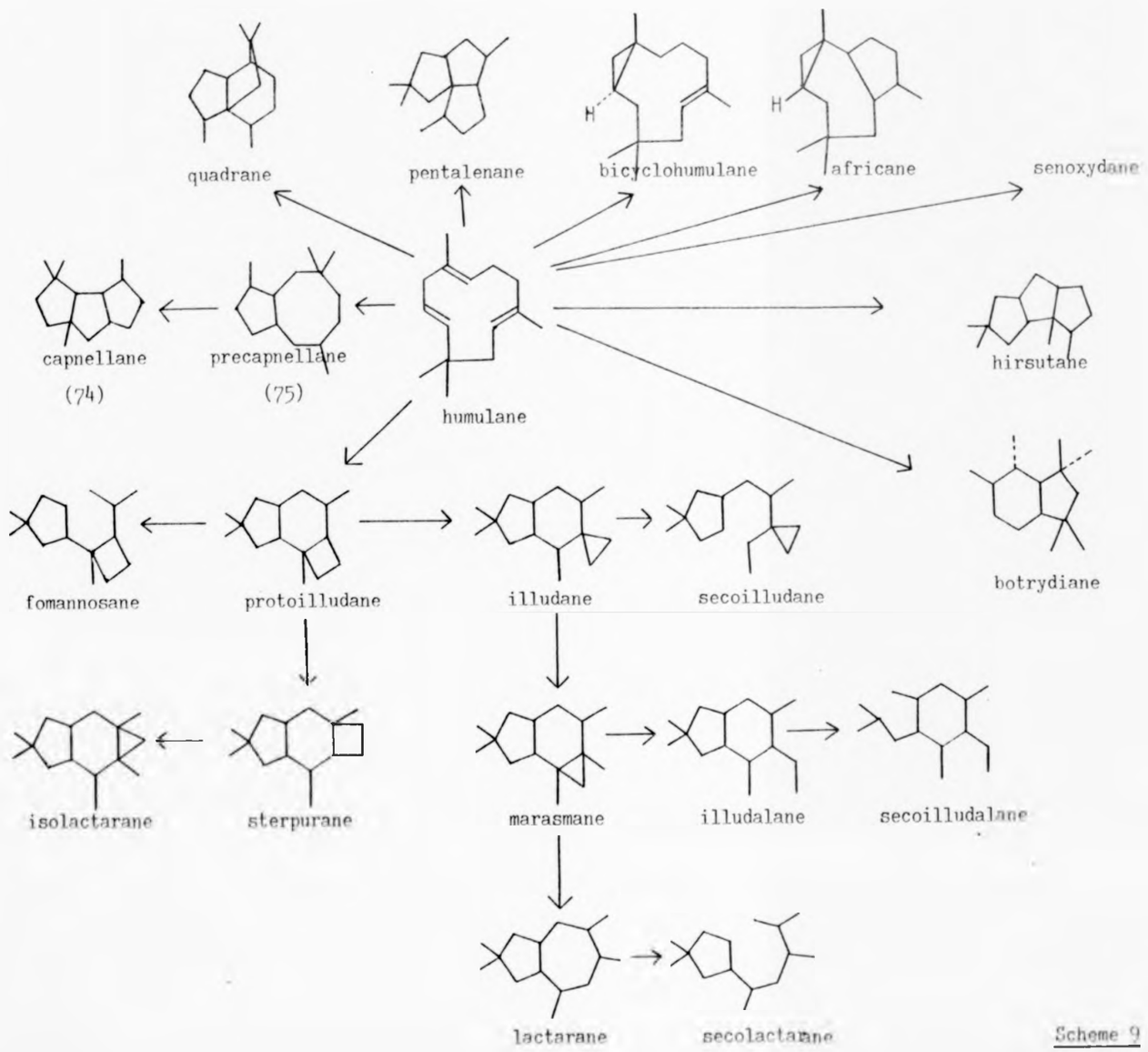
This stimulated a renaissance in humulene chemistry, as humulene could be considered to be the biogenetic precursor of all four compounds.

The number of naturally occurring compounds thought to be derived from humulene by intramolecular cyclisation and subsequent rearrangements has since increased dramatically such that there are now more than 17 different skeletal types known (Scheme 9). Many of these have been isolated from fungi, particularly Basidiomycetes.[48]

The synthesis of the numerous carbon frameworks and functionalities associated with naturally occurring compounds derived from humulene has provided a challenge for the organic chemist. The result has been the many elegant and ingenious syntheses of practically every humulene-derived metabolite present in the recent literature. It is, however, beyond the scope of this introduction to detail these syntheses, especially as they have been thoroughly reviewed recently.[49]

An interesting feature concerning the derivation of these different carbon skeletons from humulene is that except for capnellane (74) and precapnellane (75) the initiation of the various cyclisations is the enzymatic equivalent of protonation at the $\Delta^{4,5}$ double bond. As we have already seen this is the least reactive of the three double bonds towards electrophilic attack. Indeed, earlier work on the acid-catalysed rearrangements of humulene (i.e. *in vitro* protonation) demonstrated that the greater reactivity of the $\Delta^{1,2}$ double bond dictated the chemical outcome of the cyclisation modes.

The emphasis in the remainder of this introduction is on the established biosynthesis and the biomimetic-type


quadrane
pentalenane
bicyclohumulane
africane
senoxydane
capnellane
(74)
precapnellane
(75)
humulane
hirsutane
botrydiane
fomannosane
protoilludane
illudane
secoilludane
isolactarane
sterpurane
marasmane
illudalane
secoilludalane
lactarane
secolactarane

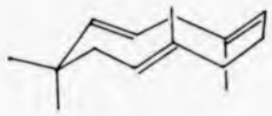
Scheme 9

syntheses of these humulene-derived compounds. At the outset it is important to appreciate the conformational properties of humulene and their influence in the ensuing cyclisation processes. Shirahama *et al.*[50] used Allinger's MM1 programme to carry out empirical force field calculations on the conformational behaviour of humulene. It was concluded that four strain minimum energy conformers of humulene, namely the CC (76), the CT (60), the TT (77) and the TC (78) conformers, with respective heats of formation of 4.47, 4.24, 7.86 and 5.30 k cal mole^{-1}, existed. The activation enthalpy for the transformation from the CT to the CC conformer by rotation of the $\Delta^{1,2}$ double bond through the humulene ring was found to be 10.63 k cal mole^{-1}. The activation enthalpy for humulene ring inversion was estimated to be 14.17 k cal mole^{-1} which is reasonable compared to the value of $\Delta G^{\neq} = 10.16 \pm 0.3$ k cal mole^{-1} obtained from an n.m.r. study.[51] Thus humulene ring inversion should be free at room temperature.

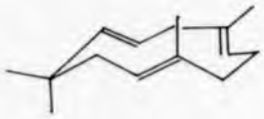
These studies indicate that in addition to the CT conformer of humulene, the CC conformer should be of comparable energy and is important in the transannular cyclisations of humulene.

The TC and TT conformers are excluded from the discussion on the transannular cyclisations of humulene as they would cyclise to give *trans* fused products (Scheme 10), which have not been found as naturally occurring compounds.

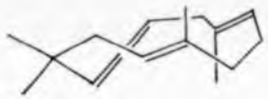
Now having examined the conformational behaviour of humulene, it is necessary to survey the biosynthesis and biomimetic chemistry of humulene-derived metabolites. For



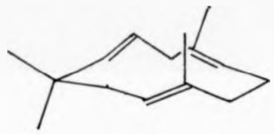
RSR - CT
(60)



RRR - CC
(76)



RSS - TT
(77)



RRS - TC
(78)

convenience the humulene-derived compounds have been divided into several classes which will be examined individually.

Africane and Bicyclohumulane

There are now four examples of the africane skeleton, which interestingly come from both plant and coral, but not fungal sources. Africanol (79)[52] and $\Delta^{9,(15)}$ africanene[53,54] (80) have both been isolated from marine sources, namely the soft corals Lemnalia africanna and Sinularia erecta respectively.

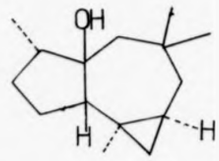
RSS - TT
(77)

RRS - TC
(78)

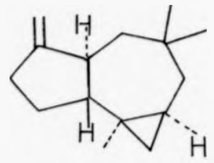
Scheme 10

The absolute configuration of $\Delta^{9,(15)}$ africanene (80) has been determined from X-ray analysis and the CD spectrum. The keto-angeloate (81)[55] and africanone (82)[56] have both been isolated from plant sources, namely Senecio oxyriifolins and Lippia integrifolia respectively. The absolute configurations of (81) and (82) have not been determined. Bicyclohumulenone (83), an example of the bicyclohumulane skeleton, has been isolated from Plagiochila acanthophylla.[57]

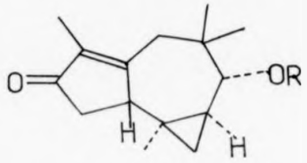
Both the africane and bicyclohumulane skeletons can be derived from humulene by initial protonation at the $\Delta^{4,5}$ double bond followed by participation of the $\Delta^{1,2}$ double



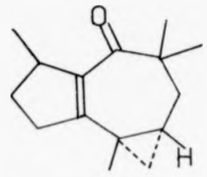
(79)



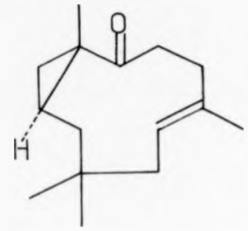
(80)



R = Angeloyl (81)



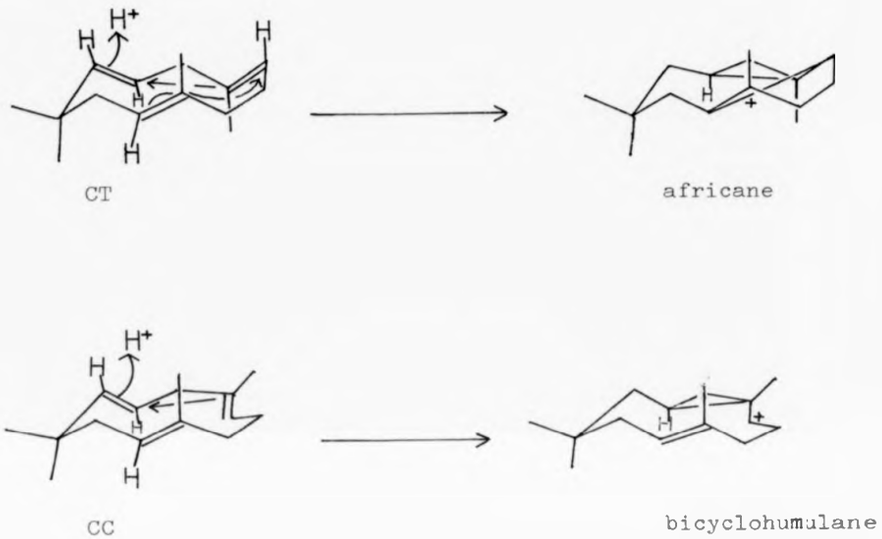
(82)



(83)

bond, then in the case of africane the $\Delta^{8,9}$ double bond. It should be noted that africane has a cis fused cyclopropane ring whilst that of bicyclohumulane is trans fused. This indicates that they have not arisen through a common intermediate but via separate pathways. This can be rationalised if the africane skeleton is formed by cyclisation of humulene in the CT conformer and the bicyclohumulane skeleton is formed by cyclisation of the CC conformer of humulene (Scheme 11).

Although there is no reported biosynthetic work on compounds of these two types, there is considerable information on their derivation from the cyclisation of humulene-4,5-epoxide (7). For the majority of transannular cyclisations of humulene it is necessary to initiate cyclisation at the least reactive $\Delta^{4,5}$ double bond. An effective method of

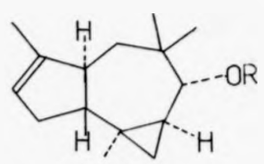


Scheme 11

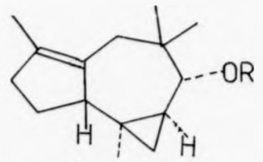
activating the $\Delta^{4,5}$ double bond of humulene to electrophilic attack is to form the 4,5 epoxide.

Roberts et al.[52] have reported the cyclisation of humulene-4,5-epoxide with boron trifluoride etherate to give the isomeric alcohols (84) and (85), which are closely related to africanol (77)[52] and the keto-angelate ester (81) of (86)[55]. The alcohol (85) was subsequently converted to the keto-alcohol (83) synthetically.[59]

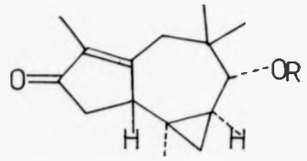
Shirahama et al.[60] also reported a similar cyclisation of humulene-4,5-epoxide (7) with trimethylsilyl trifluoromethane-sulphonate to give (84) and (85). Cyclisation of (7) with boron



R = H (84)
R = Ac (89)



R = H (85)
R = Ac (88)



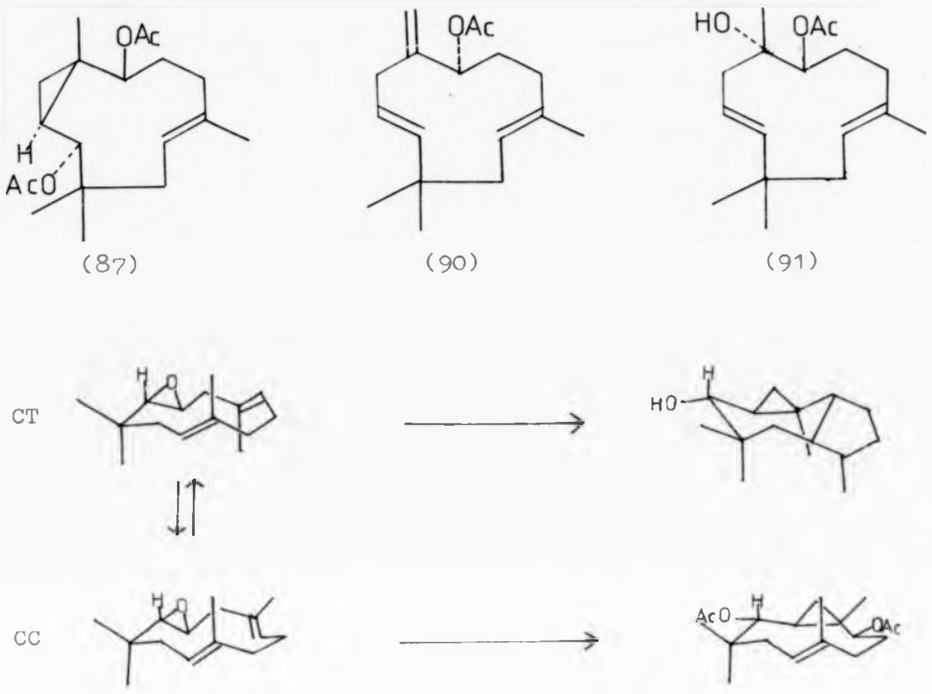
R = Angeloyl (81)
R = H (86)

trifluoride etherate in acetic anhydride gave the diacetate (87) as the sole product. The intermediates (85) and (87) were converted to the naturally occurring compounds d,l-africanol (79) and bicyclohumulenone (83).

As the conformations of humulene epoxides are thought to be similar to that of the original olefin,[61] the 4,5 epoxide of humulene can be considered in terms of the CC and CT conformers. After X-ray analysis of the diacetate (87), it was concluded that it arose from cyclisation of the CC conformer of (7), leading to a trans fused cyclopropane ring, whilst the alcohols (84) and (85) arise from the CT conformer (Scheme 12). This can be considered as an example of a conformationally selective reaction of humulene.

Treatment of humulene-4,5-epoxide with boron trifluoride etherate in acetic acid gave the diacetate (87) and the isomeric acetates (88) and (89) together with the anomalous compounds (90) and (91).[62]

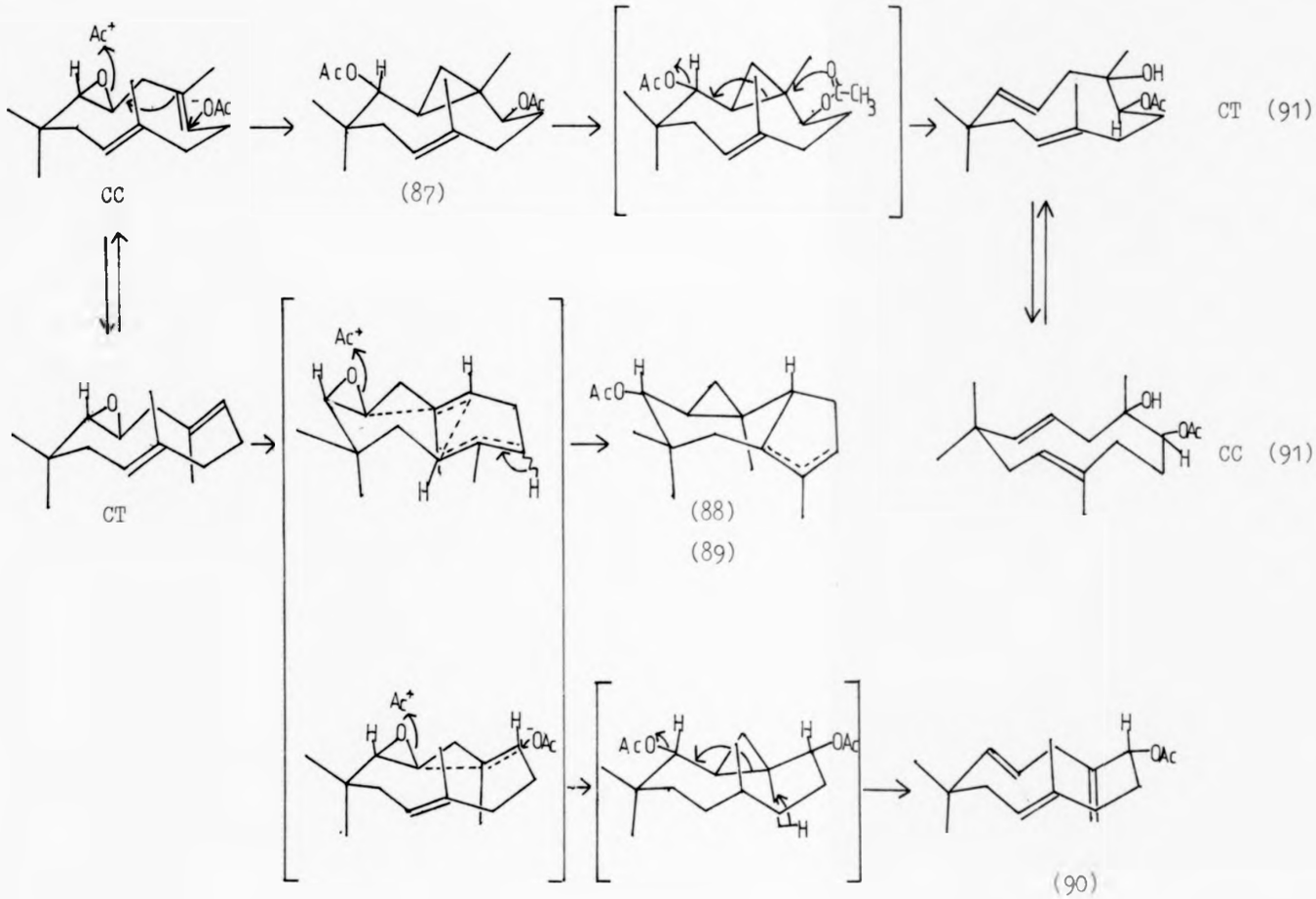
These results were interpreted in terms of the CC and CT conformers of humulene-4,5-epoxide, the nucleophilicity of the attacking reagent and of the stability of the initial



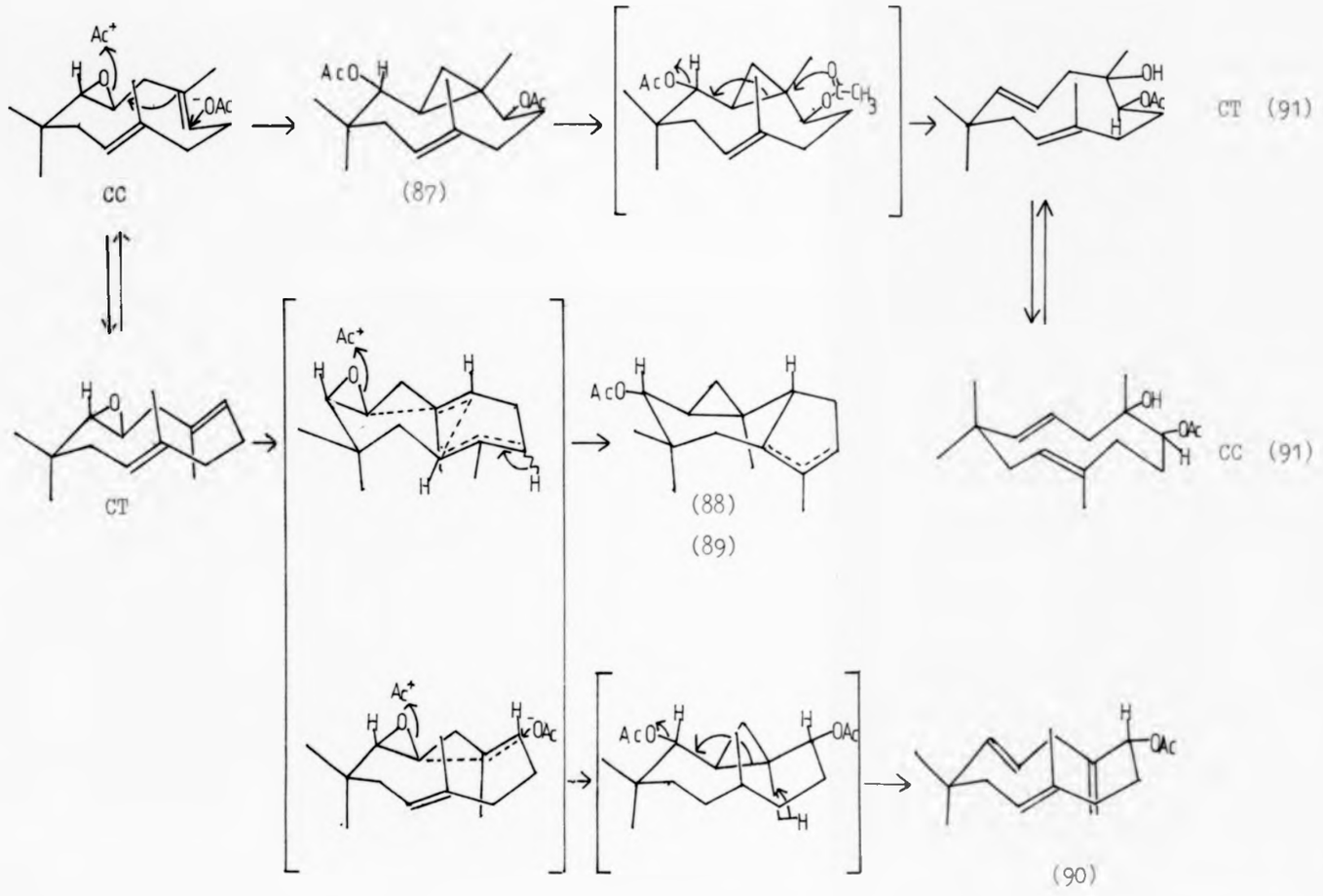
Scheme 12

products based on strain energy calculations (Scheme 13). It has already been noted that the reaction of humulene-4,5-epoxide in toluene with trimethylsilyl trifluoromethanesulphonate and in acetic anhydride with boron trifluoride etherate yields selectively CT and CC mediated products respectively.

When trimethylsilyl trifluoromethanesulphonate in toluene is used in the cyclisation only the weak triflate nucleophile is present. Thus, the C-1 cationic centre interacts preferentially with the $\Delta^{8,9}$ double bond giving products of the type (84) and (85).



Scheme 13

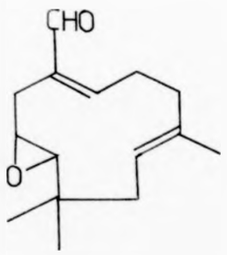


Scheme 13

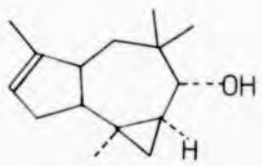
In boron trifluoride etherate and acetic anhydride the more nucleophilic acetate anion is present and the preferred reaction pathway is via acetate interaction at the C-1 cationic centre, leading to the formation of (87).

However in the boron trifluoride etherate/acetic acid system, the main nucleophilic species present, acetic acid represents an intermediate case and interaction of the C-1 cationic centre with the internal $\Delta^{8,9}$ double bond and the external acetic acid compete to give (87) and (88)/(89).

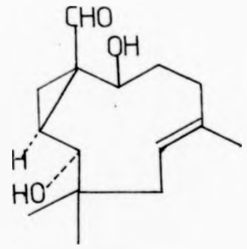
Cyclisation of (92), a derivative of humulene-4,5-epoxide with the $\Delta^{1,2}$ double bond deactivated by the presence of the C-12 aldehyde group, with boron trifluoride etherate in acetic anhydride yielded the africane and bicyclohumulane derivatives (93) and (94) respectively.[63] Interestingly cyclisation of (92) with trimethylsilyl trifluoromethane-sulphonate yielded the isomeric alcohols (95) and (96).



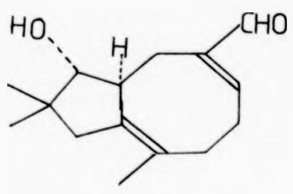
(92)



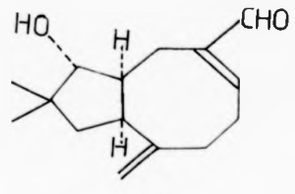
(93)



(94)



(95)



(96)

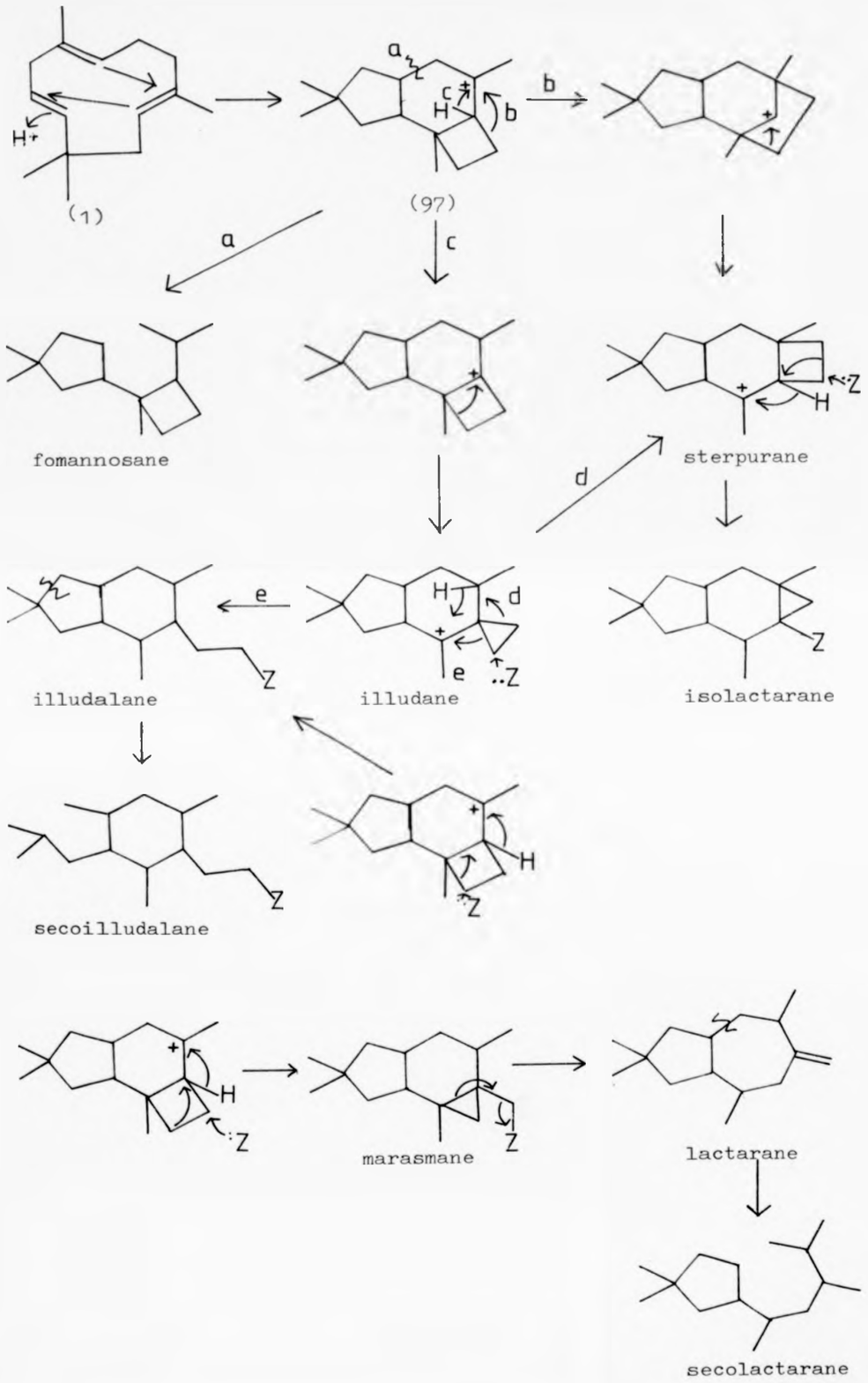
Protoilludane

The importance of the protoilludane skeleton stems from the proposal that the protoilludyl cation (97) is a central intermediate in the biogenetic pathways to the formannosanes, illudanes, sterpuranes, isolacturanes, illudalanes, seco-illudanes, marasmanes, lactaranes, and secolactaranes (Scheme 14).

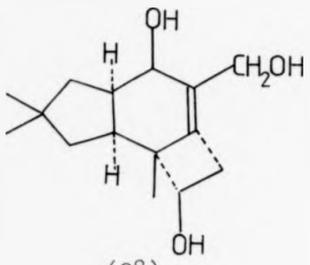
Illudol (98)[64] was the first naturally occurring compound isolated with the protoilludane skeleton. Its stereochemistry was rigidly established by a combination of X-ray analysis[65] and total synthesis[66,67], and it was found to have the cis, anti, cis stereochemistry. Thus one can infer that the stereochemistry of the protoilludyl cation would be produced from cyclisation of humulene in the RSR CT conformer* (Scheme 15).

Five other protoilludanes are now known including Δ^6 protoilludene (99), Δ^7 protoilluden-6-ol (100)[68], neoilludol (101)[69], melleolide (102)[70] an orsellinate of a protoilludane-diol, and armillol (103)[71], an isomeric alcohol also isolated as the orsellinate.

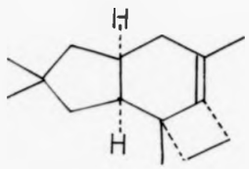
* The prefix RSR denotes the chirality of the $\Delta^{8,9}$, $\Delta^{1,2}$ and $\Delta^{4,5}$ double bonds respectively.


(1)
(97)
fomannosane
sterpurane
illudalane
illudane
isolactarane
secoilludalane
marasmane
lactarane
secolactarane

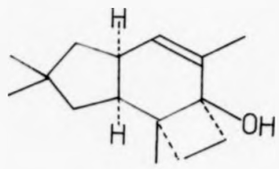
Scheme 14



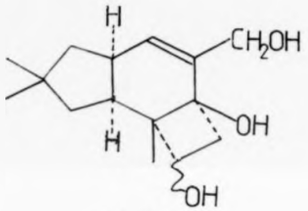
(98)



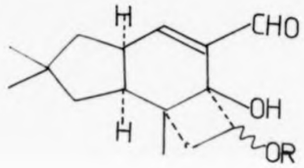
(99)



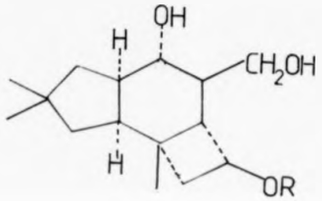
(100)



(101)

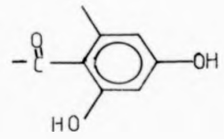


(102)



(103)

R =



RSR - CT

(60)

Scheme 15

Fomannosane

Fomannosin (104) isolated from Fomes annosus[72] has been the subject of extensive biosynthetic studies. More recently isolated from the same fungi are two isocoumarins, fomojorins S (105) and D (106)[73]. It is proposed that fomojorins S and D arise biosynthetically from mevalonate via the protoilludyl cation (97) or its equivalent. Isocoumarins more usually arise biosynthetically from polyketides. This proposal gains support from ^{13}C labelling experiments, which shows a common pathway for fomannosin and the fomojorins. [1,2-$^{13}C_2$]-Acetate was fed to cultures of Fomes annosus and the enriched fomannosin[74] and fomojorin D[75] isolated. The labelling patterns present in fomojorin D were consistent with the fomojorins having arisen from mevalonate via cleavage of the protoilludyl cation (97), pathway b in Scheme 16. Fomannosin (104) arises by oxidative cleavage of the six membered ring of the protoilludyl cation (97), equivalent to pathway 'a' in Scheme 16.

Cane and Nachbar[74] have carried out a detailed analysis of the cyclisation of farnesyl pyrophosphate to produce fomannosin (104) and, by implication, the illudane sesquiterpenes. An abbreviated expression was derived which denotes the absolute stereochemistry of the first transannular cyclisation to form the dimethylcyclopentane moiety, though this was later extended in the light of Shirahama's molecular mechanics calculations.[76] Thus fomannosin biosynthesis can be described as si,re,cis,Cis,pro-S,R, where the first si

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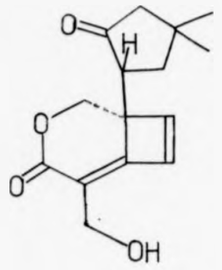
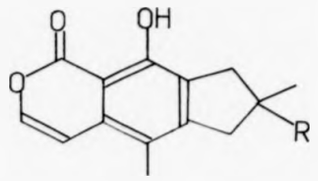
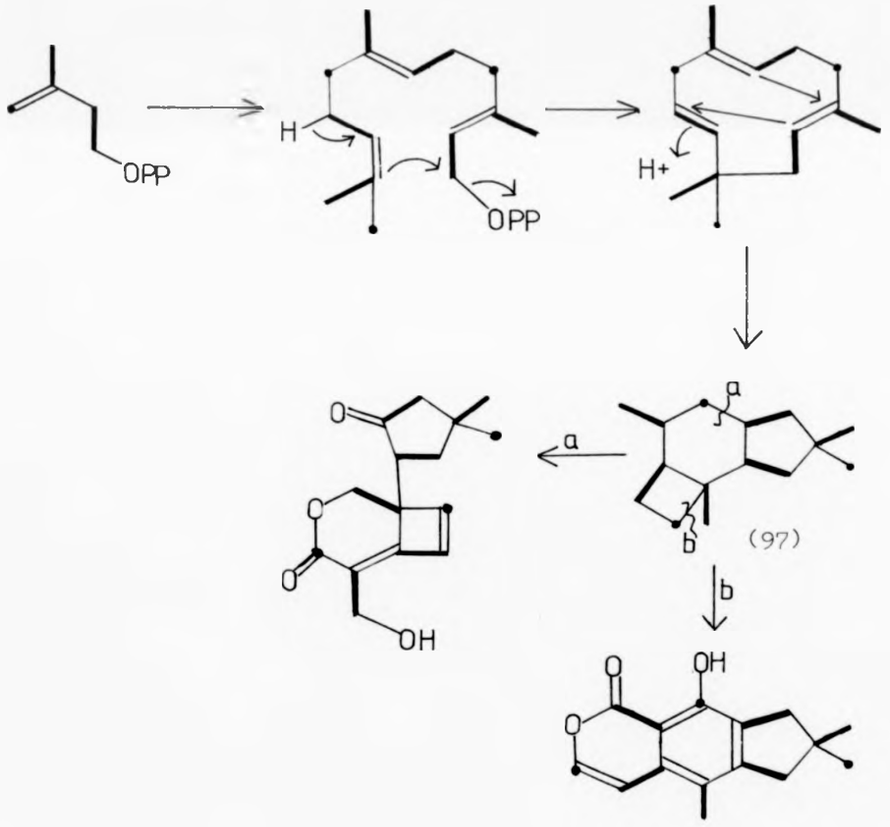


(104)

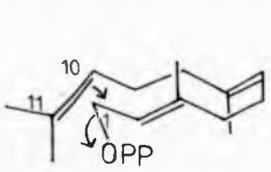


R = CO_2H (105)
R = CH_3 (106)

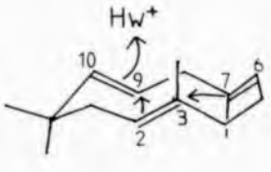


Scheme 16

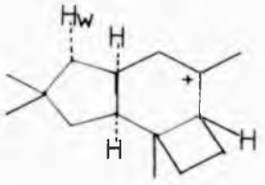
denotes the face of the $\Delta^{10,11}$ double bond* interacting at C-11 with the incipient carbonium ion at C-1 (107). Protonation can then occur on the re face of the $\Delta^{9,10}$ double bond of the humulene thus formed (108), to give a cis fused cyclopentane ring in the resulting protoilludyl cation (109). The fomannosin ultimately formed would have the methyl derived from C-2 of mevalonate Cis to the cyclobutyl substituent on the cyclopentane ring (110), the 12 pro-S proton of fomannosin would be derived from water (111) and, finally the configuration at C-9 of fomannosin would be R (112).



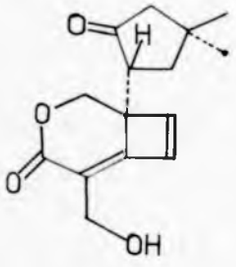
si
(107)



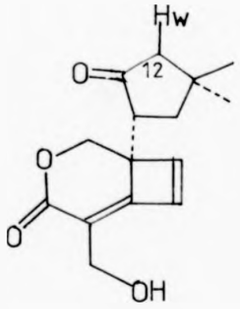
re
(108)



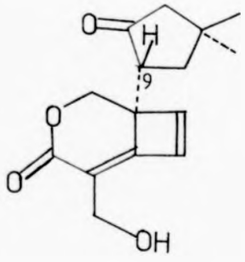
cis
(109)



Cis
(110)



pro - S
(111)



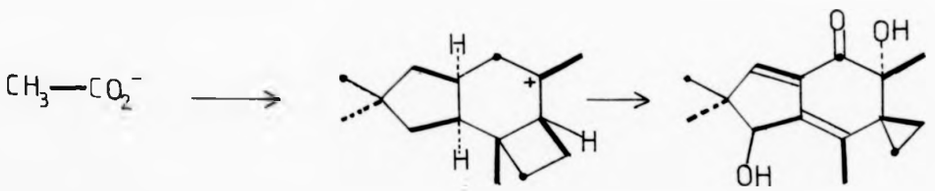
R
(112)

* For clarity farnesyl pyrophosphate numbering is used in this biosynthetic scheme.

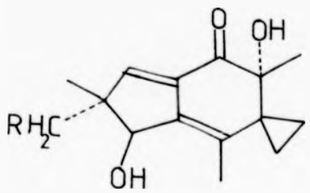
As we have already seen, protoilludane and related metabolites can only arise from a cis fused protoilludyl cation. From the absolute stereochemistry of fomannosin it becomes apparent that it can only arise from the RSR CT conformer of humulene, implying that the protoilludyl cation must also arise from this conformer of humulene.

Illudanes

The illudanes, illudins S (72) and M (73), were amongst the first metabolites isolated which were thought to be derived from humulene. Further evidence for the biosynthesis of the illudanes has since come from labelling experiments. Feeding [1,2-$^{13}C_2$] acetate produced illudin M with a labelling pattern consistent with Scheme 17.[77] Hanson et al.[77,78] also used ^{3}H and ^{14}C labelling experiments in an attempt to probe further illudin biosynthesis, but the results were inconclusive due to low incorporations of the label.

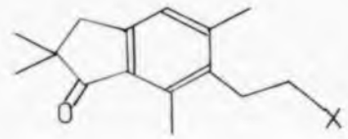


Scheme 17

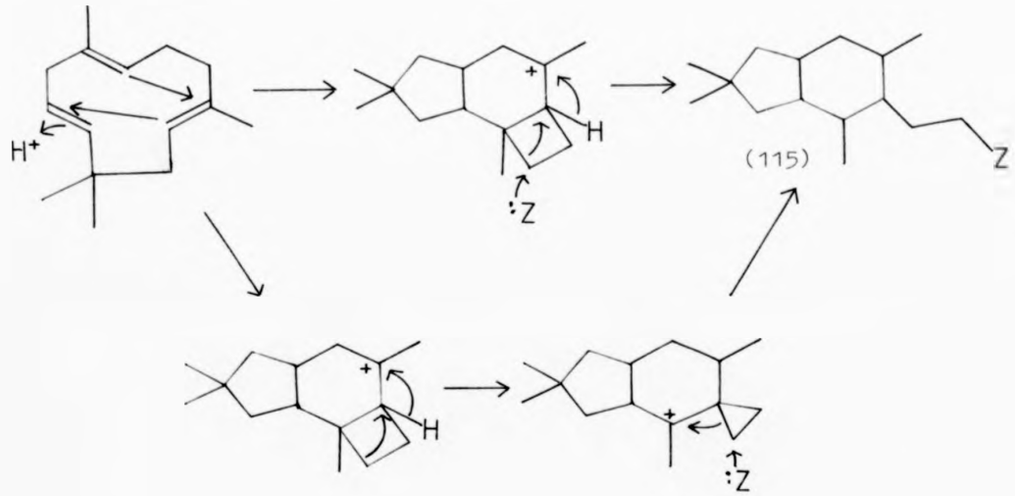


R = H (72)
R = OH (73)

An interesting relationship has developed between the pterosins, hypacrone and the recently found ptaquiloside. The pterosins, of which there are now more than twenty examples, are typified by pterosin Z (113) and H (114) and possess the illudalane skeleton (115).[79] The biosynthetic pathway to the pterosins is thought to be via humulene and the protoilludyl cation (Scheme 18).

