THE INTRAMOLECULAR ENE REACTIONS OF SOME UNSATURATED ACYLOINS

by

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A Doctoral Thesis
submitted in partial fulfilment of the
requirements for the award of
Doctor of Philosophy of the
Loughborough University of Technology
(1986)

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Department of Chemistry

TO MY FAMILY

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to Dr. B.A. Marples for his support and guidance throughout this project.

I would like to thank Mike Harris, Hansa Madha, John Kershaw, John Greenfield and the rest of the technical staff for their technical assistance; Mr D. Hunter of Fisons, Loughborough, for some high field ^{1}H n.m.r. spectra, and my colleagues for their friendship and support.

I would also like to thank my family, especially my parents for their constant encouragement throughout my academic career.

Finally, I would like to thank Mrs L. Bowen for typing this thesis.

Some of the work described has been published.

a) Ene Reactions of Unsaturated Acyloins
B.A. Marples and C.D. Spilling,
Tetrahedron Lett., 26, 6515 (1985).

SUMMARY

The reaction of 3β-tosyloxy-5α-cholesta-5,6β-diol with potassium t-butoxide in t-butanol has been further investigated.

5β-Hydroxy-4,5-secocholest-3-en-6-one was synthesised. It was shown to undergo an ene reaction in decalin in a sealed tube at 200°C to give primarily 3β-methyl-A-nor-5β-cholestan-5-ol-6-one and 6β-hydroxy-4(5-6α) abeo-cholestan-5-one. These primary products were further modified under the reaction conditions to give 3-methyl-B-nor-5β-cholest-2-en-4-one and 5β-cholestan-5-ol-6-one respectively.

The cyclohexane analogue, 3-methyl-3-(3-butenyl)-2-hydroxy-cyclohexan-1-one was synthesised. Heating under reflux in decalin gave 3β,7aβ-dimethyl-3aβ-hydroxy-octahydro-4H-inden-4-one;5β,7aβ-dimethyl-3aβ-hydroxy-octahydro-4H-inden-4-one and an unidentified minor product.

The synthesis of 5-(2-propenyl)-5β-cholestan-2-ol-3-one was partially completed.

The epimeric 5-(2-propenyl)-5α-cholestan-2-ol-3-one was synthesised. The ene reaction was observed in refluxing toluene giving 2α,5-(1-methyl-ethano)-5α-cholestan-2β-ol-3-one and 3α,5-(1-methylethano)-5α-cholestan-3β-ol-2-one.

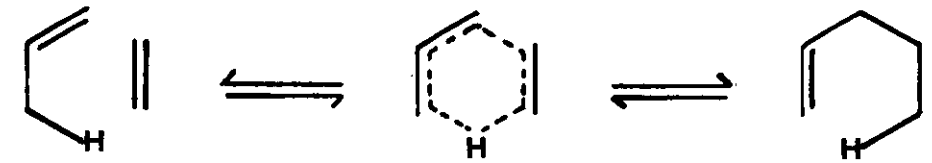
The ketone analogue, 5-(2-propenyl)-5α-cholestan-3-one underwent an ene reaction in decalin in a sealed tube at 250°C to give 2α,5-(1-methyl-ethano)-5α-cholestan-3-one.

CONTENTS

INTRODUCTION

The ene reaction was first recognised and systematically investigated by Alder[1] in 1943. It was originally defined as the "indirect substituting addition of a compound with a double bond, the enophile, to an olefin with an allylic hydrogen, the ene. It involves allylic shift of one double bond, transfer of the allylic hydrogen to the enophile and bonding of the unsaturated termini" (Scheme 1).

Scheme 1

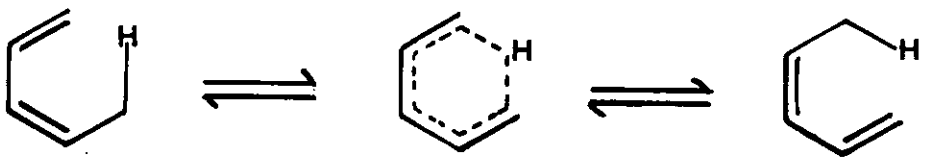


ene enophile

It is related to both the Diels-Alder reaction and the 1,5 hydrogen shift as all three reactions may be considered to involve similar cyclic six-membered transition states (Scheme 2).

Scheme 2

Diels-Alder

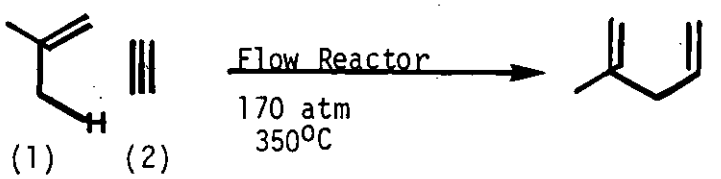


1,5 hydrogen shift

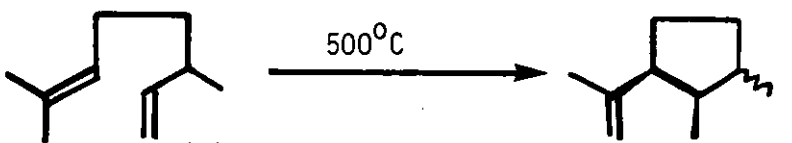
Recent calculations[2,3] suggest that the transition state of the ene reaction may be unsymmetrical, the ene-enophile carbon-carbon bond being more developed than the enophile carbon-ene hydrogen bond.

In relation to the Diels-Alder reaction where the diene is generally electron rich and the dienophile is electron deficient, the ene reaction proceeds most readily when the ene is electron rich and the enophile is electron deficient. Intermolecular ene reactions of simple unactivated olefins are unknown. Even the simplest example, the reaction of 1-methyl prop-1-ene (1) and acetylene (2) requires extreme pressure and temperature[4] (Scheme 3). Intramolecular reactions of simple 1,6-dienes (3) have been reported[5] and require temperatures in excess of 400°C.

Scheme 3



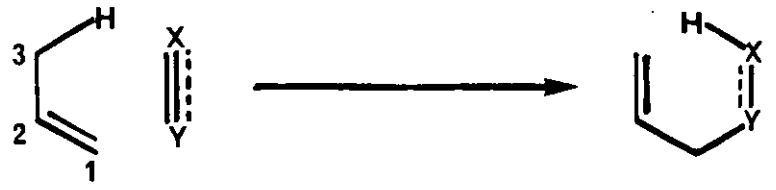
(1) (2)



(3)

The enthalpy of the reaction can be examined[6] by considering all of the bond breaking and bonding forming processes (Scheme 4).

Scheme 4



Energy expended (Bond breaking)	Energy gained (Bond making)
$D\ (C_3\text{-}H)$	$D\ (X\text{-}H)$
$D_{\Pi}\ (X{=}Y)$	$D\ (C_1\text{-}Y)$
$D_{\Pi}\ (C_2{=}C_1)$	$D_{\Pi}\ (C_2{=}C_3)$

$$\Delta G = \Delta H - T\Delta S$$

ΔH = sum of bond dissociation energies.

$$= D\ (X\text{-}H) + D\ (C_1\text{-}Y) + D_{\Pi}\ (C_2{=}C_3) - D\ (C_3\text{-}H) - D_{\Pi}\ (X{=}Y) - D_{\Pi}(C_2{=}C_1)$$

In most cases where $C_2{=}C_1$ and $C_2{=}C_3$ are not significantly strained, they will have similar dissociation energies and so $D_{\Pi}\ (C_2{=}C_3)$ and $D_{\Pi}\ (C_2{=}C_1)$ will cancel from the equation, which becomes:-

$$\Delta H = D\ (X\text{-}H) + D\ (C_1\text{-}Y) - D\ (C_3\text{-}H) - D_{\Pi}\ (X{=}Y).$$

Several conclusions can be reached:-

1) Reactivity is dependant upon the allylic hydrogen bond dissociation energy $D\ (C_3\text{-}H)$.

2) The enhanced reactivity of acetylenes compared to olefins can be attributed to the lower Π bond dissociation energy of the acetylene, $(D_{\Pi}\ (X{\equiv}Y))$.

Thermodynamic considerations also make it possible to predict the orientation of attack on the enophile. An example is the exclusive formation of alcohols with carbonyl enophiles[7](Scheme 5).

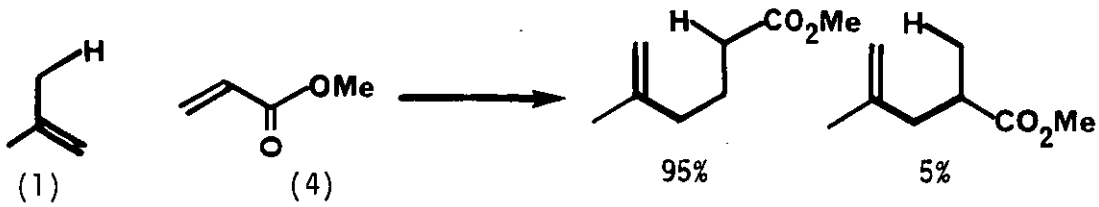
Scheme 5

D(O-H) 102 ± 2KCal/mol
D(C-C) 88 ± 2KCal/mol
190 KCal/mol

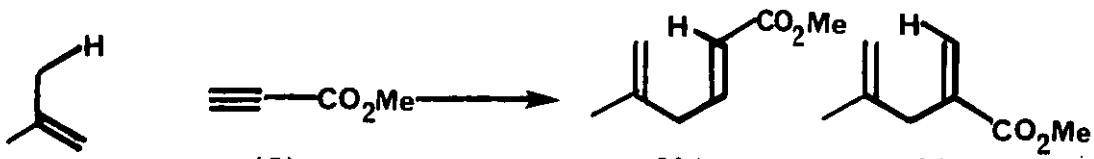
D(C-H) 98 ± 2KCal/mol
D(C-O) 79 ± 2KCal/mol
177 KCal/mol

α,β-Unsaturated carbonyl enophiles also show a preferred orientation of reaction (Scheme 6). This is exemplified by the reaction of methyl acrylate (4) and methyl propiolate (5) with 1-methylprop-1-ene (1) in which transfer of the proton to the α-carbon is preferred.[8]

Scheme 6



(1) (4) 95% 5%

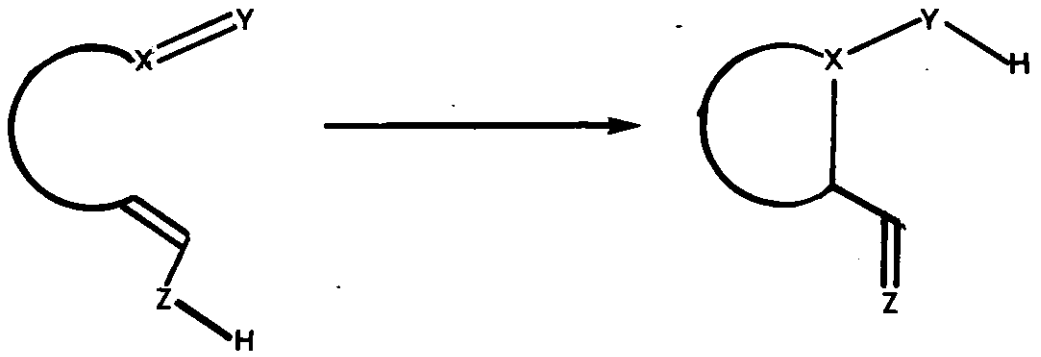


(5) 94% 6%

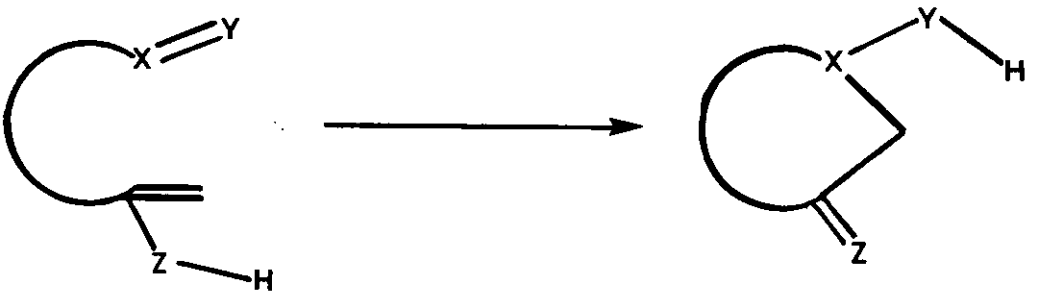
The intramolecular ene reaction benefits from entropic advantages compared to the intermolecular reaction.[9] The enhanced reactivity of an ene-enophile combination is a consequence of the compensating effect of a less negative ΔS.

Depending on the position of the bridge linking the ene and enophile, four orientations for intramolecular ene reactions are known. These are types I, II and III described by Oppolzer[9] and the more recently observed[10] type IV (Scheme 7).

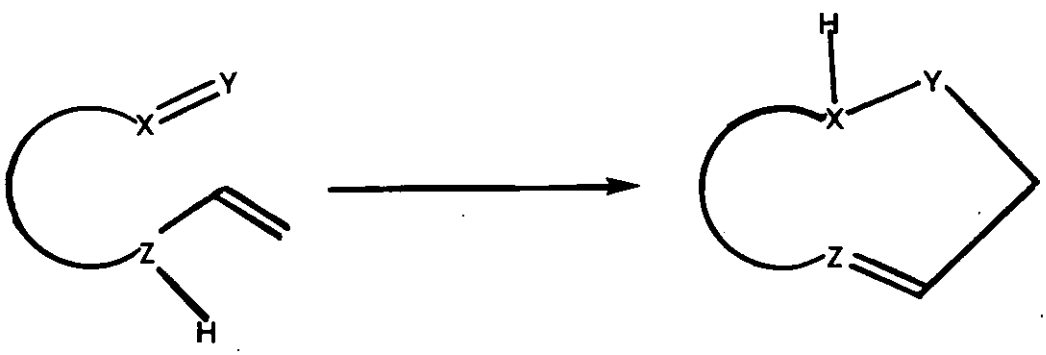
Scheme 7



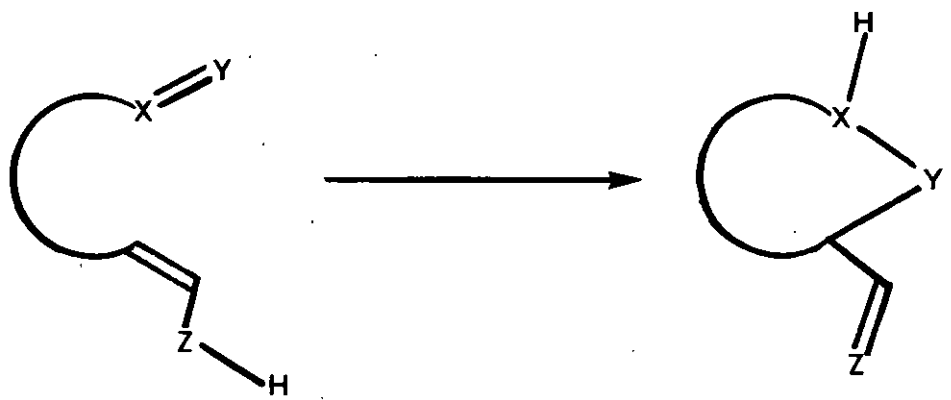
Type I



Type II



Type III



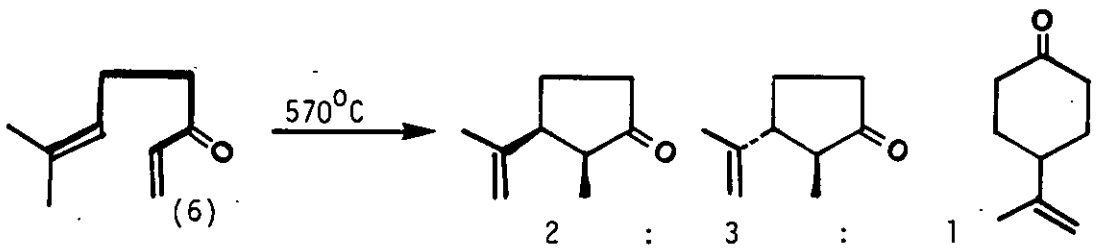
Type IV

The type I reaction is by far the most common with type III and type IV being confined to a few examples.[10,11]

Reaction leading to the formation of 5-membered rings is almost always more facile than the analogous six-membered ring formation. Seven-membered ring formation is generally not an efficient process.

The thermal cyclisation of the dienone (6) is a demonstration of the preference for five-membered ring formation even though this involves addition of the hydrogen to the β-carbon of the enone (cf Scheme 6) (Scheme 8).[12] This leads to a mixture of five and six membered ring products.

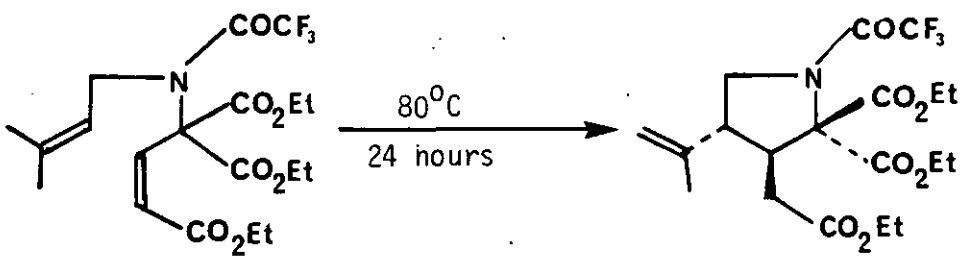
Scheme 8



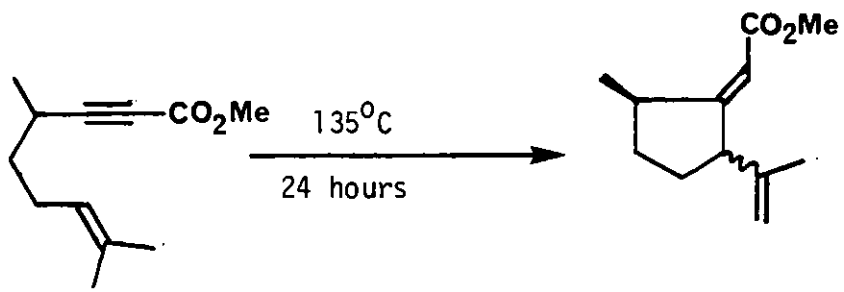
This reaction, in common with many other high temperature ene reactions, is reversible and heating the cyclohexanone product at the reaction temperature gives a partial conversion to the others.

The development of activated electron deficient enophiles has greatly expanded the synthetic utility of both the inter- and intra-molecular ene reactions. The use of conjugated acetylenic or olefinic carbonyl compounds as enophiles has been explored and is exemplified in Scheme 9.

Scheme 9



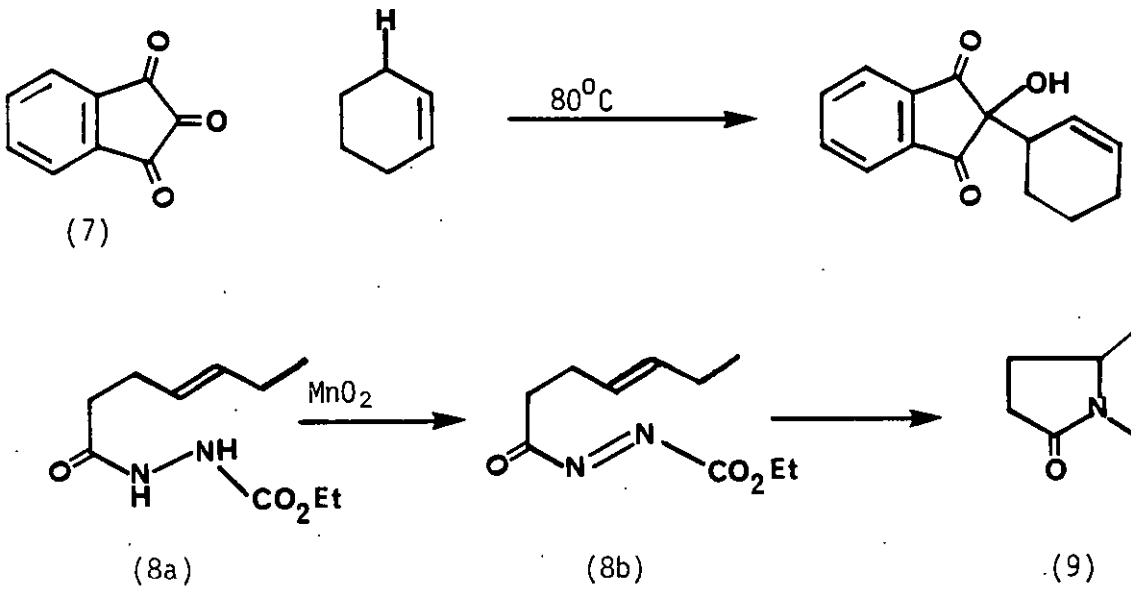
(ref. 14)



(ref. 13)

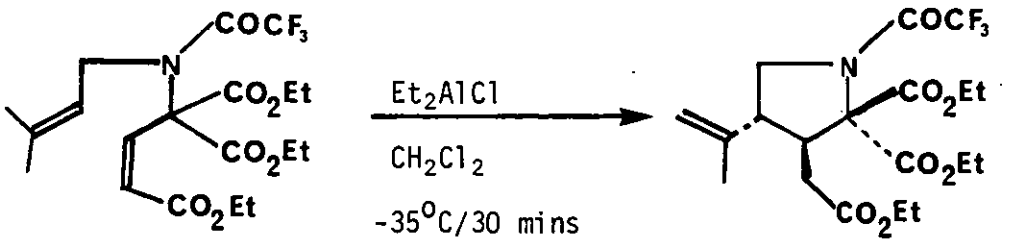
Further examples of activated enophiles includes the reaction of triketoindene (7) with cyclohexene[15] and the intramolecular cyclisation of the keto-diazocarboxylate (8b).[16] Oxidation of the hydrazide (8a) in dichloromethane at room temperature gave (8b) which immediately underwent an ene reaction to give the pyrrolidone derivative (9) (Scheme 10).

