BIOMIMETIC REARRANGEMENTS OF HUMULENE

A Thesis
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Doctor of Philosophy

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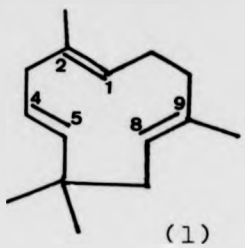
INTRODUCTION

Simple terpenoids have been known for many centuries as plant constituents whose fragrance commended them to the early investigators. Within this group of naturally-occurring compounds the C_{15} sesquiterpenes were of particular interest, largely as a result of their relatively high abundance. In 1895, Chapman isolated a new sesquiterpene, humulene (1), from oil of hops and by the preparation of various derivatives distinguished this hydrocarbon, previously called α-caryophyllene, from caryophyllene.[1] The carbon skeleton of this hydrocarbon was established but the placement of the three olefinic bonds proved difficult.[2-4] The structure was deduced correctly by degradative experiments[5] and the analysis of the nmr spectrum suggested that all the double bonds were endocyclic and had a trans configuration.[6] The structure was confirmed beyond doubt by an X-ray study of the bis-silver nitrate adduct.[7]

It is clear that humulene (1) has a widespread occurrence in Nature, as does its isomer γ-humulene (2).[8] Although many functionalised compounds of humulene exist in Nature, some of these compounds may be artifacts. Two episulphides of humulene were discovered in hop oil and were tentatively assigned structures (3) and (4).[9] On a more careful examination the structures were recently revised to (3) and (5).[10] It is thought that these compounds arise from hops which have been heavily dressed with flowers of sulphur during the growing period to control mildew.

Many oxygenated derivatives exist, such as

humuladienone (6), 1-humulenol (7), humulene-1,2-epoxide (8), humulene-4,5-epoxide (9), humulene-8,9-epoxide (10) and humulene-1,2-8,9-bisepoxide (11).[11] The novel humulene alcohol (12) has been extracted from the aerial parts of Helichrysum chionosphaerum.[12]



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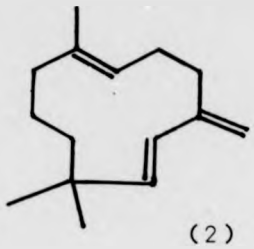

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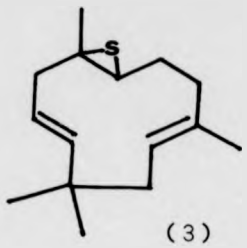

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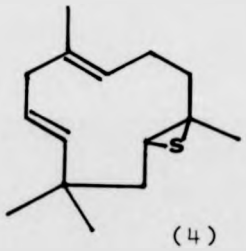

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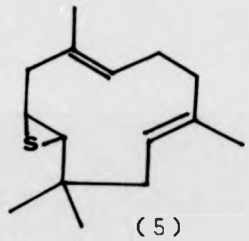

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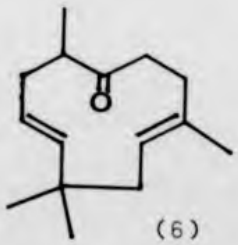

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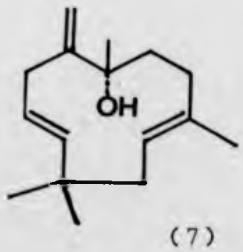

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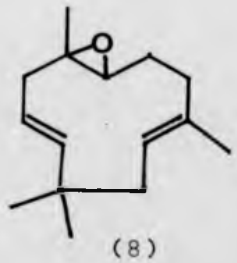

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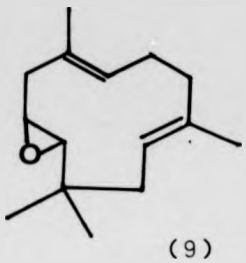

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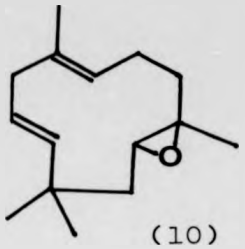

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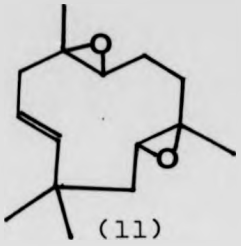

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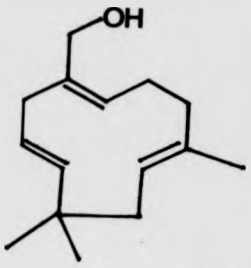
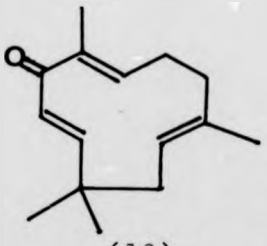


(12)

Zerumbone (13), zerumbone epoxides (14)-(16) and zerumbol (17) all display plant growth inhibiting potential.[13]



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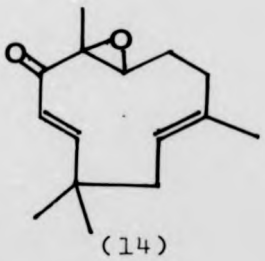

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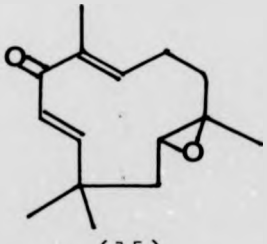

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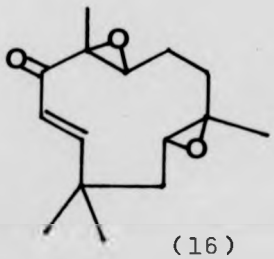

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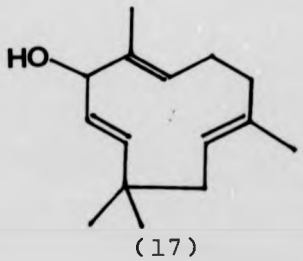
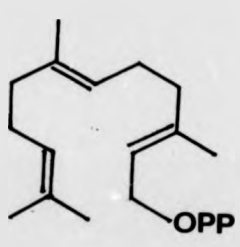


(17)

The biogenesis of humulene (1) was proposed initially in terms of the Biogenetic Isoprene Rule[14] and subsequent embellishments were added later.[15] Thus, the cyclisation of farnesyl pyrophosphate (18) *via* the intermediate cation (19) to give humulene (1) after deprotonation and subsequently to give caryophyllene (20) by a further cyclisation and deprotonation was postulated as the probable route to these compounds based on the fact that both compounds usually co-exist in Nature.



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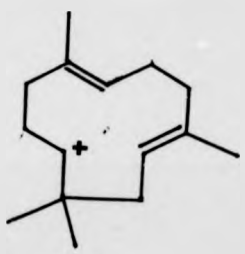

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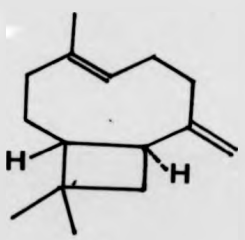


(20)

Before proceeding with the chemistry of humulene (1) it should be noted that there have been three syntheses of humulene recorded in the literature. The earliest was reported by Corey,[16] the key step in the synthesis involving the cyclisation of the dibromide (21) using nickel carbonyl to give the *cis*-isomer (22) of humulene, which on irradiation in the presence of diphenyl disulphide gave the desired product (1). An Indian research team[17] designed a scheme employing Corey's nickel carbonyl cyclisation step but achieved the all-*trans* configuration in the dibromide (23) used for cyclisation (Figure 1).

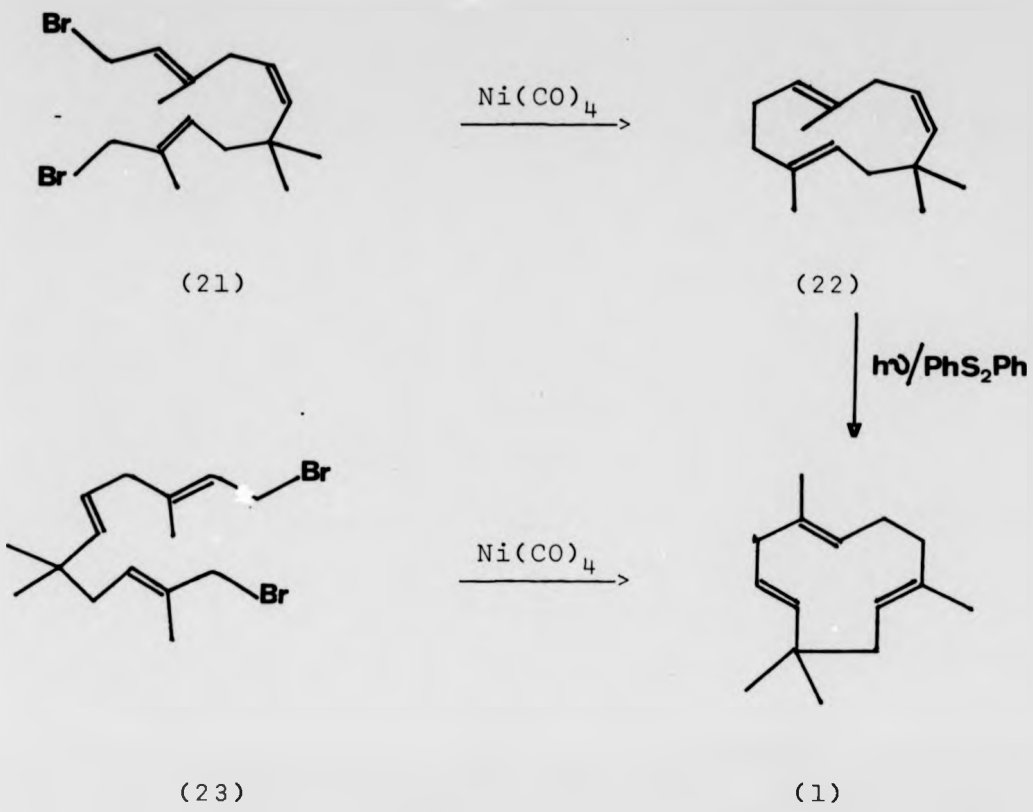
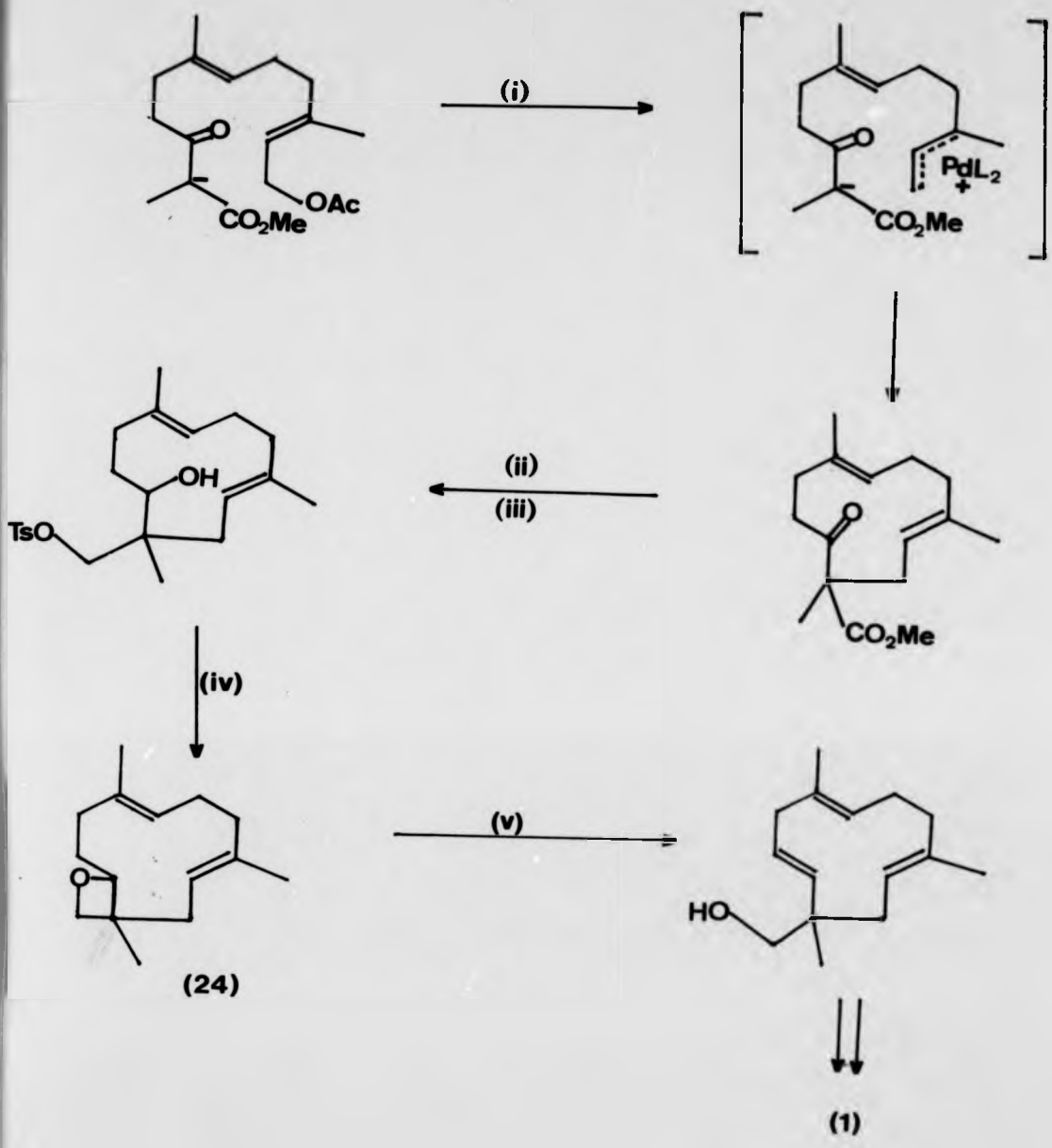


Figure 1

The latest synthesis[18] employed the use of a π-allyl palladium complex which underwent intramolecular anionic cyclisation to form the eleven-membered ring (Figure 2). The 4,5-trans-double bond was introduced via an oxetane (24) which was opened to the corresponding allylic alcohol by a cyclic syn-elimination mechanism with diethylaluminium-N-methylanilide.

The chemistry of humulene (1) may be subdivided essentially into two parts where the division is drawn chronologically. In 1965 the biosynthetic significance of humulene (1) as a precursor of structurally related tricyclic sesquiterpenoids was recognised. Before this time, humulene was considered to be

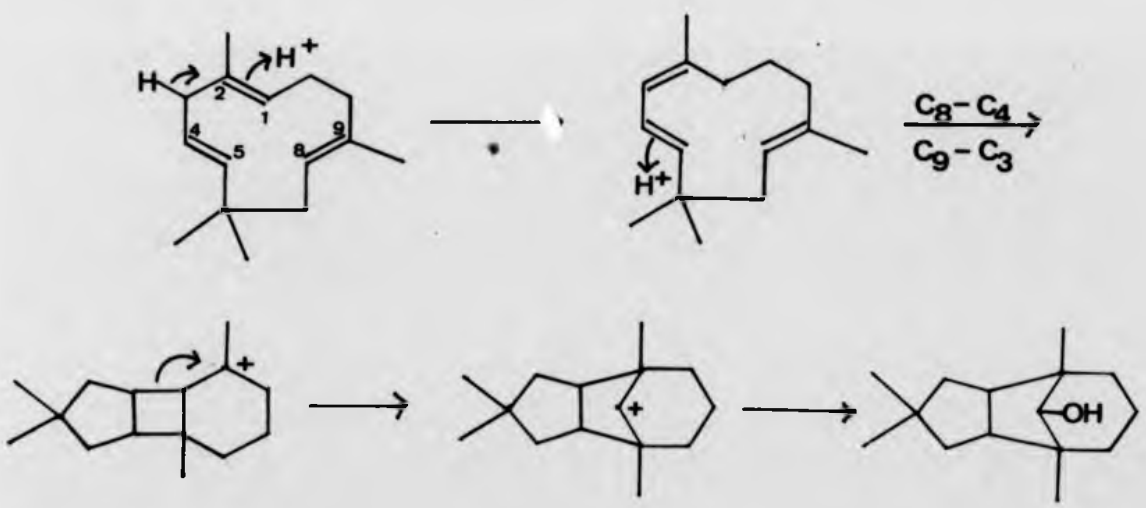


Reagents: (i) $(Ph_3P)_4Pd/Ph_2P$ ⌒ PPh_2/HMPA
(ii) $LiAlH_4$
(iii) Ts/py.
(iv) $KOBu^t$
(v) $Et_2AlNMePh$

Figure 2

a chemical curiosity and its chemical study was related to its structural elucidation and investigation of its rearrangement products. It is on this latter aspect that humulene provided interesting results which have a bearing on later chemical studies.

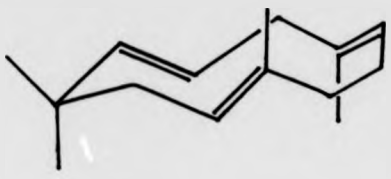
The study of the rearrangement products of humulene began with the elucidation of the structure of α-caryophyllene alcohol which was derived from humulene (1) by treatment with sulphuric acid[19,20] and possessed the symmetrical structure (25). Nickon coined the name apollan-11-ol for this compound and proposed the mechanism of formation from humulene (1) outlined in Figure 3. This mechanism was substantiated by deuterium labelling, coupled with ^{13}C nmr spectroscopy.[21]



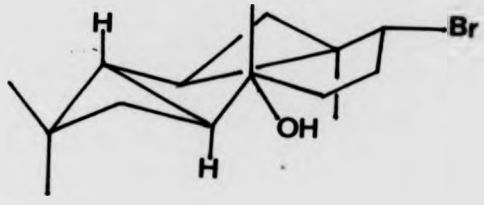
(25)

Figure 3

Pertinent to the chemistry of humulene (1) is the work of Sutherland who studied the stereoselectivity in the cyclisation of medium ring 1,5-dienes on the basis of preferred conformations.[22] Humulene was cyclised with aqueous N-bromo-succinimide[23] and it was found that the product (26) had maintained the anticipated conformation of the starting compound based upon the X-ray structure of the silver nitrate adduct.[7]

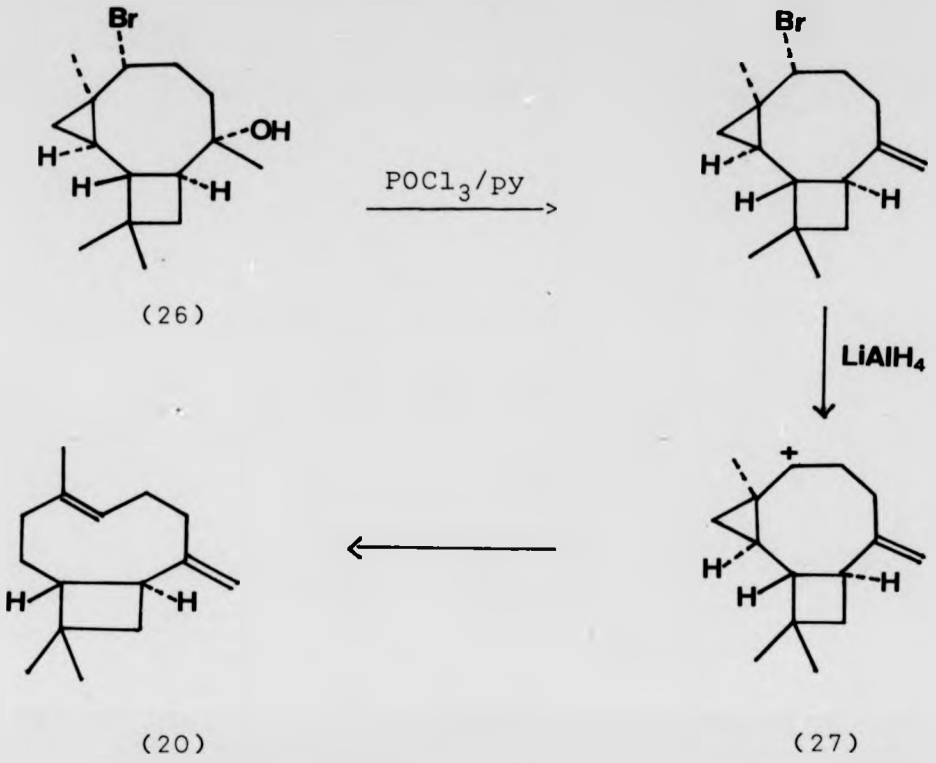


(1)



(26)

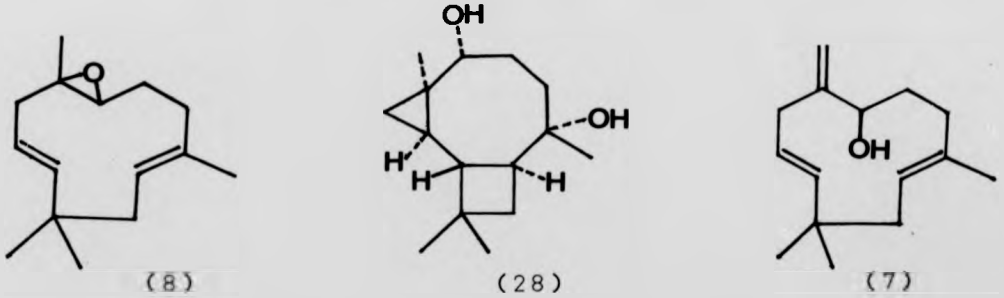
Cyclisation is initiated by electrophilic attack at the $\Delta^{1,2}$ double bond, followed by participation of neighbouring π-bonds. Strain calculations from the X-ray study had predicted the $\Delta^{1,2}$ double bond to be the most reactive. The stereochemistry of the product (26), with a trans-fused cyclobutane ring and a cis-fused cyclopropane ring, was in accord with its then accepted CT conformation. It is interesting to note that dehydration of the bromohydrin (26) followed by hydride reduction yields caryophyllene (20) (amongst other products) via the cyclopropyl carbinyl ion (27) (Figure 4).



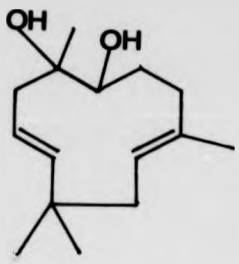
(26) (27) (20)

Figure 4

Pertinent to this work by Sutherland are the results of the acid-catalysed rearrangements of humulene-1,2-epoxide (8),[24-26] which is the major product of monoepoxidation of humulene (1). The cyclisation produced amongst other products, the tricyclic diol (28), along with humulenol (7) and the diols (29) and (30).



(8) (28) (7)



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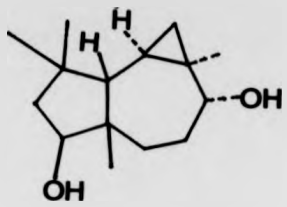


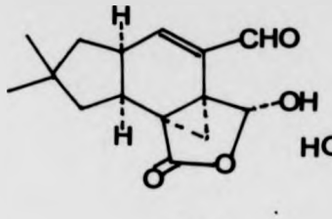
(30)

The epoxide (8) initially cyclizes to give the tricyclohumuladiol (28) which decyclizes or rearranges to (7), (29) and (30). Compound (30) is produced by loss of a hydroxyl group at C-8 in diol (28) with subsequent ring expansion to yield product (30). Tricyclohumuladiol (28) has been isolated from hop oil[27] but it is felt that it is an artefact of the isolation procedure since it was not isolated as an optically-active material. It is known that the three humulene monoepoxides are found optically-active in Nature.[11]

The year 1965 saw a turning point in the study of humulene chemistry since that year heralded the structural elucidation of the fungal metabolites marasmic acid (31),[28] hirsutic acid (32)[29] and illudin (M) and (S).[30] All these tricyclic carbon skeletons could formally be derived by intramolecular cyclisation and rearrangements of humulene. An increasing number of naturally-occurring compounds, mainly of fungal origin, have been isolated from that time and illustrate the importance of humulene in the biosynthesis of certain types of sesquiterpenoids.

The compounds considered to be derived from humulene at present, may be classified under nine general skeletal types, i.e. hirsutane (35), protoilludane (36), marasmane (37), illudane (38), africane (39), pentalenane (40), senoxydane (41),

sterpurane (42) and isolactarane (43).



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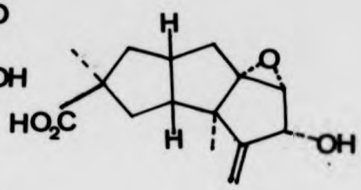

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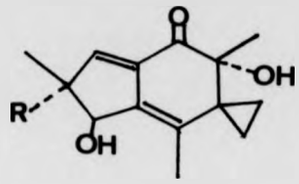
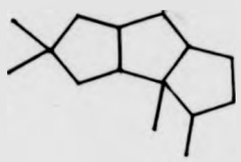


(33) R=Me
(34) R=CH_2OH



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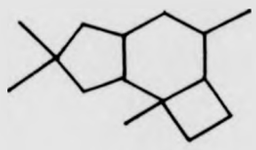

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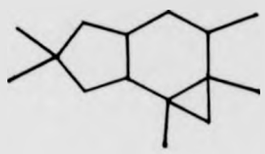

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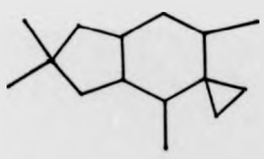

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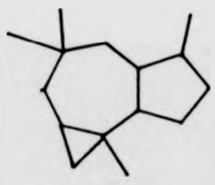

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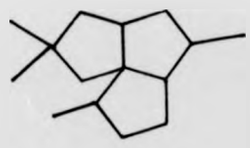

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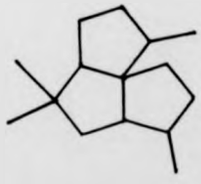

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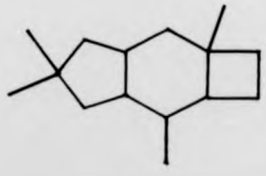

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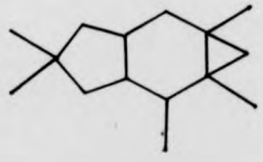
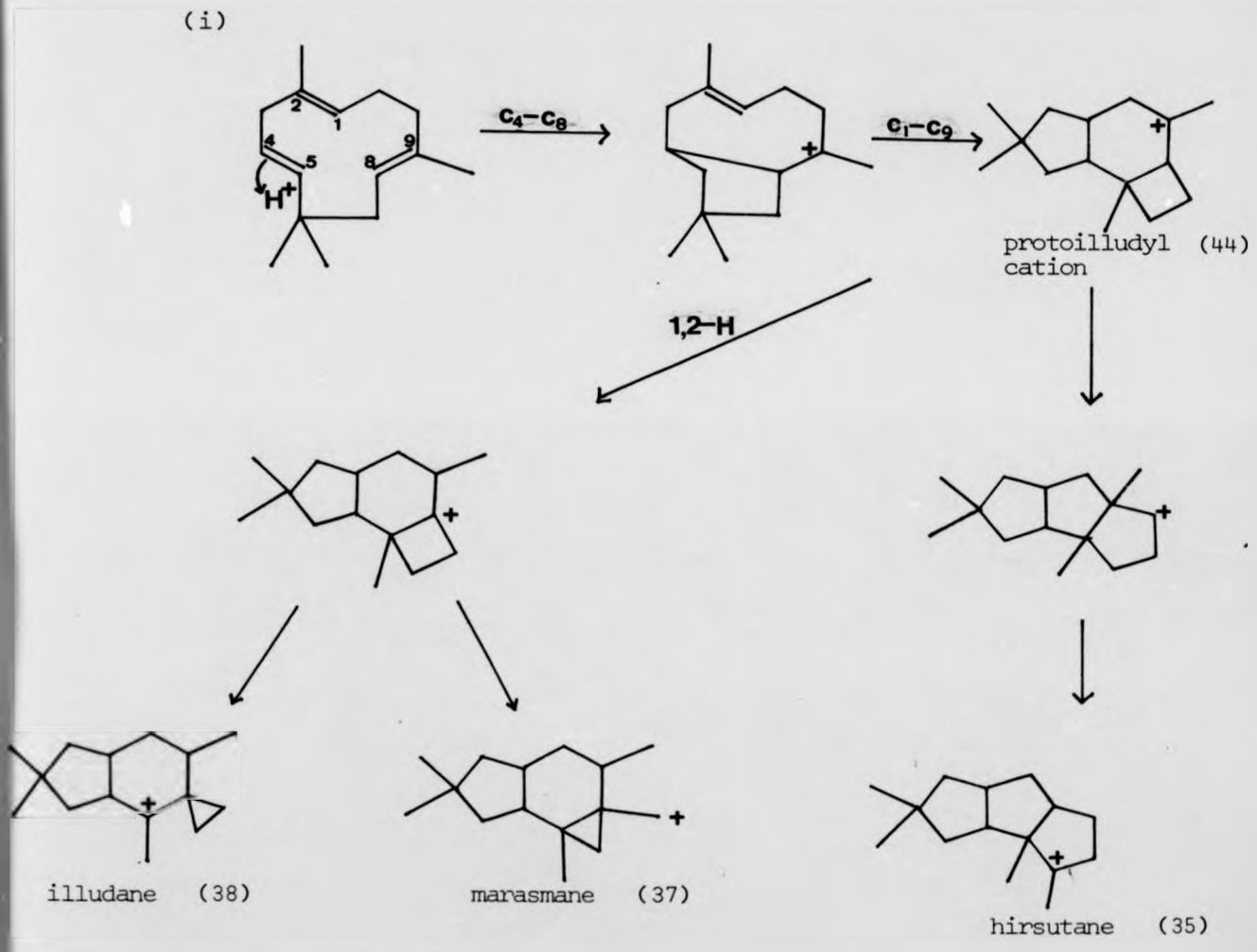


(43)

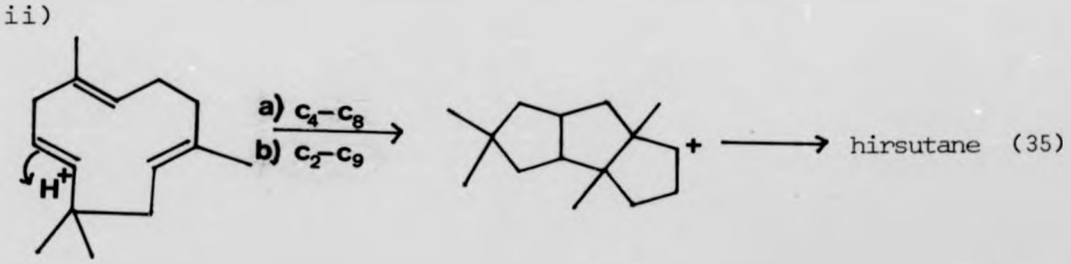
These skeletal types may be derived from humulene (1) by initial protonation of the $\Delta^{4,5}$ double bond followed by cyclisation of the remaining double bonds. The cyclisation pathways are considered in Figure 5 and it is important to note that

the protoilludyl cation (44) plays a major rôle in the biogenetic schemes. Seven of the nine skeletons may be derived from cation (44), although alternative pathways exist for hirsutane (35) and pentalenane (40).

(i)



(ii)



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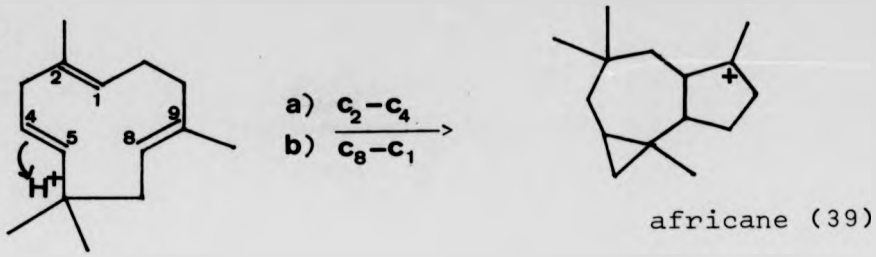
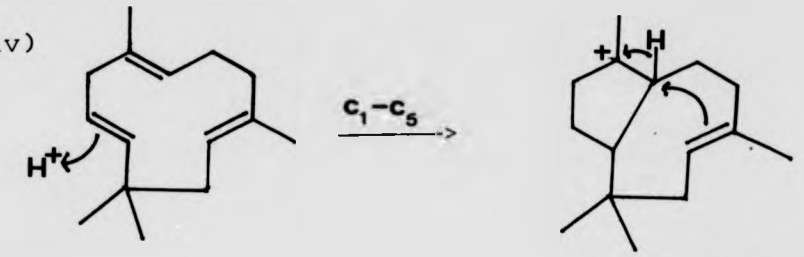
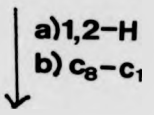
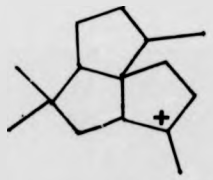


africane (39)

(iv)

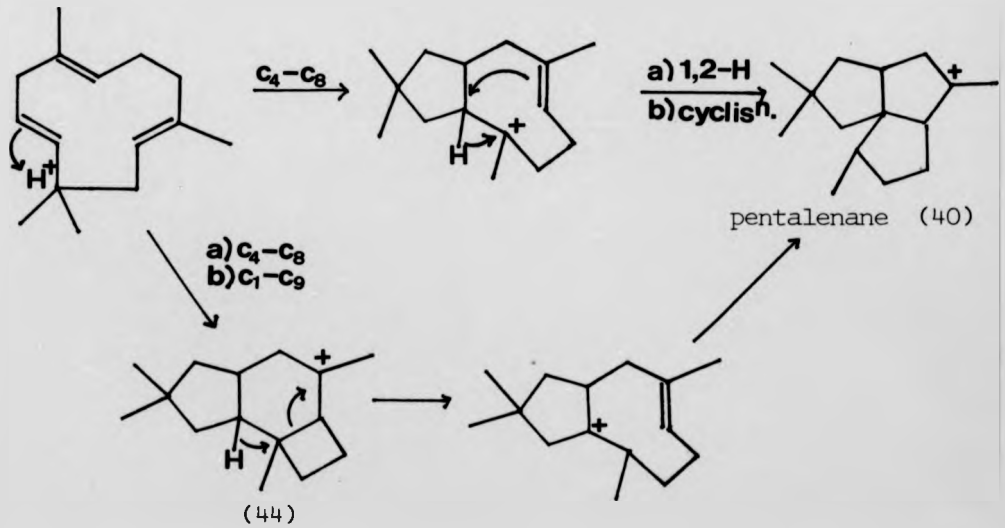






senoxydane (41)

(v)



(44)

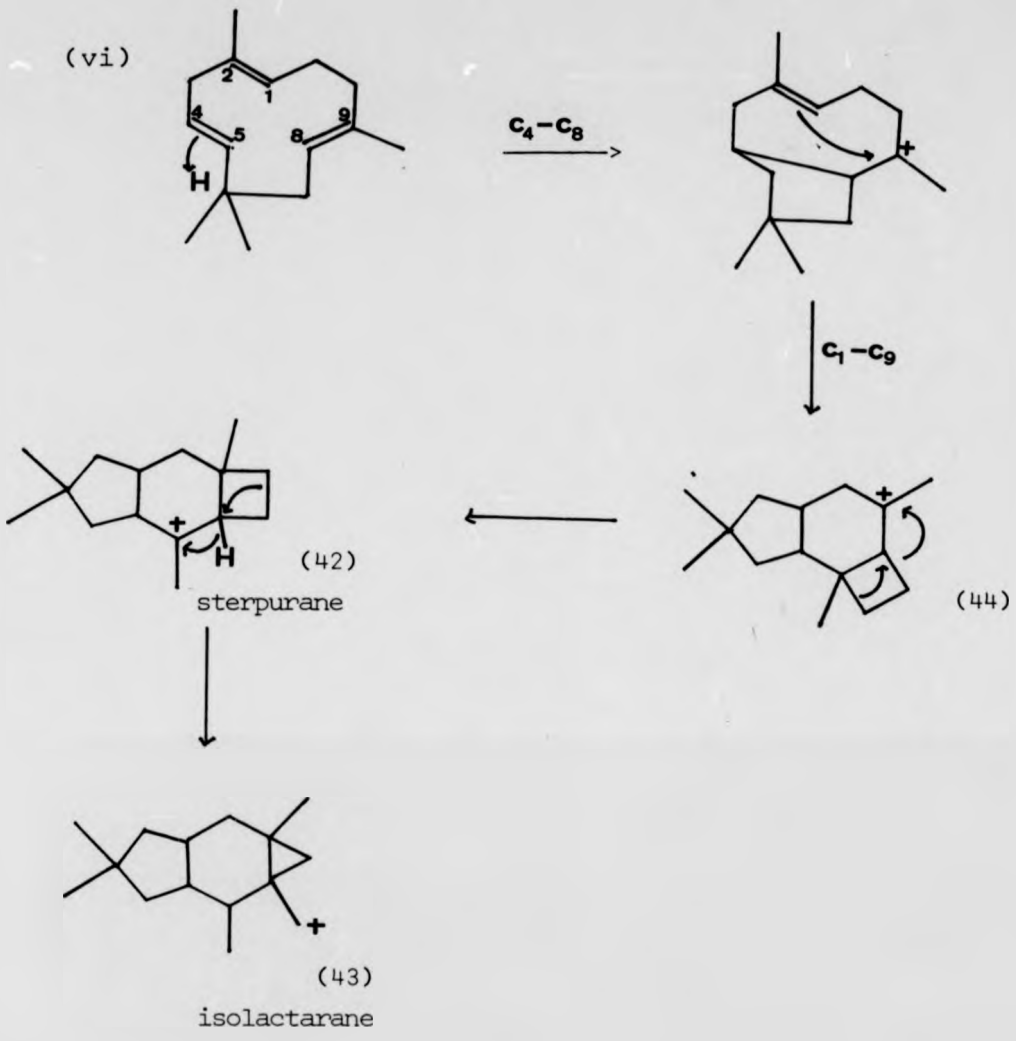
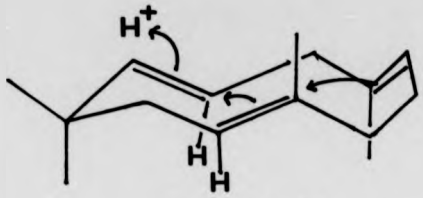


Figure 5

McMorris et al[31] isolated illudol (45) which was found to have a cis-fused hydrindane skeleton.[32] This was in keeping with humulene in the CT conformation (46),[22] the hydrogen atoms at C-4 and C-8 being cis to each other before cyclisation.



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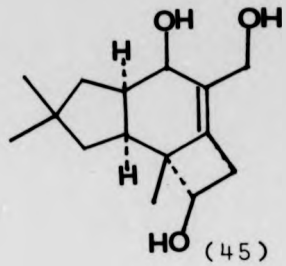
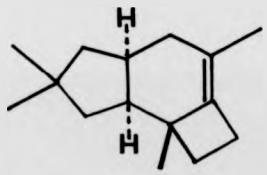


(45)

Δ^6-Protoilludane (47) and the related alcohol (48) have been isolated[33] and their structures can be rationalised by quenching of the protoilludyl cation (44).



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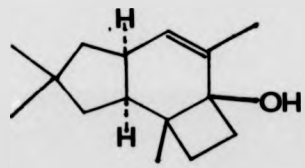
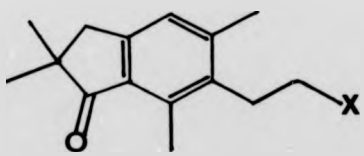
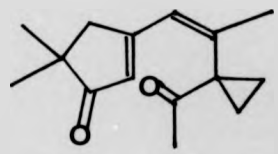


(48)

The pterosins H (49), I (50), Z (51) and hypacrone (52)[34] are closely related to illudol (45).



X=Cl (49)
X=OMe (50)
X=OH (51)



(52)

The biogenesis of the pterosins is believed to arise from the protoilludyl cation (44) and is outlined in Figure 6.[35] Hypacrone (52) is also thought to arise by cleavage of the protoilludyl cation, suggesting a common biosynthetic process in the plant for the pterosins and hypacrone.

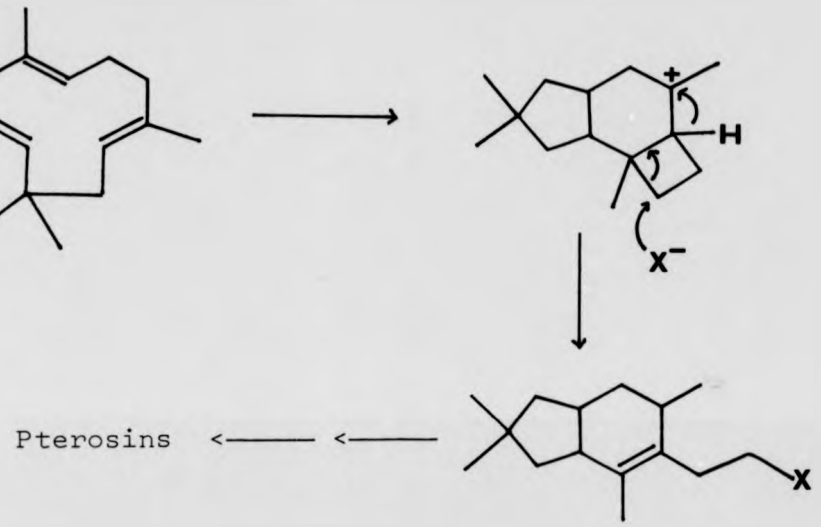
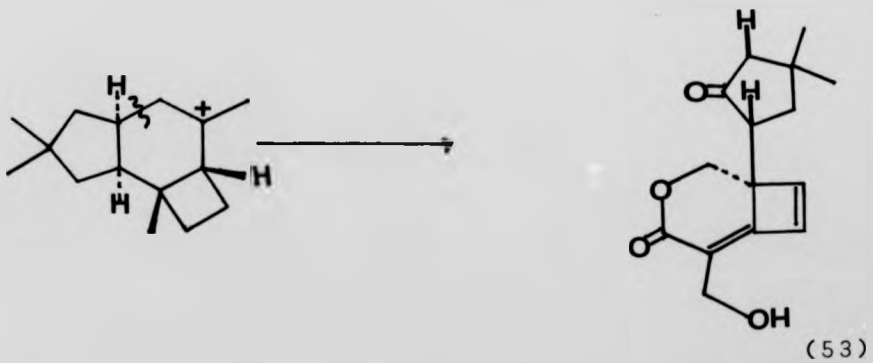


Figure 6

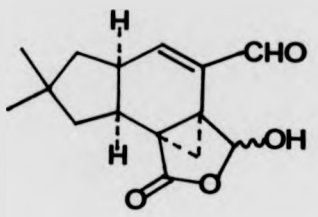
Fommanosin (53) which is isolated from the same fungus as Δ^6-protoilludane (47) was identified[36] and can be considered to be formed by oxidative cleavage of the six-membered ring of the protoilludyl cation (44) as illustrated in Figure 7.