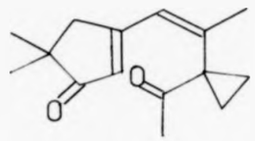


X = OH (113)
X = Cl (114)

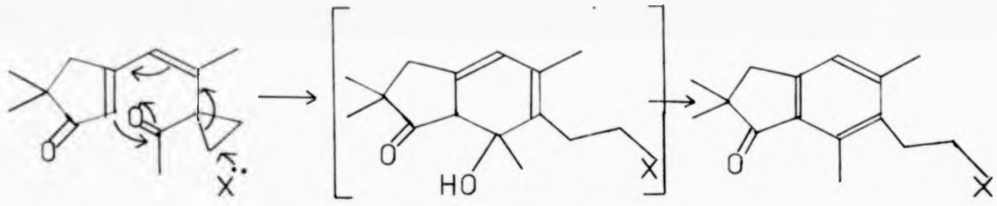


Scheme 18

Hypacrone (116) has a seco-illudane skeleton[79] and is converted to pterosin Z (113) and pterosin H (114) on treatment with sulphuric and hydrochloric acids respectively (Scheme 19).

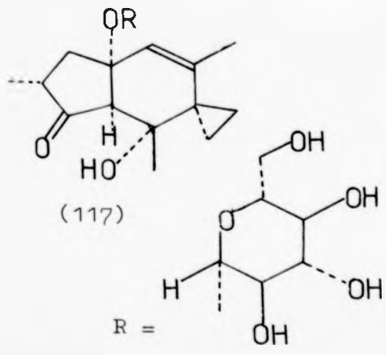


(116)

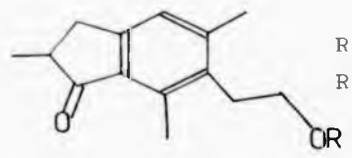


Scheme 19

Ptaquiloside (117) is an unstable sesquiterpenoid glucoside with a novel illudane skeleton and it is proposed that it can be regarded as the biosynthetic precursor to the pterosins.[81,82] It is converted under acidic or basic conditions to pterosin B (118) or O (119) depending upon the solvent used.

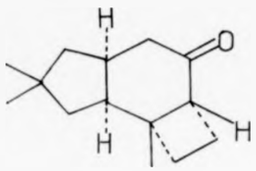


(117)

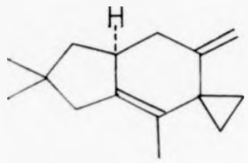


R = H (118)
R = Me (119)

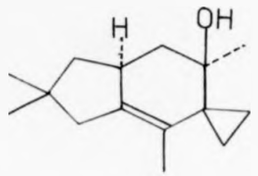
The only biogenetic-like chemistry of the illudanes has come from model studies. Shirahama et al.[83] used the ketone (120) to form $\Delta^{2,(3),7,(13)}$ illudadiene (121) and $\Delta^{2,(3)}$-7β-illudenol (122).



(120)



(121)



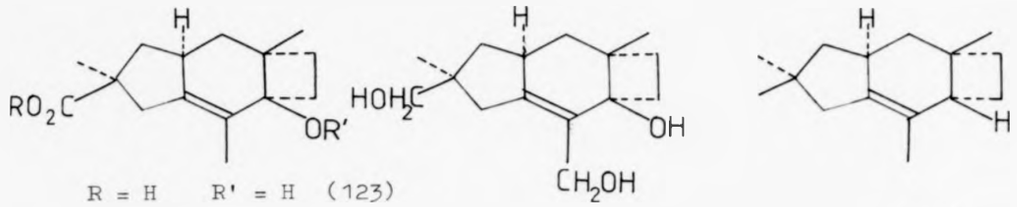
(122)

Sterpurane

In 1981 Ayer et al.[84] reported the isolation of sterpuric acid (123), hydroxysterpuric acid (124), hydroxy-sterpuric acid ethylidene acetal (125) from the fungus Sterpeum purpureum, the cause of the so-called 'silver leaf' disease common in fruit and ornamental trees. Later sterpurene-3,12,14-triol (126) and sterpurene (127)[85] were isolated from the same source.

Studies using ^{13}C acetate have produced labelling patterns consistent with the biosynthesis of sterpurane from humulene via the protoilludyl cation (97) (Scheme 20).[86] There are two possible biosynthetic routes from the proto-illudyl cation to the sterpuranes either by rearrangement consisting of two 1,2 shifts (path a), or via the illudane cation which on ring expansion and hydride shift leads to the

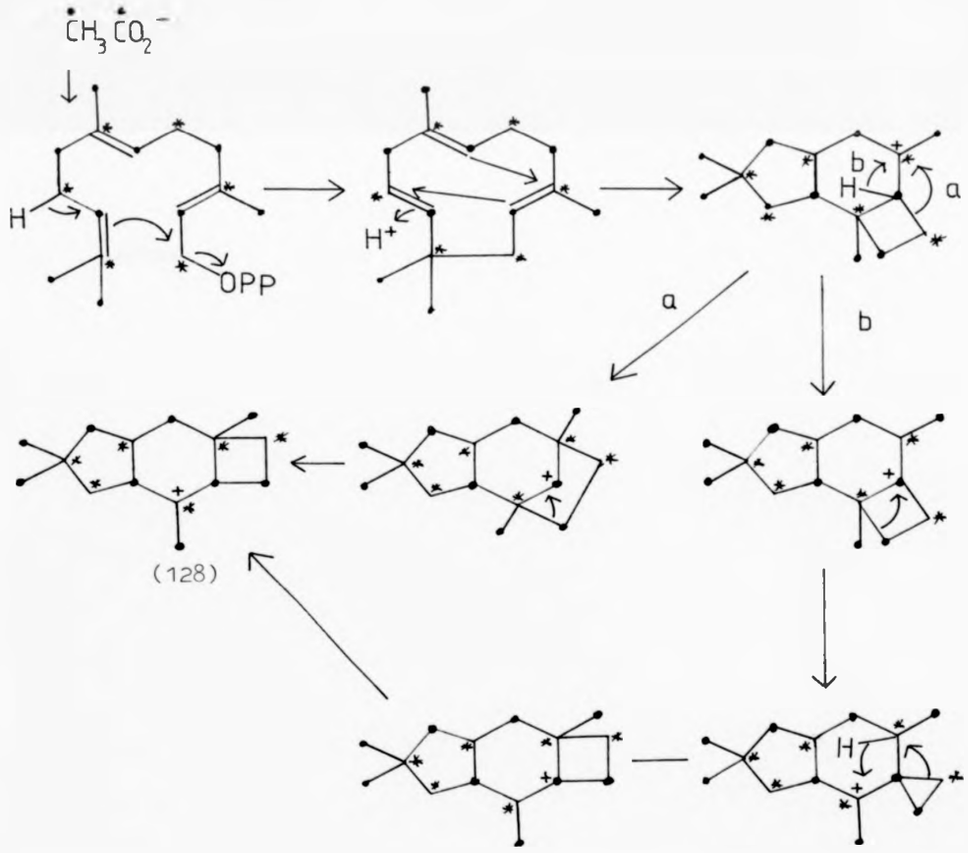
sterpuryl cation (128) (path b).



R = H R' = H (123)
R = CH_3 R' = H (124)
R = CH_3 R' = $COCH_3$ (125)

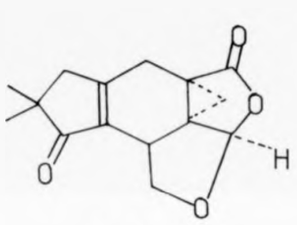
(126)

(127)

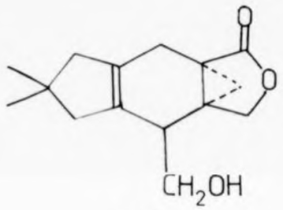


Scheme 20

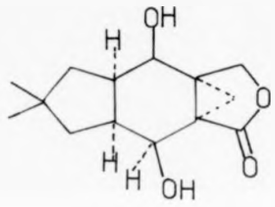
It is interesting to note that the sterpuryl cation (128) has been proposed as the precursor of the so-called isolactarane sesquiterpenoids. Sterepolide (129), dihydrosterepolide (130)[87] and isolactarorufin (131)[88] are isolated from the same fungi as the sterpuranes, and this co-existence contributes to the evidence that they both arise from the sterpuryl cation (128) (Scheme 21).



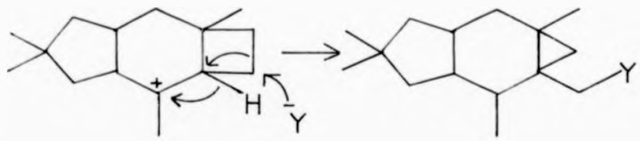
(129)



(130)



(131)



Scheme 21

A biomimetic synthesis of sterpurene (127) has been achieved.[89] Shirahama et al.[90,91] had previously undertaken the cyclisation of humulene directly using aqueous mercury (II) acetate in an oxymercuration/demercuration procedure and this resulted in the formation of the cyclic ethers (132) and (133). The use of mercury (II) nitrate similarly resulted in the formation of (134) and (135). The

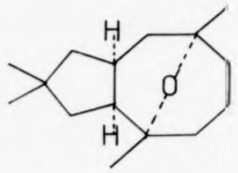
formation of these cyclic ethers can be rationalised in terms of initial electrophilic attack at the $\Delta^{1,2}$ double bond, followed by cyclisation initiated at the $\Delta^{4,5}$ double bond. The alcohol thus formed undergoes further cyclisation to give the cyclic ether (136), which can then either undergo reduction to give products of the type (132) and (133) or rearrangement and reduction to (133) and (134) (Scheme 22).[92]

Treatment of (134) with lithium in ethylamine yielded the alcohol (137) which on formolysis gave the bridged formate (138) and pentalenene (139).[91] The mechanism of this reaction was studied by deuterium labelling and it was shown that formation of (138) proceeded *via* the protoilludyl cation (Scheme 23).

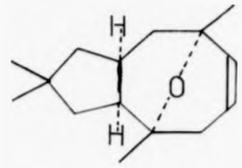
The alcohol (137) could also be converted to a methoxy ether (140), which gave a bridged bromide (141) on treatment with boron tribromide. This was thought to be analogous to the formation of the formate (138). The bridged bromide (141) was converted to racemic sterpurene (127) on treatment with silver acetate.

Marasmanes

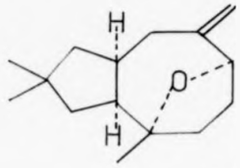
Evidence from labelling studies using [2-^{14}C]-mevalonate showed that the biosynthesis of marasmic acid (70) takes place *via* the protoilludyl cation (Scheme 24).[93] Marasmic acid had already been shown to have the same *cis*-fused hydrindane skeleton as illudol (98) from the partial X-ray structure.[65] Examples of marasmanes isolated include isovelleral (142),[94] the alcohol (143)[68] and more recently stearyl vetutinal (144).[95]



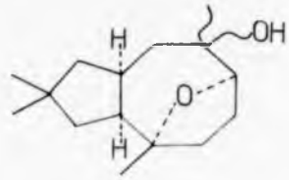
(132)



(133)



(134)



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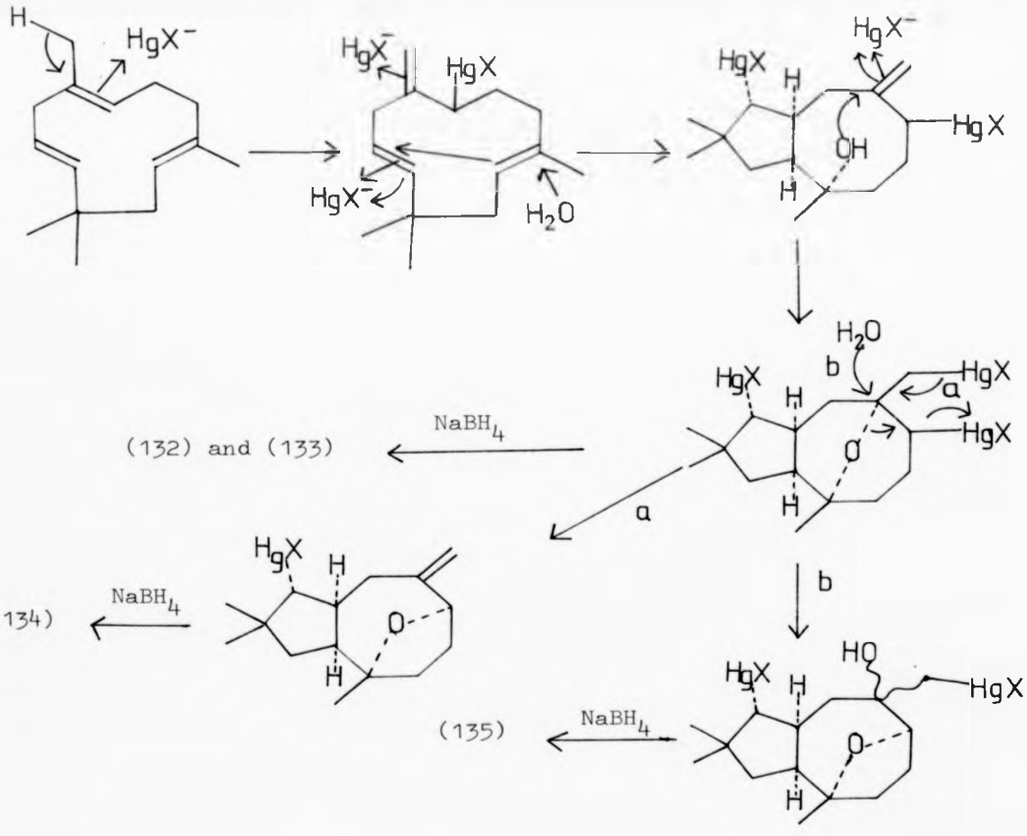
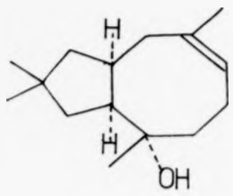


Scheme 22



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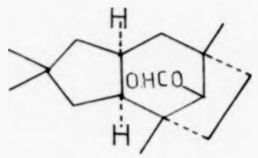

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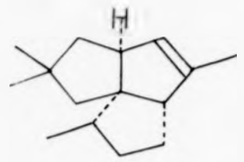
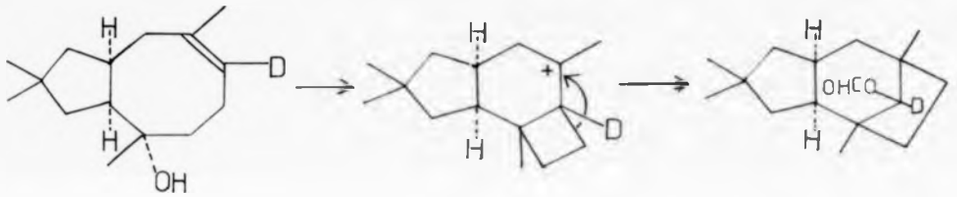
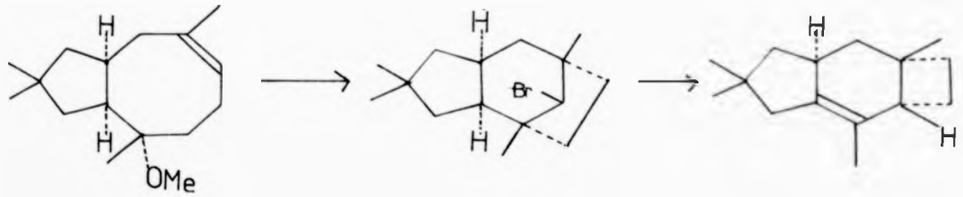


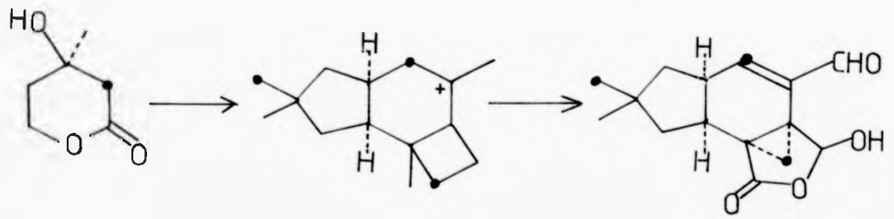
(139)



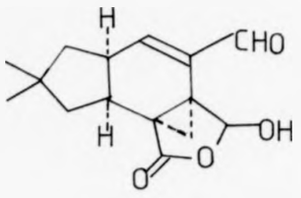
Scheme 23



(140) (141) (127)



Scheme 24



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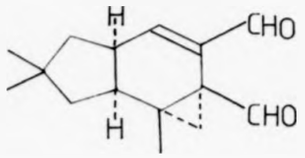
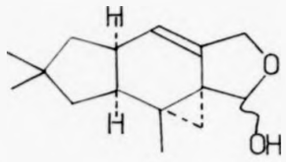
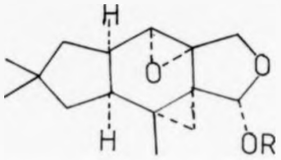


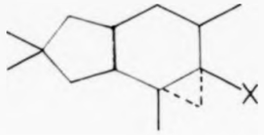
(142)



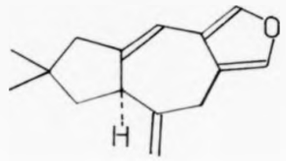
(143)



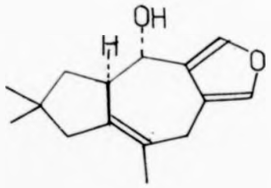
R = stearyl (144)



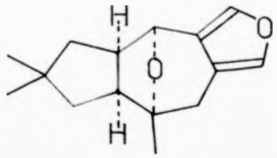
(145)



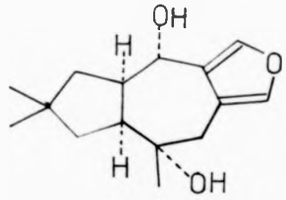
(146)



(147)



(148)



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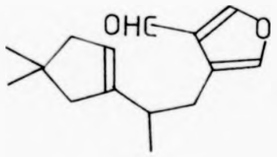

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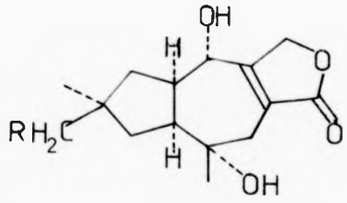
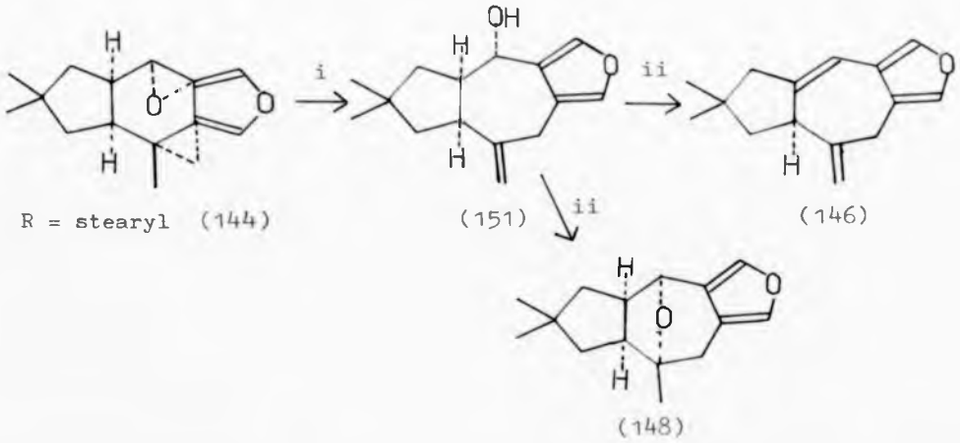


R = H (152)
R = OH (153)

Closely related to the marasmanes are the lactaranes*, which are thought to have a common biogenetic precursor (145).[33] This proposal received support from the thermal rearrangement of isovelleral (142) to the synthetic lactarane, pyrovellerofuran (146).[96] Further evidence comes from the rearrangement of stearyl velutinal (144) on silica gel to give furanol (147), furan ether A (148), furan diol (149), and lactaral (150).[97] The isolation of a novel sesquiterpenoid (151) has also been reported and is a possible intermediate in the rearrangement of stearyl velutinal (144) to pyrovellerofuran (146) (Scheme 25).[98]

There are many examples of compounds with a lactarane skeleton known, typically lactorufins A (152) and B (153) from Lactarus rufus.[99]



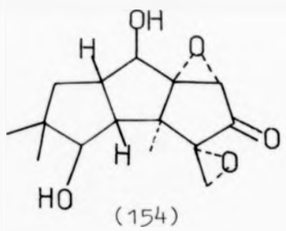
Reagents : i SiO_2
ii PPh_3 , CBr_4

Scheme 25

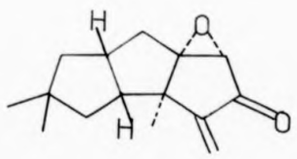
* The literature describing this class of compounds uses the names lactarane and vellerane interchangeably.

Hirsutane

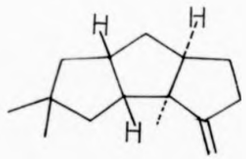
Coriolin (154)[100-101] is a sesquiterpenoid antibiotic which was shown to have a cis-anti-cis tricyclic skeleton. However in this case the gem-dimethylcyclopentane ring fusion was found to be of opposite absolute configuration to the protoilludane-derived compounds. This was also found to be so for hirsutic (71) and complicatic (155) acids.[102] The hirsutanes are thought to have a common precursor in hirsutene (156). Evidence to support this proposal comes from the isolation of hirsutene and coriolin from a common source, namely Coriblus consors.



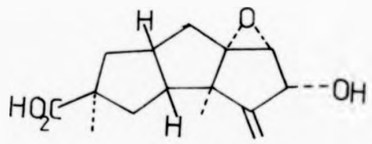
(154)



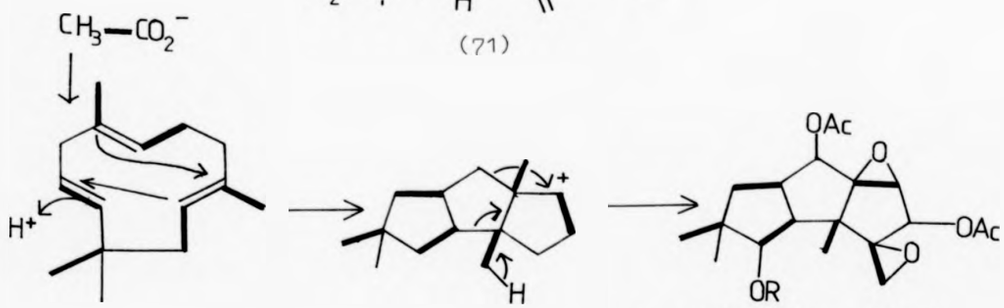
(155)



(156)



(71)

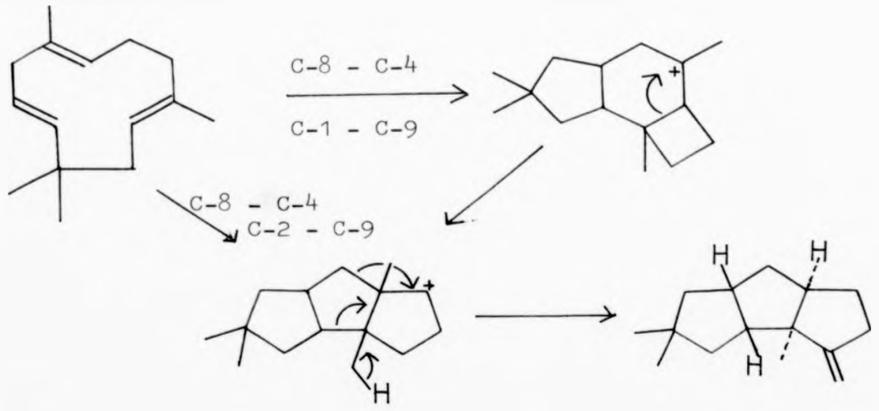


R = -COCHC6H13 (157)
OAc

Scheme 26

Conclusive evidence for the biosynthesis of the hirsutanes from humulene comes from ^{13}C labelling experiments. [1,2-$^{13}C_2$]-Acetate was fed to Coriblus consors and the labelling patterns observed in the isolated dihydrocoriolin diacetate (157) are consistent with Scheme 26.[103] It should be noted that these labelling experiments do not exclude the intermediacy of the protoilludyl cation (Scheme 27).

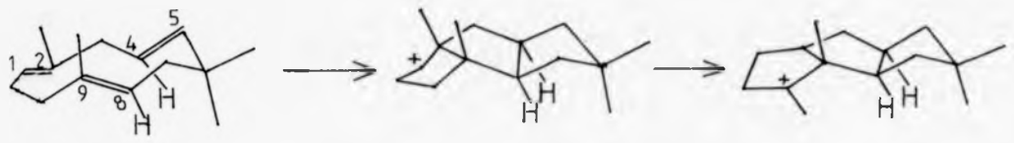
Shirahama et al.[51] considered the relative and absolute configurations of the hirsutanoids and suggested that these can be accommodated if the humulene precursor is in the conformation designated SSS-CC (Scheme 28). Therefore



Scheme 27

two separate pathways are proposed namely, RSR-CT humulene as the precursor of the protoilludanoids whilst SSS-CC humulene as the precursor of the hirsutanoids.

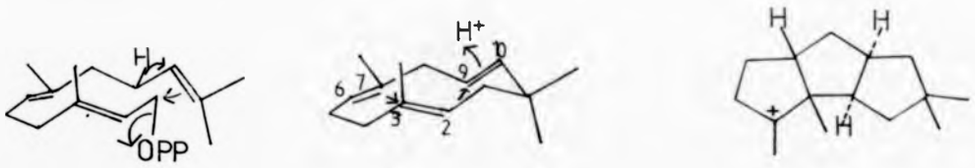
Cane and Nachbar[76] partially extended their previous analysis of formannosin biosynthesis to cover the hirsutanoids, though due to the limited amount of information available from



SSS - CC

Scheme 28

labelling experiments it was not possible to derive a full expression. Thus farnesyl pyrophosphate cyclisation is thought to occur at the re face of the $\Delta^{10,11}$ double bond. It will be remembered that the initial cyclisation for the protoilludanoids was si. The partial expression is thus re,si,cis (Scheme 29).

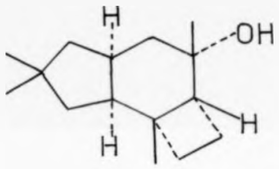


re si cis

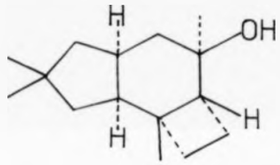
Scheme 29

There are now three biomimetic-type syntheses of hirsutene (156), although none of these can be considered truly biomimetic in view of the earlier discussion, as they involve the intermediacy of the protoilludyl cation.

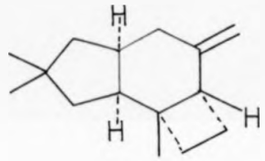
Due to the lack of progress in inducing humulene to undergo ring closures towards naturally occurring skeletons, Shirahama *et al.*[104] initiated a series of model studies. To this end the protoilludyl cation precursors, 7α-protoilludanol (158), 7β-protoilludanol (159), $\Delta^{7,(13)}$-protoilludene (160), and 7-keto-13-norprotoilludane (120) were all produced by total synthesis. The nor-ketone (120) was converted to d,l-hirsutene (156) *via* the route shown in Scheme 30.[105]



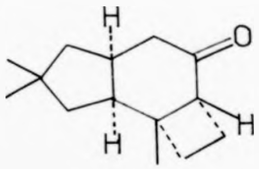
(158)



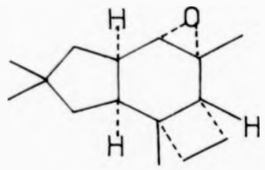
(159)



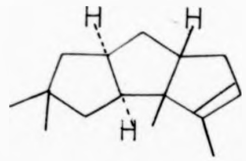
(160)



(120)



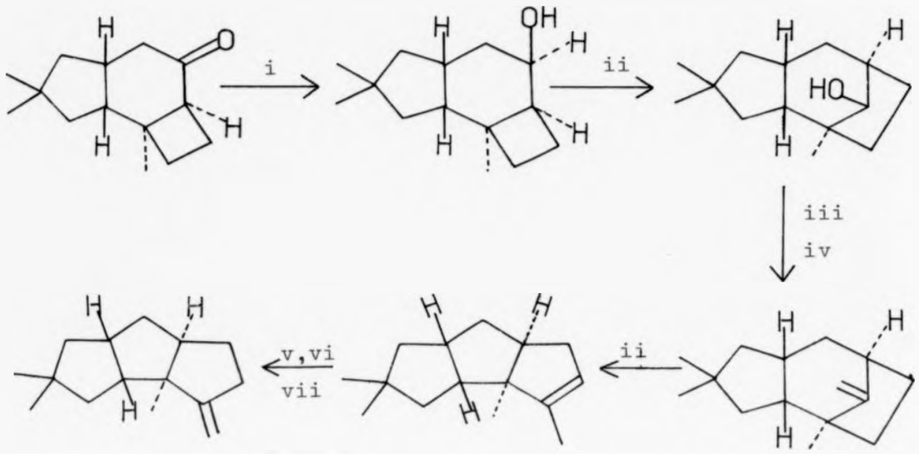
(161)



(162)

d,l-Hirsutene was also produced from $\Delta^{7,(13)}$-protoilludene (160) *via* the epoxide (161).[106]

It is relevant at this point to include a description of a set of model studies which were used by Shirahama *et al.*[107] to rationalise the formation of *endo*-hirsutene (162) from α-protoilludene-epoxide (161). The compounds (163)-(166) were prepared and treatment of (162)-(165) with formic acid at 0°C resulted in a mixture of (166)-(171). On the other hand,



Reagents : i $NaBH_4$
ii p-TSA
iii CrO_3 - H^+
iv $Ph_3P=CH_2$
v m-CPBA
vi $LiAlH_4$
vii MsCl , py

Scheme 30

treatment of (163)-(166), with formic acid at 60°C resulted in a mixture of (169)-(171) only. The exo olefin (167) remained unchanged when resubmitted to these reaction conditions, whilst the endo olefin (168) on resubmission gave a mixture of (169)-(171). These results were thought to be consistent with the mechanisms in Scheme 31.

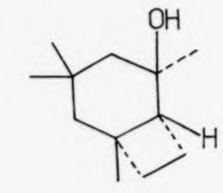
Finally humulene has been converted to hirsutene[108] by an indirect route using nor-derivatives. Starting from the previously discussed ether (134) this was converted to the bicyclic norketone (172) which was converted through a number of steps to the bridged norketone (173) which had previously been converted to hirsutene[105] (Scheme 32).

Pentalenane

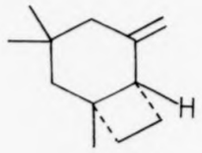
There are now a growing number of compounds isolated with a pentalenane skeleton. Pentalenic acid (174), pentalenolactones E (175), G (176), H (177), F (178), pentalenolactone (179) and the parent hydrocarbon itself, pentalenene (139), have all been isolated.[109-113]

The pentalenanes are thought to be derived from humulene *via* the protoilludyl cation (97) although an alternative and more direct mechanism may be operating which does not involve this intermediate (Scheme 33).

Cane *et al.*[114-115] have investigated pentalenane biosynthesis by using a series of ^{13}C, ^{2}H and ^{3}H labelling experiments. The labelled precursor, [u-$^{13}C_6$] glucose, was fed to cultures of *Streptomyces* UC5319 and the labelling pattern produced in the isolated pentalenolactone was consistent with Scheme 34. Similar experiments using [6,6-$^{2}H_2$] glucose as the labelled precursor give inconclusive results. ^{3}H Labelling of farnesyl pyrophosphate gave results that confirmed the scheme already proposed from ^{13}C labelling. It is concluded from this work that the pentalenanes are formed from cyclisation of humulene in the *RSR*-CT conformer.



(163)



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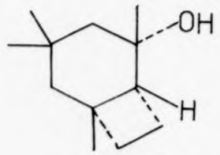

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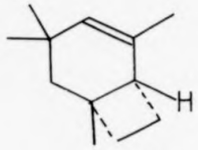

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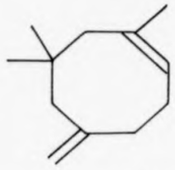

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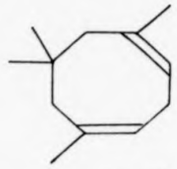

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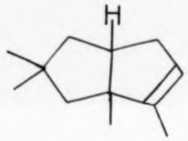

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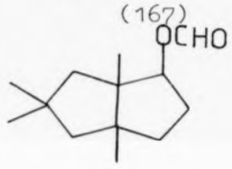

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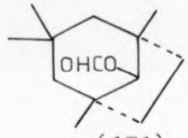
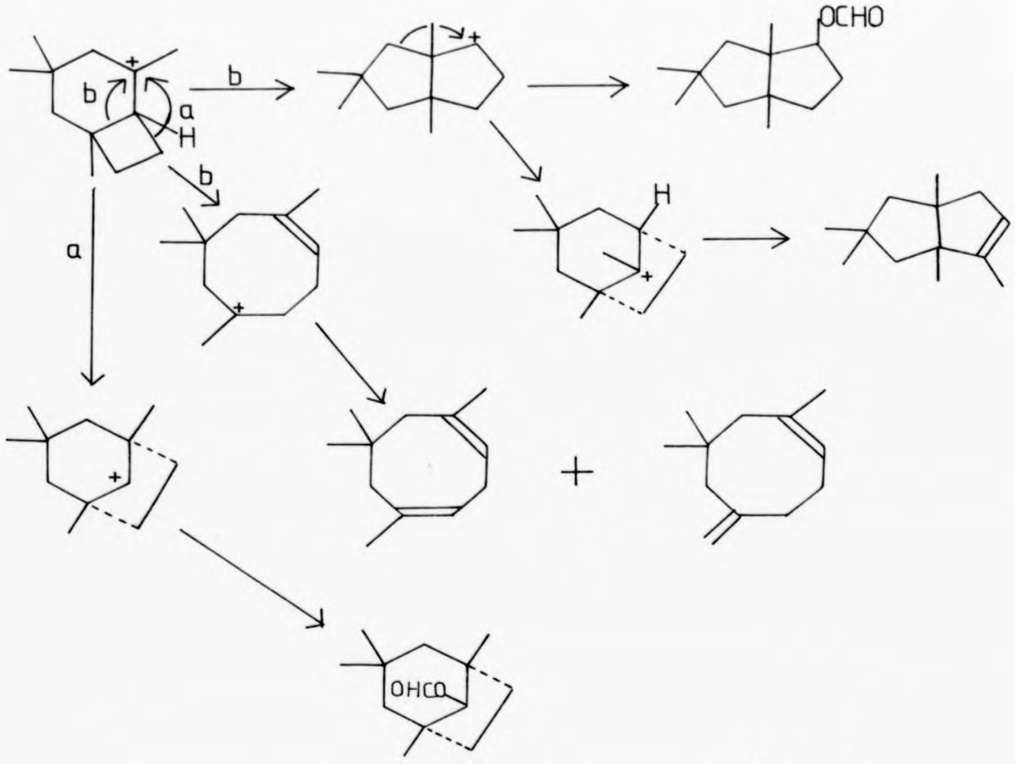
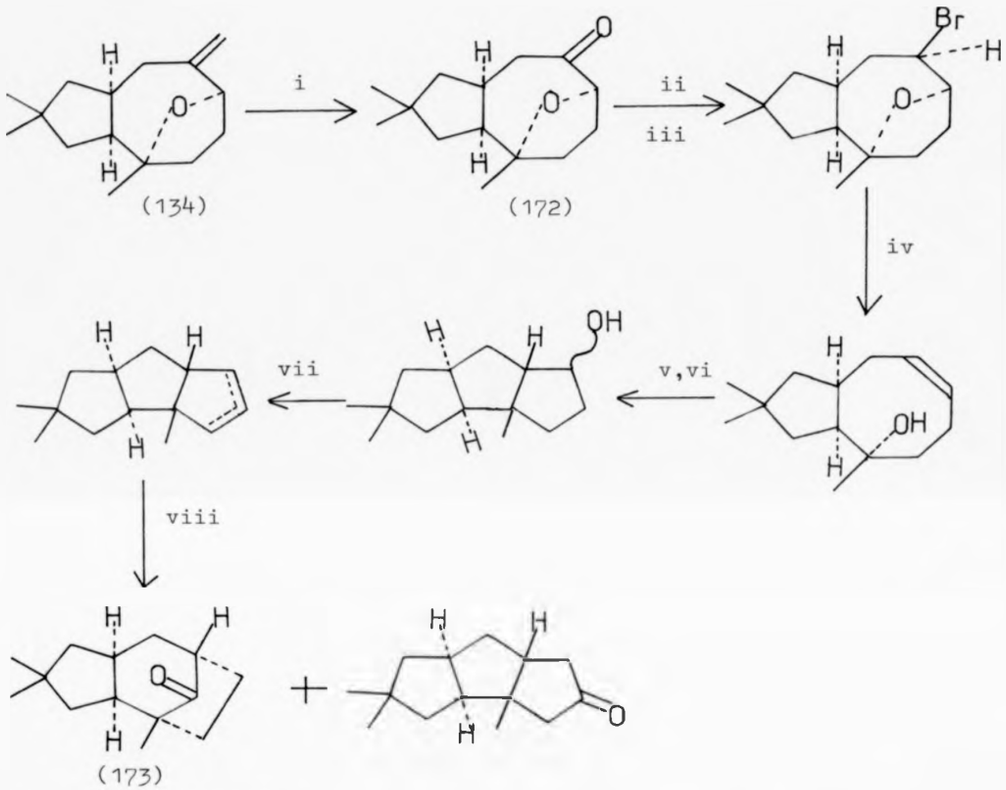


(171)



Scheme 31



Reagents : i OsO_4 , $NaIO_4$

ii DiBAL

iii PPh_3 , CBr_4

iv Zn , EtOH

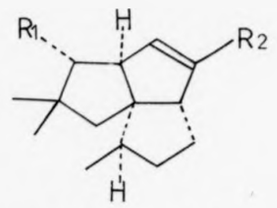
v HCO_2H , Ac_2O

vi $LiAlH_4$

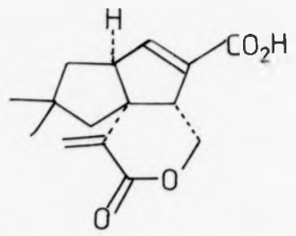
vii MsCl , py

viii $Tl(ClO_4)_3$

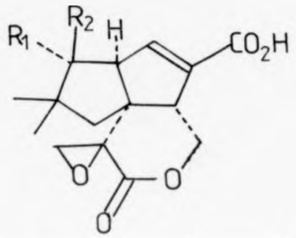
Scheme 32



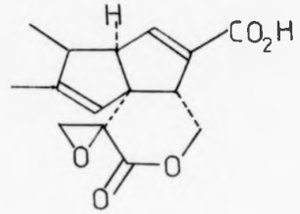
R_1 = OH R_2 = CO_2H (174)
R_1 = H R_2 = CH_3 (139)



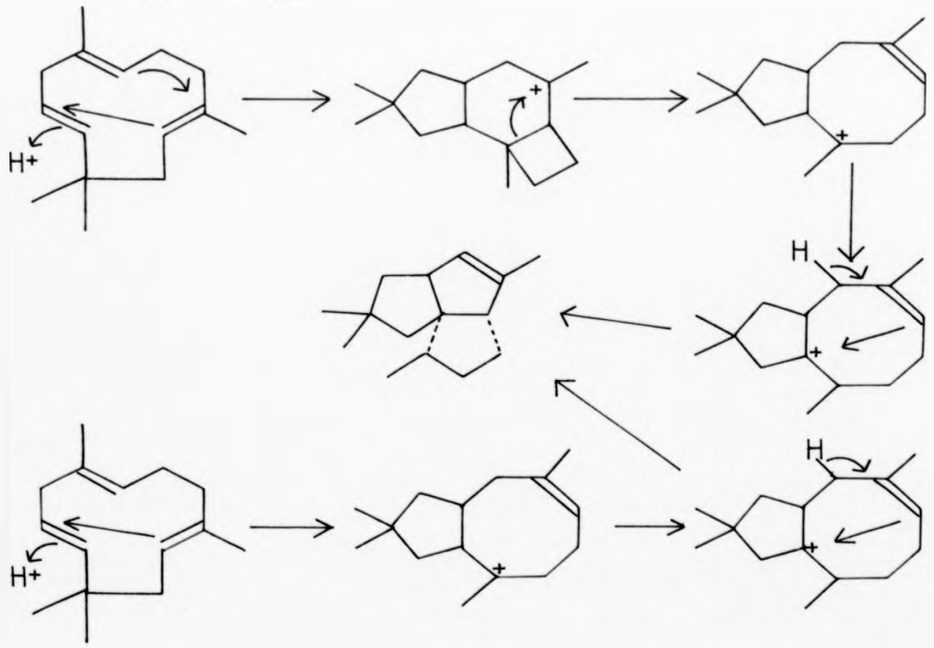
(175)



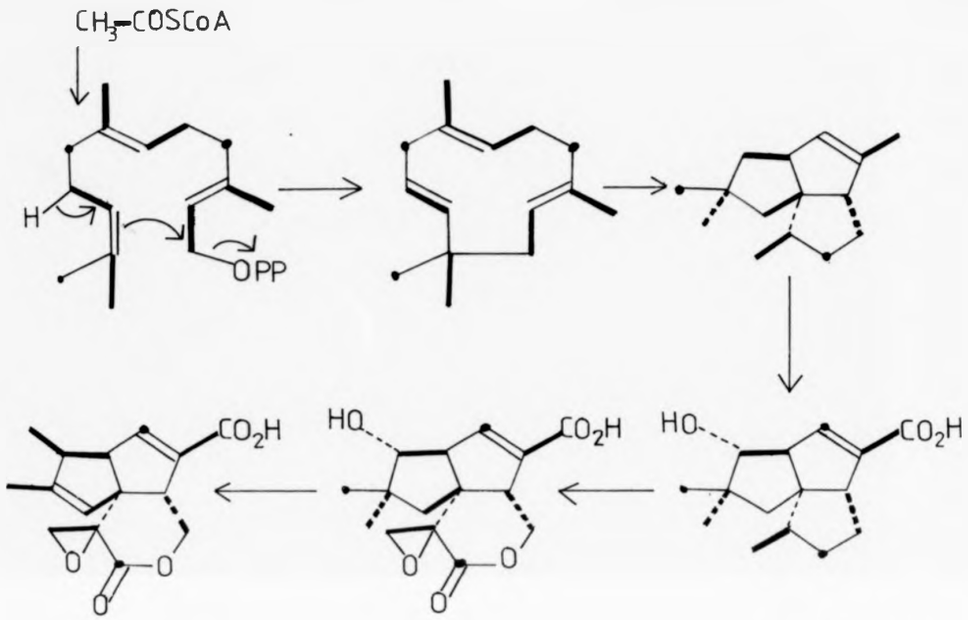
R_1 = R_2 = O (176)
R_1 = OH R_2 = H (177)
R_1 = H R_2 = H (178)



(179)



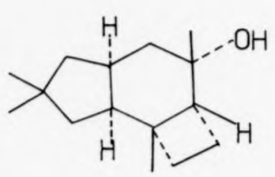
Scheme 33



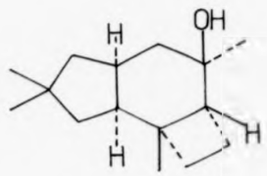
Scheme 34

The first biomimetic-type synthesis of pentalenene (139) in 1975, came from the model studies of Shirahama et al.[104,116] However, it should be noted that pentalenene was not isolated as a naturally occurring compound until 1980.[111] Formolysis of the protoilludanoids (158), (159), and (160) produced a mixture of the bridged formate (138) and pentalenene (139). The reaction was thought to proceed through the protoilludyl cation (97) and the products (138) and (139) were explained in terms of different conformers of (97) (Scheme 35).