Scheme 10

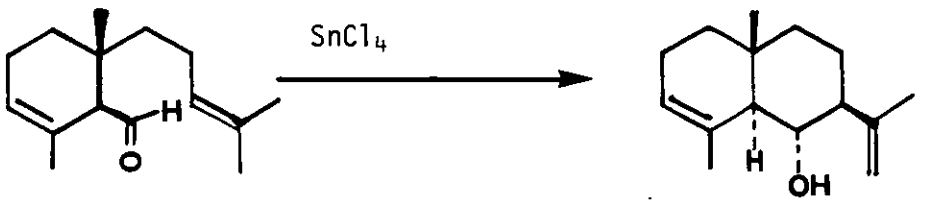


Snider[17] has investigated the use of Lewis acids to further activate α,β-unsaturated carbonyl and carbonyl enophiles. Many reactions may be carried out at room temperature or below (Scheme 11). The Lewis acid acts by co-ordinating to the carbonyl oxygen effectively withdrawing electron density from the enophile.

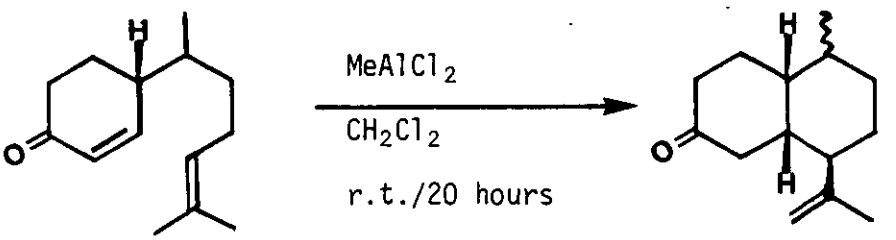
Scheme 11



(ref. 14)



(ref. 18)

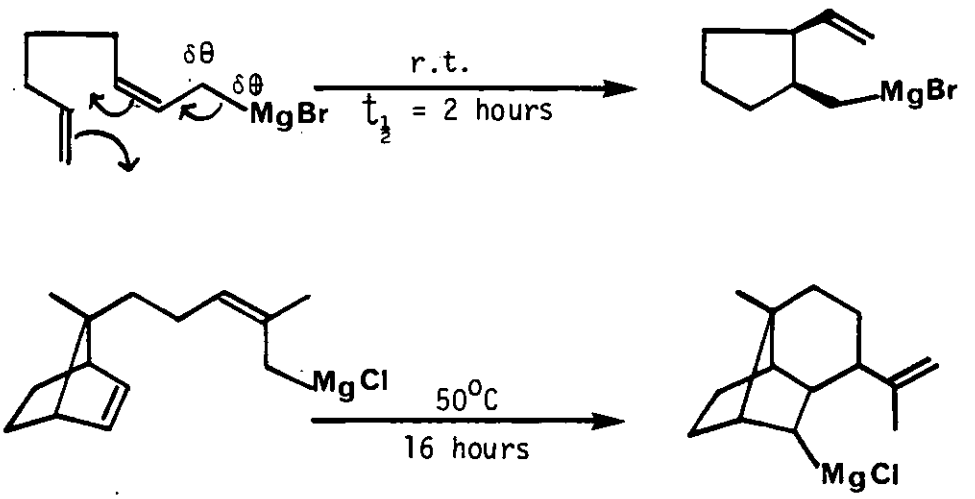


(ref. 19)

r.t. = room temperature.

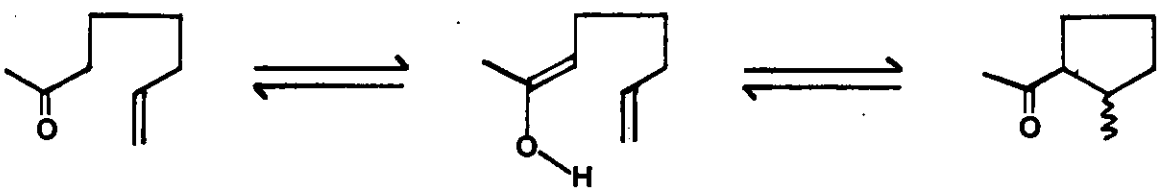
In contrast, little work has been reported on the development of activated electron rich ene systems. A related reaction is the metallo-ene reaction[20,21] which occurs at ambient temperatures. The ene may be considered as an allylic carbanion. Reaction proceeds with transfer of a metal atom, usually magnesium (Scheme 12).

Scheme 12



Conia[22] has cyclised a large number of unsaturated carbonyl compounds using the enol tautomer as the ene (Scheme 13). These reactions take place at temperatures between 270° and 350°C (cf 500°C for simple 1,6 dienes).

Scheme 13

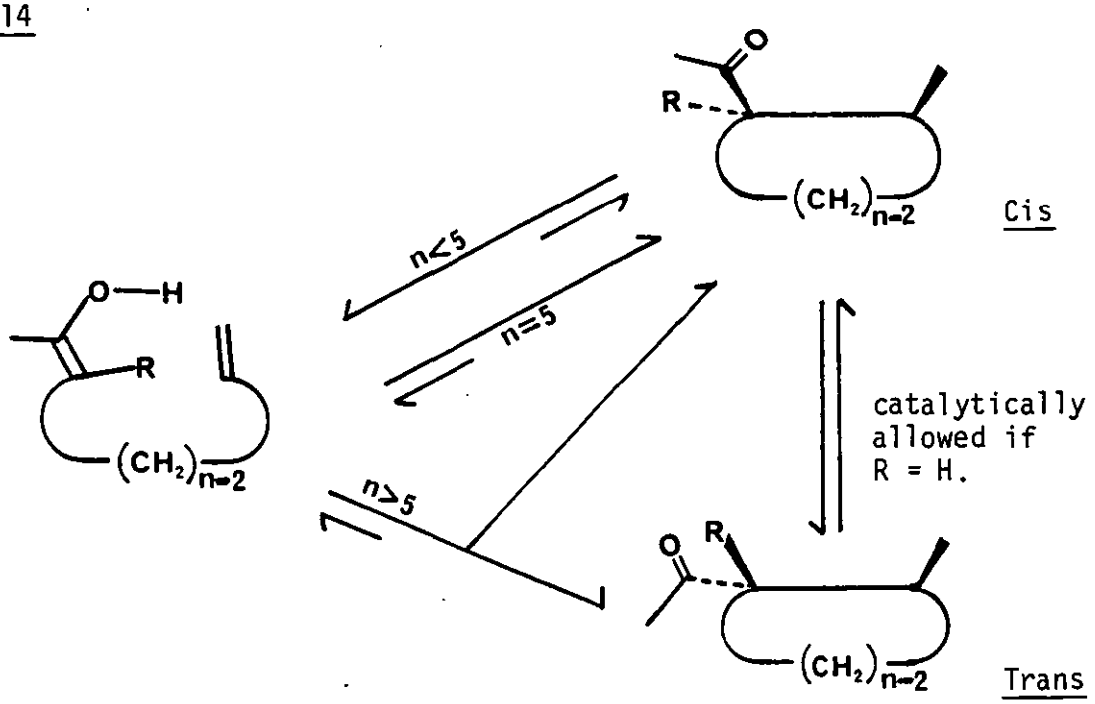


Five and six-membered rings are formed in good yield under similar conditions. Larger rings have been reported[23] but require higher temperatures and give decreased yields.

The stereochemistry of the reaction is dependant upon several factors and is generally difficult to predict, especially in reactions producing bicyclic products. Conia[22] has, however, made several generalisations based on experimental results and a study of transition state geometry (Scheme 14). A five-membered ring, when formed under kinetic control, will have cis-stereochemistry. However, six-membered ring formation

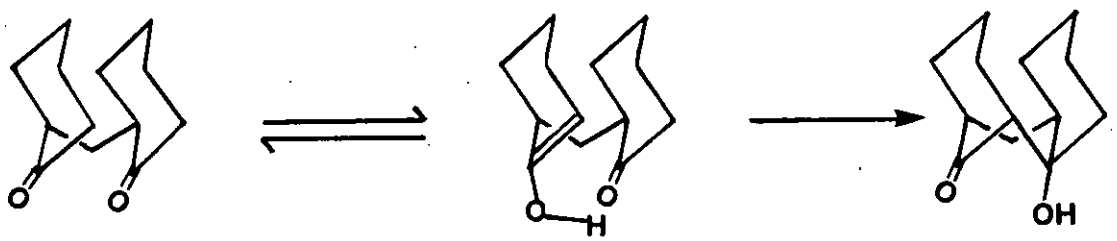
usually leads to trans-stereochemistry. Reaction reversibility and enolisation in the product may allow modification of the final product stereochemistry.

Scheme 14



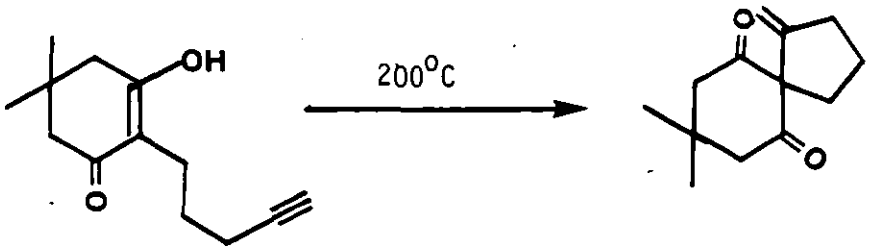
The enophile is generally an olefin or acetylene, but an example of a carbonyl enophile is the thermal 'aldol' reaction of the diketone (10)[24] (Scheme 15).

Scheme 15



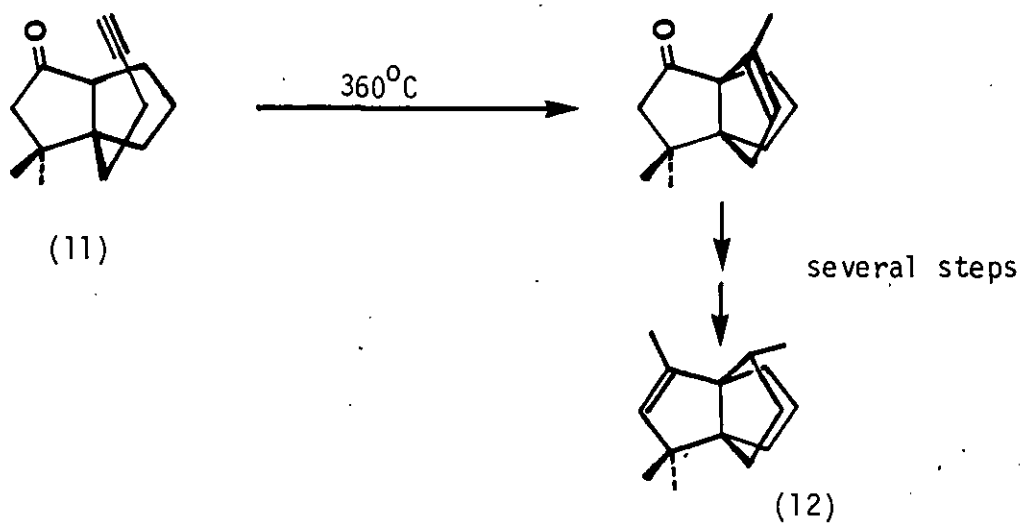
The pronounced enol character of β-diketones allow cyclisation temperatures as low as 200-250°C (Scheme 16). The low temperatures avoid exo-endo rearrangement of the double bond produced on cyclising acetylenes.[25]

Scheme 16



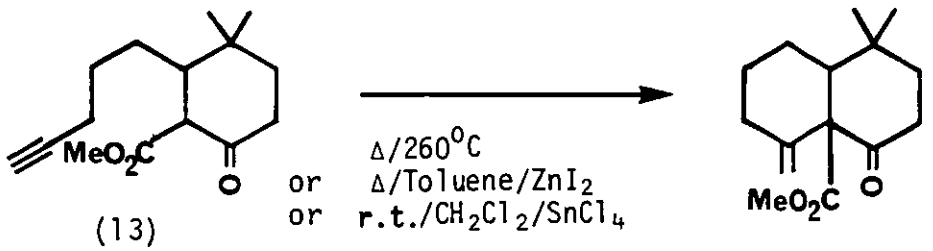
The ene reaction of unsaturated carbonyl compounds has found wide application in the synthesis of natural products. Paquette[26] cyclised the intermediate acetylenic ketone (11) in his synthesis of modhephene (12) (Scheme 17).

Scheme 17



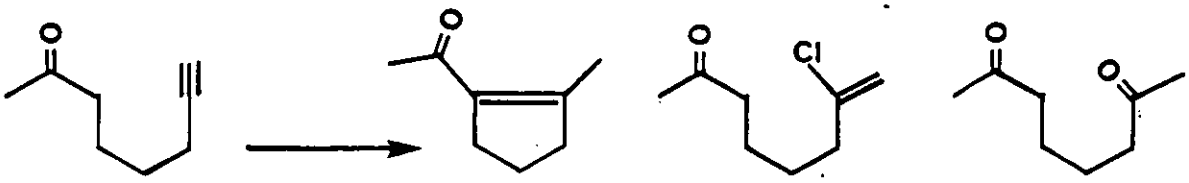
Ley and Jackson[27] used the ene reaction of an acetylenic β-keto-ester (13) in the synthesis of analogues of the insect antifedants clerodin and ajugarin (Scheme 18). The thermal cyclisation required a temperature in excess of 260°C. However, Lewis acids were found to catalyse the reaction and allow cyclisation to proceed at lower temperatures.

Scheme 18



Recently[28] Lewis acids and mercury salt/protic acid combinations have been used to catalyse the reactions of simple acetylenic ketones (Scheme 19).

Scheme 19



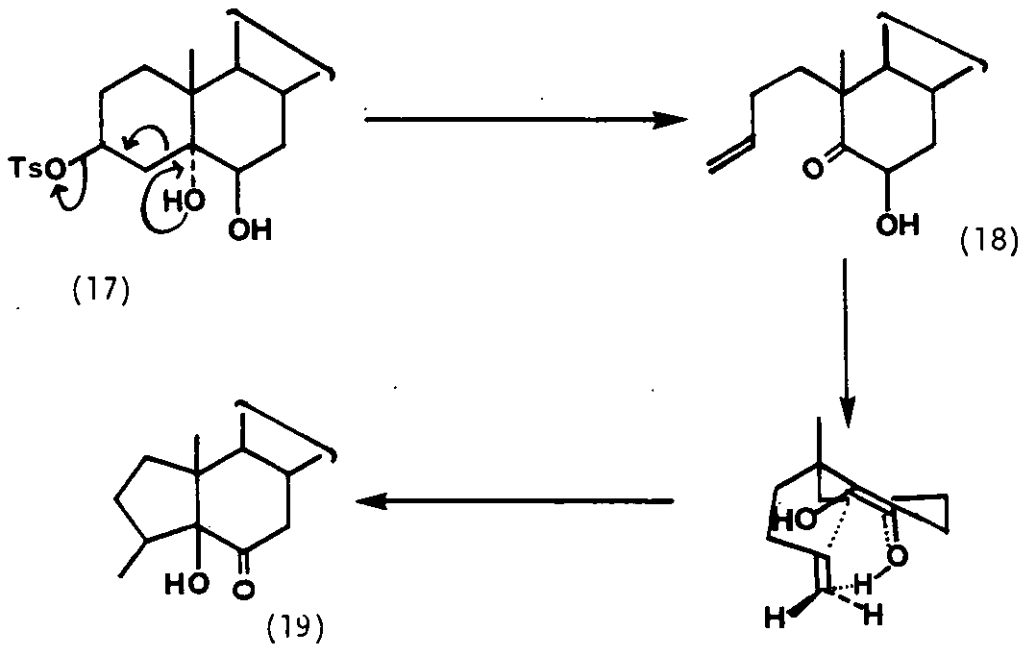
(14) (15) (16)

Condition	Yield % (14)	(15)	(16)
i) T.C.E./70°C/24 hrs HCl/H_2O, $HgCl_2$/EtOH	38	17	24
ii) T.C.E./70°C/24 hrs p.T.S.A./Et_2O, $HgCl_2/Et_2O$	78	-	-
iii) CH_2Cl_2/70°C/24 hrs $SnCl_4$	70	-	-

p.T.S.A. = p-toluenesulphonic acid
T.C.E. = 1,1,2,2-Tetrachloroethane

It was observed[29] in these laboratories that a byproduct of the reaction of the tosyloxy diol (17) with potassium t-butoxide in t-butanol at 50°C was 3β-methyl-A-nor-5β-cholestan-5-ol-6-one (19) (Scheme 20). This was believed to arise from a novel intramolecular ene reaction of the intermediate unsaturated acyloin (18) formed by fragmentation of (17).

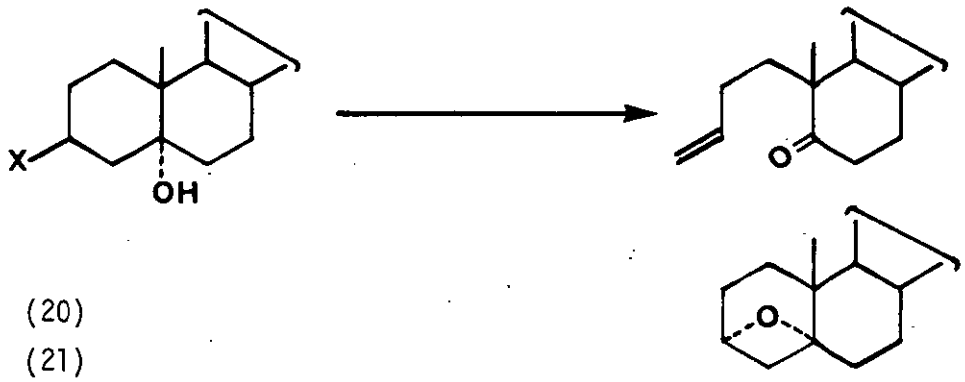
Scheme 20



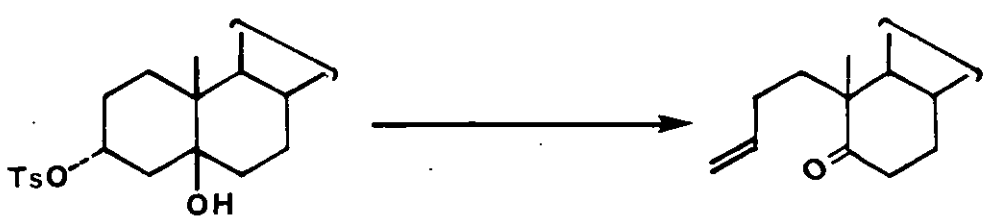
(17) (18) (19)

Fragmentations of the type described in Scheme 20 have also been observed[30] in the reactions of 3β-chloro and 3β -tosyloxy-5α-cholestan-5-ol (20) (21) and 3α-toxyloxy-5β-cholestan-5-ol (22) with potassium t-butoxide in t-butanol (Scheme 21).

Scheme 21



X = Cl (20)
X = TsO (21)

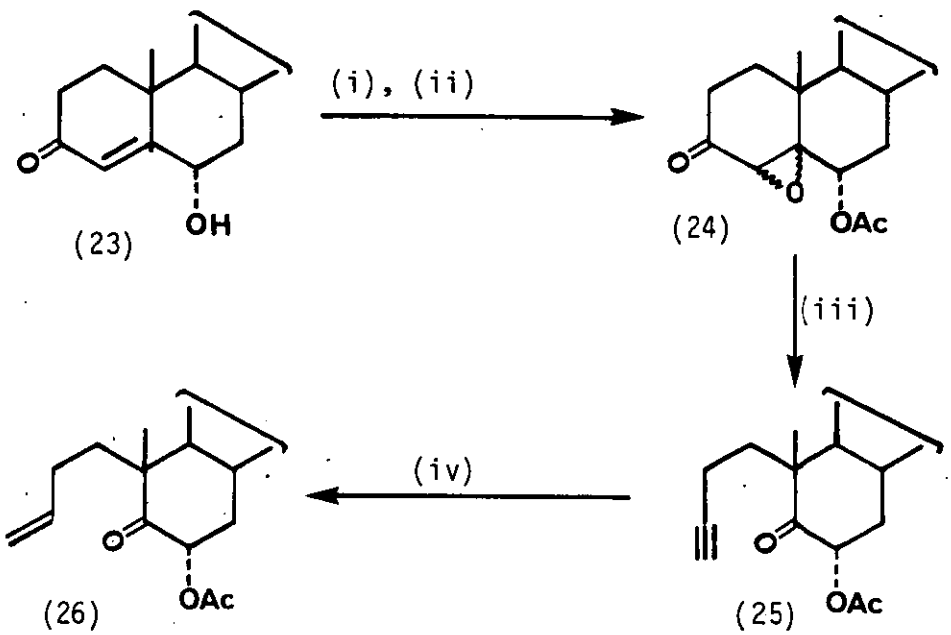


(22)

The ene reaction of the unsaturated acyloin (18) is similar to those of unsaturated ketones described previously[22], but occurs at significantly lower temperature. This enhanced reactivity may be due to the extra oxygen atom increasing the electron density of the ene.

Attempts to isolate the intermediate failed, but Silva[31] in these laboratories synthesised the 6-O-acetyl derivative (26) of the 6-epimer of the unsaturated acyloin (18) from 6α-hydroxy-cholest-4-en-3-one (23) utilising an Eschenmoser fragmentation (Scheme 22).

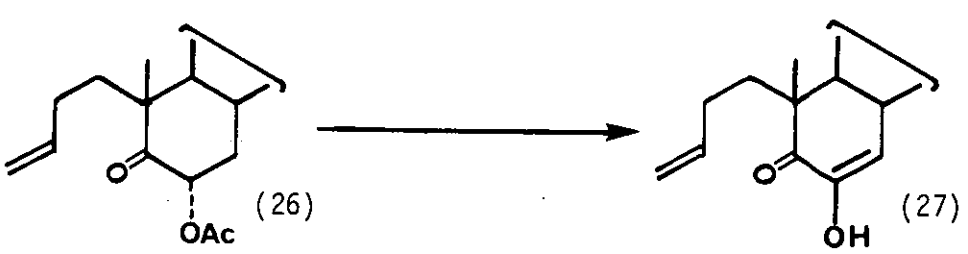
Scheme 22



Reagents: i) H_2O_2/NaOH/MeOH, ii) Ac_2O/Py, iii) EtOH/$TsNHNH_2$/50°C, iv) H_2/Pd/$BaSO_4$/EtOAc.