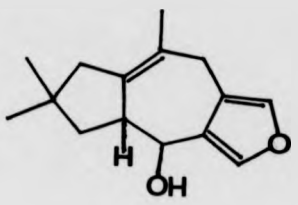
(53)

Figure 7

Marasmic acid (31)[37] proved to have the same cis-fused hydrindane skeleton as illudol (45) and evidence suggests that it is derived from the protoilludyl cation (44).[38] The related compounds with the vellerane-type skeleton, examples of which are (54) and (55), have been of interest since it has been suggested[39] that both marasmanes and velleranes may be derived from the cation (56).



(31)



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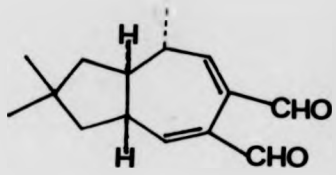
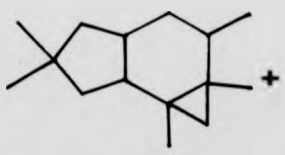
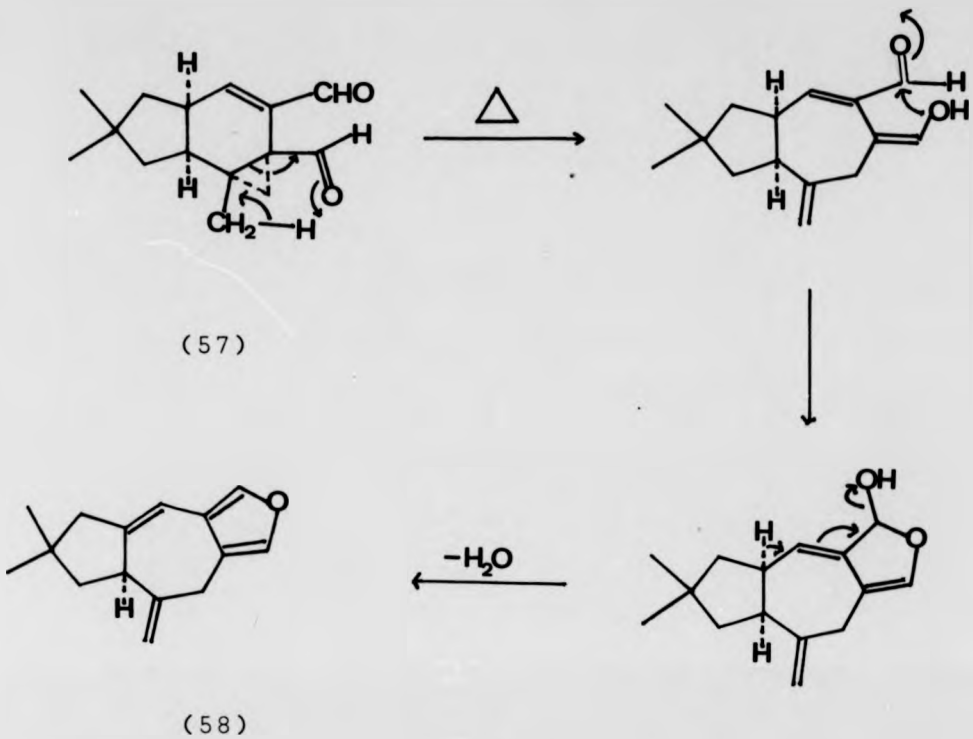


(55)



(56)

This was substantiated by the thermal rearrangement of isovelleral (57) to the vellerane type compound (58) (Figure 8).[40]



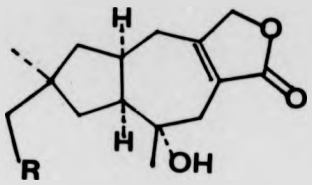
(57)

(58)

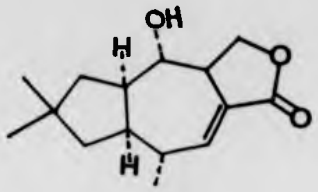
Figure 8

Closely related to the velleranes are compounds with the lactarane skeleton. The lactorufins A (59), (60) and (61)[41] have been isolated from the mushroom, Lactarius rufus, and the compounds (62) - (64) are examples of metabolites recently found in extracts of Lactarius scrobiculatus.[42]

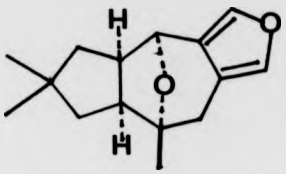
Pentalenic acid (65)[43] (isolated as the methyl ester), pentalenolactone G (66), pentalenolactone H (67) and pentalactone E (68)[44] are thought to be derived from the protoilludyl cation (44) as depicted by the mechanism (a) in Figure 9. However an alternative mechanism (b) may be operating which does not necessitate the protoilludyl cation as intermediate.



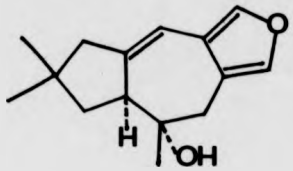
R=H (59)
R=OH (60)



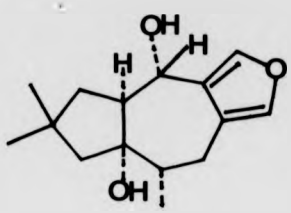
(61)



(62)



(63)



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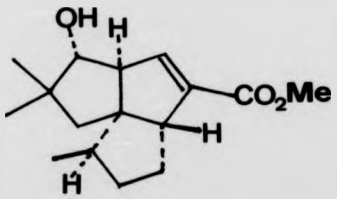
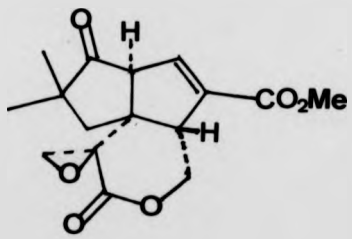


(65)



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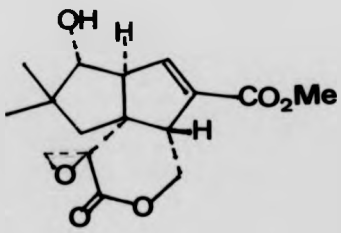

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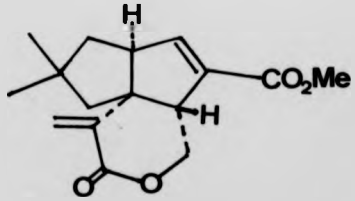


(68)

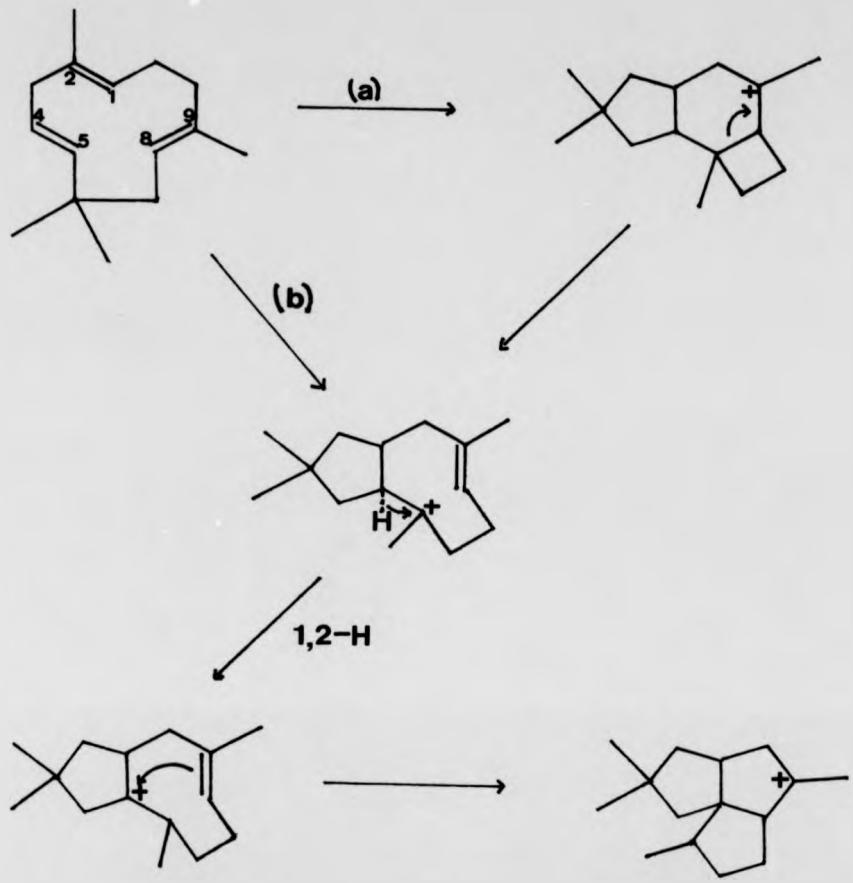
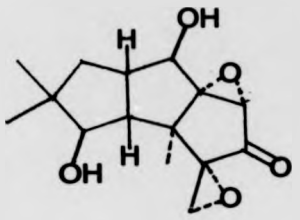


Figure 9

Coriolin (69)[45,46], a new sesquiterpenoid antibiotic was shown to have a cis fused hydrindane skeleton but it was observed that the ring fusions were of opposite absolute configuration to that found in the previously discussed hydrindane-type compounds. A similar situation was observed in complicatic (70) and hirsutic (32)[47] acids and on the basis of structural

similarities, the coriolins and the hirsutanes are thought to have hirsutene (71) as a common precursor. This hypothesis was also enhanced by the isolation of hirsutene (71) from Coriolus consors, which is known to produce coriolin (69). Interestingly, humulene was also found in the hydrocarbon mixture.



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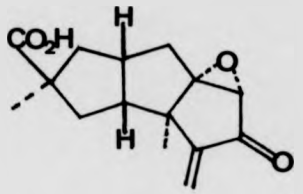

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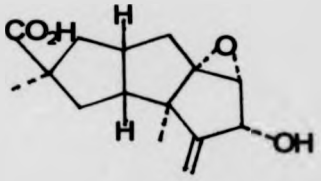

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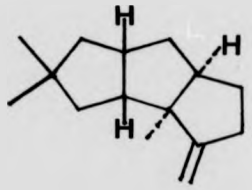


(71)

As there exists an antipodal relationship between the skeletons derived from the protoilludyl cation (44) and the hirsutane group, it was thought that the latter was not derived from the protoilludyl cation. Studies[48,49] have been carried out on the biosynthesis of these compounds using [1,2-$^{13}C_2$] acetate and [1-^{13}C] and [2-^{13}C] acetate, but these

results do not clearly indicate whether or not a protoilludyl intermediate is involved.

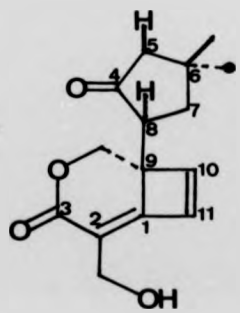
In the previous studies which have been discussed, Sutherland suggested that humulene adopted the CT conformation in solution,[22] by analogy with the silver nitrate adduct of humulene (1).[7] The experimental results for cyclisation of humulene using N-bromosuccinimide, clearly demonstrated that the resulting bromohydrin maintained the CT conformation as determined by X-ray analysis.[50]

Recent molecular mechanics calculations carried out by Matsumoto et al,[51,52] involved the energy minimisation of the four principal conformers of humulene (1) by computer methods. Four stable conformers were envisaged, i.e. CT, CC, TT and TC with the respective heats of formation (kcal/mol) 4.24, 4.47, 7.86 and 5.30. The activation enthalpy for the transformation CT to CC, which corresponds to rotation of the $\Delta^{1,2}$ double bond through the humulene ring, was calculated to be 10.63 kcal/mol. The activation enthalpy for humulene ring inversion was also estimated to be $\Delta H^{\neq}$ = 14.17 kcal/mol, which is reasonable compared to the barrier $\Delta G^{\neq}$ = 10.6 kcal/mol for humulene obtained by a nmr study[53] and humulene ring inversion should be free at room temperature.

These results strongly suggest that in addition to the known CT conformer, the new CC form should be equally stable and this new conformer is important in the transannular reactions of humulene. If the conformation is kept almost unchanged through the course of the reaction, the conformers CT and CC are well suited to the precursors of illudoids and hirsutoids respectively.

Two separate biosynthetic pathways can be suggested [CT → protoilludoid (a) and CC → hirsutanoid (d,f)] rather than assuming a single route, i.e. [CT → protoilludane → hirsutane (c,e,g)] (Figure 10). These workers had been suspicious of a single route, since the co-occurrence of hirsutanoids and other illudoids has not been discovered.

In a recent study by Cane and Nachbar[54] of the biosynthesis of fommanosin (53), it was demonstrated that labelled illudoid and hirsutanoid compounds are biosynthesised through the paths represented by the abbreviated expressions si,re,cis,cis,R and re,si,cis,cis,S respectively, noting the absolute stereochemistry of the cyclisation reaction of farnesyl pyrophosphate. The first si or re denotes which face of the distal double bond of the farnesyl pyrophosphate is attacted by the C-7 carbinyl carbon to yield the humulene indicated (Figure 10). This information is found by finding which of the methyl groups is derived from C-2 of mevalonate. The second re or si denotes the face of the $\Delta^{4,5}$ double bond which is attacted by a proton to form the cyclopentane ring. The first cis relates the C-4 and C-8 angular hydrogens. When the molecule has formed fommanosin (53) the second cis denotes the relationship of the methyl group derived from C-2 of mevalonate and the C-9 carbon of the cyclobutyl substituent. The last R or S indicates the absolute configuration of C-8.



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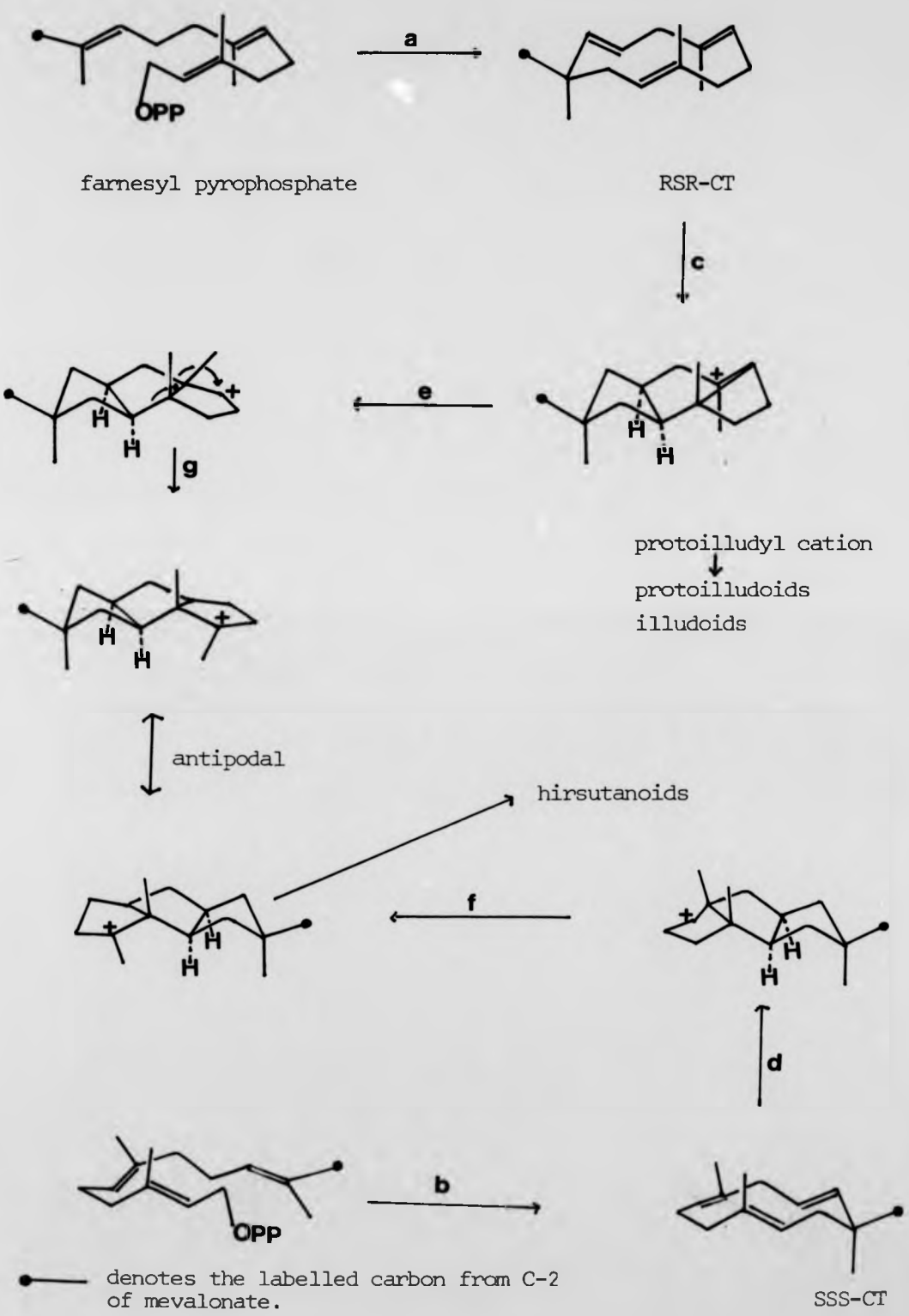

OPP
a
farnesyl pyrophosphate
RSR-CT
c
e
g
protoilludyl cation
protoilludoids
illudoids
antipodal
hirsutanoids
f
d
OPP
b
denotes the labelled carbon from C-2 of mevalonate.
SSS-CT

Figure 10

Cane and Nachbar successfully analysed the stereochemistry of formation of the cyclopentane moiety but did not examine the second transannular cyclisation to give illudoid or hirsutanoid skeletons. Matsumoto et al.[52] conclude that the absolute configuration of the products suggests that the conformation designated RSR CT-humulene is the precursor of illudoids and SSS-CC humulene is that of hirsutanoids, where the prefix RSR denotes the chirality of the three double bonds $\Delta^{8,9}$, $\Delta^{1,2}$ and $\Delta^{4,5}$ respectively.

It should be noted that the TT and TC conformers in Figure 11 are excluded as they cyclise to form trans-fused bicyclic compounds which have not been found as natural products.

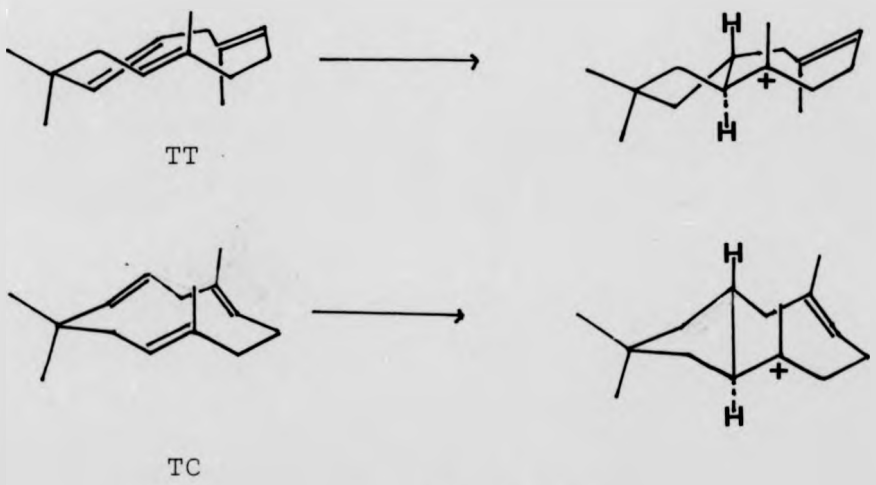
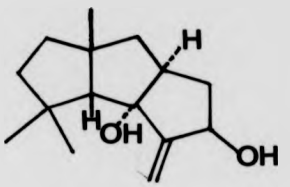


Figure 11

The group of compounds which are given the name capnellane[55] have a similar skeleton to hirsutane but differ in the positioning of the methyl groups. $\Delta^{9(12)}$-Capnellane-8β,10α-diol (72) and $\Delta^{9(12)}$-capnellane (73) are members of this

group which are derived from an isomer of farnesyl pyrophosphate (74) which undergoes a methyl migration after cyclisation.



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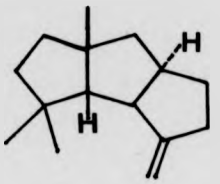

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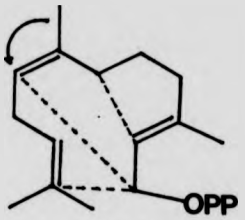
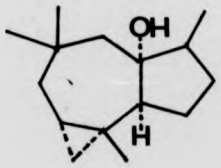


(74)

The africane-type compounds, africanol (75) and hydrocarbons (76)-(78) were isolated from a marine sponge.[56]



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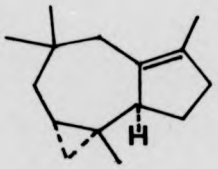

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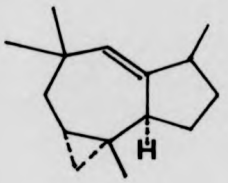

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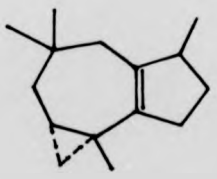
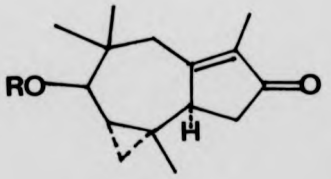


(78)

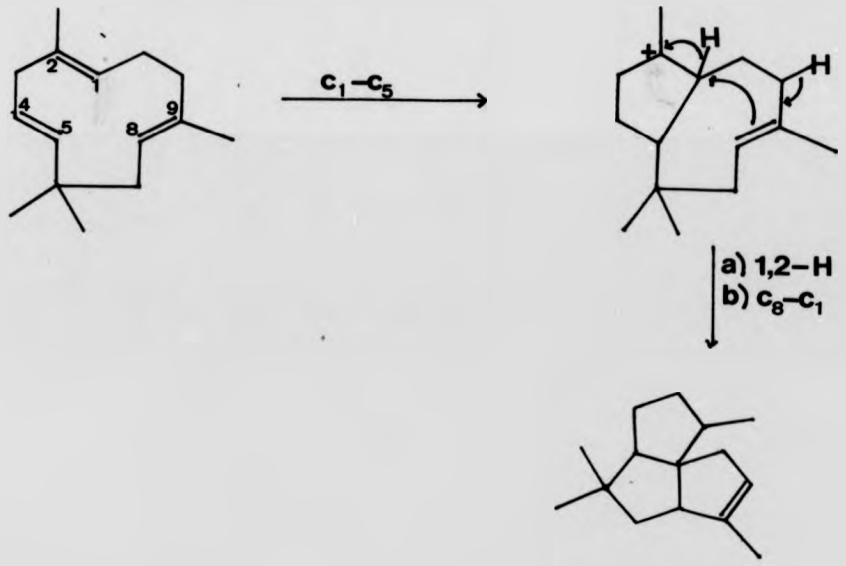


R=Ang

(79)

Recently Bohlmann and Zdero isolated the keto-angelate (79)[57] and although it was proposed that humulene-8,9-epoxide (10) was the precursor, it seems more likely to be derived from humulene-4,5-epoxide (9).

Bohlmann and Zdero have also recently isolated senoxydane (80), a sesquiterpene hydrocarbon with a new carbon skeleton from Senecio oxydontus.[58] Its formation has been postulated from humulene via initial protonation of the $\Delta^{4,5}$ double bond (Figure 12).

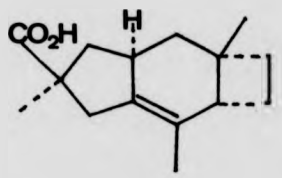


(80)

Figure 12

Ayer et al have reported the structures of sterpuric acid (81)[59] and related sterpurenes. Biosynthetic studies indicate that the sterpurenes are derived from farnesyl pyrophosphate via humulene and the protoilludyl cation (44).[60] These workers have also isolated sterepolide compounds (82) and (83),[61] which with isolactarorufin (84),[62] represent the

only known members possessing the isolactarane skeleton (43). The co-occurrence of the sterepolids and the sterpurenes, suggests the possibility that the isolactarane skeleton (43) may be derived biogenetically <u>via</u> the sterpurane cation (42) (Figure 13).



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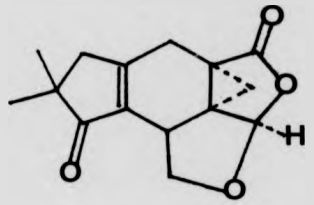

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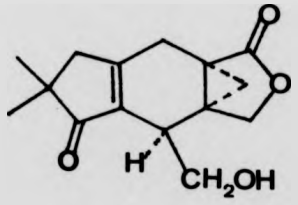

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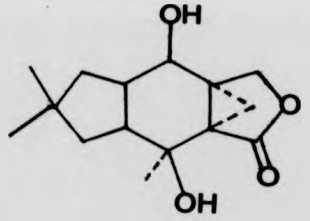

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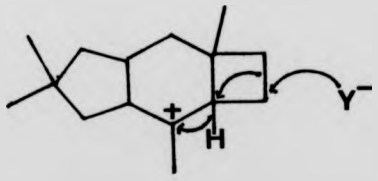
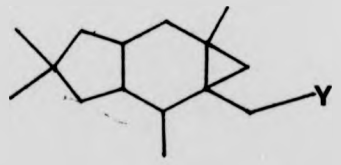


(42)



(43)

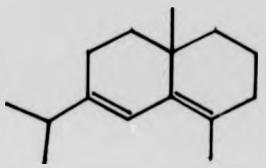
Figure 13

Before discussing attempts to synthesise some of these tricyclic compounds by biomimetic strategies, it is important to note that a significant number of them have been obtained by total synthesis, many of which are elegant in design. Most recent examples are hirsutene,[63-66] hirsutic acid,[67] coriolin,[68-71] protoilludane,[72] pentalenolactone,[73-76] illudol,[77] marasmic acid,[78,79] isomarasmic acid,[80], marasmane, isomarasmane[81] and fommanosin.[82] Biosynthetic studies have also been carried out on many of these compounds, and these include illudin M and S,[83] the pterosides,[35] marasmic acid,[38] coriolin[48] and pentalenolactone.[84]

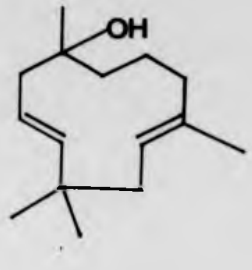
The stage is now set to discuss the more recent chemistry of humulene (1), where the emphasis has been directed towards three goals. These involve inducing humulene to undergo the postulated ring closures; investigations of the *in vitro* reactivity of protoilludyl cation equivalents; inducing functionalised derivatives of humulene to undergo cyclisation.

In considering humulene (1) first of all, Naya and Hirose[85] (and independently by Parker *et al*)[20] proved that humulol (85) was the initial product which then rearranged to the bicyclic compounds (86)-(89). Figure 14 illustrates the mechanism of formation of these bicyclic compounds. Apollan-11-ol (25) was also formed and its mechanism of formation has been discussed (Figure 3).

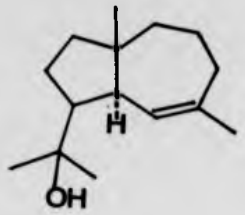
Mehta and Singh[86] also produced δ-selinene (90) from acid treatment of humulene and it is thought that this arises from rearrangement of the hydrocarbon (89).



(90)



(85)



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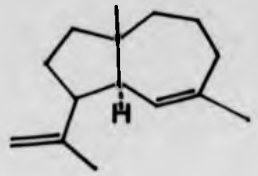
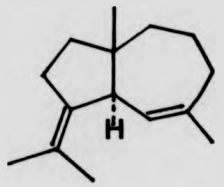


(87)



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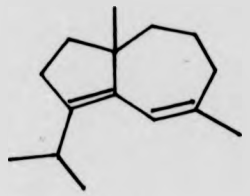

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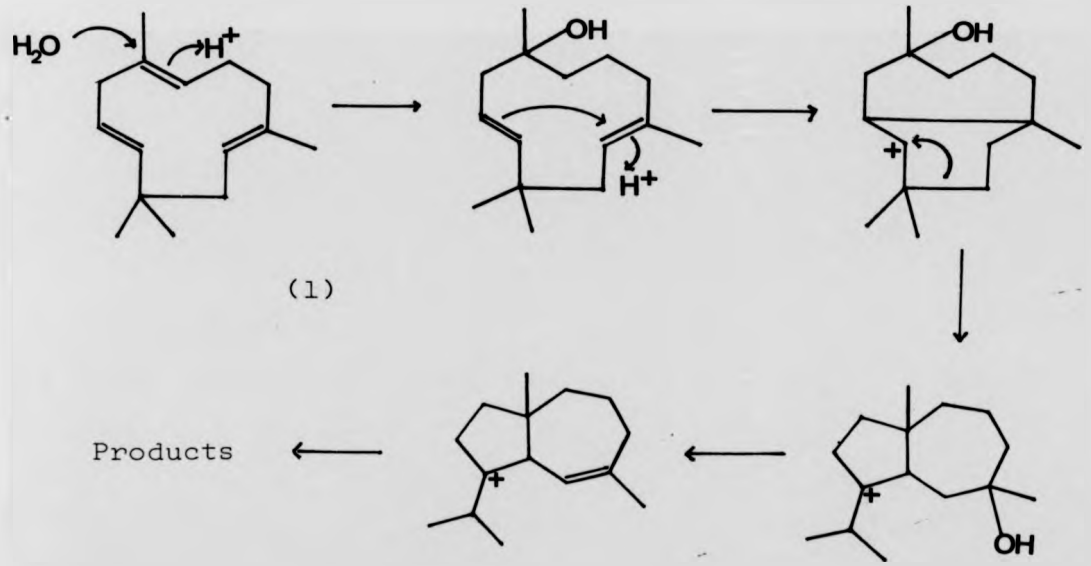


Figure 14

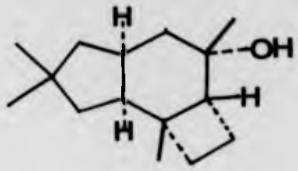
It became obvious that reactions on humulene *per se*, did not produce compounds with the skeletal type found in Nature. Therefore, it was hoped that by formation of the intermediate protoilludyl cation (44) or its equivalent, it may be induced to undergo the desired rearrangements. Matsumoto *et al*.[87] have synthesised the cationic equivalents (91), (92) and (93) and formolysis[88] of these produced the bridged compound (94) and the naturally-occurring pentalenane hydrocarbon (95).[89] The different products were explained in terms of two possible conformations (96) and (97) of the protoilludyl cation which cyclise to give (98) and (99) respectively.

The same workers have also used the ketone (100) in a biogenetic-like synthesis of $\Delta^{2(3),7(13)}$ illudadiene (101), $\Delta^{2(3)}$-7β-illudenol (102)[90] and d,l-hirsutene (71)[91] (although this is not truly biomimetic since Matsumoto *et al*[52] later postulated that hirsutene is not formed *via* the protoilludyl cation).

Matsumoto *et al* have also been conducting experiments on humulene in an attempt to cyclise the hydrocarbon directly.[92] The oxymercuration-demercuration with mercuric acetate of humulene gave the two cyclic ethers (103) and (104).

The initial attack occurs on the $\Delta^{1,2}$ double bond and subsequent attack $\Delta^{4,5}$ double bond promotes cyclisation. The reactive species may be drawn in the CT type conformation as illustrated in (105).

Treatment of ether (103) with boron trifluoride in acetic anhydride produced compounds (106) and (107).[93]



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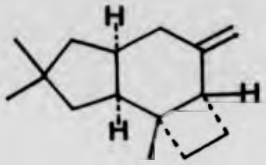

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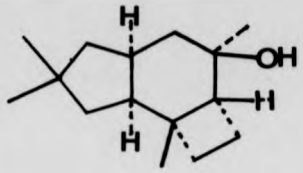
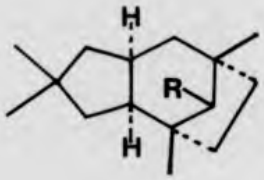
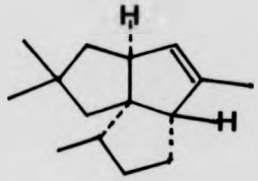


(93)



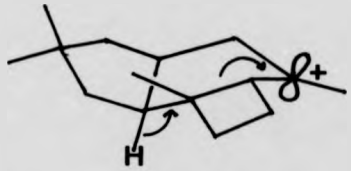
R=OCHO

(94)



(95)

(96)



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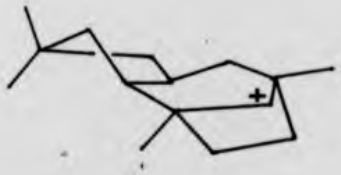

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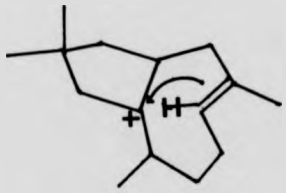

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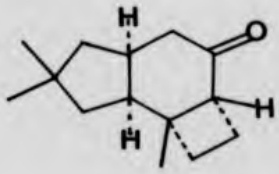

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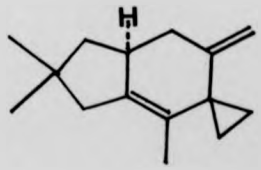

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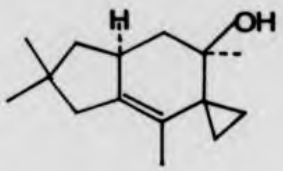

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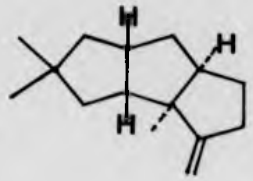

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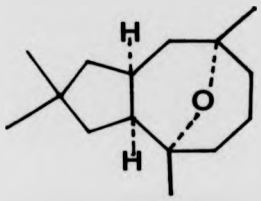

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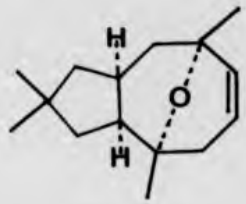

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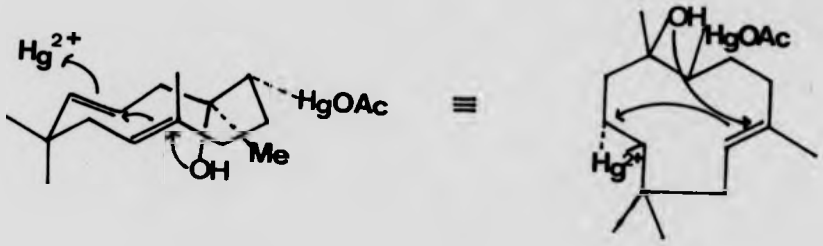

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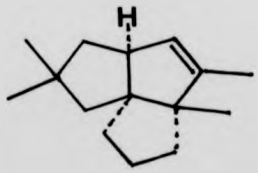

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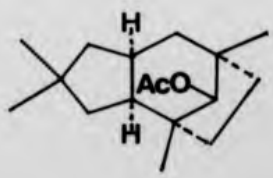
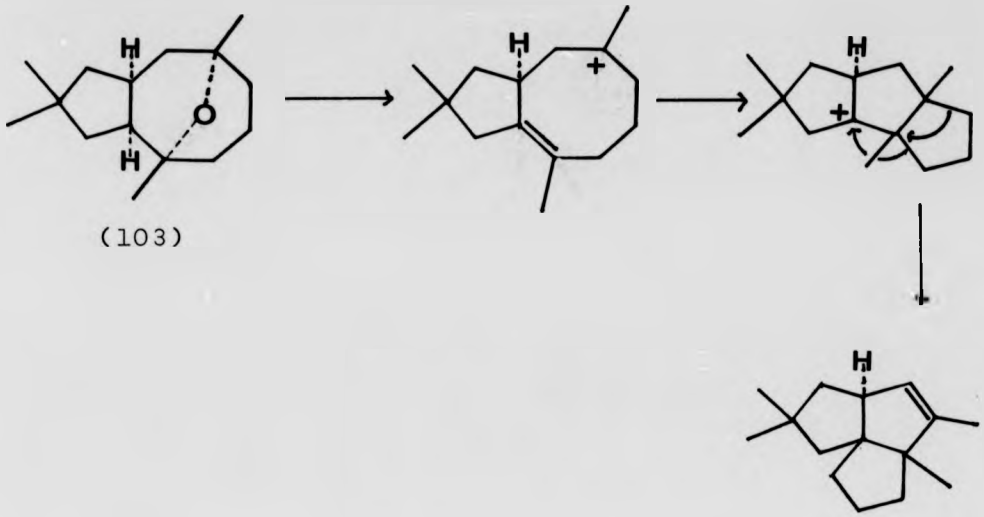


(107)

The tricyclic compound (106) arose by the rearrangement outlined in Figure 15.

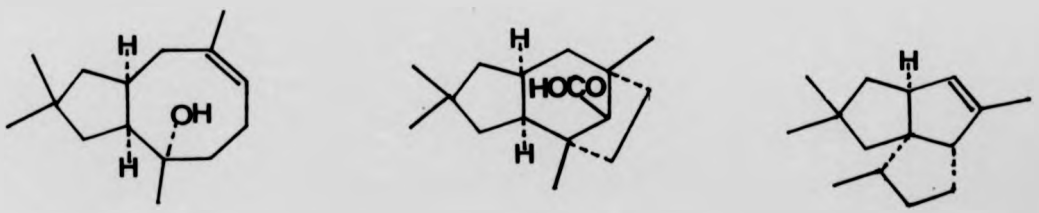


(103) (106)

Figure 15

The cyclisation of humulene with mercuric nitrate in acetic acid yielded the new cyclic ethers (106), (108) and (110). Although different products were obtained from reaction with mercuric acetate, the initial cyclisation is the same as shown in Figure 16.[94]

Reduction of (110) with lithium and ethylamine gave the alcohol (111) which on formolysis yielded (94) and pentalenane (95), both of which had been prepared from the protoilludyl precursors.



(111) (94) (95)

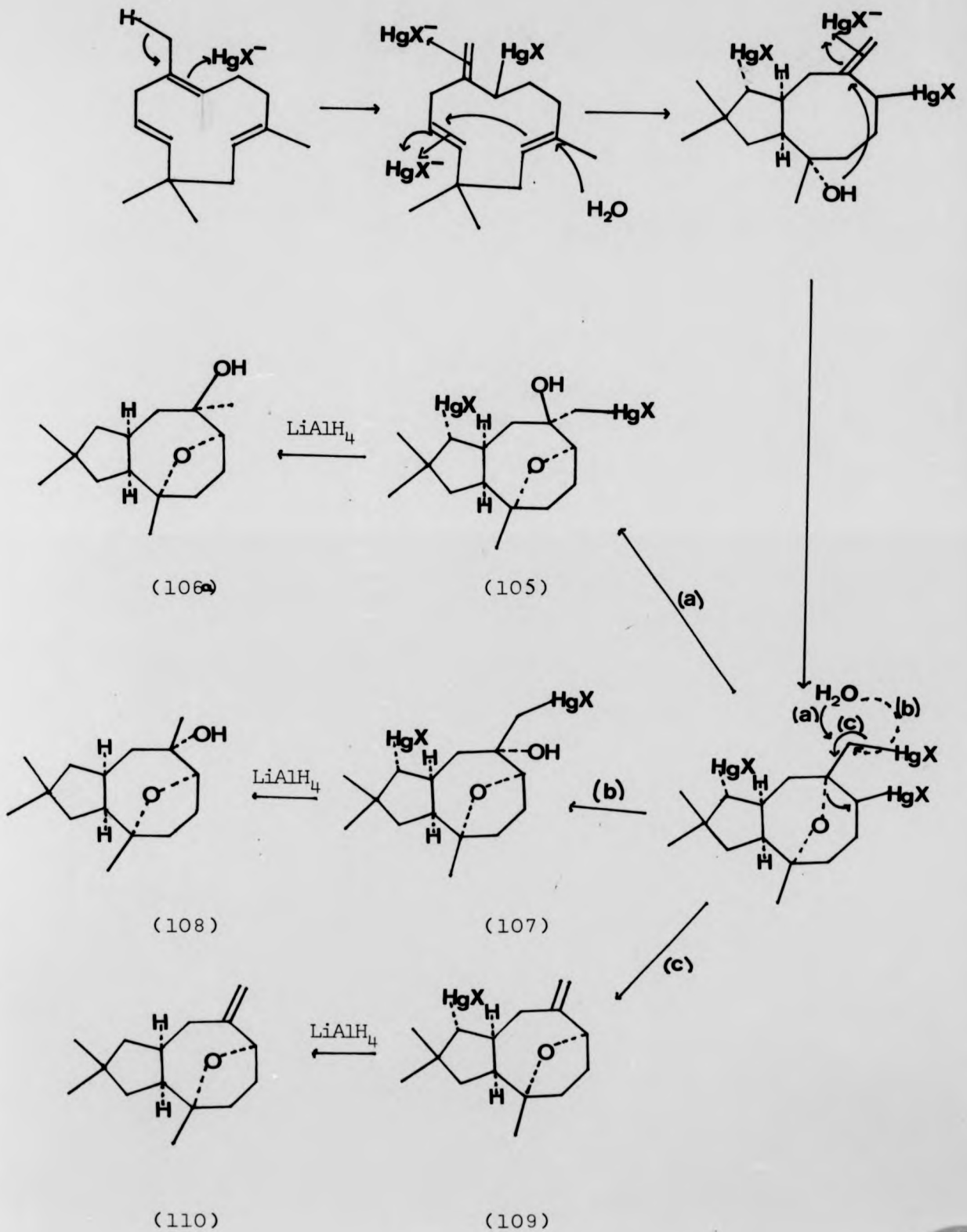

H
HgX⁻
HgX⁻
HgX
HgX⁻
H₂O
HgX⁻
HgX
HgX
H
H
HgX
OH
OH
H
O
H
LiAlH₄
HgX
OH
HgX
H
O
H
(106a)
(105)
(a)
H₂O
(a)
(b)
(c)
HgX
HgX
H
HgX
OH
H
O
H
LiAlH₄
(b)
(108)
(107)
(c)
HgX
H
O
H
LiAlH₄
(110)
(109)

Figure 16

Deuterium labelling experiments established the protoilludyl intermediate in the formation of (94) as indicated in Figure 17.