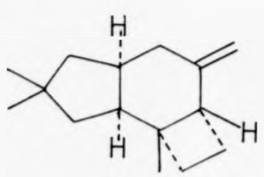
The alcohol (137), which was produced by lithium



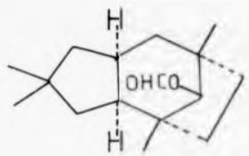
(158)



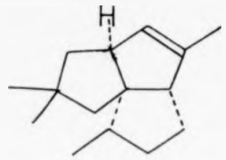
(159)



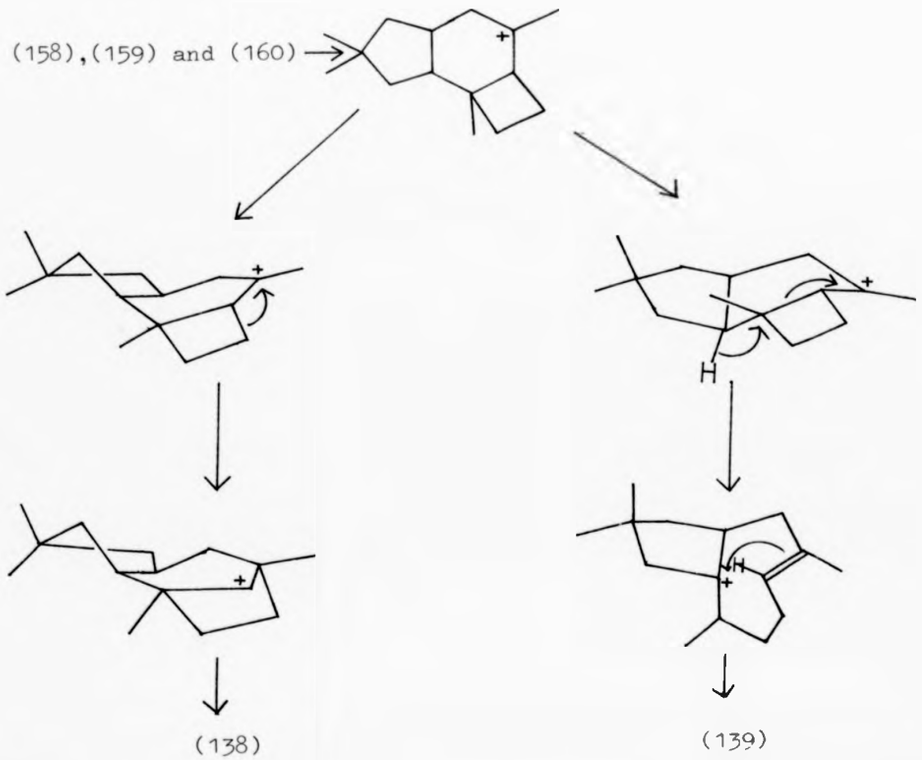
(160)



(138)



(139)



Scheme 35

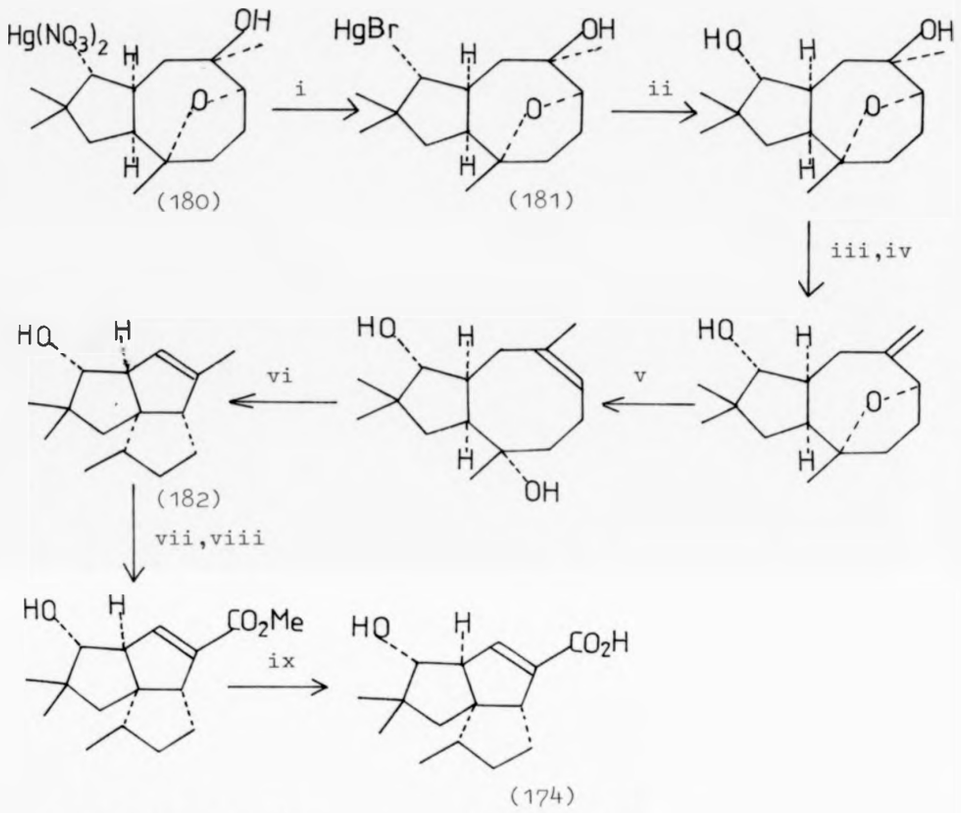
in ethylamine treatment of the cyclic ether (134), itself a product of the oxymercuration/demercuration procedure on humulene, was also converted to pentalenene. Formolysis of (137) produced the bridged formate (138) and pentalenene (139).[91]

Shirahama *et al.*[117,118] have now also converted humulene to pentalenic acid (174) and pentalenolactones E (175) and F (178). The synthesis of pentalenic acid from the previously described compound (180) is outlined in Scheme 36. Essential steps in this synthesis involve the functionalisation of C-4 *via* the bromomercurial (181), and also selective oxidation of the allylic methyl in (182).

The synthesis of pentalenolactones E (175) and F (178) uses a circuitous route to achieve functionalisation in ring C. The key feature of this synthesis is the conversion of the methoxy alkene (183) to the ketone (184). This transformation of the double bond ensures that the cyclisation is initiated at the ketonic carbon to yield the alcohol (185): the functionalisation now present provides a foothold for the lactonisation of ring C.

Capnellane

The capnellanes are skeletally similar to the hirsutanes, differing only in the position of the methyl groups. The capnellanes are probably derived from humulene but clearly there must be a methyl migration at some point in the biosynthetic pathway. Capnellanes are typified by $\Delta^{9,(12)}$ capnellene (69) and $\Delta^{9,(12)}$ capnellen-8β,10α-diol (186).[119]



(180) (181) (182) (174)

Reagents : i KBr ii O_2 , $NaBH_4$

iii Ac_2O , py , PBr_3

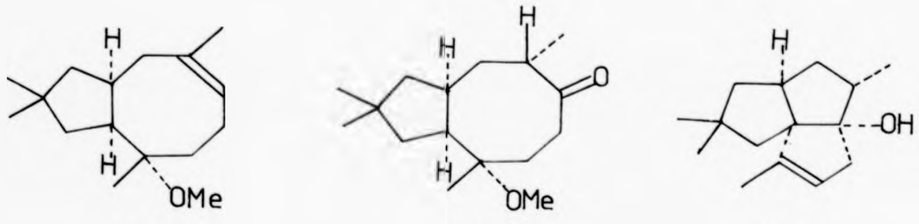
iv t-AmONa , DMSO

v Li , $EtNH_2$ vi BF_3Et_2O

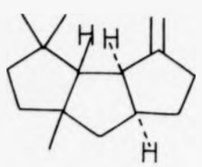
vii SeO_2 viii MnO_2 , KCN

ix KOH , MeOH , H_2O

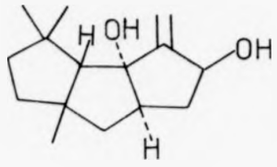
Scheme 36



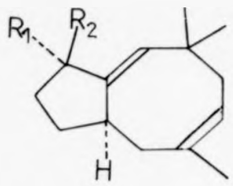
(183) (184) (185)



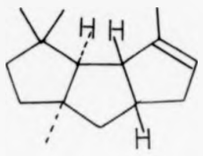
(69)



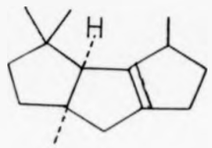
(186)



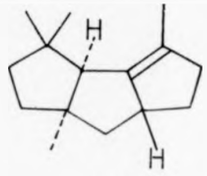
R_1 = H R_2 = CH_3 (187)
R_1 = CH_3 R_2 = H (188)



(189)



(190)

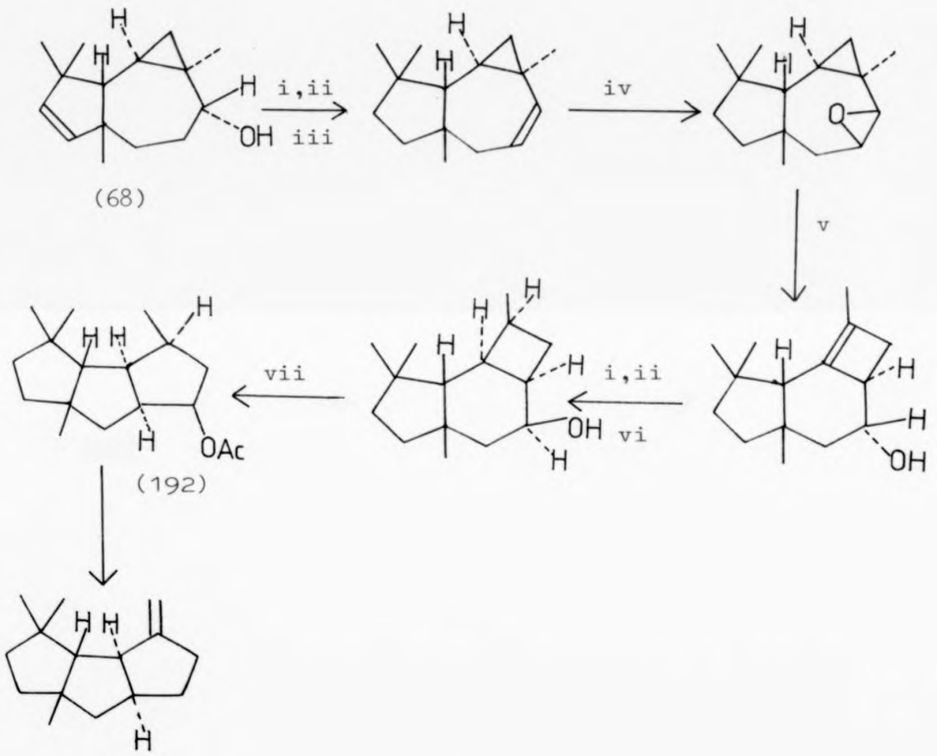


(191)

The presumed biosynthetic precursor for the capnellanes, precapnelladiene (187)[120], has recently been the subject of a study by Pattenden and coworkers.[121] Epiprecapnelladiene (188) was made by total synthesis, cyclisation of (188) with boron trifluoride etherate resulted in the formation of $\Delta^{8,9}$ capnellene (189) as the major product and $\Delta^{6,(10)}$ and $\Delta^{9,(10)}$ capnellenes (190) and (191) as the minor isomeric products.

Shirahama et al.[44,45] have reported the conversion of humulene to $\Delta^{9,(12)}$ capnellene (69). Cyclisation of humulene-1,2-epoxide (5) with trimethylsilyl trifluoromethane-sulphonate yielded the tricyclic alcohol as the major product. The alcohol (68) was then converted to the acetate (192),

proceeding through an apparent methyl migration (Scheme 37) this was converted to $\Delta^{9,(12)}$ capnellene by conventional methods.



(68) (192) (69)

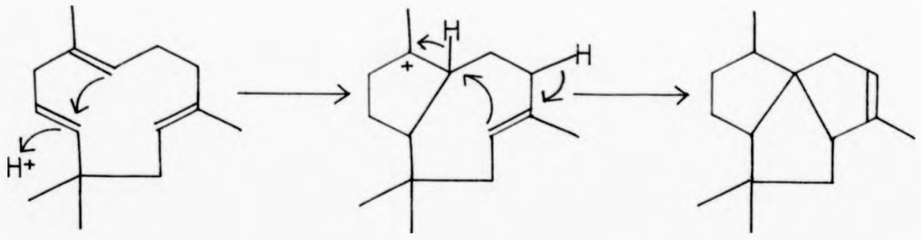
Reagents : i H_2 , PtO_2 ii CrO_3-H^+
iii Shapiro's method
iv m-CPBA
v(a) $Me_3SiTrif$ v(b) HCl
vi L-selectride
vii(a) MsCl , py , DMAP vii(b) NaOAc , AcOH

Scheme 37

Quadrane, Senoxydane and Botrydiane

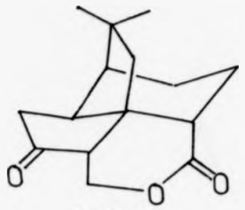
Recently it has been suggested that quadrone (193) can be derived from humulene (1). Evidence to support this proposal comes from labelling experiments.[122] [1-^{13}C] and [1,2-^{13}C] Acetate were fed to Aspergillus terrus and the labelling patterns produced in quadrone were consistent with the biosynthetic pathway shown in Scheme 38. It should be noted, however, that the labelling is also consistent with a previously suggested biosynthetic route from caryophyllene (35).[123]

Senoxydene is a sesquiterpene isolated in 1979 by Bohlmann et al.[124] from Senecio oxydontus; its structure was assigned as (194) on the basis of spectroscopic analysis. They proposed that senoxydene could be derived from humulene (Scheme 39).

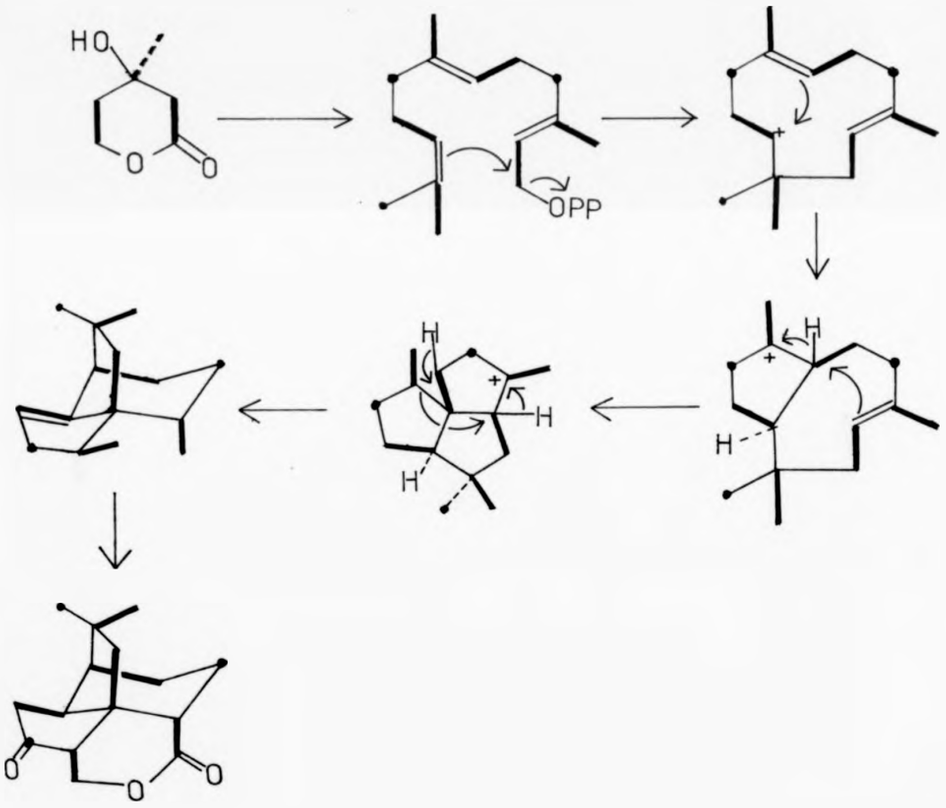


Scheme 39

However total synthesis of the hydrocarbon (194) and of its epimer (195), both of these structures being rigidly established, showed that senoxydene is not (194) or (195) and its structure is uncertain at present.[125] Despite this, one important point may be made: if the proposed biosynthesis of senoxydene is re-examined then a common pathway with quadrone can be seen.

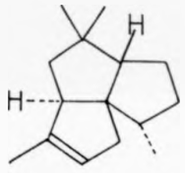


(193)

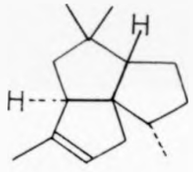


Scheme 38

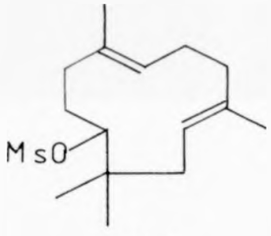
Hence the proposed biosynthetic route for both quadrone and senoxydene would involve the intermediacy of the C-5 cation. Nozaki *et al.*[126] have synthesised a C-5 cation equivalent *in vitro* in the form of 5-mesyl-humulene (196), and treatment of this with aqueous acetone or dimethylaluminium phenoxide yielded humulene as the major product. In view of this result it appears tenuous to invoke the C-5 cation of humulene in quadrone or senoxydane biosynthesis although the enzymatic process may well differ.



(194)



(195)

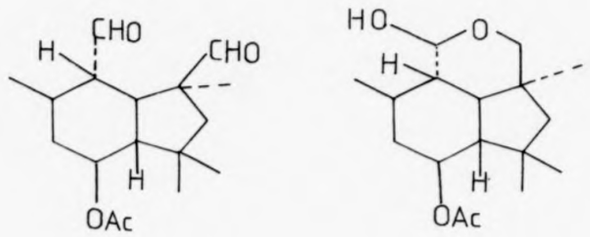


(196)

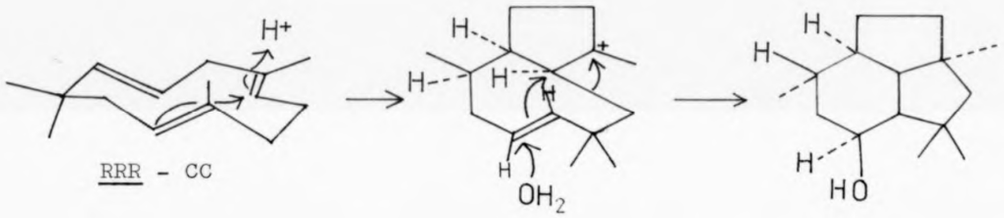
Botrydial (197) and dihydrobotrydial (198) are fungal metabolites whose biosynthesis has been investigated by ^{13}C and ^{1}H labelling.[127] It is proposed from this information that botrydial is derived from humulene (Scheme 40), although it should be noted that the proposed route would involve initial enzymatic proton at the $\Delta^{1,2}$ double bond. Stereochemical considerations indicate that the humulene cyclised would be in the RRR-CC conformer.

Z,E,E Humulene

Shirahama *et al.*[128,129] have attempted to expand on Hendrickson's suggestion[21] that several groups of sesquiterpenes such as the himachalane (199), longifolane (200),



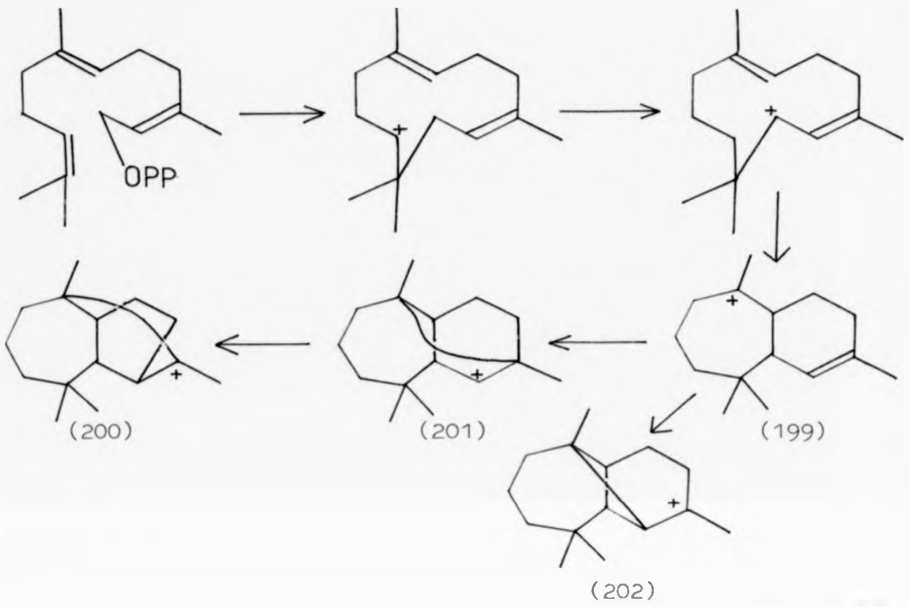
(197) (198)



Scheme 40

longibornane (201) and longipinane (202), skeletons are derived from cis-farnesyl pyrophosphate, through a protonated form of Z,E,E-humulene (Scheme 41).

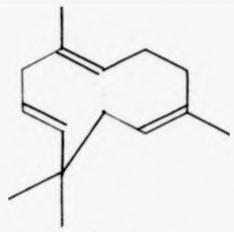
Z,E,E-Humulene (203) was synthesised from E,E,E humulene and force field calculations indicated that it consists of four minimum strain conformers, namely the TT (204), CT (205), TC (206) and CC (207) conformers with respective heats of formation of 6.29, 6.36, 6.42 and 6.71 k cal $mole^{-1}$. Thus only small differences in strain energy were calculated among the conformers and each conformer is considered to be present in a conformational equilibrium mixture.



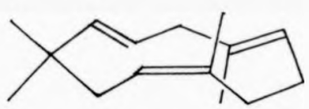
Scheme 41

Direct cyclisation of Z,E,E-humulene, by the oxymercuration/demercuration procedure used previously to cyclise E,E,E-humulene to the cyclic ether (132) produced an isomeric ether (207). It is presumed that the different geometry of the starting material leads to a different stereochemistry in the product.

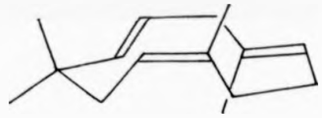
Cyclisation of Z,E,E-humulene-4,5-epoxide (209) with trimethylsilyl trifluoromethanesulphonate gave the novel isomeric alcohols (210) and (211). These were formed by the opening of the 4,5 epoxide to give the C-4 cationic centre, which subsequently interacts with the $\Delta^{1,2}$ double bond. Nozaki et al.[126] synthesised the Z,E-humulene-5-mesylate (212), treatment of this with aqueous acetone yielded the ring



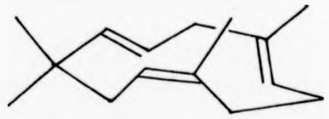
(203)



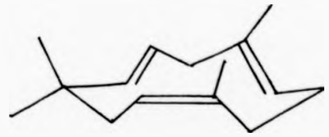
TT
(204)



CT
(205)

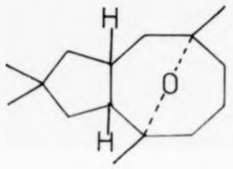


TC
(206)

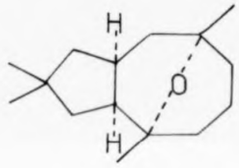


CC
(207)

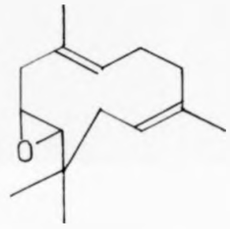
contraction products (213), (214) and (215). It is interesting to note that no cyclisation products of (209) or (212) were isolated from the generation of a cationic centre at either C-4 or C-5 of Z,E-humulene.



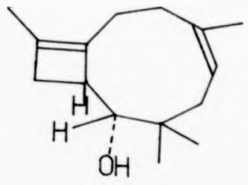
(208)



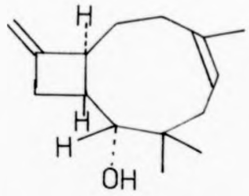
(132)



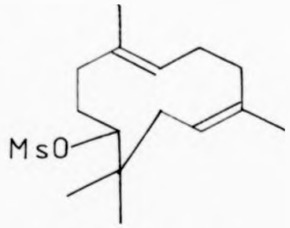
(209)



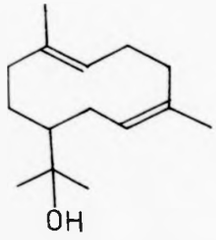
(210)



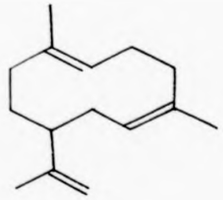
(211)



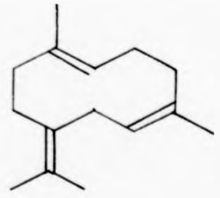
(212)



(213)

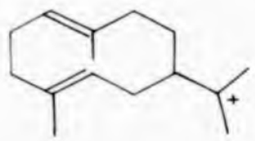


(214)



(215)

It can be seen from the information in this introduction that over the past twenty years humulene has risen in stature to become a pivotal sesquiterpene in the biogenesis of a wide variety of bicyclic and tricyclic sesquiterpenoids. It now commands a position as important as germacrene (216) in the hierarchy of biogenetically significant sesquiterpenes. In view of the increasing number of humulene-derived metabolites in recent years it will be interesting to see whether humulene will ultimately assume the dominant position.



(216)

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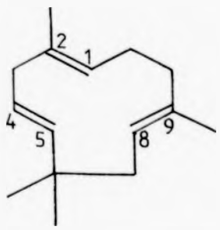
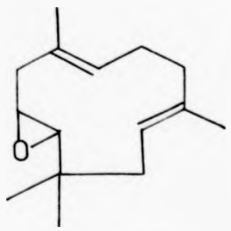
DISCUSSION

As described in the introduction the all-important feature of the intermediacy of humulene (1) in the biosynthesis of a wide variety of sesquiterpenoids is the apparent enzymatic protonation of the $\Delta^{4,5}$ double bond. The ensuing generation of a cationic centre at C-4 provides the impetus for π-participation with the $\Delta^{1,2}$ and $\Delta^{8,9}$ double bonds leading to the various bicyclic and tricyclic frameworks. Furthermore it is abundantly clear that the *in vitro* chemistry of humulene does not mirror these proposed pathways in view of the greater reactivity of the $\Delta^{1,2}$ double bond towards electrophilic attack such as protonation, epoxidation and oxymercuration. Thus any attempts to mimic the proposed biosynthetic pathways demands a regio-controlled functionalisation of humulene in such a way that generation of the C-4 cationic centre can be guaranteed.

An attractive method of achieving this objective is to form the 4,5-epoxide. Johnson and van Tamelen, in particular, have pioneered this technique to promote the



(1)



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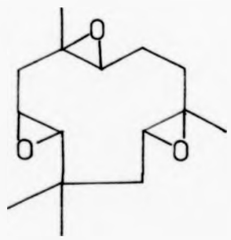
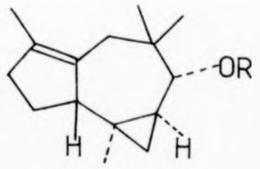


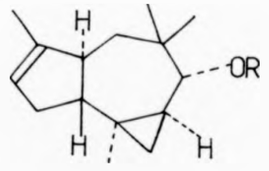
(3)

cyclisation of acyclic polyolefins with remarkable success.[1,2] It should be noted that the formation of humulene-4,5-epoxide (2)

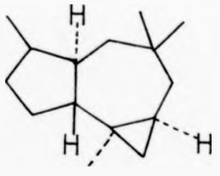
is not simple, as it requires functionalisation of the least reactive double bond. A convenient method for the formation of humulene-4,5-epoxide (2) is by deoxygenation of humulene trisepoxide (3) with two equivalents of tungsten hexachloride and n-butyllithium.[3] The conformations of humulene-4,5-epoxide (2) are thought to be similar to those of humulene itself, thus humulene-4,5-epoxide will exist as a mixture of CC, CT, TC and TT conformers. Treatment of humulene-4,5-epoxide with boron trifluoride etherate in ether or trimethylsilyl trifluoromethanesulphonate yields the alcohols (4) and (5) with an africane type skeleton (6).[4,5] The alcohols (4)



R = H (4)
R = Ac (9)



R = H (5)
R = Ac (10)



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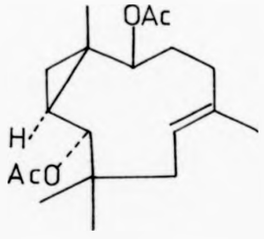

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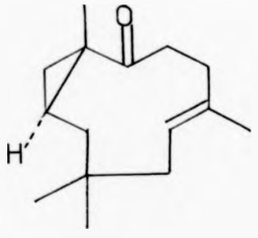


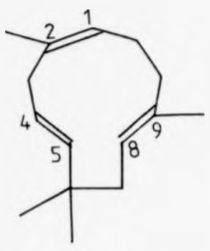
(8)

and (5) can be considered to have arisen from cyclisation of humulene-4,5-epoxide in the CT conformer. Treatment of humulene-4,5-epoxide (2) with boron trifluoride etherate in

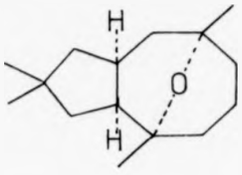
acetic anhydride yields the diacetate (7) related to bicyclohumulenone (8). The diacetate (7) can be considered to have arisen from cyclisation of humulene-4,5-epoxide in the CC conformer. These cyclisations of humulene-4,5-epoxide can be viewed as examples of a conformationally selective reaction. Treatment of humulene-4,5-epoxide with boron trifluoride etherate in acetic acid yields both CC and CT conformer-mediated products, namely the acetates (9) and (10) and the diacetate (7).[6] Thus *in vitro* cyclisation of humulene-4,5-epoxide is initiated by carbonium ion formation at C-4. Interaction with the $\Delta^{1,2}$ double bond follows to yield products of the africane (6) and bicyclohumulane (8) types.

Although these were very encouraging results and can be viewed as a biomimetic-type syntheses of the africane and bicyclohumulane compounds, Shirahama and ourselves have been unable to encourage the $\Delta^{8,9}$ double bond to participate naturally with the C-4 cationic centre, in what is probably a concerted reaction. This was essentially the objective of the work to be described since only by these means could we begin to break into the protoilludyl and related systems, i.e. towards those compounds having a gem-dimethylcyclopentane ring as a common denominator. An examination of molecular models leads to the identification of the problem as the *trans* geometry of the $\Delta^{1,2}$ double bond, which inhibits the correct alignment of the $\Delta^{4,5}$ and $\Delta^{8,9}$ double bonds. Two solutions to this problem were thought possible. Firstly, *trans*-*cis* isomerisation of the $\Delta^{1,2}$ double bond should increase the conformational mobility within the ring. Some

initial work in this field has been performed within this research group with the formation of isohumulene (11), although no transannular cyclisations have so far been attempted.[7]



(11)



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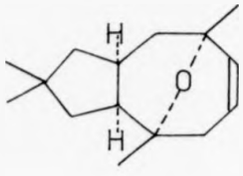
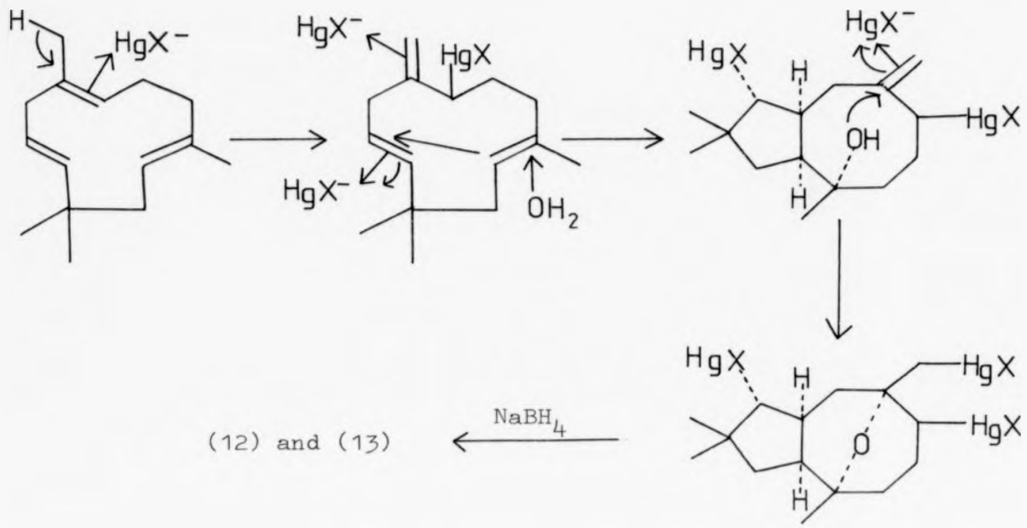


(13)

Alternatively the $\Delta^{1,2}$ double bond could be temporarily removed and replaced with a suitable functionality which would permit the regeneration of the double bond at the appropriate time. Thus two sp^2 hybridised centres would be replaced by two sp^3 hybridised centres which should increase the conformational mobility within the eleven-membered ring, allowing for a more favourable alignment of the $\Delta^{4,5}$ and $\Delta^{8,9}$ double bonds. This approach also has the advantage that as the $\Delta^{1,2}$ double bond has been removed, no products can arise from interaction of the $\Delta^{4,5}$ and $\Delta^{1,2}$ double bonds.

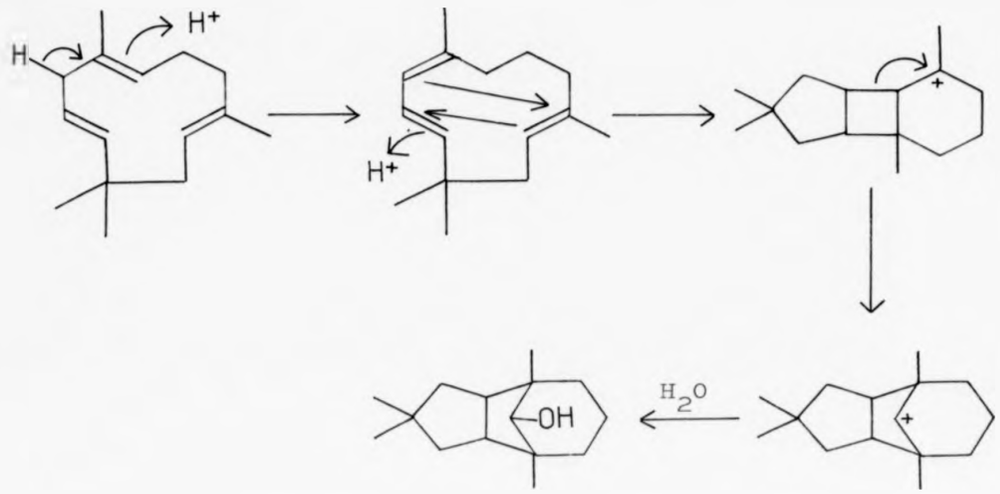
This hypothesis receives support from the work of Shirahama *et al.*[8], who cyclised humulene directly with mercury compounds, using an oxymercuration/demercuration procedure to give the cyclic ethers (12) and (13). The mechanism of the reaction was examined by deuterium labelling[9] and showed that the reaction proceeds *via* the pathway shown in Scheme 1. It is important to note that the derivative which undergoes cyclisation has an sp^3 centre at C-1.



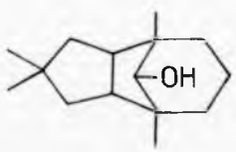
Scheme 1

Also relevant to this hypothesis is the product formed on treatment of humulene (1) with sulphuric acid, α-caryophyllene alcohol (14).[10] This reaction has been examined by deuterium labelling coupled with ^{13}C nmr spectroscopy and the proposed mechanism is outlined in Scheme 2.[11] Interestingly the initial step is the $\Delta^{1,2}$ to $\Delta^{2,3}$ double bond isomerisation, leaving an sp^3 centre at C-1. The interactions within the ring are now such that the $\Delta^{4,5}$ double bond undergoes initial protonation, followed by successive participation of the $\Delta^{8,9}$ and $\Delta^{2,3}$ double bonds.

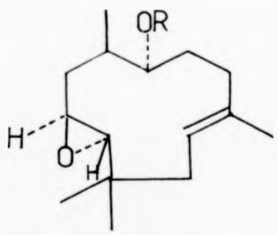
Work along these lines has already been carried out



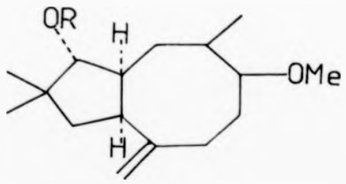
Scheme 2



(14)

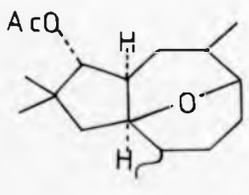


R = H (15)
R = Me (16)

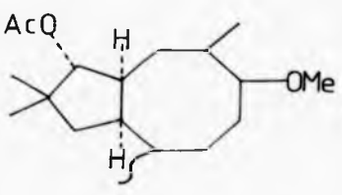


R = H (17)
R = 3,5 dinitrobenzoate (18)
R = Ac (19)

within this research group by Bryson.[7] The target molecule was envisaged as the protected isohumulol-4,5-epoxide (15). The methyl ether was chosen as the protecting group in the molecule (16). This would seem initially a strange protecting group to use as it is normally considered too stable for routine protection of alcohols. The introduction of organosilicon reagents such as trimethylsilyl iodide,[12] however, should make the dealkylation of methyl ethers a simple process. The methyl ether of isohumulol-4,5-epoxide (16) was synthesised from humulene (1) in four steps. Treatment of the epoxide (16) with boron trifluoride etherate in ether gave one major product, the alcohol (17) whose structure was established as the 5-methyl ether of 6,10,10-trimethyl-2-methylene bicyclo-[6.3.0]undeca-5,9-diol by X-ray analysis of the 3,5 dinitrobenzoate derivative (18). Surprisingly, however, treatment of the acetate (19) with trimethylsilyl iodide produced the cyclic ether (20), as did treatment of (19) with a whole range of organosilicon reagents. This proved a major barrier to further work in this field. Interestingly hydrogenation of the acetate (19) with Raney nickel as the catalyst produced the dihydro-compound (21), which when treated with trimethylsilyl iodide underwent elimination to give the alkene (22).