Deprotection of the keto-acetate (26) with sodium ethoxide in ethanol gave only the diosphenol (27) (Scheme 23).

Scheme 23



It was our aim to further investigate the ene reaction of unsaturated acyloins by:-

i) Closer examination of the original fragmentation - cyclisation reaction (Scheme 20).

ii) Synthesis of the unsaturated acyloin via 6α and 6β-acetoxy-4,5-seco-cholest-3-en-5-one and investigate its reactions under a variety of conditions.

iii) Synthesis of other unsaturated acyloins to study the general reaction.

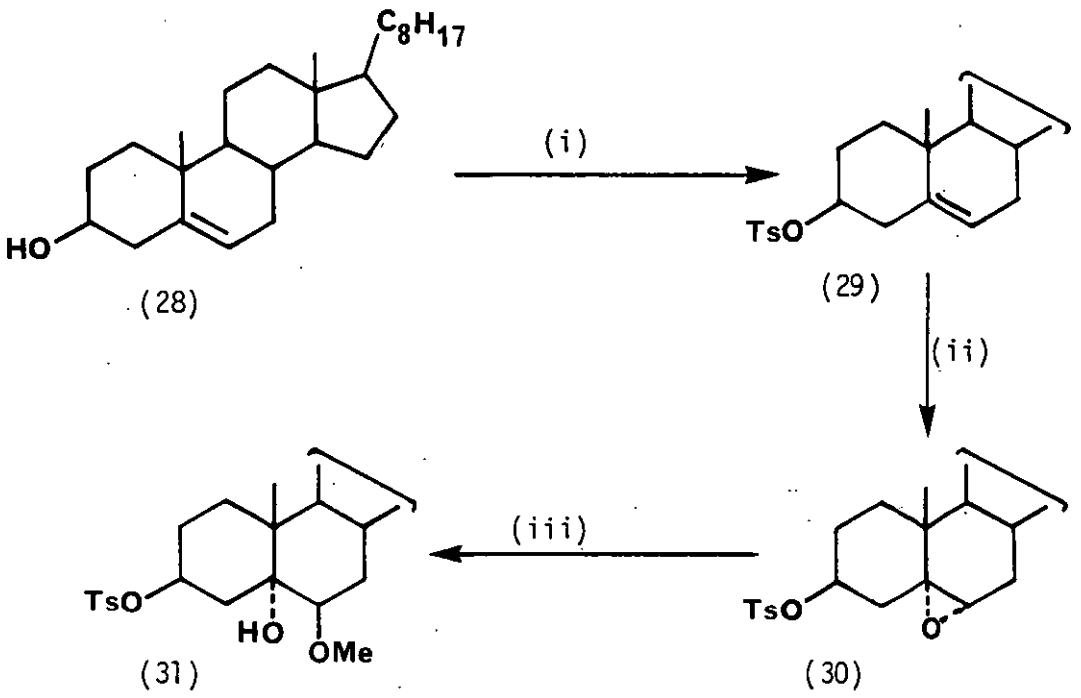
RESULTS AND DISCUSSION

Part I Preparation and Reactions of the 4,5-secocholest-3-en-5,6-acyloins.

We considered that base-catalysed fragmentation of a tosyloxy diol derivative with the 6β-hydroxyl protected would give evidence of the proposed intermediate unsaturated acyloin (18). Also, the protecting group would stop further reaction and allow investigation of the intermediate acyloin.

Treatment of cholesterol (28) with p-toluenesulphonyl chloride in pyridine gave the tosylate (29).[32] This was epoxidised with m-chloroperbenzoic acid (mCPBA) in ether/chloroform to give the α-epoxide (30)[33] which was treated with methanol and boron trifluoride etherate to give the known methoxy-tosylate (31)[31] (Scheme 24).

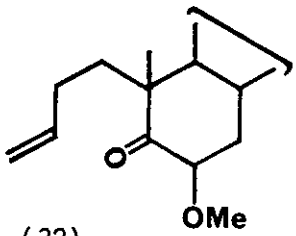
Scheme 24



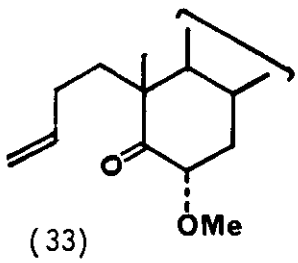
Reagents: i) TsCl/Py; ii) mCPBA/Et_2O/$CHCl_3$; iii) MeOH/BF_3.Et_2O.

Reaction of the methoxy-tosylate (31) with potassium t-butoxide in t-butanol gave a mixture from which a minor product (2%) 6β-methoxy-4,5-secocholest-3-en-5-one (32), could be separated by preparative thin layer

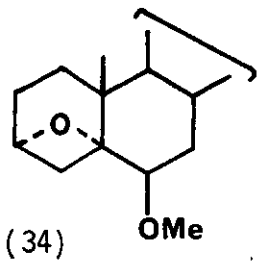
chromatography. The major fraction contained a mixture of 6α-methoxy-4,5-secocholest-3-en-5-one (33) and 6β-methoxy-5α-cholestan-3α,5-epoxide (34) in 55% yield.



(32)



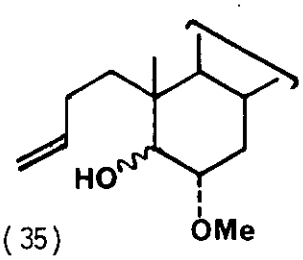
(33)



(34)

The 6β-methoxy-ketone (32) showed $\nu_{max.}$ 1720 (C=O) cm^{-1} in its infrared spectrum and its 'H n.m.r. spectrum had signals at δ 5.5 - 5.9 (m, RC<u>H</u> = CH_2), 4.9 - 5.2 (m, RCH = $C\underline{H}_2$), 3.64 (brd t, C6α-H) and 3.34 (s, OMe) which supported the assigned structure. The mass spectrum had a molecular ion at m/z 416 and a base peak at m/z 362 arising from a McLafferty rearrangement involving the loss of the butenyl chain by cleavage of the C_1-C_2 bond.

The presence of the 6α-methoxy-ketone (33) in the mixed band was confirmed by the infrared spectrum ($\nu_{max.}$ 1720 (C=O) cm^{-1}) and the 'H n.m.r. spectrum (δ 4.0, q, C6β-Me). Reduction of the mixture with sodium borohydride in methanol and preparative thin layer chromatography gave, as the minor product (2%) 6α-methoxy-4,5-secocholest-3-en-5-ξ-ol (35) and as the major product (55%) 6β-methoxy-5α-cholestan-3α,5-epoxide (34).[31]



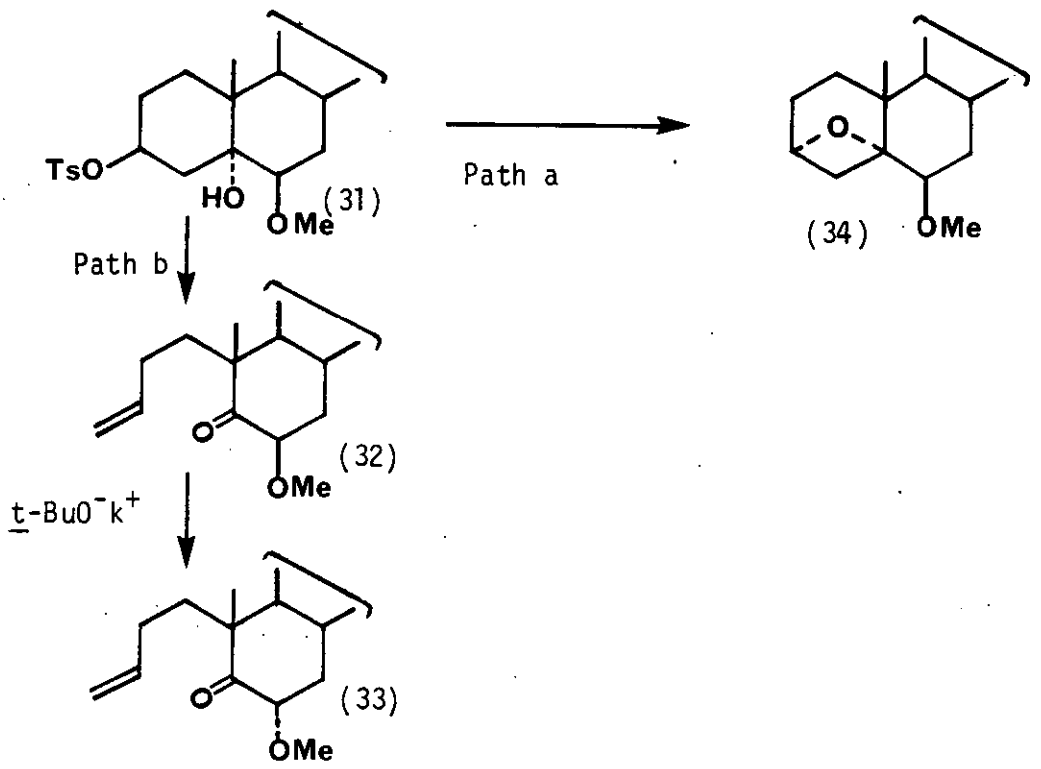
(35)

The methoxy-alcohol (35) had $\nu_{max.}$ 3580, 3470 (OH) cm^{-1} in its infrared spectrum and the 'H n.m.r. spectrum had important signals at δ 5.6 - 6.0

(m, RCH=$\underline{CH_2}$), 4.8 - 5.2 (m, RCH=$\underline{CH_2}$), 3.42 and 3.35 (s, OMe) and 3.25 (m, C6β-H). The mass spectrum had a molecular ion at m/z 418.

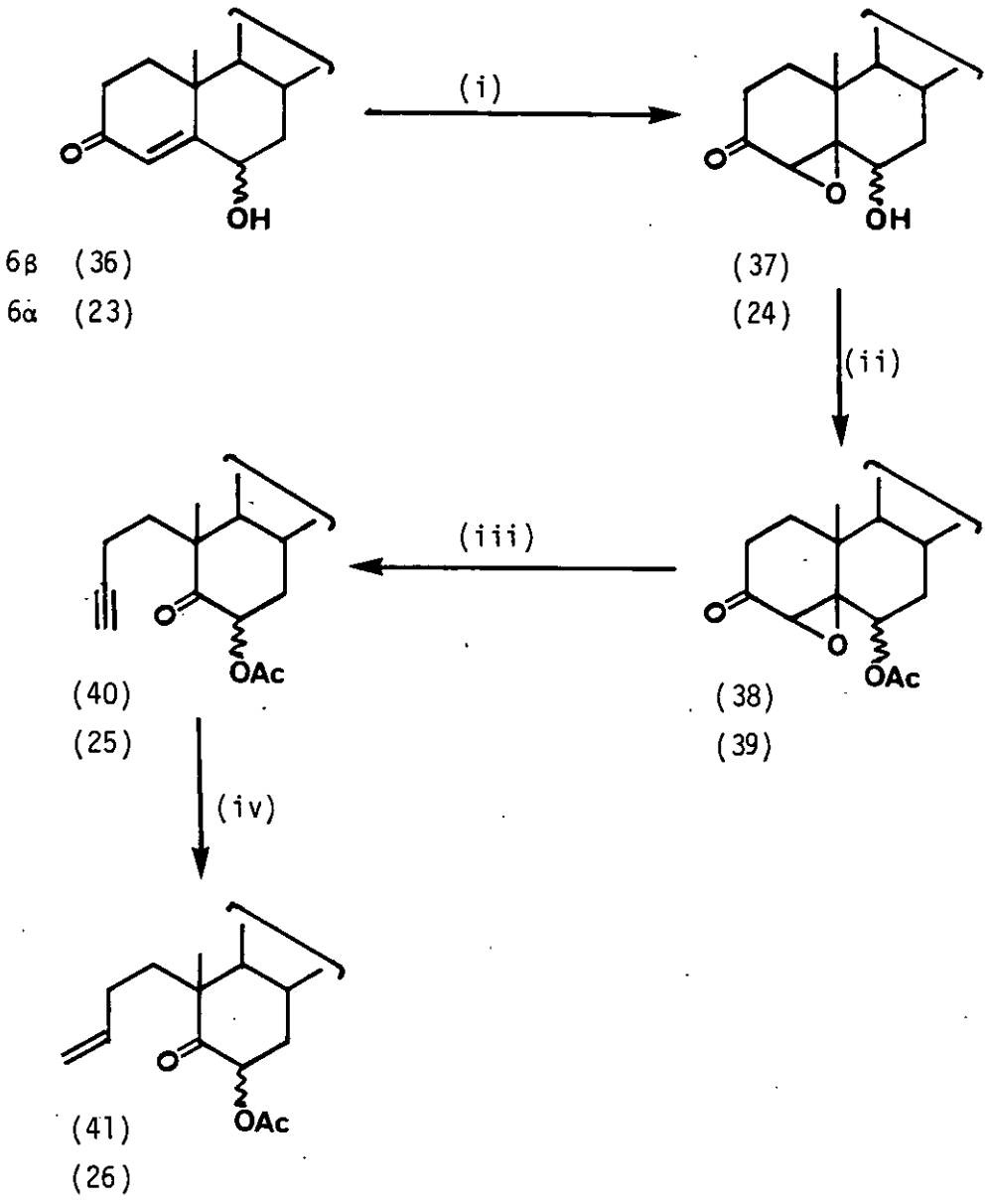
Reaction of the methoxy-tosylate (31) can proceed by two pathways. Displacement of the tosylate by the oxygen anion (Path A) leads to the oxetane (34). Fragmentation (Path B) leads to the 6β-methoxy-ketone (32) which undergoes a base-catalysed epimerisation to give the 6α-methoxy-ketone (33) (Scheme 25).

Scheme 25



Preparation of the 6-O-acetyl- derivatives of the epimeric unsaturated acyloins (41), (26) was achieved via a common route (Scheme 26) from their respective 6-hydroxycholest-4-en-3-ones (36), (23).

Scheme 26



6β (36)
6α (23)

(37)
(24)

(40)
(25)

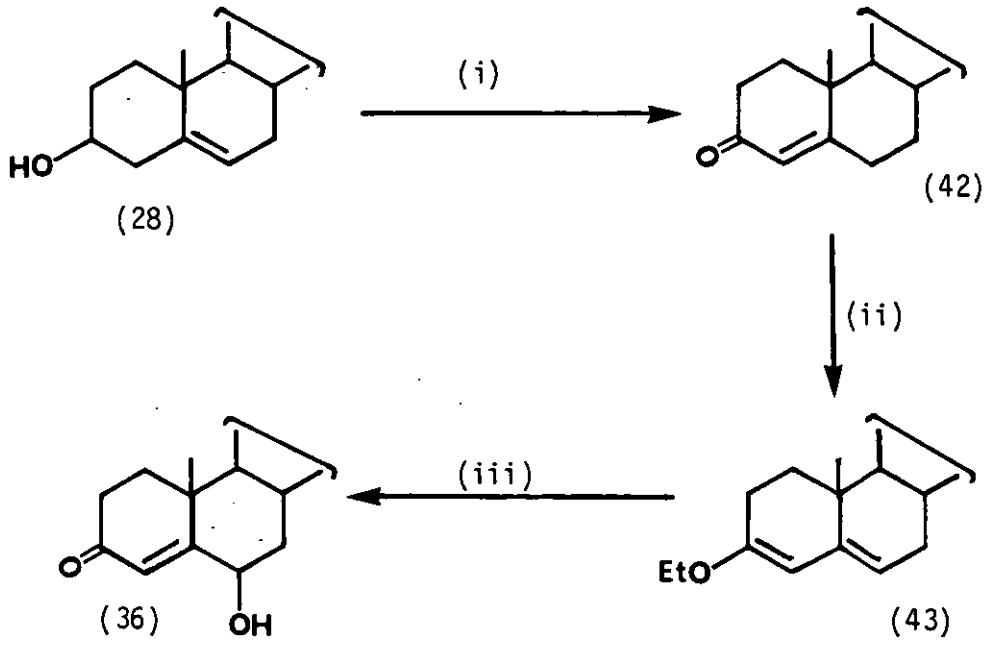
(38)
(39)

(41)
(26)

Reagents: i) H_2O_2/NaOH/MeOH; ii) Py/Ac_2O; iii) $TsNHNH_2$/EtOH/50°C; iv) H_2/Pd.$BaSO_4$/EtOAc

Cholesterol (28) was oxidised with cyclohexanone and aluminium isopropoxide in toluene to give cholestenone (42).[34] Treatment of cholestenone with triethylorthoformate and a catalytic amount of acid in ethanol gave the ethoxy-diene (43)[35] which was photolysed in oxygenated ethanol[36] to give 6β-hydroxycholest-4-en-3-one (36)[37] (Scheme 27).

Scheme 27

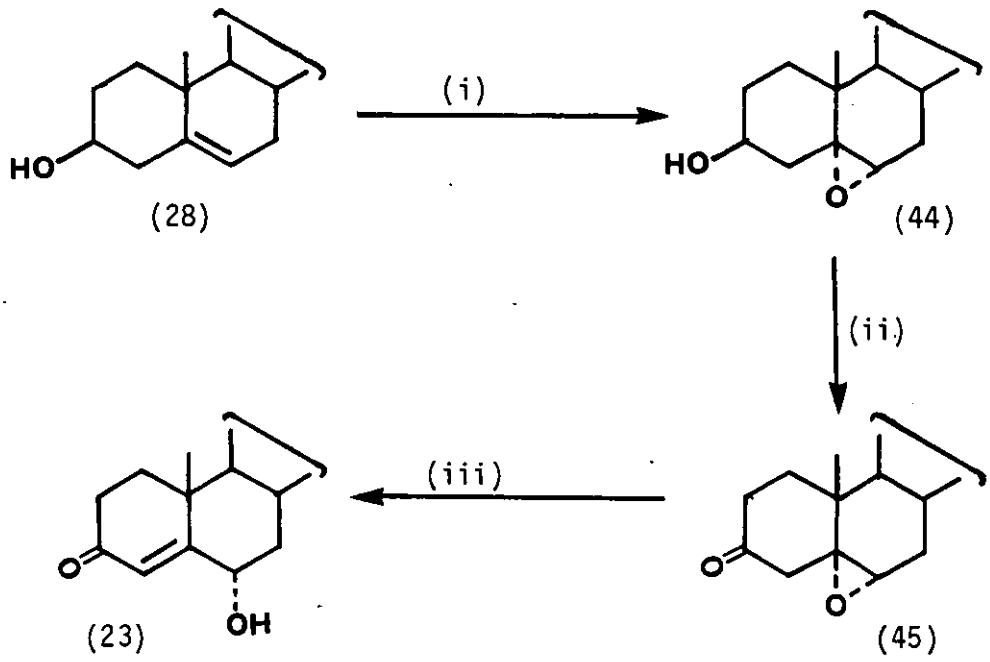


Reagents: i) Al $(O^iPr)_3$/cyclohexanone/toluene; ii) $HC(OEt)_3/H^+$/EtOH; iii) $h\nu/O_2$/EtOH.

Epoxidation of cholesterol (28) with m-chloroperbenzoic acid in ether gave the α-epoxide (44).[38] Oxidation with pyridinium chlorochromate in dichloromethane followed by isomerisation of the crude keto-epoxide (45) with triethylamine in ethanol gave 6α-hydroxycholest-4-en-3-one (23)[39] (Scheme 28).

Silva[31] previously prepared the 6α-hydroxy-enone (23) by oxidation of the epoxide (44) with chromium trioxide in pyridine. This resulted in over-oxidation and generally lower yields.

Scheme 28

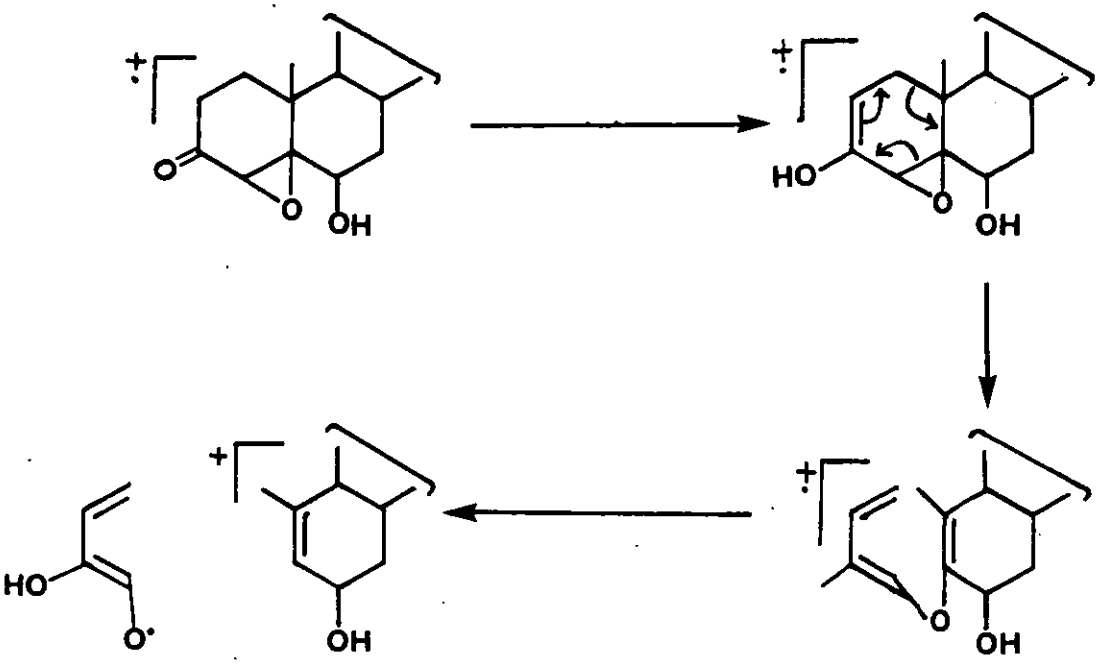


Reagents: i) mCPBA/ether; ii) $PyCrO_2Cl_2/CH_2Cl_2$; iii) $EtOH/NEt_3$.