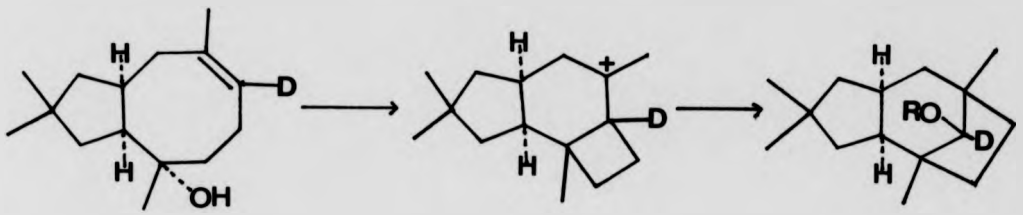
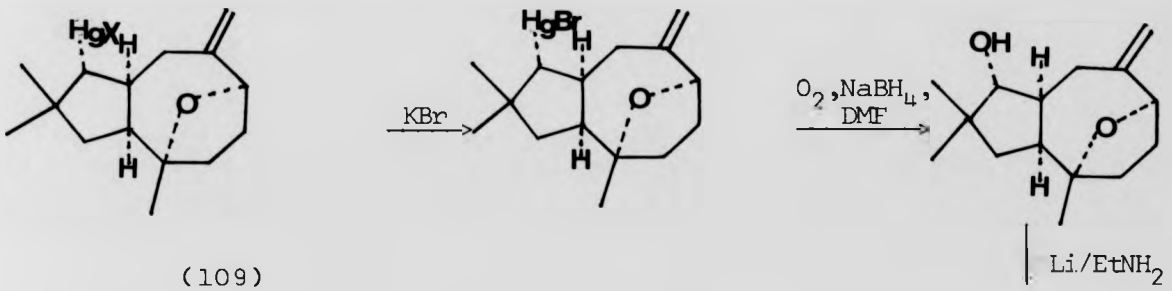


Figure 17

Matsumoto et al have also recently synthesised pentalenic acid (as the methyl ester) (62) from the compound (109)[95] and the synthesis is outlined in Figure 18.



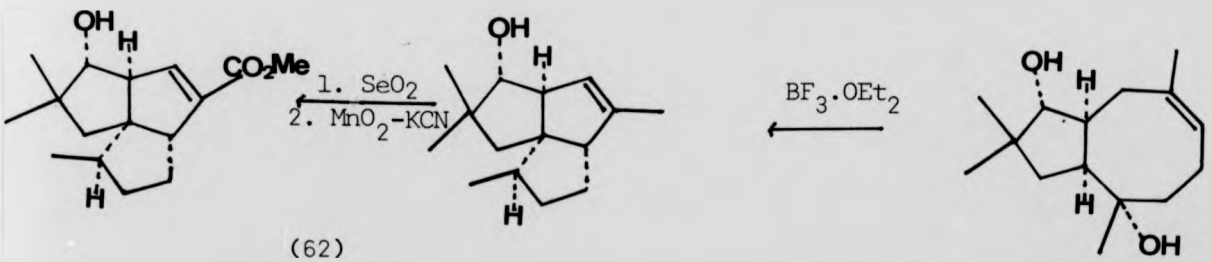
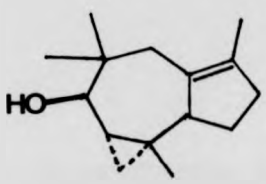


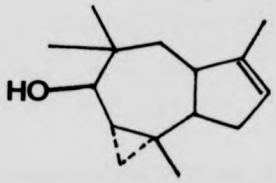
Figure 18

Thus, Matsumoto et al have formed the naturally-occurring compounds pentalenane (95) and pentalenic acid (62) by biomimetic syntheses from humulene per se.

The reaction of humulene-4,5-epoxide (9) has recently attracted the interest of two groups of workers. In the treatment of the 4,5-epoxide (9) with boron trifluoride etherate, Roberts et al[96] isolated the alcohols (112) and (113) which are related in structure and stereochemistry to africanol (75).[56]



(112)



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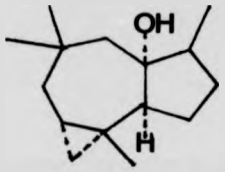

(75)

Independently, Matsumoto et al[97] synthesised dl-bicyclohumulenone[98] (114) and dl-africanol (75)[56] from humulene-4,5-epoxide (9). The 4,5-epoxide (9) was converted to bicyclohumulenediol diacetate (115) with boron trifluoride in acetic anhydride and treatment of (9) with trimethylsilyl-trifluoromethansulphonate (TMSOTf) gave (112) and (113). The intermediates (115) and (112) were converted to the natural products (114) and (75) respectively (Figure 19).

Since stable conformations of humulene epoxides are known to be similar to those of the original olefin,[99] the 4,5-epoxide (9) undoubtedly exists as a mixture of CT and CC conformations at equilibrium.[52] X-ray analysis of the diacetate (115) revealed a configuration which originates from the CC

conformer of (9) giving a trans fused cyclopropane ring. The configuration of the olefins (112) and (113) is considered to be derived from the CT conformation (Figure 19). Thus two structurally different cyclised products have been synthesised from humulene-4,5-epoxide (9) via conformationally selective transannular cyclisation reactions.

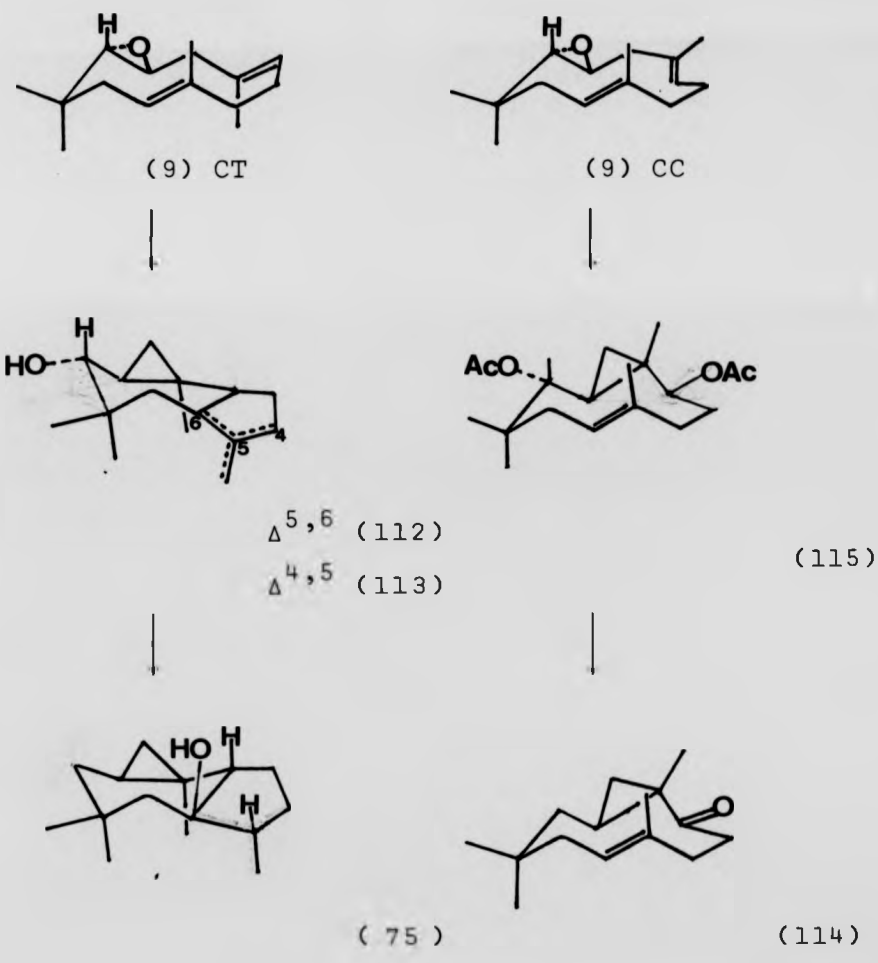

Figure 19

The treatment of humulene-4,5-epoxide (9) in more polar conditions (boron trifluoride etherate in acetic acid) has recently been studied[100] and gives rise to the diacetate (115), the tricyclic compound (117) and the seemingly anomalous products (116) and (118). The conformer-product relationship is summarised in Figure 20.

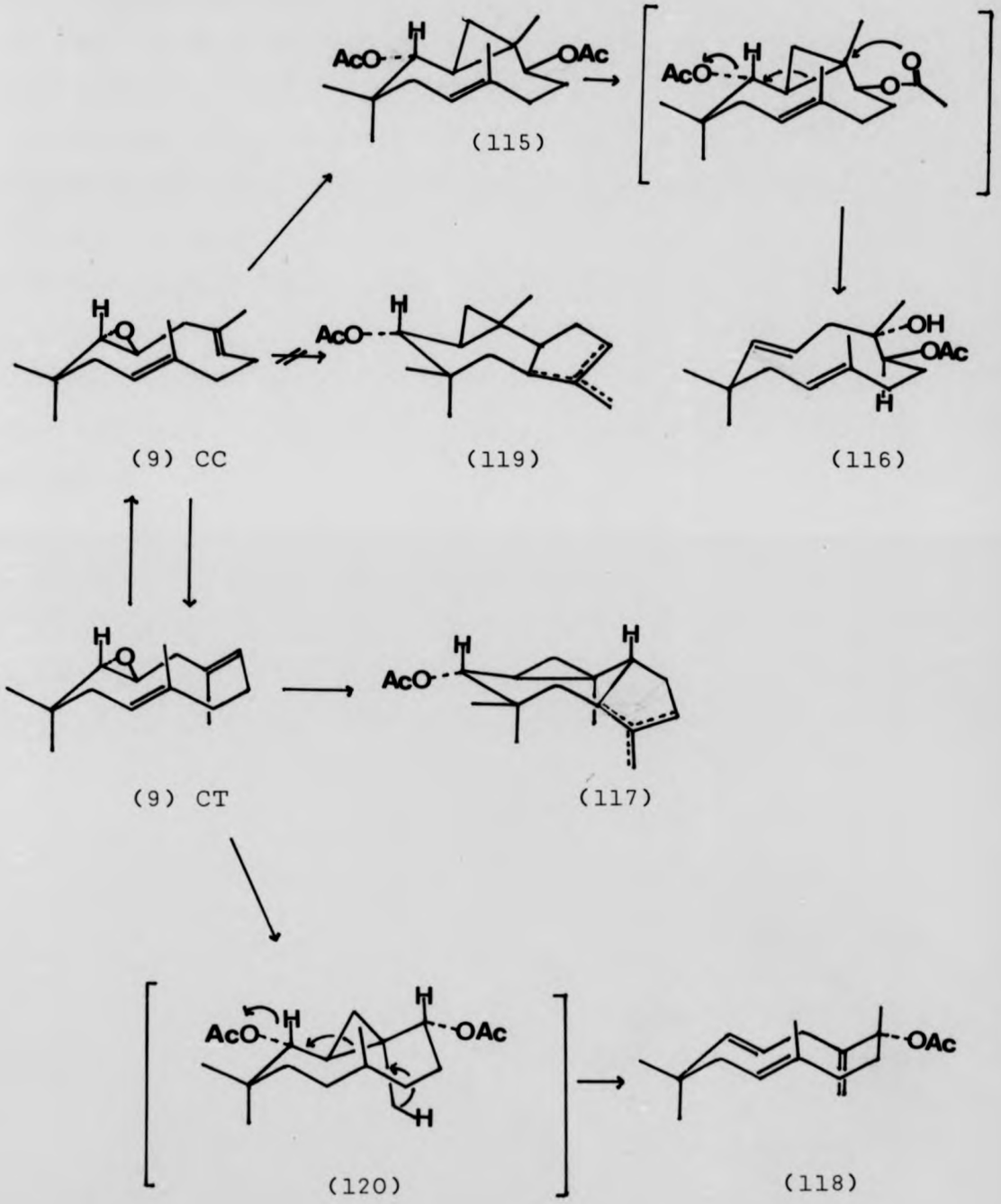
AcO
OAc
(115)
AcO
O
O
(9) CC
AcO
(119)
OH
OAc
(116)
(9) CT
AcO
(117)
AcO
OAc
(120)
OAc
(118)

Figure 20

In this reaction mixture the tricyclic compound (119) originating from (9)-CC could not be identified. These results were explained on the basis of strain energy calculations (estimated by molecular mechanics) carried out on structures (115), (119), (117) and (120) (where the acetoxyl groups were replaced by methyl groups) giving strain energies (kcal/mol) of 46.8, 52.8, 42.7 and 49.0 respectively. It was noted that reaction with TMSOTt afforded selectively (9)-CT mediated products and reaction with borontrifluoride in acetic anhydride[97] gave products resulting from the (9)-CC conformer, while this reaction in acetic acid proceeded through both conformers.

The formation of (115) and (120) and their related compounds (116) and (118) requires the acetate nucleophile. In the reaction conducted in acetic anhydride this is a powerful nucleophile (AcO^-) and the preferred reaction must be substitution, leading to either (115) or (120). Since (115) has been calculated to be more stable, this becomes the main product.

In the reaction with TMSOTf, only the poor nucleophile, trifluoromethoxide, is present leading to a preferred intramolecular attack of the $\Delta^{8,9}$ double bond and as (117) is more stable than (119), only the former is produced.

The reaction with borontrifluoride in acetic acid is considered to be an intermediate case, with acetic acid (AcOH) as the external nucleophile. Attack of the internal $\Delta^{8,9}$ double double bond at the cationic centre (C-1) or of external nucleophiles may take place to give (117), (115) and (120).

A considerable part of the research conducted by

this group, and included in this thesis, parallels the work of Matsumoto *et al* both in the synthesis of pentalenic acid (62)[95] and in the rearrangement of humulene-4,5-epoxide (9).[97,100] However, both groups have made a contribution to the growing understanding of the complexities of humulene rearrangement.

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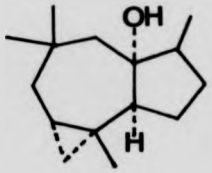
CHAPTER 1

CYCLISATION OF HUMULENE-4,5-EPOXIDE

In 1974, the first africane-type compound, africanol (1), was isolated along with hydrocarbons (2)-(4) from Lemnalia africana, a marine sponge.[1]



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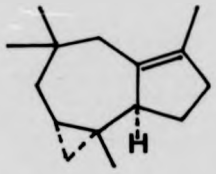

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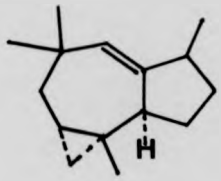

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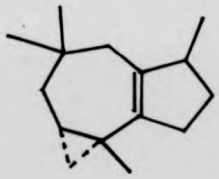
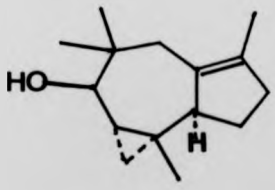
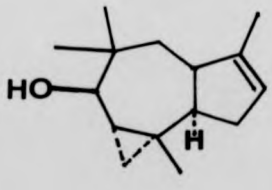


(4)

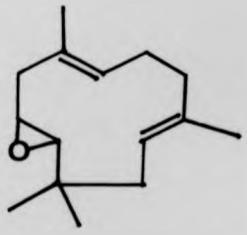
J. A. Mlotkiewicz working in this group at Stirling University, produced the alcohols (5) and (6) from the rearrangement of humulene-4,5-epoxide (7).[2,3] This was of particular interest since these alcohols are closely related in structure and stereochemistry to the naturally-occurring compounds.



(5)

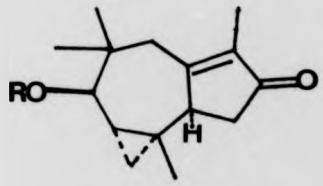


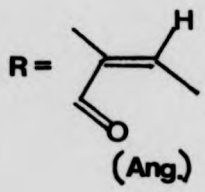
(6)



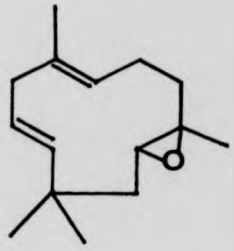
(7)

The keto-angelate (8) was later isolated by Bohlmann and Zdero,[4] who proposed that humulene-8,9-epoxide (9) was the precursor. In view of the work of Mlotkiewicz et al., it seems more acceptable to propose humulene-4,5-epoxide (7) as the biogenetic starting material.



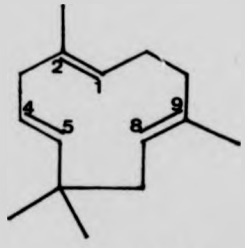


(8)



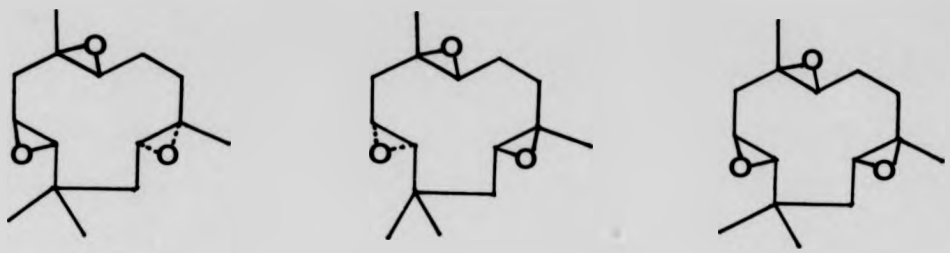
(9)

The method of synthesis of humulene-4,5-epoxide (7) was also established within the group in this department[5] and later refined by J. A. Mlotkiewicz.[3] The order of reactivity of the double bonds in humulene (10) is $\Delta^{1,2} > \Delta^{8,9} > \Delta^{4,5}$ and is explained in terms of the relative strain about each of the reactive bonds.[6] Thus functionalisation of the least reactive ($\Delta^{4,5}$) double bond is required.



(10)

Peroxyacid epoxidation of humulene using an alkaline, two-phase solvent system[7] produces practically pure tris-epoxide (11).[8] A previous method[5] produced two other tris-epoxides (12) and (13) which had to be removed by crystallisation.



(11) (12) (13)

Subsequent stereoselective deoxygenation of the trisepoxide (11) using tungsten hexachloride and n-butyl lithium[9,10] yielded the required 4,5-epoxide (7) and this was the only method permitting stereoselective reduction to the required monoepoxide.[5] It was also found[3] that the reaction conditions had to be scrupulously dry, the temperature carefully controlled and the optimum ratio of trisepoxide (11) to tungsten hexachloride:n-butyllithium had to be 1:2.3:6.9, and the work-up required the use of aqueous sodium tartrate/sodium hydroxide[9] to ensure removal of all tungsten salts. The proposed mechanism of the reaction is illustrated in Figure 1.

$$WCl_6 + 2BuLi \rightarrow Li_2WCl_6 + Bu\text{-}Bu$$

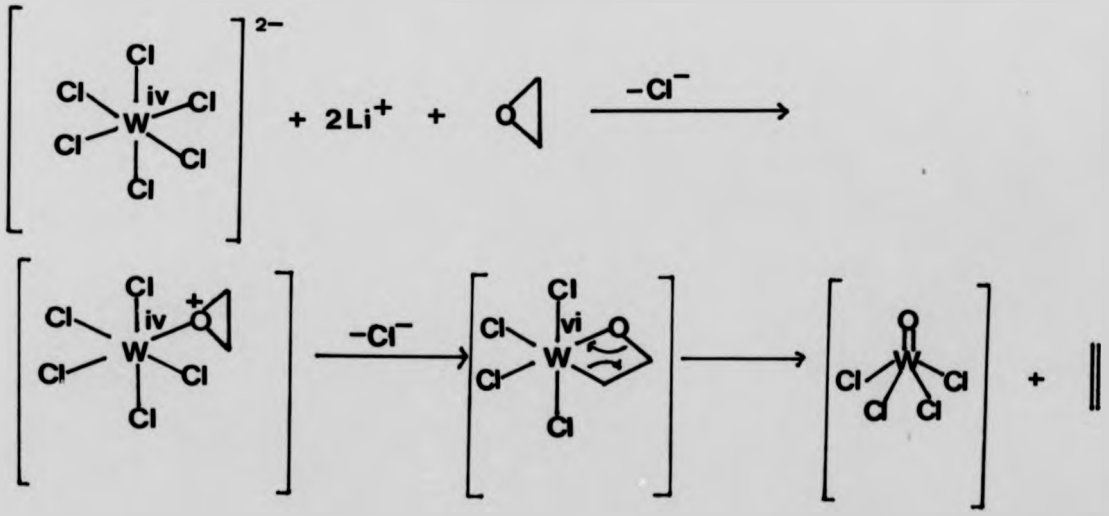


Figure 1

Apart from traces of humulene and diepoxides produced in the reaction, purification of the crude deoxygenation mixture by silica gel column chromatography yielded a further compound which crystallised on elution with diethyl ether. It appeared that this only happened when the reaction was carried out by R. Carman at I.C.I. Pharmaceuticals Division.[11] The structure of this compound was deduced by ^{13}C and ^{1}H nmr spectroscopy using lanthanide shift experiments with $Eu(fod)_3$,[12] INDOR and spin decoupling experiments and was assigned structure (14),[3] where the stereochemistry of the cyclopropyl ring fusion was unknown. Carman also reported[11] that the diol (14) formed the 4,5-epoxide (7) in the presence of acid. Mechanistically this can be explained in Figure 2 and from a model study this reaction seemed feasible for either the cis- or trans-fused cyclopropane ring.

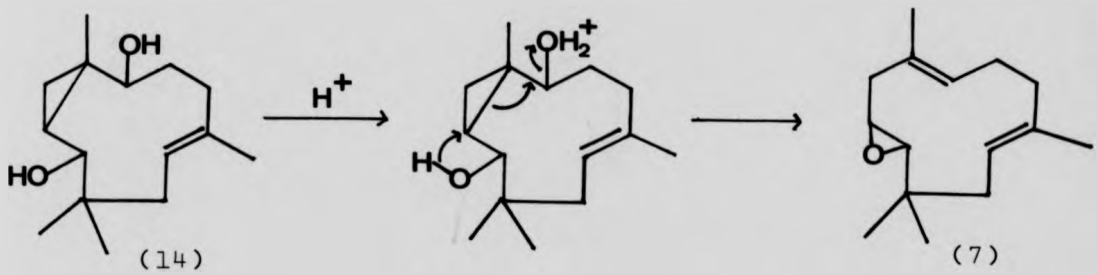


Figure 2

Possible mechanisms of formation were considered and these are illustrated in Figure 3.

Mechanism (a) in Figure 3 involves coordination of one tungsten with two epoxides of the starting material to give an intermediate complex which eventually could lead to the diol (14). The driving force behind the deoxygenation reaction is

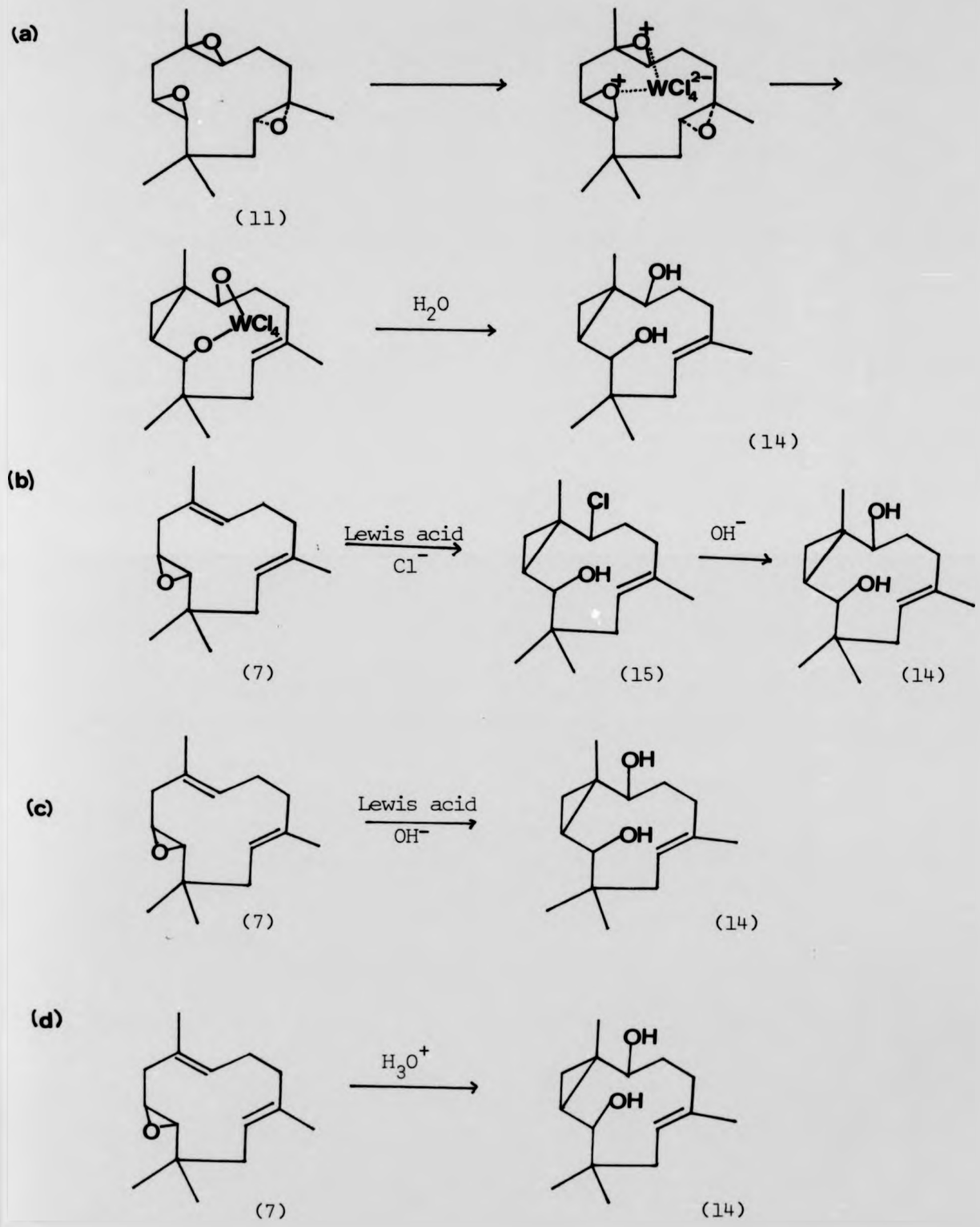

(a)
(11)
WCl_4^{2-}
WCl_4
H_2O
OH
OH
(14)
(b)
(7)
Lewis acid
Cl^-
Cl
OH
(15)
OH^-
OH
OH
(14)
(c)
(7)
Lewis acid
OH^-
OH
OH
(14)
(d)
(7)
H_3O^+
OH
OH
(14)

Figure 3

the formation of the strong W=O bond and so mechanism (a) is unlikely since it seems improbable that two single W-O bonds could survive until hydrolysis had been carried out.

An alternative mechanism (b) involved the action of a Lewis acid, possibly a tungsten species (Figure 1), upon the 4,5-epoxide (7), opening the epoxide and inducing cyclisation to form the intermediate chlorohydrin (15). The presence of lithium chloride in the reaction must be considered and the chloride could act as an external nucleophile, quenching the carbonium ion formed at C-1 after formation of the cyclopropyl ring. In the subsequent alkaline work-up conditions, hydroxide displaces the chloride to yield the diol (14). Alternatively the presence of hydroxide (formed by action of strong base on water) as the external nucleophile in the deoxygenation reaction (mechanism (c)) would give the diol (14) directly.

Mechanism (d) suggests that perhaps the diol (14) was an artefact of hydration, the reaction taking place not in the deoxygenation mixture, but on the column during purification. Wet, acidic silica could possibly induce protonation of the epoxide (7) followed by opening of the epoxide, cyclisation to give the cyclopropyl ring and quenching of the C-1 carbonium ion with water.

Neither the mechanism of formation of the diol (14) nor whether it was formed in the deoxygenation reaction or in the subsequent work-up was solved by Mlotkiewicz and Carman. Throughout this project experiments have been carried out in order to solve this problem.

Although the diol (14) was not found in the

deoxygenation conditions (by analysis directly from the reaction flask) when the reaction was carried out in the rigorously dry procedure used by Mlotkiewicz, traces of the diol could be observed when water was not so carefully excluded. The diol (14) was also isolated from these conditions where water had not been so carefully removed.

Experiments were carried out in an attempt to provide evidence for mechanism (b) of Figure 3, involving the chlorohydrin (15). Although it was difficult to mimic the supposed Lewis acid, humulene-4,5-epoxide (7) was stirred in the presence of aqueous lithium chloride, then worked up under normal alkaline conditions. However, no diol (14) was observed and this, coupled with the fact that the diol has been found in the deoxygenation reaction prior to work-up, tends to rule out mechanism (b).

The reaction of humulene-4,5-epoxide (7) in the presence of a variety of grades of wet silica were studied but no diol (14) was formed and the 4,5-epoxide (7) remained unchanged. Treatment of humulene-4,5-epoxide (7) with the weak Lewis acids, zinc chloride, magnesium bromide and lithium perchlorate in solvents which had been saturated with water, failed to produce the desired diol (14).

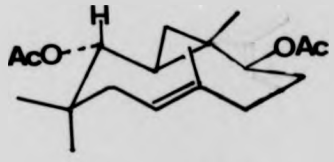
However, on examining the reaction solution of epoxide (7) with boron trifluoride etherate in wet diethyl ether by analytical tlc, it appeared that a large amount of the diol had formed, but on work-up with saturated sodium bicarbonate solution and isolation of the product, only the starting epoxide (7) was present. This suggested that the diol (14) was being formed on the analytical tlc plate and not in the reaction

solution.

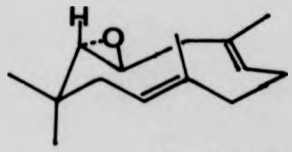
This prompted the study of the reaction of humulene-4,5-epoxide (7) in the presence of boron trifluoride etherate, water and silica. The active Lewis acid in this situation is obviously difficult to ascertain, but is likely to be a hydrate of boron trifluoride[13] bound to the surface of the silica.

Many variations were carried out, all producing different proportions of the diol (14), but the most successful technique involved applying the epoxide (7) to a preparative tlc plate followed by boron trifluoride etherate and water, then carrying out chromatography immediately by elution of the plate with diethyl ether. The diol (14) was removed from the plate and proved to be identical to the authentic material.

Very recently, Matsumoto et al.[14] have reported that treatment of humulene-4,5-epoxide with boron trifluoride/acetic anhydride yielded the diacetate (16). The X-ray crystallographic analysis revealed that the cyclopropane ring is trans-fused which suggests that the transannular cyclisation occurs from the CC conformer (17) of epoxide (7).



(16)



CC (17)

The formation of the diol (14) under the conditions described and the work of Matsumoto et al. tends to rule out mechanism (a) in Figure 3 which requires an intermediate tungsten

complex. The small amount of diol (14) produced in the deoxygenation reaction must surely be formed from humulene-4,5-epoxide (7) by action of a Lewis acid (possibly a tungsten species as in Figure 1). The quenching of the carbonium ion formed at C-1 must be by traces of hydroxide ion introduced by water (mechanism (c)).

A synthesis of the diol (14) was attempted by the reaction of the bisepoxide (18) with lithium in ethylamine,[15] hoping that (14) may be formed by the mechanism described in Figure 4.

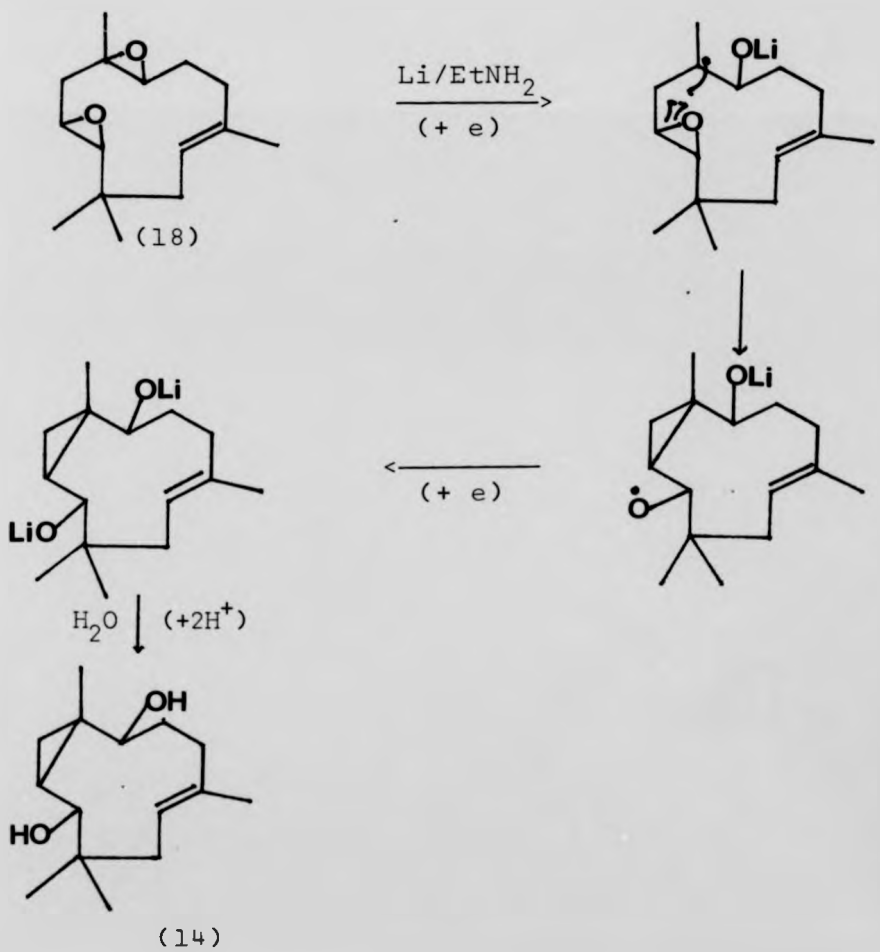
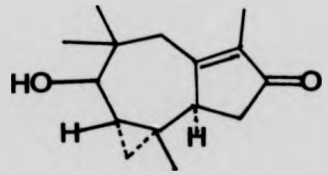


Figure 4

Humulene-1,2-4,5-bisepoxide (18)[5] was formed by monoepoxidation of humulene-4,5-epoxide (7) and subjected to conditions of dissolving metal reduction with lithium in ethylamine. The reaction was followed by analytical tlc and although a number of polar products were produced from the bisepoxide (18), none had the polarity of the desired diol (14).

The synthesis of the alcohol (19), which constitutes the sesquiterpenoid ester, 8β-angeloyloxy-senoxyri-4-en-3-one (8)[4] was thought possible from compound (5), which is the tetrasubstituted olefin formed as the major product from rearrangement of humulene-4,5-epoxide (7)[2] with boron trifluoride etherate. This synthesis has formed the second part of the research in this area.[16]



(19)

In order to synthesise this alcohol (19), a method of protecting the hydroxyl function of compound (5) followed by selective allylic oxidation was sought. This was achieved by initial acetylation of (5) with acetic anhydride in pyridine to yield the ester (20) (Figure 5). The acetate (20) was then subjected to an excess of Collins' reagent generated *in situ* in dichloromethane solution,[17,18] to yield the acetoxy-ketone (21) (27% isolated yield). The allylic oxidation was unsuccessful

with pyridinium chlorochromate under similar reaction conditions.[19]

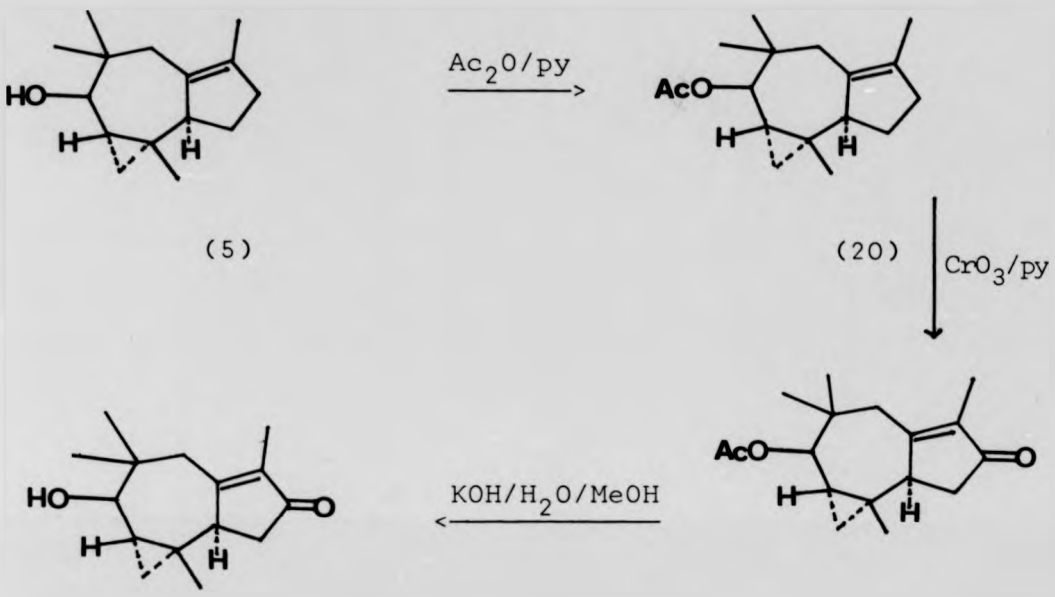


Figure 5

The spectral data were in accord with structure (21), λ_{max}^{EtOH} 240nm (ε 10,200), (λ_{calc}^{EtOH} 241nm)[20]; $\bar{\nu}$max 1730, 1700, and 1640 cm^{-1}; δ($CDCl_3$,ppm), 0.75-1.0 (3H,m), 0.8 (3H,s), 1.0 (3H,s), 1.03 (3H,s), 1.70 (3H,bs), 2.04 (3H,s), 2.25-2.8 (5H,m), and 4.7 (1H,d, J = 9 Hz).

The acetate (21) was then hydrolysed with methanolic potassium hydroxide to give the keto-alcohol (19) which proved to be identical to the hydrolysis product of (8), by infra-red,

nuclear magnetic resonance and mass spectroscopy (the synthesised compound (19) is of course racemic whereas the natural product is optically active). Professor Bohlmann of the University of Berlin kindly carried out the comparison of the 270 MHz nmr spectra of synthetic (19) and the hydrolysis product of (8).

The recent synthesis of africanol (1) and the africene (2) from the alcohol (5) (Figure 6) by Matsumoto et al.[14], completes the biomimetic syntheses of these natural products containing the africane structure.

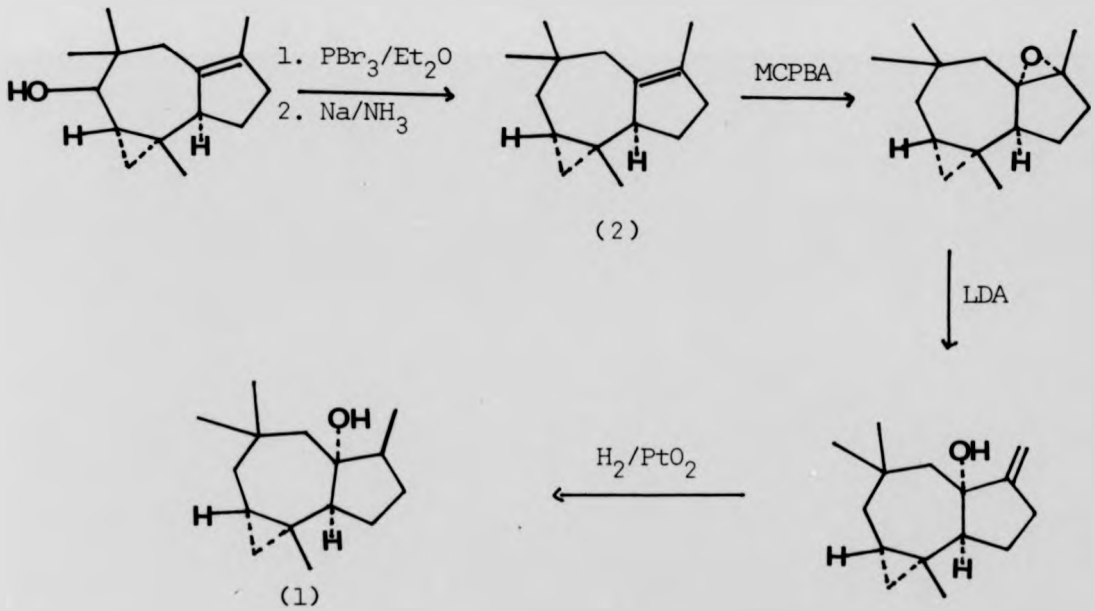


Figure 6

The same group[14] have synthesised the naturally-occurring compound bicyclohumulenone (22)[21] from the diacetate (16) and an outline of this synthesis is shown in Figure 7.