(20)



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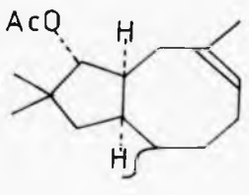
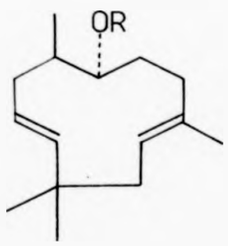


(22)

This final result provided an impetus for further work in this field, showing that if the problems that beset the deprotection stage could be overcome the $\Delta^{5,6}$ double bond could be restored.

As several new methods for methyl ether cleavage had been published following Bryson's work, it seemed logical to examine these methods before considering new protecting groups.

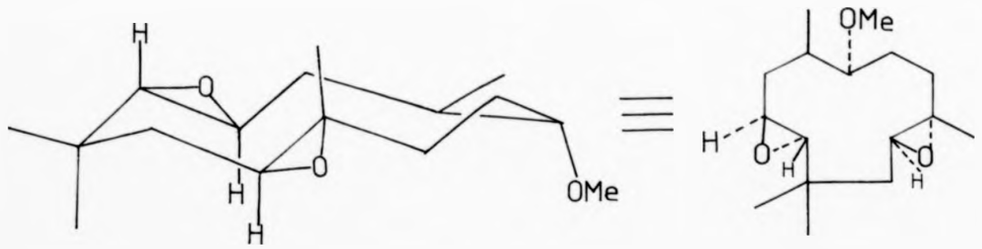
Humulene (1) was hydroborated with borane-tetrahydrofuran complex to give isohumulol (23) in low yield (∿ 36%).[13] The remaining material recovered from the reaction mixture was starting material which could be recycled. Although isohumulol was normally purified by column chromatography using Kieselgel 60, this was a lengthy and tedious process and more usually crude isohumulol was used in the protection step, and the protected isohumulol thus produced could be purified on alumina.



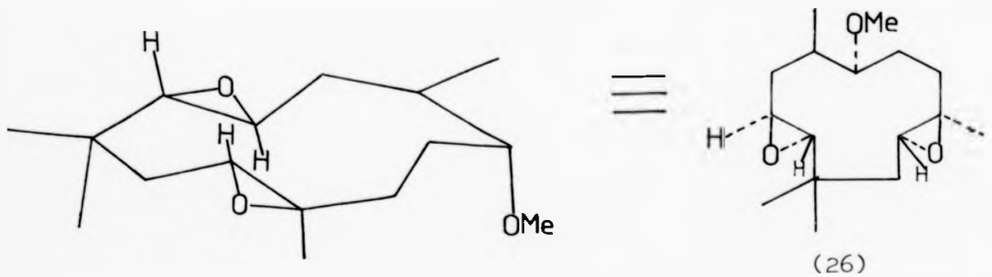
R = H (23)
R = Me (24)

Protection of isohumulol (23) as the methyl ether (24) was a straightforward process using n-butyllithium and methyl iodide. Bisepoxidation of the methyl ether (24) in a biphasic system of dichloromethane/0.5M sodium bicarbonate

solution,[14] emulsified by rapid mechanical stirring and using m-chloroperoxybenzoic acid as the epoxidation agent, gave either (25) or its diastereoisomer (26) in good yield (62%). The relative stereochemistries of (25) and (26) are depicted in Scheme 3. The stereochemistry about the C-4 - C-5 bond is the crucial feature in (25) and (26), and was inferred from the stereochemistry of the cyclisation product (17). The stereochemistry about the C-8 - C-9 bond cannot be determined in the bisepoxides (25) and (26) since the C-8 - C-9 epoxide is removed in the next step.



(25)



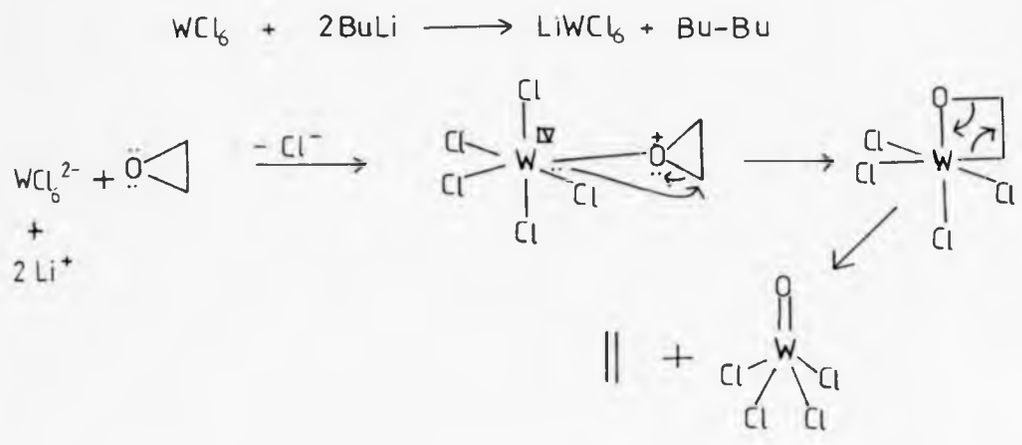
(26)

Scheme 3

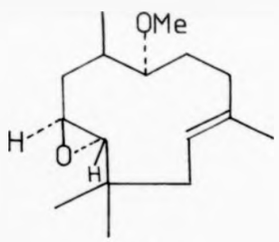
Treatment of the methyl ether of isohumulol bisepoxide (25)/(26) with tungsten hexachloride and n-butyllithium produced the 4,5-epoxide (16) in relatively good yield (37%).[15,16] This method for the deoxygenation of epoxides has been used previously by this research group for the regioselective deoxygenation of humulene trisepoxide (3) to give humulene-4,5-epoxide (2).[3] The principle reagent in this mixture is thought to be Li_2WCl_6 and the proposed mechanism of the reaction is depicted in Scheme 4. It is interesting to note that the WCl_6^{2-} ion can act as a Lewis acid as well as a reducing agent.

The methyl ether of isohumulol-4,5-epoxide (16) was then treated with boron trifluoride etherate in ether to yield the 5-methyl ether of 6,10,10-trimethyl-2-methylene bicyclo[6.3.0]undeca-5,9-diol (17) spectroscopically identical to authentic material prepared by Bryson.[7] The alcohol (17) was subsequently acylated with acetic anhydride, pyridine and N,N-dimethyl-4-aminopyridine to give the acetate (19).

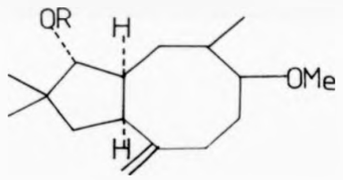
It had previously been found that the alcohol (17) could be isolated also from the crude deoxygenation mixture when longer reaction times were used.[7] Re-examination of the crude deoxygenation mixture showed that cyclised material could also be isolated under normal reaction times. If the crude bisepoxide (25/26) was recovered from the deoxygenation reaction mixture and examined by analytical tlc, it was seen to consist of two compounds Rf = 0.28 and 0.3. These could be separated by acylation of the crude reaction mixture followed by column chromatography. There were three spots



Scheme 4



(16)

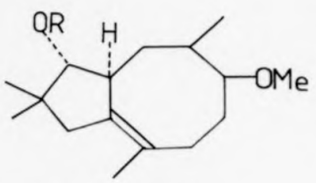


R = H (17)
R = Ac (19)

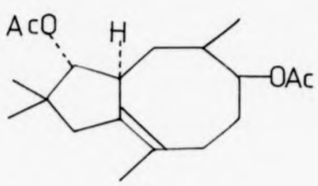
visible on analytical tlc after acylation Rf = 0.28, 0.76, 0.82. The material, Rf = 0.28 was identified as the bis-epoxide (25/26), and the material Rf = 0.76 was identified as a mixture of the acetate (19) and a new acetate. The material Rf = 0.82 was the new acetate and displayed a 90 MHz nmr spectrum with:

δ = 0.87 (3H,s), 0.99 (3H,d,J = 6Hz), 1.04 (3H,s), 1.61 (3H,s), 2.05 (3H,s), 3.24 (3H,s), 3.24 (1H,m) and 4.62 (1H,d,J = 7Hz). This was identified as the isomeric acetate (27) by comparison of the 90 MHz nmr spectrum with that of the known diacetate (28).[7]

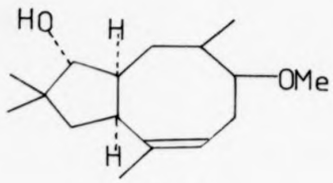
δ = 0.86 (3H,s), 0.99 (3H,d,J = 7H), 1.05 (3H,s), 1.61 (3H,s), 1.96 (3H,s), 2.09 (3H,s), 4.7 (1H,d,J = 6Hz) and 4.95 (1H,m).



R = Ac (27)
R = H (29)



(28)



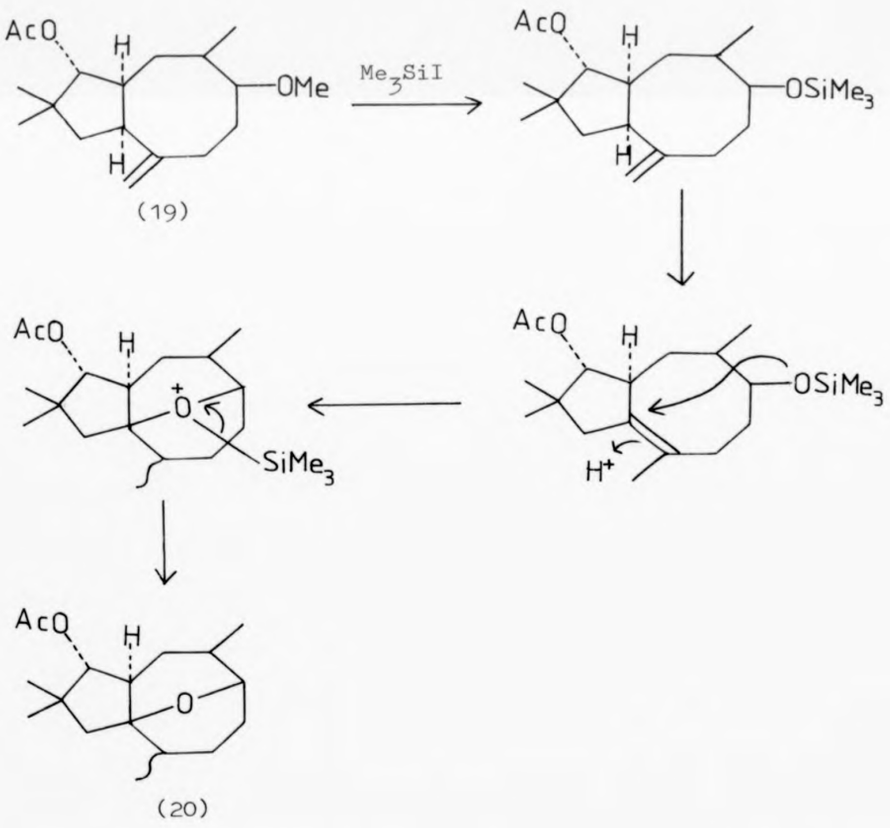
(30)

This result is interesting because not only is some species within the deoxygenation mixture, possibly the WCl_6^{2-} ion behaving as a Lewis acid, but also it can produce an isomeric product (29) to that produced by cyclisation with boron trifluoride etherate (17). There are three possible products of Lewis acid promoted cyclisation of the methyl ether of isohumulol-4,5-epoxide,[16] namely the isomeric alcohols (17), (29) and (30).

The cleavage of the methyl ether function was first attempted using the methyl ether of isohumulol (24) as a model compound. Treatment of this methyl ether with boron tribromide, 15 -crown-5 and sodium iodide[17] resulted in the formation of a plethora of products, whilst treatment with trichloromethyl silane[18] resulted in the formation of one major product which lacked any alkene protons in its nmr spectrum.

Methyl ether cleavage was also attempted on the bicyclic derivative (19). It should be remembered that this was found previously to give the cyclic ether (20), when treated with trimethylsilyl iodide generated <u>in situ</u>.[19] The

mechanism proposed for the formation of the cyclic ether (20) is outlined in Scheme 5. It is interesting to note that a proton source is mandatory for this mechanism, although there is not an obvious proton source within the reaction mixture, especially as the reaction was performed in the presence of a variety of bases and propene.[7] Isomerisation of the exocyclic double bond to the endo position is also required to explain C-O bond formation to C-1.

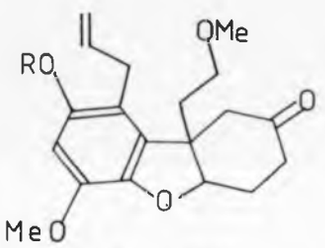


(19)

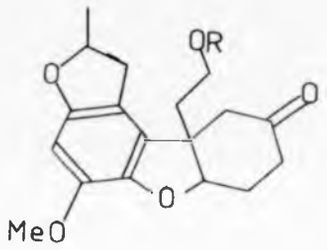
(20)

Scheme 5

An analogous reaction to this has appeared in the recent literature.[20] It was found that treatment of the methyl ether (31) with trimethylsilyl iodide did not give the expected alcohol (32), but instead gave the ethers (33) and (34). It was suggested that the initial step was indeed methyl ether cleavage of (31) to give (32), followed by cyclisation of the o-allyl phenol system due to the presence of adventitious hydrogen iodide.



R = Me (31)
R = H (32)

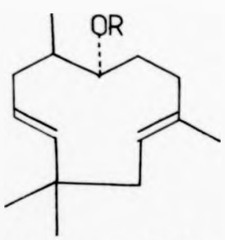


R = H (33)
R = Me (34)

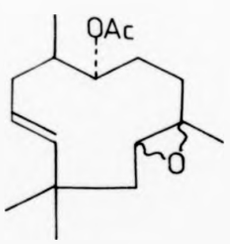
Treatment of the bicyclic derivative (19) with trimethylsilyl iodide generated *in situ*[19] from trimethylsilyl chloride and sodium iodide the resulting product was not the cyclic ether (20) but showed loss of the alkene protons at 4.76 and 4.98 ppm and the methyl ether protons at 3.25 ppm and the proton at 4.54 ppm. If the bicyclic derivative (19) was treated with trimethylsilyl iodide generated *in situ* in the presence of hexamethyldisilazane as a hydrogen iodide scavenger, then no reaction occurred. However if the same reaction mixture was heated to 50°C, one major product was formed, identified as the cyclic ether (20). Treatment of the bicyclic derivative (19) with trichloromethyl silane[18] gave the cyclic ether (20) as expected.

Since the methyl ether as a protecting group was presenting problems it seemed wise to abandon its use. The overall strategy, however, seemed to be ideal for obtaining the cis fused bicyclo[6.3.0]undecane system. Therefore it was decided to continue along these lines, altering the protecting group to one that, although less stable, may be cleaved under mild or neutral conditions.

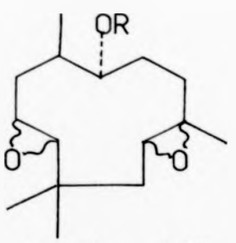
At this point the use of esters as a protecting group for isohumulol (23) was considered. The ester group would have many advantages, it is easily formed and can be hydrolysed under a variety of conditions. The use of two esters was examined, namely the acetoxy ester and the p-phenyl benzoate ester. Isohumulol (23) was easily esterified with acetic anhydride, pyridine and N,N-dimethyl-4-aminopyridine or p-phenyl benzoyl chloride and pyridine to give the acetate (35) and the p-phenyl benzoate (36) of isohumulol respectively.



R = Ac (35)
R = p-phenyl benzoate (36)



(37)



R = Ac (38)
R = p-phenyl benzoate (39)

Bisepoxidation of (35) under the same conditions used for the formation of the methyl ether bisepoxide (25/26) i.e. biphasic system, dichloromethane/0.5M sodium bicarbonate

solution, rapid mechanical stirring with m-chloroperoxybenzoic acid as the epoxidation agent,[14] gave only the monoepoxidised product (37). However if this monoepoxide was resubmitted to these conditions and the stirring rate lowered to a normal level, one major bisepoxide (38) was formed. This could be one of four diastereoisomers and insight into its relative stereochemistry could be gained from spectroscopic data. In particular it was possible to compare the key ^{13}C nmr chemical shifts that were assigned for the methyl ether bisepoxide of known stereochemistry about C-4 and C-5 (25/26) and the bisepoxide (38). (Table 1). The ^{13}C chemical shifts of C-4 and C-5 in (25/26) and (38) compare very well, however there is not such a good comparison between the ^{13}C chemical shifts of C-8 and C-9 in (25/26) and (38). It seems reasonable to assume that if (38) had a different configuration about the C-4 - C-5 bond from (25/26) then the ^{13}C chemical shifts would differ due to changes in conformation, steric effects and subtle electronic effects.[21] Hence (38) was assigned as having the same stereochemistry about the C-4 - C-5 bond as (25/26) with the stereochemistry about C-8 - C-9 in (38) unknown and possibly different from (25/26). Bisepoxidation of the p-phenyl benzoate (36) went smoothly under biphasic conditions (dichloromethane/0.5M sodium bicarbonate solution) at normal stirring rates with m-chloroperoxybenzoic acid as the epoxidation agent[14] to give one major bisepoxide (39).

The deoxygenation procedure with tungsten hexachloride and n-butyllithium should be compatable with esters, stigmasterol acetate bisepoxide (40) has been deoxygenated to

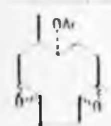
TABLE 1

*these are tentative assignments only

MOLECULE — ^{13}C NMR SPECTRUM ($CDCl_3$)

(25/26)

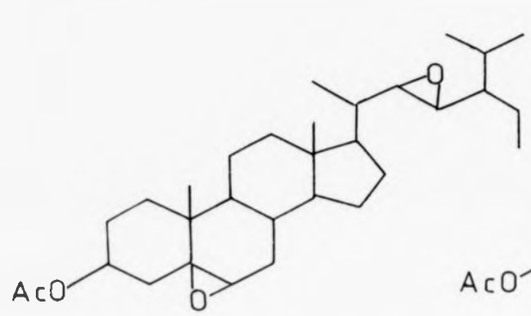
Assignment*				C-11		C-2	C-6	C-3	C-10	C-7	C-4	OCH_3	C-8	C-9	C-5	C-1
δ	12.9	17.7	20.6	24.0	28.4	31.8	33.0	35.5	35.7	40.0	56.9	57.1	59.0	61.0	67.2	82.0
Multiplicity	q	q	q	t	q	d	s	t	t	t	d	q	d	s	d	d



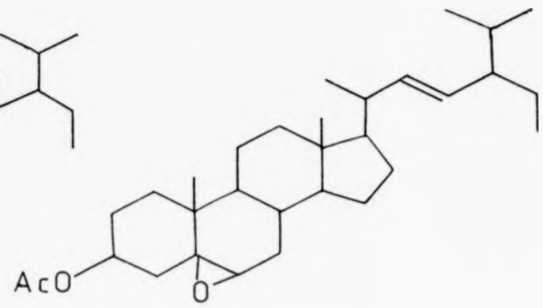
(40)

Assignment*					C-11		C-6	C-3	C-10	C-2	C-7	C-4	C-8	C-9	C-5	C-1	R-C=O
δ	13.15	17.1	20.7	21.1	22.6	28.3	33.02	35.0	35.3	35.7	40.4	56.6	59.3	61.0	67.2	73.7	171.0
Multiplicity	q	q	q	q	t	q	s	t	t	d	t	d	d	s	d	d	s

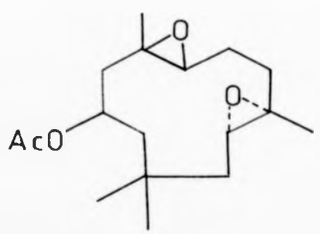
the monoepoxide (41).[15] Also relevant is the deoxygenation of the bisepoxide (42) to the acetate of 4-hydroxy-4,5-dihydrohumulene (43).[22]



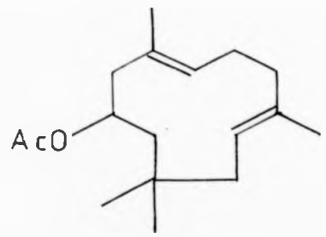
(40)



(41)



(42)

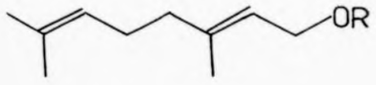


(43)

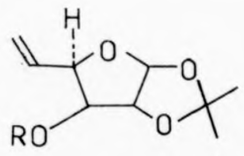
However attempted deoxygenation of (38) and (39) with tungsten hexachloride and n-butyllithium for prolonged periods resulted in the recovery of starting material only. This result was unexpected. It was thought that some type of tungsten complex was being formed within the reaction mixture, as the solution gradually became an orange-yellow colour on addition of the ester instead of the more usual blue solution, and this may have inhibited the deoxygenation reaction. However this is purely speculative, and this result

was discouraging and due to the previous success with an ether protecting group, a new type of ether protecting group was sought.

At this point our attention was attracted by a paper by Oikawa *et al*.[23] who had used 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to cleave *p*-methoxy benzyl ethers in the presence of many other protecting groups and functionalities. Of particular interest was a modification which allowed the reaction to be performed under neutral conditions. It was found that *p*-methoxy benzyl ethers (PMBz) such as (44) containing two double bonds, or cyclic systems such as (45) could be cleaved to give the corresponding alcohols (46) and (47) in high yield (> 80%).



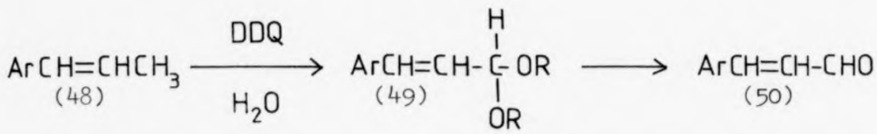
R = PMBz (44)
R = H (46)



R = PMBz (45)
R = H (47)

Benzylic oxidation by DDQ has been well studied, an example of which is the oxidation of 1-arylpropenes (48) with DDQ in benzene or dioxan containing water to give the product (50). The formation of aldehydes may be explained by successive hydride abstractions from (48) to give the hemiacetal or acetal (49) which undergoes hydrolysis to give (50).

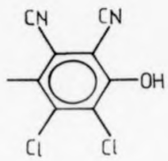
The oxidation of *p*-methoxy benzyl ethers is thought to be a similar process[24] (Scheme 6).

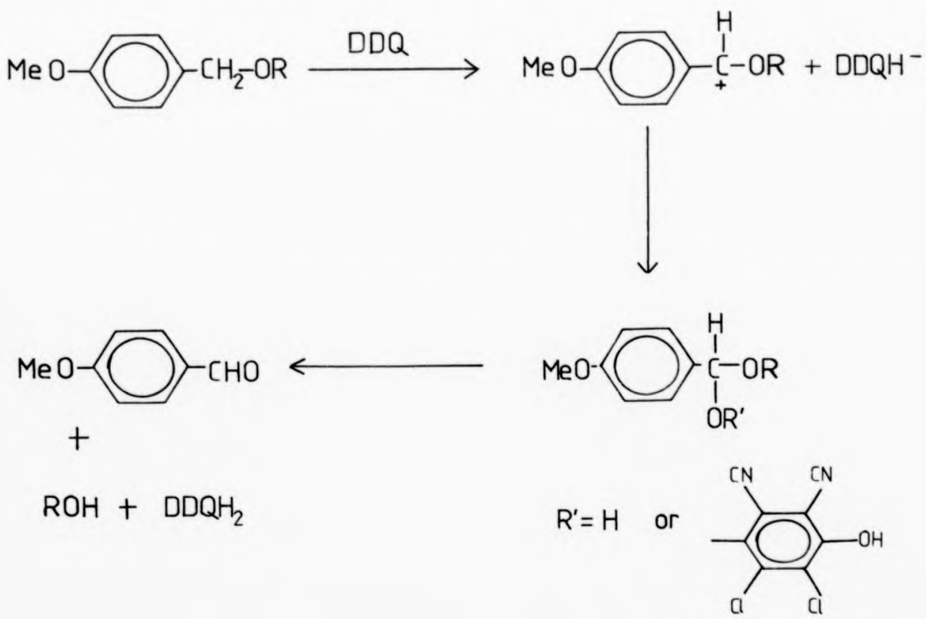


Ar = Ph—

Ar = $MeOC_6H_4$ —

R = H or

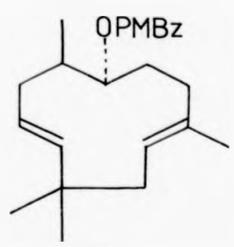




Scheme 6

There are other methods in the literature for the cleavage of p-methoxy benzyl ethers including oxidation with stable radical cations of triaryl amines[25] and electrochemical oxidation.[26] However, cleavage with DDQ should provide a quick clean method.

It seemed practical, at this point, to test the cleavage of p-methoxy benzyl ethers with DDQ by forming the p-methoxy benzyl ether of isohumulol (51). Isohumulol (23) was treated with 1 eq. of sodium hydride and p-methoxy benzyl chloride in tetrahydrofuran. p-Methoxy benzyl chloride cannot be obtained commercially, but it can be conveniently prepared from p-methoxybenzyl alcohol and concentrated hydrochloric acid.[27] This gave the p-methoxy benzyl ether (51) in low yield (∿ 30%) unacceptable for a protection step. The base in the reaction was changed to n-butyllithium, but in this case no reaction took place and starting material only was recovered. Instead of altering the base, the amount of sodium hydride in the reaction mixture was increased from 1 eq. to 10 eq. and this succeeded in improving the yield of (51) to an acceptable level (∿ 80%).

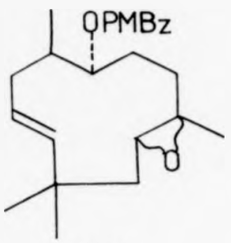


(51)

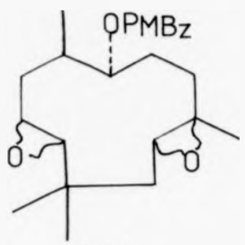
Treatment of the p-methoxy benzyl ether of isohumulol (51) with DDQ in dichloromethane and water[23] resulted in the cleavage of the p-methoxy benzyl ether to give isohumulol (23) and p-methoxy benzaldehyde. One major problem was encountered, namely the production of $DDQH_2$ within the reaction mixture, which was allegedly insoluble in dichloromethane and water. This was found not to be the case and it did not precipitate out as expected. A tedious work-up procedure resulted, although the yield of recovered isohumulol remained high (∿ 82%).

Bisepoxidation of the p-methoxy benzyl ether of isohumulol (51) was first attempted using a biphasic system (dichloromethane/0.5M sodium bicarbonate solution) with m-chloroperoxybenzoic acid as the epoxidation agent and normal stirring rates.[14] This resulted in the formation of the corresponding 8,9-epoxide (52) (7%) and the bisepoxide (53) (7%), both in low yield. If the same conditions were retained and the stirring rate increased then a slightly higher yield of the bisepoxide (53) was obtained (13%), but this was still unacceptably low. Treatment of (51) with m-chloroperoxybenzoic acid in dichloromethane with the absence of base gave the bisepoxide (53) in a better yield (∿ 38%).

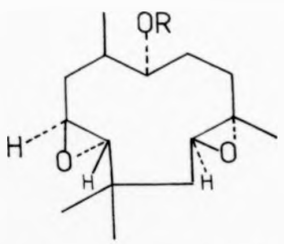
Again the p-methoxy benzyl ether of isohumulol bisepoxide (53) can exist as four diastereoisomers (54)-(57). It is known from the series of methyl ether protected compounds that the required stereochemistry for the bisepoxide would be (54) or (55). The stereochemistry about the C-8 - C-9 bond is not critical as this epoxide will be removed at the deoxygenation



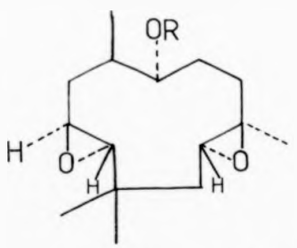
(52)



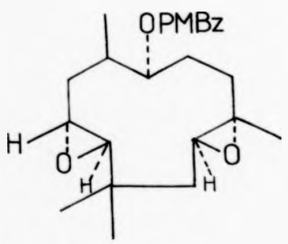
(53)



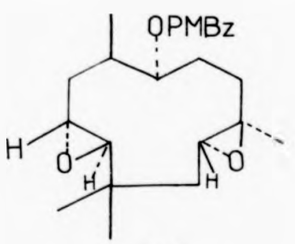
R = Me (25)
R = PMBz (54)



R = Me (26)
R = PMBz (55)



(56)



(57)

step. Again a ^{13}C nmr spectral comparison of the methyl ether bisepoxides (25) and (26), with the p-methoxy benzyl ether bisepoxide (53) was useful (Table 2). From this it can be seen that there is a reasonable correlation between the ^{13}C chemical shifts of (25/26) and (53). In particular there is a good comparison between the C-4, C-5, C-8 and C-9 ^{13}C chemical shifts in (25/26) and (53). Hence it is reasonable to assume that (53) has either the structure (54) or (55).

Initial problems were encountered when the deoxygenation of the p-methoxy benzyl ether bisepoxide (54/55) was attempted. Treatment of (54/55) with tungsten hexachloride and n-butyllithium[15,16] under the conditions previously used for the deoxygenation of the bisepoxide (25/26), showed that the main reaction was removal of the protecting group, and hence p-methoxy benzyl alcohol was recovered. However by variation of the reaction temperature, it was found that at lower temperatures the 4,5-epoxide (58) could be formed in low yields (∿ 14%), the remaining material recovered was starting material. By extending the reaction times, it was hoped that a better yield could be achieved, but removal of the protecting group again began to predominate. Hence it was reasoned that lowering the reaction temperature lowered the rate of deoxygenation to an unacceptable level, and that increasing the reaction time increased the amount of side reactions due to the presence of a Lewis acid. The logical step was to increase the concentration of the tungsten reagent, and thus increase the deoxygenation rate at lower temperatures. If the bisepoxide (54/55) was treated with two equivalents of tungsten

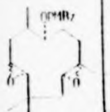
TABLE 2

*these are tentative assignments only

COMPOUND — ^{13}C NMR SPECTRUM ($CDCl_3$)

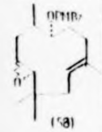
(25/26)

Assignment*				C-11		C-2	C-6	C-3	C-10	C-7	C-4	-OCH₃	C-8	C-9	C-5	C-1
δ	12.9	17.2	20.7	24.0	28.4	31.8	33.0	35.5	37.7	40.0	56.9	57.1	59.8	61.8	67.2	82.0
Multiplicity	q	q	q	t	q	d	s	t	t	t	d	q	d	s	d	d



(53)

Assignment*				C-11		C-2	C-6	C-3	C-10	C-7	-OCH₃	C-4	C-8	C-9	C-5	-OCH₂-	C-1				
δ	12.9	17.25	20.4	24.0	28.4	31.8	33.0	35.5	35.8	40.1	55.3	56.6	59.3	61.7	67.4	69.7	77.2	114.2	129.6	130.15	159.65
Multiplicity	q	q	q	t	q	d	s	t	t	t	q	d	d	s	d	t	d	d	d	s	s



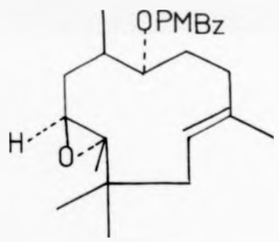
(58)

Assignment*				C-11		C-2	C-3	C-6	C-10	C-7	-OCH₃	C-4	C-5	-OCH₂-	C-1		C-8			C-9	
δ	13.2	16.7	19.9	26.6	28.0	32.5	35.25	35.25	36.6	39.7	55.1	56.5	69.0	69.6	76.6	114	121.65	129.0	131.0	137.0	159.4
Multiplicity	q	q	q	t	q	d	t	s	t	t	q	d	d	t	d	d	d	d	s	s	s

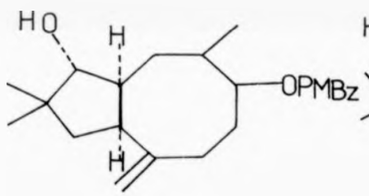
(16)

Assignment*				C-11		C-2	C-3	C-6	C-10	C-7	C-4	-OCH₃	C-5	C-1	C-8	C-9
δ	13.2	16.7	20.1	26.6	28.1	32.6	35.2	35.4	37.3	39.9	56.6	56.9	68.6	81.0	122.1	136.9
Multiplicity	q	q	q	t	q	d	t	s	t	t	d	q	d	d	d	s

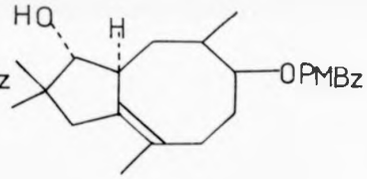
hexachloride/n-butyllithium at -15°C for 1 hour, followed by warming to room temperature for 50 minutes, a reasonable yield of 4,5-epoxide (58) was obtained. The other material recovered from the reaction was a mixture of the cyclised isomers (61) and (60) and starting material (54/55). An important point to note was since room temperature is variable (!) the reaction rate would vary accordingly, on each occasion the progress of each reaction was monitored carefully by analytical tlc. The yield of 4,5-epoxide (58) was not improved when the tungsten reagent concentration was increased to three equivalents



(58)



(60)



(61)

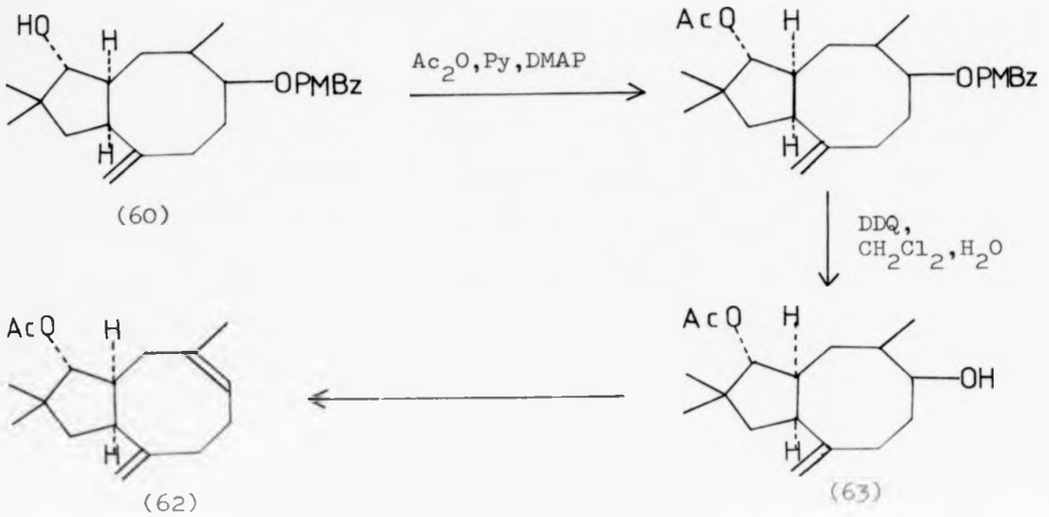
(∿ 42%) and in fact the work-up procedure became difficult due to the large concentration of tungsten salts.

Hence a viable method was realised for the production of the p-methoxy benzyl ether of isohumulol-4,5-epoxide (58) in reasonable yield. A comparison of the ^{13}C nmr chemical shift data of (58) with that for the methyl ether 4,5-epoxide (16) showed a very good correlation and again this seems to support the evidence that these compounds have the same relative stereochemistry (Table 2).

Treatment of the p-methoxy benzyl ether of isohumulol-4,5-epoxide (58) with boron trifluoride etherate in ether at

room temperature resulted in the formation of the 5-*p*-methoxy benzyl ether of 6,10,10-trimethyl-2-methylene bicyclo[6.3.0]undeca-5,9-diol (60) (19%) corresponding to the methyl ether (17) previously formed. This yield could be improved to 65% if the reaction was performed at 0°C. As the structure of the 3,5-dinitrobenzoate derivative of the methyl ether (18) had been rigorously established by X-ray analysis it was important that (17) and (60) were established as having the same relative stereochemistry. A comparison of ^{1}H and ^{13}C nmr chemical shift data (Table 3) showed that there was a reasonable correlation between (17) and (60). Of particular importance was that the coupling constant between the proton at C-9 and the proton at C-8 remained the same (10 Hz). If the ring fusion had either of the *trans* stereochemistries then this coupling would have been somewhat different. Again ^{13}C nmr chemical shift data showed a reasonable correlation.

From this point on it was anticipated that it would be a relatively easy matter to convert (60) to the diene (62) (Scheme 7). The initial step was planned as the protection of the C-9 hydroxyl group as the acetate since this would permit differentiation between the C-5 and C-9 hydroxyl groups once the C-5 hydroxyl group had been regenerated. Cleavage of the *p*-methoxy benzyl ether should be a straightforward matter using DDQ in dichloromethane/water. However some uncertainty remained about the best method for the dehydration of the C-5 hydroxyl group.



Scheme 7

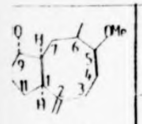
To this end a series of model studies was instituted using isohumulol (23) as the model compound. Isohumulol has several advantages as a model compound. It is freely available and both humulene and isohumulol are well characterised and familiar compounds. Also it contains a medium sized ring with a fair degree of flexibility as is the case in (63).

Treatment of isohumulol (23) with mesyl chloride in pyridine did not result in immediate elimination but led to the formation of the mesylate (64) (50%). This was also the case if the base was changed to triethylamine. If the isohumulol (23) and mesyl chloride in pyridine reaction mixture was heated the sole identified product was still the mesylate (64). Hence it was concluded that the treatment of the C-5

TABLE 3

*these are tentative assignments

COMPOUND — $^{1}H/^{13}C$ NMR CHEMICAL SHIFT DATA

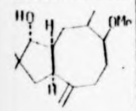


(17)

	3H	3H	3H	1H	3H	1H			1H	1H	
δ	0.85	0.95	1.08	3.07	3.3	3.33			4.67	4.99	
	d J=6Hz	s	s	d J=10Hz	s	m			s	s	

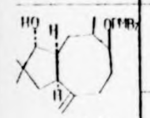
(60)

	3H	3H	3H	1H	1H	3H	2H	1H	1H	4H	
δ	0.87	0.88	1.01	3.08	3.5	3.77	4.4	4.89	5.02	6.84	7.26
	d J=6Hz	s	s	d J=10Hz	m	s	s	s	s	AA'BB'q J=9Hz	



(17)

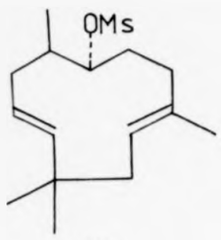
Assignment*				C-7	C-3	C-6	C-10	C-4	C-8	C-11	C-1	-OCH$_3$		C-5	C-9	C=CH$_2$				C-2	
δ	14.2	20.5	27.1	30.4	32.4	36.3	39.0	40.8	42.4	43.8	46.4	56.2		83.4	84.7	112.6				152.7	
Multiplicity	q	q	q	t	t	d	s	t	d	t	d	q		d	d	t				s	



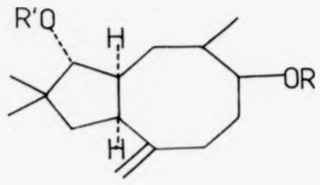
(60)

Assignment*				C-7	C-3	C-6	C-10	C-4	C-1	C-11	C-8	-OCH$_3$		C-5	C-9	C=CH$_2$				C-2	
δ	14.9	20.4	27.1	30.8	32.5	36.9	39.0	40.6	42.3	43.7	46.7	55.3	70.1	86.5	84.9	112.5	113.7	129.0	131.3	152.7	159.0
Multiplicity	q	q	q	t	t	d	s	t	d	t	d	q	t	d	d	t	d	d	s	s	s

hydroxy group in (63) would probably result in the formation of the mesylate (65) which could then be treated with a base such as 1,8-diazabicyclo[5.4.0]undeca-7-ene (DBU) to bring about elimination.[28]



(64)



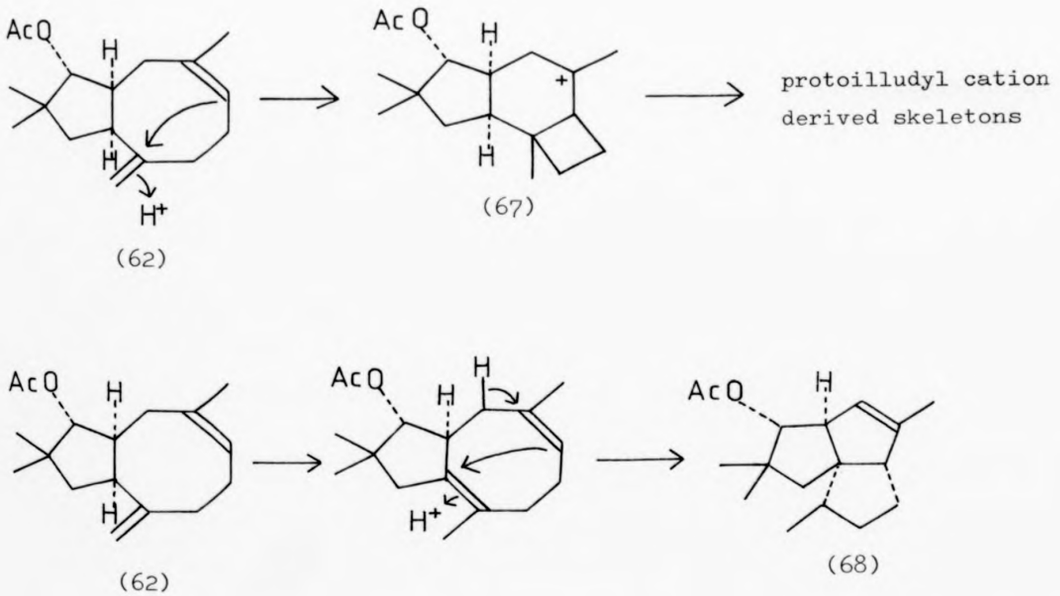
R = PMBz	R' = H	(60)
R = PMBz	R' = Ac	(66)
R = H	R' = Ac	(63)
R = Ms	R' = Ac	(65)

Treatment of the 5-p-methoxy benzyl ether of 6,10,10-trimethyl-2-methylene-bicyclo[6.3.0]undeca-5,9-diol (60) with acetic anhydride in pyridine with a catalytic amount of N,N-dimethyl-4-aminopyridine resulted in the smooth formation of the acetate (66). The cleavage of the p-methoxy benzyl ether in (66) with DDQ in dichloromethane/water went in high yield to give the alcohol (63) (83%).[23]

As anticipated treatment of (63) with mesyl chloride in pyridine resulted in the formation of the mesylate (65). This compound was heated with DBU for 22 hours after which time elimination had taken place to form the acetate of 9-hydroxy-6,10,10-trimethyl-2-methylene-bicyclo[6.3.0]undeca-5-ene (62).