The hydroxy-enones (37) and (23) were epoxidised with alkaline hydrogen peroxide in methanol to give, after recrystallisation, the epoxides (37) and (24) respectively. The epoxides were assigned the 4β,5β-stereochemistry by analogy with other reported[40,41] epoxidations of steroid Δ^4-3-ketones.

The epoxy-ketone (36) had important signals at δ 3.48 (brd s, C6α-H, $W_{\frac{1}{2}}$ 6Hz), 3.02 (s, C4α-H) and 1.36 (s, C10β-Me) in its ^1H n.m.r. spectrum. The mass spectrum had a molecular ion at m/z 416 which fragmented with the loss of C_4H_5O to m/z 331. A possible rationalisation of this fragmentation is shown in Scheme 29.

Scheme 29

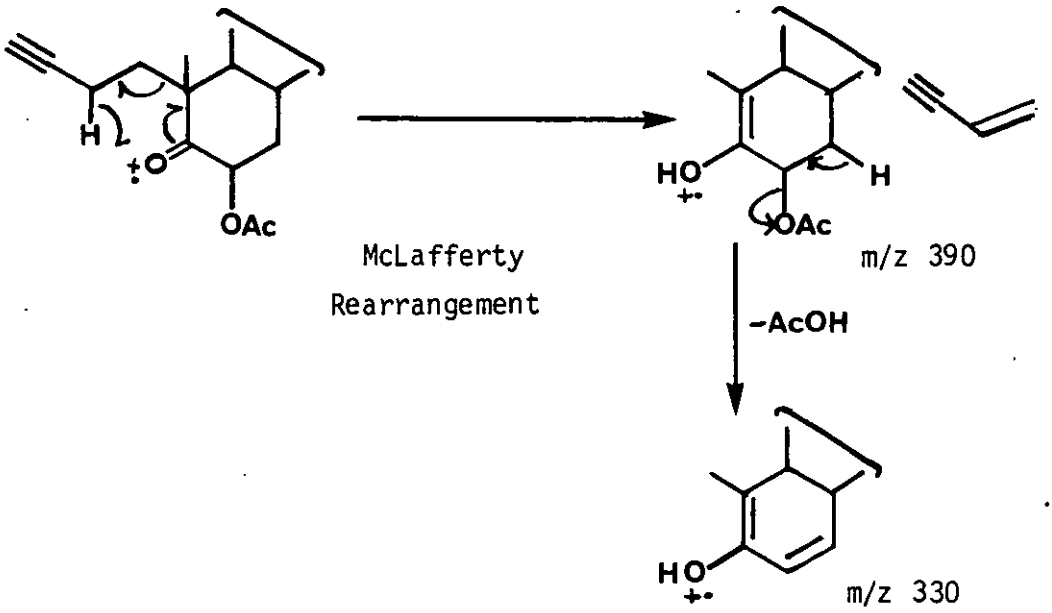


The epoxy-ketone (24) had similarly characteristic signals in its ^{1}H n.m.r. spectrum at δ 4.14 (q, C6β-H, J 5 and 11Hz), 3.46 (s, C4α-H) and 1.14 (s, C10β-Me) and mass spectrum similar to that of (36).

Acetylation with acetic anhydride in pyridine gave respectively the epoxy-acetates (38) and (39), which underwent an Eschenmoser fragmentation[42] when treated with p-toluene sulphonhydrazide in ethanol to give the acetylenes (40) and (25).

The presence of the terminal acetylene in (40) was confirmed by the infrared spectrum ($\nu_{max.}$ 3310 and 2120 (C≡C-H) cm^{-1}). The ^{1}H n.m.r. spectrum had an important signal at δ 5.39 (brd t, C6α-H, $J_{(apparent)}$ 9Hz), which confirmed retention of the 6β-OAc stereochemistry under the reaction conditions. The mass spectrum showed a molecular ion at m/z 442 which fragmented with the loss of the butynyl chain to afford a peak at m/z 390, which further fragmented with the loss of acetic acid to give a peak at m/z 330 (Scheme 30).

Scheme 30

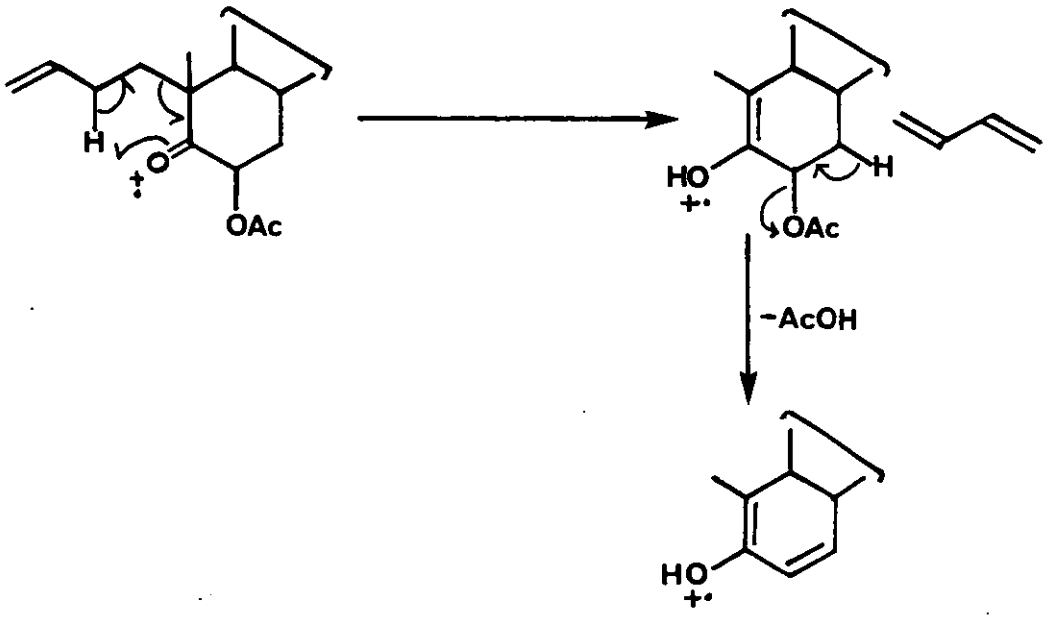


The acetylene (25) had a similar mass spectrum and characteristic infrared ($\nu_{max.}$ 3315 and 2120, (C≡C-H) cm^{-1}) and ^1H n.m.r. (δ 5.46, q, C6β-H, J 6 and 11Hz) spectra.

The acetylenes (40) and (25) were partially hydrogenated in ethyl acetate solution using 5% palladium-on-barium sulphate catalyst poisoned with quinoline to give the olefins (41) and (26).

The olefin (41) had infrared (ν_{max} 3080 and 1640 (RCH=CH)cm^{-1}). and ^1H n.m.r. (5.6-6.0, m, R$\underline{CH}$=CH_2 and 4.85-5.15, m, RCH=$C\underline{H_2}$) spectra that confirmed the presence of a terminal olefin. Its mass spectrum had a molecular ion at m/z 444 which fragmented with the loss of the butenyl group to afford a peak at m/z 390. Further fragmentation by the loss of acetic acid gave the base peak at m/z 330 (Scheme 31).

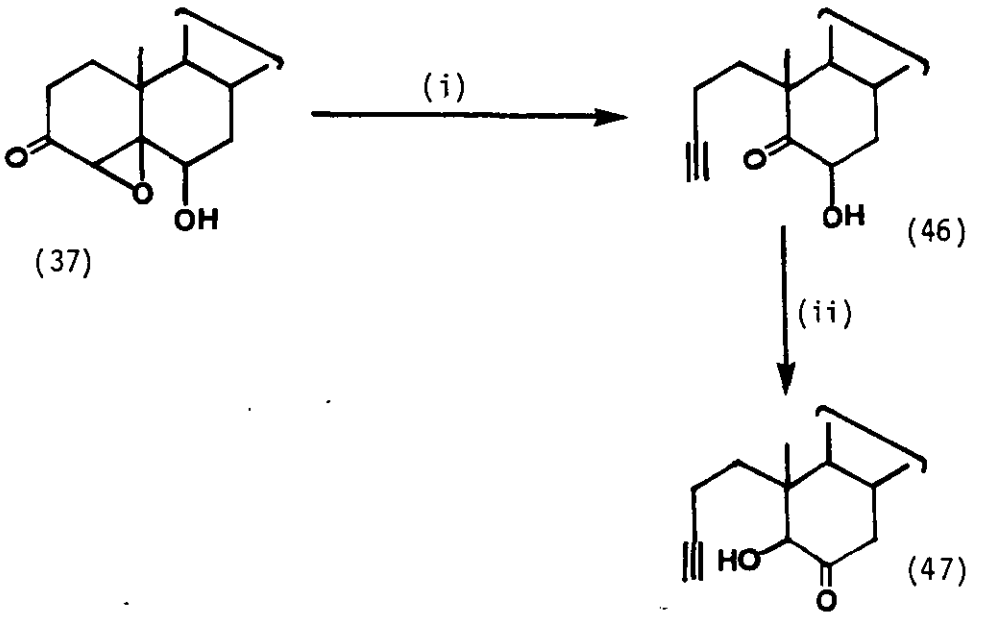
Scheme 31



The olefin (26) gave a similar mass spectrum. Its infrared spectrum had $\nu_{max.}$ 3075 and 1640 (RCH = CH_2)cm^{-1} and its ^1H n.m.r. spectrum had important peaks at δ 5.6 - 6.1 (m, R$\underline{C}$H = CH_2) and 4.85 - 5.20 (RCH = $C\underline{H}_2$).

6β-Hydroxy-4β,5-epoxy-5β-cholestan-3-one (37) also underwent an Eschenmoser fragmentation[42] to give, in the crude product, the 6β-acetylenic acyloin (46). Attempted purification by preparative thin layer chromatography on silica gel caused isomerisation to the 5β-acetylenic acyloin (47) (Scheme 32). This approach to the synthesis of the unsaturated acyloin (48) proved to be inefficient, compared to using the epoxy-acetate (38), due mainly to difficulties in purification of the product.

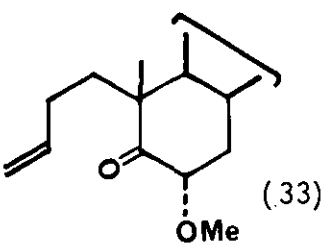
Scheme 32



Reagents: i) EtOH/$TsNHNH_2$/50°C; ii) Silica, preparative t.l.c.

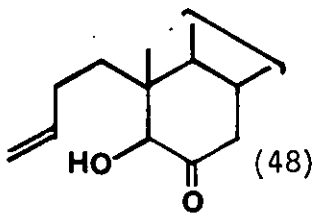
The infrared spectrum of the acetylenic acyloin (47) had ν_{max} 3280, 2120 (C≡C-H), 3520 (OH) and 1715 (C=O) cm^{-1} confirming the presence of a terminal acetylene and an acyloin. The ^1H n.m.r. spectrum had important signals at 3.55 (s, OH, D_2O exchangeable) and 4.08 (s, C5α-H) which supported the assigned regiochemistry. The 5-acyloin (47) is presumably more thermodynamically stable than the 6β-acyloin (46) and it is assumed that the 5β-equatorial conformation would be preferred.

Attempted hydrolysis of the 6β-acetoxy-ketone (41) using concentrated hydrochloric acid in methanol gave the 5α-methoxy-ketone (33) previously obtained in the reaction of 3β-tosyloxy-6β-methoxy-5α-cholestan-5-ol (31) with potassium t-butoxide in t-butanol.

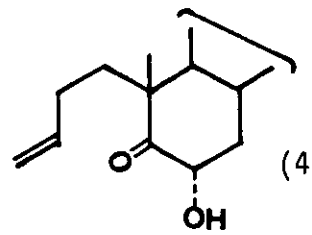


(33)

Hydrolysis of the 6β-acetoxy-ketone (41) was best achieved with concentrated hydrochloric acid in 90% aqueous ethanol, giving 5β-hydroxy-4,5-secocholest-3-en-5-one (48). Both the 6α- and 6β-acetoxy-ketone (26) and (41) underwent hydrolysis when treated with dilute hydrochloric acid (2M) in ethanol, although a longer reaction time was required. The milder conditions of this reaction allowed the isolation, by preparative t.l.c., of the 5β-acyloin (48) as the major product and 6α-hydroxy-4,5-secocholest-3-en-5-one (49) as the minor product.



(48)



(49)

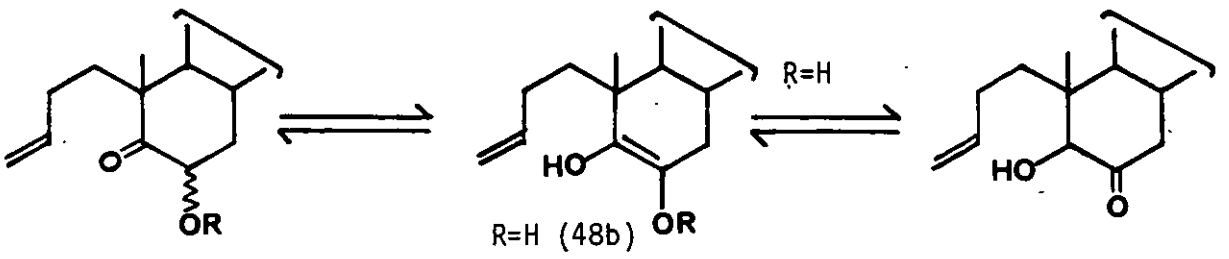
33%	from (26)	26%
30%	from (41)	24%

The 5β-acyloin (48) had ν_{max} 3070 and 1640 (RCH=CH), 3470 (OH) and 1710 (C=O) cm^{-1} in its infrared spectrum which confirmed the presence of the terminal olefin and acyloin. Its 'H n.m.r. spectrum had important signals at δ 4.25 (brd s, OH, D_2O exchangeable) and 4.08 (s, C5α-H) which confirmed the assigned regiochemistry. Its mass spectrum had a molecular ion at m/z 402 which fragmented with the loss of the butenyl chain to give a peak at m/z 348.

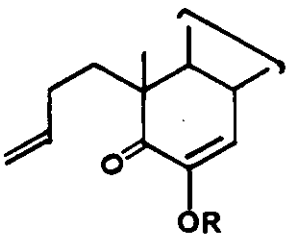
The 6α-acyloin (49) gave a similar mass spectrum. Its infrared spectrum had $\nu_{max.}$ 3070 and 1640 ($RCH=CH_2$), 3470 (OH) and 1700 (C=O) cm^{-1}. Its 'H n.m.r. spectrum had important signals at δ 4.38 (q, C6β-H, J 7 and 11Hz) and 3.90 (brd s, OH, D_2O exchangeable) which confirmed the assigned regio and stereochemistry.

Isomerisation presumably proceeds by acid catalysed enolisation of the acyloin to an enediol intermediate (48b) (Scheme 33).

Scheme 33



Hydrolysis of the 6β-acetoxy-ketone (41) with deoxygenated ethanolic potassium hydroxide under an inert atmosphere gave only the 5β-acyloin (48). However, if the hydrolysis was performed in the presence of air, the diosphenol (27) was the major isolable product. The diosphenol had $\nu_{max.}$ 3430 (OH), 3080 ($RCH=CH_2$), 1670 (C=O), 1650 (C=C) cm^{-1} in its infrared spectrum and the ^1H n.m.r. spectrum showed important signals at δ 6.09 (s, OH, D_2O exchangeable), 6.01 (d, C7- H J 2Hz) 5.55 - 6.0 (m, $R\underline{C}H=CH_2$) and 4.9 - 5.2 (m, $RCH=C\underline{H}_2$). The mass spectrum had a molecular ion at m/z 400 which fragmented with the loss of the butenyl chain to give the base peak at m/z 346. Acetylation with acetic anhydride in pyridine gave the diosphenol acetate (51) which showed a downfield shift of 0.36 ppm for the C7-H signal in the ^1H n.m.r. spectrum.



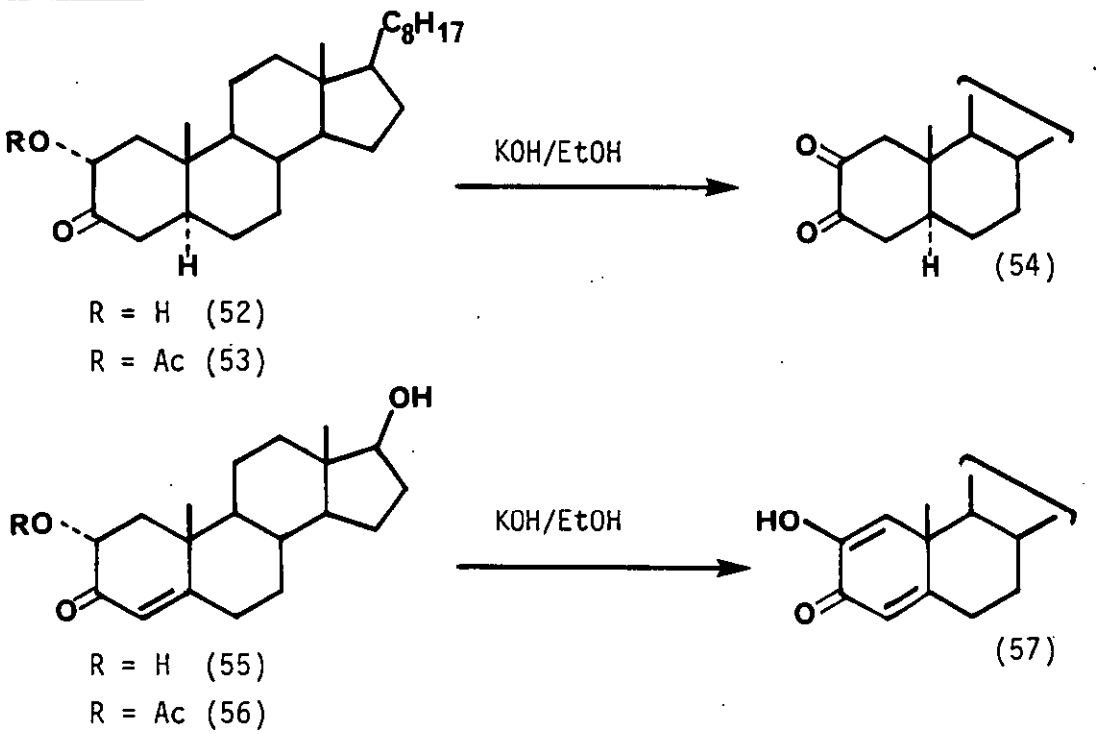
R = H (27)
R = Ac (51)

Treatment of the 5β-acyloin (48) with either ethanolic potassium hydroxide or potassium t-butoxide in t-butanol, in the presence of air, also gave the diosphenol (27).

Several examples of the base catalysed autoxidation of acyloins have been reported[43,44,45] (Scheme 34). Typically, when 5α-cholestan-2α-ol-3-one (52) or its acetate (53) are treated with ethanolic potassium hydroxide in the presence of oxygen, the diosphenol(54) is formed.

Similarly, 2α-hydroxy or 2α-acetoxy-androst-4-en-17β-ol-3-one (55) (56) gave the diosphenol (57).

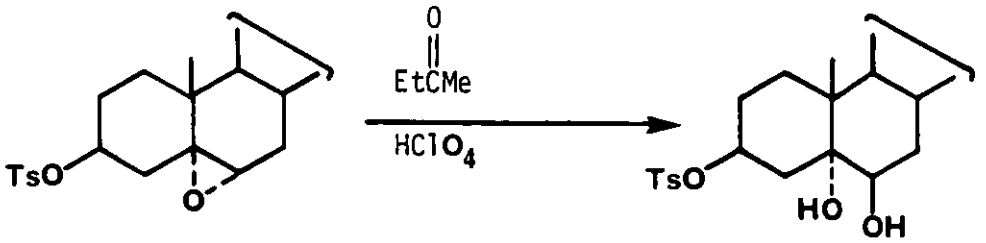
Scheme 34



The 5β-acyloin (48) failed to cyclise in a deoxygenated solution of potassium t-butoxide in t-butanol at reflux and only starting material was recovered. Failure of the isolated acyloin (48) to cyclise under the original conditions[29] promoted us to re-investigate the reaction in which 3β-methyl-A-nor-5β-cholestan-5-ol-6-one (19) is produced from the tosyloxy diol (17).

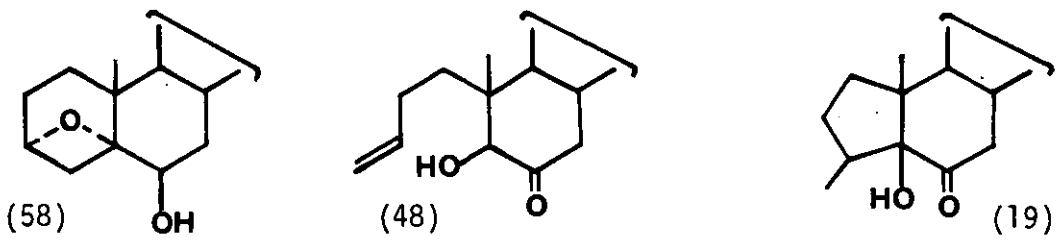
The tosyloxy-epoxide (30)[33] was treated with perchloric acid in methyl ethyl ketone to give the tosyloxy diol (17)[46] (Scheme 35).

Scheme 35



(30) (17)

Reaction of (17) in a deoxygenated solution of potassium t-butoxide in t-butanol at 50°C gave a mixture. Separation by preparative thin layer chromatography gave 3β-methyl-A-nor-cholestan-5-ol-6-one (19) (11%), 5β-hydroxy-4,5-secocholest-3-en-5-one (48) (4%) and 6β-hydroxy-5α-cholestan-3α,5-epoxide (58)[47] (49%).