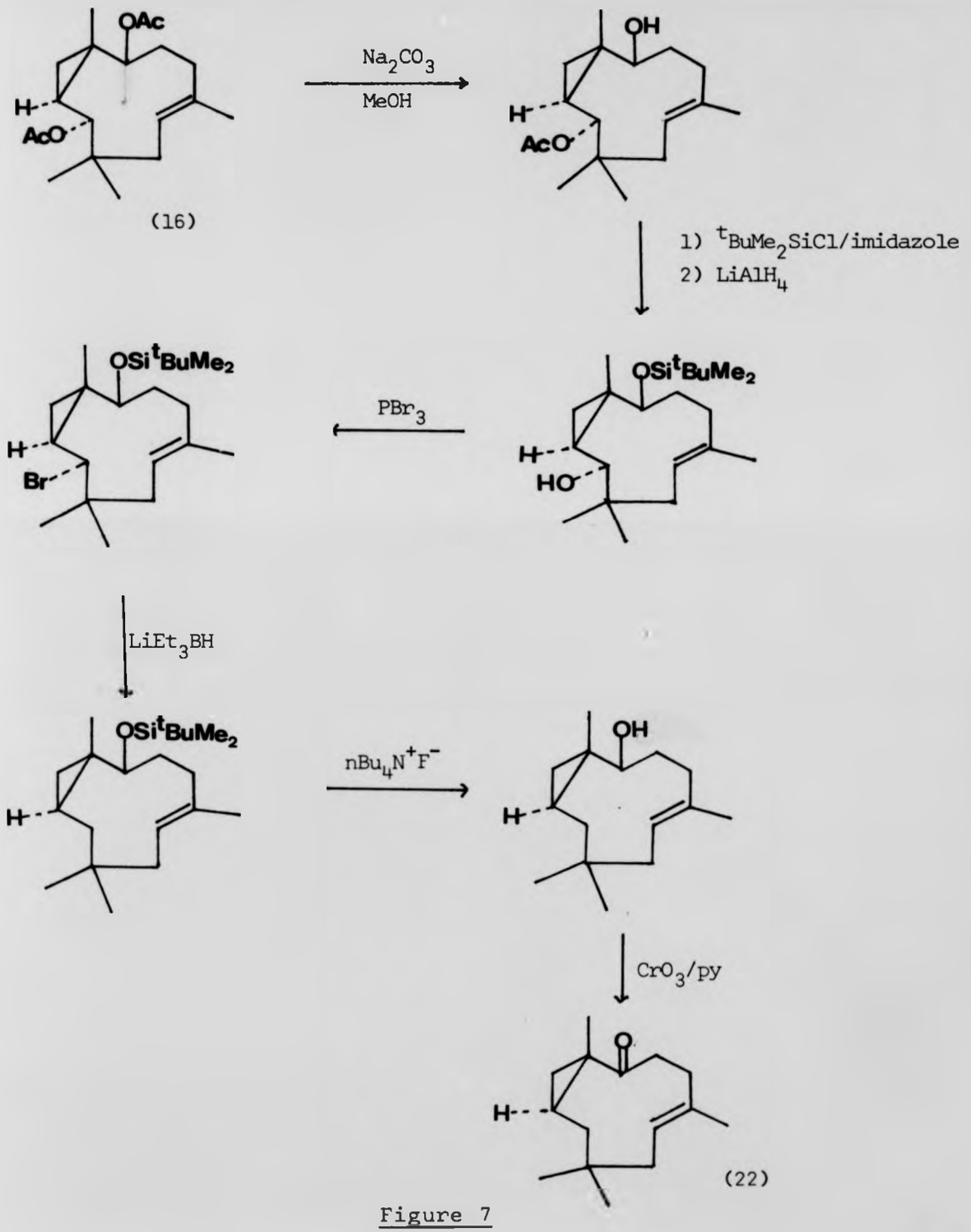
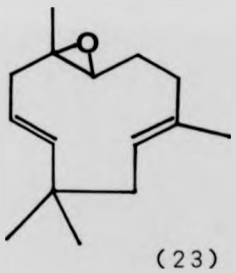

OAc
H
AcO
(16)
Na_2CO_3
MeOH
OH
H
AcO
1) $^tBuMe_2SiCl$/imidazole
2) $LiAlH_4$
OSi^tBuMe_2
H
Br
PBr_3
OSi^tBuMe_2
H
HO
$LiEt_3BH$
OSi^tBuMe_2
H
$nBu_4N^+F^-$
OH
H
CrO_3/py
O
H
(22)

Figure 7

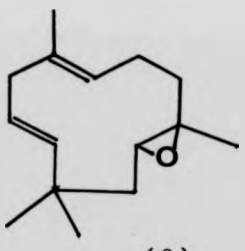
CHAPTER 2

REARRANGEMENT OF HUMULENE-8,9-EPOXIDE

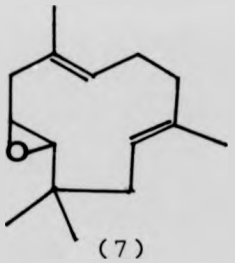
The three monoepoxides of humulene (23), (9) and (7) are all naturally-occurring and may serve as *in vivo* precursors of other bicyclic and tricyclic sesquiterpenoids. As previously mentioned, the *in vitro* cyclizations of two of these monoepoxides have been studied. Acid-catalysed cyclization of the 1,2-epoxide (23) leads to two principle tricyclic diols (24) and (25)[22,23] (see Introduction) and rearrangement of the 4,5-epoxide has been discussed in Chapter 1. In the light of these interesting results, the acid-catalysed rearrangement of humulene-8,9-epoxide (9) was studied.



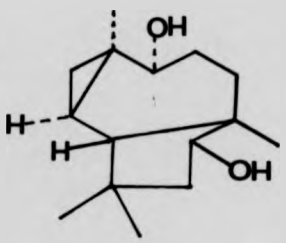
(23)



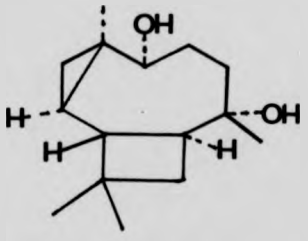
(9)



(7)



(24)



(25)

Formation of the 8,9-epoxide (9) from humulene, requires the functionalisation of a less reactive double bond. The epoxidation of humulene with one equivalent of *m*-chloroperoxybenzoic acid in chloroform at room temperature as carried

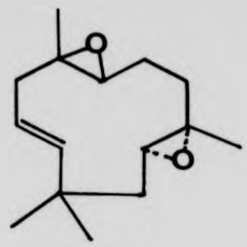
out by A. Sattar,[24] produced the three monoepoxides 1,2-epoxide (23), 8,9-epoxide (9) and 4,5-epoxide (7) in the approximate ratio 16:3:1 (from glc).

The monoepoxidation of humulene was repeated using a two-phase solvent system (sodium bicarbonate solution and dichloromethane)[7] at room temperature and this procedure produced the epoxides in approximately the same ratio as above (15:3:1) (calculated from isolated yields). Decreasing the temperature to 0°C increased the proportions of 8,9 epoxide (9) and 4,5-epoxide (7) relative to 1,2-epoxide (23) giving (23), (9) and (7) in the ratio 11:3:1. The use of chloroform as the organic solvent gave a similar composition of epoxides.

It is known[25,26] that the use of relatively polar solvents such as dichloromethane and chloroform increases the effective steric bulk of the peroxyacid in the transition state, so it was reasoned that using a less polar solvent, such as carbon tetrachloride, should decrease the selectivity of the epoxidising reagent. Thus it was found that reaction in carbon tetrachloride and sodium bicarbonate solution at 0°C yielded the most favourable proportion of 8,9-epoxide (9) where the monoepoxides were produced in the ratio 10:4:1 [compounds (23):(9):(7)].

An alternative approach to producing the 8,9-epoxide (9) is to carry out selective deoxygenation of the known humulene-1,2-8,9-bisepoxide (26) and this had been already successfully achieved by A. Sattar[5] using tungsten hexachloride and n-butyl lithium.[9,10] However, these reagents are very expensive, so an alternative reagent for selective deoxygenation

was sought.



(26)

Although there are many literature methods for deoxygenation of epoxides to produce olefins,[27] most are nonstereospecific and again involve expensive reagents requiring prolonged reaction times. The readily available reagents trifluoroacetyl iodide with sodium iodide, however, are known to generate olefins of the same geometry as the epoxide in high yields *via* the mechanism given in Figure 8.[28]

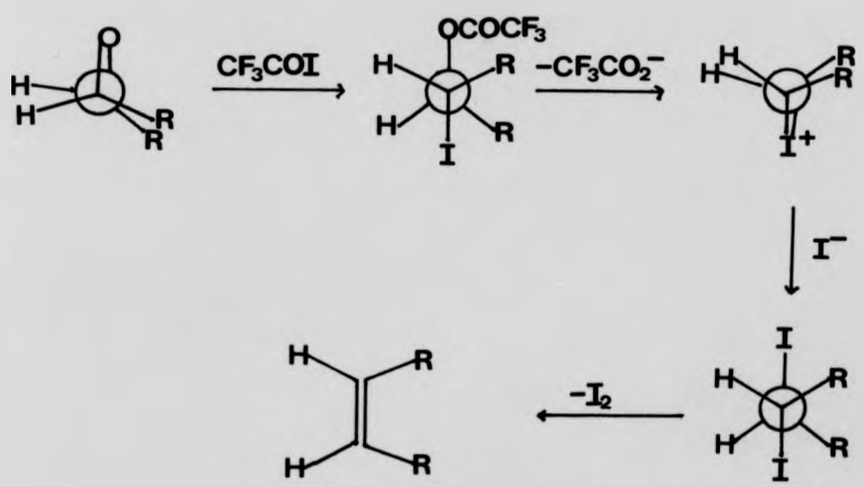


Figure 8

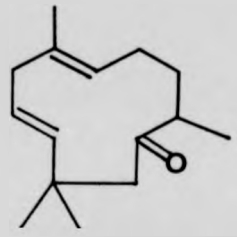
Deoxygenation reactions were carried out on humulene-1,2-epoxide (23) and the bisepoxide (26) using this method and although the 1,2-epoxide (23) was converted to humulene (10), selective deoxygenation of the bisepoxide (26) was not achieved. Similar results were obtained using diphosphorus tetraiodide.[27]

Thus, a sufficient quantity of the 8,9-epoxide (9), was synthesised by monoepoxidation of humulene under the conditions most favourable for its formation, as described above.

A study of the rearrangement of the 8,9-epoxide (9) in protic and Lewis acids was undertaken. Small scale reactions with p-toluenesulphonic acid, acetic acid, trifluoroacetic acid, sulphuric acid, boron trifluoride etherate, aluminium and tin (IV) chloride were studied with respect to solvent, temperature, concentration and reaction time.

The epoxide (9) demonstrated a remarkable stability in protic acids. High temperatures ($\sim 70^{\circ}C$) were required to induce rearrangement and a plethora of compounds resulted (> 20 from analytical tlc). Since large quantities of compound (9) were not easily produced, conditions favouring a narrower range of products were sought.

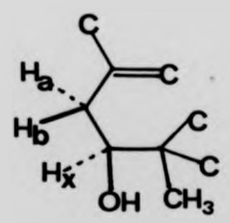
The presence of a Lewis acid in a suitable solvent produced this desired effect. The 8,9-epoxide (9), on treatment with boron trifluoride etherate in toluene produced the new ketone (27) at room temperature (circa 50% yield).



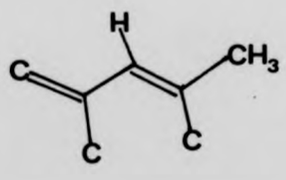
(27)

This ketone exhibited $\bar{\nu}_{max}$ 1695 cm^{-1} and the nmr was in good agreement with this structure 2.5-3.1 ppm integrating for five protons (2 x H-3, 2 x H-7 and 1 x H-9) and 1.2 ppm (3H,d,J = 9 Hz) for the new secondary methyl group. The H-1 proton (4.8 ppm) is shielded in comparison with the starting epoxide (9) and molecular models suggest that the ketone at C-8 could be responsible for this shielding. There are many literature analogies for this epoxide-ketone conversion in similar reaction conditions.[29]

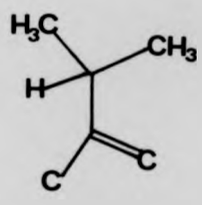
The most interesting results have stemmed from the reaction of the epoxide (9) with tin (IV) chloride. At low temperature (- 60°C) in chloroform solution using a fifteen molar excess of tin (IV) chloride, the epoxide is rapidly converted to one major alcohol, $C_{15}H_{24}O$, in 25% yield (a number of hydrocarbons are also produced in the reaction). The alcohol has the spectral data: λ_{max}^{EtOH} 245nm (ε = 11,280); $\bar{\nu}_{max}$ 3620 and 1070 cm^{-1}; $\delta(CDCl_3,ppm)$ 0.89 (3H,s), 0.91 (3H,d,J=7Hz), 0.94 (3H,d,J=7Hz), 1.76 (3H,bs), 2.3-2.8 (5H,m), 3.83 (1H,X part of an ABX system, $J_{AX} \sim J_{BX} \sim$ 9Hz), and 5.90 (1H,bs). Simplification of the nmr spectrum was achieved in the presence of $Eu(fod)_3$ and with double irradiation experiments. This, with the aid of the uv data enabled the part structures (A) - (C) to be constructed.



(A)

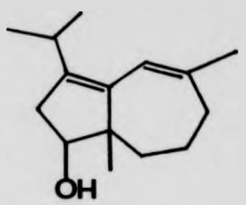


(B)

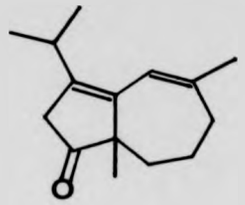


(C)

With a possible mechanism in mind, these part structures were assembled to give structure (28) as the rearrangement product. Oxidation of (28) with pyridinium chlorochromate[19] gave the corresponding ketone (29) ($\bar{\nu}_{max}$ 1745 cm^{-1}).

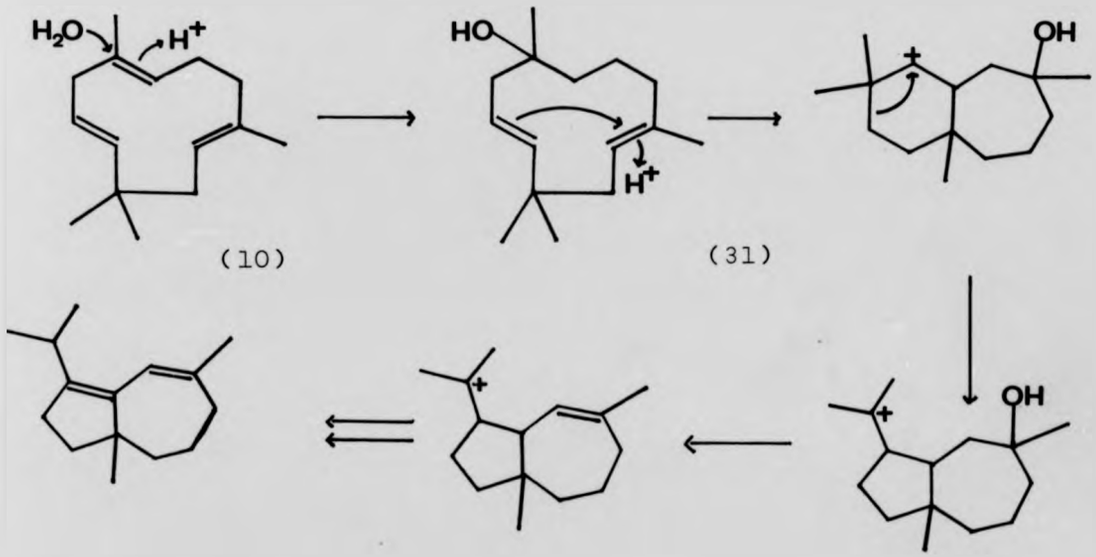


(28)



(29)

The structure of (28) is closely related to that of the diene (30) obtained from humulene (10) itself upon treatment with various acid catalysts (Figure 9). Humulol (31) is the initial product which undergoes subsequent rearrangement to give the bicyclic diene (30).[30-32]

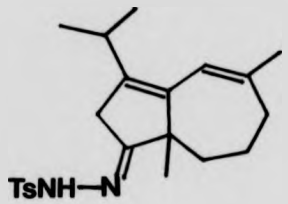


(10) (31)

(30)

Figure 9

To confirm the proposed structure, the alcohol (28) was converted to the hydrocarbon (30) and a comparison made with authentic material produced by acid-catalysed rearrangement of humulene (10). The ketone (29) was reacted with tosylhydrazine to give the tosylhydrazone derivative (32) which was reduced to the hydrocarbon (30) with sodium borohydride in dioxan.[33]

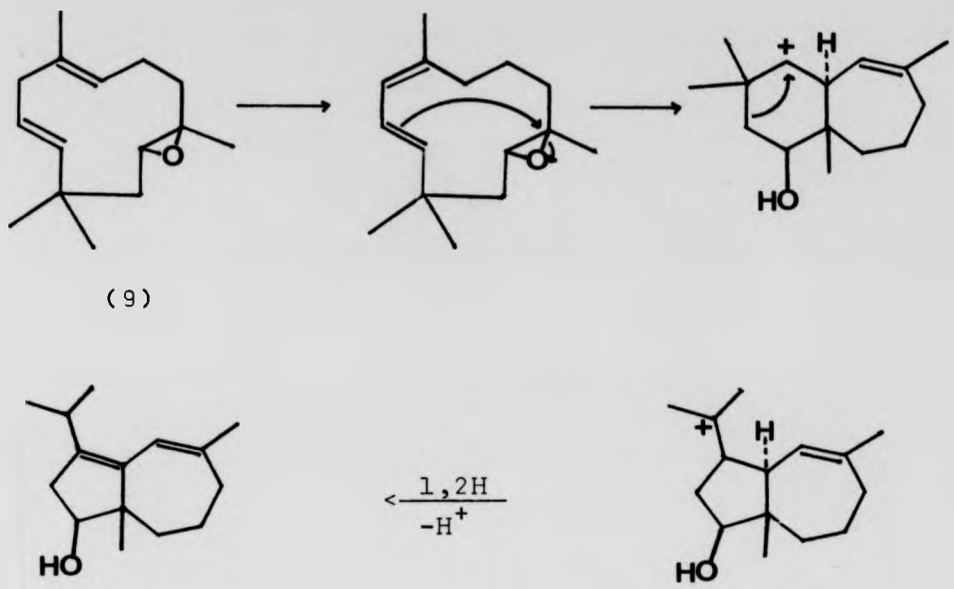


(32)

The hydrocarbon (30) was derived from humulene and the material obtained by reduction of the tosylhydrazone proved to be identical by comparison of nmr, ir and uv spectra, by analytical tlc and glc and by glc-mass spectrometry.

A probable mechanism for the formation of the alcohol is shown in Figure 10. Although it may seem possible that cyclization could occur from the 8,9-epoxide directly, molecular models indicate that participation of the $\Delta^{4,5}$ double bond in the opening of the 8,9-epoxide can best be achieved after either isomerization or hydration of the $\Delta^{1,2}$ double bond.

In partial support of this hypothesis, humulol (31) was converted to the hydroxy-epoxide (33) by epoxidation with one equivalent of m-chloroperoxybenzoic acid. Treatment of (33) with tin (IV) chloride under identical conditions as used for

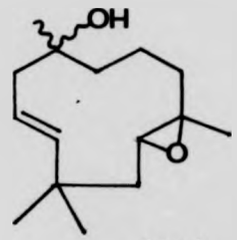


(9)

(28)

Figure 10

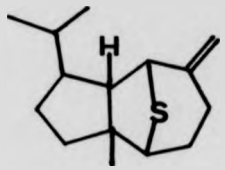
the 8,9-epoxide (9), gave the alcohol (28) in better yield (40%). The formation of (28) from the hydroxy-epoxide (33) directly parallels the formation of the diene (30) from humulol (31) (Figure 9).



(33)

Although the alcohol (28) is not a known naturally-occurring compound, it is interesting to note that the carbon

skeleton embodied in (28) is the same as that of mintsulphide (34), a recently identified constituent of peppermint oil.[34]



(34)

CHAPTER 3

PREPARATION AND REACTIONS OF 4,5-EPOXYISOHUMULYL METHYL ETHER. ISOLATION OF A NOVEL CYCLIC ETHER.

An important feature in the proposed cyclization pathways of humulene, is that the protoilludyl cation (35) plays a pivotal rôle in the biogenetic scheme. The routes leading to the protoilludoids, illudoids (36) and pentalenoids (37) are illustrated in Figure 11.

A biomimetic synthesis of the protoilludane (35) and pentalenane skeleton (37) was thought possible from humulene (10). Initiation of the cyclization is required at the $\Delta^{4,5}$ double bond of humulene, followed by participation of the $\Delta^{8,9}$ double bond. Epoxidation of the $\Delta^{4,5}$ double bond was considered and the opening of the epoxide ring in acid conditions thought an ideal method to initiate cyclization. The $\Delta^{1,2}$ double bond would have to be temporarily removed to prevent its participation in the cyclization (as occurs in the formation of the africane skeleton).[2] This would also facilitate the interaction of the $\Delta^{8,9}$ double bond in the opening of the 4,5-epoxide by removing two sp^2 centres within the ring, so increasing its conformational mobility. Cyclization with the $\Delta^{1,2}$ double bond present would also produce a strained trans-cyclooctene ring if the desired cyclization was successful.

The necessity of removing the trans-$\Delta^{1,2}$ double bond in order that the desired cyclization may take place is borne out by the work of Matsumoto et al.[35] in the cyclization of humulene with mercuric acetate (Figure 12). Before cyclization takes place, oxymercuration occurs across the $\Delta^{1,2}$ double bond

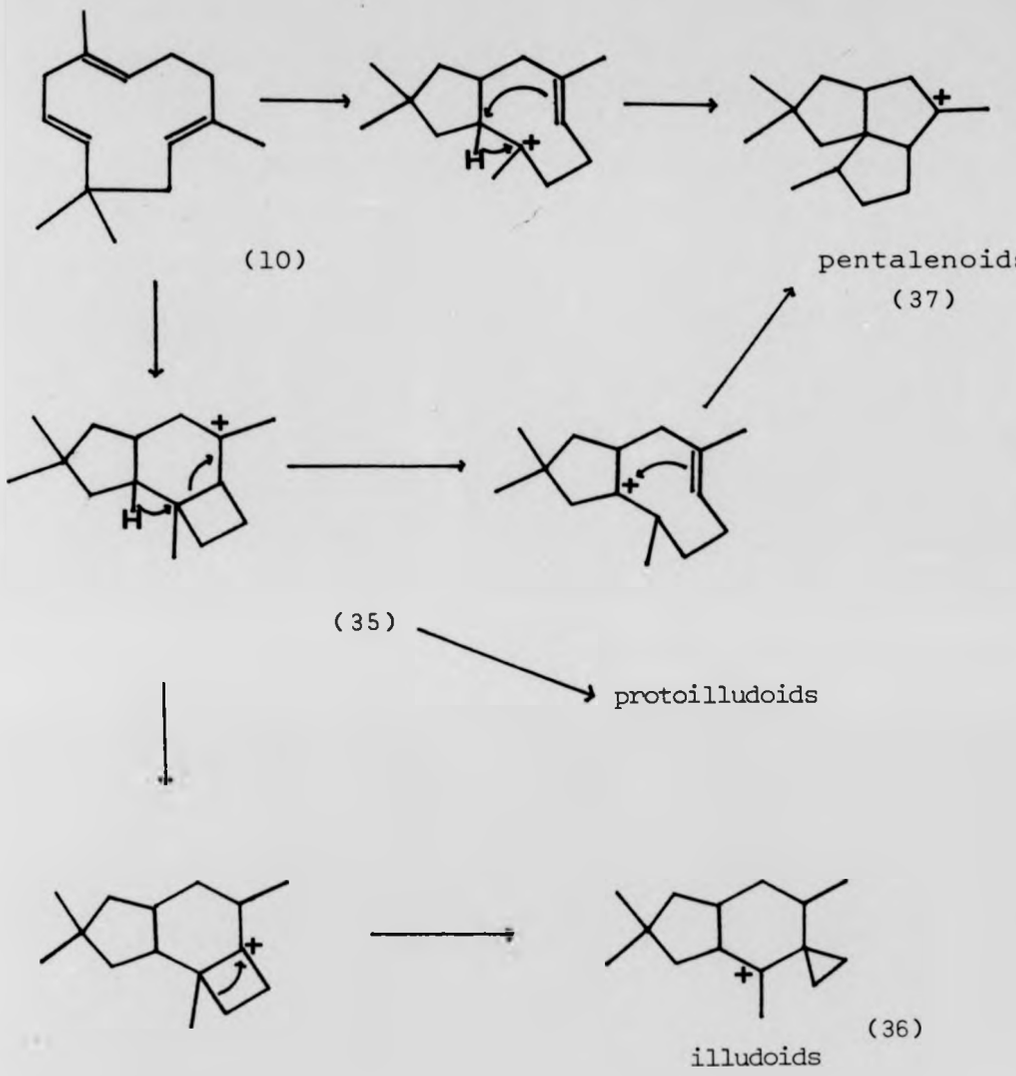


Figure 11

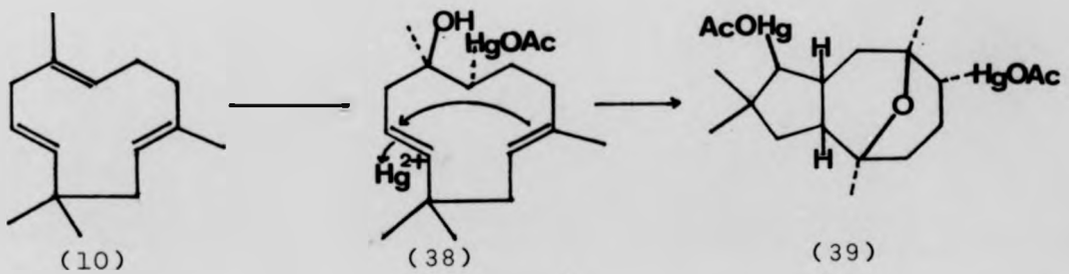
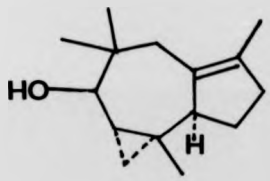


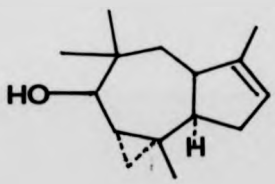
Figure 12

to give (38) and subsequent electrophilic addition to the $\Delta^{4,5}$ double bond by mercury, promotes cyclization yielding (39).

Some preliminary work in this area was carried out in this department by J. A. Mlotkiewicz.[3] The first approach considered was to complex selectively the $\Delta^{1,2}$ double bond to a metal as a π-olefin complex[36] and then to promote cyclization of the 4,5-epoxide (7) by participation of the $\Delta^{8,9}$ double bond. Complexes were formed with silver, iron and copper ions but on reaction with Lewis acid, the alcohols (5) and (6) were produced, which result from participation of the $\Delta^{1,2}$ double bond.



(5)



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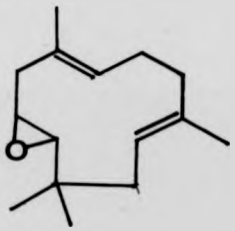
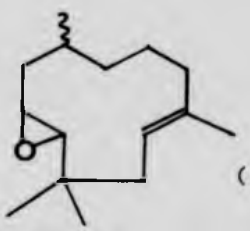
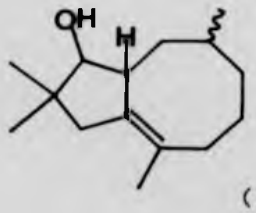


(7)

Conversion of the bond between C-1 to C-2 from sp^2 to sp^3 character gives enhanced flexibility of the ring system and allows greater mobility of the $\Delta^{8,9}$ double bond. As a model study, J. A. Mlotkiewicz[3] synthesised 1,2-dihydrohumulene-4,5-epoxide (40) and subjected this compound to acid catalysed rearrangement. There were problems encountered with this experiment in that (40) existed as an inseparable mixture of diastereoisomers (each of which exist as a racemate) but cyclization of this mixture appeared to give the desired bicyclic alcohol (41) (as a mixture of epimers).

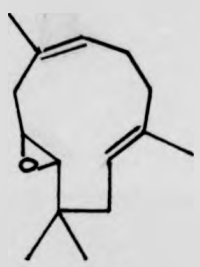


(40)

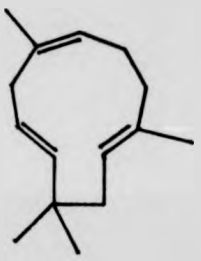


(41)

An alternative strategy considered was the isomerization of the $\Delta^{1,2}$ double bond to the cis-configuration and it was hoped that the 4,5-epoxide (42) may cyclize in the desired manner. Although sp^2 centres are retained at C-1 and C-2, the conformational mobility of the ring system is enhanced by the cis-configuration, allowing greater interaction of the $\Delta^{8,9}$ double bond with the 4,5-epoxide than in the trans-configuration. The preparation of isohumulene (43) is discussed in Chapter 4.

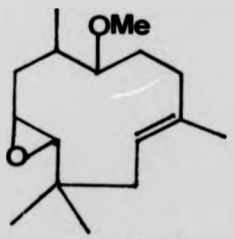


(42)



(43)

The strategy adopted was to remove temporarily the $\Delta^{1,2}$ double bond and to replace this bond after cyclization had been achieved. Hydration of the $\Delta^{1,2}$ double bond (in an anti-Markownikoff sense), followed by protection of the hydroxyl group at C-1 (as the methyl ether) seemed a reasonable solution and enabled the trisubstituted bond to be reintroduced after cyclization. Thus, epoxide (44) was the desired compound for cyclization study.



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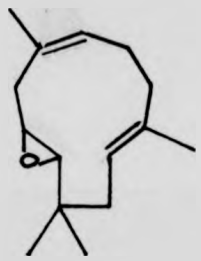
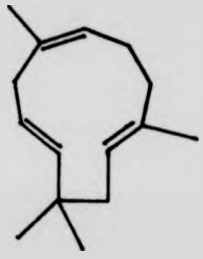


(42)



(43)

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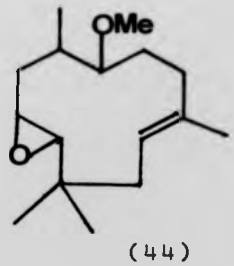


(44)

The choice of the methyl ether as the protecting group for the alcohol requires explanation. Although the methyl group has been considered too stable to be used for the routine protection of alcohols, the recent introduction of the reagent, iodotrimethylsilane,[37] for the hydrolysis of aliphatic and aromatic ethers (in high yields) now makes the dealkylation of methyl ethers a simple and efficient process.

It was hoped that on treatment with a suitable acid, compound (44) would cyclize to give C_4-C_9 bond formation and produce (45) (where the position of the olefinic bond was uncertain) (Figure 13).

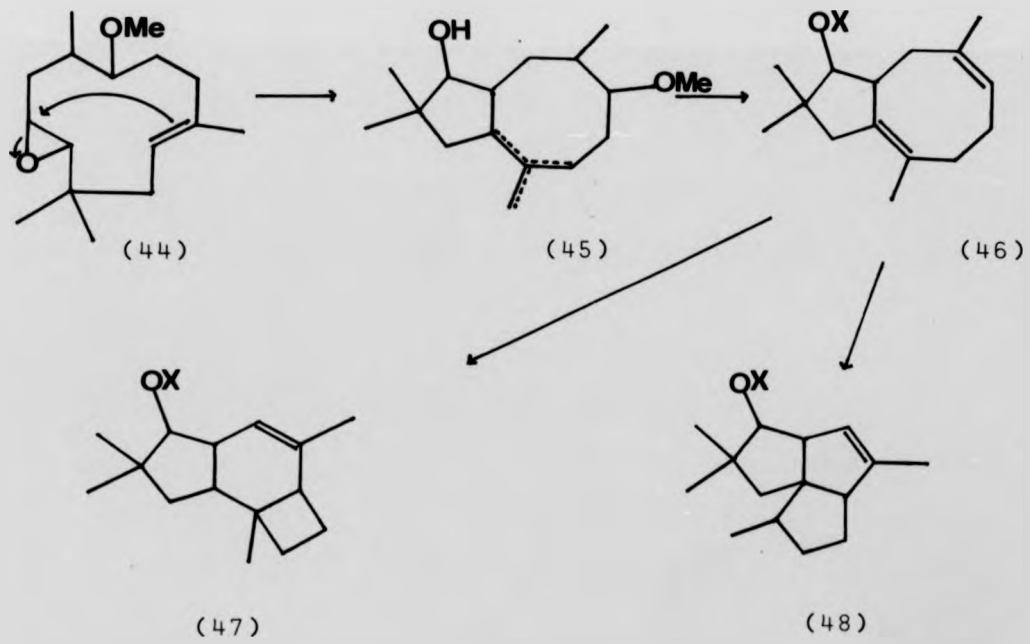
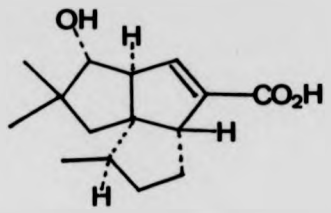


Figure 13

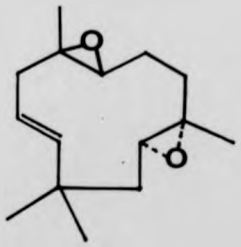
Protection of the hydroxyl group on the cyclopentane ring, demethylation and dehydration would reintroduce the original $\Delta^{1,2}$ double bond. Isomerization of the other double bond to the

tetrasubstituted position would yield the diene (46). It was hoped that treatment of this diene (or of a monoepoxide) under suitable conditions would produce compounds possessing the protoilludane skeleton (47) or the pentalenane skeleton (48) and this seemed reasonable considering the biosynthetic analogies (Figure 11). It is interesting to note that the synthesis of pentalenic acid (49)[38] appeared possible from compound (48), by oxidation of the vinylic methyl group.



(49)

Various strategies were considered for the synthesis of compound (44). It was thought that (44) may be formed by selective hydroboration-oxidation of humulene-4,5-epoxide (7) at the $\Delta^{1,2}$ double bond, followed by methylation. Although boranes are known to react with epoxides,[39] the reaction is comparatively slow in comparison to the reaction with olefins. Indeed, the hydroboration of the bisepoxide (26) has been successfully achieved to produce the alcohol (50).[5]



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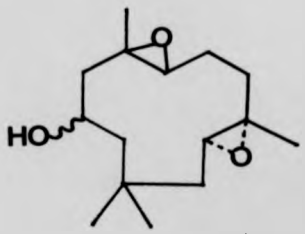
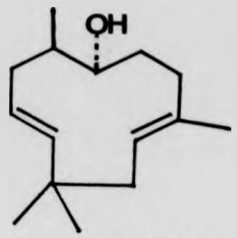


(50)

Hydroboration-oxidation reactions with several hydroborating reagents (borane-tetrahydrofuran,[40] 9-borabicyclo[3.3.1]nonane,[41] borane-methyl sulphide[42] and catecholborane[43]) were carried out on humulene-4,5-epoxide (7), to give a plethora of products. However, the reaction with humulene (10) itself produced isohumulol (51)[32] as the major product (60%).



(51)

An alternative approach was to synthesise isohumulol (51) and then carry out monoepoxidation hoping that some of the 4,5-epoxide (52) may be formed (Figure 14). There was a precedent for electrophilic attack occurring at the 4,5-double bond in that cyclisation of (38) (Figure 12) occurs by initial addition of the mercuric ion at C-5.[35]

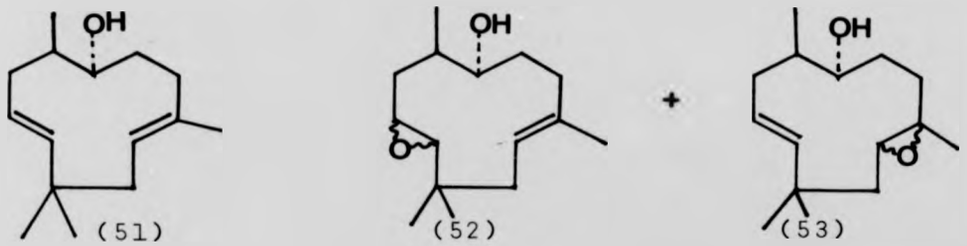


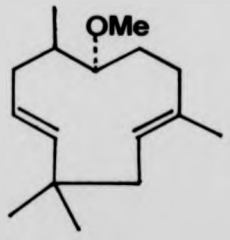
Figure 14

The formation of isohumulol (51) had previously only been carried out by lithium-ethylamine reduction of humulene-1,2-epoxide (23).[32] The alcohol (51) was prepared by this method

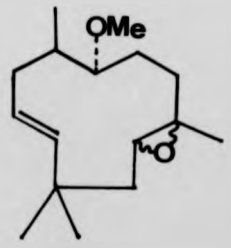
or by hydroboration-oxidation of humulene with borane-tetrahydrofuran. Monoepoxidation of isohumulol (51) with m-chloroperoxybenzoic acid,[7] trifluoroperoxyacetic acid[44] and benzonitrile-hydrogen peroxide,[45] all produced the 8,9-epoxide (53) exclusively. The 8,9-epoxide (53) was characterised by its nmr spectrum: $\delta(CDCl_3,ppm)$ 4.9-5.1 (2H,m, for 1 x H-4 and 1 x H-5), 2.6 (1H,m, for 1 x H-8), and 1.0 (3H,s, for the new methyl signal of the 8,9-epoxide).

The solution to the functionalisation of the less reactive, disubstituted, $\Delta^{4,5}$ double bond appeared to be by formation of the bisepoxide, then selective deoxygenation of the 8,9-epoxide.

The hydroxyl function of isohumulol (51) was protected by formation of the methyl ether by reaction with n-butyllithium and a large excess of methyl iodide to produce compound (54) (75% isolated yield). Methylation was unsuccessful with both sodium hydride/methyl iodide[46] and imidazole/methyl-iodide in dimethylformamide,[47] although cyclohexanol was converted to the corresponding methyl ether under these conditions. Monoepoxidation of the methyl ether (54) produced only the 8,9-epoxide (55).



(54)



(55)

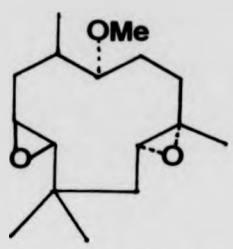
Reaction of the methyl ether (54) with two equivalents of m-chloroperoxybenzoic acid in dichloromethane and sodium bicarbonate solution[7] produced three of the four possible diastereoisomers of the bisepoxide (56)-(59) (each diastereoisomer exists as a racemate).

It should of course be noted that it is not completely correct to denote the substituents in terms of cis and trans since the undecane ring allows considerable conformational mobility. However, where the conformation of the ring is such that it almost lies in the plane of the paper (as drawn in (56)-(59), with H-1, H-5 and H-8 protons pointing towards the centre of the ring) the substituents have the relative stereochemistry depicted.

One of these isomers (isomer A) had a markedly different polarity on analytical tlc (Rf 0.25 in 25% ethyl-acetate/petrol ether 60-80^{o}) and as a consequence could be separated by chromatography on silica. The other two isomers (isomers B and C) although partially resolved on analytical tlc (Rf 0.43 and 0.45) proved to be inseparable on a preparative scale and consisted of a 1:1 mixture (as estimated from the nmr spectrum). The bisepoxides A, B and C were produced in the approximate ratio 2:1:1 under these conditions.

The epoxidation conditions were varied with respect to organic solvent and temperature and the composition of the bisepoxides compared (from isolated products) but the three isomers A, B and C were always produced in the same ratio. However, the rate at which the organic and aqueous phases were mixed, was critical. The two phases were normally mixed by

means of a magnetic stirrer and fast stirring by this method gave the mixture of isomers A, B and C in the ratio 2:1:1. Rapid mixing with a mechanical stirrer (which effectively produced an emulsion), resulted in the formation of isomer A as the major product with only a trace of isomers B and C (circa 20:1:1).