The stage is now set to discuss the effects of protonation, cyclisation and rearrangement upon the diene (62). At this point only pathways that lead from the diene (62) to naturally occurring sesquiterpene skeletons will be considered.

Initial protonation at the C-2 methylene would lead to the formation of the C-2 cation, participation of the $\Delta^{5,6}$ double bond would then give the protoilludyl cation derivative (67), which could subsequently undergo rearrangement to give a wide variety of proto-illudyl cation derived skeletons. Alternatively the initial step could be acid catalysed isomerisation of the C-2 methylene to the $\Delta^{1,2}$ double bond. This is not an unreasonable proposal in view of the fact that this isomerisation must be invoked to explain the formation of the ether (20). Protonation at the $\Delta^{1,2}$ double bond followed by participation of the $\Delta^{5,6}$ double bond would lead to the formation of the pentalenane cation derivative (68) (Scheme 8).

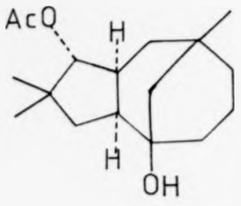


Scheme 8

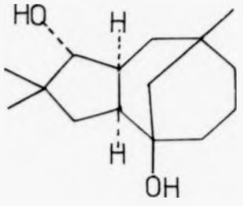
A series of small scale experiments were set up to examine the effects of various acids upon the diene (62), the reactions being monitored by analytical tlc. It was found that no reaction occurred with boron trifluoride etherate or trifluoroacetic acid, whilst sulphuric acid in ether and p-toluene sulphonic acid in benzene both led to the formation of one major product Rf = 0.34 (30% ethyl acetate/pet.ether). Two new compounds Rf = 0.65 and 0.6 (30% ethyl acetate/pet. ether) were formed when the diene (62) was treated with formic acid in acetic anhydride, whilst three new compounds Rf = 0.5, 0.33 and 0.1 (10% ethyl acetate/pet.ether) were formed when (62) was treated with formic acid alone.

Large scale treatment of the diene (62) with p-toluene sulphonic acid in benzene followed by quenching with water resulted in the formation of one major alcohol (39%). This was identified as 4,4,8-trimethyltricyclo[6.3.1.$0^{2,6}$]-dodeca-1,5-diol (69) from its 90 MHz nmr spectrum.
δ = 0.91 (3H,s), 0.97 (3H,s), 1.14 (3H,s), 2.03 (3H,s), 2.2-2.6 (2H,m), 4.45 (1H,d,J = 2.5Hz).

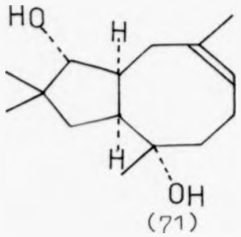
Shirahama et al.[29] have reported the formation of a similar compound, namely the diol (70), from the treatment of the alcohol (71) with boron trifluoride etherate. Also isolated from the reaction mixture were 10 α-hydroxy penta-lenene (72) and the novel compounds (73)-(75). The reported nmr spectrum of the diol (70) was brief but seemed to confirm our assignment.
δ = 0.9 (3H,s), 0.97 (3H,s), 1.08 (3H,s), 3.34 (1H,d,J = 3Hz).



(69)



(70)



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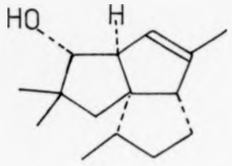
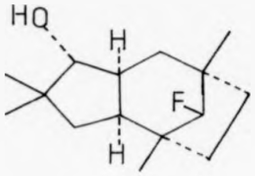
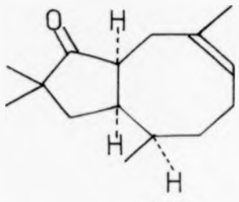


(72)



(73)



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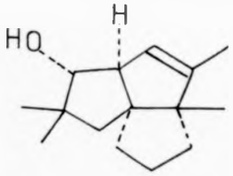

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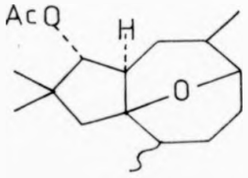

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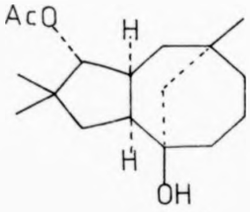

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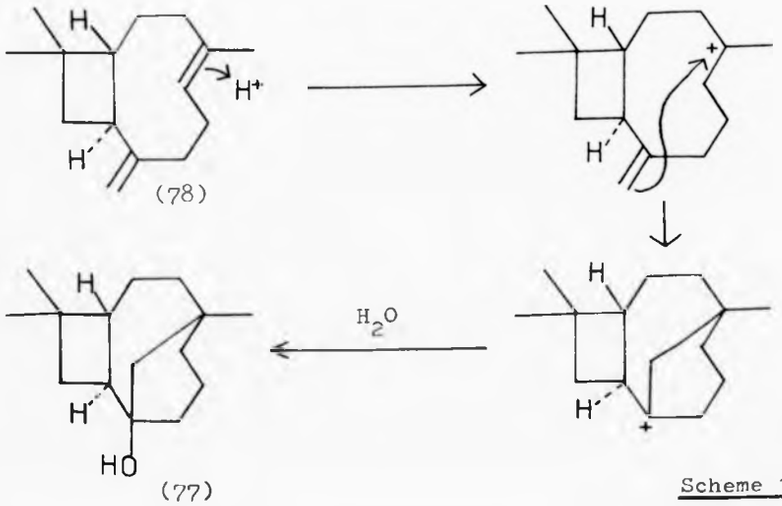


Scheme 10

TABLE 4

Tricyclic alcohol (69).

M^+ (found) = 280.2030; M^+ (calculated for $C_{17}H_{28}O_3$) = 280.2038

m/e: (relative intensity), 280 (1.5), 2.37 (55.7), 111 (100), 43 (39.9), 41 (25.9)

M^+-169 (found) = 111.0816; M^+-169 (calculated for $C_7H_{11}O$) = 111.0810.

β-caryophyllene alcohol (77).

M^+ (found) = 222.1981; M^+ (calculated for $C_{15}H_{26}O$) = 222.1983

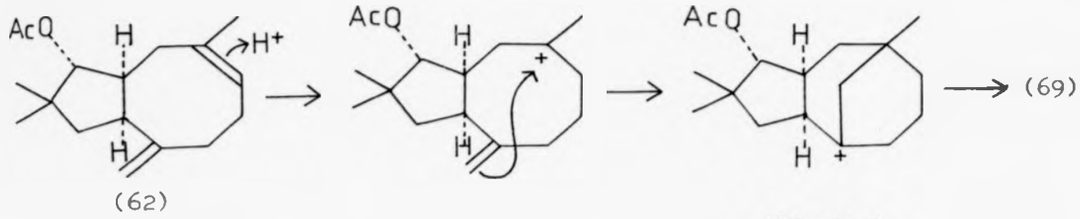
m/e: (relative intensity), 222 (0.6), 204 (12.7), 111 (100), 41 (50.4)

M^+-111 (found) = 111.0814; M^+-111 (calculated for $C_7H_{11}O$) = 111.0810.

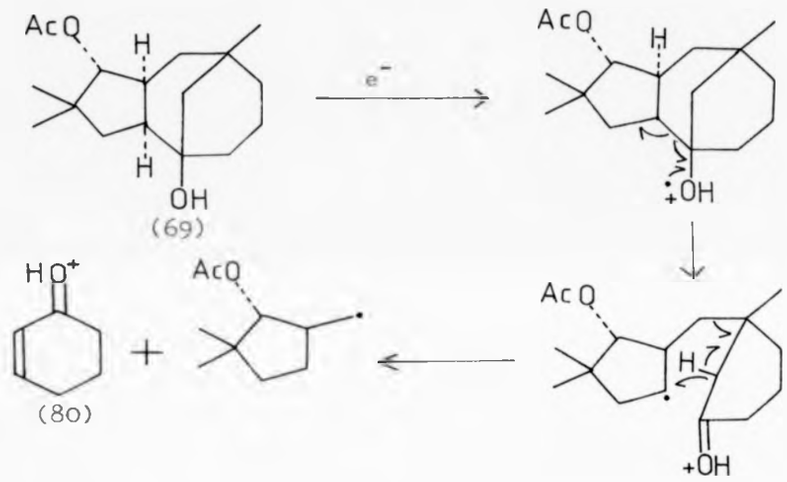
Initial protonation occurs at the $\Delta^{5,6}$ double bond of (62) and the carbonium ion thus formed interacts with the C-2 methylene group and cyclises to give the most stable carbonium ion, which is quenched by the addition of water to give (69). An examination of molecular models shows that (69) must have the stereochemistry depicted, its isomer (79) would be far more sterically congested.

It was also found that the mass spectrum of (69) displayed a characteristic loss of $C_7H_{11}O$ corresponding to the cleavage of the C-1 - C-2 and C-7 - C-8 bonds. This would lead to the loss of the ion (80) (Scheme 11). If this is correct it would not be unreasonable to expect a similar loss from β-caryophyllene alcohol (77) and this was found to be the case as shown in Table 4.

Large scale treatment of the diene (62) with formic acid resulted in the formation of a mixture with at least



Scheme 9

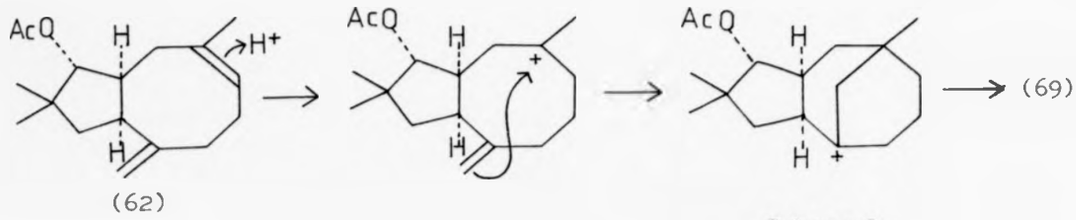


Scheme 11

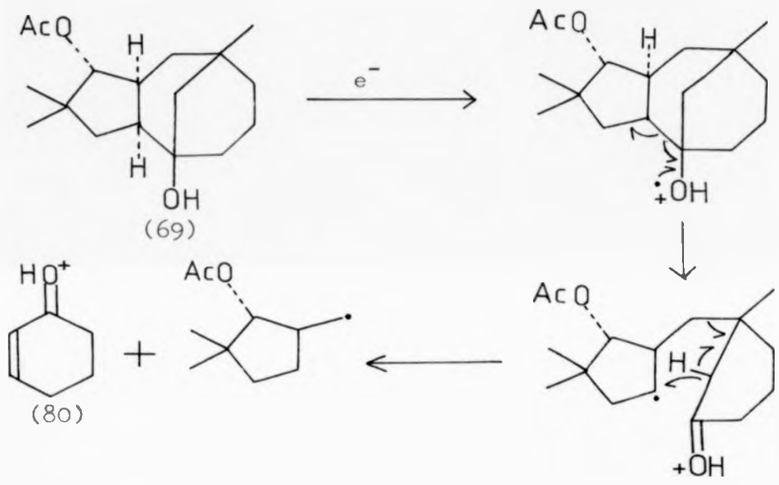
three components by analytical tlc Rf = 0.5, 0.33 and 0.1 (10% ethyl acetate/pet.ether). The most polar fraction Rf = 0.5 contained a mixture of unidentified compounds. The fraction Rf = 0.33 contained a formate, identified as (81) from its 90 MHz nmr spectrum (13%).

δ = 0.94 (3H,s), 0.97 (3H,s), 1.16 (3H,s), 2.07 (3H,s), 2.2-2.7 (2H,m), 4.5 (1H,d,J = 2.5Hz) and 8.0 (1H,s).

The fraction Rf = 0.1 contained the tricyclic alcohol (69) (16%).



Scheme 9



Scheme 11

three components by analytical tlc Rf = 0.5, 0.33 and 0.1 (10% ethyl acetate/pet.ether). The most polar fraction Rf = 0.5 contained a mixture of unidentified compounds. The fraction Rf = 0.33 contained a formate, identified as (81) from its 90 MHz nmr spectrum (13%).

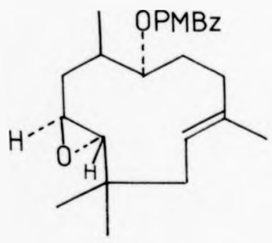
δ = 0.94 (3H,s), 0.97 (3H,s), 1.16 (3H,s), 2.07 (3H,s), 2.2-2.7 (2H,m), 4.5 (1H,d,J = 2.5Hz) and 8.0 (1H,s).

The fraction Rf = 0.1 contained the tricyclic alcohol (69) (16%).

From these results it is obvious that protonation in the diene (62) occurs at the $\Delta^{5,6}$ double bond, whereas if the required sesquiterpenoid frameworks are to be obtained then protonation must occur at the C-2 methylene group.

It was already known that the isomeric alcohol (61) was produced when the bisepoxide (54/54) was treated with tungsten hexachloride/n-butyllithium. It is thought that some species within this reaction mixture is acting as a Lewis acid to bring about cyclisation of the 4,5-epoxide (58). Hence, it was reasonable to suggest that variation of the Lewis acid used to cyclise the 4,5-epoxide (58) might lead to an improved yield of (61).

Initially the solvent used for the boron trifluoride etherate-induced cyclisation of the 4,5-epoxide (58) was varied. Thus the 4,5-epoxide (58) was reacted with boron trifluoride etherate in benzene, or chloroform, or acetic anhydride, or acetic anhydride ether. However all these gave many products by analytical tlc. Lowering the reaction temperature of the 4,5-epoxide (58) with boron trifluoride



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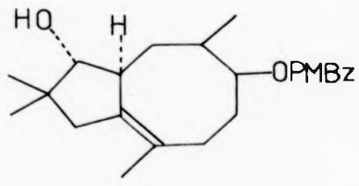

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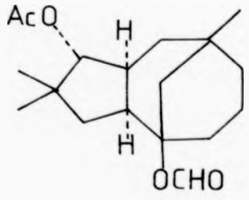
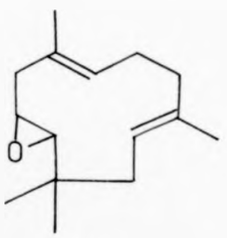


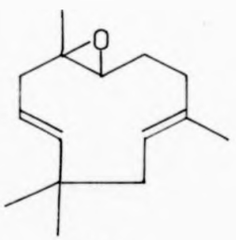
(81)

etherate in ether to -78°C completely halted the reaction. Treatment of the 4,5-epoxide (58) with perchloric acid in

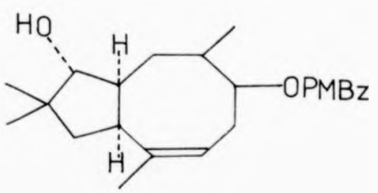
chloroform, tin (IV) chloride in benzene or nitromethane, or chloroform all produced numerous products by analytical tlc. However initially promising was the use of trimethylsilyl trifluoromethanesulphonate in toluene, this reagent having been extensively used by Shirahama et al.[5,31] for the cyclisation of humulene-4,5-epoxide (2) and humulene-1,2-epoxide (82). Treatment of the 4,5-epoxide (58) with trimethylsilyl trifluoromethanesulphonate in toluene at -78°C for 30 minutes followed by quenching of the reaction and desilylation with 10% potassium fluoride in methanol solution produced four compounds on analytical tlc, one of which had an Rf = 0.32 similar to that of the alcohol (60). The reaction was repeated using a reaction time of 7.5 minutes.



(2)



(82)



(83)

Although this produced apparently one product by analytical tlc with an Rf similar to that of the alcohol (60), silver nitrate impregnated tlc clearly showed the presence of two products, one of which had an Rf identical to that of the alcohol (60).

This reaction was repeated on the 4,5-epoxide (58) on a larger scale and it was found that a white crystalline material appeared in the product mixture on standing. This

could be conveniently filtered off and washed with cold hexane to give a white crystalline solid (42%) identified from its spectroscopic data as 2,6,10,10-tetramethyl-5,9-dihydroxy-bicyclo[6.3.0]undeca-2-ene (83) (Table 5). The residue from the filtration usually contained both the isomeric alcohols (60) and (83). Several interesting features of the reaction emerged, firstly the isomers (83) and (60) were usually produced in an approximate 1:1 ratio, as determined from the 90 MHz nmr integrals, although obviously not all of (83) would crystallise. There was a limitation to the size of the reaction. Using approximately 400mg of 4,5-epoxide (58) the isomers were produced in the ratio (83):(60), 8:7. However when the reaction size was increased to 500mg of 4,5-epoxide the ratio of isomers (83):(60) became 8:4, but in the former case 42% of (83) crystallised out, whilst in the latter only 32% of (83) could be induced to crystallise.

A further investigation was undertaken of this reaction. It was found that resubmission of (83) or (60) to the cyclisation conditions yielded starting material only i.e. there was no isomerisation taking place. Small variations in temperature did not produce any important results. The raising of the reaction temperature of (58) with trimethylsilyl trifluoromethanesulphonate to -72°C produced a ratio of (83):(60) of 11.5:8 whereas lowering the temperature to -94°C resulted in no reaction. Only after 40 minutes at -94°C was there a significant reaction, when the ratio of isomers (83):(60) was 9:7.

From this reaction and its variants nothing could

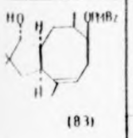
TABLE 5

* these are tentative assignments only

COMPOUND — NMR

(60)

	3H	3H	3H	1H	1H	3H	2H	1H	1H	4H	
δ	0.85	0.95	1.08	3.08	3.5	3.77	4.4	4.69	5.02	6.84	7.26
	d J=6Hz	s	s	d J=10Hz	m	s	s	s	s	AA'BB'q	J=9Hz

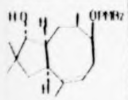


(83)

	3H	3H	3H	3H	2H	1H	3H	2H		1H	4H	
δ	0.94	1.00	1.07	1.68	2.98 -3.3	3.54	3.79	4.38	4.68	5.5	6.86	7.29
	s	d J=7Hz	s	s	m	m	s	ABq	J=12Hz	t	AA'BB'q	J=9Hz

(60)

Assignment*				C-7	C-3	C-6	C-10	C-4	C-8	C-11	C-1	-OCH$_3$	-O-CH$_2$-	C-5	C-9	C=CH$_2$				C-2	
δ	14.9	20.4	27.1	30.8	32.5	36.9	39.0	40.6	42.3	43.7	46.7	55.3	70.1	80.5	84.9	112.5	113.7	129.0	131.3	152.7	159.0
Multiplicity	q	q	q	t	t	d	s	t	d	t	d	q	t	d	d	t		d	s	s	s



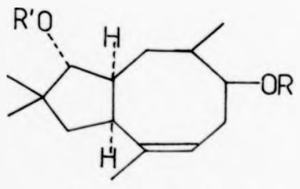
(83)

Assignment*					C-4	C-7	C-6	C-11	C-10	C-8	C-1	-OCH$_3$	O-CH$_2$-	C-5	C-9		C-3			C-2	
δ	21.5	23.2	24.1	27.8	29.2	30.1	36.5	39.2	39.4	42.1	53.1	55.3	70.3	80.0	83.9	113.7	123.3	129.2	131.4	137.5	159.5
Multiplicity	q	q	q	q	t	t	d	t	s	d	d	q	t	d	d	d	d	d	s	s	s

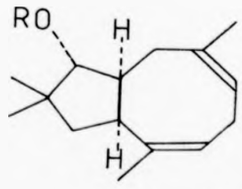
be positively concluded about the subtle factors controlling the reaction course and hence the amount of each isomer produced.

The net result was the alcohol (83) was obtained in reasonable yield and was easily purified. It was also assumed that (83) has the same relative stereochemistry as (60) from comparison of ^{1}H and ^{13}C nmr spectroscopic data (Table 5). It should then have been a relatively straightforward matter to convert the alcohol (83) to the diene (84), using the methodology developed for the synthesis of the diene (62).

Thus the alcohol (83) was treated with acetic anhydride and pyridine containing a catalytic amount of N,N-dimethyl-4-aminopyridine to give the acetate (85) in high yield (96%). This was treated with DDQ in dichloromethane/water to deprotect the p-methoxybenzyl ether to give the alcohol (86) (93%). The alcohol was then mesylated with mesyl chloride in pyridine to give the mesylate (87) (85%).

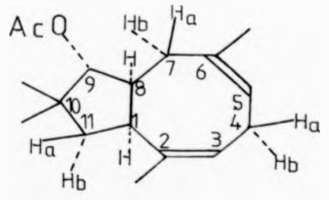


R = PMBz R' = H (83)
R = PMBz R' = Ac (85)
R = H R' = Ac (86)
R = Ms R' = Ac (87)



R = Ac (84)
R = H (88)

Demesylation of (87) went smoothly in DBU to give the diene (84) (71%) and the deacylated diene (88) (13%). Examination of the 90 MHz nmr spectrum of (84) showed that an anomalously low field proton was appearing at ∿ 3.35 ppm δ = 1.0 (3H,s), 1.02 (3H,s), 1.67 (3H,s), 1.76 (3H,s), 2.10 (3H,s), 2.80 (1H,6s), 3.35 (1H,m), 4.59 (1H,d,J = 9Hz), 5.16-5.61 (2H,m). Clearly the nmr spectrum of the diene (84) was more complex than expected. For this reason a 360 MHz ^{1}H spectrum of (84) was obtained, with extensive decoupling. The results of this allowed the tentative assignment of every proton in the spectrum, along with an estimation of the coupling constants as shown in Table 6.



(84)

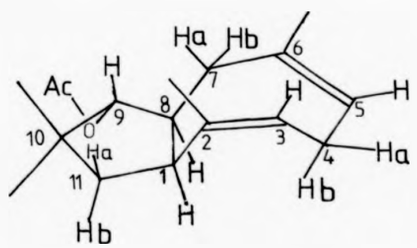
δ = 0.965 (3H,s), 0.986 (3H,s), (H-15/H-16), 1.55 (1H,m)(H-7_b), 1.62 (3H,s)(H-12), 1.63 (2H,m)(H-11), 1.72 (3H,s)(H-13), 2.06 (3H,s)(H-14), 2.2 (1H,m)(H-7_a), 2.29 (1H,m)(H-4_a), 2.4 (1H,m)(H-8), 2.82 (1H,m)(H-4_b), 3.33 (1H,q)(H-1), 4.54 (1H,d)(H-9), 5.23 (1H,d)(H-5) and 5.4 (1H,t)(H-3).

Estimated coupling constants (Hz)

$J_{8-9} = 9.6$	$J_{4a-4b} = 14$	$J_{11b-1} = 13$
$J_{8-7b} = 0$	$J_{4a-5} = 8$	$J_{11a-11b} = 14$
$J_{8-7a} = 16$	$J_{4a-3} = 7$	$J_{11a-1} = 9$
$J_{8-1} = 12$	$J_{4b-5} = 0$	
$J_{7a-7b} = 14$	$J_{4b-3} = 7$	

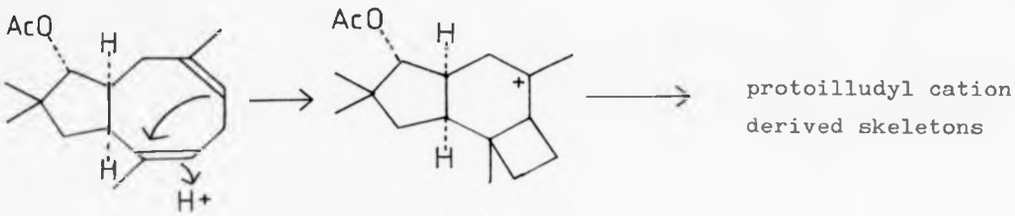
TABLE 6

This spectrum contains some interesting features. The proton H-1 is the proton appearing at 3.33 ppm, this is because this proton lies in the plane of the $\Delta^{2,3}$ double bond, and the π electron system of the double bond will have a significant deshielding effect on this proton.[32] The H-7a proton must also lie in the plane of the $\Delta^{5,6}$ double bond, along with the H-4b proton. There is a zero coupling constant between H-4b and H-5, and this provides enough information for the molecule to be drawn in what is probably its preferred conformation (89).



(89)

The protonation of the diene (84) can occur primarily at either the $\Delta^{2,3}$ double bond or the $\Delta^{5,6}$ double bond. Only initial protonation at the $\Delta^{2,3}$ double bond followed by participation of the $\Delta^{5,6}$ double bond can lead to the protoilludyl cation derivative (67) and hence to the many protoilludyl cation derived skeletons.

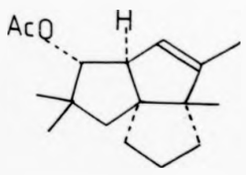


(84) (67)

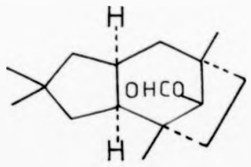
A series of trial cyclisations were undertaken on the diene (84). Treatment of (84) with sulphuric acid in ether, boron trifluoride etherate in ether or benzene produced many compounds whilst no reaction occurred with formic acid in acetic hydride or trifluoroacetic and in ether. The use of p-toluene sulphonic acid in benzene produced five compounds by analytical tlc, whilst with formic acid and trifluoromethanesulphonic acid in dichloromethane only one product was produced.

The reaction of the diene (84) with formic acid was investigated further. It was found, in fact, that the product mixture showed three spots on analytical tlc, one Rf = 0.6 (15% ethyl acetate/pet.ether) composed of a mixture of two alkenes as determined from the 90 MHz nmr spectrum. The major component of this mixture was later tentatively assigned

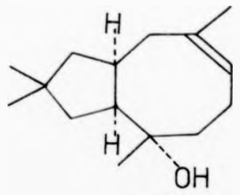
as (90), although not enough material was available to confirm this. The second fraction Rf = 0.49 (15% ethyl acetate/pet.ether) contained one major formate which was purified by sublimation. This formate displayed the ^{1}H 90 MHz nmr spectrum:
δ = 0.88 (3H,s), 0.93 (3H,s), 0.97 (3H,s), 1.1 (3H,s), 2.05 (3H,s), 4.55 (1H,d,J = 3Hz), 4.68 (1H,s) and 8.21 (1H,s). Again it was noted that the H-5 to H-6 coupling constant had decreased to 3 Hz. The spectrum seemed reminiscent of that of the formate (91)[33,34] produced on treatment of (92) with formic acid in acetic anhydride, the other product of this reaction being pentalenene (93).
(91) δ = 0.88 (3H,s), 0.94 (3H,s), 0.99 (3H,s), 1.09 (3H,s), 4.64 (1H,d,J = 1Hz) and 8.10 (1H,d,J = 1Hz).



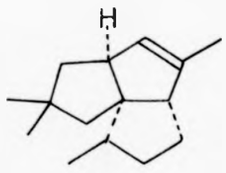
(90)



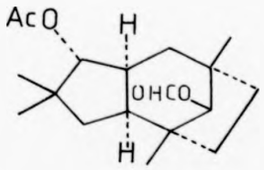
(91)



(92)



(93)



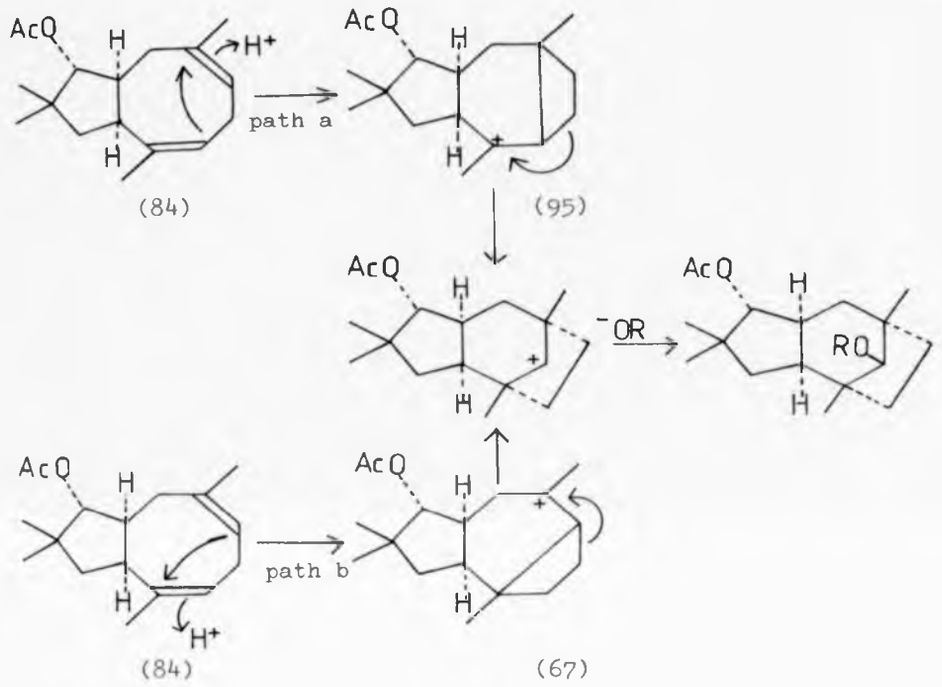
(94)

Hence the formate was identified as the 5-acetate, 11-formate of 1,4,4,8-tetramethyltricyclo[6.2.1.O.^{2,6}]undeca-5,11-diol (94), and this identification was confirmed by the ^{13}C and mass spectral data. The third fraction Rf = 0.19 (15% ethyl acetate/pet.ether) was an unidentified alcohol.

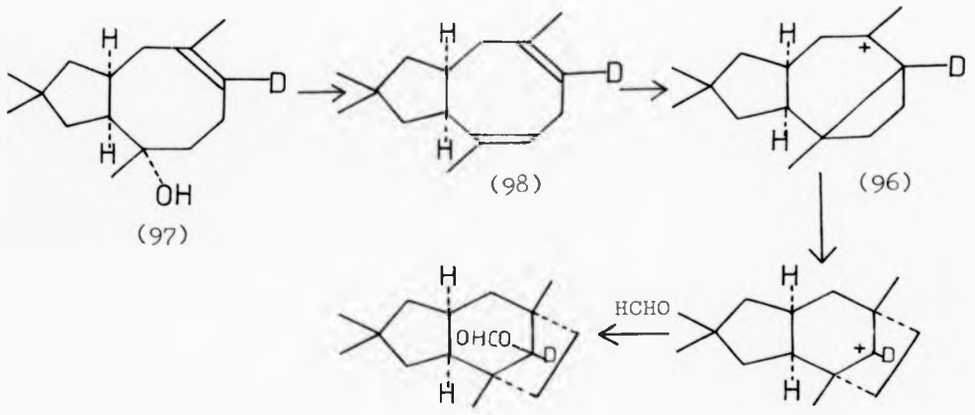
The mechanism of formation of (94) can be rationalised in two ways (Scheme 12), path a, *via* the sterpuryl-type cation (95) and path b *via* the protoilludyl type cation (67). Shirahama *et al.*[33] used ^{2}H labelling experiments to show that the formate (91) is produced from (97) *via* the protoilludyl cation intermediate (96) (Scheme 13). It should be noted that it is not necessary to invoke the intermediacy of the diene (98) as the carbonium ion (99) could be formed directly from (97). It was important to establish that the formate (91) was formed *via* the protoilludyl cation (96) as Shirahama *et al.*[35] interpreted the treatment of the methoxy ether (100) with boron tribromide to give the bromide (101) as an analogous process. The bromide (101) was used in a biomimetic synthesis of sterpurene (102) from humulene (1). It has recently been established that sterpurene (102) is formed *via* the protoilludyl cation (103), not by direct cyclisation of the intermediate diene (104).[36]

It was not possible within the limitations of our experimentation to discover the mechanistic details of the cyclisation of the diene (84) to give the formate (94). The diene (84) could cyclise *via* path a or path b (Scheme 12), or indeed both paths a and b (Scheme 12) could be operating simultaneously.

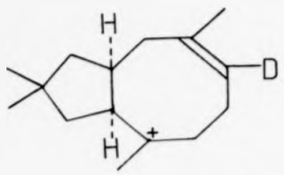
It was hoped that monitoring the cyclisation of the



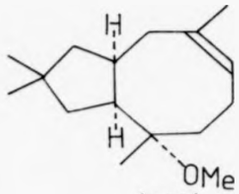
Scheme 12



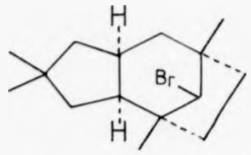
Scheme 13



(99)



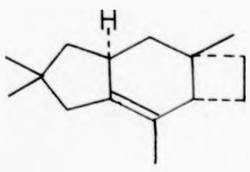
(100)



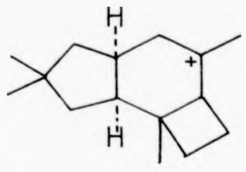
(101)

diene (84) by some acid, with nmr spectroscopy would reveal some details of the cyclisation mechanism. The acid chosen was trifluoroacetic acid as it is not visible in the ^{1}H nmr spectrum. The diene (84) was dissolved in deuterochloroform under nitrogen and trifluoroacetic acid was added. After 15 minutes the alkene proton at 5.23 ppm was no longer visible in the 90 MHz nmr spectrum whilst the alkene proton at 5.4 ppm remained visible for ~ 24 hours. The isolated product from this reaction was the trifluoroacetate (105). However, no conclusions could be drawn from this experiment.

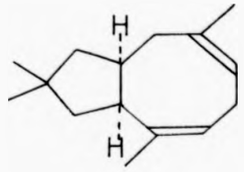
Treatment of the diene (84) with p-toluene sulphonic acid in benzene formed a reaction mixture which showed five spots on analytical tlc. Rf = 0.71, 0.61, 0.49, 0.44 and 0.28 (10% ethyl acetate/pet.ether). Only the compound



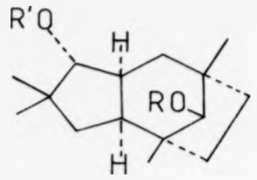
(102)



(103)



(104)

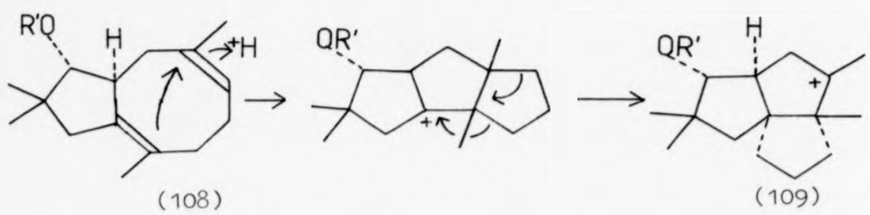


R' = Ac	R = CF_3CO	(105)
R' = Ac	R = Ts	(106)
R' = H	R = CF_3SO_2	(107)

corresponding to Rf = 0.28 was positively identified as the tosylate (106) (14%). Likewise treatment of the diene (88) with trifluoromethanesulphonic acid formed the trifluoromethanesulphonate (107) as the major compound (37%).

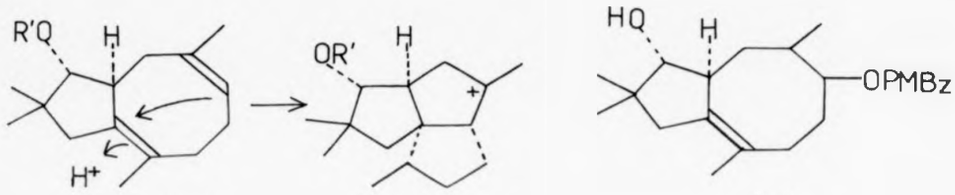
Although the cyclisation of the dienes (62) and (84) with a variety of acids had produced some encouraging results, we still had not been able to obtain any of the desired humulene derived sesquiterpene skeletons. It was thought that an examination of the cyclisation of the diene (108) might be fruitful, this could happen in two possible ways. Initial protonation could occur at the $\Delta^{5,6}$ double bond in (108), participation of the $\Delta^{1,2}$ double bond followed by rearrangement would lead to the novel compound (109) (Scheme 14).[33] However initial protonation of the $\Delta^{1,2}$ double bond in (108) followed by participation of the $\Delta^{5,6}$ double bond would lead to the pentalenane skeleton (110).

Although it was known that the isomeric alcohol (61) could be obtained by deoxygenation of the diene (54/55) with tungsten hexachloride and n-butyllithium, there were difficulties envisaged in the purification of this material.



(108) (109)

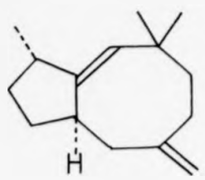
Scheme 14



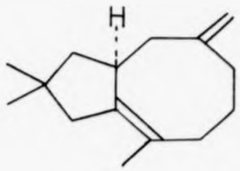
(108) (110) (61)

It was thought that it may be possible to isomerise the C-2 methylene of (62) or the $\Delta^{2,3}$ double bond of (84) into the $\Delta^{1,2}$ double bond position. There are many methods available for the isomerisation of double bonds and we were encouraged by the work of Pattenden et al.[37,38] who was able to isomerise the exo-methylene group in (111) and (112) into the endo position giving (113) and (114) respectively.