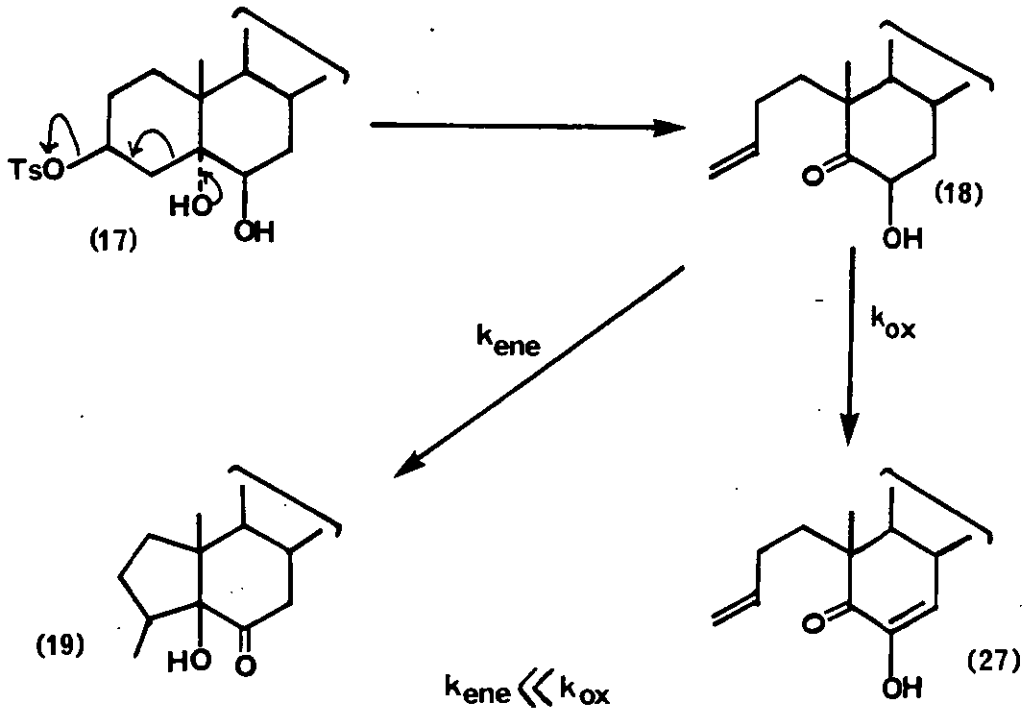


(58) (48) (19)

These results are similar to those obtained by Marples et al[29]. However, isolation of the 5β-acyloin (48) from this reaction is an indication of its role as an intermediate in the production of the A-nor-ketol (19). Further evidence was gained by repeating the reaction in the presence of air. Separation of the reaction mixture by preparative thin layer chromatography gave only the oxetane (58) (53%) and the disophenol (27) (17%). The yield of the diosphenol is comparable with the sum of the yields of the A-nor-ketol (19) and the 5β-acyloin (48) in the absence of air.

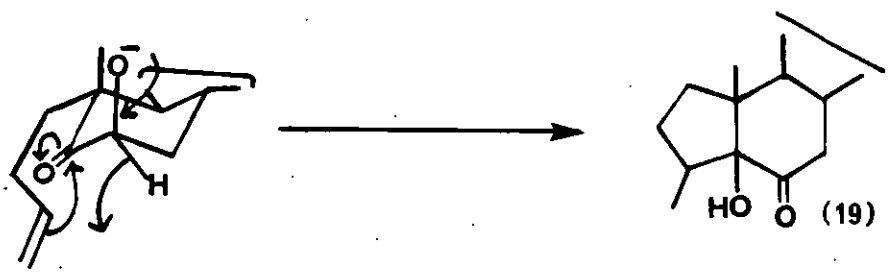
It is assumed that autoxidation of the acyloin (18) produced by fragmentation of the tosyloxy diol (17) is a fast process compared to the ene reaction (Scheme 36). The acyloin is therefore 'trapped' by oxidation to the diosphenol (27).

Scheme 36



It is possible that the A-nor-ketol (19) may arise from the 5β-acyloin by a direct hydride transfer from C6α to the olefin (C4) (Scheme 37).

Scheme 37

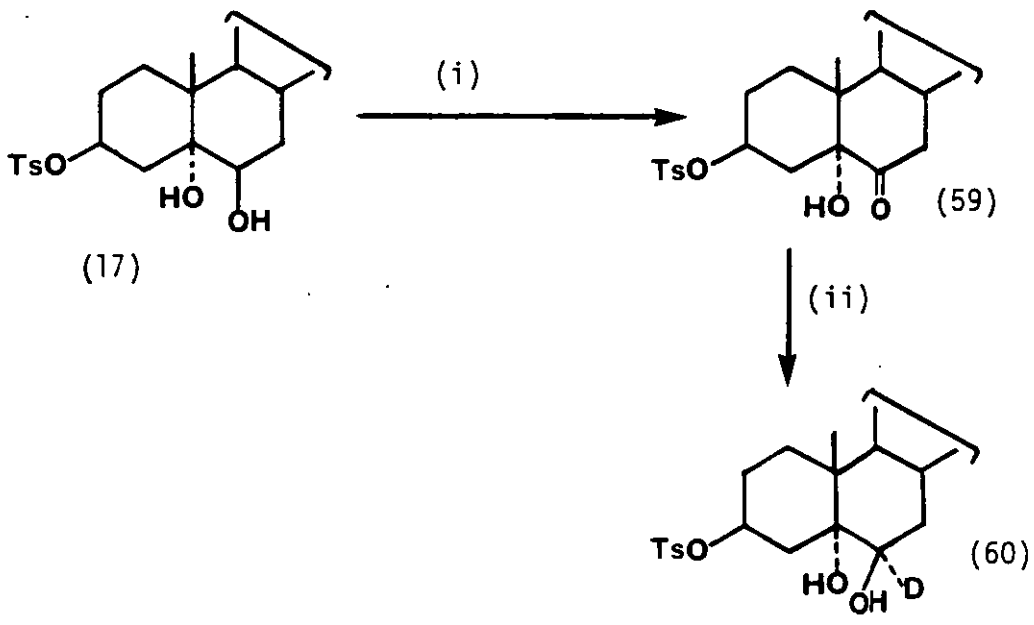


This mechanism appeared unlikely, but to examine the role of the 6α-hydrogen in the production of the A-nor-ketol (19), the 6α-^{2}H derivative of the tosyloxy diol was synthesised.

Oxidation of the tosyloxy diol (17) with pyridinium chlorochromate in dichloromethane gave the tosyloxy ketol (59)[48] which was reduced with sodium borodeuteride in methanol to give the [6α-^{2}H]-tosyloxy diol (60) (Scheme 38).

The absence of a signal at δ 3.58 (C6α-H) in ^{1}H n.m.r. confirmed the introduction of deuterium into the 6α-position.

Scheme 38



Reagents: i) $PyCrO_2Cl_2/CH_2Cl_2$; ii) $NaBD_4$/MeOH.

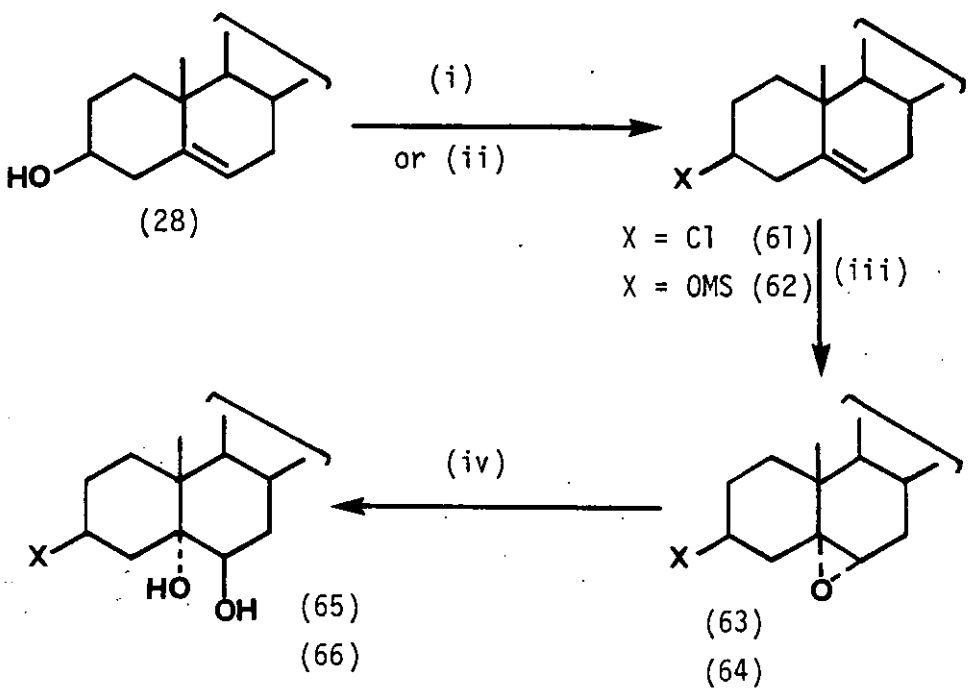
Treatment of (60) with potassium t-butoxide in deoxygenated t-butanol and separation of the products by preparative thin layer chromatography gave the A-nor-ketol (19) in only 2% yield. Its mass spectrum had a molecular ion at m/z 402 indicating the loss of deuterium during the reaction. The 5β-acyloin (48) (9%) was isolated and the presence of the signal at δ 4.08 (C5α-H) confirmed the loss of deuterium. As expected, the [6α-^{2}H] -oxetane derivative (58) (57%) was also isolated. The absence of a signal at δ 3.87 (C6α-H) in the ^{1}H n.m.r. spectrum confirmed the retention of deuterium.

This result ruled out the hydride shift mechanism since deuterium is absent in the A-nor-ketol (19). The hydrogen must come either directly or indirectly from the solvent as in the proposed ene mechanism. The increase in the level of the 5β-acyloin (48), in the product, over that of the A-nor-ketol (19) is thought to be due to a kinetic isotope effect and is discussed later as part of the overall mechanism.

It was envisaged that changing either the leaving group or the relative stereochemistry of the 3-tosyloxy and 5-hydroxy groups, would alter the course of the reaction sufficiently to give an increase of the fragmentation reaction at the expense of oxetane (58) formation. Increased fragmentation should lead to increased A-nor-ketol (19) formation.

Cholesterol (28) was treated with thionyl chloride to give the chloride (61)[49], and with mesyl chloride in pyridine to give the mesylate (62)[50]. Treatment of these derivatives with m-chloroperbenzoic acid in ether afforded the chloro-epoxide (63)[51] and the mesyloxy-epoxide (64)[46] which were hydrolysed with aqueous perchloric acid to give the chloro diol (65)[51] and the mesyloxy diol (66) respectively (Scheme 39).

Scheme 39



Reagents: i) $SOCl_2$; ii) $MeSO_2Cl/Py$; iii) $mCPBA/Et_2O$; iv) $HClO_4/EtCOMe$

The chloro diol (65) gave only the oxetane (58) (35%) after heating with 3 moles of potassium t-butoxide in t-butanol solution for 18 hours. A considerable quantity of the starting material was recovered.

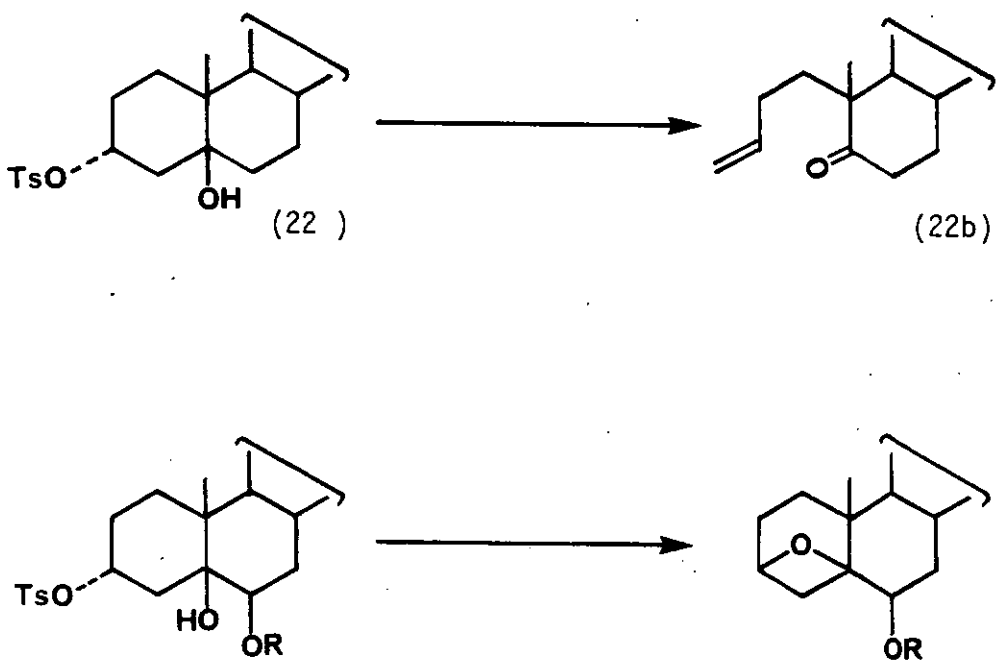
The mesyloxy diol (66) on treatment with potassium t-butoxide in t-butanol gave a mixture. Separation by thin layer chromatography gave the

A-nor-ketol (19) (2%), the 5β-acyloin (48) (10%) and the oxetane (58) (54%).

This represents an overall decrease in the amount of fragmentation. More surprisingly, formation of the A-nor-ketol (19) has been affected, resulting in the isolation of mainly 5β-acyloin (48).

3α-Tosyloxy-5β-cholestan-5-ol (22) has been reported[30] to give only 4,5-secocholest-3-en-5-one (22b) on reaction with potassium t-butoxide in t-butanol (Scheme 40). The analogous reactions of 3α-tosyloxy-6β-cholestane-5,6β-diol (67) with sodium hydride in D.M.F., or 3α-tosyloxy-6β-acetoxy-5β-cholestan-5-ol with potassium t-butoxide in t-butanol, gave 6β-hydroxy-3β,5-epoxy-5β-cholestane (68)[52].

Scheme 40



R = H (67) , NaH/D.M.F.
R = Ac (69) , Bu^tOK/Bu^tOH

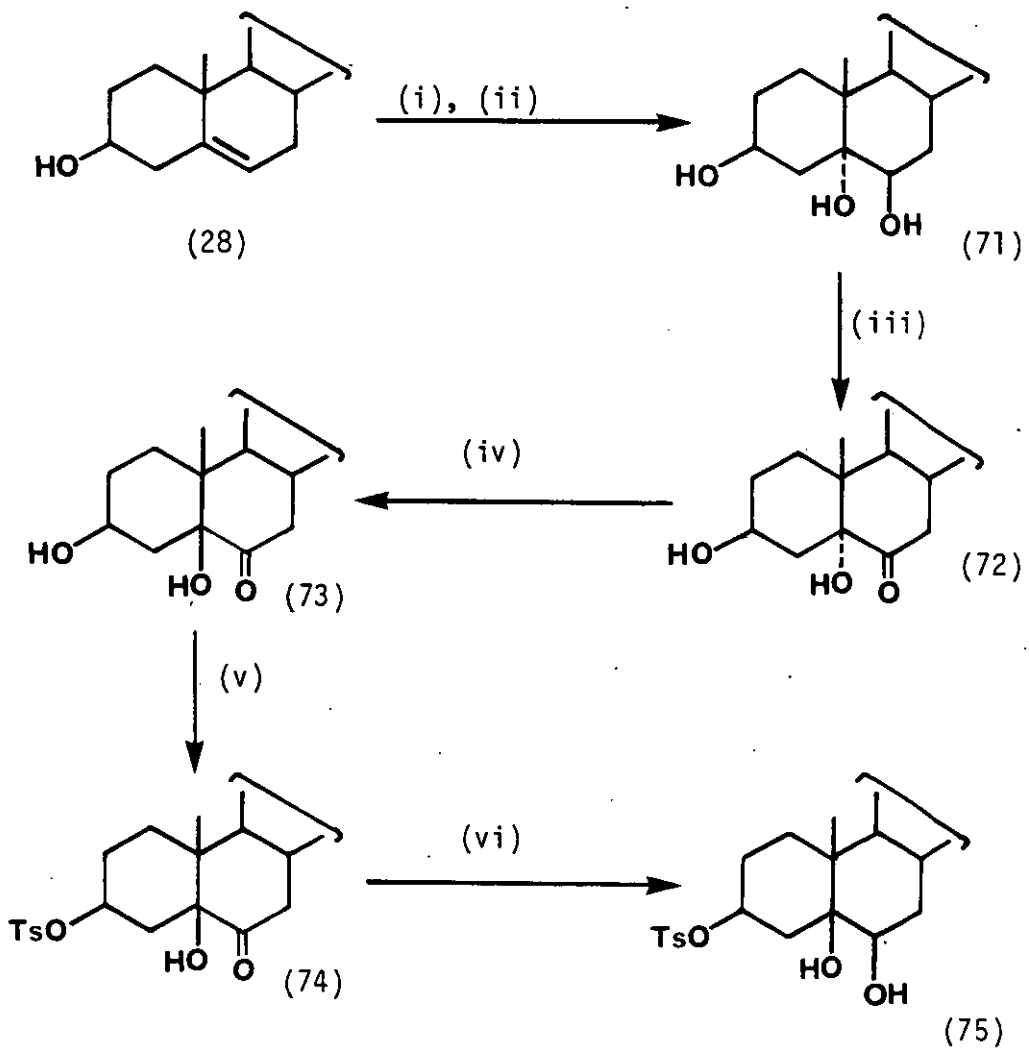
R = H (68), 52%
R = H (68), 16%
R = Ac (70), 11%

We considered that a 3β, 5β tosyloxy, hydroxy geometry would remove competing oxetane formation and increase the yield of the fragmentation

product. 3β-Tosyloxy-5β-cholestane-5,6β-diol was prepared, although it is realised that the tosyloxy-hydroxy geometry is less than ideal for the fragmentation reaction (see below).

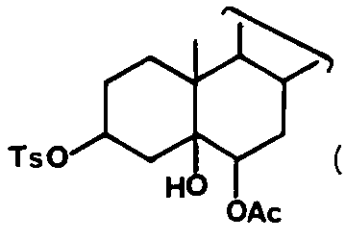
Treatment of cholesterol (28) with performic acid, followed by hydrolysis of the formate, gave the triol (71)[53] which was oxidised selectively to the 5α-dihydroxy ketone (72)[53] with N-bromosuccinimide (N.B.S.) in aqueous dioxan. Epimerisation in refluxing methanolic potassium hydroxide[58] gave the 5β-dihydroxy-ketone (73).[54] Reaction with p-toluenesulphonyl chloride in pyridine gave the tosyloxy ketone (73)[71] and reduction with sodium borohydride in methanol gave the tosyloxy diol (75) (Scheme 41).

Scheme 41



Reagents: i) HCO_2H/H_2O_2; ii) NaOH/MeOH/H_2O; iii) N.B.S./  /H_2O
iv) KOH/MeOH; v) TsCl/Py; vi) $NaBH_4$/MeOH

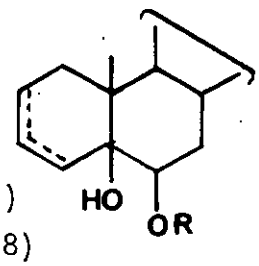
The tosyloxy diol (75) stereochemistry was confirmed by the 'H n.m.r. spectrum which had important signals at δ 4.97 (brd s, C3α-H, $W_{\frac{1}{2}}$ 7Hz) and 3.53 (brd s, C6α-H, $W_{\frac{1}{2}}$ 6Hz). Compound (75) was converted to the monoacetate (76) by treatment with acetic anhydride in pyridine. The signal at δ 4.76 (brd s, C6α-H) in the 'H n.m.r. spectrum confirmed the acetylation of the 6β-OH.



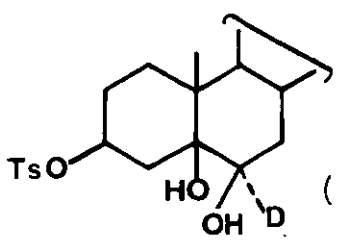
(76)

Reaction of the tosyloxy diol (75) with potassium t-butoxide in t-butanol was extremely variable due to competing thermal decomposition. The best result in terms of A-nor-ketol yield consisted of the A-nor-ketol (19) (45%), the 5β-acyloin (48) (5%) and an olefinic diol (77) (18%).

The olefinic diol (77) was identified from the infrared spectrum ($\nu_{max.}$ 3450,(OH)cm^{-1}) and the 'H n.m.r. spectrum which had important signals at δ 5.2 - 6.0 (m, olefinic protons) and 3.69 (brd s, C6α-H, $W_{\frac{1}{2}}$ 6Hz). The mass spectrum had a molecular ion at m/z.402. Acetylation afforded the monoacetate (78), the 'H n.m.r. spectrum of which showed the 6α-H signal at δ 4.87.