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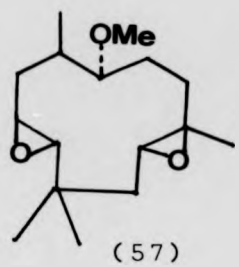
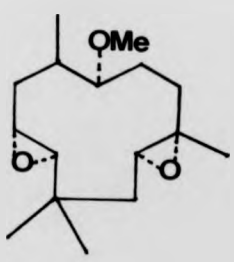
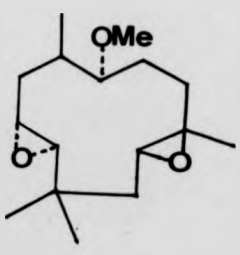


(57)



(58)



(59)

The epoxidation presumably involves the initial rapid oxidation of the $\Delta^{8,9}$ double bond, followed by a slower, rate determining oxidation of the $\Delta^{4,5}$ double bond. Under the conditions of vigorous stirring, epoxidation is much more stereoselective and this is most likely related to the nature of the peroxyacid in the transition state.[25,26]

If one assumes that the conformational barrier is substantially lower than the reaction barrier of epoxidation (Curtin-Hammett principle[48]) the ratio of the diastereoisomeric products will be determined by the relative free energies of the transition states.[49] With this approach the change in the ratio of the products is due to the change in the relative energies of the transition state.

If the conformational barrier is substantially higher than the reaction barriers, the ratio of products will be related to the conformational equilibrium of the starting compound. It should be noted that in the past there has been a definite connection with choice of reaction conditions and conformation of the substrate in solution in relation to the oxidation of squalene.[50]

The free energy surface of this epoxidation reaction probably lies between these two limiting cases where the product ratio is dependent upon both the equilibrium population of the conformations and the relative free energies of the transition states. Under conditions of vigorous stirring, both the conformational equilibrium and the relative activation energies for epoxidation may change in favour of the formation of isomer A.

The selective deoxygenation of the bisepoxide A and the mixture of isomers B and C, was carried out using n-butyl lithium and tungsten hexachloride.[9,10] The reaction with bisepoxide A produced the 4,5-epoxide D and the deoxygenation of the mixture of B and C yielded the 4,5-epoxide E which had the opposite configuration. These epoxides had virtually identical spectral characteristics, but as with the bisepoxides,

had quite different Rf values on analytical and preparative tlc, the more polar bisepoxides producing the more polar monoepoxide D (Rf D = 0.52, 25% ethyl acetate/petrol ether 60-80° and Rf E = 0.69).

The 4,5-epoxide stereoisomers D and E were treated with boron-trifluoride etherate and tin(IV) chloride under varying temperature and molar ratio of Lewis acid. The isomer D, rapidly produced a major alcohol (50%), $C_{16}H_{28}O_2$, with two mole equivalents of boron-trifluoride etherate in diethyl ether at room temperature. Isomer E was completely unreactive in these conditions (even after 48 hours) and required a large excess of tin(IV) chloride in chloroform and long reaction times to bring about rearrangement. Although epoxide E produced a multitude of products under these conditions, the alcohol resulting from rearrangement of D was not one of these compounds (as determined by analytical tlc and nmr).

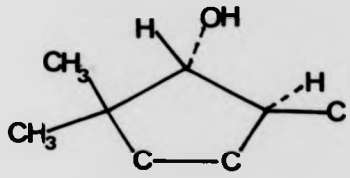
The alcohol derived from rearrangement of isomer D exhibited the spectral characteristics:

$\bar{\nu}_{max}$ 3450, 1620, 1080, and 890 cm^{-1}:

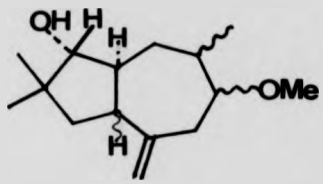
$\delta(CDCl_3$,ppm) 0.85 (3H,d,J = 7Hz), 0.95 (3H,s), 1.08 (3H,s), 3.12 (1H,d,J = 10Hz), 3.32 (3H,s), 3.33 (1H,m), 4.74 (1H,bs), and 5.06 (1H,bs).

The nmr spectrum was simplified with $Eu(fod)_3$ and double irradiation experiments were carried out. Oxidation of the alcohol with pyridinium chlorochromate[19] gave a ketone with $\bar{\nu}_{max}$ 1750 cm^{-1} indicating a cyclopentanone moiety. The part structure F could be assembled from this information and

this, combined with the ^{13}C off-resonance nmr data and a mechanistic rationale (Figure 13) inferred that the compound had structure (60).

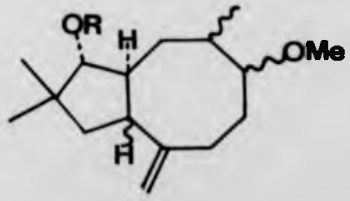


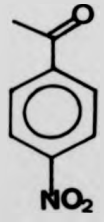
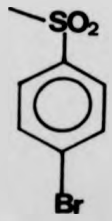
(F)

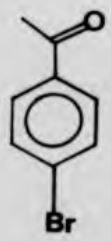
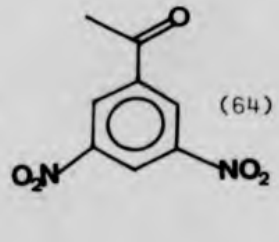


(60)

Since this compound was a key intermediate in the planned synthesis, the structure and stereochemistry had to be unambiguously determined. Therefore, an attempt was made to prepare a crystalline derivative for X-ray analysis. Various esters were formed by reaction with the corresponding acid chloride [p-nitrobenzoate (61), p-bromobenzene sulphonate (62) and p-bromobenzoate] (63) , but these could not be isolated in a crystalline form. However, the 3,5-dinitrobenzoate (64) was crystalline (mp 150-152^{o}C) and the X-ray analysis was kindly carried out by Drs. J. Murray-Rust and P. Murray-Rust in this department.[51]

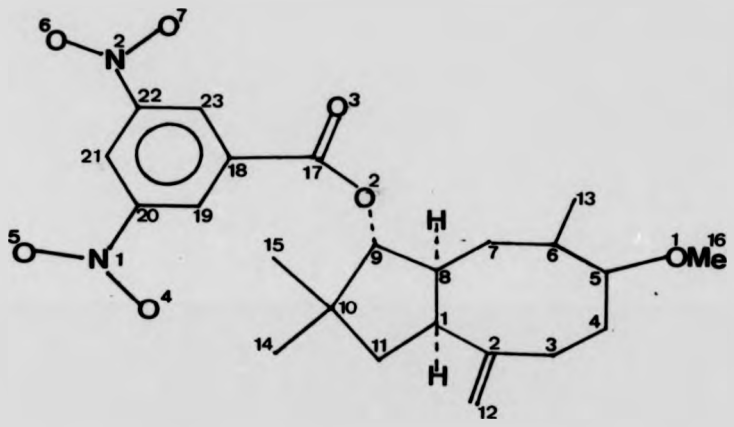


R=  (61) R=  (62)

=  (63) =  (64)

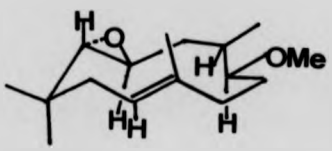
The structure determined was thus confirmed and the compound had the stereochemistry shown in structure (65) (see also Appendix 1).

Crystal data: $P2_{1/n}$, a = 15.37(5), b = 8.79(6), c = 18.16(6) Å, $\beta = 80.44(3)^6$ and R = 0.072 for 1113 observed reflexions.



(65)

From the stereochemistry of the parent alcohol, it was possible to predict from which of the two possible diastereoisomeric epoxides the alcohol was derived. Thus the isomer denoted as D must have the stereochemistry shown in structure (66) and isomer E has structure (67) (both shown as the CC conformers).



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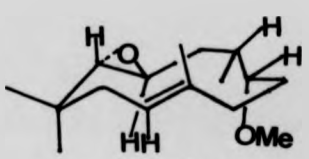


(67)

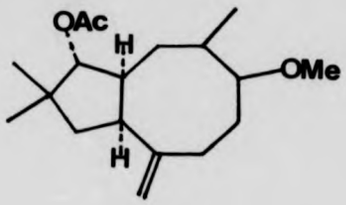
It is also possible to extrapolate this reasoning to the bisepoxides and isomers B and C must possess structures (58) and (59) and isomer A will have either structure (56) or (57).

It was observed that this alcohol (60) was also found in the crude reaction mixture from deoxygenation of the bis-epoxide (isomer A), when longer reaction times were used. Indeed, on studying the reaction by analytical tlc, beyond the point of maximum formation of the 4,5-monoepoxide (66), it was found that the gradual formation of the alcohol (60) coincided with a simultaneous loss of the epoxide (66). Presumably a tungsten species is acting as a Lewis acid in the rearrangement of epoxide (66). This rearrangement in the deoxygenation conditions is of particular interest in view of the postulated rearrangement of the 4,5-epoxide (7) itself under identical conditions to produce the diol (14) (Chapter 1).

From examination of the structure (65) it was thought that the reintroduction of the original $\Delta^{1,2}$ double bond present in humulene (but with the cis relationship) should be facile, since the H-2 proton and the methoxyl group can adopt an anti-periplanar relationship. This was to be brought about by demethylation and dehydration. Before methods of inducing this elimination could be tried, the hydroxyl group on the cyclopentane ring had to be protected. This was successfully achieved by forming the acetate (68).

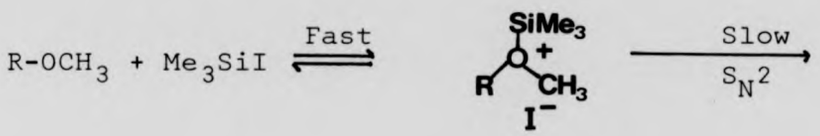
A number of methods exist in the literature for the demethylation of methyl ethers involving the use of a thiol and a Lewis acid.[52,53] However, demethylation using iodotrimethyl-silane seemed the most efficient and mildest method.[37] This

reagent can also be generated *in situ*, from chlorotrimethylsilane and sodium iodide.[54]



(68)

The suggested mechanism of this reaction (Figure 15), involves the action of iodotrimethylsilane on the ether to produce a silylated oxonium ion in a fast reversible step. A slow, irreversible S_N2 attack by iodide produces an alkyl trimethylsilyl ether which can be easily converted to the alcohol upon hydrolysis.



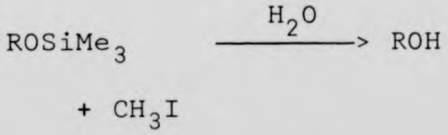
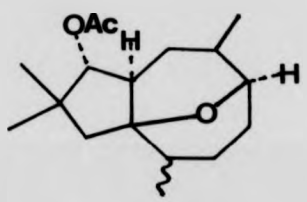


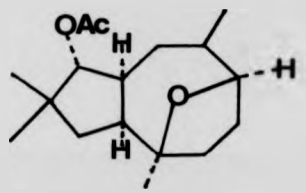
Figure 15

Demethylation reactions were attempted using both iodotrimethylsilane and the reagent generated *in situ*.[54] The compound $C_{17}H_{26}O_3$ was the only major product of these conditions

(∿ 67%) and was slightly less polar than the starting material on analytical tlc. The 90 MHz ^{1}H nmr spectrum revealed that the protons due to the methoxyl group (3.3 ppm) and the exo-methylene group (4.7 and 5.1 ppm) had disappeared. There was a decrease in the coupling constant of the H-9 and H-8 protons (with respect to the starting acetate (68)). From this information structures (69) or (70) were tentatively proposed and it was impossible to conclusively distinguish between the two structures from the off-resonance ^{13}C spectrum.



(69)



(70)

A 360 MHz ^{1}H nmr spectrum was required to unravel the methyl region (0.9-1.2 ppm) and this gave the following information: $\delta(CDCl_3$,ppm), 0.91 (3H,s), 0.99 (3H,d,J = 7Hz), 1.05 (3H,d,J = 7Hz), 1.16 (3H,s), 1.58 (1H,d,J = -13Hz) and 1.66 (1H,d,J = -13Hz) - AB system, 2.14 (3H,s), 3.36 (1H,m), and 4.70 (1H,d,J = 2.5Hz).

The presence of two methyl doublets and the AB system due to the methylene protons of the cyclopentane ring, points to the compound having the oxane structure (69).

The vicinal coupling constant due to splitting of the H-8 and H-9 (H-9 at 4.70 ppm,d,J = 2.5Hz) requires comment. From molecular models it appears that on forming the oxane (69) the H-C-C-H bond angle between H-8 and H-9 decreases to

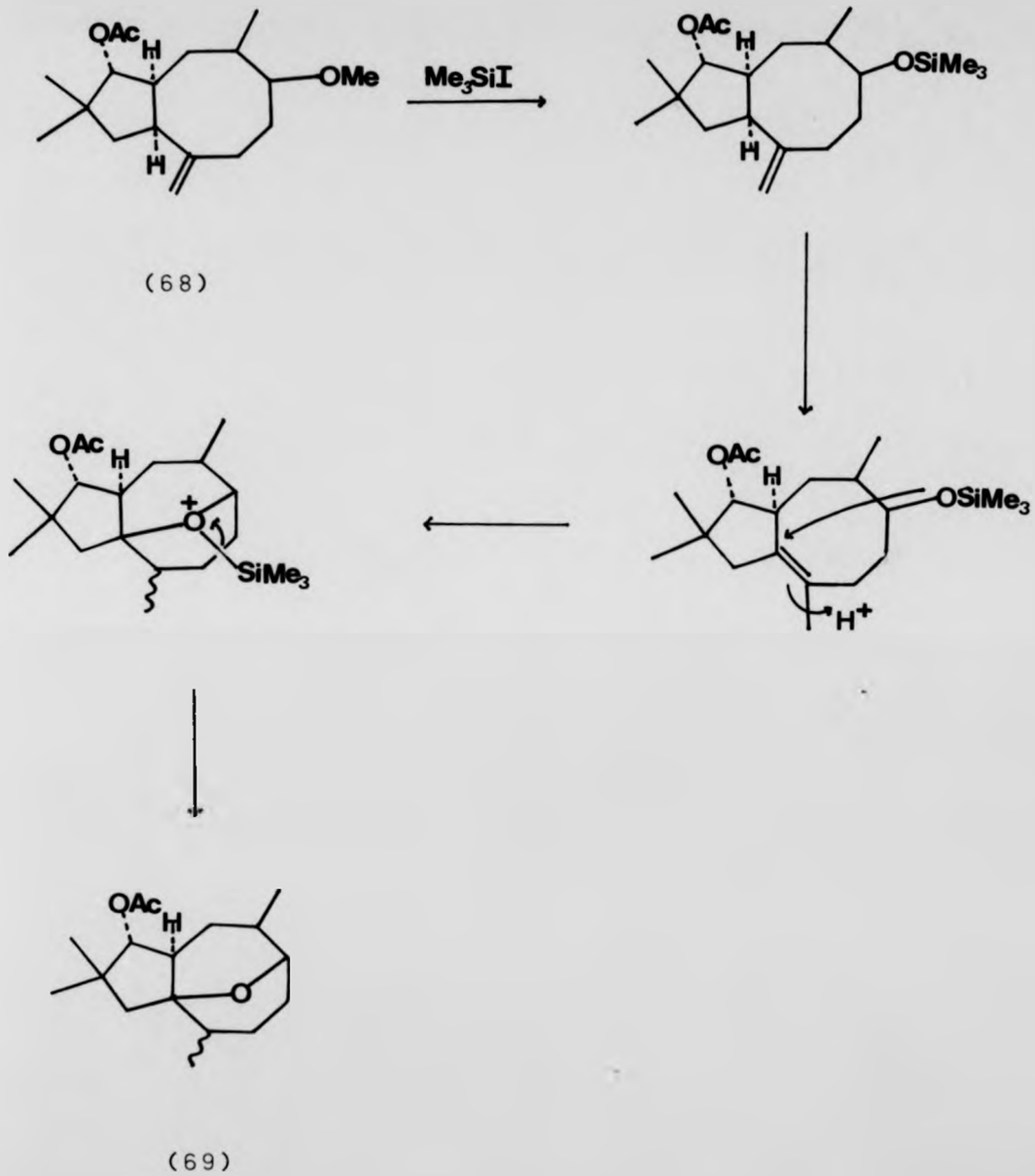
approximately 110° and this is reflected in the decrease of the coupling constant.

The mechanism of formation of compound (69) is not fully understood and no literature analogies can be found. It is known that cyclization takes place before the work-up procedure, as the course of the reaction has been studied by nmr spectroscopy. Although the methyl and methylene regions of the spectrum were complex (0.8-2.0 ppm), it was possible to monitor the disappearance of the exomethylene group (4.7 and 5.1 ppm), the H-9 proton (4.55 ppm) and the methoxyl protons (3.3 ppm). New signals could be observed at 2.1 ppm (s) due to the formation of iodomethane and at 0 ppm from either the trimethylsilyl ether or hexamethyldisiloxane production. The build up of the H-9 signal (4.7 ppm, d,J = 2.5Hz) of the cyclized product was also clear.

The mechanism depicted in Figure 16 is considered possible at this stage and requires one mole equivalent of protons (and a proton source was also thought necessary for isomerization of the exomethylene double bond).

Reaction in the presence of base, such as solid sodium bicarbonate or triethylamine, which should remove any protons present, did not affect the reaction. Indeed, the addition of pyridine catalysed the reaction by acting as a nucleophilic catalyst[55] (the use of 4-dimethylaminopyridine also exemplies this). The saturation of the reaction with propene[37] (to remove hydrogen iodide) did seem to retard the reaction, although the same product was formed.

The relatively mild method of cleaving methyl ethers using the organosilane reagents, methylthiotrimethylsilane and phenylthiotrimethylsilane, in combination with zinc iodide and



(68)

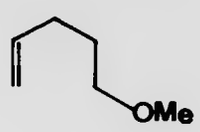
(69)

Figure 16

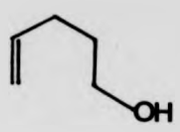
tetra n-butylammonium iodide,[56] was also carried out on compound (68). Because of the relative stability of the reagents, and the possibility to vigorously exclude moisture, this method was supposed to prevent adventitious formation of

hydrogen iodide. However, compound (69) was also the major product under these conditions.

A further study of this unprecedented reaction was carried out using 5-methoxypent-1-ene (71) as a model compound. The reaction of compound (71) with iodotrimethylsilane[37] gave a plethora of volatile products and although these compounds were not positively identified, it was apparent that 4-penten-1-ol (72) was not formed.



(71)



(72)

The demethylation reaction using iodotrimethylsilane[37] was also carried out on isohumulyl methyl ether (54) and the reaction monitored by analytical tlc. Although a number of unidentified, less polar compounds were produced, no isohumulol was formed.

Further model studies are required on this reaction, where demethylation is being carried out in the presence of an olefinic bond within the molecule. For example, the demethylation of (73) should provide a suitable model system for examination. The corresponding alcohol (74) has been synthesised by monohydroboration - oxidation of 1,5-dimethyl-1,5-cyclooctadiene (75).[57]

Cleavage of the methyl ether of compound (68) was attempted with boron trifluoride etherate and acetic anhydride. This reaction is known to produce the corresponding acetate.

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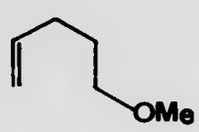
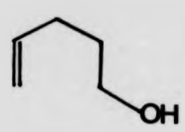


(71)



(72)

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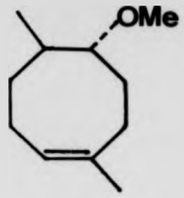
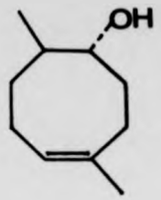
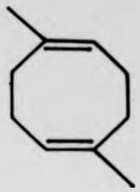


(73)

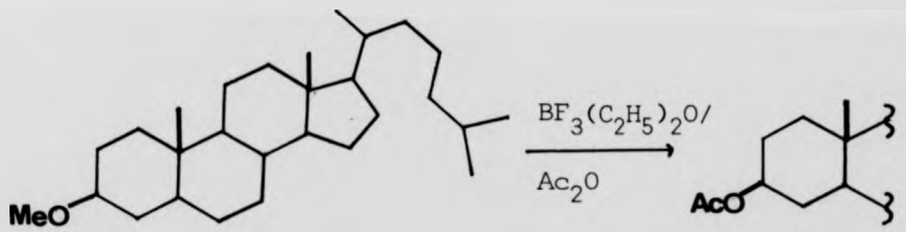


(74)



(75)

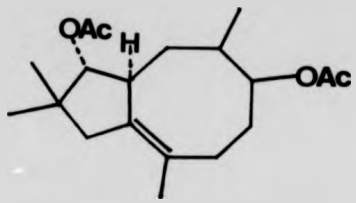
For example, cholestanyl methyl ether (76), has been reported to give cholestanyl acetate (77)[58] (some epimeric acetate and elimination product also formed) (Figure 17).



(76) (77)

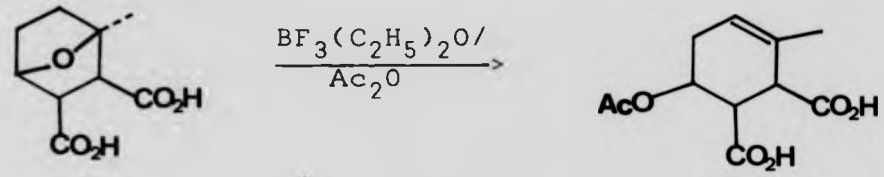
Figure 17

However, these conditions produced (69) exclusively and on longer reaction times (or on treatment of (69) itself) the oxane ring was cleaved to produce the bicyclic compound (78). Compound (64) had the spectral characteristics: $\bar{\nu}_{max}$ 1725 cm^{-1}; $\delta(CDCl_3,ppm)$, 0.90 (3H,s), 1.05 (3H,d,J = 7Hz), 1.10 (3H,s), 1.64 (3H,bs), 2.00 (3H,s), 2.12 (3H,s), 4.72 (1H,d,J = Hz), and 4.95 (1H,m).



(78)

The cleavage of cyclic ethers with boron trifluoride etherate and acetic anhydride is well precedented. It is known for example that compound (79) yields the acetate (80) under such conditions.[59] (Figure 18).

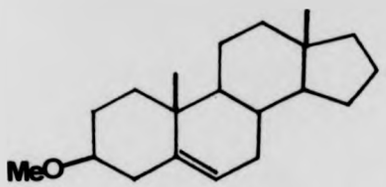


(79) (80)

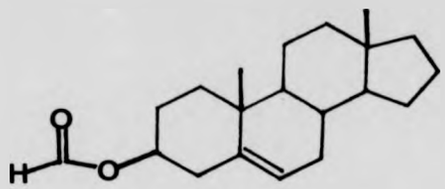
Figure 18

An alternative method of demethylation involved oxidative cleavage of the ether. This method, reported by Harrison and Harrison,[60] involves oxidation of the methyl ether with chromium trioxide and acetic acid to the corresponding formate, which on hydrolysis yields the desired alcohol. Thus, 3β-methoxyandrost-5-ene (81) (after prior protection of the

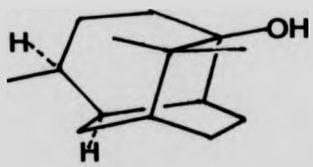
double bond as the dibromide) yielded 3β-formyloxyandrost-5-ene (82) which on alkaline hydrolysis yielded the secondary alcohol. This reaction has also been used to generate the tertiary alcohol, patchouli alcohol (83), from the methyl ether (84).[61]



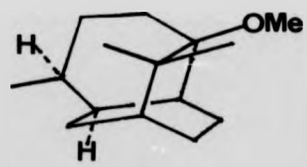
(81)



(82)



(83)



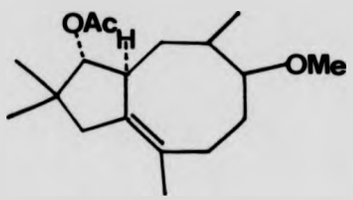
(84)

Oxidative cleavage of the methyl ether of compound (68) was attempted using chromium trioxide in acetic acid but a multitude of compounds (> 10 from analytical tlc) resulted from these conditions.

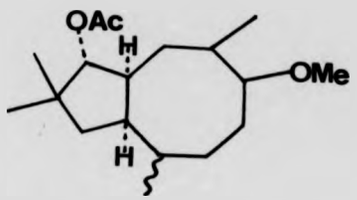
To overcome the concurrent cyclization which took place with demethylation of compound (68), the exomethylene double bond was removed by hydrogenation. Hydrogenation with palladium on charcoal[62] gave an approximately 1:1 mixture of two compounds G and H. Compound G had the nmr spectrum: $\delta(CDCl_3$,ppm) 0.90 (3H,s), 0.95 (3H,d,J = 7Hz), 1.06 (3H,s), 1.65 (3H,bs), 2.10 (3H,s), 3.28 (3H,s), 3.33 (1H,m), and

4.75 (1H,d,J = 7Hz). Compound H had the spectral characteristics: δ($CDCl_3$,ppm), 0.85 (3H,d,J = 7Hz), 0.90 (3H,s), 1.03 (3H,d,J = 7Hz), 1.05 (3H,s), 2.07 (3H,s), 3.30 (3H,s), 3.31 (1H,m), and 4.60 (1H,d,J = 7Hz).

These spectral data combined with the knowledge that palladium promotes double bond migration,[62] suggested that compound G was the isomer (85) and compound H was the desired dihydro-compound (86).



(85)

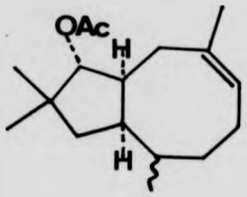


(86)

The ability of metals to promote double bond migration parallels their ability to catalyse olefin hydrogenation, i.e. Pd > Rh > Pt > Ru. However, Raney nickel, even though it is a good catalyst for double bond hydrogenation, does not promote migration at low temperatures and pressures.[62] Thus, using Raney nickel as the catalyst in ethanol, compound (86) was formed exclusively.

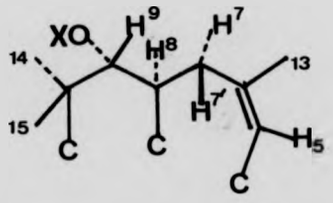
Demethylation of the dihydro-derivative (86) with iodotrimethylsilane,[37] methylthiotrimethylsilane and phenylthiotrimethylsilane[56] was carried out in an endeavour to produce the corresponding alcohol. In all cases, the compound $C_{17}H_{28}O_2$ was the only product (∿ 70%) which was characterised by the 360 MHz ^1H nmr spectrum: δ($CDCl_3$,ppm) 0.89 (3H,s), 0.98 (3H,d,J=7Hz), 1.03 (3H,s), 1.74 (3H,bs), 2.05 (3H,s), 2.56 (1H,t,J = 13Hz),

4.61 (1H,d,J = 6Hz), and 5.33 (1H,t,J = 8Hz). From these data, structure (87) was tentatively proposed, being derived from (86) by elimination of methanol to give the trisubstituted olefin. However the triplet at 2.56 ppm (J = 13Hz) seemed rather anomalous.



(87)

The partial structure (88) portrays the region of interest within compound (87).

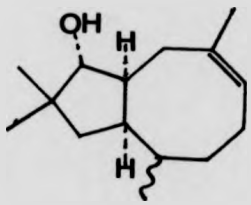


X = $\overset{O}{\overset{\|}{C}}-CH_3$

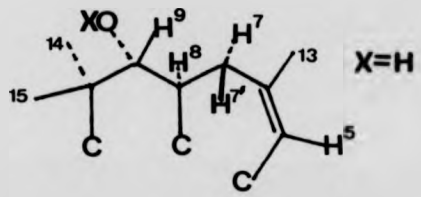
(88)

Molecular models show H-7' to have an antiperiplanar relationship with H-8. Therefore it was thought possible that $J_{8,7'}$ may have the same approximate magnitude as the geminal coupling $J_{7,7'}$ (i.e. 13Hz), giving the triplet signal for H-7'. The slight downfield chemical shift (2.56 ppm) may be due to the deshielding effect of the carbon-carbon double bond. Since H-7' lies in the plane of this bond, the deshielding effect of the π-electron system will be significant for this proton.[63]

To confirm this hypothesis, the alcohol (89) was formed by alkaline hydrolysis of (87) and the 90 MHz nmr spectrum of this compound simplified by the addition of $Eu(fod)_3$ and spin decoupling techniques. The results of this work, which are given in Table 1, support the proposed structure (87).



(89)



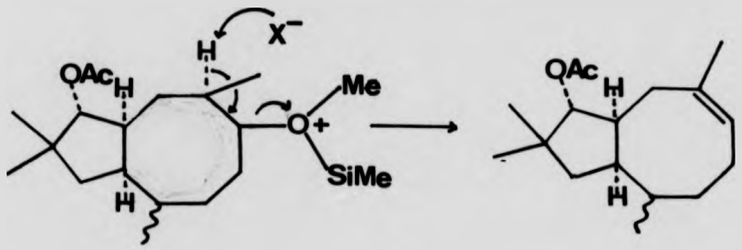
(88)

TABLE 1

Results of Decoupling for Partial Structure (88) where X=H

Irradiation of signal	Observed signal before irradiation	Observed signal on irradiation
H-9 (d,J=6Hz)	H-8(m)	– sharpens
H-8(m)	H-9(d) H-7(bd,J=13Hz) H-7'(t,J=13Hz)	– (s) – sharpens – (d,J=13Hz)
H-7(bd,J=13Hz)	H-7'(t,J=13Hz)	– (d,J=13Hz)
H-7'(t,J=13Hz)	H-7(bd,J=13Hz)	– (bs)
CH_3-13(bs)	H-5(t,J=8Hz)	– sharpens
H-5(t,J=8Hz)	CH_3-13(bs)	– sharpens

This elimination reaction of compound (86) with organosilane reagents is also unprecedented and presumably proceeds through the path illustrated in Figure 19.



(86) (87)

X = I^-

= MeS^-

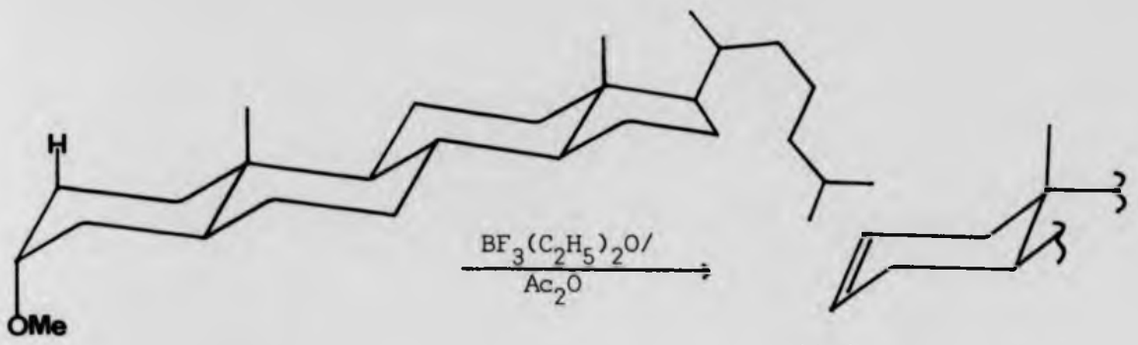
= PhS^-

Figure 19

In this mechanism, iodide (or a mercaptide) acts as a base in the trans elimination process with methoxytrimethylsilane as the leaving group. Although there are no analogous reactions for these particular conditions, boron trifluoride in acetic anhydride causes elimination of methanol in a similar manner to that shown in Figure 19 (where the methoxyl group is favourably aligned for acid catalysed elimination). In the treatment of cholestan-3α-ol methyl ether (90) for example, 2-cholestene (91) was the major product.[58] (Figure 20).

The action of boron trifluoride in acetic anhydride on compound (86) also brought about its rapid conversion to the olefin (87).

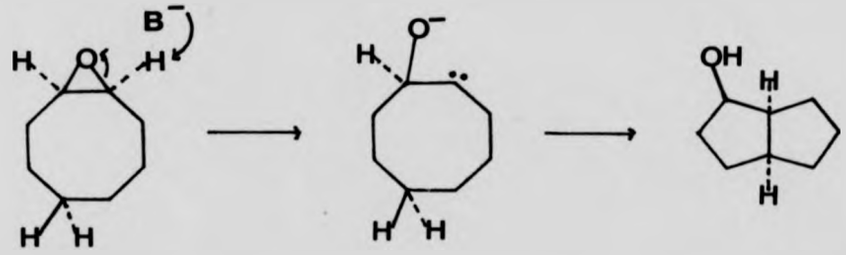
Although compound (87) was not part of the original synthetic strategy (Figure 13), a route to the pentalenane skeleton (48) was considered via the epoxide of (87). The



(90) (91)

Figure 20

reaction of cis-cyclooctene oxide (92) with strong base is known to form the bicyclic alcohol (93)[64] (70%) by an intramolecular alkylation involving a carbene (Figure 21). If this reaction was successful on the epoxide of (87), the pentalenane skeleton would be achieved.

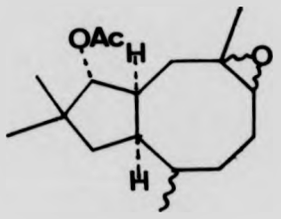


(92) (93)

Figure 21

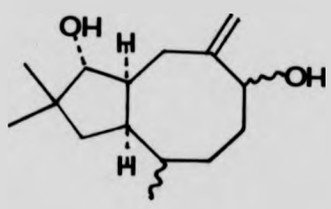
Compound (87) was treated with one mole equivalent of m-chloroperoxybenzoic acid[7] to yield the corresponding epoxide (94) (the spectral data was in accord with this structure).

Treatment of this epoxide with lithium diethylamide



(94)

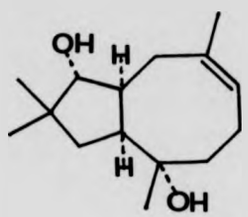
did not give a transannular reaction, but caused isomerisation of the epoxide to give the probable structure (95) (with ester hydrolysis in the work up procedure). Compound (95) exhibited: $\bar{\nu}_{max}$ 3455, 1620, 1090, and 890 cm^{-1};
$\delta(CDCl_3, ppm)$ 3.10 (1H,d,J = 10Hz), 3.45 (1H,bt,J = 8Hz), 4.90 (1H,bs), and 5.1 (1H,bs). This rearrangement of epoxides under basic conditions is well precedented.[65]



(95)

Although the biomimetic synthesis of a pentalenane (48) or protoilludane (47) skeleton was not achieved during the period of research, it is important to note the work of Matsumoto *et al.*[66] in the synthesis of pentalenic acid (see

Introduction). This biomimetic synthesis was published at the time of writing and the formation of the pentalenane skeleton (in 20% yield) was brought about by treatment of the alcohol (96) with boron trifluoride etherate. The similarity in the synthetic planning is apparent.

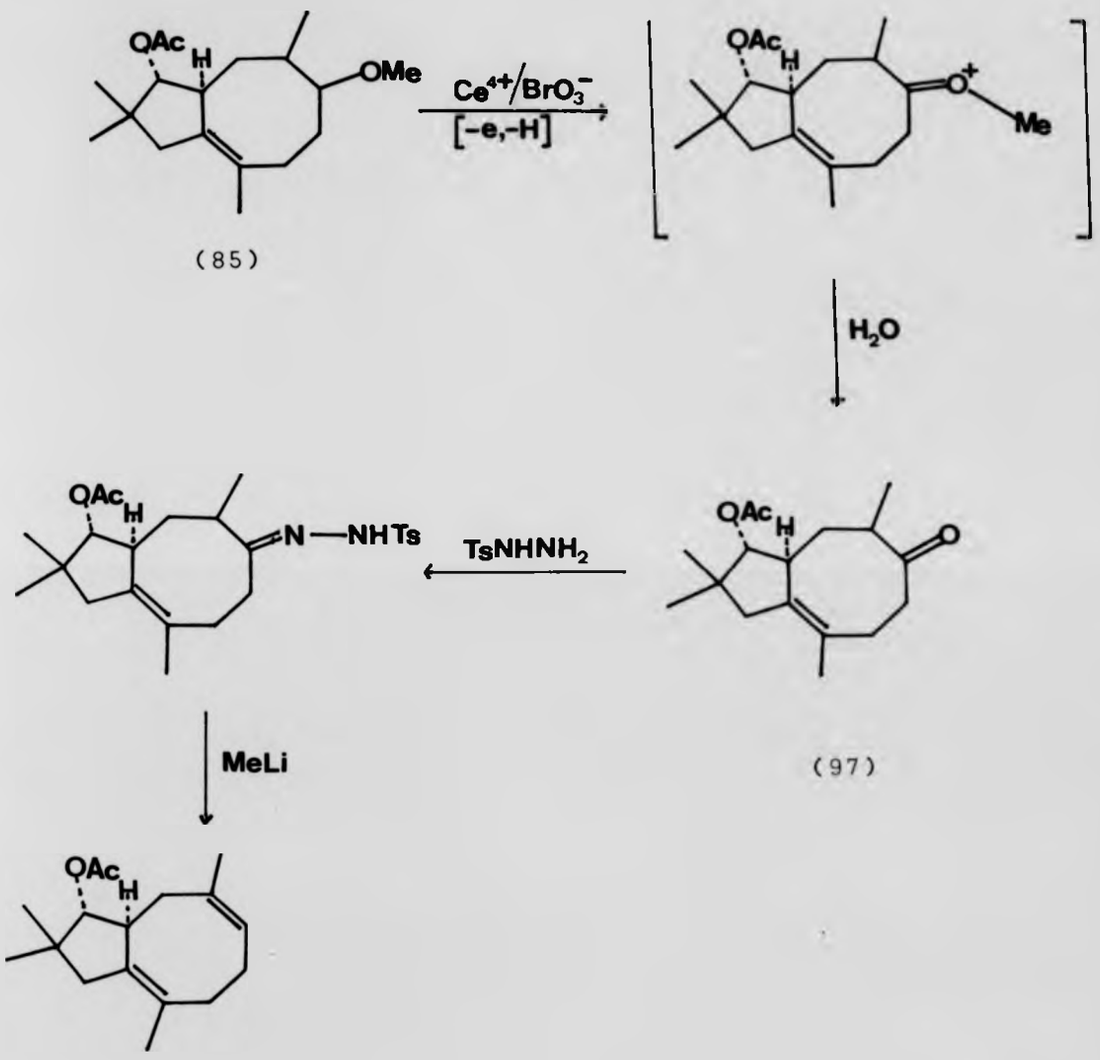


(96)

Although the original synthetic scheme has foundered on the demethylation of compound (68) there are alternative schemes which could be employed.

For example, the formation of the ketone (97) may be possible from (85) by the mild oxidative technique using sodium bromate and a catalytic amount of ceric ammonium nitrate.[67] The ketone (97) may be converted to the diene (98) *via* a tosylhydrazone/methyllithium route.[68] (Figure 22).

The diene (98) is the target molecule of the original synthetic scheme (Figure 13) and may cyclize in appropriate acidic conditions to give compounds possessing the pentalenane (48) or protoilludane skeletons (47).



(85)

(97)

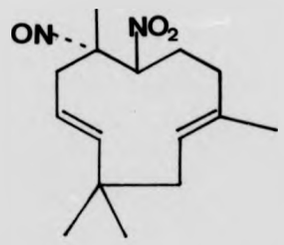
(98)

Figure 22

CHAPTER 4

PREPARATION OF ISOHUMULENE

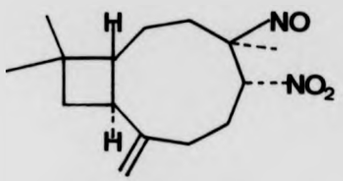
Some terpenes used to be characterised by allowing them to react with dinitrogen trioxide to produce crystalline nitrosite derivatives. Chapman first prepared humulene nitrosite (99) almost one hundred years ago,[69,70] and the same nitrosite was used by Mitchell in his early pioneering work on the Cotton effect[71] and in his studies on asymmetrical photochemical reactions involving circularly polarised light.[72] The structural elucidation of the nitrosite (99) was published recently by Porte *et al.*[73], but in fact this had already been carried out in unpublished work by J. A. Mlotkiewicz.[74]



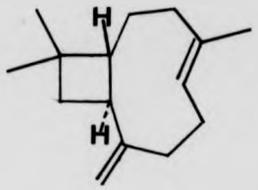
(99)

Early work on the formation of caryophyllene nitrosite (100) showed that an isomeric form of caryophyllene (101), namely isocaryophyllene (102), was the main product in the reaction of caryophyllene (101) with dinitrogen trioxide.