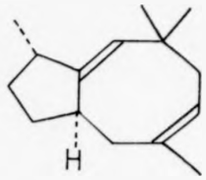
The mechanism of rhodium trichloride trihydrate isomerisation is not fully understood. When cis,cis-1,3-cyclooctadiene is treated with rhodium trichloride trihydrate in ethanol a dimeric complex (115) is formed, this complex yields cis,cis-1,5-cyclooctadiene on treatment with aqueous potassium cyanide.[39] There are two proposed mechanisms for



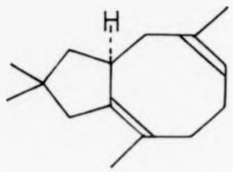
(111)



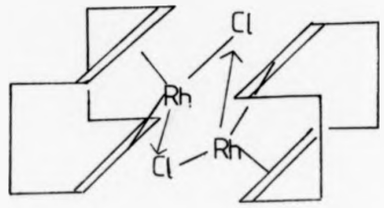
(112)



(113)

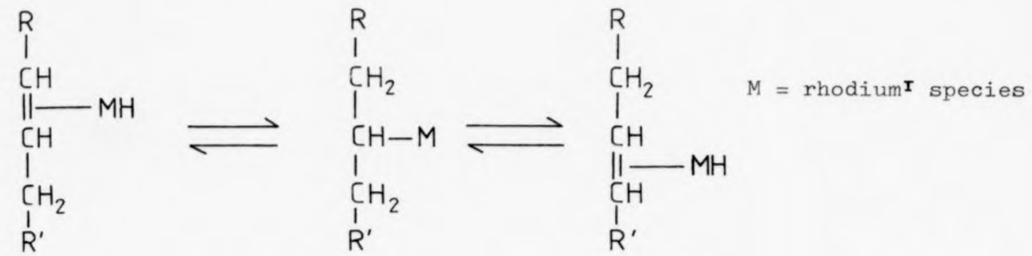


(114)

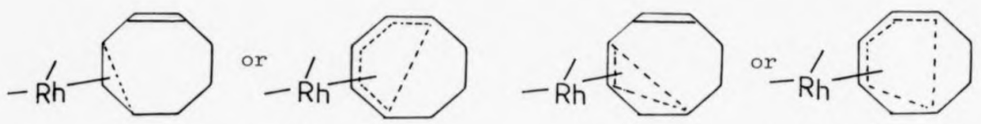


(115)

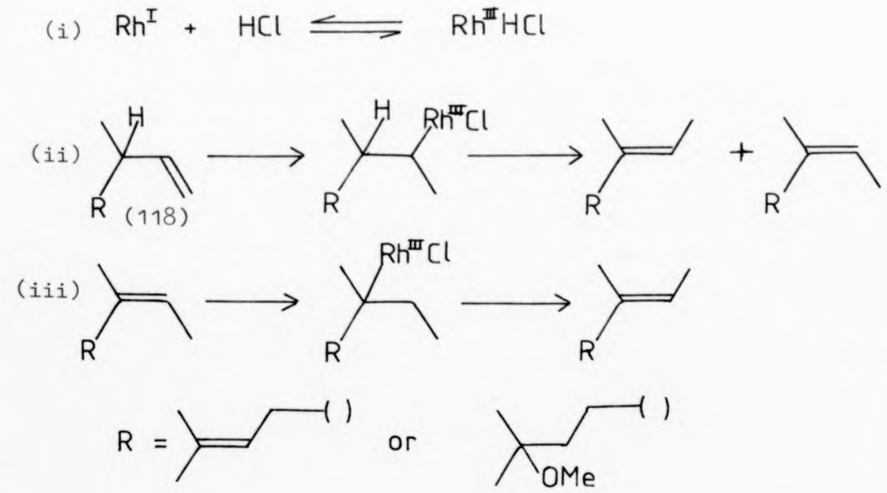
the formation of the complex (115): addition and elimination of a long lived metal hydride could occur (Scheme 15),[40] alternatively rearrangement could occur through a transitory π-allyl complex (116) (117).[39] In the former case a source of a rhodium hydride species is mandatory and it is known that rhodium trichloride trihydrate oxidises ethanol to give a catalytically active rhodium hydride species with simultaneous production of hydrogen chloride.[41] Similarly when rhodium trichloride trihydrate is used in acetone there exists a source of a Rh^{I} species and hydrogen chloride. The mechanism proposed for the isomerisation of the alkene (118) by this reagent is shown in Scheme 16.[42] The reaction is inhibited by the addition of potassium carbonate, hence the presence of



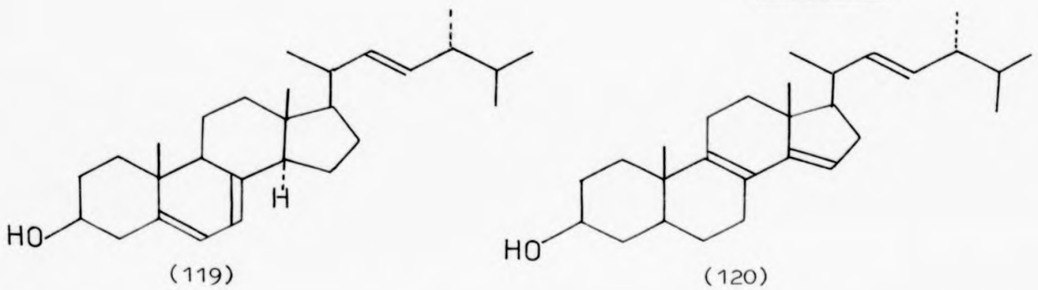
Scheme 15



(116) (117)



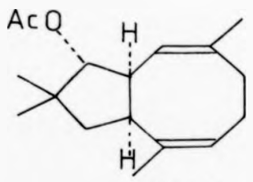
Scheme 16



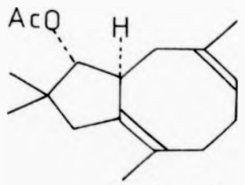
(119) (120)

hydrogen chloride is essential. However, when ergosterol (119) was treated with rhodium trichloride trihydrate in ethanol in the presence of potassium carbonate ergosterol B_1 (120) was the major product.[43] Hence a rhodium hydride species was able to bring about isomerisation independently of the production of hydrogen chloride. Therefore it seems likely that more than one mechanism can operate in the isomerisation of alkenes by rhodium trichloride trihydrate.

Treatment of a mixture of the isomeric alcohols (60) and (61) with rhodium trichloride trihydrate in ethanol produced a plethora of products. However, a similar treatment of the diene (84) produced one major compound, tentatively identified as the isomeric diene (121). In the absence of detailed mechanistic information it is not possible to speculate why the alcohol (60) was not isomerised to (61) or why the diene (121) was produced instead of the desired diene (122).



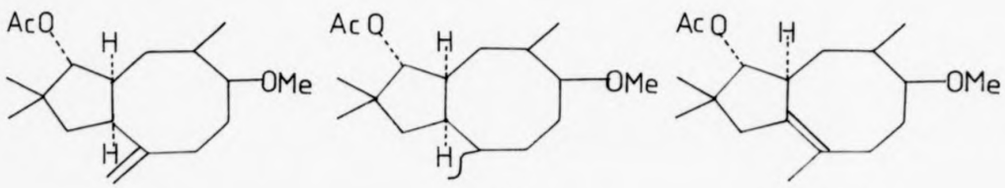
(121)



(122)

Two other methods of double bond isomerisation were attempted. Iodine has been used for double bond isomerisations.[44] However, treatment of the diene (62) with a catalytic amount of iodine in toluene resulted in the recovery of starting material only. It had been noted by Bryson that

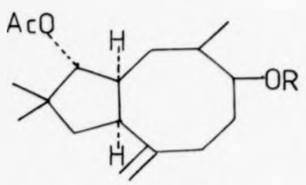
attempted hydrogenation of the methyl ether (19) with palladium on charcoal resulted in the formation of (21) and (123)[7]. Palladium is known for its ability to promote bond migration.[45] Thus it was hoped that hydrogenation of the



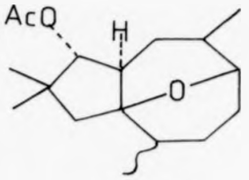
(19) (21) (123)

p-methoxy benzyl ethers (66), (76), with palladium on charcoal would have two effects; it would bring about double bond isomerisation and it would remove the p-methoxy benzyl group. Thus isomerisation and deprotection could be brought about in one step. However hydrogenation of (66) with palladium on charcoal resulted in the production of a vast array of compounds.

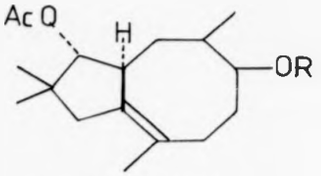
It was becoming apparent that isomerisation of the exo-methylene or the $\Delta^{2,3}$ double bond to the $\Delta^{1,2}$ double bond position was not as easy as was first thought. Therefore, an alternative method for the formation of the $\Delta^{1,2}$ double bond isomer was examined. Bryson had found that on treatment of the cyclic ether (20) with boron trifluoride etherate in acetic anhydride, the diacetate (28) was formed. It was also claimed that the diacetate (28) could be formed in a similar manner from the methyl ether (19). There is precedent in the literature for the cleavage of cyclic ethers with boron



R = PMBz (66)
R = Me (19)

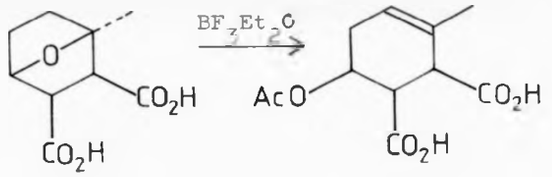


(20)



R = Ac (28)
R = PMBz (76)

trifluoride etherate and acetic anhydride. For example, (124) yields the acetate (125) under these conditions.[46]



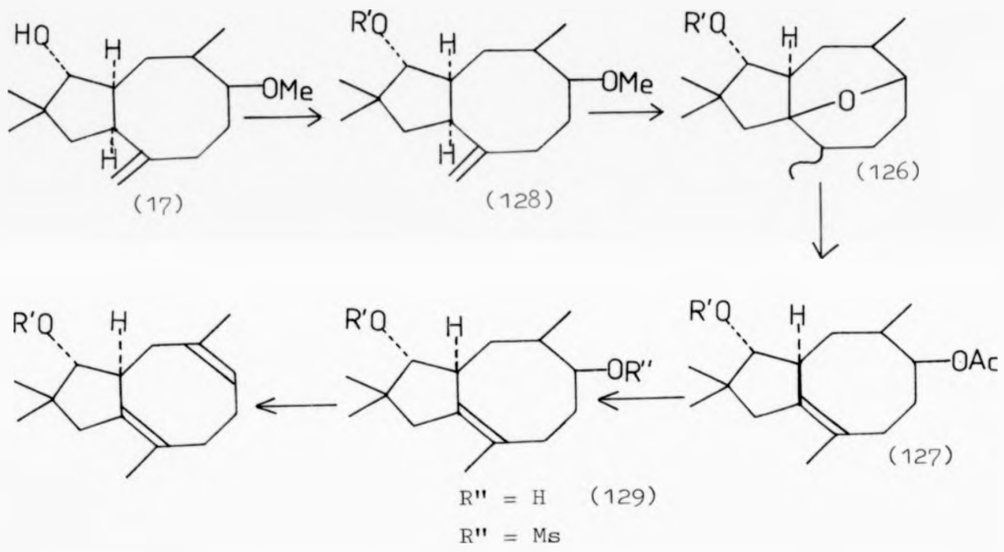
(124) (125)

Treatment of the cyclic ether (20) with boron trifluoride etherate and acetic anhydride resulted in the formation of the diacetate (28) in a reasonable yield (60%). However similar treatment of the methyl ether (19) gave a plethora of products. The latter result was disappointing as it would have provided a convenient direct route to the $\Delta^{1,2}$ double bond isomer.

Selective hydrolysis of the diacetate (28) was then attempted. It can be seen from previous work that it is important to be able to differentiate between the C-5 and C-9 hydroxy groups. However the diacetate (28) did not undergo selective hydrolysis when treated with potassium carbonate in

methanol/water. The rates of hydrolysis of the C-5 and C-9 acetate groups were almost identical, with possibly the C-9 acetate being hydrolysed a little faster.

As the diacetate (28) could not be selectively hydrolysed, a new strategy was evolved for differentiating between the protected C-5 and C-9 hydroxyl groups (Scheme 17).



Scheme 17

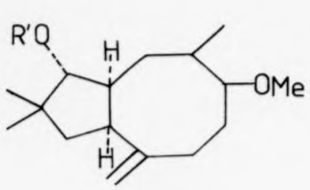
Thus the major requirement for the new strategy would be a new protecting group R' for the C-9 hydroxy group. The new C-9 protecting group should be able to withstand the step of ether formation (126) and must be hydrolysed at a different rate, or cleaved under different conditions to the acetate group in (127).

The synthesis would start from the alcohol (17), the initial step being protection of the C-9 hydroxyl group.

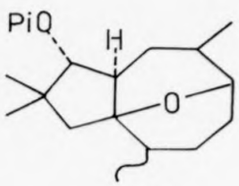
This would be followed by formation of the cyclic ether (126) on treatment of (128) with trimethylsilyl iodide. The cyclic ether (126) would then be treated with boron trifluoride etherate in acetic anhydride to yield the acetate (127). The acetate would then be selectively hydrolysed to the alcohol (129), which can be converted as before to the diene (108).

The protecting group was chosen as the pivaloate ester. This has several advantages: it should be easily formed and should be more stable to hydrolysis than the acetate group; it adds molecular weight to the molecule, a distinct advantage when working with small quantities; finally, as it is an ester it should not interfere with the formation of the cyclic ether (126).

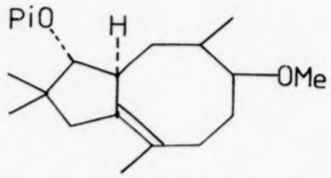
Treatment of the alcohol (17) with pivaloyl chloride in pyridine with a catalytic amount of N,N-dimethyl-4-amino-pyridine for 60 hours afforded the pivaloate (130) in good yield (∿ 80%). This was easily converted to the cyclic ether (131) on treatment with trimethylsilyl iodide generated *in situ* from trimethylsilyl chloride and sodium iodide.[19] It was observed that when a mixture of (130) and (132) was used as the substrate then (131) was the sole detectable product by analytical tlc, Rf = 0.67 (25% ethyl acetate/pet.ether) (67%). However, when (131) only was used as the substrate then two compounds were detected on analytical tlc, Rf = 0.67 and 0.6. The least polar compound was identified as the cyclic ether (131) (50%). The most polar compound was isolated and identified as the pivaloate of 1,4,4,8-tetramethyl 12-oxa-tricyclo[7.2.1.$O^{2,6}$]dodeca-5-ol (133). This product



R = H (17)
R = Pi (130)

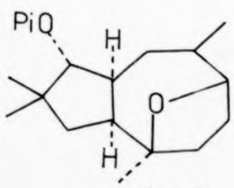


(131)

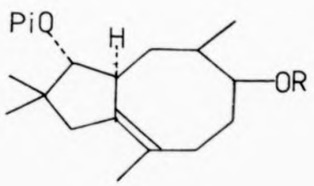


(132)

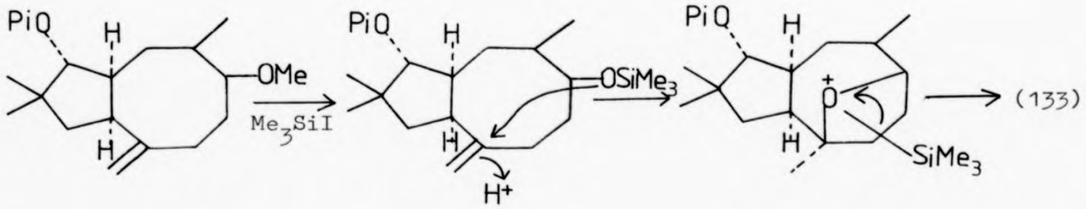
would be formed in the same manner as (131), except cyclic ether formation would take place prior to isomerisation (Scheme 18).



(133)



R = Ac (134)
R = H (135)
R = Ms (137)

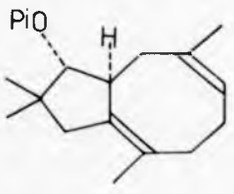


Scheme 18

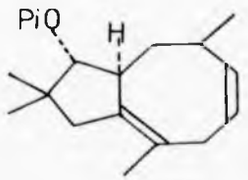
The cyclic ether (131) was treated with boron trifluoride etherate and acetic anhydride to give the acetate (134). The acetate group in (134) was selectively hydrolysed in the presence of the pivaloate group with 5% potassium

hydroxide in ethanol solution, to give the alcohol (135) in high yield (82%). The alcohol (135) could then be treated in the usual manner to yield the diene (138). Treatment of the alcohol (135) with mesyl chloride in pyridine went smoothly to form the mesylate (137). Demesylation with DBU of (137) led to the formation of a mixture of compounds with identical Rf values by analytical tlc, Rf = 0.68 (25% ethyl acetate/ pet.ether). The mixture contained two compounds using silver nitrate impregnated tlc plates, Rf = 0.56 and 0.39 (10% ethyl acetate/pet.ether). These could be separated by silver impregnated silica column chromatography to give two compounds, identified by ^{1}H and ^{13}C nmr spectroscopy as the isomeric dienes (138) (26%) and (139) (31%). Clearly this was a disappointing result, although it is not too surprising in view of the increased mobility within the cyclooctane ring. With the double bond in the C-1 - C-2 position not only does the C-6 proton attain the necessary 180° bond angle for mesylate elimination, but also one of the C-4 protons can also reach the required position.

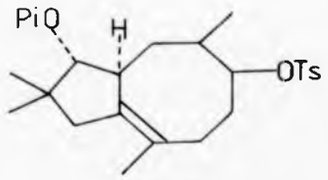
It was thought that the yield of the desired diene (138) might be improved by increasing the bulk of the leaving



(138)



(139)



(140)

group, hence altering the conformational mobility of the cyclooctane ring. The tosylate (140) was formed by treatment of (135) with p-toluene sulphonyl chloride and pyridine. However, treatment of (140) with DBU still yielded a mixture of (138) and (139).

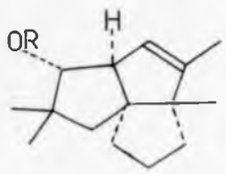
The demesylation of (137) was also attempted using a different base in an attempt to improve the yield of (138). Treatment of (137) with potassium t-butoxide in presence of dimethyl sulphoxide gave two unknown polar products, whereas in t-butanol no reaction occurred.

Enough of the desired (138) could be obtained from the treatment of the mesylate (137) with DBU to attempt a cyclisation. Treatment of (138) with boron trifluoride etherate in dichloromethane[29] resulted in the clean formation of one major product Rf = 0.69 using silver nitrate impregnated tlc (10% ethyl acetate/pet.ether). This compound was identified by its ^{1}H nmr spectrum;

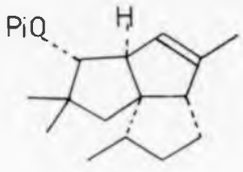
δ = 0.94 (3H,s), 0.97 (3H,s), 1.02 (3H,s), 1.19 (9H,s), 1.43 and 1.85 (2H,ABq,J = 14Hz), 1.55 (3H,q,J = 2Hz and J = 1.5Hz), 2.47 (1H,dd with long range coupling, J = 2.5Hz, J = 5.5Hz long range, J = 2Hz), 4.39 (1H,d,J = 5.2Hz) and 5.31 (1H, bt ,J = 1.5Hz, J = 2.5Hz), as (141) and this was confirmed by the ^{13}C nmr spectrum. Partial confirmation of this structure (141) was obtained by comparison with the ^{1}H nmr spectrum of (75) supplied by Professor Shirahama, but his spectrum was of poorer quality hence a positive correlation between (141) and (75) was not possible.

The mechanism proposed for the formation of (141)

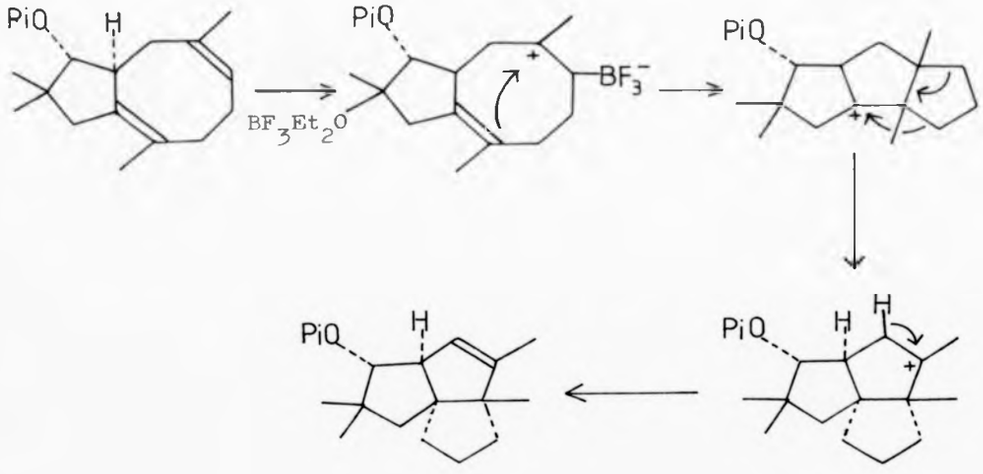
involves initial attack of boron trifluoride etherate at the $\Delta^{5,6}$ double bond, followed by participation of the $\Delta^{1,2}$ double bond and rearrangement (Scheme 19).[38] To form the required pentalenane derivative (142), it would be necessary to have initial attack of boron trifluoride etherate at the $\Delta^{1,2}$ double bond (Scheme 20).



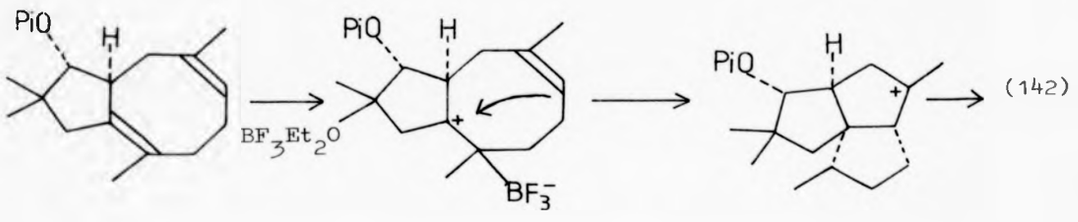
R = H (75)
R = Pi (141)



(142)



Scheme 19

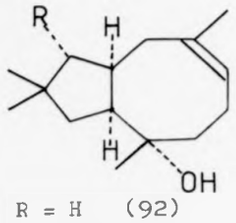


Scheme 20

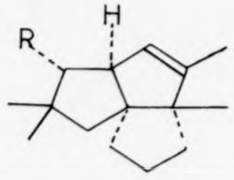
This result is interesting in the light of the work by Shirahama *et al.*[29] and more recently by Pattenden *et al.*[38] Shirahama *et al.*[29] reported that treatment of the diol (71) with boron trifluoride etherate in dichloromethane gave 10α-hydroxypentalenene (72) (20%) along with other products (70), (73)-(75). Treatment of the alcohol (92) with formic acid in acetic anhydride resulted in the formation of pentalenene (93) and the formate (91).[33,34] The treatment of the diol (71) under the same conditions yielded the formate (143) as the sole product.

Pattenden *et al.*[38] have elegantly synthesised the diene (114) and treatment of this with boron trifluoride etherate in dichloromethane gave pentalenene (93) (35%) with the tricyclic compound (144) as a minor isomeric product. This latter hydrocarbon was the sole product when the isomeric diene (112) was treated in the same manner.

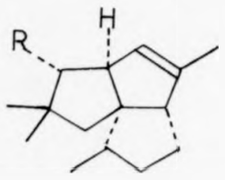
Although the diol (71) can be considered as a precursor of the diene (145), the distribution of products (70), (72)-(75) clearly implicate the transient formation of the other two isomeric dienes (146) and (147). Thus it can be seen that compounds (114), (145) and (138) all share the basic 2,6,10,10-tetramethylbicyclo[6.3.0]undeca-1,5-diene framework, differing only in the substitution at C-9. In (114) there is no oxygen substituent at C-9 and it can be cyclised with boron trifluoride etherate in dichloromethane to give pentalenene (93) as the major product, with (144) as a minor isomeric product. When the substituent at C-9 is a hydroxyl group, then treatment of (145) under the same conditions



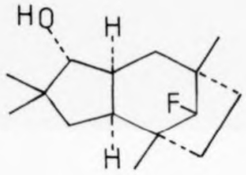
R = H (92)
R = OH (71)



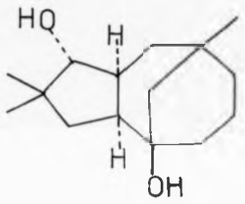
R = H (144)
R = OH (75)
R = OCHO (143)
R = OPi (141)



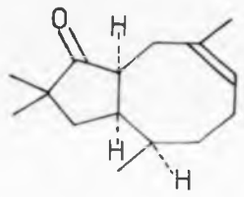
R = H (93)
R = OH (72)



(73)



(70)



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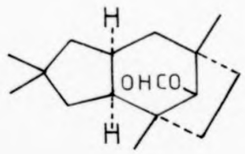

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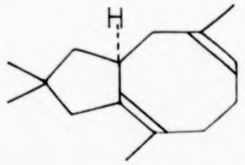
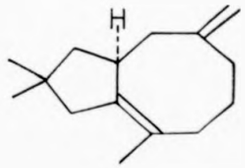
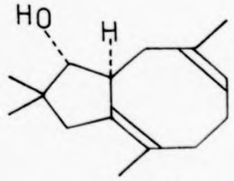


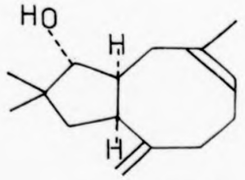
(114)



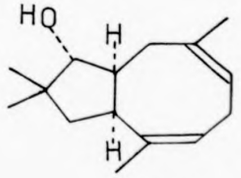
(112)



(145)



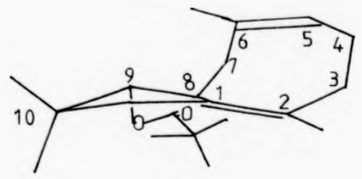
(146)



(147)

yields 10α-hydroxy pentalenene (72) (20%) and the tricyclic alcohol (75) (10%). However when the hydroxy group at C-9 is protected as the pivaloate ester (138), the sole product is the tricyclic compound (141). This is not a very good comparison as (71) does not give solely (145). Even so in (114) and (145) the major products are those from initial attack at the $\Delta^{1,2}$ double bond, electronically, it is reasonable to expect initial attack at this bond to be favoured. In (138) the pivaloate group sterically hinders the β-face of the molecule, preventing electrophilic attack at the $\Delta^{1,2}$ double bond and attack at the $\Delta^{5,6}$ double bond is preferred (148).

Logically the next step in this work to test this hypothesis is to remove the offending source of steric congestion by hydrolysis of the pivaloate group in (138) to generate a pure sample of the hydroxy-diene (145). It is anticipated that treatment of this compound with boron trifluoride etherate in dichloromethane should give 10α-hydroxypentalenene (72) as a major product.



(148)

EXPERIMENTAL

Melting points are uncorrected and were determined on a Köffler hot-stage apparatus; boiling points are not corrected. Kieselgel 60 GF_{254} (Art.7730, Merck) silica was used for all preparative thin layer chromatography. Analytical tlc plates Kieselgel 60 F_{254} (Art.5735) were eluted with 25% ethyl acetate/petroleum ether solution unless otherwise stated and viewed under ultra-violet light (∿ 254 nm) and stained with ceric ammonium sulphate/sulphuric acid solution followed by heating to approximately 150°C. Petroleum ether refers to the fraction of boiling range 40-60°C and all organic solvents were dried over magnesium sulphate unless otherwise stated. Where necessary, solvents were purified and dried,[48] and reagents were either distilled or recrystallised.

Infra-red spectra were recorded on a Perkin-Elmer S57 grating infra-red spectrometer and, unless stated, were obtained from liquid films. Nuclear magnetic resonance spectra were recorded on a Hitachi Perkin-Elmer R24 (60 MHz), a Perkin-Elmer R32 (90 MHz), a Bruker WP80 (80 MHz), or a Bruker WH360 (360 MHz) (Edinburgh) nmr spectrometer using deuterated chloroform as a solvent unless otherwise stated. Tetramethylsilane was used as an internal standard and all spectral values are quoted in parts per million. Mass spectra were determined on a Jeol JMS D100 mass spectrometer combined with a Jeol JCS 20K gas chromatograph and using an Intsem Data Mass Maxi data processing system.

1. Hydroboration of humulene (1)[13]

Humulene (1) (7g, 0.029 mol) was dissolved in tetrahydrofuran (100 ml) at 0°C and 1M borane-tetrahydrofuran complex (in tetrahydrofuran, 25 ml) was added under nitrogen. The reaction mixture was stirred for 45 minutes then quenched with 30% hydrogen peroxide (40 ml) and 10% potassium hydroxide solution (40 ml) and the solution stirred for a further 2 hours at room temperature. The reaction mixture was extracted with ether and the ethereal solution washed with 10% ferrous sulphate solution, dried, and the solvent removed on the rotary evaporator to yield a colourless oil (7.2g). Column chromatography using Kieselgel 60 (Art.7730), eluting with 50% ethyl acetate/pet.ether gave isohumulol (23) (1.8g, 36%) and humulene (4.8g).

Rf = 0.15 (10% ethyl acetate/pet.ether)

δ = 0.86 (3H,d,J = 6Hz), 1.02 (3H,s), 1.07 (3H,s), 1.57 (3H,bs), 3.75 (1H,m), and 4.8-5.3 (3H,m).

2. Formation of the methyl ether (24)

Isohumulol (23) (6.87g, 0.031 mol) was dissolved in tetrahydrofuran (300 ml) at 0°C and 1M-n-butyllithium (in hexane, 46 ml, 0.046 mol) added under nitrogen. The solution was stirred for 10 minutes at this temperature and then methyl iodide (19.5 ml, 0.309 mol) was added gradually. The reaction mixture was allowed to warm up to room temperature and stirred for 56 hours. The reaction mixture was then poured into a separating funnel containing ether and water and shaken well. The ethereal layer was separated, dried, and the solvent removed. Column chromatography of the crude product using

Kieselgel 60 (Art.7730) eluting with pet.ether gave methyl ether (24) (5.78g, 79%).

Rf = 0.51 (10% ethyl acetate/pet.ether)

δ = 0.87 (3H,d,J = 6Hz), 1.03 (3H,s), 1.07 (3H,s), 1.59 (3H,s), 3.29 (3H,s), 3.31 (1H,m), and 4.75-5.3 (3H,m).

$\bar{\nu}_{max}$ = 2920(b), 1450(b), 1380(b), and 1090(b) cm^{-1}.

3. Formation of the bisepoxide (25/26)[14]

Methyl ether (24) (9.05g, 0.038 mol) dissolved in dichloromethane (350 ml) was added to 0.5M sodium bicarbonate solution (350 ml) and then subjected to rapid mechanical stirring until a white emulsion was formed. To this stirred solution was then added m-chloroperoxybenzoic acid (85%, 16.34g, 0.08 mol), and the stirring continued for 4 hours. The reaction solution was then poured into a separating funnel; the dichloromethane layer was separated and washed with 2M sodium hydroxide solution, dried; and the solvent removed on the rotary evaporator to yield crude material (9.5g). From this 4.4g of methyl ether bisepoxide ( ) were removed by filtration. Column chromatography of the residue using Kieselgel 60 (Art.7730) eluting with 15% ethyl acetate/pet. ether yielded a further amount of methyl ether bisepoxide (1.92g). Total yield of methyl ether bisepoxide (6.32g, 62%).

Rf = 0.28

δ = 0.84 (3H,d,J = 6Hz), 0.86 (3H,s), 1.06 (3H,s), 1.30 (3H,s), 3.25 (1H,m), and 3.31 (3H,s).

^{13}C nmr spectrum ($CDCl_3$).

δ = 12.9 (q), 17.2 (q), 20.7 (q), 24.0 (t), 28.4 (q), 31.8 (d), 33.0 (s), 35.5 (t), 35.7 (t), 40.0 (t), 56.9 (d), 57.1 (q), 59.8 (d), 61.8 (s), 67.2 (d), and 82.0 (d).

ν_{max} = 2930(b), 1460, 1380, and 1090 cm^{-1}.

4. Formation of methyl ether 4,5-epoxide (16)[15,16]

(a) Formation of the tungsten reagent

Tetrahydrofuran (250 ml) was stirred at -78°C under nitrogen for 10 minutes. To this was added tungsten hexachloride (4.45g, 0.011 mol), and the reaction mixture stirred vigorously for 15 minutes, then 1.6M n-butyllithium (in hexane, 20.1 ml, 0.033 mol) was added slowly such that the temperature of the reaction mixture did not rise above -65°C. When the addition was complete the reaction mixture was stirred at -78°C for a further 10 minutes and then gradually allowed to warm up to room temperature.

(b) Deoxygenation of the methyl ether bisepoxide (25/26)

The tungsten reagent was cooled to 10°C and the bisepoxide (25/26) (3g, 0.011 mol) added. The reaction mixture was stirred at room temperature for 45 minutes, and then heated rapidly in a preheated oil bath (80°C) to 60-65°C and held at this temperature for 45 minutes. The progress of the reaction was followed by analytical tlc, aliquots of the reaction mixture (0.25 µl) being removed and worked up at regular intervals. The reaction mixture was then cooled to room temperature and poured into a separating funnel containing ether and washed with 2M sodium hydroxide, 1.5M sodium potassium tartrate solution, dried and removal of solvent on the rotary evaporator gave a green-blue oil (3.1g). Column chromatography of the oil on Kieselgel 60 (Art.7730) eluting with 15% ethyl acetate/pet.ether gave methyl ether (24) (0.44g), methyl ether bisepoxide (25/26) (1.32g) identical to the starting material and methyl ether 4,5-epoxide (16) (0.58g, 37%).

Rf = 0.72

δ = 0.75 (3H,s), 0.8 (3H,d,J = 6Hz), 1.02 (3H,s), 1.66 (3H,s), 3.25 (1H,bs), 3.31 (3H,s), 5.20 (1H,dd,J = 4Hz and J = 11Hz).

$\bar{\nu}_{max}$ = 2930(b), 1460, 1380, 1240, and 1090 cm^{-1}.

5. Deoxygenation of methyl ether bisepoxide, acetylation of resulting cyclised alcohols (17),(29)

The formation of tungsten reagent was carried out as described above using tungsten hexachloride (5.05g, 0.0127 mol), 1.6M n-butyllithium (24 ml, 0.038 mol) and tetrahydrofuran (250 ml).

Continuing as for part 4(b) using the bisepoxide (25/26) (3.41g, 0.0127 mol), gave crude deoxygenated material (3.41g). Column chromatography using Kieselgel (Art.9385) eluting with 10% ethyl acetate/pet.ether gave a crude mixture of the bisepoxide (25/26) and cyclised alcohol (17)(29)(2.5g).

To the crude mixture (2.5g) in pyridine (15 ml) at room temperature, was added excess acetic anhydride (0.87 ml) and N,N-dimethyl-4-aminopyridine (10 mg). The reaction mixture was stirred for 15 hours. The reaction was quenched by addition of sat.sodium bicarbonate solution and then the reaction mixture was extracted with ether. The ethereal extracts were washed with sat.copper sulphate solution, dried, and removal of solvent yielded crude material (2.2g). Column chromatography of this material on Kieselgel (Art.9385) eluting with 5% ethyl acetate/pet.ether gave Rf = 0.82, the acetate (27) (300 mg) and a mixture of acetates Rf = 0.76 (27) and (19) (600 mg).

Rf = 0.82

δ = 0.87 (3H,s), 0.99 (3H,d,J = 6Hz), 1.04 (3H,s), 1.61 (3H,s), 2.05 (3H,s), 3.24 (3H,s), 3.24 (1H,m), and 4.62 (1H,d,J = 7Hz).

Rf = 0.76

significant peaks at δ = 1.61, 2.05, 3.24, 4.6, 4.76 and 4.98.

6. Cyclisation of the epoxide (16)

Methyl ether 4,5-epoxide (16) (0.67g, 2.65 mmol) was dissolved in ether (15 ml) at room temperature and boron trifluoride etherate (3.27 ml, 0.0265 mol) was added. The reaction mixture was stirred for 30 min, after which time it was quenched by the addition of sat.sodium bicarbonate solution. The reaction mixture was then extracted with ether and the ethereal extracts washed with sat.sodium chloride solution, dried, and removal of solvent on the rotary evaporator gave 0.57g crude material. Column chromatography on Kiesel (Art.9385) eluting with 30% ether/pet.ether gave the alcohol (17) (0.27g, 47%).

Rf = 0.30

= 0.85 (3H,d,J = 6Hz), 0.95 (3H,s), 1.08 (3H,s), 3.07 (1H,d,J = 10Hz), 3.3 (3H,s), 3.33 (1H,m), 4.67 (1H,s), and 4.99 (1H,s).

7. Acylation of crude alcohol (17)

To the crude alcohol (0.84g) stirred in pyridine (10 ml) at room temperature, was added acetic anhydride (0.47 ml) and N,N-dimethyl-4-aminopyridine (10 mg). The

reaction mixture was stirred for 1 hour and then quenched by the addition of sat.sodium bicarbonate solution. The reaction mixture was extracted with ether and the ethereal extracts washed with sat.copper sulphate solution, dried, and removal of solvent on the rotary evaporator gave 750 mg crude material. This was subjected to column chromatography Kieselgel (Art.9385) eluting with ethyl acetate/pet.ether and yielded methyl ether bisepoxide (25/26) (210 mg) and acetoxy methyl ether (19) (410 mg, 56%).

Rf = 0.7

δ = 0.79 (3H,d,J = 6Hz), 0.96 (3H,s), 1.0 (3H,s), 2.05 (3H,s), 3.25 (3H,s), 3.33 (1H,m), 4.54 (1H,d,J = 10Hz), 4.76 (1H,s), and 4.98 (1H,s).

$\bar{\nu}_{max}$ = 2920(b), 1735, 1635, 1460, 1370, 1235, 1090, and 1040 cm^{-1}.

8. Attempted Methyl ether cleavage

(a) 15-Crown-5, boron tribromide and sodium iodide[17]

Methyl ether (24) (200 mg, 8.47 mmol) was dissolved in dichloromethane (3 mls) and stirred at -30°C under nitrogen. To this was added 15-Crown-5 (1.12g, 5.08 mmol) dissolved in dichloromethane and saturated with sodium iodide (13 ml). The reaction mixture was stirred for 10 minutes and then boron tribromide (0.243 ml, 2.54 mmol) was added and the reaction mixture was stirred for 3 hours at this temperature, and then allowed to warm up to room temperature for a further 2½ hours. Saturated sodium bicarbonate solution was then added, the dichloromethane layer separated, dried and removal

of solvent on the rotary evaporator gave 190 mg crude material. Column chromatography using Alumina (type UG) eluting with pet.ether gave two fractions. One [Rf 0.68 (10% ethyl acetate/ pet.ether)] was judged by its nmr spectrum to contain at least four compounds, the other contained greater than five compounds on analytical tlc.

(b) Sodium iodide and trichloromethyl silane[18]

Sodium iodide (380 mg, 2.54 mmol) was dissolved in acetonitrile (10 ml) and stirred under nitrogen at room temperature. To this was added successively trichloromethyl silane (380 mg, 2.54 mmol) and methyl ether (24) (500 mg, 2.12 mmol), and the stirring continued for 5 hours. After this time, the reaction was quenched by the addition of water, and the reaction mixture extracted with ether. The ethereal extracts were washed with sat.sodium thiosulphate solution and sat. sodium chloride solution, dried, and removal of solvent on the rotary evaporator gave 510 mg crude material. Column chromatography of this using Kieselgel (Art.9385) eluting with pet.ether gave 70 mg of an oil identical to isohumulol on analytical tlc. The nmr spectrum of this oil however showed retention of the O-Me peak at 3.29 ppm but loss of the alkene protons between 4.75-5.3 ppm.

9. Attempted methyl ether cleavage of (19)

(a) Trimethylsilyl iodide generated *in situ*[19] in the presence of hexamethyldisilazane

Acetoxy methyl ether (19) (50 mg, 0.17 mmol), was dissolved in acetonitrile (4 ml) at -10°C and hexamethyldisilazane (0.042 ml, 0.2 mmol) was added under nitrogen with

stirring. To this solution was added successively sodium iodide (25 mg, 0.17 mmol) and trimethylsilyl chloride (0.0215 ml, 0.17 mmol), and the reaction mixture was allowed to warm up to room temperature and stirred for 24 hours. The reaction was quenched by addition of sat.sodium bicarbonate solution and ether. The ethereal extracts were separated and washed with sat.sodium thiosulphate solution, dried, and removal of solvent on the rotary evaporator gave 50 mg of material identical with the starting material.

(b) Trimethylsilyl iodide generated in situ[19]

Sodium iodide (10 mg, 0.068 mmol) was dissolved in acetonitrile (2.5 ml) and stirred under nitrogen. Acetoxy methyl ether (19) (20 mg, 0.068 mmol) and trimethylsilyl chloride (8.6 µl, 0.068 mmol) were added successively. The reaction was monitored by analytical tlc for 24 hours after which time one major compound Rf=0.71 was formed. The reaction was quenched by addition of water and the reaction mixture extracted with ether. The ethereal extracts were washed with sat.sodium thiosulphate solution, dried, and removal of solvent on the rotary evaporator gave 15 mg yellow oil, the nmr spectrum of which shows loss of the O-Me protons at 3.25 ppm and the alkene protons at 4.76 and 4.98 ppm and the acetoxy proton at 4.54 ppm, but the retention of the acetoxy protons at 2.05 ppm.

(c) Trichloromethyl silane and sodium iodide[18]

Sodium iodide (10.2 mg, 0.068 mmol) was dissolved in acetonitrile (2.5 ml) and stirred under nitrogen at room temperature and then acetoxymethyl ether (19) (20 mg, 0.068 mmol)

and trichloromethylsilane (0.0102g, 0.068 mmol) were added successively. The reaction was stirred for 24 hours and monitored by analytical tlc. After this time the reaction was quenched by the addition of water, the reaction mixture extracted with ether and the ethereal extracts washed with sat.sodium thiosulphate solution, dried, and removal of solvent on the rotary evaporator gave a yellow oil, the cyclic ether (20) (15 mg).

Rf = 0.71

δ = 0.91 (3H,s), 0.98 (3H,d,J = 7Hz), 1.07 (3H,d,J = 7Hz), 1.17 (3H,s), 2.03 (3H,s), 3.3 (1H,m), and 4.72 (1H,d, J = 2.5Hz).