R = H (77)
R = Ac (78)



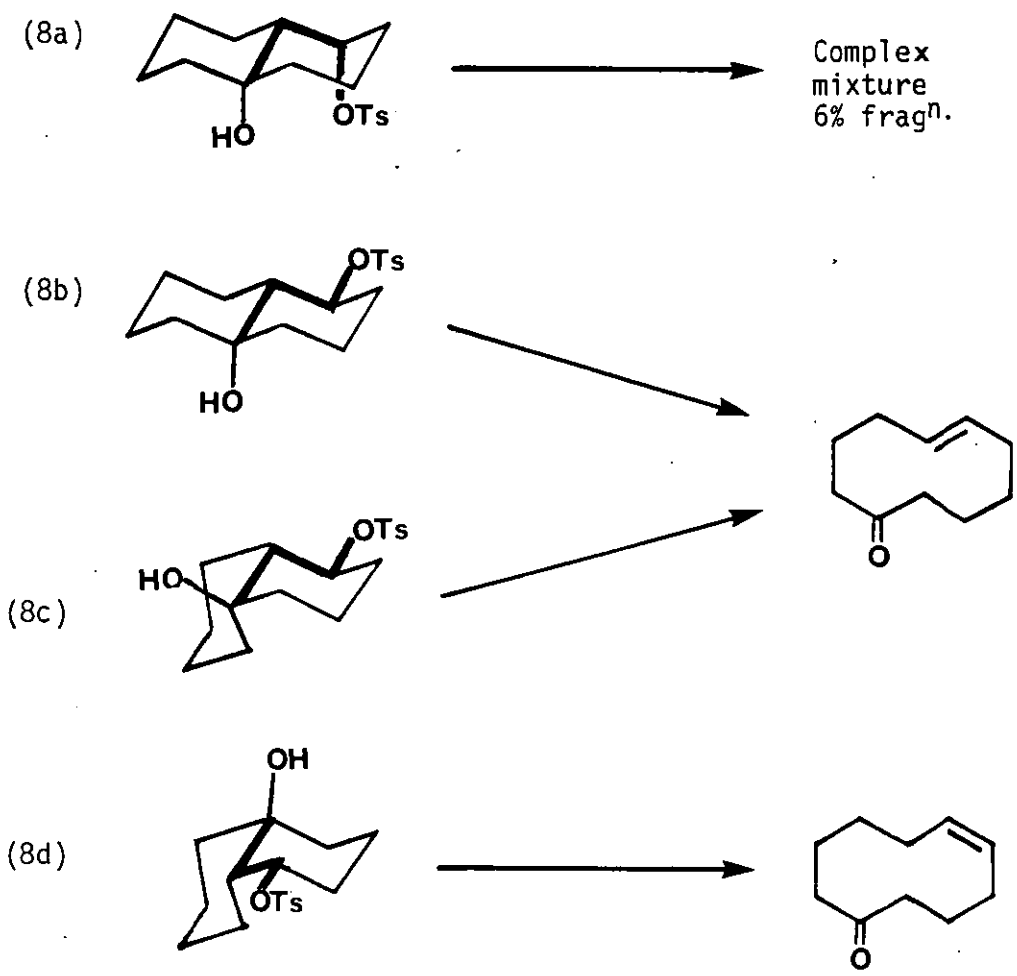
(79)

The 6α-^{2}H derivative of the tosyloxy diol (75) was prepared by reduction of the tosyloxy ketone (74) with sodium borodeuteride in methanol.

Treatment of (79) with potassium t-butoxide in t-butanol again gave varying results. The best result (based on the yield of (19)) gave, after preparative thin layer chromatography, a band containing a mixture of A-nor-ketol (19) and diosphenol (27) (47%), the 5β-acyloin (5%) and the dihydroxy-[6α-^{2}H]-olefin (13%). Acetylation of the mixture and further chromatography gave the A-nor-ketol (19) (26%) and the diosphenol acetate (51) (12%). Only the dihydroxy olefin (77) showed retention of deuterium. The diosphenol was a product of incomplete deoxygenation of the t-butanol solution. Yields of the A-nor-ketol (19) were found to be generally lower.

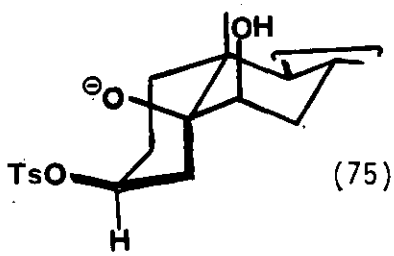
Wharton and Hiegel[55] have reported the base catalysed fragmentations of some tosyloxy-hydroxy-decalins (8 a-d) (Scheme 42). Fragmentation would appear to require the carbon-tosylate and fragmenting carbon-carbon bonds to be anti. The hydroxyl geometry is less important.

Scheme 42

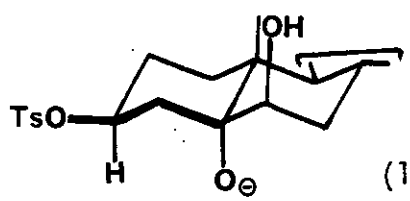


The small amount of fragmentation that occurs with compound (8a) is thought to arise from a non-concerted reaction pathway.

The tosyloxy diol (75) is unable to obtain the correct conformation for oxetane formation which requires attack of the oxy-anion on the opposite side of the carbon atom to the leaving tosylate anion. However, it is also not in the ideal conformation for fragmentation, although fragmentation is observed, presumably by a non-concerted pathway. This is reflected in the increased reaction time, 16 hours compared to 2 hours for the tosyloxy-5α-diol (17).



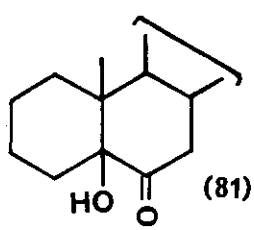
(75)



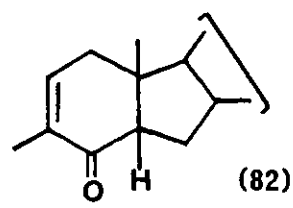
(17)

The series of reactions described contribute a great deal of circumstantial evidence in favour of the proposed ene reaction for the formation of the A-nor-ketol (19). The failure of the acyloin to cyclise under the original conditions of reaction seems to refute this. Comparison with the ene reactions of unsaturated ketones led us to believe that elevating the reaction temperature would lead to a cyclisation.

Cyclisation was achieved by heating the 5β-acyloin (48) in decalin in a sealed tube for 5½ hours at 200°C. Separation of the products by preparative thin layer chromatography gave 5β-cholestan-5-ol-6-one (81)[56] in 13% yield and 3-methyl-B-nor-5β-cholest-2-en-4-one in 26% yield.



(81)

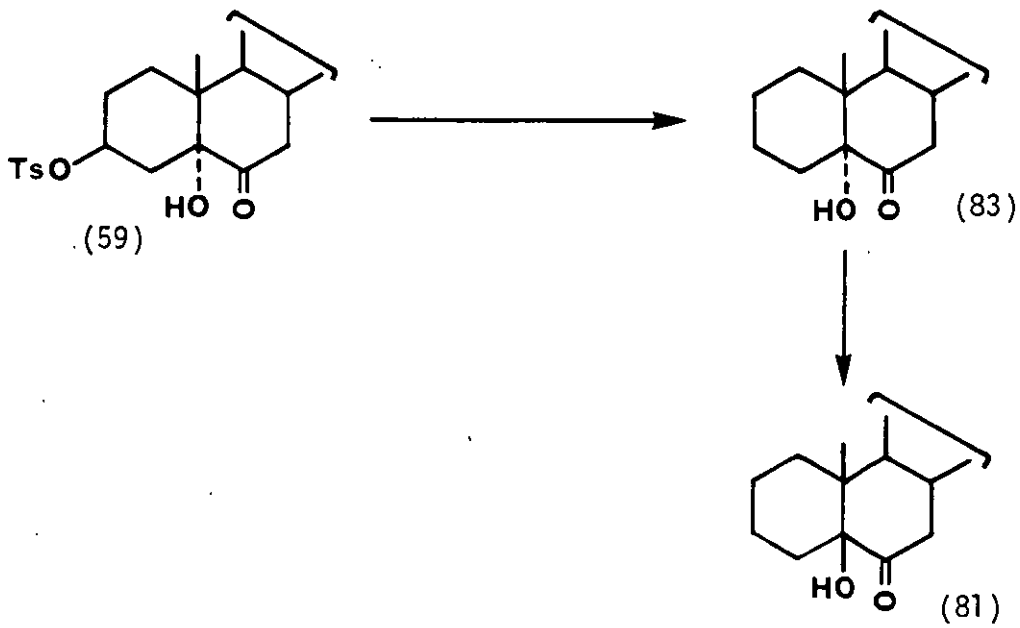


(82)

The 5β-ketol (81) had $\nu_{max.}$ 3465 (OH) and 1695 (C=O) cm^{-1}. The ^1H n.m.r. spectrum had important signals at δ 3.9 (s, OH, D_2O exchangeable), 0.71 (s, C10 β-Me) and 0.66 (s, C13 β-Me). The mass spectrum had molecular ion m/z 402. The mixed melting point with an authentic sample gave no depression.

An authentic sample of the 5β-ketol (81) was prepared according to Scheme 43. The tosyloxy ketol (59) was reduced with zinc and sodium iodide in refluxing dimethoxy ethane[57] to give the 5α-ketol (83). Epimerisation of (83) in methanolic potassium hydroxide[58] gave the 5β-ketol (81).

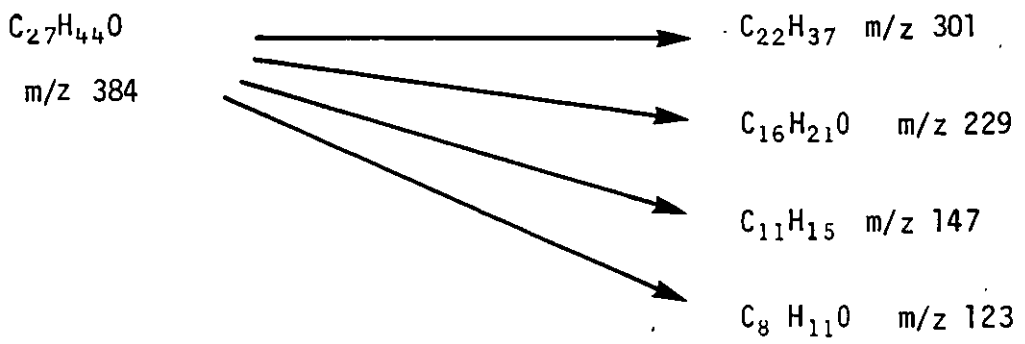
Scheme 43



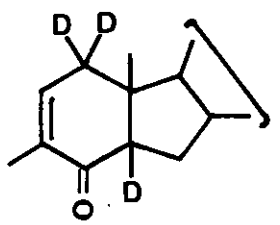
Reagents i) Zn/NaI/$CH_3OCH_2CH_2OCH_3$; ii) KOH/MeOH

The structure assignment of the B-nor-enone (82) was supported by the infrared spectrum ($\nu_{max.}$ 1665 (C=O) cm^{-1}) and the ultra-violet spectrum ($\lambda_{max.}$ 240 nm) which confirmed the presence of an α-substituted α,β-unsaturated ketone. The ^1H n.m.r. spectrum had signals at δ 6.50 (m, RCH=CMeCO) and 1.80 (RCH=CMeCO). Double irradiation of the methyl signal at δ 1.80 caused the multiplet at δ 6.50 to collapse to a double doublet (J 5.8 and 2.8 Hz) illustrating the spin-spin coupling between the C-2 and C-1 protons. Double

irradiation of the multiplet at δ 6.50 caused the methyl signal to collapse to a double doublet (J 1.2 and 2.4 Hz) illustrating the long range coupling between the methyl and C-1 protons. The 5β-configuration was assigned on the basis of thermodynamic stability and supported by the low-field position of the C10β-Me signal (δ 25.7) in the ^{13}C n.m.r. spectrum. The full ^{13}C data are given in Appendix I. The mass spectrum had a molecular ion at m/z 384 which fragments as shown below:-

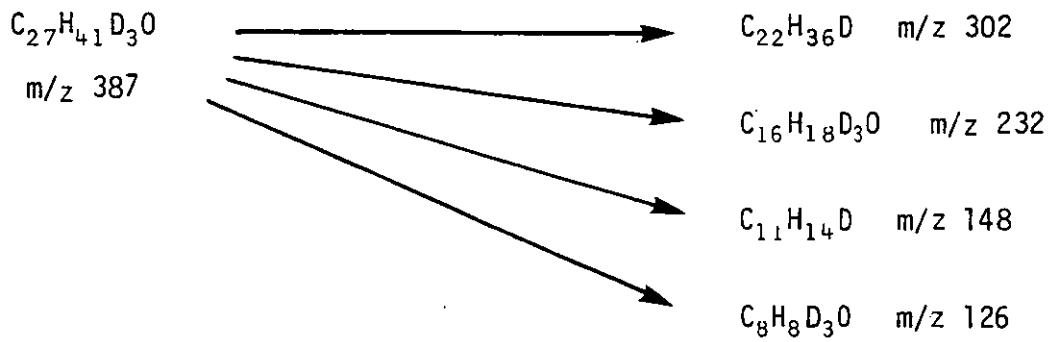


Further evidence in support of the structure (82) was the observation that a maximum of 3-deuterium atoms (C-1 and C-5) were incoporated when treated with $NaOD/D_2O$ in refluxing dioxan giving (84).

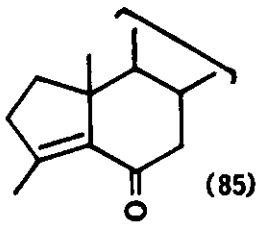


(84)

The mass spectrum showed a molecular ion at m/z 387 ($C_{27}H_{41}D_3O$) which fragmented as shown below:-

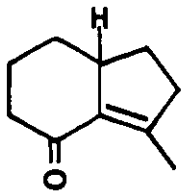


Although the expected A-nor-ketol (19) was not obtained on heating the 5β-acyloin (48) in decalin, under similar conditions, it was partially converted to the B-nor-enone (82). It was also found to be susceptible to acid catalysed rearrangement since on treatment with p-toluenesulphonic acid in benzene solution, it was converted to the B-nor-enone (82) in 49% yield and 3-methyl-A-nor-cholest-3-en-6-one (85) in 32% yield.



(85)

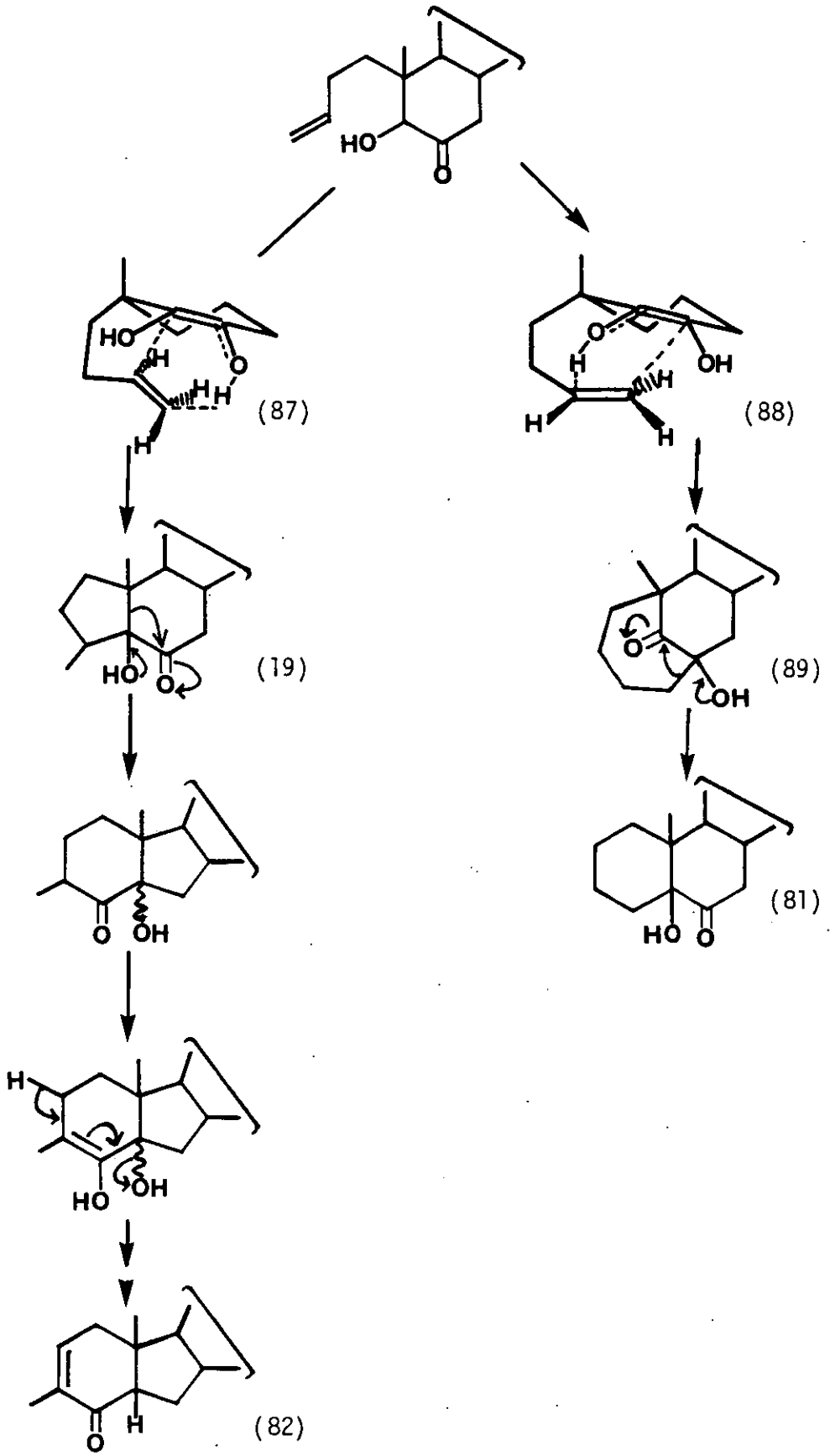
(86)



The A-nor-enone (85) infrared spectrum, ($\nu_{max.}$ 1680 (C=O), 1625 (C=C) cm^{-1}) and the ultra-violet spectrum ($\lambda_{max.}$ 260 nm) were in accord with the assigned structure. The observed $\lambda_{max.}$ and the calculated $\lambda_{max.}$ (242 nm, Woodward rule[59]) differ by 18 nm, but a similarly large $\lambda_{max.}$ (260 nm) is observed in the ultra-violet spectrum of hydrindenone (86)[60]. The ^1H n.m.r. spectrum had an important signal at δ 2.03 (brd s, RCMe=CR-C=O). The mass spectrum had a molecular ion at m/z 384, which fragmented with the loss of methyl to give m/z 369.

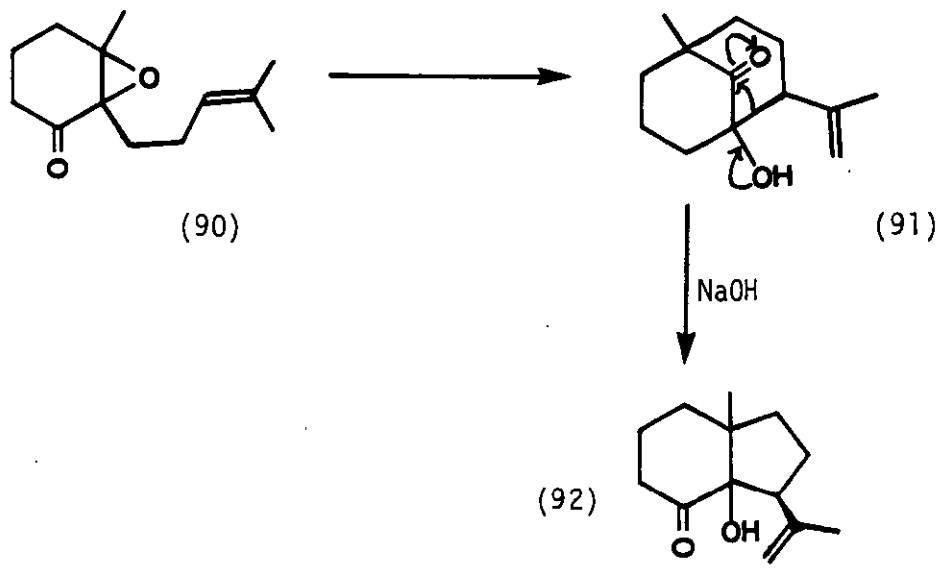
It is assumed at elevated temperature the 5β-acyloin (48) was converted to the dienediol (48b) which reacted in the conformations (87) and (88) to give, respectively, the A-nor-ketol (19) and 6β-hydroxy-4(5-6α)-abeo-cholestan-5-one (89) as the primary products (Scheme 44). Under the reaction conditions, these primary products are further modified to give the B-nor-enone (82) and 5β-cholestan-5-ol-6-one (81). It is possible for the 5β-ketol (81) to arise directly from the dienediol but models suggest that the transition state would be too strained.

Scheme 44



Modification of the primary products involves acyloin (α-ketol) rearrangements. Several examples of similar arrangements have been observed.[58,61] It was reported that the epoxide undergoes a cyclisation to give the bridged ketone (91) which is converted by acyloin rearrangement to the hydrindanolone (92) (Scheme 45).