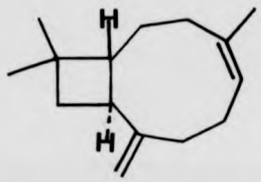
The formation of isocaryophyllene (102) and caryophyllene nitrosite (100) is illustrated in Figure 23 (homolytic fission of the N-N bond of N_2O_3 giving the two radicals $\dot{N}O_2$ and $\dot{N}O$). It has also been shown that if caryophyllene nitrosite is heated



(100)

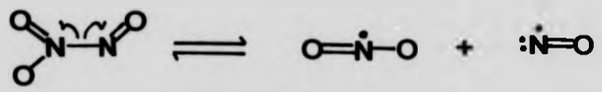


(101)



(102)

in ethanol, isocaryophyllene is formed. The inherent strain of the trans-double bond in the ring system has been relieved by isomerisation via a tertiary radical intermediate. From the product ratio of approximately 80% isocaryophyllene to 10% nitrosite, it would appear that loss of $\dot{N}O_2$ is energetically more favourable than addition of $\dot{N}O$. However, it is unusual that the elimination process predominates in this reaction since radical combination reactions are known from polymerisation studies to have a very low activation energy, suggesting that the reaction of the β-nitro radical with $\dot{N}O$ would be fast. This anomaly is explained in terms of the sterically hindered



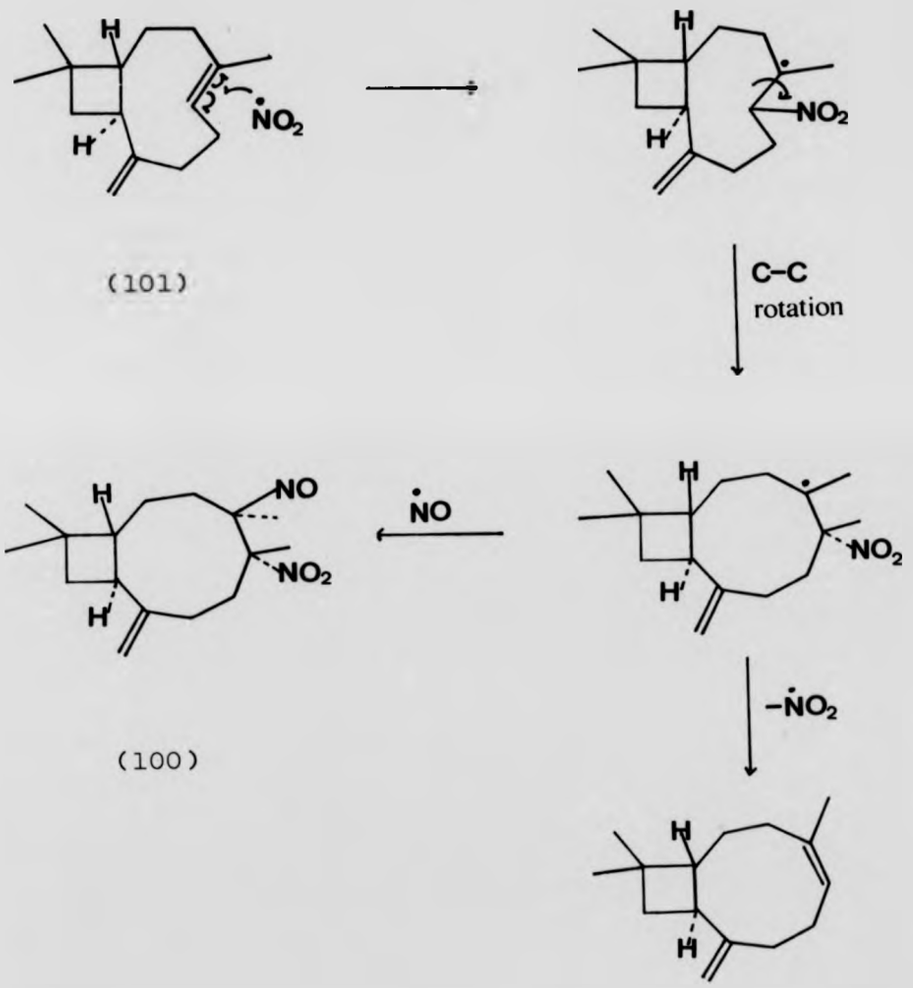


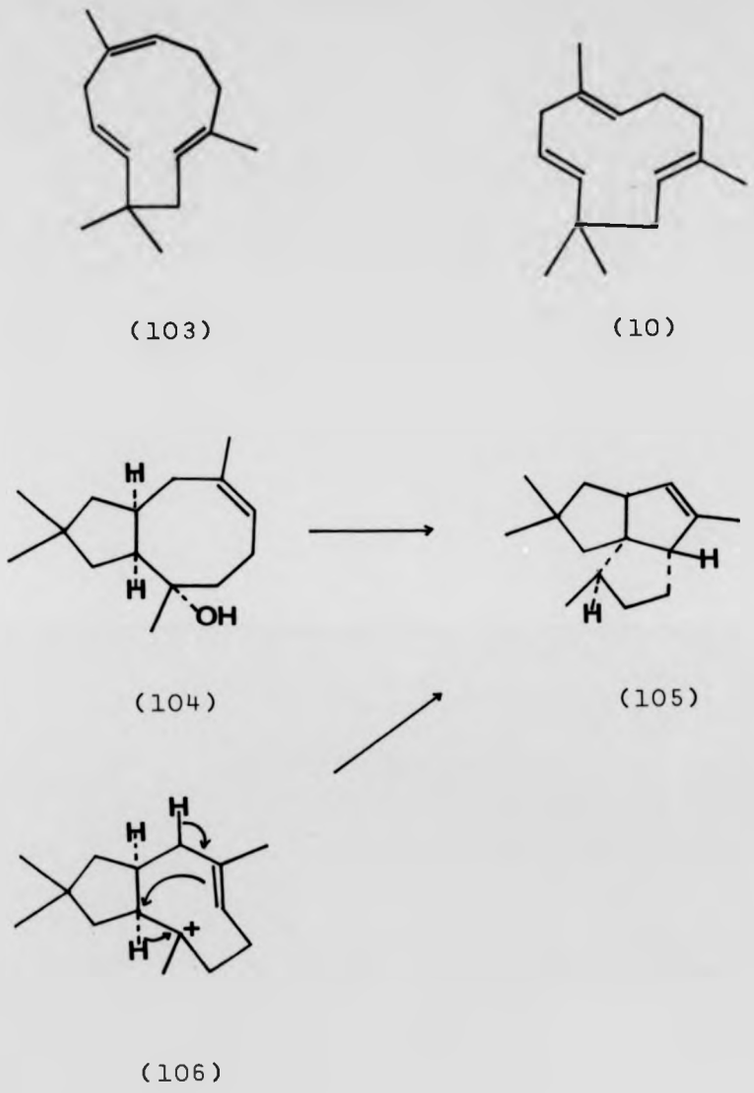
Figure 23

combination of $\dot{N}O$ with the preferred conformation of the β-nitro radical and can be compared favourably with the preferred trans addition of dinitrogen tetroxide to the $\Delta^{9,10}$-octalin and the preferred exo-cis-addition to norbornene.[75]

In the light of this work which had been carried out on the conversion of caryophyllene (101) and caryophyllene nitrosite (100) to isocaryophyllene (102), the analogous formation of the hitherto unknown compound, isohumulene (103) was thought possible from humulene nitrosite (99) or humulene (10). This molecule would be very interesting in terms of its possible rearrangement products.

From molecular models it is apparent that the presence of a cis-$\Delta^{1,2}$ double bond in the eleven-membered ring of humulene, greatly increases the conformational mobility, facilitating π-bond interaction of the $\Delta^{4,5}$ and $\Delta^{8,9}$ double bonds and thus lowering the activation energy required for rearrangement. The hypothesis that isohumulene may, in fact, be the biosynthetic precursor of a number of cyclised products was considered. Although this compound has not been found in Nature, it was reasoned that since its reactivity is presumably greater than that of humulene, it would undergo more rapid cyclisation. This hypothesis seemed to be substantiated by the work of Matsumoto et al. in the formolysis of (104),[76] which cyclises to give the naturally-occurring pentalenane (105) (Figure 24).

In compound (104) the original $\Delta^{1,2}$ double bond of humulene has been reintroduced as the cis-isomer and cyclises to give pentalenane with the same stereochemistry as the naturally-



(103) (10)

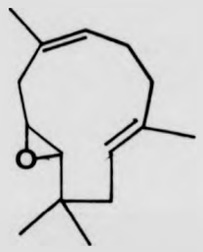
(104) (105)

(106)

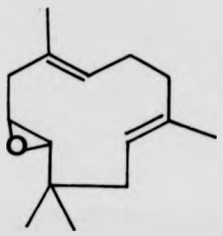
Figure 24

occurring compound. However, the biogenesis of pentalenane invokes the trans isomer (106) in the cyclization pathway (although a conformation of this isomer also gives the pentalenane of correct stereochemistry).

A study of the 4,5-epoxide of isohumulene (107) was also thought worthy of attention in view of the proposed increased interaction of the $\Delta^{8,9}$ double bond with the 4,5-epoxide with respect to humulene-4,5-epoxide (7).



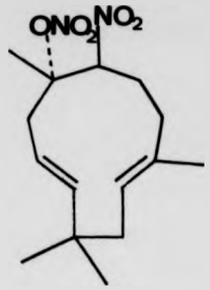
(107)



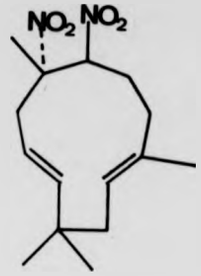
(7)

It was also reasoned that isomerisation of the trans $\Delta^{1,2}$ double bond to the cis configuration may alter the reactivity of the double bonds towards epoxidation (reactivity in humulene is $\Delta^{1,2} > \Delta^{8,9} > \Delta^{4,5}$).

Humulene nitrosite was prepared by the early literature[70] method by reaction of humulene with dinitrogen trioxide generated in situ (aqueous sodium nitrite and glacial acetic acid) giving an isolated yield of 10% after 30 minutes at 10°C. Humulene was recovered from this reaction (~ 60%) and the other products generated have been identified by Mlotkiewicz[74] and Porte et al.[73] and consist of nitronitratohumulene (108) and dinitrohumulene (109).



(108)



(109)

Heating humulene nitrosite (99) (in refluxing ethanol for 8 hours) produced the nitrosate (109) as the major compound (60%) and some hydrocarbon material which had an identical polarity to humulene on silica analytical tlc. However, examination of this material on silica impregnated with silver nitrate and by glc (apiazon), revealed the presence of two components (one of which was identical in Rf and Rt to humulene) in the approximate ratio of 1:1.

These compounds were separated by chromatography over silica impregnated with silver nitrate (humulene was bound tightly to this system as expected from formation of the bis-silver nitrate complex.[77]) The nmr spectrum of this humulene was identical to starting material;

$\delta(CDCl_3$,ppm) humulene, 1.10 (6H,s,gem-dimethyl group),
1,45 (3H,d,J = 1.8Hz,trans allylic coupling),
1.60 (3H,d,J = 1.8Hz,transallylic coupling),
1.90 (2H,d,J = 7Hz, 2 x H-7), 2.5 (2H,d,J = 7Hz, 2 x H-3),
4.70-5.00 (2H,m,1 x H-1 and 1 x H-8), 5.10 (1H,d,J = 16Hz,
1 x H-5), and 5.5 (1H,m,J = 7Hz and 16 Hz, 1 x H-4).

The new hydrocarbon (10% yield), $C_{15}H_{24}$, exhibited a similar ir spectrum to humulene but the nmr spectrum was quite

different;

$\delta(CDCl_3, ppm)$, 1.0 (6H,s,gem-dimethyl group),

1.65 (3H,d,J = 0.5 Hz,cis-allylic coupling),

1.75 (3H,d,J = 1.8Hz,trans-allylic coupling),

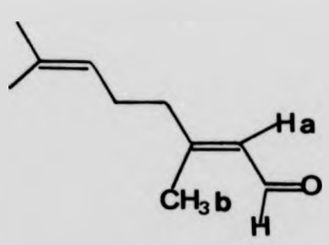
2.70 (2H,d,J = 6Hz, 2 x H-3), and 5.0-5.4 (4H,m).

This spectrum indicated that the two doubly allylic H-3 protons remained and the allylic coupling of one of the vinylic methyl groups (0.5Hz) was diagnostic of a cis-coupling.

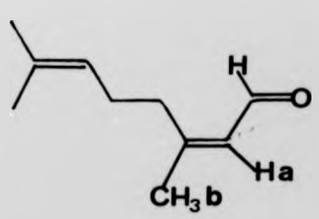
On the basis of the spectral evidence and on the analogous reaction of caryophyllene nitrosite (100) being converted to isocaryophyllene (102), this hydrocarbon was assumed to have the desired structure of isohumulene (103).

It is interesting to note that in 1960 S. Dev,[78] proposed (103) as the structure of humulene itself, after examination of an early nmr spectrum of the compound.

The obvious technique to verify the cis-$\Delta^{1,2}$ double bond in compound (103) is the nuclear Overhauser effect (NOE). The NOE is a change in the integrated nmr absorption intensity of a nuclear spin when the nmr adsorption of another spin is saturated. The spacial dependence of the NOE has been used by many workers to elucidate molecular structures and, for example, Ohtsuru et al.[79] used the NOE to confirm the configurations of citral a (110) and citral b (111).



(110)



(111)

The saturation of CH_3b in citral a (110) gave no observable enhancement of the Ha resonance, while in citral b (111), the resonance of Ha was enhanced by 18%. As the largest enhancement would be expected for the methyl group closest to Ha, these results confirmed that CH_3b was *trans* to Ha in citral a (110) and *cis* to it in citral b (111).

The NOE experiment was carried out on humulene (10) and isohumulene (103) by Dr. F. G. Riddell in this department. Both vinylic methyl groups in (10) and (103) were saturated and the integration of the olefinic regions carried out. There was no observable NOE on irradiation of either methyl groups, in either compound. However, this result may be due to experimental technique, and this experiment has to be repeated on compounds known to exhibit the NOE (on camphene, for example).

Although the allylic coupling constant of 0.5Hz was indicative of a *cis* coupling in compound (103), it was thought that measurement of the vicinal ^{13}C-^{1}H coupling constant would be more diagnostic since this value varies markedly with configuration.[80] The 80 MHz ^{13}C spectra of humulene and isohumulene were recorded, but the chemical shift of the allylic carbons were so close, that it was felt that the off-resonance-decoupled spectra would be too complicated to distinguish the signals. However, this work is to be repeated in the future by Dr. J. E. Anderson at the University College, London, using a 200 MHz instrument, which should give better resolution.

Another interesting nmr experiment has been carried out by Dr. F. G. Riddell involving the temperature dependence of the isohumulene spectrum. This work had been carried out on humulene by Anderson *et al.*[81] and the free energy of activation for ring inversion calculated to be $\Delta G^{\neq} = 10.6 \pm 0.3$ kcal/mol

at -81°C (the activation enthalpy was later estimated to be $\Delta H^{\neq}$ = 14.17 kcal/mol by Matsumoto et al.[82]).

The spectrum of humulene at ambient temperature shows a sharp singlet for the gem-dimethyl group, but below -81°C this signal becomes a narrowly-spaced symmetrical doublet. At low temperature, humulene adopts the most stable mirror-image conformations RSR-CT (112) and SRS-CT (113) which can be related by ring inversion and this involves rotation of all the double bonds through the ring (the activation energies for all the conformational changes have been calculated by Matsumoto et al.[82]). The correlation diagram for the eight minimum energy conformations of humulene is given in Figure 25.

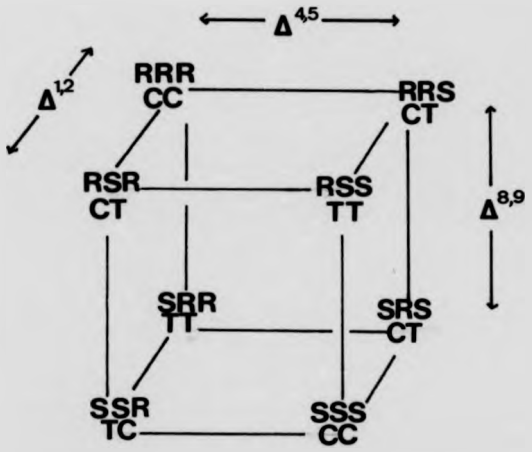
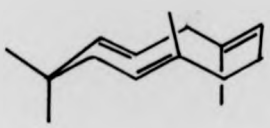
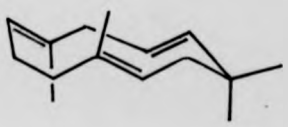


Figure 25



RSR-CT (112)



SRS-CT (113)

At -81°C the two methyl groups on C-6 in (112) and (113) are chemically different as are the pairs of hydrogen atoms on carbons 3, 7, 10 and 11. This gives rise to the observed doublet for the gem-dimethyl at C-6 but while broadening of the other signals was observed, these changes were not so clear.

This work was repeated with the ^1H nmr spectrum of humulene in perdeuterioacetone and a coalescence temperature of -84°C observed ($\Delta\nu$ = 1.9 Hz* at -90°C) giving a calculated activation energy for ring inversion[83] $\Delta G^{\neq}$ = 10.6 kcal/mol which was identical to that of Anderson *et al.*[80]

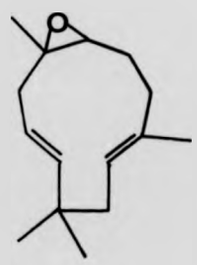
The experiment with isohumulene in deuteriochloroform gave a much higher temperature of coalescence of -34°C ($\Delta\nu$ = 6.16 Hz* at -64°C) and therefore a higher energy of activation for ring inversion $\Delta G^{\neq}$ = 12.6 ($\pm$ 0.3) kcal/mol. This higher energy for ring inversion is a reflection on the unfavourable process of rotating the *cis*-$\Delta^{1,2}$ double bond through the ring and from molecular models it is apparent that this conformational change in fact requires the flipping of the C-11 methylene group through the ring. The inversion of the $\Delta^{4,5}$ and $\Delta^{8,9}$ double bonds simply requires the rotation of olefinic protons through the ring and these conformational changes should remain relatively low energy prossesses, as in humulene itself.

Isohumulene could also be prepared from humulene by prolonged reaction time (48 hours) at room temperature with dinitrogen trioxide (12% yield). This is analogous to the isomerization of caryophyllene, however it should be noted that dinitrohumulene (109) was the major product (40%) and a small amount of humulene was recovered (10%). This, combined

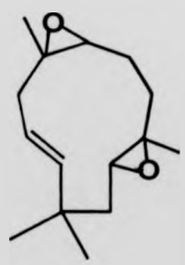
* (80MHz)

with the fact that humulene nitrosite produces approximately a 1:1 mixture of humulene and isohumulene, suggests that the all trans-isomer humulene is thermodynamically as stable as isohumulene (unlike the caryophyllene nitrosite reaction where isocaryophyllene is the only product).

Epoxidation of isohumulene (103) with one mole equivalent of m-chloroperoxybenzoic acid[7] produced one major compound, $C_{15}H_{24}O$ with the nmr spectrum: $\delta(CDCl_3,ppm)$, 1.0 (3H,s), 1.1 (3H,s), 1.3 (3H,s), 1.6 (3H,bs), and 5.0-5.5 (3H,m). The absence of the doubly allylic protons on C-3 (2.7 ppm in isohumulene) suggested that this was isohumulene-1,2-epoxide (114). The reaction of two equivalents of m-chloroperoxybenzoic acid with isohumulene produced isohumulene-1,2-8,9-bisepoxide (115) which displays the nmr spectrum: $\delta(CDCl_3,ppm)$ 1.1 (6H,s), 1.2 (3H,s), 1.3 (3H,s), and 5.2-5.5 (2H,m). Thus the order of reactivity remains $\Delta^{1,2} > \Delta^{8,9} > \Delta^{4,5}$.

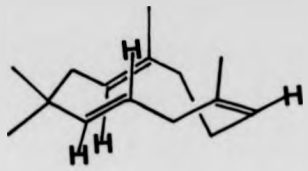


(114)

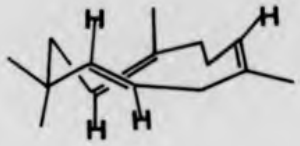


(115)

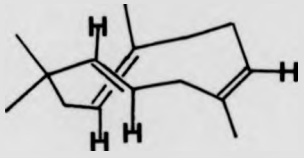
This work has stimulated a study of the conformational behaviour of isohumulene (103) by empirical force field calculations.[84] Some calculations are being carried out at the



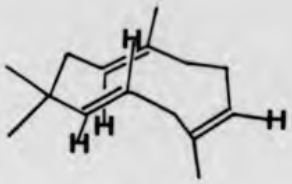
(TT)



(CT)



(CT^*)



(TT^*)

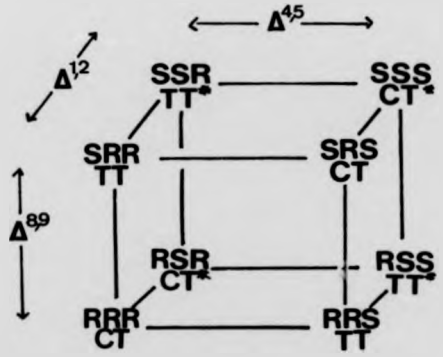


Figure 26

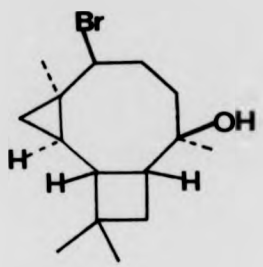
time of writing by Dr. W. V. Steele in this department and the results are very interesting especially in the light of the work of Matsumoto *et al.*[82] on humulene, where cyclization pathways of the most stable conformers could be predicted.

The preliminary results reveal that isohumulene exists mainly (98.3%) as the conformation designated TT (*vide infra*) which has a calculated heat of formation ΔH_f^o = 3.7 kcal/mol. The CT conformer (1.2%) and the CT* conformer (0.5%) have the heats of formation 5.1 and 6.8 kcal/mol respectively (see Appendices 2, 3 and 4). The other possible conformer (TT*) does not appear to exist and obviously possesses a relatively high heat of formation. The correlation diagram for the conformations of isohumulene is given in Figure 26.

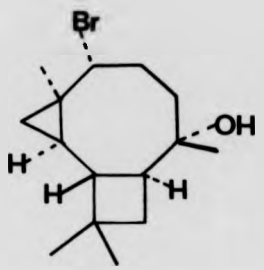
It is reasonable to assume that isohumulene (103) (or the 4,5-epoxide (107)) would adopt the TT conformation in any biogenetic type cyclization, by analogy of the work of Matsumoto *et al.*[82] on the cyclization of humulene. This being true, C_4-C_8 bond formation would produce a *trans*-fused ring junction and such compounds have not been found as natural products. These initial results of the conformational study invalidate the original hypothesis that isohumulene may be a biogenetic precursor to some metabolites.

An *in vitro* study of acid-catalysed cyclization of isohumulene would be worthy of attention. In view of the epoxidation results (*vide supra*) the initial electrophilic attack should occur at the $\Delta^{1,2}$ double bond and the TT conformation is ideally arranged for C_2-C_4 and C_5-C_8 bond formation. Thus treatment of isohumulene with, for example,

aqueous N-bromosuccinimide may produce the bromohydrin (116). This would make an interesting comparison to the treatment of humulene (10) with aqueous N-bromosuccinimide[85] which gives the bromohydrin (117) whose stereochemistry reveals that cyclization occurs <u>via</u> the CT conformation of humulene.



(116)



(117)

EXPERIMENTAL

Melting points are uncorrected and were determined on a Kofler hot-stage apparatus; boiling points are not corrected. Kieselgel GF_{254} (Merck) silica was used for all preparative thin layer chromatography. Analytical tlc plates were eluted with 20% ethyl acetate/petroleum ether solution unless otherwise stated and stained with iodine vapour and/or ceric ammonium sulphate followed by heating to approximately 150°C. Petroleum ether refers to the fraction of boiling range 60-80°C and all organic solvents were dried over magnesium sulphate unless otherwise stated. Where necessary, solvents were purified and dried, and reagents were either distilled or recrystallised.

Infra-red spectra were recorded on a Perkin-Elmer 557 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) or a Brücker WP80 (80 MHz) nmr spectrometer using deuterated chloroform as 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 Instem Data Mass Maxi data processing system. Gas-liquid chromatographic analyses were carried out on a Perkin-Elmer F11 Gas Chromatograph. Microanalyses were carried out in the department by Mrs. G. Berry.

1. Preparation of humulene trisepoxide (11)[7]

Humulene (10) (97% purity, 15g, 73.4 mmol) was dissolved in dichloromethane (400 ml) and aqueous sodium bicarbonate solution added (600 ml). The mixture was stirred magnetically at room temperature and m-chloroperoxybenzoic acid added slowly (85% purity, 47.69g, 0.235 mols). On completion of the peroxy acid addition the reaction mixture was stirred for 12 hours at room temperature.

The two layers were separated and the organic layer was washed with 1M aqueous sodium hydroxide solution (500 ml) followed by water (500 ml), and then dried. The solution was filtered and the solvent removed under vacuum to yield a yellow-green oil which was dissolved in a small amount of petroleum ether. A white solid precipitated which was removed by filtration and washed with petroleum ether. The filtrate and washings were recycled through the process of solvent removal, precipitation, and filtration until 16.3g (88%) of the trisepoxide (11) was obtained, mp. 114-118°C. Analytical tlc showed one spot Rf.0.12.

δ = 0.88 (3H,s), 1.10 (3H,s), 1.38 (6H,s), and 2.20-3.10 (4H,m).

2. Preparation of humulene-4,5-epoxide (7)[9,10]

Tetrahydrofuran (dried by 24 hours reflux over sodium, then 24 hours reflux over lithium aluminium hydride) (250 ml) was distilled directly into a pre-dried 3-necked 500 ml conical flask which was fitted with a magnetic follower and an alcohol thermometer carried in a thermometer pocket/pressure vent fitted with a silica gel guard tube. Nitrogen was dried by passing it

through concentrated sulphuric acid and introduced into the flask through a Subaseal stopper. With a glass stopper in the third port, the tetrahydrofuran was cooled to -70°C and stirred, maintaining that temperature with an acetone/Drikold bath. Resublimed tungsten hexachloride (15.78g, 0.04 moles), previously packed in glass ampoules under nitrogen, was transferred to the flask from a glass reservoir when the solvent temperature had stabilised below -70°C, vigorous stirring being required to keep the solid mobile. Immediately on addition of the tungsten hexachloride, a Subaseal stopper was fitted to the third port and the mixture stirred for 15 minutes at -70°C. n-Butyllithium (1.6M in hexane, 74.6 ml, 0.12 mols) was introduced through the subaseal by a hypodermic syringe, care being taken to ensure that the reaction temperature did not rise above -65°C. On completion of the addition, the mixture was stirred for 10 minutes at -70°C then allowed to warm to room temperature where the colour changed from pea-green to dark blue/black and all solids dissolved. The solution was cooled to 10°C and humulene trisepoxide (11) (4.37g, 17.3 mmol) was quickly added. A reflux condenser was fitted to the centre port, the thermometer was transferred to the third port and the mixture stirred at room temperature for 5 minutes after which it was heated rapidly to 45-50°C using a pre-heated oil bath (80°C). After stirring at that temperature for 45 minutes, the reaction mixture was cooled to 10°C, poured into a separating funnel containing ether (50 ml) and an aqueous solution (1.5M in sodium tartrate and 2M in sodium hydroxide, 500 ml). The mixture was shaken vigorously, the ethereal layer separated, shaken again with aqueous sodium tartrate/sodium hydroxide solution (500 ml), washed with brine, dried, filtered

and the solvent removed under vacuum leaving a greenish-yellow oil, crude yield 4.3g. Analytical tlc showed predominantly the desired epoxide (7) Rf 0.55, with humulene Rf 0.73, humulene-1,2-epoxide (23) Rf 0.49, humulene diepoxides Rf ∿ 0.3 and some unreacted trisepoxide (11) as the other significant components. The epoxide (7) was purified by high pressure column chromatography using Kieselgel 60 (Art.7739) (ratio 2:1) and eluting with 2% ether/pet.ether. A pale yellow oil was obtained (2.19g, 57%).

δ = 0.71 (3H,s), 1.05 (3H,s), 1.50 (3H,s), 1.60 (3H,s), 2.40-3.00 (2H,m), and 4.85 (2H,m).

3. Formation of the diol (14)[11] in the preparation of humulene-4,5-epoxide (7)

The diol (14) was formed in the deoxygenation conditions above when the tetrahydrofuran was dried by addition of lithium aluminium hydride only and then distilled directly into the reaction flask. Tungsten hexachloride was stored in a desiccator (over silica gel) and added to the reaction vessel directly from these conditions.

After elution of the 4,5-epoxide (7) from the chromatography column, elution with ether gave the diol (14) fraction which yielded colourless crystals (0.25g from 4.37g of trisepoxide): mp 109-111°C.

$\bar{\nu}_{max}$ (nujol): 3320, 1660, 1095, 1022, and 925 cm^{-1}.

δ = 0.36-1.09 (3H,m), 0.93 (3H,s), 0.95 (3H,s), 1.09 (3H,s), 1.63 (3H,bs), 2.78 (1H,dd), 2.95 (1H,d), and 5.26 (1H,br.dd).

M^+ = 238

Rf = 0.22 (100% ethyl acetate).

4. Attempted formation of diol (14) by action of aqueous lithium chloride and sodium hydroxide on humulene-4,5-epoxide (7)

Humulene-4,5-epoxide (10 mg) was dissolved in tetrahydrofuran (0.5 ml) and added to an aqueous solution of lithium chloride (10 mg in 1 ml) and the solution shaken for 30 minutes. An aqueous solution (2 ml) of 2M sodium hydroxide and 1.5M sodium tartrate with diethyl ether (1 ml) (to imitate work-up procedure in part 2) was added, but no reaction was observed after 1 hour (as followed by analytical tlc).

5. Attempted formation of diol (14) from humulene-4,5-epoxide (7) on silica

Small quantities of humulene-4,5-epoxide (10 mg) were dissolved in anhydrous ether (2 ml) and different chromatography silicas (300 mg) (which had been exposed to atmospheric moisture) added to the solutions. Types of silicas used were BDH 60-120 mesh, Fisons 100-200 mesh (M and B), Koch-Light 50-100 mesh and Kieselgel 60 (Art.7739). The solutions were monitored by analytical tlc every 30 minutes but no reaction occurred over 8 hours.

6. Attempted formation of diol (14) by treatment of humulene-4,5-epoxide with aqueous magnesium bromide, zinc chloride and lithium perchlorate

Small quantities of humulene-4,5-epoxide (10 mg) were dissolved in tetrahydrofuran (2 ml) and the desired aqueous solution of Lewis acid (above, 40 mg in 0.5 ml) added to the stirred solution. The solutions were monitored at room temperature and at reflux, but no diol (14) was formed after 8 hours, although other compounds were formed (> 6 by analytical tlc).

7. Attempted formation of diol (14) from humulene-4,5-epoxide (7) with boron-trifluoride etherate in diethyl ether (saturated with water)

The epoxide (7) (180 mg) was dissolved in diethyl ether (which had been thoroughly shaken with water) and boron trifluoride etherate (1.5 ml) added to the stirred solution. After 5 hours analytical tlc showed that most of the epoxide (7) had reacted to produce the diol (14). The reaction was quenched with sodium bicarbonate solution and the product isolated. The product proved to be humulene-4,5-epoxide (7) (180 mg) by analytical tlc and nmr.

8. Attempted formation of diol (14) from epoxide (7)

These reactions could not be monitored by analytical tlc since reaction was occurring on the silica itself. The formation of the diol (14) was confirmed by its isolation and characterisation by nmr. Recovered epoxide (7) was also identified by nmr.

(a) With silica and boron-trifluoride etherate in diethyl ether

Quantities of (7) (100 mg) were stirred in diethyl ether solution (10 ml) which had been saturated with water, with varying amounts of boron-trifluoride etherate (0.5, 1, 1.5, 2 and 2.5 ml) and silica used for analytical tlc (100, 200, 300, 400 and 500 mg). No diol was isolated in any case and epoxide (7) was the only compound recovered.

(b) On gravity columns

Quantities of (7) (50 mg) were added to the top on a short pad of silica (2g of Kieselgel 60 Art.7739) with increasing portions of boron-trifluoride etherate (0.5-2.5 ml)

4. Attempted formation of diol (14) by action of aqueous lithium chloride and sodium hydroxide on humulene-4,5-epoxide (7)

Humulene-4,5-epoxide (10 mg) was dissolved in tetrahydrofuran (0.5 ml) and added to an aqueous solution of lithium chloride (10 mg in 1 ml) and the solution shaken for 30 minutes. An aqueous solution (2 ml) of 2M sodium hydroxide and 1.5M sodium tartrate with diethyl ether (1 ml) (to imitate work-up procedure in part 2) was added, but no reaction was observed after 1 hour (as followed by analytical tlc).

5. Attempted formation of diol (14) from humulene-4,5-epoxide (7) on silica

Small quantities of humulene-4,5-epoxide (10 mg) were dissolved in anhydrous ether (2 ml) and different chromatography silicas (300 mg) (which had been exposed to atmospheric moisture) added to the solutions. Types of silicas used were BDH 60-120 mesh, Fisons 100-200 mesh (M and B), Koch-Light 50-100 mesh and Kieselgel 60 (Art.7739). The solutions were monitored by analytical tlc every 30 minutes but no reaction occurred over 8 hours.

6. Attempted formation of diol (14) by treatment of humulene-4,5-epoxide with aqueous magnesium bromide, zinc chloride and lithium perchlorate

Small quantities of humulene-4,5-epoxide (10 mg) were dissolved in tetrahydrofuran (2 ml) and the desired aqueous solution of Lewis acid (above, 40 mg in 0.5 ml) added to the stirred solution. The solutions were monitored at room temperature and at reflux, but no diol (14) was formed after 8 hours, although other compounds were formed (> 6 by analytical tlc).

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7. Attempted formation of diol (14) from humulene-4,5-epoxide (7) with boron-trifluoride etherate in diethyl ether (saturated with water)

The epoxide (7) (180 mg) was dissolved in diethyl ether (which had been thoroughly shaken with water) and boron trifluoride etherate (1.5 ml) added to the stirred solution. After 5 hours analytical tlc showed that most of the epoxide (7) had reacted to produce the diol (14). The reaction was quenched with sodium bicarbonate solution and the product isolated. The product proved to be humulene-4,5-epoxide (7) (180 mg) by analytical tlc and nmr.

8. Attempted formation of diol (14) from epoxide (7)

These reactions could not be monitored by analytical tlc since reaction was occurring on the silica itself. The formation of the diol (14) was confirmed by its isolation and characterisation by nmr. Recovered epoxide (7) was also identified by nmr.

(a) With silica and boron-trifluoride etherate in diethyl ether

Quantities of (7) (100 mg) were stirred in diethyl ether solution (10 ml) which had been saturated with water, with varying amounts of boron-trifluoride etherate (0.5, 1, 1.5, 2 and 2.5 ml) and silica used for analytical tlc (100, 200, 300, 400 and 500 mg). No diol was isolated in any case and epoxide (7) was the only compound recovered.

(b) On gravity columns

Quantities of (7) (50 mg) were added to the top on a short pad of silica (2g of Kieselgel 60 Art.7739) with increasing portions of boron-trifluoride etherate (0.5-2.5 ml)

and the pad immediately eluted with diethyl ether (saturated with water). Compound (7) (50 mg) was the only substance recovered in each case.

(c) On preparative tlc plates impregnated with boron-trifluoride etherate

A preparative tlc plate was eluted with a 10% solution of boron-trifluoride etherate in diethyl ether and allowed to dry. Epoxide (7) (100 mg) was applied to the plate in the normal manner and the plate eluted with diethyl ether (containing water). The edges of the plate were developed and the band corresponding to the diol (Rf 0.2) removed to yield 10 mg of the diol (14). No epoxide (7) was recovered and several bands less polar than (14) were present on the plate.

(d) On a preparative tlc plate

Epoxide (7) (100 mg) was applied to a preparative tlc plate followed by boron-trifluoride etherate (1 ml) and water (1 ml) (added quickly by Pasteur pipette). The plate was immediately eluted with diethyl ether and chromatography carried out in the normal way. Thus, 22 mg of diol (14) was isolated and 70 mg of the epoxide (7) recovered.

9. Formation of humulene-1,2-4,5-bisepoxide (18)[5]

The 4,5-epoxide (7) (50 mg, 0.25 mmol) in dichloromethane (30 ml) was stirred with 0.5M sodium bicarbonate solution (40 ml) and 85% m-chloroperoxybenzoic acid (51 mg, 0.25 mmol) was added. After 1 hour analytical tlc revealed one major spot (Rf 0.25). The organic layer was separated and washed with 1M sodium hydroxide solution followed by water and then dried. Preparative tlc (10% ethyl acetate/pet.ether) yielded the desired bisepoxide (18) (an oil, 35 mg, 60%).

δ = 0.8 (3H,s), 1.1 (3H,s), 1.4 (3H,s), 1.7 (3H,bs), 2.3-2.8 (3H,m), and 5.15 (1H,br,dd,J = 3Hz and 8Hz). (Identical to spectrum of compound produced by A. Sattar.[5])

10. Reduction of humulene-1,2-4,5-bisepoxide (18) with lithium in ethylamine

The bisepoxide (18) (20 mg, 0.08 mmol) was dissolved in ethylamine (3 ml) at -23°C (carbon tetrachloride/Drikold bath) and lithium shot (200 mg) added. The reaction was followed by analytical tlc (100% ethyl acetate) and after 3 hours all of the bisepoxide had reacted producing more polar products (74) but none had the polarity of the desired diol (14).

11. Preparation of alcohols (5) and (6)[2]

Humulene-4,5-epoxide (5) (500 mg, 2.27 mmol) was dissolved in anhydrous ether (10 ml) and the solution stirred magnetically and cooled to -70°C using an acetone/Drikold bath. Boron-trifluoride etherate (280 µl, 2.27 mmol) was added quickly by microsyringe, the solution was stirred at -70°C for 1 hour, allowed to warm to room temperature and then stirred for a further 12 hours. The solution was worked up using saturated sodium bicarbonate solution and ether, the ethereal layer being dried, filtered and the solvent removed under vacuum to give a green-brown oil, crude yield 470 mg. Analytical tlc showed a small amount of non-polar material, a small amount of unreacted starting material and a large polar spot Rf 0.31. This material was separated by high pressure column chromatography on Kieselgel HF_{254} (Type 60) (ratio 20:1) using 5% ether/pet.ether as eluant to give a pale yellow oil (300 mg) which was subsequently separated into two compounds (5) and (6) by column chromatography using Hi-Flosil-Ag 20% $AgNO_3$ support (60-200 mesh) (ratio 33:1) and eluting with 2% ethyl acetate/pet.ether.

(5) mp. 63-64°C, yield 140 mg (28%)

$\bar{\nu}_{max}(CHCl_3)$ = 3610, 3060, 1050, 1030, and 1010 cm^{-1}

δ = 0.45-0.8 (3H,m), 0.90 (3H,s), 0.92 (3H,s), 1.00 (3H,s), 1.67 (3H,bs), and 3.23 (1H,d,J = 9.5Hz).

(6) yield 160 mg (32%)

$\bar{\nu}_{max}$ = 3610, 3060, 3040, 1650, 1055, 1030, 1012, and 8.25 cm^{-1}

δ = 0.3-0.9 (3H,m), 1.02 (9H,s), 1.64 (3H,bs), 3.21 (1H,d,J = 8Hz) and 5.33 (1H,m).

12. Acetylation of alcohol (5)[16]

The alcohol (5) (393 mg, 1.79 mmol) was dissolved in dry pyridine (0.5 ml) then acetic anhydride (219 mg, 2.15 mmol) was added and the mixture was allowed to stand at 0°C overnight. The reaction was worked up by adding cold water and extracting well with ice-cold saturated copper sulphate solution (2 x 5 ml), ice-cold saturated sodium carbonate solution (5 ml) and ice-cold water. The ether extract was dried, filtered and the solvent removed under vacuum. The crude oil was purifed by column chromatography using Kieselgel 60 (Art.9385) and eluting with 2% ether/pet.ether to give the ester (20) (320 mg, 68%).

Rf = 0.42.

δ = 0.45-0.8 (3H,m), 0.90 (3H,s), 0.92 (3H,s), 1.00 (3H,s), 1.70 (3H,bs) and 4.65 (1H,d,J = 9.5Hz).

M^+ (found = 262.1935; M^+ (calculated for $C_{17}H_{26}O_2$) = 262.1933.

13. Allylic oxidation of acetate (20) with Collins' reagent[17,18]

Chromium trioxide (1.83g, 18.3 mmol) was added to an ice-cold, rapidly stirred solution of dry pyridine (2.89g) in distilled dichloromethane (30 ml) under nitrogen. The deep burgundy solution was stirred for 5 minutes then allowed to

warm up to room temperature. The ester (20) (320 mg, 1.22 mmol) was added in dichloromethane solution and the reaction left for 24 hours. The reaction mixture was poured from the flask, the precipitate in the flask washed with ether and the washings combined with the organic layer. This was washed with saturated sodium bicarbonate solution, saturated copper sulphate solution and then with brine. The organic layer was dried, filtered and the solvent removed under vacuum to give a crude oil. Purification by column chromatography using Kieselgel 60 (Art.9385) and 3-40% ether/pet.ether gave the acetoxy-ketone (21) (90 mg, 27%).

mp. 78-79°C; Rf = 0.25.

λ_{max}^{EtOH} = 240 nm (ε = 10,200)

$\bar{\nu}_{max}(CHCl_3)$ = 1730, 1700 and 1640 cm^{-1}

δ = 0.73-1.0 (3H,m), 0.8 (3H,s), 1.0 (3H,s), 1.03 (3H,s), 1.70 (3H,bs), 2.04 (3H,s), 2.25-2.8 (5H,m) and 4.7 (1H,d,J = 9Hz).

M^+ (found) = 276.1733; M^+ (calculated for $C_{17}H_{24}O_3$) = 276.1725.

14. Attempted allylic oxidation with pyridinium chlorochromate[19]

Pyridium chlorochromate (244 mg, 1.134 mmol) was dissolved in dichloromethane (5 ml) and stirred at room temperature. The ester (33 mg, 0.126 mmol) was added in dichloromethane solution (1 ml) and the reaction monitored by analytical tlc over 48 hours. In this time, the acetate (20) remained unreacted.

15. Saponification of the keto-ester (21)[16]

The keto-ester (21) (80 mg, 0.29 mmol) was dissolved in methanol (10 ml) and potassium hydroxide solution (80 mg in 4 ml of water) was added. The solution was stirred at 70°C for

1 hour in an oil bath. Analytical tlc showed that the ester had been hydrolysed. The methanol was removed on the rotary evaporator, a small amount of water was added to the solution and the solution extracted with ether. The ethereal layer was dried, filtered and the solvent removed under vacuum. The keto-alcohol (19) was separated by preparative tlc using 50% ethyl acetate/pet.ether to give 43 mg (63%) of a colourless oil, Rf 0.23.