(d) Trimethylsilyl iodide generated *in situ* in the presence of hexamethyldisilazane with heating

Sodium iodide (10 mg, 0.068 mmol) was dissolved in acetonitrile (3 ml) and stirred under nitrogen. Acetoxy methyl ether (19) (20 mg, 0.068 mmol) was added and then hexamethyldisilazane (15.8 µl, 0.075 mmol) and trimethylsilyl chloride (8.6 µl, 0.068 mmol) were added successively and the reaction mixture heated to 50°C and stirred for 24 hours monitoring by analytical tlc. After this time the reaction mixture was refluxed for 6 hours and then cooled to room temperature and quenched by the addition of water and ether. The ether layer was separated, washed with sat. sodium thiosulphate solution, and then dried and removal of solvent on the rotary evaporator gave a clear oil, Rf=0.71 nmr identical to that of the cyclic ether (20) (20 mg).

10. Formation of the acetate of isohumulol (23)

Crude isohumulol (23) (1.2g) was dissolved in pyridine (6 ml) and acetic anhydride (3 ml) was added and the reaction stirred for 5 hours. After this time, the reaction mixture was poured into a separating funnel containing water and extracted with ether. The ethereal solution was washed successively with sat.copper sulphate solution and sat.sodium bicarbonate solution and then dried, and the solvent removed on the rotary evaporator to give crude material (1.16g). Column chromatography in alumina (type UG) eluting with 1-2% ethyl acetate/pet.ether gave the acetate of isohumulol (35) (0.39g, 26.2% from humulene).

Rf = 0.45 (10% ethyl acetate/pet.ether)

δ = 0.84 (3H,d,J = 5Hz), 0.93 (3H,s), 1.06 (3H,s), 1.18 (3H,s), 1.63 (3H,s), 2.04 (3H,s), and 4.87-5.3 (4H,m).

$\bar{\nu}_{max}$ 2920(b), 1730, 1450, 1370, and 1240 cm^{-1}.

M^+ (found) = 264.2086; M^+ (calculated for $C_{17}H_{28}O_2$) = 264.2089.

11. Formation of the p-phenyl benzoate ester of isohumulol (23)

Crude isohumulol (23) (2g) was dissolved in pyridine at room temperature (10 ml) and p-phenyl benzoyl chloride (1.09g) was added and the reaction mixture stirred for 15 hrs. After this time the reaction mixture was poured into a separating funnel containing water and extracted with ether. The ethereal solution was washed with sat.copper sulphate solution, and then dried and removal of solvent

on the rotary evaporator gave 1.8g crude product. Column chromatography on alumina (type UG) eluting with 1-2% ethyl acetate/pet.ether gave the p-phenyl benzoate ester of isohumulol (36) (0.54g, 68%).

Rf = 0.76

δ = 0.95 (3H,d,J = 6Hz), 1.03 (3H,s), 1.21 (3H,s), 1.56 (3H,s), 4.7-5.5 (4H,m), and 7.1-8.1 (9H,m).

$\bar{\upsilon}_{max}$ = 2920(b), 1720, 1620, 1460, 1280, and 1120 cm^{-1}.

12. Bis-epoxidation of the acetoxy ester of isohumulol (35)

(a) Mono-epoxidation

The acetoxy ester of isohumulol (35) (0.39g, 1.47 mmol) dissolved in dichloromethane (200 ml) was added to 0.5M sodium bicarbonate solution (200 ml) and m-chloroperoxy benzoic acid (85%, 0.6g, 2.95 mmol) was added and the reaction mixture stirred rapidly with a mechanical stirrer until a white emulsion was formed, for 1 hour. After this time, the dichloromethane layer was separated and washed with 2M sodium hydroxide solution, dried and the solvent removed on the rotary evaporator to give 0.29g clear oil, Rf=0.25. The nmr spectrum showed it to be a mixture, and to have retained the alkene protons between 4.92 and 5.46 ppm. This oil was not investigated further but resubmitted to epoxidation conditions.

(b) The presumed mono epoxide (37) (0.29g) was dissolved in dichloromethane (50 ml) and 0.5M sodium bicarbonate solution (60 ml) and m-chloroperoxy benzoic acid (85%, 0.231g) added and the reaction mixture stirred for 15 hours. After

this time the dichloromethane layer was separated and washed with 2M sodium hydroxide solution, dried and removal of solvent on the rotary evaporator yielded 0.25g white crystals. Column chromatography using Kieselgel (Art.9385) eluting with 10% ethyl acetate/pet.ether gave two compounds Rf = 0.28 and 0.2. The less polar material was identified as the semi-crystalline bisepoxide (38) (110 mg, 36%), and the more polar material was unidentified (20mg, 6.5%).

Rf = 0.28

δ = 0.88 (3H,d,J = 8Hz), 0.96 (3H,s), 1.07 (3H,s), 1.33 (3H,s), 2.05 (3H,s), 2.41 (1H,d,J = 3Hz), 2.58 (2H,m), and 5.15 (1H,d,J = 9Hz).

^{13}C nmr spectrum ($CDCl_3$).

δ = 13.15(q), 17.1(q), 20.6(q), 21.1(q), 22.6(t), 28.33(q), 33.02(s), 35.0(t), 35.3(t), 35.7(d), 40.4(t), 56.6(d), 59.3(d), 61.0(s), 67.2(d), 73.7(d), 171.0(s).

m/e: (relative intensity) = 221 (0.4), 43 (100), 41(41), 55(36.8).

Rf = 0.2

δ = 0.88(s), 1.1(s), 1.27(s), 1.53(s), 2.05(s), and 4.6-4.95(m).

13. Bisepoxidation of the p-phenyl benzoate ester of isohumulol (39)[14]

The p-phenyl benzoate ester (36) (470 mg, 1.17 mmol) was dissolved in dichloromethane (40 mls) and 0.5M sodium bicarbonate solution (50 mls) and m-chloroperoxybenzoic acid (85%, 0.498, 2.45 mmol) were added and the

reaction solution stirred for 24 hours. After this time the dichloromethane layer was separated, washed with 2M sodium hydroxide solution, dried, and removal of solvent on the rotary evaporator gave 420 mg crude material. Column chromatography on Kieselgel (Art.9385) eluting with 10% ethyl acetate/pet.ether gave two compounds Rf = 0.58 and 0.41 the less polar, a clear oil was unidentified (80 mg, 16.4%) and the more polar bisepoxide (39) (260 mg, 51%).

Rf = 0.58 nmr spectrum showed retention of alkene protons between 5.1-5.5 ppm.

Rf = 0.41

δ = 1 (3H,d,J = 6Hz), 1.03 (3H,s), 1.07 (3H,s), 1.3 (3H,s) 2.82-3.28 (2H,m), 5.43 (1H,d,J = 9Hz) and 7.18-8.1 (9H,m).

14. Deoxygenation of the bisepoxide (38)[15,16]

Formation of the tungsten reagent was performed as in part 4(a) using tungsten hexachloride (0.67g, 1.69 mmol), 1.6M n-butyllithium (3.17 ml, 5.07 mmol) and tetrahydrofuran (150 ml).

The tungsten reagent was cooled to 10°C and then the bisepoxide (38) (0.5g, 1.69 mmol) was added in tetrahydrofuran and the reaction mixture stirred at room temperature for 45 minutes. The reaction mixture was then heated rapidly with a pre-heated oil bath (80°C) to reflux, and held at this temperature for 3 hours, monitoring the progress of the reaction by analytical tlc. After 3 hours the reaction mixture was cooled to room temperature, poured into a

separating funnel containing ether and washed with 2M sodium hydroxide, 1.5M sodium potassium tartrate solution. The ethereal solution was dried and the solvent removed to yield 0.61g blue-green oil. Column chromatography on Kieselgel (Art.9385) eluting with 10% ethyl acetate/pet.ether gave recovered starting material (400 mg).

15. Deoxygenation of the bisepoxide (39)[15,16]

Formation of tungsten reagent as part 4(a) using tungsten hexachloride (0.239g, 0.599 mmol), 1.6M n-butyllithium (1.12 ml, 1.79 mmol), and tetrahydrofuran (100 mls).

The tungsten reagent was cooled to 10°C and the bisepoxide (39) (250 mg, 0.599 mmol) was added. The reaction mixture was stirred for 45 minutes and then heated rapidly to reflux in a pre-heated oil bath (80°C) and held at this temperature for 18 hours. After this time the reaction mixture was cooled to room temperature, poured into a separating funnel containing ether and washed with 2M sodium hydroxide, 1.5M sodium potassium tartrate solution, dried and the solvent removed on the rotary evaporator. Column chromatography of the crude material using alumina (type UG) eluting with 10% ethyl acetate/pet.ether gave recovered starting material (220 mg).

16. p-Methoxy-benzyl chloride[27]

p-Methoxy-benzyl alcohol (20g, 0.145m) was stirred with concentrated hydrochloric acid (10M, 28.98 ml, 0.299m) for 15 minutes. The reaction mixture was then poured into a separating funnel and the organic layer separated and dried

with calcium chloride for 30 minutes. This crude p-methoxy benzyl chloride was distilled under vacuum (2 mm Hg, 75°C) to yield 12.67g colourless oil (72%). The pure p-methoxy benzyl chloride could be stored at less than 0°C until needed. δ = 3.63 (3H,s), 4.4 (2H,s), and 6.94 (4H,m).

17. Attempted formation of the p-methoxy benzyl ether (51)

(a) Sodium hydride

Isohumulol (23) (0.8g, 3.6 mmol) was dissolved in tetrahydrofuran (100 ml) and sodium hydride (0.26g, 0.0108 mol) and p-methoxy benzyl chloride (1.128g, 7.2 mmol) were added and the reaction mixture refluxed for 20 hours. After this time the reaction mixture was cooled to room temperature and ether/methanol (1:1) added, followed by sat.ammonium chloride solution. The organic layer was then separated, dried, and removal of solvent yielded 1.5g crude material. Column chromatography on Kieselgel 60 (Art.7730) eluting with pet.ether gave the p-methoxy benzyl ether (51) (430 mg, 35%).

Rf = 0.58 (10% Ethyl acetate/pet.ether).

δ = 0.89 (3H,d,J = 6.5Hz), 0.96 (3H,s), 1.0 (3H,s), 1.55 (3H,bs), 3.47 (1H,m), 3.79 (3H,s), 4.32, and 4.62 (2H,ABq,J = 12Hz), 4.82-5.02 (2H,m), and 6.91 and 7.35 (4H,AA'BB'q,J = 9Hz).

$\bar{\nu}_{max}$ = 2930(b), 1620(w), 1520, 1465(b), 1380, 1255, and 1065(b) cm^{-1}.

M^+ (found) = 342.2567; M^+ (calculated for $C_{23}H_{34}O_2$) = 342.2559.

(b) n-Butyllithium

Isohumulol (23) (1g, 4.5 mmol) was stirred in tetrahydrofuran (100 ml) at 0°C under nitrogen, 1.6M n-butyllithium (in hexane, 5.6 ml, 9.0 mmol was added and the stirring continued for 15 minutes. p-Methoxy benzyl chloride (1.41g, 9.0 mmol) was then added and the reaction mixture allowed to warm up to room temperature and stirred for 48 hours. After this time the reaction mixture was examined by analytical tlc: no reaction had taken place.

(c) Excess sodium hydride

Isohumulol (23) (3g, 0.0135 m) was dissolved in tetrahydrofuran (100 mls) and sodium hydride (50% dispersion in oil, washed with tetrahydrofuran, 6.48g, 0.135 mol) was added, and the solution stirred for 30 minutes. p-Methoxy benzyl chloride (3.17g, 0.0203 m) was added and the reaction mixture refluxed for 24 hours. The reaction mixture was then cooled to room temperature and methanol added slowly, followed by sat.ammonium chloride solution and ether and this solution was stirred for 30 minutes. The ethereal solution was then separated and dried and removal of solvent on the rotary evaporator yielded 6.28g yellow oil. Column chromatography of this using alumina (type UG) eluting with 10% ether/pet.ether yielded the p-methoxy benzyl ether (51) (3.62g, 78%).

18. Cleavage of the p-methoxy benzyl ether (51)[23]

p-Methoxy benzyl ether (51) (300 mg, 0.87 mmol) was dissolved in dichloromethane (shaken with water, 50 mls) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.19g, 0.87

mmol) was added and the reaction mixture stirred in the air for 1 hour monitoring the reaction by analytical tlc. After this time water was added and the dichloromethane solution was separated and washed with sat.sodium chloride solution. Passage down a short silica column, Kieselgel 60 (Art.7730) and removal of the solvent on the rotary evaporator yielded an oil. Column chromatography using Kieselgel 60 (Art.7730) eluting with dichloromethane yielded isohumulol (23) (100 mg, 82%) identical to authentic material by analytical tlc and nmr spectroscopy.

19. Formation of the bisepoxide (54/55)

(a) Biphase system, normal stirring

p-Methoxy benzyl ether (51) (500 mg, 1.6 mmol) was dissolved in dichloromethane (30 ml). To this solution was added 0.5M sodium bicarbonate solution and m-chloroperoxybenzoic acid (85%, 680 mg, 3.4 mmol) and the reaction stirred for 23 hours at room temperature, monitoring the reactions progress by analytical tlc. A further addition of m-chloroperoxybenzoic acid (85%, 680 mg, 3.4 mmol) was made after this time and the reaction mixture stirred for a further 24 hours. The dichloromethane layer was then separated, washed with 2M sodium hydroxide solution and then dried, and the solvent removed on the rotary evaporator to yield a yellow oil (310 mg). Column chromatography using Kieselgel (Art.9385) eluting with 10% ethyl acetate/pet.ether gave two products Rf = 0.63 and 0.4. The less polar was identified as the 8,9 epoxide (52) (35 mg, 7%), the more polar was

identified as the bisepoxide (54/55) (40 mg, 7%).

Rf = 0.63 (30% ethylacetate/pet.ether)

δ = 0.84 (3H,d,J = 6Hz), 0.93 (3H,s), 1.03 (3H,s), 1.2 (3H,s), 3.28 (1H,m), 3.76 (3H,s), 4.2 and 4.53 (2H,ABq, J = 12Hz), 5.03 (2H,m), 6.78 and 7.18 (4A,AA'BB'q, J = 9Hz).

Rf = 0.4 (30% ethyl acetate/pet.ether).

mp = 92-93°C

δ = 0.6 (3H,s), 0.88 (3H,d,J = 6Hz), 0.99 (3H,s), 1.24 (3H,s), 3.3 (1H,m), 3.72 (3H,s), 4.27 and 4.57 (2H,ABq,J = 12Hz), 6.76 and 7.24 (4H,AA'BB'q,J = 9Hz).

^{13}C nmr spectrum ($CDCl_3$)

δ = 12.9(q), 17.25(q), 20.4(q), 24.0(t), 28.4(q), 31.8(d), 33.0(s), 35.5(t), 35.8(t), 40.1(t), 55.3(q), 56.6(d), 59.3(d), 61.7(s), 67.4(d), 69.7(t), 77.2(d), 114.2(d), 129.6(d), 130.45(s), 159.65(s).

$\bar{\nu}_{max}$ = 2920(b), 1615, 1510, 1465, 1250 and 1065(b) cm^{-1}.

M^+ (found) = 374.2443; M^+ (calculated for $C_{23}H_{34}O_9$) = 374.2457.

(b) Biphase system, vigorous stirring

p-Methoxy benzyl ether (51) (500 mg, 1.6 mmol) was dissolved in dichloromethane (200 ml) to which was added 0.5M sodium bicarbonate solution (250 ml). The solution was stirred vigorously with a mechanical stirrer until a white emulsion was formed. m-Chloroperoxybenzoic acid (85%, 0.68g, 3.4 mmol) was added to the stirred solution and the stirring continued for 6 hours, when further m-chloroperoxybenzoic acid (85%, 0.68g, 3.4 mmol) was added and the stirring continued

for 1 hour. The organic layer was then separated, washed with 2M sodium hydroxide solution and then dried, removal of the solvent on the rotary evaporator yielded 0.75g crude material. Column chromatography using Kieselgel 60 (Art.7730) eluting with 30% ether/pet.ether yielded the bisepoxide (54/55) (70 mg, 13%).

(c) Dichloromethane solution

p-Methoxy benzyl ether (51) (9.47g, 0.029 mol) was dissolved in dichloromethane (250 ml) and m-chloroperoxy benzoic acid (85%, 12.13g, 0.059 mol) was added and the reaction mixture stirred for 2 hours at room temperature. After this time the reaction mixture was washed with 2M sodium hydroxide solution, dried, and the solvent removed on the rotary evaporator to give 7.73g crude material. Column chromatography using Kieselgel 60 (Art.7730) eluting with 40% ether/pet.ether gave the bisepoxide (54/55) as white crystals (4.09g, 38%).

20. Monodeoxygenation of the bisepoxide (54/55)[15,16]

A series of experiments were performed to assess the optimum conditions for deoxygenation of the bisepoxide (54/55) using varying ratios of tungsten reagent to reactant and various temperatures. The results are summarised in the Table.

(a) Methyl ether conditions

Formation of the tungsten reagent was performed as in part 4(a) using tungsten hexachloride (0.26g, 0.67 mmol) 1.6M n-butyllithium (in hexane, 1.25 ml, 0.02 mol) and tetrahydrofuran (50 ml).

The tungsten reagent was cooled to 10°C and the bisepoxide (54/55) (0.25g, 0.68 mmol) was added. The reaction mixture was stirred at room temperature for 45 minutes and then heated to rapidly reflux in a preheated oil bath (80°C) and held at this temperature for 2 hours. The reaction mixture was then cooled to room temperature and poured into a separating funnel containing ether. The ethereal layer was washed with 2M sodium hydroxide, 1.5M sodium potassium tartrate solution and then dried, removal of the solvent on the rotary evaporator yielded 290 mg crude material. Column chromatography using Kieselgel 60 (Art.7730) eluting with 40% ether/pet.ether yielded one major compound Rf = 0.62. The nmr spectrum identified this compound as p-methoxy benzyl alcohol.

(b) Lower temperature

Formation of the tungsten reagent was performed as in part 4(a) using tungsten hexachloride (0.79g, 2.0 mmol), 1.6M n-butyllithium (in hexane, 3.8 ml, 6.0 mmol) and tetrahydrofuran (100 ml).

The tungsten reagent was cooled to -2°C and the bisepoxide (54/55) (0.75g, 2.0 mmol) was added and the reaction mixture stirred at this temperature for 1.5 hours, monitoring the progress by analytical tlc. The reaction mixture was then stirred at 0-10°C for 45 minutes and then at room temperature for 1.5 hours. After this time the reaction mixture was worked up as for part 20(a) to yield 600 mg crude material. Preparative tlc, eluting with 70% ether/pet.ether yielded the epoxide (58) (100 mg, 14%) and recovered starting material (250 mg).

Rf = 0.55 (30% ethyl acetate/pet.ether)

δ = 0.54 (3H,s), 0.86 (3H,d,J = 8Hz), 0.98 (3H,s,1.61 (3H,s), 3.42 (1H,m), 3.76 (3H,s), 4.63 and 4.65 (2H,ABq,J = 12Hz), 4.79 (1H,bd), 6.84 and 7.26 (4H,AA'BB'q,J = 9Hz).

^{13}C nmr spectrum ($CDCl_3$)

δ = 13.2(q), 16.7(q), 19.9(q), 26.6(t), 28.0(q), 32.5(d), 35.25(t), 35.25(s), 36.6(t), 39.7(t), 55.3(q), 56.5(d), 69.0(d), 69.6(t), 76.6(d), 114.0(d), 121.65(d), 129.6(d), 131.0(s), 137.0(s), 159.4(s).

$\bar{\nu}_{max}$ = 2940(b), 1720(b), 1615, 1460(b), 1320 and 1245 cm^{-1}

M^+ (found = 358.2489; M^+ (calculated for $C_{23}H_{34}O_3$) = 358.2508.

(c) Prolonged reaction times at room temperature

Formation of the tungsten reagent was performed as in part 4(a) using tungsten hexachloride (0.79g, 2.0 mmol), 1.6M n-butyllithium (in hexane, 3.8 ml, 6.0 mmol) and tetrahydrofuran (100 ml).

The tungsten reagent was cooled to 10°C and the bisepoxide (54/55) (0.75g, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 12 hours. After this time the reaction was worked up as for part 20(a) to yield 770 mg crude material, which appeared from analytical tlc and the nmr spectrum to be a mixture of compounds, of which p-methoxy benzyl alcohol was the major component.

(d) Two equivalents of tungsten reagent, lower temperature

Formation of the tungsten reagent was performed as in part 4(a) using tungsten hexachloride (0.79g, 2.0 mmol),1.6M n-butyllithium (in hexane, 36.2 ml, 0.056 mol) and tetrahydrofuran (350 ml).

The tungsten reagent was cooled to -10 - -15°C and the bisepoxide (54/55) (3.5g, 9.35 mmol) added and the reaction mixture stirred at this temperature for 1 hour. The reaction mixture was then allowed to warm up to room temperature and stirred for 50 minutes carefully monitoring the progress by analytical tlc. The reaction was worked up as for part 20(a) to yield a crude blue oil (3.6g). Column chromatography using Kieselgel 60 (Art.7730) eluting with 20% ethyl acetate/pet.ether yielded the epoxide (58) (1.62g, 45%) together with a mixture of starting material (54/55) and cyclised alcohols (60) and (61).

(e) Three equivalents of tungsten reagent, lower temperatures

Formation of the tungsten reagent was performed as in part 4(a) using tungsten hexachloride (2.38g, 60 mmol), 1.6M n-butyllithium (in hexane, 11.28 ml, 0.018 mol), and tetrahydrofuran (100 ml).

The tungsten reagent was cooled to -15°C and the bisepoxide (54/55) (750 mg, 2.0 mmol) added. The reaction mixture was maintained at this temperature for 2½ hours after which it was worked up as for part 20(a) to yield a crude green oil (0.97g). Column chromatography using Kieselgel (Art.9385) eluting with 50% ether/pet.ether yielded impure epoxide (58) (430 mg) which was further subjected to preparative tlc eluting with 30% ethyl acetate/pet.ether to yield the epoxide (58) (300 mg, 42%). On the basis of the results presented in the Table it was decided that the conditions used in experiment (d) were those most suitable for the deoxygenation of (54/55).

Experiment	No. of equivalent of tungsten reagent	Conditions	Yield of epoxide (58)
20(a)	1	45 minutes at room temperature reflux for 2 hours	-
20(b)	1	1.5 hours at -2°C 45 minutes at 0-10°C	14%
20(c)	1	12 hours at room temperature	-
20(d)	2	1 hour at -15°C 50 minutes at room temperature	48%
20(e)	3	2.5 hours at -15°C	42%

21. Cyclisation of the epoxide (58)

(a) Room temperature, boron trifluoride etherate

The epoxide (58) (160 mg, 0.45 mmol) was dissolved in ether (5 ml) and boron trifluoride etherate (0.112 ml, 0.89 mmol) was added. The reaction mixture was stirred for 1.5 hours at room temperature, monitoring the progress by analytical tlc. Sat.sodium bicarbonate solution was then added gradually. The ether layer was separated and then dried and the solvent removed to yield a crude yellow oil (170 mg). Preparative tlc eluting with 30% ethyl acetate/pet.ether yielded the 5-p-methoxy benzyl ether of 6,10,10-trimethyl bicyclo[6.3.0]undeca-5,9-diol (60) (30 mg, 19%).

Rf = 0.4 (30% ethyl acetate/pet.ether)

δ = 0.87 (3H,d,J = 8Hz), 0.88 (3H,s), 1.01 (3H,s), 3.08 (1H,d,J = 10Hz), 3.5 (1H,m), 3.77 (3H,s), 4.4 (2H,s), 4.69 (1H,s), 5.02 (1H,s), 6.84, 7.26 (4H,AA'BB'q,J = 9Hz).

^{13}C nmr spectrum

δ = 14.9(q), 20.4(q), 27.1(q), 30.8(t), 32.5(t), 36.9(d), 39.0(s), 40.6(t), 42.3(d), 43.7(t), 46.7(d), 55.3(q), 70.1(t), 80.5(d), 84.9(d), 112.5(t), 113.7(d), 129.0(d), 131.3(s), 152.7(s), 159.0(s)

$\bar{\nu}_{max}$ = 3200-3600(b), 2965(b), 1615, 1515, 1460, 1250, and 1080(b) cm^{-1}.

M^+ (found) = 358.2514; M^+ (calculated for $C_{23}H_{34}O_3$) = 358.2509.

(b) Low temperature, boron trifluoride etherate

The epoxide (58) (100 mg, 0.28 mmol) was dissolved in ether (10 ml) and cooled to 0°C. Boron trifluoride etherate (0.069 ml, 0.56 mmol) was added and the reaction mixture stirred at this temperature for 2 hours. Sat.sodium bicarbonate solution was then added and the reaction mixture extracted with ether. The ethereal extracts were washed with sat.sodium chloride solution and then dried, and the solvent removed on the rotary evaporator to yield crude material (100 mg). Column chromatography using Kieselgel (Art.9385) eluting with 30% ether/pet.ether gave the alcohol (60) (65 mg, 65%).

22. Acetalylation of the alcohol (60)

The alcohol (60) (225 mg, 0.63 mmol) was dissolved in pyridine (3 ml). Acetic anhydride (0.106 ml, 0.94 mmol) and N,N-dimethyl-4-aminopyridine (10 mg) were added and the reaction mixture stirred at room temperature for 24 hours. Sat.sodium bicarbonate solution was then added, and the reaction extracted with ether. The ethereal extracts were

washed with sat.copper sulphate solution and then dried and the solvent removed on the rotary evaporator to yield the acetate (66) (200 mg, 80%).

Rf = 0.59 (30% ethyl acetate/pet.ether)

δ = 0.85 (3H,d,J = 7Hz), 0.92 (3H,s), 0.99 (3H,s), 2.07 (3H,s), 3.49 (1H,m), 3.74 (3H,s), 4.39 (2H,s), 4.58 (1H,d,J = 10Hz), 4.79 (1H,s), 5.03 (1H,s), 6.83 and 7.24 (4H,AA'BB'q,J = 9Hz).

$\bar{\nu}_{max}$ = 2930(b), 1740, 1615, 1515, 1370, 1250(b) and 1055(b) cm^{-1}

M^+ (found) = 400.2575; M^+ (calculated for $C_{25}H_{26}O_4$) = 400.2614.

23. Deprotection of the p-methoxy benzyl ether (66)[23]

The acetate (66) (600 mg, 1.5 mmol) was dissolved in dichloromethane (shaken with water, 50 ml) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.34g, 1.5 mmol) was added and the reaction mixture stirred at room temperature for 50 minutes. Water (100 ml) was then added and the solution filtered. The dichloromethane solution was washed with water, separated, and the solvent removed on the rotary evaporator to yield a brown oil. This was passed down a short silica Kieselgel 60 (Art.7730) eluting with ether this gave 500 mg of impure product. Column chromatography using Kieselgel (Art.9385) eluting with pet.ether yielded the alcohol (63) (350 mg, 83%).

Rf = 0.215

δ = 0.89 (3H,d,J = 7.5Hz), 0.97 (3H,s), 1.01 (3H,s), 2.10 (3H,s), 3.89 (1H,m), 4.57 (1H,d,J = 10Hz), 4.83 (1H,s), 5.12 (1H,s)

$\bar{\nu}_{max}$ = 3600(b), 2915(b), 1713, 1460(b), 1240, and 1045 cm^{-1}

M^+ (found) = 280.2010; M^+ (calculated for $C_{17}H_{28}O_3$) = 280.2038

24. Model studies, dehydration of isohumulol (23)

(a) Mesyl chloride and pyridine

Isohumulol (23) (0.5g, 2.25 mmol) was dissolved in pyridine (5 ml) to which was added mesyl chloride (0.19 ml, 2.5 mmol) and the reaction mixture stirred for 15 minutes at room temperature. After this time sat.sodium bicarbonate solution was added and the solution extracted with ether. The ethereal solution was washed with sat.copper sulphate solution and then dried, and the solvent removed on the rotary evaporator to yield a clear oil, which was identified as the mesylate (64) (340 mg, 50%).

Rf = 0.35 (5% ethyl acetate/pet.ether)

δ = 0.93 (3H,d,J = 7Hz), 1.03 (3H,s), 1.11 (3H,s), 1.6 (3H,s), 2.94 (3H,s) and 4.82-5.33 (4H,m)

$\bar{\nu}_{max}$ = 2940(b), 1460(b), 1350(b), 1165 and 910 cm^{-1}

M^+ (found) = 300.1757; M^+ (calculated for $C_{16}H_{28}O_3S$) = 300.1759

(b) Mesyl chloride and triethylamine

Isohumulol (23) (500 mg, 2.25 mmol) was dissolved in triethylamine (3 ml) to which was added mesyl chloride (0.192 ml, 2.5 mmol) and the reaction mixture stirred for 3 hours at room temperature. Sat.sodium bicarbonate solution was then added and the reaction mixture extracted with ether. The ethereal solution was washed with sat.copper sulphate solution and then dried and the solvent removed on the rotary evaporator to yield a yellow oil identical to the mesylate (64) (410 mg, 60%).

(c) Mesyl chloride and pyridine with heating

Isohumulol (23) (250 mg, 1.1 mmol) was dissolved in pyridine (1 ml), cooled to 0°C, and then mesyl chloride (0.096 ml, 1.2 mmol) was added. The reaction mixture was stirred at this temperature for 30 minutes and then heated to 45°C and stirred at this temperature for 46 hours monitoring the progress by analytical tlc. After this time the reaction mixture was cooled to room temperature and extracted with ether. The ethereal solution was washed successively with 5% tartaric acid solution and 5% sodium bicarbonate solution, and then dried and the removal of solvent on the rotary evaporator yielded a brown oil identical to the mesylate (64) (180 mg, 53%).

25. Dehydration of the alcohol (63)

(a) Formation of the mesylate (65)

The alcohol (63) (24.7 mg, 0.088 mmol) was dissolved in pyridine (2 mls). Mesyl chloride (0.02 ml, 0.26 mmol) was added and the reaction mixture stirred at room temperature for 1 hour. Sat.sodium bicarbonate solution was then added and the reaction mixture extracted with ether. The ethereal solution was washed with sat.copper sulphate solution and then dried and the solvent removed on the rotary evaporator to yield the mesylate (65) (31 mg, 98%).

Rf = 0.37 (30% ethyl acetate/pet.ether)

δ = 0.93 (3H,d,J = 8Hz), 0.96 (3H,s), 1.0 (3H,s), 2.10 (3H,s), 3.0 (3H,s), 4.53 (1H,d,J = 9Hz), 4.86 (1H,s), 4.88 (1H,bm), 5.11 (1H,s)

$\bar{\nu}_{max}$ = 2960(b), 1730, 1360(b), 1250(b), 1150 and 910 cm^{-1}

M^+ -95 (found) = 262.1941; M^+ -95 (calculated for $C_{17}H_{26}O_2$) = 262.1933.

(b) Formation of the diene (62)

The mesylate (65) (250 mg, 0.69 mmol) was dissolved in 1,8-diazabicyclo[5.4.0]undeca-7-ene (1.04 ml, 6.9 mmol) under nitrogen. The reaction mixture was heated to 70°C and held at this temperature for 22 hours, it was then cooled to room temperature, and water was added and the aqueous solution extracted with ether. The ethereal solution was washed with sat.sodium chloride solution and then dried, and the solvent removed on the rotary evaporator to yield crude material (193 mg). Column chromatography using Kieselgel (Art.9385) eluting with 30% ether/pet.ether gave the diene (62) (137 mg, 75%).

Rf = 0.65 (30% ethyl acetate/pet.ether)

δ = 1.0 (3H,s), 1.1 (3H,s), 1.7 (3H,s), 2.09 (3H,s), 4.77 (1H,d,J = 9Hz), 4.85 (1H,s), 5.02 (1H,s), 5.4 (1H,t,J = 7Hz and J = 9Hz)

$\bar{\nu}_{max}$ = 2930(b), 1745, 1460, 1370, 1245, and 1040(b) cm^{-1}

M^+ (found) = 262.1933; M^+ (calculated for $C_{17}H_{26}O_2$) = 262.1933

26. Cyclisation of the diene (62)

Reactions were followed by analytical tlc, aliquots of the reaction mixture ($\sim$ 5 μl) being removed and worked up.

(a) Boron trifluoride etherate

The diene (62) (5 mg, 0.019 mmol) was dissolved in ether (1 ml) and cooled to 0°C. Boron trifluoride etherate

(2.3 µl, 0.019 mmol) was added and after 30 minutes at this temperature no reaction was observed on analytical tlc. The reaction mixture was allowed to warm up to room temperature and stirred for 93 hours. After this time, still no reaction had occurred.

(b) Sulphuric acid in ether

The diene (62) (6 mg) was stirred in 5% concentrated sulphuric acid in ether (1 ml) and after 6 hours at room temperature the reaction was complete. One major product Rf = 0.26 (20% ethyl acetate/pet.ether) was formed. The ethereal layer was washed with 10% potassium hydroxide solution and then dried and the solvent removed on the rotary evaporator to yield an oil identified as the alcohol (69) (6 mg, 93%).

(c) p-Toluene sulphonic acid

The diene (62) (10 mg, 0.038 mmol) was dissolved in benzene (2 ml) and p-toluene sulphuric acid (19.1 mg, 0.097 mmol) was added and the reaction mixture refluxed for 1½ hours. After this time, analytical tlc showed the reaction mixture to contain one major product, identical to that formed in part (b) and several minor products.

(d) Trifluoroacetic acid

The diene (62) (2 mg) was stirred with trifluoroacetic acid (1 ml) at room temperature and after 3 hours only starting material was visible on analytical tlc.

(e) Formic acid and acetic anhydride

The diene (62) (5 mg) was dissolved in acetic anhydride (0.5 ml) and formic acid (90%, 1.62 ml) was added and the reaction mixture stirred at room temperature for 2 hours. After this time, no reaction was visible on analytical

tlc, the reaction mixture was then heated to 100°C and after 1 hour two new compounds were visible on analytical tlc. Rf = 0.65 and 0.6 (30% ethyl acetate/pet.ether).

(f) Formic acid

The diene (62) (4.5 mg) was stirred in formic acid (90%, 3 ml) at room temperature for 24 hours. After this time, two new compounds were visible on analytical tlc. Rf = 0.57 and 0.33 (30% ethyl acetate/pet.ether).

27. Large scale cyclisation of the diene

(a) p-Toluene sulphonic acid

The diene (62) (47.8 mg, 0.18 mmol) was dissolved in benzene (3 ml), p-toluene sulphonic acid (86.3 mg, 0.46 mmol) was added and the reaction mixture refluxed for 3.5 hours. After this time the reaction mixture was cooled to room temperature and ether and sat.sodium bicarbonate solution added. The ethereal layer was separated, and then dried and the solvent removed on the rotary evaporator to yield a yellow oil (59.1 mg). Column chromatography using Kieselgel (Art.9385) eluting with 30% ether/pet.ether gave the alcohol (69) (20 mg, 39%).

Rf = 0.34 (30% ethyl acetate/pet.ether)

δ = 0.91 (3H,s), 0.97 (3H,s), 1.14 (3H,s), 2.03 (3H,s), 2.2-2.6 (2H,m), 4.45 (1H,d,J = 2.5 Hz)

D_2O, after addition of D_2O a peak at 1.4 ppm disappeared.

$\bar{\nu}_{max}$ = 3600-3330, 2920(b), 1725, 1465, 1375, 1250(b) and 1020(b) cm^{-1}

M^+ (found) = 280.2030; M^+ (calculated for $C_{17}H_{28}O_3$) = 280.2038

m/e: (relative intensity), 280(1.5), 237 (55.7), 111 (100), 43 (39.9), 41 (25.9)

M^+ -169 (found) = 111.0816; M^+ -169 (calculated for $C_7H_{11}O$) = 111.0810.

(b) Formic acid

The diene (62) (50 mg) was dissolved in formic acid (90%, 3 ml) and the reaction mixture stirred at room temperature for 4 hours. Sat.sodium bicarbonate solution was then added, and the reaction mixture extracted with ether. The ethereal solution was washed with sat.sodium bicarbonate solution and then dried and the solvent removed on the rotary evaporator to yield crude product (55 mg). Column chromatography using Kieselgel (Art.9385) eluting with 10% ethyl acetate/pet.ether three fractions, the least polar Rf = 0.5 (10% ethyl acetate/pet.ether) contained a mixture of unidentified compounds (20 mg). The fraction Rf = 0.33 contained the formate (81) (8 mg, 13%) and the most polar fraction Rf = 0.1 contained the alcohol (69) (8.3 mg, 16%).

Rf = 0.33 (10% ethyl acetate/pet.ether)

δ = 0.94 (3H,s), 0.97 (3H,s), 1.16 (3H,s), 2.07 (3H,s), 2.2-2.7 (2H,m) and 4.5 (1H,d,J = 2.5Hz), 8.0 (1H,s)

$\bar{\nu}_{max}$ = 2910(b), 1725, 1465, 1375, 1240 and 1185 cm^{-1}

m/e: (relative intensity), 202 (100), 187 (32.1), 111 (23.7), 95 (27.1), 43 (51.8).

28. Trial cyclisations of the epoxide (58)

Reactions were followed by analytical tlc, aliquots of the reaction mixture ($\sim$ 5 µl) being removed and worked up.

(a) Boron trifluoride etherate in benzene

The epoxide (58) (12 mg, 0.033 mmol) was dissolved in benzene (2 ml) and boron trifluoride etherate (4.5 µl, 0.039 mmol) was added. After 2 hours at room temperature, the reaction mixture showed a plethora of products on analytical tlc.

(b) Boron trifluoride etherate in ether at low temperatures

The epoxide (58) (11.5 mg, 0.032 mmol) was dissolved in ether (2 ml) and the solution cooled to -78°C, under nitrogen. Boron trifluoride etherate (4.3 µl, 0.035 mmol) was added and the reaction mixture stirred at this temperature for 1.5 hours, after which time no reaction had occurred.

(c) Trimethylsilyl trifluoromethanesulphonate in toluene

The epoxide (58) (10.5 mg, 0.029 mmol) was dissolved in toluene (2 ml) and the solution cooled -78°C, under nitrogen. Trimethylsilyl trifluoromethanesulphonate (6.9 µl, 0.038 mmol) was added and the reaction mixture stirred for 30 minutes, after which time, 10% potassium fluoride in methanol (5 ml) was added. The reaction mixture was warmed to room temperature and stirred for 12 hours, after this time four products were present on analytical tlc one of which had an Rf similar to that of the alcohol (60).

(d) Boron trifluoride etherate and acetic anhydride in ether

The epoxide (58) (10 mg, 0.028 mmol) was dissolved in ether (2 ml) and cooled to 0°C. Acetic anhydride (5.3 µl, 0.058 mmol) and boron trifluoride etherate (7 µl, 0.058 mmol) were added successively and the reaction stirred for 6 hours. No reaction occurred at this temperature. The solution was

allowed to warm up to room temperature and stirring was continued for 72 hours, after which time a plethora of products were visible on analytical tlc.

(e) Boron trifluoride etherate in acetic anhydride

The epoxide (58) (8.1 mg, 0.027 mmol) was dissolved in acetic anhydride (3 ml) and boron trifluoride etherate (14.2 µl, 0.11 mmol) was added. The reaction mixture was stirred for 72 hours at room temperature, after which time two unidentified products were visible by analytical tlc.

(f) Boron trifluoride etherate in chloroform

The epoxide (58) (10 mg, 0.028 mmol) was dissolved in chloroform (3 ml) and boron trifluoride etherate (7 µl, 0.056 mmol) was added. The reaction mixture was stirred for 30 minutes at room temperature, after which time a plethora of products were visible on analytical tlc.

(g) Perchloric acid in chloroform

The epoxide (58) (10 mg, 0.028 mmol) was dissolved in chloroform (3 ml) and perchloric acid (60%, 2.8µl, 0.028 mmol) was added. The reaction mixture was stirred for 30 minutes at room temperature, after which time a plethora of products were visible on analytical tlc.

(h) Trimethylsilyl trifluoromethanesulphonate in toluene - shorter reaction time

The epoxide (58) (10 mg, 0.028 mmol) was dissolved in toluene (3 ml) and the solution cooled to -78°C, under nitrogen. Trimethylsilyl trifluoromethanesulphonate (6.6 µl, 0.036 mmol) was added and the reaction mixture was stirred for 7.5 minutes after which time 10% potassium fluoride in methanol (5 ml) was added and the reaction mixture stirred

at room temperature for 2 hours. Analytical tlc of the reaction mixture showed one product with an Rf identical to that of the alcohol (60). However silver nitrate impregnated tlc showed that the reaction mixture contained two products - one identical to the alcohol (60).

(i) Tin (IV) chloride in benzene

The epoxide (58) (7.2 mg, 0.02 mmol) was dissolved in benzene (2 ml) and tin (IV) chloride (3.5 µl, 0.03 mmol) was added. The reaction mixture was stirred for 2 hours at room temperature after which time a plethora of products were visible on analytical tlc.

(j) Tin (IV) chloride in nitromethane

The epoxide (58) (10 mg, 0.028 mmol) was dissolved in nitromethane (2 ml) and the solution cooled to 0°C. Tin (IV) chloride (5 µl, 0.042 mmol) was added and the reaction mixture stirred for 2 hours at this temperature after which time a plethora of products were visible on analytical tlc.

(k) Tin (IV) chloride in chloroform

The epoxide (10.5 mg, 0.029 mmol) was dissolved in chloroform (2 mls) and the solution cooled to 0°C. Tin (IV) chloride (5.2 µl, 0.044 mmol) was added. The reaction was stirred for 30 minutes at this temperature after which time a plethora of products were visible on analytical tlc.