Scheme 45



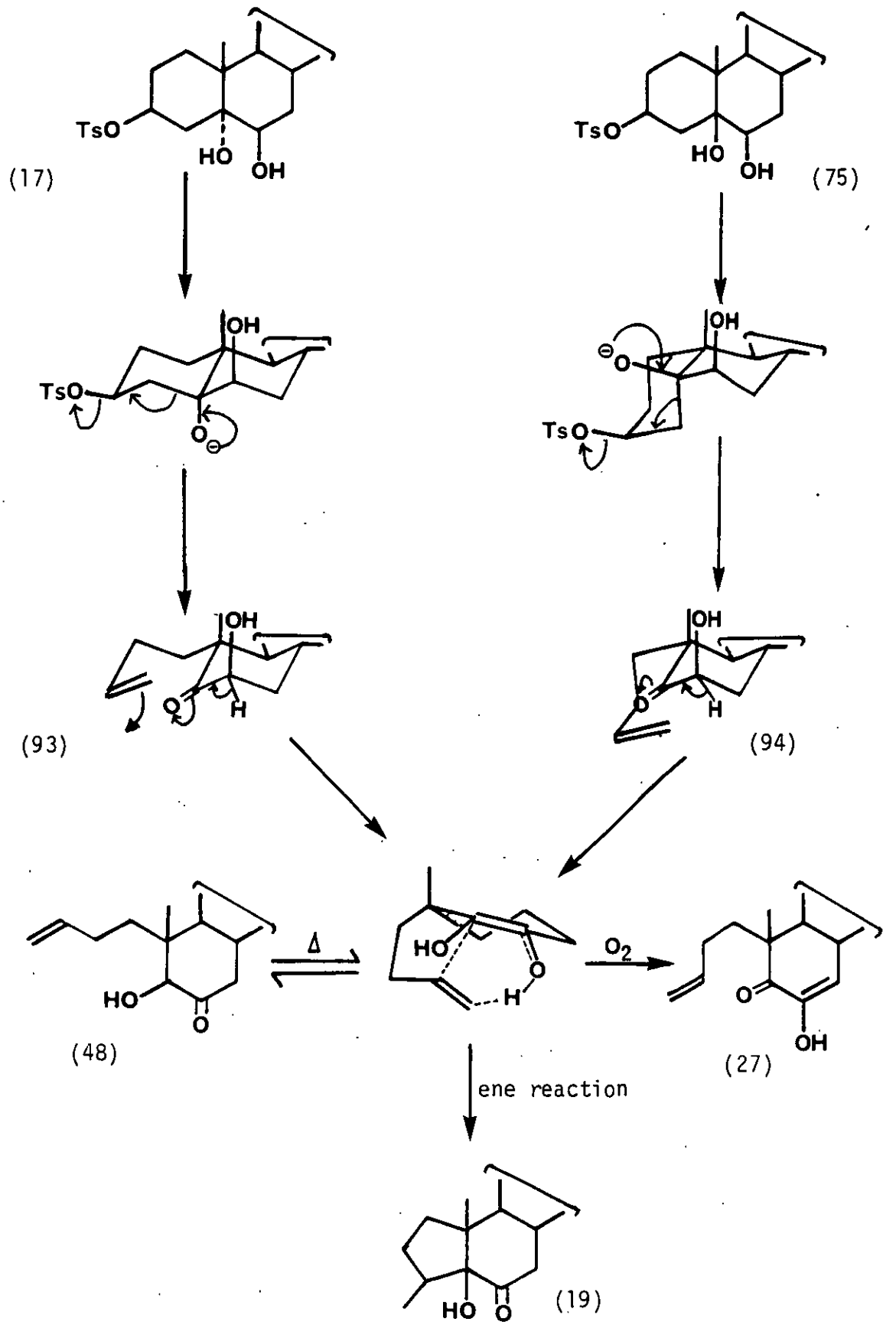
The observed reaction of the 5β-acyloin (48) occurs at relatively low temperature compared with unsaturated ketones.[22] It is unusual in that one of the products (89) is formed by carbon-carbon bond formation to the terminal alkene carbon.

The reactions studied suggest that the A-nor-ketol (19) does arise from an ene reaction of the 6β-acyloin (18). Failure of the isomeric 5β-acyloin to cyclise in a solution of potassium t-butoxide in t-butanol may be a function of attaining the appropriate conformation, an obstacle overcome by performing the reaction at elevated temperature in a sealed tube. Alternatively, fragmentation of the tosyloxy diols (17) or (75) produce the 6β-acyloin (18) in situ in a conformation (93) or (94) which requires minimum

bond rotation for this to be achieved. Enolisation to the diene-diol (48b) would have to be fast compared to the rate at which the chain unfolds. This enolisation would be assisted by the drive to remove the 6β-hydroxy/10β-methyl steric interaction. Introduction of a deuterium at the 6α-position presumably induces a kinetic isotope effect which slows the rate of enolisation to a rate at which chain unfolding is comparable or faster. Addition of air allows a rapid and efficient oxidation of the intermediate to the diosphenol (27) at a rate faster than the ene reaction (Scheme 46).

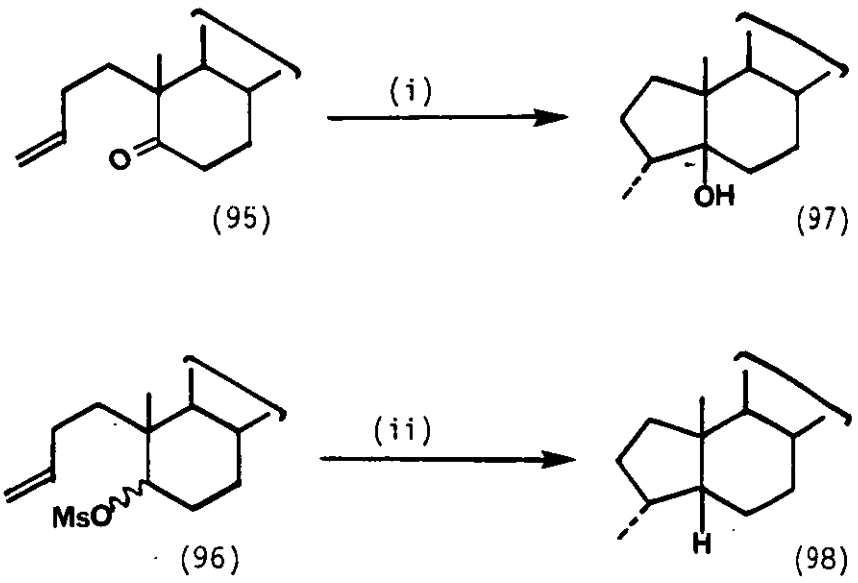
The role of the mesyloxy group in slowing the ene reaction is not understood. It may be that the mesyloxy diol (66) fragments through a different transition state that allows the chain to unfold before the acyloin can enolise.

Scheme 46


TsO
HO
OH
(17)
TsO
HO
OH
(75)
OH
TsO
O
OH
O
TsO
OH
O
H
(93)
OH
O
H
(94)
HO
O
(48)
Δ
HO
O
H
O2
O
OH
(27)
ene reaction
HO
O
(19)

Prahdan[62 63 64] has shown that the 4,5-secocholest-3-ene derivatives (95) and (96) undergo reductive radical cyclisation to give the A-nor-cholestane derivatives (97) and (98) respectively (Scheme 47).

Scheme 47



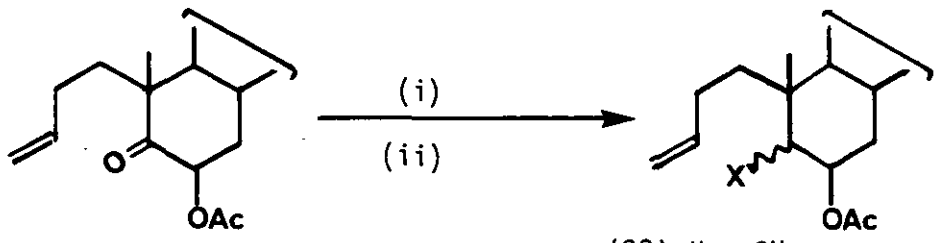
Reagents: i) Na/THF or $Li/NH_{3(l)}$ ii) Zn/NaI/D.M.E.

The 3-methyl stereochemistry was found to be α, whereas the ene reaction gives the A-nor-ketol (19) with β-stereochemistry. It was decided to investigate the affect of 6-substituents on similar cyclisations.

The diosphenol (27) failed to cyclise when treated with sodium in anhydrous T.H.F. and only starting material was isolated.

Reduction of the keto-acetate (41) with sodium borohydride in methanol gave the hydroxy-acetate (99). Treatment with mesyl chloride in pyridine gave the mesyloxy-acetate (100) (Scheme 48).

Scheme 48

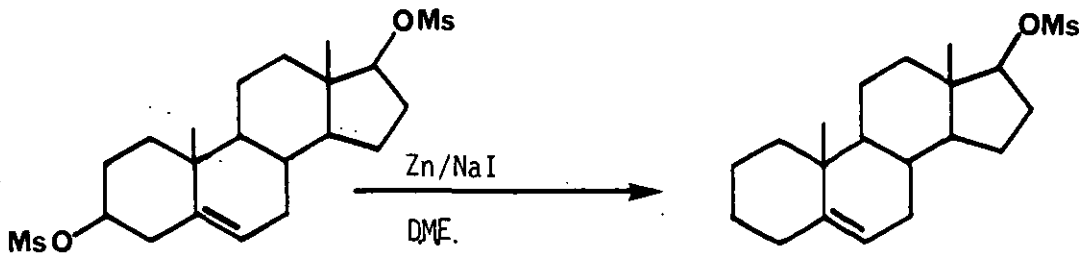


(99) X = OH
(100) X = OMs

Reagents: i) $NaBH_4$/MeOH; ii) CH_3SO_2Cl/Py

Attempted reductive cyclisation of (100) with zinc and sodium iodide in dimethoxyethane proved unsuccessful. It is assumed that 6-acetate has significantly increased the steric hinderance on the 5-position making reaction slow. It has been shown[57] that this reaction is subject to steric hinderance. An example (Scheme 49) is the selective removal of the 3-mesyloxy group from compound (101), the 17-mesyloxy being more sterically hindered and unreactive.

Scheme 49

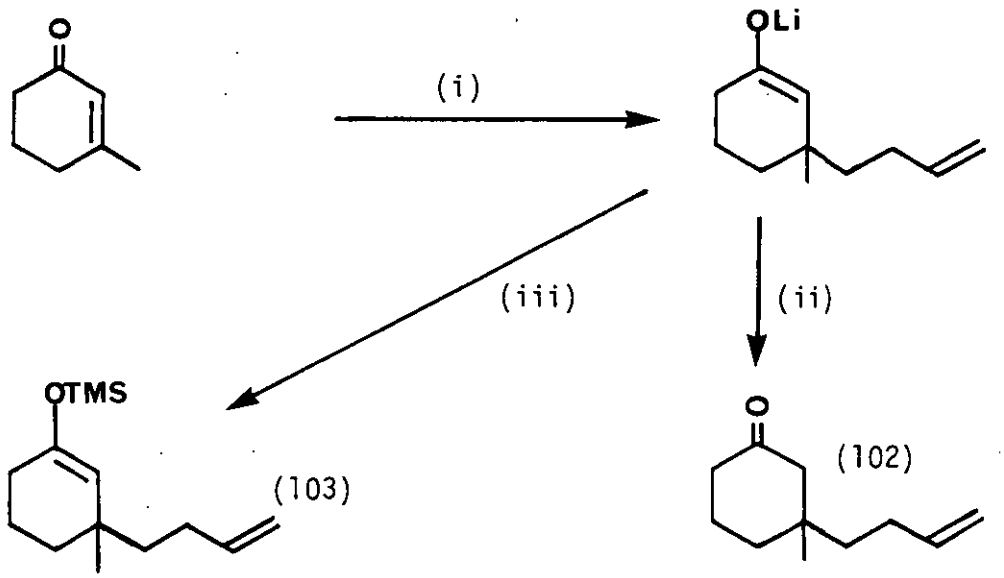


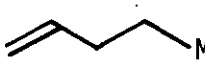
101

Part II Preparation and Reactions of 3-methyl-3-(3-butenyl)-2-hydroxy-cyclohexan-1-one

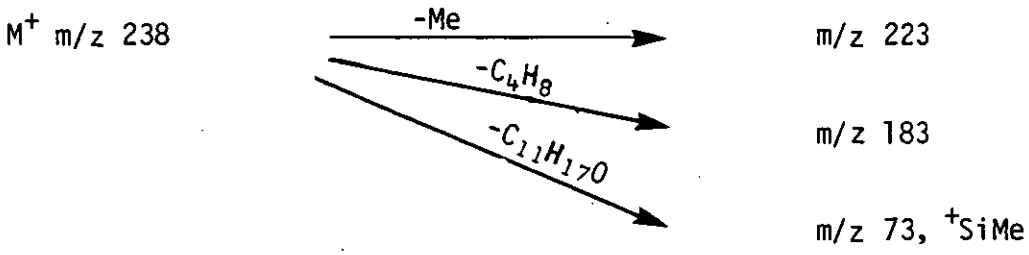
The mixed cuprate derived from methyl lithium, 3-butenyl magnesium bromide and copper (I) iodide was reported[65] to selectively transfer the butenyl moiety in a 1,4 addition reaction with a variety of enones. When 3-methyl-2-cyclohexen-1-one was added to a solution of the mixed cuprate, a smooth reaction occurred giving, on aqueous work up, the ketone (102)[65], or on quenching with trimethylsilylchloride in triethylamine, the trimethylsilylenol ether (103) (Scheme 50).

Scheme 50



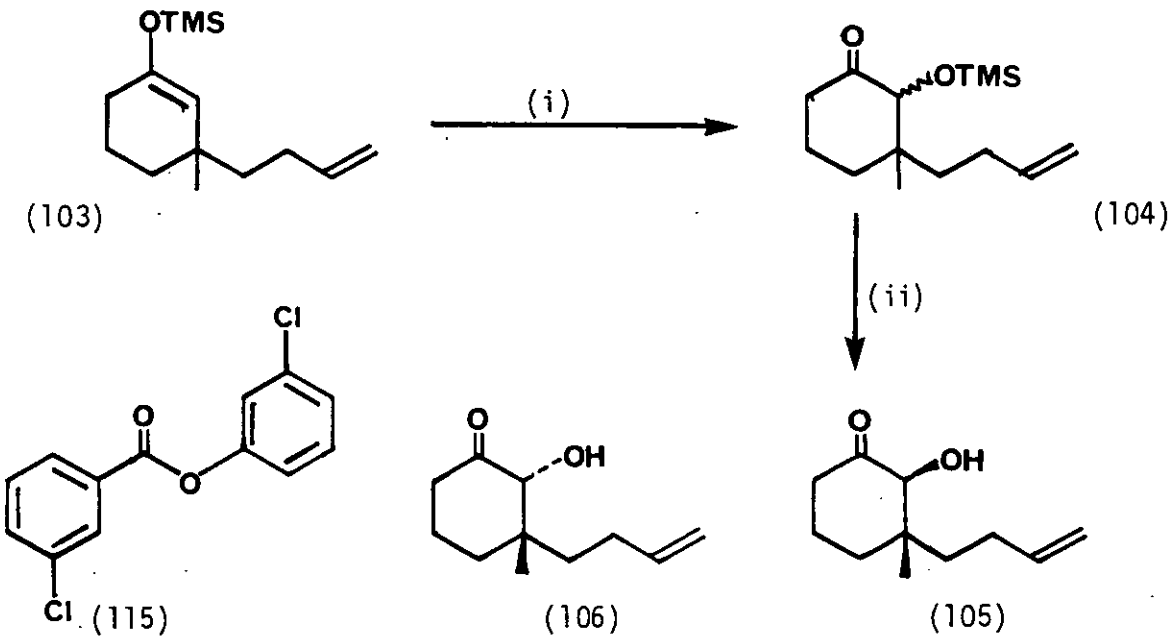
Reagents: i) MeLi/  MgBr/CuI/Et_2O/THF/-40°C; ii) NH_4Cl/H_2O; iii) Me_3SiCl/Et_3N

The infrared ($\nu_{max.}$ 3080, 1640,(RCH=CH_2) and 1660,(C=C-OSiMe_3)cm^{-1} and ^1H n.m.r. (δ 5.4 -5.9, m, RC<u>H</u>=CH_2, 4.65 - 5.0, m, RCH=C<u>H</u>$_2$, 4.50, s, <u>H</u>C=CR-O-SiMe_3) spectra confirmed the presence of a terminal olefin and a silyl enol ether. Fragmentations of the molecular ion m/z 238 are given below.



The silylenol ether (103) was oxidised with m-chloroperbenzoic acid in ether. The m-chlorobenzoic acid derivatives (see below) were removed and the resulting α-silyloxy-ketone (104) was hydrolysed to give a mixture of the isomeric acyloins (105) and (106) (Scheme 51).

Scheme 51

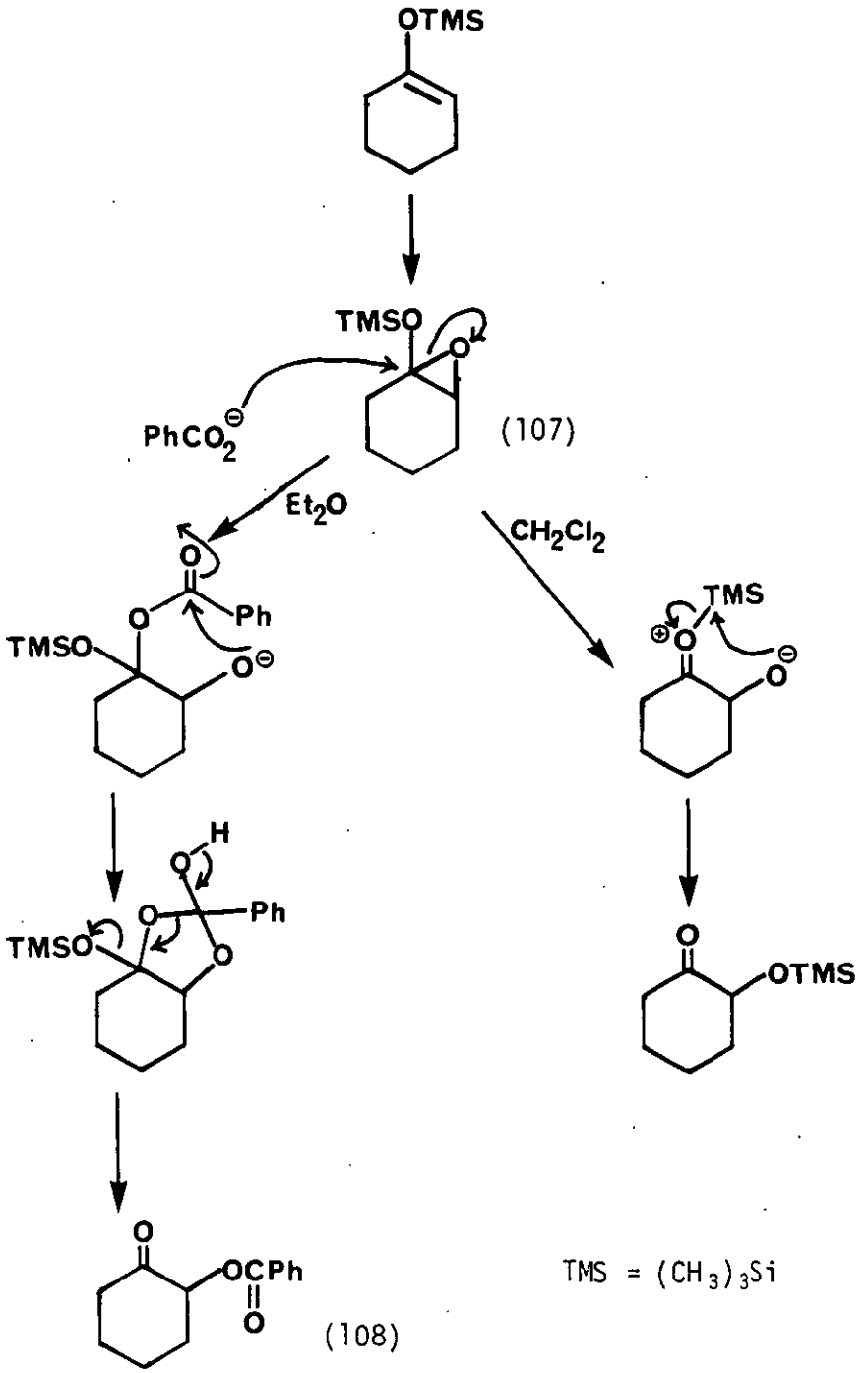


Reagents: i) mCPBA/Et_2O/$NaHCO_3$; ii) EtOH/H_2O/HCl

Isolation of the acyloins was complicated by the formation of m-chlorobenzoic acid derivatives. The major derivative being an ester (115) derived from two acid molecules. m-Chlorobenzoate esters of the acyloins (105) and (106) were also formed. Boeckman and Ramiah reported[66] the occurrence of ester formation when using ether as solvent. Oxidations performed in dichloromethane or hexane gave mainly α-silyloxy ketones. It is thought that the nucleophilicity of the acid is enhanced due to the higher bascity of ether.

This increases the rate of attack on the intermediate epoxyether (107) leading to the ester (108). In non-polar media, internal transfer of silicon is more rapid (Scheme 52).

Scheme 52

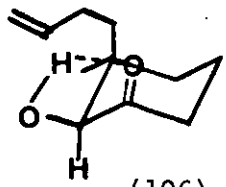


The acyloin isomers were separated by flash chromatography to give, as the least polar isomer, trans-3-methyl-r-3-(3-butenyl)-2-hydroxy-cyclohexan-1-one (105) and, as the most polar product, cis-3-methyl-r-3-

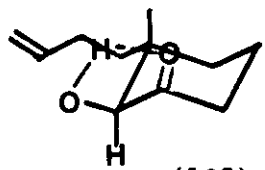
(3-butenyl)-2-hydroxycyclohexan-1-one (106).

The acyloins had $\nu_{max.}$ 3485 (OH) 1710 (C=O) for (105) and 3485 (OH), 1708 (C=O) cm^{-1} for (106) in the infrared spectra. The ^1H n.m.r. spectra had important peaks at δ 4.0 (s, C2-H), 3.6 (brd s, OH), 0.74 (s, Me) for (105) and 3.95 (s, C2-H), 3.78 (brd s, OH), 1.14 (s, Me) for (106) which confirmed the assigned regio- and stereo-chemistry.

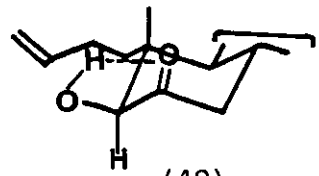
The methyl signal (δ0.74) in the ^1H n.m.r. spectrum of (105) compares with the C10β methyl signal (δ0.69) for the steroid 5β-acyloin (48).