$\lambda_{max}^{CCl_4}$ = 253 nm (ε = 12,200)

$\bar{\nu}_{max}(CCl_4)$ = 3430, 1685, 1630, and 1030 cm^{-1}

δ = 0.5-1.0 (3H,m), 0.72 (3H,s), 0.91 (3H,s), 1.02 (3H,s), 1.65 (3H,bs), and 3.22 (1H,d,J = 8 Hz).

M^+ (found) = 234.1624; M^+ (calculated for $C_{15}H_{22}O_2$) = 234.1620.

16. Monoepoxidation of humulene (10)

Humulene (10) (1g, 4.9 mmol) was dissolved in dichloromethane (40 ml) and stirred rapidly (magnetically) with 0.5M sodium bicarbonate solution (60 ml) at room temperature. m-Chloroperoxybenzoic acid (85%, 0.994g, 4.9 mmol) was added and the reaction stirred for a further 2 hours. The reaction was worked up in the normal way (part 1) and 1.08g of a colourless oil collected. Analytical tlc revealed a small amount of humulene remaining (Rf 0.73), some humulene-4,5-epoxide (7) (Rf .55), a large spot for humulene-1,2-epoxide (23) and humulene-8,9-epoxide (9) (Rf 0.49) and some humulene-1,2-8,9-bisepoxide (Rf 0.30). High pressure column chromatography using Kieselgel 60 (Art.7739, ratio 20:1) and 3% ether/pet.ether separated humulene (100 mg), humulene-4,5-epoxide (39 mg, 4%) and a mixture of humulene-8,9-epoxide (9) and humulene-1,2-epoxide (23) (720 mg). Compounds (9) and (23) were further separated using Hi-Flosil-Ag, 20% $AgNO_3$

support (ratio 33:1) and eluting with 10% ethyl acetate/ pet.ether to give the 1,2-epoxide (23) (600 mg, 55%) and 8,9-epoxide (9) (120 mg, 11%). (On analytical tlc impregnated with $AgNO_3$, 40% ethyl acetate/pet.ether, Rf 23 = 0.45, Rf (9) = 0.30).

This reaction was repeated with other solvents and at 0°C (salt/ice bath) using the procedure described and the results are summarised in Table 2. The total yield of mono-epoxides (23) + (9) + (7) was always ∿ 760 mg.

TABLE 2

Variation of product ratio with solvent and temperature

Solvent	Temperature	Ratio of (23):(9):(7)*
CH_2Cl_2	18°C	15:3:1
CH_2Cl_2	0°C	11:3:1
$CHCl_3$	0°C	12:3:1
CCl_4	0°C	10:4:1

* Calculated from duplicated results.

17. Preparation of humulene-1,2-8,9-bisepoxide (26)

Epoxidation of humulene (15.24g, 7.45 mmols) in the normal way[7] (part 1) with m-chloroperoxybenzoic acid (25.74g, 14.91 mmol) yielded 15.5g of a viscous oil after 8 hours. This oil was dissolved in a little pet.ether from which a white solid precipitated, and this was removed and washed with cold pet.ether. The filtrate and washings were recycled through the process of solvent removal, precipitation and filtration until 12.5g (80%) of the bisepoxide (26) was collected (mp. 105.5°C).

Rf = 0.30

δ = 1.06 (3H,s), 1.18 (3H,s), 1.28 (6H,s), and 5.3-5.5 (2H,m).

The spectrum was identical to that of authentic material.[86]

18. Reaction of humulene-1,2-epoxide (23) with trifluoroacetyl iodide and sodium iodide[28]

Sodium iodide (272 mg, 1.816 mmol), which had been dried in a vacuum oven, was stirred with acetonitrile (1 ml) (distilled from P_2O_4) and tetrahydrofuran (1 ml) (distilled from $LiAlH_4$). Trifluoroacetic anhydride (95 mg, 0.454 mmol) was injected into the reaction vessel and after 5 minutes the deep yellow solution was cooled in an ice bath. The epoxide (23) (100 mg, 0.454 mmol) was injected in tetrahydrofuran solution and after 5 minutes the ice bath was removed and the reaction mixture was worked up by dilution with aqueous sodium thiosulphate solution and extracted with ether. Preparative tlc (2% ethyl acetate/pet.ether) yielded 60 mg of humulene (64%).

19. Reaction of humulene-1,2-8,9-bisepoxide (26) with trifluoroacetyl iodide and sodium iodide[28]

The reaction with bisepoxide (26) (100 mg, 0.424 mmol) in the conditions above (part 18) using sodium iodide (254 mg, 1.696 mmol) and trifluoroacetic anhydride (89mg, 0.424 mmol) was monitored by analytical tlc and after 24 hours there was no trace of monoepoxides, although a plethora of more polar compounds were formed.

20. Reaction of humulene-1,2-epoxide (23) with diphosphorus tetraiodide[27]

A solution of epoxide (23) (100 mg, 0.424 mmol) in dry ether (5 ml) and pyridine (0.5 ml) was added to a stirred suspension of P_2I_4 (251 mg, 0.424 mmol) in ether (5 ml). The mixture was stirred for 4 hours at room temperature, then quenched by the addition of water and extracted with ether.

The ethereal layer was washed with saturated copper sulphate solution and aqueous sodium thiosulphate solution. The organic solution was dried and the solvent removed on a rotary evaporator. Preparative tlc of the crude product yielded 54 mg of humulene (58%).

21. Reaction of humulene-1,2-8,9-bisepoxide (26) with diphosphorus tetraiodide[27]

The above reaction was repeated with the bisepoxide (100 mg, 0.424 mmol) and P_2I_4 (235 mg, 0.424 mmol). The reaction was monitored by analytical tlc and after 8 hours the bisepoxide had completely reacted to yield many more polar products, but no monoepoxide (9) was produced.

22. Attempted rearrangement of humulene-8,9-epoxide (9) with protic acids

These reactions were carried out on 10 mg samples of humulene-8,9-epoxide and monitored by analytical tlc.

(a) With p-toluenesulphonic acid (PTSA).

The epoxide (9) was dissolved in anhydrous ether (5 ml) and PTSA (10 mg) added to the stirred solution at room temperature. No reaction had occurred after 24 hours. The reaction was repeated in toluene at room temperature to give an identical result but at reflux (111°C), a multitude of products with the polarity of hydrocarbons were produced.

(b) With glacial acetic acid

The epoxide (9) was stirred with glacial acetic acid (1 ml) and acetone (1 ml) for 24 hours, at room temperature and at 70°C. At the end of this period, no reaction had occurred in either case.

(c) With trifluoroacetic acid

The epoxide (9) was stirred with trifluoroacetic acid (1 ml) and acetone (1 ml) at room temperature. After 48 hours most of (9) remained but a number of more polar compounds were produced. The reaction was repeated at 50°C to produce the same product range after 6 hours.

(d) With sulphuric acid

Compound (9) dissolved in acetone (1.5 ml) was treated with 1.8M sulphuric acid (1.5 ml) for 24 hours at room temperature. After this time all the epoxide had reacted to give a plethora of more polar compounds (78). At 70°C the same product range was produced in 1 hour.

23. Reaction of humulene-8,9-epoxide (9) with Lewis acids

A series of reactions which were monitored by analytical tlc were carried out on quantities of epoxide (9) (10 mg) and the conditions are summarised in Table 3.

From the conditions giving least product range, scale up reactions were carried out.

(a) With boron-trifluoride etherate in toluene

The epoxide (9) (50 mg, 0.23 mmol) was dissolved in toluene, then boron-trifluoride etherate (65 mg, 0.46 mmol) added and the reaction stirred for 30 minutes at room temperature. The reaction was quenched with aqueous sodium bicarbonate and a little ether added. Analytical tlc of the organic layer revealed the formation of a major less polar compound (Rf 0.76) and preparative tlc (eluted with 10% ethyl acetate/pet.ether) yielded 27 mg of the ketone (27) as a colourless oil (54%).

TABLE 3

Small scale reaction conditions for rearrangement of (9) with Lewis acids

Lewis acid	Mole equivalents of acid	Solvent	Temperature (°C)
$BF_3(C_2H_5)_2O$	1,3	diethyl ether, toluene	-70, 18.
$SnCl_4$	1,5,15,30	toluene, pet.ether, CCl_4, $CHCl_3$	-60, 18.
$AlCl_3$	1,5	toluene, $CHCl_3$, CCl_4	-60, 18.

$\bar{\nu}_{max}$ = 3020, 2920, 1695 and 1640 cm^{-1}

δ = 1.05 (6H,s), 1.20 (3H,d,J = 9Hz), 1.70 (3H,bs), 2.5-3.1 (5H,m), 4.8 (1H,br.dd), and 5.1-5.9 (2H,m).

M^+ (found) = 220.1830; M^+ (calculated for $C_{15}H_{24}O$) = 220.1827.

(b) Treatment of 8,9-epoxide (9) with tin(IV) chloride in chloroform

The epoxide (9) (200 mg, 0.91 mmol) was stirred at -60°C (chloroform/Drikold bath) in chloroform (25 ml) and tin(IV) chloride (3.6g, 13.65 mmol) injected into the solution (under nitrogen). After 2 hours the reaction was quenched with saturated

sodium bicarbonate solution and the organic layer dried. Analytical tlc of this layer revealed a major more polar compound Rf 0.38 (uv active) and some hydrocarbons (which increased with reaction time). Preparative tlc (10% ethyl acetate/pet.ether) yielded 60 mg of a colourless oil (25%).

λ_{max}^{EtOH} = 245 nm (ϵ = 11,280)

$\bar{\nu}_{max}$ = 3620 and 1070 cm^{-1}

δ = 0.89 (3H,s), 0.91 (3H,d,J = 7Hz), 0.94 (3H,d,J = 7Hz), 1.76 (3H,bs), 2.3-2.8 (5H,m), 3.83 (1H, X part of an ABX system, $J_{AX} \sim J_{BX} \sim$ 9Hz), and 5.90 (1H,bs).

M^+ (found) = 220.1822; M^+ (calculated for $C_{15}H_{24}O$) = 220.1827.

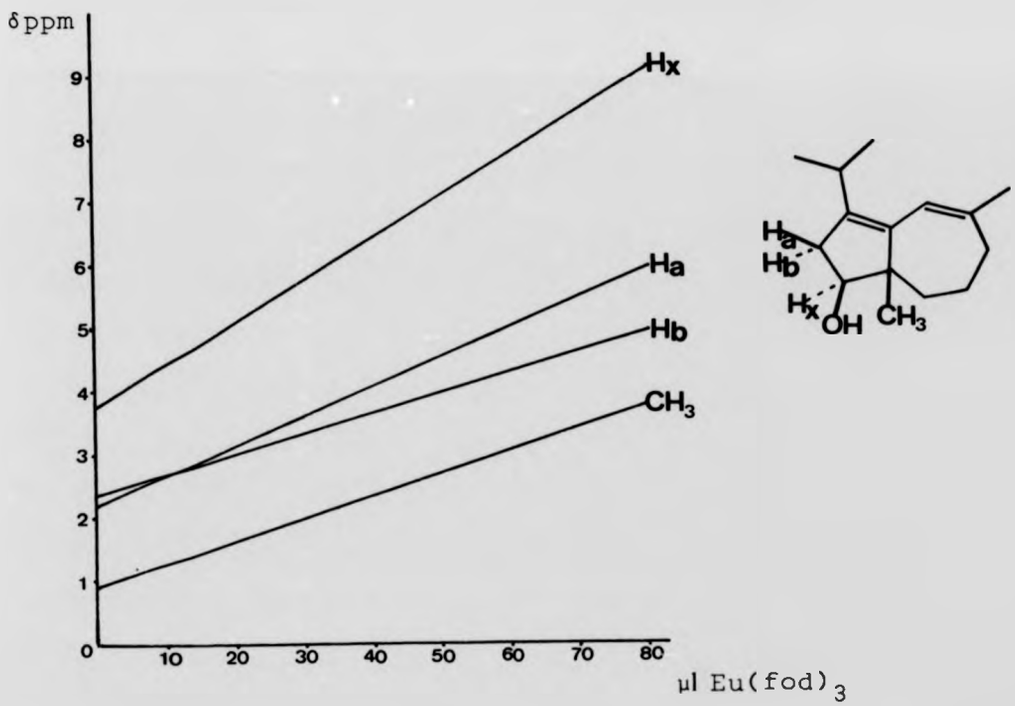

Figure 21

Variation of chemical shift with increasing concentration of $Eu(fod)_3$.*

* 10^{-4} mole $Eu(fod)_3$ in 1ml. $CDCl_3$. 0.1 mmol of (28) in 0.3ml $CDCl_3$.

sodium bicarbonate solution and the organic layer dried. Analytical tlc of this layer revealed a major more polar compound Rf 0.38 (uv active) and some hydrocarbons (which increased with reaction time). Preparative tlc (10% ethyl acetate/pet.ether) yielded 60 mg of a colourless oil (25%).

λ_{max}^{EtOH} = 245 nm (ε = 11,280)

$\bar{\nu}_{max}$ = 3620 and 1070 cm^{-1}

δ = 0.89 (3H,s), 0.91 (3H,d,J = 7Hz), 0.94 (3H,d,J = 7Hz), 1.76 (3H,bs), 2.3-2.8 (5H,m), 3.83 (1H, X part of an ABX system, $J_{AX} \sim J_{BX} \sim$ 9Hz), and 5.90 (1H,bs).

M^+ (found) = 220.1822; M^+ (calculated for $C_{15}H_{24}O$) = 220.1827.

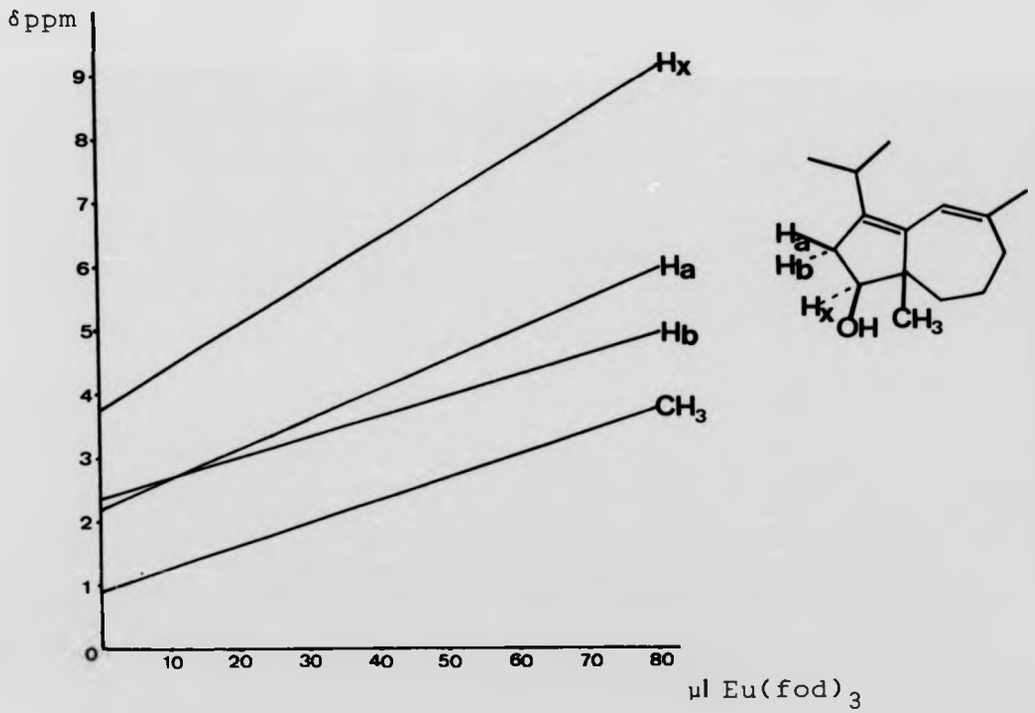

Figure 21

Variation of chemical shift with increasing concentration of $Eu(fod)_3$.*

* 10^{-4} mole $Eu(fod)_3$ in 1ml. $CDCl_3$. 0.1mmol of (28) in 0.3ml $CDCl_3$.

24. Oxidation of alcohol (28) with pyridinium chlorochromate[19]

The alcohol (28) (35 mg, 0.16 mmol) was added to a suspension of pyridinium chlorochromate (52 mg, 0.24 mmol) in dichloromethane (5 ml) and stirred at room temperature for 45 minutes. The reaction mixture was then passed through a short pad of fluorosil (2g) and flushed with dichloromethane. The solvent was removed to give 30 mg of a colourless oil which analytical tlc revealed to consist of mainly one compound (Rf 0.64). Preparative tlc (10% ethyl acetate/pet.ether) gave 20 mg of the ketone (29) (57%).

$\bar{\nu}_{max}$ = 1745 cm^{-1}

δ = 0.89 (3H,s), 0.91 (3H,d,J = 7Hz), 0.94 (3H,d,J = 7Hz), 1.76 (3H,bs), 2.7 (2H,bs), and 5.90 (1H,bs).

M^+ = 218.

25. Formation of tosylhydrazone (32)

The ketone (29) (12 mg, 5.5 x 10^{-2} mmol) was refluxed in methanol (3 ml) with tosylhydrazine (20 mg, 0.11 mmol) for 6 hours. The methanol was removed on the rotary evaporator and the crude product separated by preparative tlc (10% ethyl acetate/pet.ether) to yield the desired tosylhydrazone (an oil, 14 mg, 71%).

δ = 0.89 (3H,s), 0.91 (3H,d,J = 7Hz), 0.94 (3H,d,J = 7Hz), 1.76 (3H,bs), 2.7 (2H,bs), 5.90 (1H,bs), and 7.0-7.7 (4H,A_2X_2 system).

Rf = 0.35.

26. Reduction of tosylhydrazone (32) with sodium borohydride in dioxane[33]

The tosylhydrazone (14 mg, 2.9 x 10^{-2} mmol) was dissolved in dioxane (5 ml), sodium borohydride (38 mg, 1 mmol) added and the reaction mixture refluxed for 6 hours. The reaction

was quenched with water and ether added. Preparative tlc (pet.ether) of the crude material yielded 6 mg of the desired hydrocarbon (30).

Rf = 0.70

λ_{max}^{EtOH} = 1380, 1375, 1370, 1360, and 860 cm^{-1}

δ = 0.90 (3H,d,J = 7Hz), 0.92 (3H,s), 0.94 (3H,d,J = 7Hz), 1.72 (3H,s), and 5.90 (1H,s).

glc (5% Apiazon L), $pN_2 = O_2 = H_2$ = 20 lb/in^2, 195°C

Rf = 5.7 minutes.

glc - mass spectrum, m/e (rel.intensity) 204 (M^+, 63), 189 (100), 161 (91), and 105 (32).

Authentic material prepared from humulene,[31] gave identical spectral and analytical data. A 1:1 mixture of authentic (30) and (30) which had been prepared from (28), was indistinguishable by glc - mass spectrometry.

27. Preparation of humulol (31)[30]

Humulene (2g, 9.8 mmol) was mixed with 80% aqueous acetic acid (30 ml) and the heterogeneous mixture stirred magnetically and heated at 100°C for 2 hours. The mixture was cooled, neutralised with saturated sodium bicarbonate solution and then extracted with ether. The ethereal layer was washed with water, dried, filtered and the solvent evaporated to give a green-brown oil. The crude product was purified by high pressure column chromatography (Kieselgel 60, Art.7739, ratio 20:1) and eluting with 5% ether/pet.ether to give humulol as a pale yellow oil, yield 520 mg (24%).

δ = 0.99 (3H,s), 1.02 (3H,s), 1.11 (3H,s), 1.52 (3H,d,J = 1Hz), and 4.55-5.48 (3H,m).

28. Monoepoxidation of humulol (31) with m-chloroperoxybenzoic acid

Humulol (448 mg, 2.04 mmol) and 85% m-chloroperoxybenzoic acid (414 mg, 2.04 mmol) were reacted under the conditions for epoxidation described in part 1,[7] using dichloromethane (40 ml) and 0.5M sodium bicarbonate solution (60 ml). The organic layer gave 450 mg of a yellow, viscous oil which was separated by Kieselgel HF_{254} and 30% ether/pet.ether giving 225 mg (46% of the desired epoxide (33).

Rf = 0.12.

$\bar{\nu}_{max}$ ($CHCl_3$) = 3610, 1380, 1365, 1130, 1090, and 1075 cm^{-1}

δ = 1.05 (3H,s), 1.17 (3H,s), 1.29 (6H,s), 2.72-2.90 (1H,dd,J = 10Hz and 2Hz), and 5.21-5.81 (2H,m).

M^+ (found) = 238.1938; M^+ (calculated for $C_{15}H_{26}O_2$) = 238.1933.

29. Reaction of epoxide (33) with tin(IV) chloride

Reaction of (33) (200 mg, 0.84 mmol) in the conditions described in 23(b) with tin(IV) chloride (3.3g, 12.6 mmol) gave 80 mg of alcohol (28) (40%).

30. Hydroboration of humulene (10)[40]

Humulene (500 mg, 2.45 mmol) was dissolved in tetrahydrofuran (25 ml, $LiAlH_4$ dried) at 0°C and 1M borane-tetrahydrofuran complex (in tetrahydrofuran, 0.82 ml) added under nitrogen. The reaction was stirred for 30 minutes then quenched with 30% hydrogen peroxide (25 ml) and 10% potassium hydroxide solution (25 ml). The reaction 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 490 mg of a colourless, viscous oil. High pressure column

chromatography using Kieselgel 60 (Art.7739) (ratio 20:1) and eluting with 10% ether/pet.ether gave 326 mg of isohumulol (60%).

Rf = 0.40.

δ = (3H,d,J = 6Hz), 1.02 (3H,s), 1.07 (3H,s), 1.57 (3H,bs), 3.63 (1H,m), and 4.7-5.3 (3H,m).

m/e: (relative intensity), 222 (64,M^+), 151 (29), 123 (26), 110 (100), 95 (50), and 82 (98).

Data identical to authentic material.[32]

31. Hydroboration of humulene-4,5-epoxide (7)

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

(a) With borane-tetrahydrofuran[40]

Epoxide (7) (10.6 mg, 4.82×10^{-2} mmol) and 1M borane-tetrahydrofuran (16 µl, 1.6×10^{-2} mmol) were reacted in the conditions described in part 30. Analytical tlc of the isolated product revealed a multitude of more polar compounds (79).

(b) With 9-boranbicyclo[3.3.1]nonane (9-BBN)[41]

Epoxide (7) (35 mg, 0.159 mmol) was dissolved in tetrahydrofuran (1 ml) under nitrogen at room temperature and 0.5M 9-BBN (0.32 ml, 0.159 mmol) added. After 24 hours little of the 4,5-epoxide remained and a large number of more polar compounds were formed.

(c) With borane-methyl sulphide (BMS)[42]

Epoxide (7) (150 mg, 0.682 mmol) was dissolved in tetrahydrofuran (5 ml) and 1M BMS (0.227 ml, 0.227 mmol) injected into the solution under nitrogen. The reaction was stirred at room temperature for 3 hours to give a product range similar to part 31(a).

(d) With catecholborane

Epoxide (7) (30 mg, 0.136 mmol) was dissolved in tetrahydrofuran at room temperature under nitrogen and 1M catecholborane (in tetrahydrofuran, 0.136 ml) added at room temperature. After 24 hours most of the epoxide (7) had reacted to give a plethora of more polar compounds.

32. Lithium ethylamine opening of humulene-1,2-epoxide (23)[32]

A dark blue solution of (23) (1.9g, 8.6 mmol) and lithium (3g) in ethylamine (100 ml) was cooled in a carbon tetrachloride/Drikold bath, and stirred for 3 hours. After this time analytical tlc showed complete disappearance of starting material. Saturated ammonium chloride solution was added and the ethylamine evaporated. The organic material was extracted with ether, dried and the solvent evaporated to give 1.9g of crude material. High pressure column chromatography with Kieselgel 60 Art.7739 and eluting with 10% ether/pet.ether gave 1g of the desired isohumulol (52%).

33. Monoepoxidation of isohumulol (51)

(a) With m-chloroperoxybenzoic acid

Isohumulol (180 mg, 0.811 mmol) was reacted with 85% m-chloroperoxybenzoic acid (165 mg, 0.811 mmol) in the conditions already described for epoxidation (part 1),[7] in dichloromethane (40 ml) and 0.5M sodium bicarbonate solution (60 ml). Analytical tlc of the crude product revealed one major spot Rf 0.31 (50% ethyl acetate/pet.ether). Preparative tlc (25% ethyl acetate/pet.ether) yielded 130 mg of the epoxide (53) (67%).

$\delta(CCl_4)$ = 0.85 (3H,d,J = 6Hz), 1.00 (3H,s), 1.29 (6H,s), 2.60 (1H,m), 3.48 (1H,m), and 4.9-5.1 (2H,m).

M^+ (found) = 238.1944; M^+ (calculated for $C_{15}H_{26}O_2$) = 238.1933.

(b) With trifluoroperoxyacetic acid[44]

Trifluoroperoxyacetic acid (0.45 mmol) was prepared by addition of trifluoroacetic anhydride (76 µl, 0.54 mmol) to a suspension of hydrogen peroxide (13 µl, 86%, 0.45 mmol) in dichloromethane (2 ml) (in an ice bath). This suspension was gradually added to a stirred solution of (51) (100mg, 0.42 mmol) dissolved in dichloromethane (1 ml) containing sodium carbonate (143 mg, 1.35 mmol). The reaction mixture was refluxed for 30 minutes then cooled and the insoluble salts filtered and the solution dried and solvent removed. Preparative tlc yielded 65 mg of (53) as the only major product (61%).

(c) With benzonitrile-hydrogen peroxide[45]

A mixture of isohumulol (146 mg, 0.658 mmol), hydrogen peroxide (30%, 52 µl, 0.658 mmol), benzonitrile (68 mg, 0.658 mmol), methanol (3 ml) and potassium bicarbonate (100 mg) was stirred for 48 hours. The mixture was then diluted with water and extracted with ether. Preparative tlc of the crude product gave 95 mg of the epoxide (53) (61%).

35. Formation of the methyl ether (54)

(a) With n-butyllithium and methyl iodide

Isohumulol (211 mg, 0.959 mmol) was dissolved in tetrahydrofuran (10 ml, $LiAlH_4$ dried) and 2M n-butyllithium (0.625 ml, 1.15 mmol) added at ice bath temperature. Methyl iodide (2.04g, 14.38 mmol) was added gradually and the solution allowed to stir at room temperature for 24 hours. The reaction solution was then poured into a separating funnel containing ether and water, shaken well, the ethereal layer separated,

dried, and the solvent removed. Preparative tlc of the crude product (pet.ether) gave 170 mg of the methyl ether (54) (75%).

Rf = 0.62

$\bar{\nu}_{max}$ = 2960, 2930, 2880, and 1090 cm^{-1}

δ = 0.83 (3H,d,J = 6Hz), 1.02 (3H,s), 1.07 (3H,s), 1.57 (3H,bs), 3.29 (3H,s), 3.31 (1H,m), and 4.8-5.3 (3H,m).

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

δ = 13.4(q), 17.0(q), 24.4(q), 26.8(t), 29.9(q), 33.1(d), 37.5(t), 38.1(t), 39.5(s), 42.1(t), 56.9(q), 81.9(d), 122.9(d), 124.1(d), 136.5(s), and 140.4(d).

M^+ (found) = 236.2125; M^+ (calculated for $C_{16}H_{28}O$) = 236.2140.

(b) With sodium hydride and methyl iodide[46]

Isohumulol (51) (100 mg, 0.45 mmol) was added to a suspension of sodium hydride (21.6 mg, 0.9 mmol) in tetrahydrofuran (3 ml) followed by methyl iodide (128 mg, 0.9 mmol) and the reaction refluxed. The reaction was followed by analytical tlc and after 6 hours most of the alcohol (51) remained although several (74) less polar products were formed.

(c) With imidazole/dimethylformamide (DMF)/methyl iodide[47]

Isohumulol (51) (100 mg, 0.45 mmol), imidazole (216 mg, 4.5 mmol), methyl iodide (319 mg, 2.25 mmol) and DMF (2 ml) were stirred at 25°C. The reaction mixture was monitored by analytical tlc, but after 48 hours no reaction had occurred.

36. Monoepoxidation of the methyl ether (54)

The methyl ether (54) (50 mg, 0.212 mmol) and m-chloroperoxybenzoic acid (85%, 43 mg, 0.212 mmol) were reacted under the normal epoxidation conditions (part 1).[7] Preparative

tlc of the crude product gave 35 mg of the epoxide (55).

Rf = 0.30

$\delta(CCl_4)$ = 0.85 (3H,d,J = 6Hz), 1.00 (3H,s), 1.29 (6H,s), 2.60 (1H,m), 3.30 (3H,s), 3.31 (1H,m), and 4.5-5.1 (2H,m).

37. Reaction of methyl ether (54) with 2 mole equivalents of m-chloroperoxybenzoic acid

The methyl ether (54) (500 mg, 2.12 mmol) was reacted with m-chloroperoxybenzoic acid (431 mg, 4.24 mmol) in organic solvent (200 ml of CH_2Cl_2 or CCl_4) and 0.5M of aqueous sodium bicarbonate solution (250 ml). The isomer A and isomers (58) and (59) (B and C) (see Discussion) were separated by high pressure column chromatography using Kieselgel 60 Art.7739 and eluting with 10% ether/pet.ether. The overall yield of bisepoxide (A + B + C) was always ~ 340 mg (60%) in all cases. The effect of solvent, temperature and stirring speed is summarised in Table 4.

38. Deoxygenation of bisepoxides[9,10]

(a) Of isomer A

Isomer A (2.38g, 8.88 mmol), tungsten hexachloride (3.53g, 8.88 mmol) and 1.6M n-butyl lithium 16.6 ml, 26.6 mmol) were reacted in the conditions for deoxygenation described in part 2, except that the reaction mixture was held for 45 minutes at room temperature when addition of the epoxide was complete. Work-up procedure gave 2g of a yellow-green oil which on high pressure column chromatography using Kieselgel 60 (Art.7739) (ratio 20:1) and eluting with 5% ether/pet.ether, gave 900 mg of epoxide (66) (40%).

tlc of the crude product gave 35 mg of the epoxide (55).

Rf = 0.30

$\delta(CCl_4)$ = 0.85 (3H,d,J = 6Hz), 1.00 (3H,s), 1.29 (6H,s), 2.60 (1H,m), 3.30 (3H,s), 3.31 (1H,m), and 4.5-5.1 (2H,m).

37. Reaction of methyl ether (54) with 2 mole equivalents of m-chloroperoxybenzoic acid

The methyl ether (54) (500 mg, 2.12 mmol) was reacted with m-chloroperoxybenzoic acid (431 mg, 4.24 mmol) in organic solvent (200 ml of CH_2Cl_2 or CCl_4) and 0.5M of aqueous sodium bicarbonate solution (250 ml). The isomer A and isomers (58) and (59) (B and C) (see Discussion) were separated by high pressure column chromatography using Kieselgel 60 Art.7739 and eluting with 10% ether/pet.ether. The overall yield of bisepoxide (A + B + C) was always ∿ 340 mg (60%) in all cases. The effect of solvent, temperature and stirring speed is summarised in Table 4.

38. Deoxygenation of bisepoxides[9,10]

(a) Of isomer A

Isomer A (2.38g, 8.88 mmol), tungsten hexachloride (3.53g, 8.88 mmol) and 1.6M n-butyl lithium 16.6 ml, 26.6 mmol) were reacted in the conditions for deoxygenation described in part 2, except that the reaction mixture was held for 45 minutes at room temperature when addition of the epoxide was complete. Work-up procedure gave 2g of a yellow-green oil which on high pressure column chromatography using Kieselgel 60 (Art.7739) (ratio 20:1) and eluting with 5% ether/pet.ether, gave 900 mg of epoxide (66) (40%).

TABLE 4

Variation of diastereoisomers with epoxidation conditions

Solvent	Temperature (°C)	Stirring	Isomer A % Yield	Isomers (58) + (59) % Yield)
CCl_4	18	magnetic (fast)	29	32
CH_2Cl_2	0	magnetic (fast)	25	24
CH_2Cl_2	18	magnetic (slow)	26	33
CH_2Cl_2	18	magnetic (fast)	35	30
CH_2Cl_2	18	mechanical (vigorous)	60	6

Isomer A

mp. 102-104°C

Rf = 0.25

$\bar{\nu}_{max}$ = 2930, 1130, 1090, 790, and 760 cm^{-1}

δ = 0.84 (3H,d,J = 6Hz), 0.87 (3H,s), 1.05 (3H,s), 1.30 (3H,s), 3.27 (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), 31.7(d), 33.0(s), 35.5(t), 35.7(t), 40.1(t), 56.8(d), 57.0(q), 59.6(d), 61.6(s), 67.0(d) and 81.9(d).

M^+ (found) = 268.2030; M^+ (calculated for $C_{16}H_{28}O_3$) = 268.2038.

Isomers (58) and (59)

Rf = 0.43, 0.45.

$\bar{\nu}_{max}$ = 2930, 1130, 1090, 790, and 760 cm^{-1}

The ^1H nmr spectrum was of two almost identical spectra, superimposed upon each other and the isomers (58) and (59) were present in almost equal quantities (from integration of methoxyl groups).

δ = 0.84 (3H,d,J 2 6Hz), 0.88 (3H,s), 1.02 (3H,s), 1.28 and 1.30 (3H,s), and 3.28 and 3.35 (3H,s).

M^+ = 268.

Rf (25% ethyl acetate/pet.ether) = 0.52.

$\bar{\nu}_{max}$ = 2930, 1120, 1090, 790, and 760 cm^{-1}

δ = 0.79 (3H,s), 0.90 (3H,d,J = 6Hz), 1.05 (3H,s), 1.67 (3H,bs), 3.30 (1H,m), 3.32 (3H,s), and 5.20 (1H,br.dd, J = 4Hz and 10Hz).

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

δ = 13.2(q), 16.7(q), 20.1(q), 26.6(t), 28.1(q), 32.6(d), 35.2(t), 35.4(s), 37.3(t), 39.9(t), 56.6(d), 56.9(q), 68.6(d), 81.0(d), 122.1(d), and 136.9(s).

M^+ (found) = 252.2095; M^+ (calculated for $C_{16}H_{28}O_2$) = 252.2090.

Analytical tlc revealed that if the deoxygenation reaction was continued for 6 hours at room temperature, epoxide (66) gradually disappeared to produce alcohol (60) (Rf 0.22). Isolation of the alcohol (60) proved difficult from these conditions, since (60) had a similar polarity to that of bis-epoxide A (Rf 0.25), which was unreacted.

(b) Of isomers (58) and (59)

The deoxygenation procedure described in 38(a) was carried out on a mixture of (58) and (59) (1.34g, 5 mmol) with tungsten hexachloride (1.99g, 5 mmol) and 1.5M n-butyl lithium (10 ml, 15 mmol). Prolonged reaction (6 hours) did not affect the reaction mixture. High pressure column chromatography yielded 0.68g of monoepoxide (67) (54%).

Rf (25% ethyl acetate/pet.ether) = 0.69.

$\bar{\nu}_{max}$ = 2930, 1120, 1090, 790, and 760 cm^{-1}

δ = 0.80 (3H,d,J = 6Hz), 0.90 (tH,s), 1.69 (3H,bs), 3.28 (1H,m), 3.30 (3H,s), and 5.20 (1H,br.dd,J = 4 and 11Hz).

M^+ = 252.

39. Reaction of 4,5-monoepoxide diastereoisomers (66 and 67) with boron-trifluoride etherate and tin(IV) chloride

Quantities of both isomers (10 mg) were dissolved in solvent (2 ml) and reacted in the conditions described in Table 5. Reaction was monitored by analytical tlc.

TABLE 5

Conditions for Lewis acid catalysed rearrangement of (66) and (67)

Epoxide	Lewis acid	Molar ratio of acid	Temp. (°C)	Solvent
66	$BF_3(C_2H_5)_2O$	1,2,10	18,-70	Ether
67	$BF_3(C_2H_5)_2O$	1,2,10	18,-70	Ether
67	$SnCl_4$	1,2,10	18,-60	$CHCl_3$

Reaction of (66) in the conditions giving least product range is described in 39(a). Compound (67) gave no reaction with boron-trifluoride etherate after 48 hours in any of the conditions described. With a ten-fold molar excess of tin(IV) chloride at room temperature some reaction had occurred after 12 hours giving a multitude of non-polar compounds.

(a) Reaction of (66) with boron-trifluoride etherate

The epoxide (66) (100 mg, 0.397 mmol) was dissolved in anhydrous diethyl ether (25 ml) at room temperature and boron-trifluoride etherate (113 mg, 0.794 mmol) added. After 1 hour the reaction was quenched with saturated sodium bicarbonate solution, the ethereal layer dried and solvent

removed. Analytical tlc of the crude product revealed one major more polar spot (Rf = 0.22 in ethyl acetate/pet.ether) and preparative tlc (10% ethyl acetate/pet.ether) gave 51 mg of the alcohol (60) (51%).

glc (Apiazon L, 10%), pN_2 = 30 lb.in^{-2}, pO_2 = H_2 = 20 lb.in^{-2}
218°C, Rt = 13.6 minutes.

$\bar{\nu}_{max}$ = 3450, 1620, 1080, and 890 cm^{-1}

δ = 0.85 (3H,d,J = 7Hz), 0.95 (3H,s), 1.08 (3H,s), 3.12 (1H,d,J = Hz), 3.32 (3H,s), 3.33 (1H,m), 4.74 (1H,bs), and 5.06 (1H,bs).

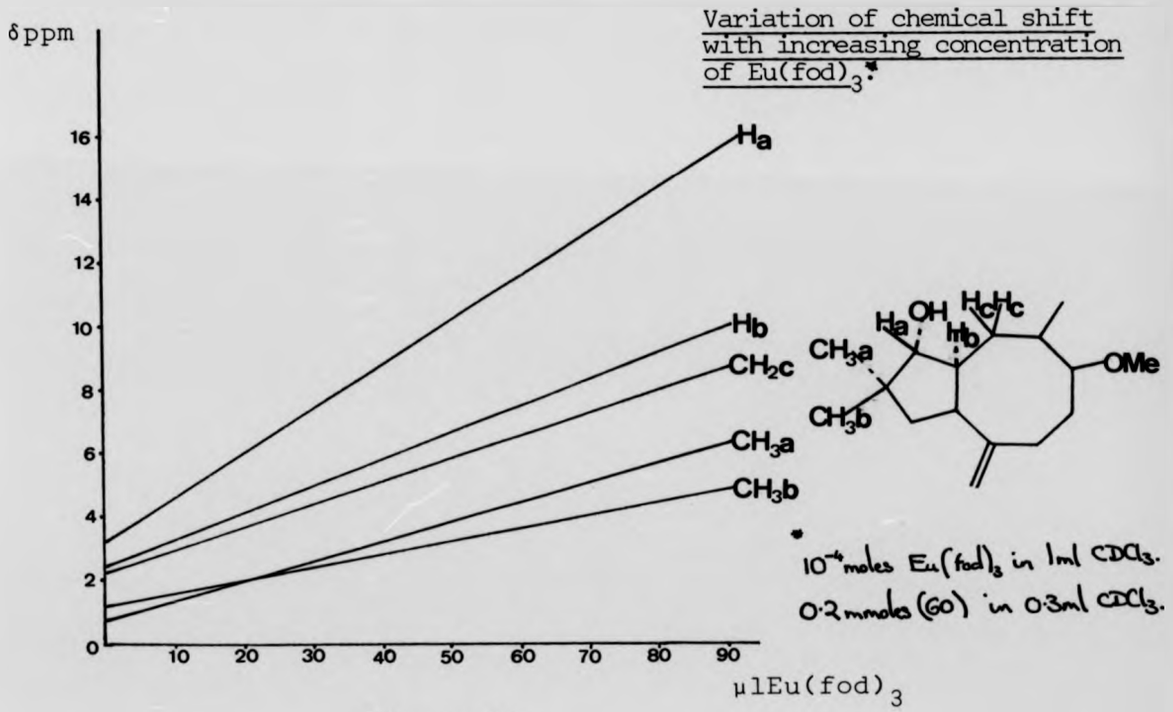

Figure 22

^{13}C nmr ($CDCl_3$)

δ = 14.2(q), 20.5(q), 27.1(q), 30.4(t), 32.4(t), 36.3(d), 39.0(s), 40.8(t), 42.4(d), 43.8(t), 46.4(d), 56.2(q), 83.4(d), 84.7(d), 112.6(t), and 152.7(s).

M^+ (found) = 252.2098; M^+ (calculated for $C_{16}H_{28}O_2$) = 252.2090

3,5-dinitrobenzoate derivative mp. 150-152°C.

Crystal data. $P2_{1/n}$, a = 15.37(5), b = 8.79(6), c = 18.16(6) Å, β = 80.44(3)°, and R = 0.072 for 1113 observed reflexions.

40. Preparation of 3,5-dinitrobenzoate derivative (64)

Alcohol (60) (97 mg, 0.385 mmol) was dissolved in dry pyridine (6 ml) with 3,5-dinitrobenzoyl chloride (133 mg, 0.577 mmol) and heated to 80°C for 2 hours. At the end of this period, sodium bicarbonate solution was added to the cooled reaction with some ether. The ethereal layer was washed with saturated copper sulphate solution and brine, dried and the solvent removed. Preparative tlc (10% ethyl acetate/pet.ether) separated 70 mg of the ester (64) (41%). The ester was recrystallised from pet.ether (mp. 150-152°C).

Rf = 0.63 (25% ethyl acetate/pet.ether).