29. Formation of the alcohol (83)[5,31]

The epoxide (58) (1g, split into three portions, (a) 0.35g, 0.86 mmol, (b) 0.39g, 1.0 mmol) and (c) 0.26g, 0.7 mmol, each treated as a separate experiment until the reaction

had been quenched), was dissolved in toluene (10 ml) and cooled to -78°C under nitrogen. Trimethylsilyl trifluoromethanesulphonate ((a) 0.23 ml, 1.3 mmol, (b) 0.25 ml, 1.4 mmol and (c) 0.17 ml, 0.95 mmol) was added and the reaction mixture stirred at this temperature for exactly 5 minutes. The reaction was then quenched by the addition of 10% potassium fluoride in methanol and stirred for 3 hours at room temperature. After this time, water (10 mls) was added and the reaction mixtures combined in a separating funnel and extracted with ether. The ethereal extracts were washed with sat.sodium chloride solution, and then dried and the solvent removed on the rotary evaporator to yield an oil (0.98g) which crystallised slowly on standing. The crystals were filtered and washed with cold hexane to give the 5-p-methoxy benzyl ether of 2,6,10,10-tetramethyl-5,9-dihydroxybicyclo[6.3.0]undeca-2-ene (83) (420 mg, 42%) and a mixture of alcohols (83) and (60) (540 mg).

Rf = 0.32

mp = 128-130°C (the material was not re-crystallised)

δ = 0.94 (3H,s), 1.0 (3H,d,J = 7Hz), 1.07 (3H,s), 1.68 (3H,s), 2.98-3.3 (2H,m), 3.54 (1H,m), 3.79 (3H,s), 4.38 and 4.68 (2H,ABq,J = 12Hz), 5.55 (1H,t), 6.86 and 7.29 (4H,AA'BB'q, J = 9Hz).

^{13}C nmr spectrum ($CDCl_3$)

δ = 21.5(q), 23.2(q), 24.1(q), 27.8(q), 29.2(t), 30.1(t), 36.5(d), 39.2(t), 39.4(s), 42.1(d), 53.1(d), 55.3(q), 70.3(t), 80.0(d), 83.9(d), 113.7(d), 123.3(d), 129.2(d), 131.4(s), 137.5(s), 159.5(s)

$\bar{\nu}_{max}$ = 3450(vw), 2910(b), 1515, 1465(b), 1250 and 1090(b) cm^{-1}

M^+ (found) = 358.2514; M^+ (calculated for $C_{23}H_{34}O_3$) = 358.2509

30. Attempted large scale formation of the alcohol (83)[5,31]

The epoxide (58) (0.5g, 1.4 mmol) was dissolved in toluene (20 ml) and cooled to -78°C under nitrogen. Trimethylsilyl trifluoromethanesulphonate (0.33 ml, 1.8 mmol) was added and the reaction mixture stirred at this temperature for 10 minutes. 10% Potassium fluoride in methanol was then added and the reaction mixture stirred at room temperature for 2.5 hours. The work up procedure was then performed as for part 29 to give a brown solid (0.5g). Column chromatography using Kieselgel (Art.9385) eluting with 15% ethyl acetate/pet.ether gave a clear oil which crystallised on standing (430 mg). Ratio of isomers (83):(60) in mixture = (8):(4). The crystals were removed by filtration and washed with 30% ether/pet.ether to yield the alcohol (83) (0.16g, 32%).

31. Resubmission of the alcohols (83) and (60) to cyclisation conditions

(a) The alcohol (83) (15 mg, 0.042 mmol) was dissolved in toluene (2 ml) and cooled to -78°C under nitrogen. Trimethylsilyl trifluoromethanesulphonate (10 µl, 0.054 mmol) was added and the stirring continued for 5 minutes. 10% Potassium fluoride in methanol (10 mls) was then added and the reaction mixture stirred for 2 hours at room temperature. The reaction mixture was worked up as for part 29 to yield white crystalline alcohol (83) (14 mg) no other isomers being visible on silver nitrate impregnated tlc.

(b) The alcohol (60) (15 mg, 0.042 mmol) was dissolved in toluene (2 ml) and cooled to -78°C under nitrogen. Trimethylsilyl trifluoromethanesulphonate (10 µl, 0.054 mmol) was

added and the experiment continued as for part (a). This yielded an oil, the alcohol (60) (11 mg), no other isomers being visible on silver nitrate impregnated tlc.

32. Effect of temperature variation on the formation of the alcohol (83)

All three experiments were performed using the same proportions, varying only the temperature as stated.

(a) The epoxide (58) (30 mg, 0.084 mmol) was dissolved in toluene (2 ml) and the solution cooled to -72°C. Trimethylsilyl trifluoromethanesulphonate (20 µl, 0.11 mmol) was added and the reaction mixture stirred for 5 minutes. Then 10% potassium fluoride in methanol (10 ml) was added and the reaction mixture stirred for a further 2.5 hours at room temperature. The reaction was worked up as for part 29(a) to yield a yellow oil (30 mg).

Estimation of isomer content. Ratio of (83):(60) = 11.5:8.

(b) Procedure and proportions as for part (a), the temperature used in this case was -94°C. The work up procedure yielded starting material (30 mg).

(c) Procedure and proportions as for part (a). The temperature used in this case was -94°C and the reaction mixture was stirred for 40 minutes at this temperature after the addition of trimethylsilyl trifluoromethanesulphonate. The work up procedure yielded an oil (30 mg).

Estimation of isomer content. Ratio of (83):(60) = 9:7.

33. Formation of the acetate (85)

The alcohol (83) (0.645g, 1.8 mmol) was dissolved in pyridine (30 ml) and acetic anhydride (0.275 ml, 2.7 mmol) and N,N-dimethyl-4-aminopyridine (10 mg) were added successively. The reaction mixture was stirred for 16 hours at room temperature. After this time, sat.sodium bicarbonate solution was added and the reaction mixture extracted with ether. The ethereal solution was washed with sat.copper sulphate solution and then dried, and the solvent removed on the rotary evaporator to yield the acetate (85) (0.69g, 96%).

Rf = 0.59 (30% ethyl acetate/pet.ether)

δ = 0.95 (3H,d,J = 6Hz), 0.97 (3H,s), 1.06 (3H,s), 1.74 (3H,s), 2.05 (3H,s), 3.17 (1H,m), 3.53 (1H,m), 3.77 (3H,s), 4.33 and 4.6 (2H,ABq,J = 12Hz), 4.58 (1H,d, J = 11Hz), 5.54 (1H,t), 6.85 and 7.26 (4H,AA'BB'q,J = 9Hz)

$\bar{\nu}_{max}$ = 2910(b), 1740, 1615, 1515, 1465, 1380, 1245 and 1040(b) cm^{-1}

M^+ (found) = 400.2649; M^+ (calculated for $C_{25}H_{36}O_4$) = 400.2614

34. Formation of the alcohol (86)[23]

The acetate (85) (0.69g, 1.7 mmol) was dissolved in dichloromethane (shaken with water, 50 ml) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.39g, 1.7 mmol) added and the reaction stirred in the air for 1 hour. The dichloromethane solution was then washed with water, and passed down a short silica column, Kieselgel 60 (Art.7730), eluting with ethyl acetate. Removal of the solvent on the rotary evaporator yielded a brown oil which was subjected to column chromatography using Kieselgel (Art.9385) eluting with 40% ether/hexane to yield the alcohol (86) (0.45g, 93%).

Rf = 0.215

mp = 89-92°C (the material was not recrystallised)

δ = 0.98 (3H,s), 0.99 (3H,d,J = 7Hz), 1.06 (3H,s), 1.79 (3H,s), 2.08 (3H,s), 3.19 (1H,m), 3.83 (1H,m), 4.59 (1H,d,J = 12Hz), 5.59 (1H,t)

M^+ (found) = 280.2049; M^+ (calculated for $C_{17}H_{28}O_3$) = 280.2039

35. Formation of the mesylate (87)

The alcohol (86) (0.45g, 1.6 mmol) was dissolved in pyridine (15 ml) and mesyl chloride (0.37 ml, 4.8 mmol) was added. The reaction mixture was stirred for 30 minutes at room temperature. Sat.sodium bicarbonate solution was then added and the reaction mixture extracted with ether. The ethereal extracts were washed with sat.copper sulphate solution, and then dried and the solvent removed on the rotary evaporator to yield the mesylate (87) (0.49g, 85%).

Rf = 0.37 (30% ethyl acetate/pet.ether)

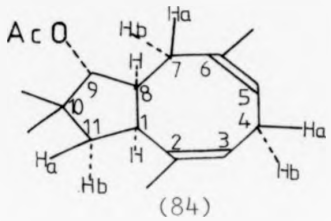
δ = 0.99 (3H,s), 1.03 (3H,d,J = 7Hz), 1.07 (3H,s), 1.77 (3H,s), 2.07 (3H,s), 3.01 (3H,s), 3.17 (1H,m), 4.58 (1H,d,J = 12Hz), 4.88 (1H,m), 5.57 (1H,t)

36. Formation of the diene (84)

The mesylate (84) (0.49g, 1.36 mmol) was dissolved in 1,8-diazobicyclo[5.4.0]undeca-7-ene (4.5 ml, 13.6 mmol) under nitrogen. The reaction mixture was heated to 80°C and held at this temperature for 18 hours, it was then cooled to room temperature and water added and the aqueous solution extracted with ether. The ethereal solution was washed with water and sat.sodium chloride solution successively, and then

dried and the solvent removed on the rotary evaporator to yield crude material (0.35g). Column chromatography on Kieselgel (Art.9385) eluting with 20% ether/hexane yielded the diene (84) (0.255g, 71%) and the deprotected diene (88) (40 mg, 13%).

Rf = 0.58 (20% ethylacetate/pet.ether)



(84)

δ = 0.965 (3H,s), 0.986 (3H,s), 1.55 (1H,m), 1.62 (3H,s), 1.63 (2H,m), 1.72 (3H,s), 2.06 (3H,s), 2.2 (1H,m), 2.29 (1H,m), 2.4 (1H,m), 2.82 (1H,m), 3.33 (1H,q), 4.54 (1H,d), 5.23 (1H,d) and 5.4 (1H,t)

Estimated coupling constants (Hz)

J_{8-9} = 9.6	J_{4a-4b} = 14	J_{11b-1} = 13
J_{8-7b} = 0	J_{4a-5} = 8	$J_{11a-11b}$ = 14
J_{8-7a} = 16	J_{4a-3} = 7	J_{11a-1} = 9
J_{8-1} = 12	J_{4b-5} = 0	
J_{7a-7b} = 14	J_{4b-3} = 7	

^{13}C nmr spectrum ($CDCl_3$)

δ = 21.1(q), 21.75(q), 22.5(q), 27.2(q), 27.2(t), 28.1(q), 33.4(t), 37.8(d), 40.0(s), 40.5(t), 49.2(d), 85.9(d), 120.9(d), 122.6(d), 137.6(s), 138.3(s), 171.0(s)

$\bar{\nu}_{max}$ = 2920(b), 1740, 1450(b), 1375, 1240(b), 1040(b) and 910 cm^{-1}

M^+ (found) = 262.1951; M^+ (calculated for $C_{17}H_{26}O_2$) = 262.1933

Deprotected diene (88)

Rf = 0.48 (20% ethyl acetate/pet.ether)

δ = 0.97 (3H,s), 1.07 (3H,s), 1.73 (6H,s), 2.82 (1H,m), 3.11 (1H,m), 3.35 (1H,q), 5.2-5.6 (2H,m)

$\bar{\nu}_{max}$ = 3500-3100(vb), 2920(b), and 1750-1600(vb) cm^{-1}

M^+ (found) = 220.1826; M^+ (calculated for $C_{15}H_{24}O$) = 220.1827

37. Trial cyclisations of the diene (84) and deprotected diene (88)

Reactions were followed by analytical tlc, aliquots of the reaction mixture (∿ 5 µl) being removed and worked up.

(a) p-Toluene sulphuric acid in benzene

The diene (84) (1.3 mg) was dissolved in benzene (1.5 ml) and p-toluene sulphuric acid was added. The reaction mixture was heated to 60°C and maintained at this temperature for 24 hours. Four products were visible on analytical tlc Rf = 0.69, 0.49, 0.35 and 0.14 (15% ethyl acetate/pet.ether).

(b) Formic acid

The diene (84) (1.6 mg) was dissolved in formic acid (90%, 0.5 ml) and silica, Kieselgel 60 (Art.7730), 15 mg was added. The reaction was stirred at room temperature and after 24 hours one major product Rf = 0.49 (15% ethyl acetate/pet.ether) was visible on analytical tlc.

(c) Formic acid and acetic anhydride

The diene (84) (2.5 mg was dissolved in acetic anhydride (0.5 ml) and formic acid (90%, 5 µl) was added. The reaction mixture was stirred for 24 hours under nitrogen, after which time only starting material was visible on analytical tlc.

Deprotected diene (88)

Rf = 0.48 (20% ethyl acetate/pet.ether)

δ = 0.97 (3H,s), 1.07 (3H,s), 1.73 (6H,s), 2.82 (1H,m), 3.11 (1H,m), 3.35 (1H,q), 5.2-5.6 (2H,m)

$\bar{\nu}_{max}$ = 3500-3100(vb), 2920(b), and 1750-1600(vb) cm^{-1}

M^+ (found) = 220.1826; M^+ (calculated for $C_{15}H_{24}O$) = 220.1827

37. Trial cyclisations of the diene (84) and deprotected diene (88)

Reactions were followed by analytical tlc, aliquots of the reaction mixture ($\sim$ 5 µl) being removed and worked up.

(a) p-Toluene sulphuric acid in benzene

The diene (84) (1.3 mg) was dissolved in benzene (1.5 ml) and p-toluene sulphuric acid was added. The reaction mixture was heated to 60°C and maintained at this temperature for 24 hours. Four products were visible on analytical tlc Rf = 0.69, 0.49, 0.35 and 0.14 (15% ethyl acetate/pet.ether).

(b) Formic acid

The diene (84) (1.6 mg) was dissolved in formic acid (90%, 0.5 ml) and silica, Kieselgel 60 (Art.7730), 15 mg was added. The reaction was stirred at room temperature and after 24 hours one major product Rf = 0.49 (15% ethyl acetate/pet.ether) was visible on analytical tlc.

(c) Formic acid and acetic anhydride

The diene (84) (2.5 mg was dissolved in acetic anhydride (0.5 ml) and formic acid (90%, 5 µl) was added. The reaction mixture was stirred for 24 hours under nitrogen, after which time only starting material was visible on analytical tlc.

(d) Sulphuric acid in ether

The diene (84) (1.3 mg) was dissolved in 10% sulphuric acid in ether (2 ml), and the reaction mixture stirred for 15 hours at room temperature. After this time a plethora of products were visible on analytical tlc.

(e) Boron trifluoride etherate in ether

The diene (1.7 mg) was dissolved in ether (2 ml) and boron trifluoride etherate (6 µl) was added. The reaction mixture was stirred for 12 hours at room temperature. Then a plethora of products were visible on analytical tlc.

(f) Boron trifluoride etherate in benzene

The diene (84) (2 mg) was dissolved in benzene (2 ml) and boron trifluoride etherate (10 µl) was added. The reaction mixture was refluxed for 6 hours and after this time a plethora of products were visible on analytical tlc.

(g) Trifluoroacetic acid in ether

The diene (84) (2 mg) was dissolved in ether (2 ml) and trifluoroacetic acid (1.2 µl) was added. The reaction mixture was stirred for 24 hours at room temperature, after which time only starting material was visible on analytical tlc.

(h) Trifluoromethanesulphonic acid in dichloromethane

The diene (88) (2.7 mg) was dissolved in dichloromethane (2 ml) under nitrogen and cooled to -15°C. Trifluoromethanesulphonic acid (6.5 µl) was added. The reaction mixture was stirred at this temperature for 15 minutes and after this time one major product Rf = 0.14 (20% ethyl acetate/pet.ether) was visible on analytical tlc.

38. Cyclisation of the diene (84) and the deprotected diene (88)

(a) Formic acid

The diene (84) (50.3 mg) was dissolved in formic acid (90%, 5 ml) and silica, Kieselgel 60 (Art.7730) was added. The reaction mixture was refluxed for 2 hours and then cooled to room temperature. Sat.sodium bicarbonate solution was added and the reaction mixture extracted with ether. The ethereal solution was washed with sat.sodium bicarbonate solution, and then dried and the solvent removed on the rotary evaporator to yield an oil (53.8 mg). Column chromatography using Kieselgel (Art.9385) eluting with 15% ether/hexane gave three fractions Rf = 0.6, 0.48 and 0.19 (15% ethyl acetate/pet.ether). The least polar Rf = 0.6 contained a mixture of unidentified alkenes, the major component of which was later tentatively assigned as (70), (11.4 mg). The fraction Rf = 0.49 contained a mixture of solid formates, (35 mg) which were purified by sublimation (0.05 mm Hg, 80-100°C) to give one major formate (94) (20 mg, 34%). The most polar fraction Rf = 0.19 was an unidentified oil (4.4 mg).

Rf = 0.6 (15% ethyl acetate/pet.ether)

δ = 0.97 (6H,s), 1.0 (3H,d,J = 5Hz), 1.59 (3H,m), 2.06 (3H,s), 2.5 (1H,m), 4.45 (1H,d,J = 7Hz), 5.32 (1H,s)

Rf = 0.49 (15% ethylacetate/pet.ether)

δ = 0.88 (3H,s), 0.93 (3H,s), 0.97 (3H,s), 1.1 (3H,s), 2.05 (3H,s), 4.55 (1H,d,J = 3Hz), 4.68 (1H,s), 8.21 (1H,s)

^{13}C nmr spectrum ($CDCl_3$) using DEPT[47]

δ = 21.0 (CH_3), 22.95 (CH_3), 22.95 (CH_3), 24.85 (CH_3),

29.6 (CH_3), 30.5 (CH_2), 35.6 (CH_2), 36.3 (CH_2), 40.5 (C), 41.52 (C), 41.8 (C), 41.86 (CH), 42.4 (CH_2), 47.05 (CH), 83.0 (CH), 89.2 (CH), 160.7 (CH), 170.8 (C)

$\bar{\nu}_{max}$ = 2940(b), 1725, 1420, 1380, and 1255(b) cm^{-1}

M^+ (found) = 308.2012; M^+ (calculated for $C_{18}H_{28}O_4$) = 308.1988

m/e: (relative intensity), 248 (46.5), 233 (62.6), 202)62.0), 187 (54.7), 174 (73), 95 (90.6), 43 (100)

Rf = 0.19 (15% ethyl acetate/pet.ether)

δ = 0.94 (3H,s), 1.07 (6H,s), 1.1 (3H,s), 3.5 (1H,d,J = 3.5Hz), 4.54 (1H,s).

(b) Trifluoroacetic acid - an nmr experiment

The diene (84) (21.5 mg) was dissolved in $CDCl_3$ (25.0 µl) containing 1% tetramethyl silane, and carefully transferred to a 5 mm nmr tube. The tube was flushed with nitrogen and trifluoroacetic acid (25 µl) was added. The progress of the reaction was monitored by 90 mHz nmr spectroscopy. After 15 minutes the proton at 5.23 ppm was no longer visible whilst the proton at 4.54 ppm had become a broad multiplet. The peak at 5.4 ppm remained visible for 24 hours, further trifluoroacetic acid (25 µl) was then added and the reaction monitored for a further 24 hours. There were no protons then present in the region 5-5.5 ppm and the region 4.5-4.9 ppm appeared to contain three singlets. The reaction mixture was poured into a separating funnel containing sat.sodium bicarbonate solution and extracted with ether. The ethereal extracts were washed with 10% potassium hydroxide solution, and then dried and the solvent removed on the rotary evaporator to yield a yellow oil (21.4 mg). Column chromato-

graphy using Kieselgel (Art.9385) eluting with 15% ether/hexane yielded two fractions Rf = 0.55 and 0.48 (15% ethyl acetate/pet.ether). The least polar fraction Rf = 0.55 was shown by nmr to contain at least three components (2.7 mg), whilst the most polar fraction Rf = 0.48 contained the trifluoroacetate (105) (11.4 mg, 38%).

Rf = 0.48 (15% ethyl acetate/pet.ether)

δ = 0.91 (3H,s), 0.93 (3H,s), 0.97 (6H,s), 2.03 (3H,s), 4.56 (1H,d,J = 2Hz), 4.71 (1H,s).

$\bar{\nu}_{max}$ = 2950(b), 1780, 1730, 1470, 1375 and 1165(b) cm^{-1}

m/e: (relative intensity), 316 (50.9), 301 (59.3), 202 (46.5), 95 (57.7), 43 (100).

(c) p-Toluene sulphonic acid in benzene

The diene (84) (50 mg, 0.2 mmol) was dissolved in benzene (7 ml) and p-toluene sulphonic acid (0.13g, 0.66 mmol) was added. The reaction mixture was refluxed for 3 hours and then cooled to room temperature. Sat.sodium bicarbonate solution was added and the reaction mixture extracted with ether. The ethereal extracts were washed with sat.sodium bicarbonate solution, and then dried and the solvent removed on the rotary evaporator to yield a crude yellow oil (50 mg). Column chromatography using Kieselgel (Art.9385) eluting with 15% ether/hexane yielded five fractions, Rf = 0.71, 0.61, 0.49, 0.44 and 0.28 (10% ethyl acetate/pet.ether). The most polar fraction Rf = 0.28 was identified as the tosylate (106) (12.6 mg, 14%). The remaining fractions were unidentified mixtures.

Rf = 0.28 (10% ethyl acetate/pet.ether)

δ = 0.79 (3H,s), 0.90 (3H,s), 0.93 (3H,s), 1.04 (3H,s), 2.05 (3H,s), 2.45 (3H,s), 4.27 (1H,s), 4.53 (1H,d,J = 2Hz), 7.35 and 7.85 (4H,AA'BB'q,J = 8Hz)

$\bar{\nu}_{max}$ = 2940(b), 1730, 1600(w), 1465, 1360(b), 1250(b) and 1170 cm^{-1}

m/e: (relative intensity), 202 (100), 187 (40.6), 95 (56.2), 91 (46.9), 43 (61.5).

(d) Trifluoromethanesulphonic acid in dichloromethane

The diene (88) (12.7 mg, 0.06 mmol) was dissolved in dichloromethane (3 ml) and the solution cooled to 0°C under nitrogen. Trifluoromethanesulphonic acid (30.7 µl, 0.34 mmol) was added and the reaction mixture stirred for 15 minutes. Water was then added, and the aqueous solution saturated with sodium chloride and then extracted with ether. The ethereal extracts were dried and the solvent removed on the rotary evaporator to yield a black oil (16.6 mg). Column chromatography using Kieselgel (Art.9385) eluting with 40% ether/pet.ether gave a white crystalline solid, the triflate (107) (8 mg, 37%).

Rf = 0.37 (20% ethyl acetate/pet.ether)

mp = 94-96°C (the material was not recrystallised)

δ = 0.93 (3H,s), 1.05 (6H,s), 1.09 (3H,s), 3.52 (1H,d,J = 3Hz), 4.54 (1H,s)

$\bar{\nu}_{max}$ = 3500-3200(vb), 2940(b), 1420, 1250, 1215, 1150, and 940 cm^{-1}.

m/e: (relative intensity), 370 (6), 107 (42.2), 105 (42.6), 95 (96.4), 91 (57.7), 69 (60.3), 41 (100).

39. Attempted isomerisation

(a) Rhodium trichloride trihydrate in ethanol[37,38]

The alcohols (60) and (61) (50 mg, 0.18 mmol) were dissolved in ethanol (5 ml) and rhodium trichloride trihydrate (50 mg, 0.18 mmol) was added. The reaction mixture was refluxed for 1 hour after which time a plethora of products were visible by analytical tlc.

(b) Isomerisation of the diene (84) with rhodium trichloride trihydrate

The diene (84) (17 mg, 0.06 mmol) was dissolved in ethanol (5 ml) and rhodium trichloride trihydrate (17 mg, 0.06 mmol) was added. The reaction mixture was refluxed for 1 hour and then cooled to room temperature. 2.5% Potassium cyanide solution was added and the reaction mixture stirred for 1 hour. It was then extracted with hexane and the combined hexane extracts washed with water, and sat.sodium chloride solution successively. The hexane solution was dried, and the solvent removed on the rotary evaporator to yield one major compound identical on analytical tlc to the starting material but with a different Rf on silver nitrate impregnated tlc. This was tentatively assigned as the isomeric diene (121) (12 mg, 67%).

Rf = 0.56 (15% ethyl acetate/pet.ether)

δ = 1.03 (3H,s), 1.1 (3H,s), 1.58 (3H,bs), 1.68 (3H,bs), 2.08 (3H,s), 3.3 (1H,m), 4.8 (1H,d,J = 6Hz), 5.05-5.5 (2H,m).

(c) Iodine

The diene (62) (40 mg, 0.15 mmol) was dissolved in toluene (1 ml) and iodine (3.7 mg, 0.015 mmol) in toluene

(0.74 ml) was added. The reaction mixture was refluxed for 24 hours and then cooled to room temperature. The reaction mixture was then washed with 2M sodium thiosulphate solution and then dried and the solvent removed on the rotary evaporator to yield starting material (40 mg).

(d) Palladium on charcoal

The acetates (66) and (76) (260 mg) were dissolved in ethyl acetate (20 ml) and stirred with palladium on charcoal (80 mg) at room temperature under an atmosphere of hydrogen for 1.5 hours. The flask was then isolated and stirred under a residual volume of hydrogen for 16 hours. The catalyst was then removed by filtration. Analytical tlc of the reaction mixture revealed a vast array of compounds.

40. Formation of the diacetate (28)

(a) From the ether (20)

The ether (20) (50 mg) was dissolved in ether (10 ml) and acetic anhydride (1 ml) and boron trifluoride etherate (1 ml) were added successively. The reaction mixture was stirred for 16 hours at room temperature. Sat.sodium bicarbonate solution was then added and the reaction mixture extracted with ether. The ethereal extracts were washed with sat.sodium bicarbonate solution, and then dried and the solvent removed on the rotary evaporator to yield crude material (50 mg). Column chromatography using Kieselgel (Art.9385) eluting with 10% ether/pet.etheryielded the diacetate (28) (35 mg, 60%).

Rf = 0.37 (10% ethyl acetate/pet.ether)

δ = 0.86 (3H,s), 0.99 (3H,d,J = 7Hz), 1.05 (3H,s), 1.61 (3H,s), 1.96 (3H,s), 2.09 (3H,s), 4.7 (1H,d,J = 6Hz), 4.95 (1H,m).

(b) From the acetate (19)

The acetate (19) (100 mg) was dissolved in ether (4 ml) and acetic anhydride (0.5 ml) and boron trifluoride etherate (0.5 ml) were added successively. The reaction mixture was stirred for 48 hours at room temperature. After this time numerous products were visible on analytical tlc.

41. Hydrolysis of the diacetate (28)

The diacetate (28) (29 mg, 0.09 mmol) was dissolved in methanol/water (1:1, 2 ml) and sodium carbonate (10.5 mg, 0.1 mmol) was added. The reaction mixture was refluxed for 2.5 hours and then cooled to room temperature. Sat.sodium bicarbonate solution was added and the aqueous mixture extracted with ether. The ethereal extracts were dried and the solvent removed on the rotary evaporator to yield a mixture of starting material and the first hydrolysis product (20 mg) Rf = 0.18 (10% ethyl acetate/pet.ether). The nmr spectrum revealed a diminished doublet at 4.7 ppm ratio of the proton 4.95 ppm:4.7 ppm = 9:6.5.

42. Formation of the pivaloate (130)

The alcohol (17) (0.17g, 0.67 mmol) was dissolved in pyridine (7.5 ml) and pivaloyl chloride (0.25 ml, 2.02 mmol) and N,N-dimethyl-4-aminopyridine (10 mg) were added successively. The reaction mixture was stirred for 60 hours at room temperature. Sat.sodium bicarbonate solution was added and the reaction mixture extracted with ether. The ethereal extracts were washed with sat.copper sulphate solution, and then dried

and the solvent removed on the rotary evaporator to yield the pivaloate (130) (180 mg, 80%).

Rf = 0.6

δ = 0.79 (3H,d,J = 6Hz), 0.99 (3H,s), 1.21 (3H,s), 1.25 (9H,s), 3.29 (3H,s), 3.32 (1H,m), 4.56 (1H,d,J = 10Hz), 4.81 (1H,s), 5.07 (1H,s)

$\bar{\nu}_{max}$ = 2920(b), 1735, 1635, 1460, 1370, 1235 and 1090 cm^{-1}

m/e: (relative intensity), 235 (1.7), 187 (10.2), 93 (13.1), 85 (16.2), 57 (100), 41 (52.3).

43. Formation of the ether (131)[19]

The pivaloates (130) and (132) (1.82g, 5.4 mmol) were dissolved in acetonitrile (50 ml) and the solution stirred under nitrogen. Sodium iodide (3.25g, 0.02 mol) and trimethylsilylchloride (2.76 ml, 0.02 mol) were added successively and the stirring continued for 20 hours. Water was then added and the reaction mixture extracted with ether. The ethereal extracts were washed with 20% sodium thiosulphate solution, and then dried and the solvent removed on the rotary evaporator to yield crude material (1.65g). Column chromatography using Kieselgel (Art.9385) eluting with 15% ethylacetate/pet.ether yielded the ether (131) (1.17g, 67%).

Rf = 0.67

δ = 0.94 (3H,s), 0.99 (3H,d,J = 6Hz), 1.08 (3H,s), 1.14 (3H,d,J = 6Hz), 1.19 (9H,s), 3.55 (1H,m), 4.64 (1H,d,J = 2Hz)

$\bar{\nu}_{max}$ = 2930(b), 1725, 1470(b), 1290 and 1165(b) cm^{-1}

M^+ (found) = 322.2504; M^+ (calculated for $C_{20}H_{34}O_3$) = 322.2508

44. Cyclisation of the pivaloate (130)[19]

The pivaloate (130) (210 mg, 0.62 mmol) was treated by the procedure outlined in part 43, using acetonitrile (50 ml), trimethylsilyl chloride (270 mg, 2.5 mmol) and sodium iodide (0.37g, 2.5 mmol). The crude yield was 200 mg. Column chromatography using Kieselgel (Art.9385) eluting with 20% ether/hexane gave three fractions, the least polar contained the ether (131) (100 mg, 50%), the next contained a mixture of (131) and (133) (35 mg) whilst the most polar fraction contained the 5-pivaloate of 1,4,4,8-tetramethyl-12-oxatricyclo[7.2.1.$O^{2,6}$]dodecane-5-ol (133) (30 mg, 15%).

Rf = 0.6

δ = 0.95 (3H,s), 1.0 (3H,d,J = 7Hz), 1.2)15H,s), 3.85 (1H,m), 4.56 (1H,d,J = 1Hz)

$\bar{\nu}_{max}$ = 2950(b), 1720, 1460(b), 1370(b), 1285, and 1160 cm^{-1}

M^+ (found) = 322.2488; M^+ (calculated for $C_{20}H_{34}O_3$) = 322.2508

45. Formation of the acetate (134)

The ether (131) (0.82g) was dissolved in ether (20 ml) and acetic anhydride (5 ml) and boron trifluoride etherate (5 ml) were added successively. The reaction mixture was stirred for 15 hours at room temperature. The reaction mixture was then treated by the work up procedure outlined in part 40(a) to give crude material (0.86g). Column chromatography using Kieselgel (Art.9385) eluting with 5% ethyl acetate/pet.ether yielded the 9-pivaloate, 5-acetoxy 2,6,10,10-tetramethyl-5,9-dihydroxybicyclo[6.3.0]undeca-1-ene as a waxy solid (134) (0.53, 57%).

Rf = 0.58

mp = 53-63°C (the material was not recrystallised)

δ = 0.87 (3H,s), 0.97 (3H,d,J = 7Hz), 1.03 (3H,s), 1.21 (9H,s), 1.6 (3H,s), 1.96 (3H,s), 4.63 (1H,d,J = 8Hz), 4.94 (1H,m)

$\bar{\nu}_{max}$ = 2920(b), 1730, 1460(b), 1370(b), 1250, and 1160 cm^{-1}

m/e: (relative intensity) = 262 (87.4), 187 (100), 160 (37.5), 57 (45.3).

46. Hydrolysis of the acetate (134)

The acetate (134) (0.51g) was dissolved in 5% potassium hydroxide in ethanol (25 ml). The reaction mixture was stirred for 56 hours at room temperature. Water was then added and the aqueous solution extracted with ether. The ethereal extracts were dried and the solvent removed on the rotary evaporator to yield crude material (0.44g). Column chromatography using Kieselgel (Art.9385) eluting with 15% ethyl acetate/pet.ether yielded the alcohol (135) as a waxy solid (0.37g, 82%).

Rf = 0.46

mp = 73-76°C (the material was not recrystallised)

δ = 0.83 (3H,s), 1.03 (3H,s), 1.04 (3H,d,J = 7Hz), 1.75 (3H,s), 3.65 (1H,m), 4.71 (1H,d,J = 7Hz)

$\bar{\nu}_{max}$ = 3550, 2920(b), 1730, 1460(b), 1370(b), 1285 and 1160 cm^{-1}

M^+ (found) = 322.2507; M^+ (calculated for $C_{20}H_{34}O_3$) = 322.2508

47. Dehydration of the alcohol (135)

(a) Formation of the mesylate (137)

The alcohol (135) (0.37g, 1.3 mmol) was treated by the procedure outlined in part 25(a) using pyridine (7.5 ml) and mesyl chloride (0.3 ml, 3.9 mmol). This yielded the mesylate (137) (0.38g, 83%).

Rf = 0.38

δ = 0.88 (3H,s), 1.04 (3H,s), 1.1 (3H,d,J = 6Hz), 1.23 (9H,s), 1.66 (3H,s), 2.9 (3H,s), 4.57 (1H,d,J = 7Hz) and 4.75 (1H,m)

$\bar{\nu}_{max}$ = 2920(b), 1730, 1340(b), 1285, 1170, and 910 cm^{-1}

m/e: (relative intensity), 298 (93.9), 283 (45.7), 187 (100), 57 (59.3)

(b) Formation of the diene (138)

The mesylate (137) (0.56g, 1.4 mmol) was treated by the procedure outlined in part 36 using 1,8-diazabicyclo-[5.4.0]undeca-7-ene (5.2 ml, 0.035 mol) and heating the reaction mixture for five hours only. This yielded crude material (330 mg) which contained three compounds on silver nitrate impregnated tlc Rf = 0.62, 0.56 and 0.39 (10% ethyl acetate/pet.ether). Column chromatography using 10% silver nitrate impregnated silica gradient eluting with 0-10% ether/hexane gave two fractions Rf = 0.56 and 0.39. The less polar fraction contained the diene (138) (110 mg, 26%). The more polar fraction contained the diene (139) (130 mg, 31%).

Rf = 0.56 (silver nitrate impregnated tlc, 10% ethyl acetate/pet.ether)

δ = 0.82 (3H,s), 0.9 (3H,s), 1.16 (9H,s), 1.5 (3H,s), 1.69 (3H,s), 4.77 (1H,d,J = 10Hz), and 5.2 (1H,d,J = 7Hz)

^{13}C nmr spectrum ($CDCl_3$) using DEPT.[47]

δ = 19.3 (CH_3), 21.1 (CH_3), 26.7 (CH_2 + CH_3), 27.3 (3 x CH_3), 27.6 (CH_3), 33.55 (CH_2), 34.3 (CH_2), 38.889 (C), 38.928 (C), 43.95 (CH_2), 46.5 (CH), 83.7 (CH), 123.4 (CH), 127.8 (C), 131.55 (C), 134.1 (C), and 178.3 (C)

M^+ (found) = 304.2394; M^+ (calculated for $C_{20}H_{32}O_2$) = 304.2402

Rf = 0.39 (silver nitrate impregnated tlc, 10% ethyl acetate/ pet.ether)

δ = 0.87 (3H,s), 0.98 (3H,s), 1.03 (3H,d,J = 7Hz), 1.25 (9H,s), 1.72 (3H), 4.67 (1H,d,J = 7Hz), 5.23 (1H,dd, J = 10Hz,J = 6Hz), and 5.85 (1H,ddd,J = 2Hz,J = 10Hz, J = 18Hz)

^{13}C nmr spectrum ($CDCl_3$) using DEPT.[47]

δ = 20.1 (CH_3), 20.8 (CH_3), 23.7 (CH_3), 26.1 (CH_3), 27.2 (3 x CH_3), 33.3 (CH), 34.2 (CH_2), 38.9 (C), 39.7 (C), 41.2 (CH_2), 44.1 (CH_2), 49.2 (CH), 86.8 (CH), 129.8 (CH), 132.0 (C), 134 (C), 137.0 (CH), 178.4 (C).

M^+ (found) = 304.2406; M^+ (calculated for $C_{20}H_{32}O_2$) = 304.2403

48. Formation of the tosylate (140)

The alcohol (135) (100 mg, 0.31 mmol) was dissolved in pyridine (3 ml) and p-toluene sulphonyl chloride (89 mg, 0.46 mmol) was added. The reaction mixture was stirred for 60 hours at room temperature. Further p-toluene sulphonylchloride (356 mg, 1.84 mmol) was then added and the reaction mixture stirred for 24 hours. Sat.sodium bicarbonate solution was added and the solution extracted with ether. The ethereal extracts were washed with sat.copper sulphate solution

and then dried and the solvent removed on the rotary evaporator to yield 120 mg crude material. Column chromatography using Kieselgel (Art.9385) eluting with 15% ethyl acetate/pet.ether yielded the tosylate (140) (120 mg, 78%) as a waxy solid.

Rf = 0.59

δ = 0.83 (3H,s), 0.87 (3H,d,J = 6Hz), 0.89 (3H,s), 1.19 (9H,s), 1.56 (3H,s), 2.43 (3H,s), 4.55 (1H,d,J = 7Hz), 4.68 (1H,m), 7.32 and 7.75 (4H,AB,J = 9Hz).

$\bar{\nu}_{max}$ = 2910(b), 1725, 1600, 1320, 1285, 1190, and 910.

49. Dehydration of the mesylate (137) and tosylate (140)

(a) Treatment of the tosylate (140) with 1,8-diazabicyclo[5.4.0]undeca-7-ene

The tosylate (140) (10 mg) was dissolved in 1,8-diazabicyclo[5.4.0]undeca-7-ene (0.5 ml) and heated to 65°C under nitrogen. After 2.5 hours no starting material was present by analytical tlc, however silver nitrate impregnated tlc showed two products corresponding to the dienes (138) and (139).

(b) The mesylate (137) with potassium t-butoxide in dimethyl sulphoxide

The mesylate (137) (5 mg, 0.012 mmol) was dissolved in dimethyl sulphoxide (0.5 ml) and potassium t-butoxide (1.68 mg, 0.015 mmol) was added. The reaction mixture was stirred at room temperature, and after 30 minutes two polar products had formed on analytical tlc which did not correspond to the dienes (138) and (139).

(c) The mesylate (137) with potassium t-butoxide in t-butanol

The mesylate (137) (5 mg) was dissolved in t-butanol

(0.5 ml) and potassium t-butoxide (2 mg) added. After the reaction had been stored for 2 hours at room temperature no reaction had occurred by analytical and silver impregnated nitrate tlc.

50. Cyclisation of the diene (138)[29]

The diene (138) (50 mg, 0.16 mmol) was dissolved in dichloromethane (1 ml) and the solution cooled to less than 5°C, boron trifluoride etherate (20.2 µl, 0.16 mmol) was added and the solution maintained at this temperature for 15 hours. After this time dichloromethane was added and the solution washed with sat.sodium bicarbonate solution, dried and the solvent removed to yield the alkene (141) (40 mg, 80%).

Rf = 0.69 (silver nitrate impregnated tlc, 10% ethyl acetate/ pet.ether)

δ = 0.94 (3H,s), 0.97 (3H,s), 1.02 (3H,s), 1.19 (9H,s), 1.43 and 1.855 (2H,ABq,J = 13.6 Hz), 1.55 (3H,q,J = 2Hz, J = 1.5Hz), 2.47 (1H,dd with long range coupling, J = 2.5Hz,J = 5.5Hz, long range J = 2Hz), 4.39 (1H,d,J = 5.2Hz), and 5.31 (1H,bt,J = 1.5Hz,J = 2.5Hz)

^{13}C nmr spectrum ($CDCl_3$) using DEPT.[47]

δ = 13.1 (CH_3), 22.9 (CH_3), 23.5 (CH_3), 23.6 (CH_2), 27.2 (3 x CH_3), 27.7 (CH_3), 38.8 (C), 39.4 (CH_2), 42.8 (C), 45.3 (CH_2), 47.3 (CH_2), 58.2 (C), 59.2 (C), 64.4 (CH), 87.1 (CH), 125.5 (CH), 145.2 (C), 178.0 (C)

$\bar{\nu}_{max}$ = 2940(b), 1725, 1480, 1285, and 1150 cm^{-1}

M^+ (found) = 304.2417; M^+ (calculated for $C_{20}H_{32}O_2$) = 304.2403

m/e: (relative intensity), 202 (46.5), 188 (15.2), 187 (100).

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