δ = 0.76 (3H,d,J = 7Hz), 1.07 (3H,s), 1.03 (3H,s), 3.21 (3H,s), 3.30 (1H,m), 4.85 (1H,d,J = 10Hz), 4.87 (1H,bs), 5.09 (1H,bs), and 9.0-9.2 (3H,m).

The p-nitrobenzoate (61), p-bromobenzene sulphonate (62) and p-bromobenzoate (63) esters were prepared by the same procedure from the corresponding acid chloride, but these did not produce crystalline compounds.

41. Preparation of acetate (68)

The alcohol (60) (300 mg, 1.19 mmol), acetic anhydride (182 mg, 1.78 mmol) and p-dimethylaminopyridine (10 mg) were dissolved in pyridine (5 ml) and the reaction solution stirred at room temperature for 30 minutes. The reaction was quenched with sodium bicarbonate solution and ether added. The ethereal solution was washed with saturated copper sulphate solution and brine, dried and solvent removed. Preparative tlc (10% ethyl acetate/pet.ether) separated 208 mg of acetate (68) (60%) which crystallised on standing (mp. 55°C).

Rf = 0.50 (25% ethyl acetate/pet.ether).

$\bar{\nu}_{max}$ = 2930, 1730, 1630, 1240, 1090, and 1030 cm^{-1}

$\delta(CCl_4)$ = 0.79 (3H,d,J = 6Hz), 0.92 (3H,s), 0.98 (3H,s), 2.00 (3H,s), 3.19 (3H,s), 3.25 (1H,m), 4.45 (1H,d,J = 10Hz), 4.75 (1H,bs), and 4.96 (1H,bs).

M^+ (found) = 294.2185; M^+ (calculated for $C_{18}H_{30}O_3$) = 294.2195.

42. Oxidation of alcohol (60) with pyridinium chlorochromate[19]

The alcohol (60) (230 mg, 0.913 mmol) was dissolved in a suspension of pyridinium chlorochromate (300 mg, 1.37 mmol) in dichloromethane (25 ml) and the reaction carried out as in part 24. Preparative tlc (5% ether/pet.ether) of the crude product gave 180 mg of a ketone (79%).

Rf = 0.49 (25% ethyl acetate/pet.ether)

$\bar{\nu}_{max}$ = 2930, 1750, 1630, and 1090 cm^{-1}

$\delta(CCl_4)$ = 0.85 (3H,d,J = 6Hz), 1.05 (6H,s), 3.26 (3H,s), 3.28 (1H,m), 4.75 (1H,bs), and 4.83 (1H,bs).

M^+ (found) = 250.1926; M^+ (calculated for $C_{16}H_{26}O_2$) = 250.1933.

43. Attempted demethylation of compound (68)

(a) With iodotrimethylsilane

Compound (68) (500 mg, 1.70 mmol) was dissolved in chloroform (10 ml) and iodotrimethylsilane (1.7g, 8.5 mmol) added under nitrogen. The reaction was stirred for 16 hours at room temperature and quenched with methanol. Ether was added and the organic solvent washed with sodium thiosulphate solution, dried and solvent removed by rotary evaporation. High pressure column chromatography using Kieselgel 60 (Art.7739) and eluting with 5% ether/pet.ether yielded 320 mg of ether (69) (an oil, 67%).

Rf = 0.61 (25% ethyl acetate/pet.ether)

$\bar{\nu}_{max}$ = 2920, 1730, 1240, and 1035 cm^{-1}

δ = 0.91 (3H,s), 0.99 (3H,d,J = 7Hz), 1.05 (3H,d,J = 7Hz), 1.16 (3H,s), 1.58 (1H,d,J = -13Hz) and 1.66 (1H,d,J = -13Hz)-AB system, 2.14 (3H,s), 3.36 (1H,m), and 4.70 (1H,d,J = 2.5Hz).

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

δ = 14.4(q), 21.2(q), 22.5(q), 23.6(t), 24.3(t), 24.5(q), 28.2(q), 31.1(d), 31.7(t), 37.8(d), 40.5(s), 50.3(d), 52.1(t), 75.6(d), 80.6(s), 88.6(d), and 170.4(s).

M^+ (found) = 280.2019; M^+ (calculated for $C_{17}H_{28}O_3$) = 280.2038.

Reaction in the presence of solid sodium bicarbonate (200 mg) or triethylamine (2 ml), did not affect the reaction. The addition of pyridine (1 ml) decreased the reaction time to 4 hours and with p-dimethylaminopyridine (10 mg) added to the reaction solution, the reaction occurred within 1 hour at room temperature. The addition of propene (by saturation of the chloroform used for the reaction) retarded the reaction and 30 hours was required to give an equivalent yield of (69).

(b) With iodotrimethylsilane generated in situ[54]

Compound (68) (30 mg, 0.119 mmol), potassium iodide (198 mg, 0.119 mmol) were stirred in acetonitrile under nitrogen. Analytical tlc revealed that there was no change in the reaction mixture after 15 hours. After this time, work-up (as in part 43a) yielded 17 mg of ether (69) (52%). Some starting material (68) (10 mg) was recovered.

(c) Reaction with methylthiotrimethylsilane and phenylthiotrimethylsilane[56]

Compound (68) (10 mg, 3.4×10^{-2} mmol), methylthio-

trimethylsilane (41 mg, 3.4×10^{-2} mmol) [or phenylthiotrimethylsilane (52 mg)], zinc iodide (54 mg, 0.17 mmol), and tetra n-butylammonium iodide (19 mg, 5.1×10^{-2} mmol) were added to dichloromethane (5 ml) and the mixture refluxed. Analytical tlc of the reaction showed that (69) was the major product after 4 hours (some less polar compounds also produced).

44. Attempted demethylation of 5-methoxy-pent-1-ene (71)

5-Methoxy-pent-1-ene (71) (400 mg, 4 mmol, bp 96-98°C), was reacted with iodotrimethylsilane (1.2g, 6 mmol) in deuteriochloroform (25 ml), under nitrogen. The reaction was followed by nmr and by analytical tlc (Rf desired product (72), in 25% ethyl acetate/pet.ether = 0.13 and Rf (71) = 0.66). After 24 hours analytical tlc revealed that (71) had completely reacted. However, there was no trace of alcohol (72) and it seemed that the products formed were too volatile for analytical tlc analysis. The nmr of the crude reaction mixture after 24 hours revealed that the methoxyl group (3.28 ppm) had disappeared, as had the olefinic proton at 4.7-5.1 ppm. Small scale fractional distillation of the crude product(s) was difficult and the compound(s) formed had bp < 85°C.

This reaction was not investigated further.

45. Attempted demethylation of isohumulyl methyl ether (54) with iodotrimethylsilane[37]

Compound (54) (142 mg, 0.602 mmol) was reacted with iodotrimethylsilane (241 mg, 1.204 mmol) in chloroform (5 ml) under nitrogen at room temperature. Analytical tlc of the reaction mixture after 24 hours revealed that most of the methyl ether (54) had reacted to give less polar products (> 4). No isohumulol (51) was formed.

46. Reaction of (68) with boron-trifluoride etherate in acetic anhydride

Compound (58) (100 mg, 0.34 mmol) was dissolved in ether (20 ml) and acetic anhydride (2 ml), then boron-trifluoride etherate (2 ml) added at room temperature. The reaction was followed by analytical tlc. After 30 minutes, the reaction was quenched with aqueous sodium bicarbonate solution and 65 mg of ether (69) isolated (68%) by preparative tlc.

When the reaction was left for 4 hours, the ether (69) gradually reacted to produce the diacetate (78) (Rf. in 10% ethyl acetate/pet.ether = 0.33).

47. Reaction of ether (69) with boron-trifluoride etherate in acetic anhydride

Compound (69) (50 mg, 0.178 mmol) was dissolved in ether (10 ml) and boron-trifluoride etherate (1 ml) and acetic anhydride (1 ml) added immediately. The reaction was stirred for 4 hours at room temperature then worked-up in the manner outlined in part 46. The diacetate (78) was thus isolated (71%).

$\bar{\nu}_{max}$ = 1725 cm^{-1}

δ = 0.90 (3H,s), 1.05 (3H,d,J = 7Hz), 1.10 (3H,s), 1.64 (3H,bs), 2.00 (3H,s), 2.12 (3H,s), 4.72 (1H,d,J = 7Hz), and 4.95 (1H,m).

48. Attempted oxidative cleavage of methyl ether in (68)[60]

Compound (68) (20 mg) was oxidised by a suspension of chromium trioxide (200 mg) in a mixture of acetic acid (0.5 ml) and dichloromethane (10 ml) for 2 hours at room temperature. Analytical tlc revealed mainly starting material present, although many (> 6) more polar spots had developed.

49. Hydrogenation of (68)[62]

(a) With palladium on charcoal

The acetate (68) (200 mg, 0.680 mmol) was dissolved in ethyl acetate (20 ml) and stirred with palladium on charcoal (80 mg) at room temperature under an atmosphere of hydrogen (1 atmos.). After 12 hours the catalyst was removed by filtration and the solvent removed by rotary evaporation. Preparative tlc (10% ethyl acetate/pet.ether) isolated 80 mg of (85) (40%) and 90 mg of crystalline (86) (45%).

(85) an oil, Rf = 0.62 (25% ethyl acetate/pet.ether).

δ = 0.90 (3H,s), 0.95 (3H,d,J = 7Hz), 1.06 (3H,s), 1.65 (3H,bs), 2.10 (3H,s), 3.28 (3H,s), 3.33 (1H,m), and 4.75 (1H,d,J = 7Hz)

M^+ = 294.

(86) mp 47°C, Rf = 0.52 (25% ethyl acetate/pet.ether).

$\bar{\nu}_{max}$ = 2930, 1730, 1240, 1090, 1035, and 750 cm^{-1}

δ = 0.85 (3H,d,J = 7Hz), 0.90 (3H,s), 1.03 (3H,d,J = 7Hz), 1.05 (3H,s), 2.07 (3H,s), 3.30 (3H,s), 3.31 (1H,m), and 4.60 (1H,d,J = 7Hz).

M^+ (found) = 296.2345; M^+ (calculated for $C_{18}H_{32}O_3$) = 296.2351.

(b) With Raney nickel

Reaction of the acetate (68) (200 mg, 0.68 mmol) in ethanol with Raney nickel (Crosfield, Grade 102, 100 mg) for 12 hours, yielded 185 mg of the dihydro compound (86) (92%).

49. Attempted demethylation of (86)

(a) With iodotrimethylsilane[37]

Compound (86) (100 mg, 0.338 mmol) was dissolved in chloroform (10 ml), then p-dimethylaminopyridine (10 mg) and iodotrimethylsilane (338 mg, 1.69 mmol) added under nitrogen.

The reaction was worked up in the same manner as part 43(a) after 3 hours, to give 56 mg of olefin (87) (63%, an oil).

Rf = 0.60 (25% ethyl acetate/pet.ether).

$\bar{\nu}_{max}$ = 2950, 2920, 2860, 1730, 1240, and 1030 cm^{-1}

δ = 0.89 (3H,s), 0.98 (3H,d,J = 7Hz), 1.03 (3H,s), 1.74 (3H,bs), 2.05 (3H,s), 2.56 (1H,t,J = 13Hz), 4.61 (1H,d,J = 6Hz), and 5.33 (1H,t,J = 8Hz).

M^+ (found) = 264.2069; M^+ (calculated for $C_{17}H_{28}O_2$) = 264.2089.

(b) With methylthiotrimethylsilane and phenylthiotrimethylsilane[56]

Compound (86) (100 mg, 0.338 mmol), methylthiomethylsilane (406 mg, 3.38 mmol), [or phenylthiotrimethylsilane (514 mg)], zinc iodide (540 mg), and tetra n-butylammonium iodide (200 mg) were dissolved in dichloromethane (25 ml) and the reaction refluxed for 3 hours. The reaction was quenched with 5% barium hydroxide solution and some dichloromethane added. Processing the organic phase as usual gave 61 mg of olefin (87) (68%).

50. Saponification of ester (87)

Ester (87) (40 mg, 0.151 mmol) was dissolved in methanol (5 ml) and then potassium hydroxide solution (40 mg in 2 ml of water) added. The reaction and work-up procedure was identical to part 15. In this way 30 mg of the alcohol (89) (88%) was isolated.

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

$\bar{\nu}_{max}$ = 3430 and 1030 cm^{-1}

δ = 0.89 (3H,s), 0.98 (3H,d,J = 7Hz), 1.03 (3H,s), 1.74 (3H,bs), 2.05 (3H,s), 2.56 (1H,t,J = 13Hz), 3.48 (1H,d,J = 6Hz), and 5.33 (1H,t,J = 8Hz).

M^+ = 222.

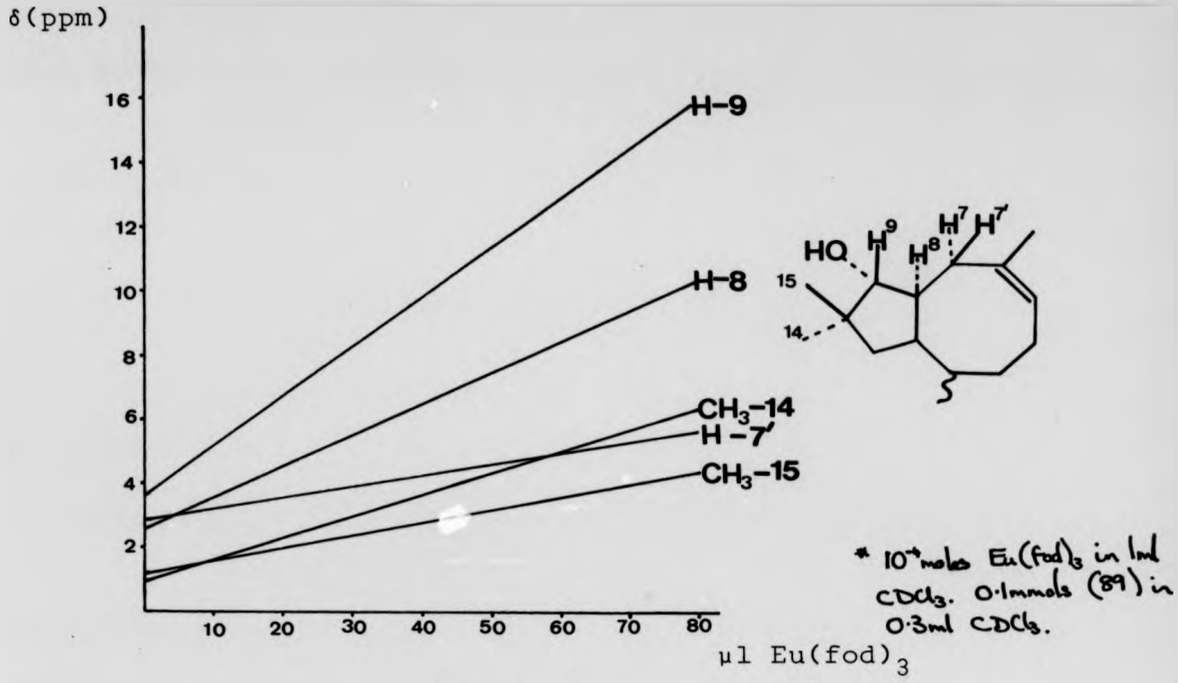

Figure 23

Variation of chemical shift with increasing concentration of $Eu(fod)_3$*

51. Reaction of (86) with boron trifluoride etherate in acetic anhydride

Compound (86) (100 mg, 0.338 mmol) was dissolved in diethyl ether (20 ml) and acetic anhydride (2 ml) with boron trifluoride etherate (2 ml) added at room temperature. The reaction was stirred for 30 minutes then quenched with saturated bicarbonate solution. The ethereal layer was separated, dried and the solvent removed. Preparative tlc (10% ethyl acetate/pet.ether) yielded 62 mg of olefin (87) (68%).

52. Epoxidation of (87)

Compound (87) (100 mg, 0.378 mmol) was dissolved in dichloromethane (40 ml) and stirred with 0.5M sodium bicarbonate solution (60 ml). m-Chloroperoxybenzoic acid (85%, 115 mg,

0.567 mmol) was added and the reaction left for 12 hours at room temperature. Work-up (as in part 1) and preparative tlc (10% ethyl acetate/pet.ether) yielded 75 mg of epoxide (94) (71%) which was a viscous oil.

Rf = 0.44

$\delta(CCl_4)$ = 0.90 (3H,s), 1.00 (3H,d,J = 7Hz), 1.14 (3H,s), 1.27 (3H,s), 2.00 (3H,s), 2.48 (1H,t,J = 8Hz), and 4.40 (1H,d,J = 4Hz).

M^+ = 280

53. Reaction of epoxide (94) with lithium diethylamide[64]

1.2M n-butyllithium (0.2ml, 0.192 mmol) was added to a flame dried flask, followed by diethylamine (25 µl, 0.192 mmol) at -5°C under nitrogen. This solvent was brought to room temperature and epoxide (94) (18 mg, 6.4×10^{-2} mmol) added in ether (2 ml). The reaction was refluxed for 24 hours after which time, analytical tlc (ethyl acetate only) revealed that all the epoxide had reacted to give a major more polar spot (Rf 0.75). Water and ether were added and the ethereal layer separated, dried and the solvent removed. Preparative tlc (50% ethyl acetate/pet.ether) gave 10 mg of (95) (67%).

$\bar{\nu}_{max}$ = 3455, 1620, 1090, and 890 cm^{-1}

$\delta(CCl_4)$ = 0.90 (3H,s), 1.00 (3H,d,J = 7Hz), 1.03 (3H,s), 3.10 (1H,d,J = 10Hz), 3.45 (1H,bt,J = 8Hz), 4.90 (1H,bs), and 5.10 (1H,bs).

54. Preparation of humulene nitrosite (99)[70]

Humulene (97%, 7.3g, 3.58×10^{-2} mmol) in pet.ether (100 ml) was cooled to -10°C in an ice/salt bath. Saturated aqueous sodium nitrite (100 ml) was added and, with vigorous mechanical

stirring, glacial acetic acid (100 ml) was added dropwise over 30 minutes. After addition of the acetic acid, the mixture was stirred for a further 1 hour, then cooled using an acetone/Drikold bath. Blue crystals of (99) were collected by filtration, washed with ice-cold water and finally with ice-cold ethanol. Further crystals were separated from the mother liquor. The total yield was 1.2g of (99) (12%). 4.4g of humulene was recovered (60%).

mp. 114°C

Rf = 0.35 (10% ethyl acetate/pet.ether)

δ = 0.98 (3H,s), 1.00 (3H,s), 1.15 (3H,s), 1.70 (3H,s), 4.8-5.29 (3H,m), and 6.12 (1H,bd,J = 9Hz).

55. Reaction of humulene nitrosite (99) in refluxing ethanol

Humulene nitrosite (200 mg, 0.714 mmol) was refluxed for 8 hours in ethanol and as the reaction continued, the blue colour gradually disappeared to give a pale yellow solution. On cooling, colourless needle crystals of dinitrohumulene (109) were deposited and these were filtered off to give 125 mg of material (60%). Preparative tlc of the crude material obtained from rotary evaporation of the ethereal solution gave 28 mg of hydrocarbon which had the same polarity as humulene. Separation of this material by preparative tlc which had been impregnated with silver nitrate (10% w/w in SiO_2) gave 12 mg of humulene (8%) and 16 mg of isohumulene (11%).

dinitrohumulene (109) mp. 168°C

Rf = 0.34 (10% ethyl acetate/pet.ether)

δ = 1.05 (3H,s), 1.08 (3H,s), 1.68 (3H,s), 1.90 (3H,s), and 4.65-5.52 (4H,m,olefinic protons and $CH-NO_2$).

humulene (10) bp. 110-12°C/5-7 mm.

Rf = 0.82 (10% ethyl acetate/pet.ether)

Rf = 0.36 (ethyl acetate, $AgNO_3$ impregnated analytical plate)

glc (Apiazon L, 10%) $pH_2 = O_2 = N_2 = 20$ lb. in^{-2}

215°C, Rt = 5.6 minutes

δ = 1.10 (6H,s), 1.45 (3H,d,J = 1.8Hz), 1.60 (3H,d,J = 1.8Hz), 1.90 (2H,d,J = 7Hz), 2.50 (2H,d,J = 7Hz), 4.70-5.00 (2H,m), 5.10 (1H,d,J = 16Hz), and 5.50 (1H,m,J = 7Hz and 16Hz).

^{13}C nmr spectrum (acetone-d_6)

δ = 141.0, 139.0, 133.0, 128.0, 126.3, 125.3, 42.4, 40.7, 40.1, 37.6, 27.3 (2**C**), 23.8, 18.0, and 15.1.

isohumulene (103) bp. 101-105°C/5-7mm.

Rf = 0.82 (10% ethyl acetate/pet.ether)

Rf = 0.78 (ethyl acetate, $AgNO_3$ impregnated analytical plate)

glc (Apiazon L, 10%) $pH_2 = O_2 = N_2 = 20$ lb. in^{-2}

215°C Rt = 5.2 minutes.

δ = 1.0 (6H,s), 1.65 (3H,d,J = 0.5Hz), 1.75 (3H,d,J = 1.8Hz), 2.70 (2H,d,J = 6Hz), and 5.0-5.4 (4H,m).

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

δ = 141.0, 132.8, 126.5, 125.1, 122.2, 189.8, 51.0, 43.5, 37.5, 37.0, 31.2, 27.8 (2**C**), 26.0, and 21.7.

M^+ (found) = 204.1866; M^+ (calculated for $C_{15}H_{24}$) = 204.1878.

Found: C, 88.1%; H, 11.8%. $C_{15}H_{24}$ requires C, 88.23%; H, 11.76%.

56. Prolonged reaction of humulene with dinitrogen trioxide

Humulene (200 mg, 0.98 mmol) was dissolved in pet.ether (2 ml) and stirred with glacial acetic acid (2 ml) and saturated sodium nitrite solution (2 ml) at room temperature. The reaction

was followed by glc and after 48 hours was worked-up by the initial addition of ether and water. The ethereal layer was washed with sodium bicarbonate solution, dried and solvent removed by rotary evaporation. Preparative tlc with Kieselgel GF_{254} and with silica impregnated with silver nitrate yielded 116 mg of dinitrohumulene (109) and 24 mg of isohumulene (12%). Humulene (10) was also recovered (20 mg).

57. Formation of isohumulene-1,2-epoxide (114)

Isohumulene (125 mg, 0.613 mmol) was reacted with one mole equivalent of 85% m-chloroperoxybenzoic acid (125 mg, 0.613 mmol) under the normal conditions for epoxidation described in part 1.

Preparative tlc (10% ethyl acetate/pet.ether) of the crude product yielded 70 mg of the 1,2-epoxide (114) (53%). Some isohumulene (20 mg) was recovered and 25 mg of the bis-epoxide (115) was also produced.

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

$\delta(CDCl_3)$ = 1.0 (3H,s), 1.1 (3H,s), 1.3 (3H,s), 1.6 (3H,bs), and 5.0-5.5 (3H,m).

Found: C, 82.0%; H, 11.0%. $C_{15}H_{24}O$ requires C, 81.8%; H, 10.9%.

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

58. Formation of isohumulene-1,2-8,9-bisepoxide (115)

Isohumulene (125 mg, 0.612 mmol) was reacted with two mole equivalents of 85% m-chloroperoxybenzoic acid (250 mg, 1.224 mmol) under the conditions described in part 1. Preparative tlc of the crude epoxidation mixture yielded 95 mg of the bis-epoxide (115).

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

δ = 1.1 (6H,s), 1.2 (3H,s), 1.3 (3H,s) and 5.2-5.5 (2H,m).

Found: C, 76.3%; H, 10.3%. $C_{15}H_{24}O_2$ requires

C, 76.3%; H, 10.2%.

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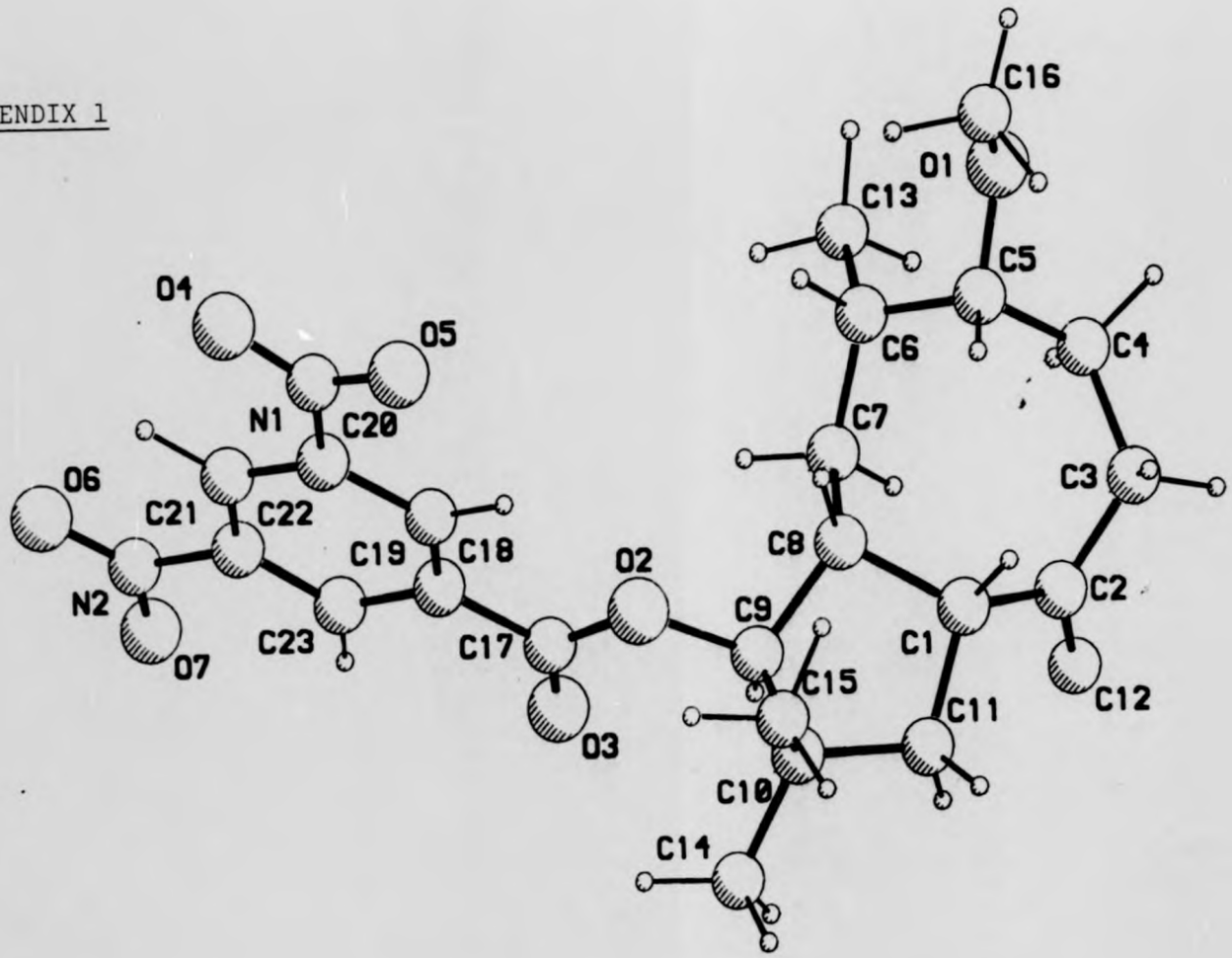
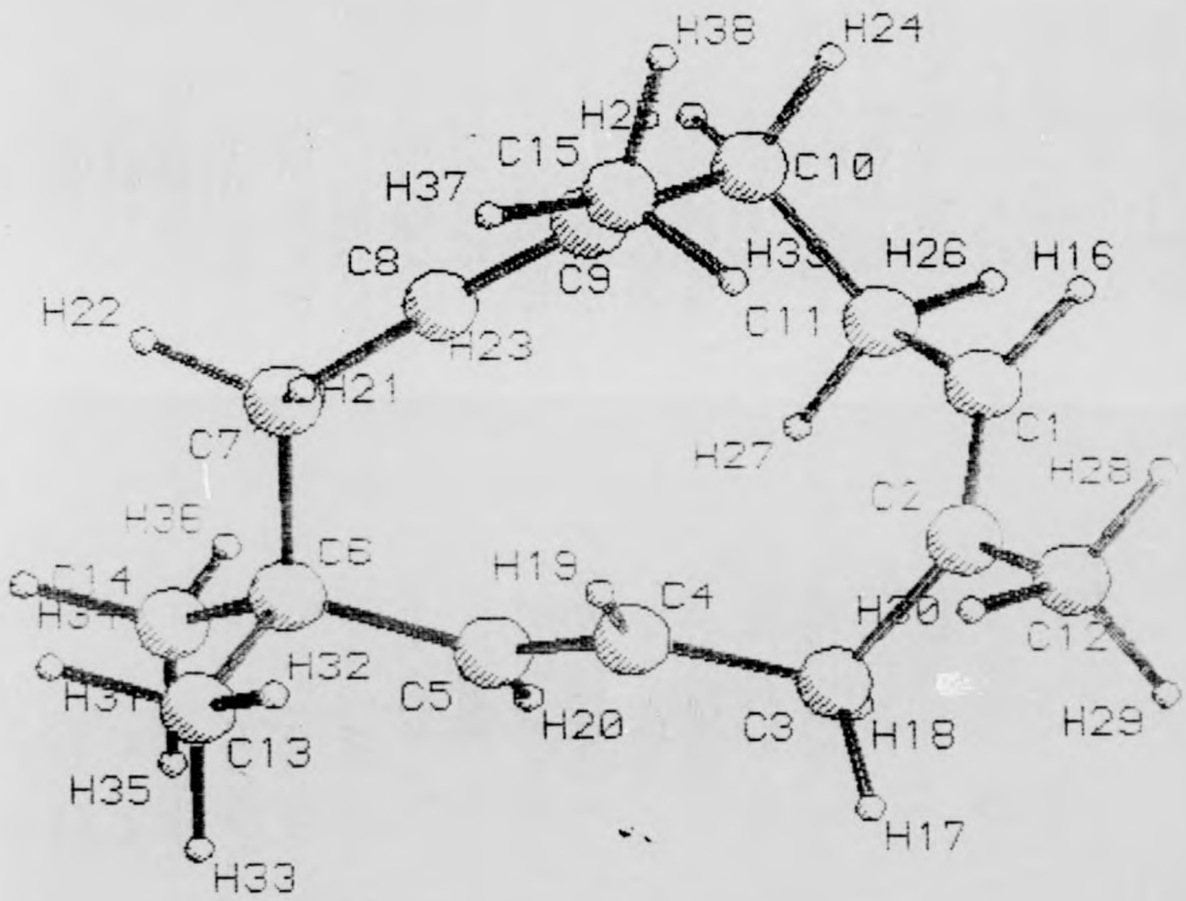
APPENDIX 1



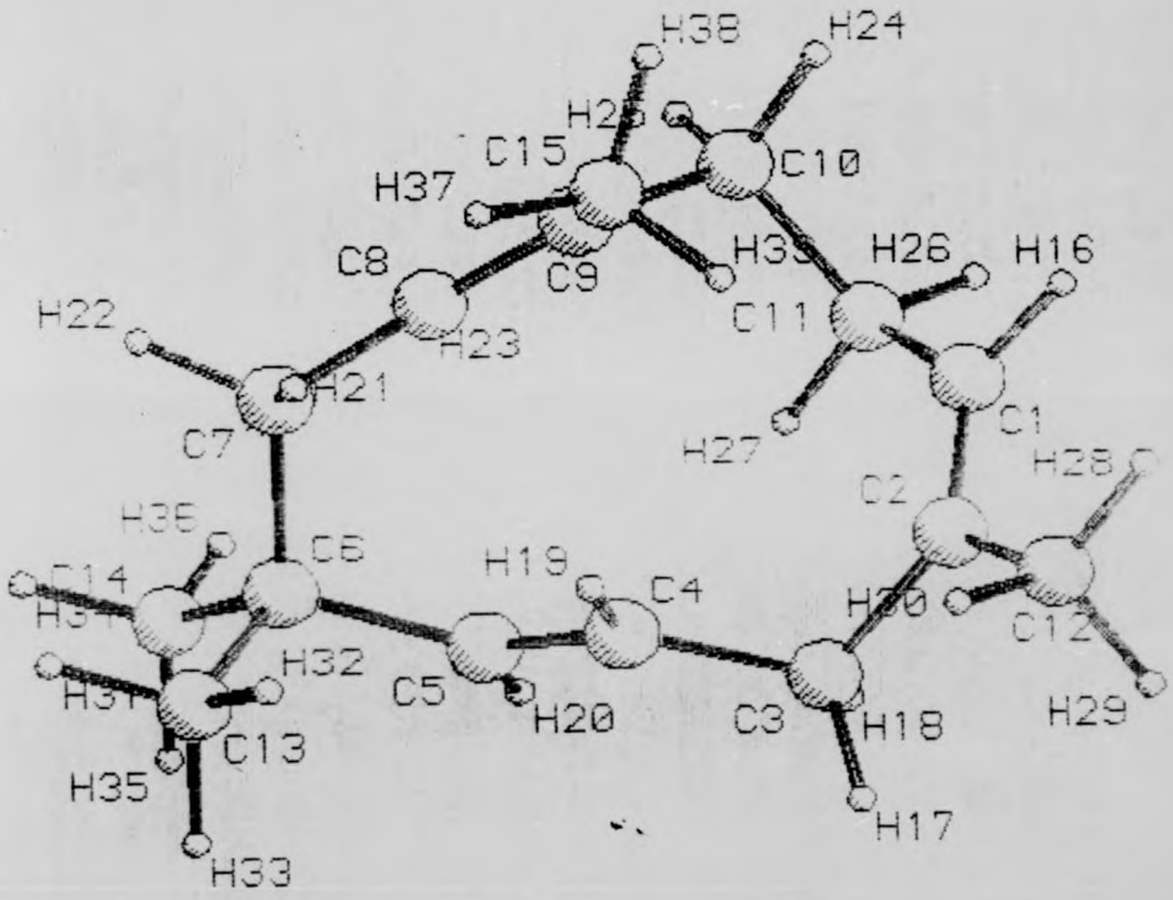
The 3,5-dinitrobenzoate derivative (64)

APPENDIX 2



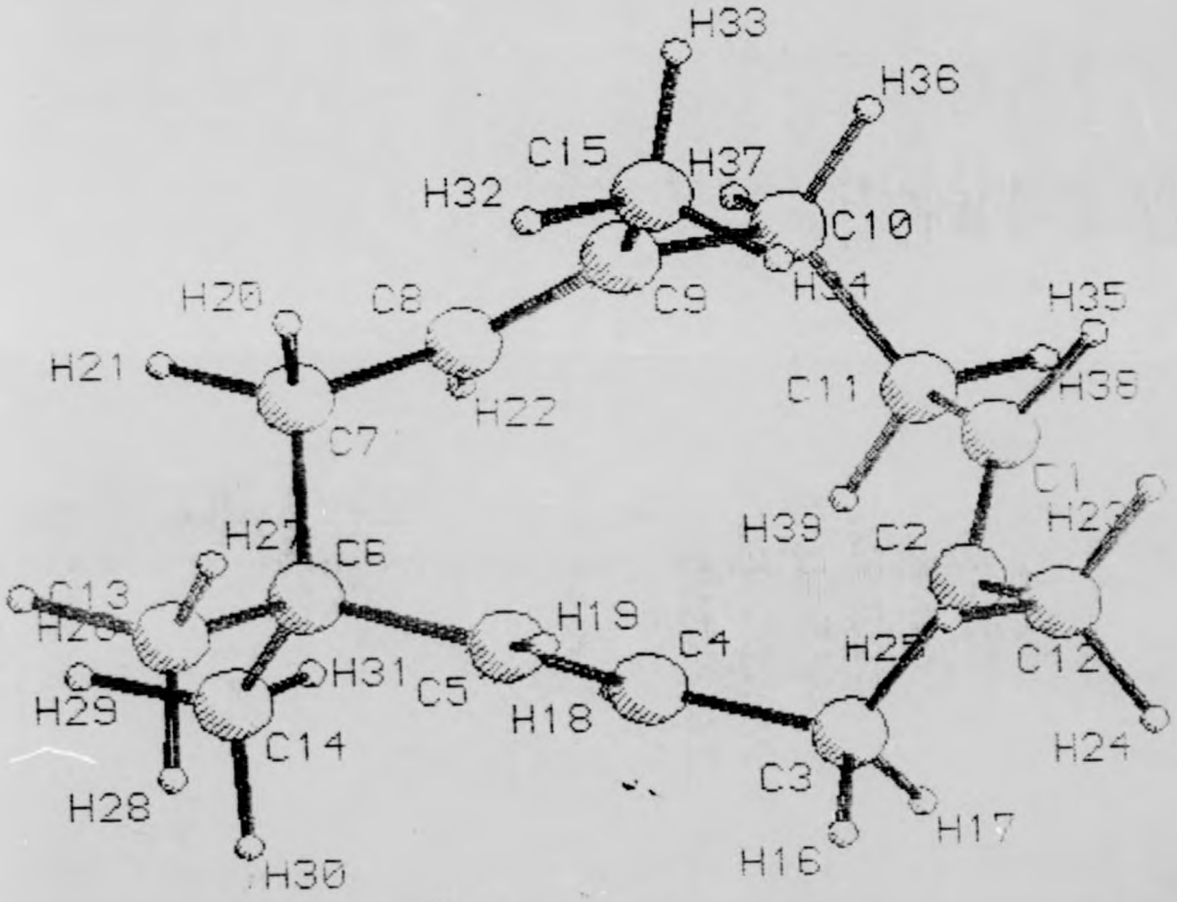
The TT conformer of isohumulene (103)

APPENDIX 2



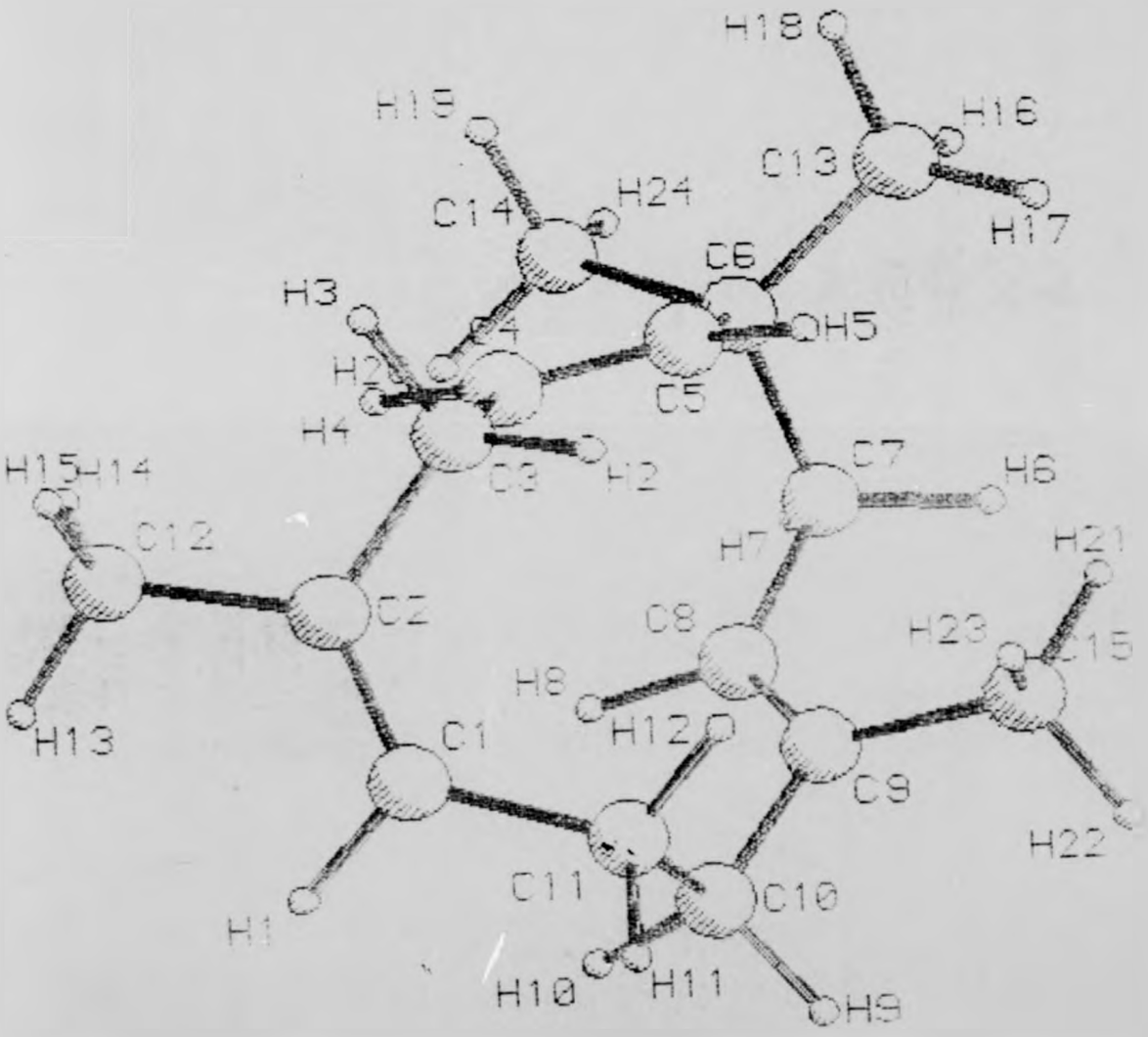
The TT conformer of isohumulene (103)

APPENDIX 3



The CT conformer of isohumulene (103)

APPENDIX 4



The CT* conformer of isohumulene (103)

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