(106)

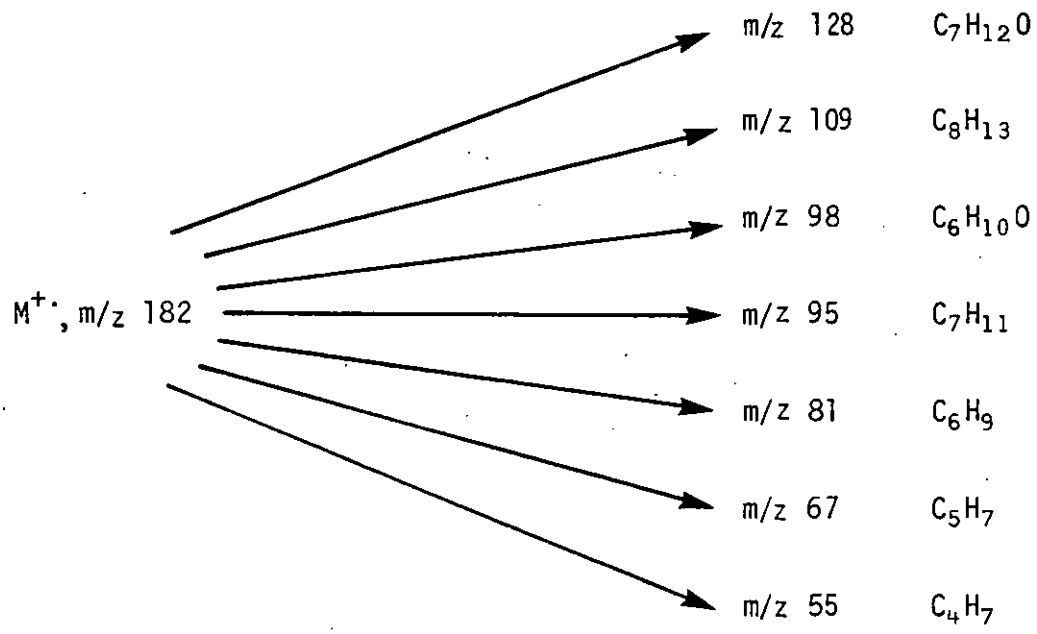


(105)



(48)

The mass spectra showed similar fragmentations of the molecular ions at m/z 182 and these are shown below:-

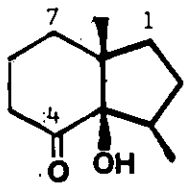


The acyloins (105) and (106) failed to cyclise in a deoxygenated solution of potassium t-butoxide in t-butanol. However, when heated under reflux in decalin solution, in an argon atmosphere for 24 hours, cyclisation occurred

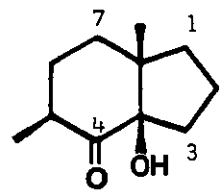
and three products were isolated by flash chromatography.

The least polar product was identified as 3β, 7aβ-dimethyl-3aβ-hydroxy-octahydro-4H-inden-4-one (109). Its structure elucidation was supported by the infrared spectrum which had $\nu_{max.}$ 3495 (OH) and 1700 (C=O) cm^{-1} and the 'H n.m.r. spectrum which had important signals at δ 3.7 (s, OH), 0.99 (s, C7a-Me) and 0.81 (d, C3-Me). The ^{13}C n.m.r. spectrum had important signals at δ 215.0 (C=O), 89.3 (C3a), 54.2 (C7a), 42.6 (C3), 19.3 (C7a-Me) and 13.0 (C3-Me). The full ^{13}C data are given in Appendix I.

The mass spectrum had a molecular ion m/z 182, for which major fragmentations led to ions at m/z 112 ($C_7H_{12}O$), m/z 111 ($C_7H_{11}O$) and m/z 98 ($C_6H_{10}O$).



(109)



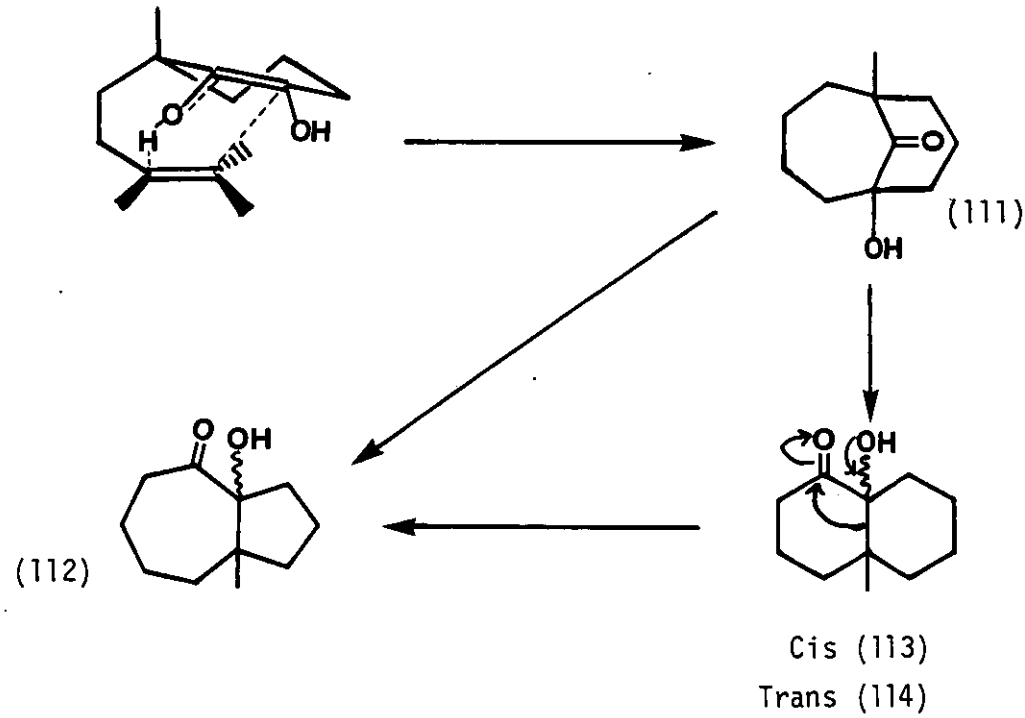
(110)

The major product was identified as 5β,7aβ-dimethyl-3aβ-hydroxy-octahydro-4H-inden-4-one (110). The proposed structure was supported by the infrared spectrum which had $\nu_{max.}$ 3495 (OH) and 1695 (C=O) cm^{-1}. The 'H n.m.r. spectrum had important signals at δ 4.02 (s, OH), 1.05 (d, C5-Me) and 0.92 (s, C7a-Me) and the ^{13}C n.m.r. spectrum had peaks at δ 214.3 (C=O), 88.2 (C3a), 54.9 (C7a), 39.7 (C5), 18.2 (C7a-Me) and 14.5 (C5-Me). The mass spectrum had molecular ion at m/z 182 which fragmented as above, (109).

An unidentified minor product, possibly (111) or (112) had $\nu_{max.}$ 3495 (OH) and 1712 (C=O) cm^{-1} in its infrared spectrum. The 'H n.m.r. spectrum had important signals at δ 3.88 (s, OH) and 1.07 (s, Me). The mass spectrum had a molecular ion at m/z 182. It is assumed that this minor product results from endo ring closure by analogy with the steroid 5β-acyloin (48). It may therefore be either the bridge ketol (111) or the seven-membered ketol (112) from its rearrangement (Scheme 53). The decalones (113) and (114) are also rearrangement products of (111) but their spectroscopic data[67] do not fit

the minor product.

Scheme 53



The 'H n.m.r. spectra of the hydrindanolones (109) and (110) showed angular (7a) methyl at chemical shifts which compare well with literature values for similar systems[61,68].

The cis hydroxyl, 7a-methyl geometry is assumed on the basis of thermodynamic stability through intramolecular hydrogen bonding. This is supported by the sharpness and dilution independance of the OH 'H signals in the 'H n.m.r. spectra.

Further evidence for the proposed structures (109) and (110) was gained from aromatic solvent-induced shifts (ASIS) and lathanide-induced shifts (LIS). The 'H n.m.r. spectrum of (109) in benzene solution had signals at δ0.93 (C7a-Me) and δ 0.77 (C3-Me). These signals are respectively upfield of those in

$CDCl_3$ by 0.06 and 0.04 ppm. Similar upfield shift of the signals for the C5-Me (δ 0.96) and the C7a-Me (δ0.87) of 0.09 and 0.05 ppm respectively were observed in the ^1H n.m.r. spectrum of (110) in benzene. The larger shift of the C5-methyl in (110) may be attributed to a π - π interaction between the carbonyl and the solvating benzene molecule decreasing the deshielding effect of the carbonyl and illustrating the close proximity of this methyl group to the carbonyl. 2-Methyl cyclohexanone in benzene solution exhibits a similar upfield shift of 0.09 ppm. for the signal for the methyl group in its ^1H n.m.r. spectrum.

The 90 MHz ^1H n.m.r. spectra of (109) and (110) were obtained in the presence of increasing concentrations of the lanthanide shift reagent, europium (III) tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate) (Eu(fod $_3$)). The results are tabulated below and represented in graphical form (least squares line fit).

(109) So = 0.000907 moles

L/S	7a-Me		3-Me	
	δ/ppm	Δδ	δ/ppm	Δδ
0.000	0.99	0.00	0.81	0.00
0.0149	1.04	0.05	0.88	0.07
0.0287	1.10	0.11	0.99	0.18
0.0425	1.17	0.18	0.19	0.28
0.0563	1.21	0.22	0.15	0.34
0.0669	1.26	0.27	0.24	0.43
0.0754	1.31	0.32	1.30	0.49
1.00		4.20		6.55

(110) So = 0.000879 moles

L/So	7a-Me		5-Me	
	δ/ppm	Δδ	δ/ppm	Δδ
0.000	0.92	0.00	1.05	0.00
0.0132	1.02	0.10	1.10	0.05
0.0307	1.15	0.23	1.13	0.08
0.0417	1.23	0.31	1.19	0.14
0.0548	1.34	0.42	1.23	0.18
0.0680	1.45	0.53	1.27	0.22
0.08660	1.66	0.74	1.35	0.30
1.00		8.33		3.23

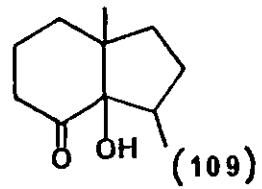
Assuming linearity and a 1:1 complex, the slope of the graph gives the shift for the Lo/So = 1[69],

then $\Delta\delta_i \propto R_i^3$

$\Delta\delta_i$ = change in chemical shift for proton i

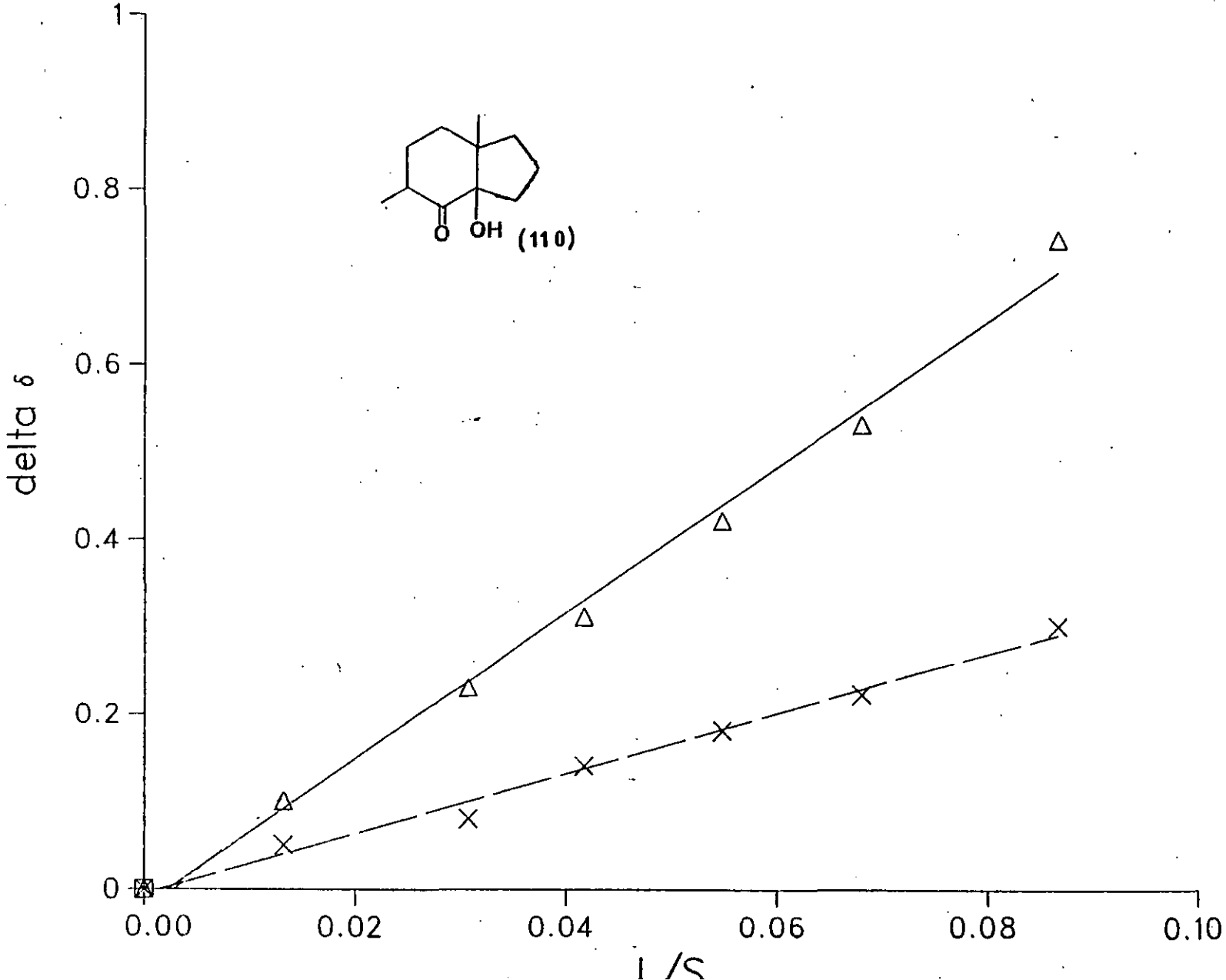
R_i = distance of proton i from centre of lathanide atom.

Lanthanide shift experiment, isomer 1

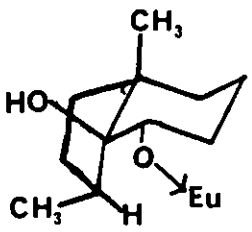


(109)

Lanthanide shift experiment, isomer 2

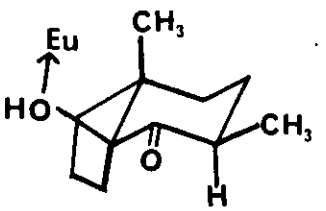


In this case $Eu(fod)_3$ is not the ideal reagent since it is able to bond to both the carbonyl and hydroxyl oxygens, depending on steric accessibility. The result for hydrindanolone (109) is best explained with the lanthanide co-ordinated to the carbonyl oxygen.



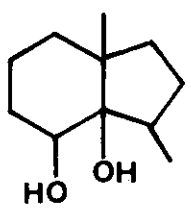
(109)

The greater slope for the C3-methyl compared to the angular methyl reflects its proximity to the lanthanide atom. However, the result for hydrindanolone (110) is best explained with the lanthanide co-ordinated to the hydroxyl oxygen. The angular methyl is then closer to the lanthanide atom and therefore gives the greater slope. The change in co-ordination site may be due to the steric hindrance caused by the C3-methyl and the C5-methyl respectively.

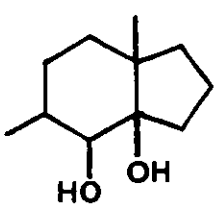


(110)

Reduction of (109) and (110) with sodium borohydride in methanol gave the diols (119) and (120).

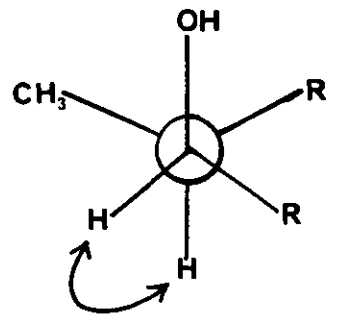


(119)



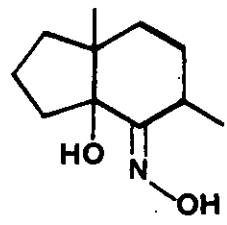
(120)

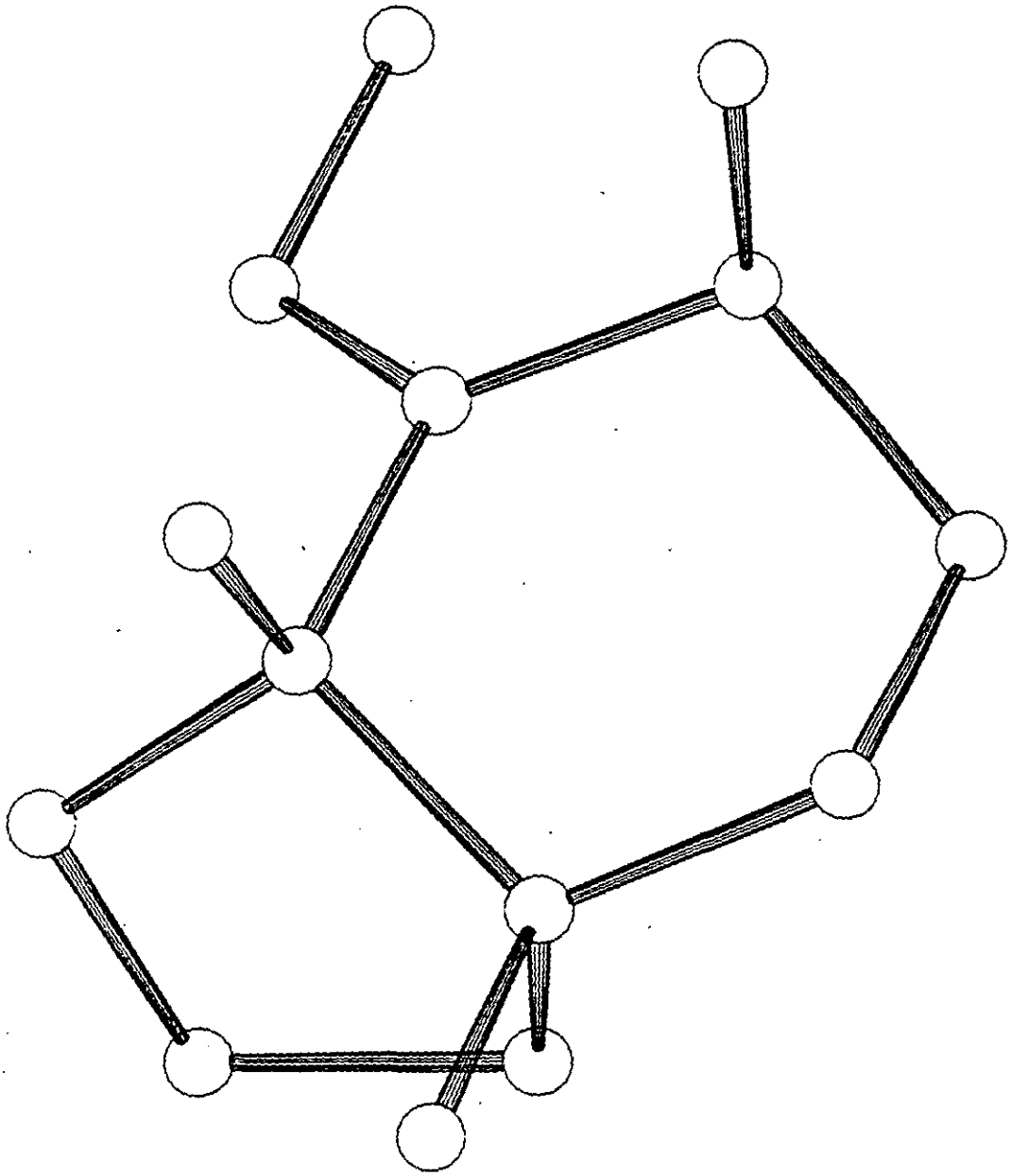
The assigned structure (119) was supported by the 'H n.m.r. spectrum which had an important signal at δ 3.74 (m, C4α-H, $W_{\frac{1}{2}}$ 10Hz). The diol (120) had a similarly important signal in its 'H n.m.r. spectrum at δ 3.58 (brd s, C4α-H, $W_{\frac{1}{2}}$ 4Hz). The spin-spin coupling of the C4α-H to only the C5α-H reflected in the small $W_{\frac{1}{2}}$



(120)

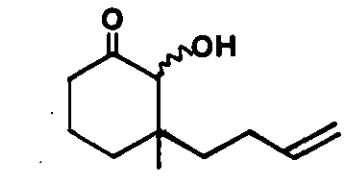
Final proof of the structure (110) was achieved through X-ray chrystallography on the crystalline oxime derivative. Direct methods were employed using SHELLEX and the present convential R is 0.0553 from the 2408 observed reflections (diffractometer data). Full data will be published elsewhere.



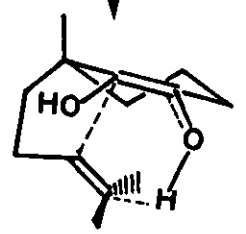


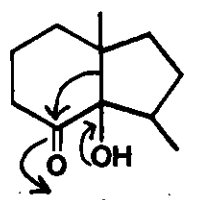
It is assumed that the acyloins (105) and (106) undergo the ene reaction as the enediol to give initially hydrindanolone (109) and compound (111) (Scheme 54). Hydrindanolone (109) undergoes a thermal acyloin rearrangement to give the isomeric hydrindanolone (110).

Scheme 54

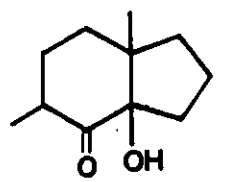


(105) (106)



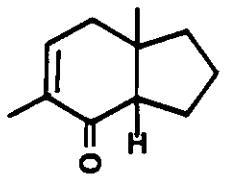


(109)



(110)

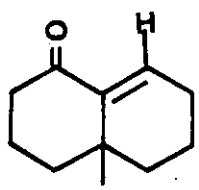
One experiment performed by heating the acyloins at double the concentration in decalin resulted in dehydration of the primary products. Separation of the mixture by flash column chromatography and preparative thin layer chromatography gave, as the major product, 5,7a-dimethyl-1,2,3,3a,7,7a-hexahydro-4H-iden-4-one (121) (20%) and an unidentified minor product (122) (5%).



(121)

The structural assignment for (121) was supported by its infrared (1665, (C=O,**enone**)cm^{-1} and its ^1H n.m.r. (δ 6.47, m, RC<u>H</u>=CMe-C=O and 1.78, brd s, RCH=C<u>Me</u>-C=O) spectra which compared well with steroid B-nor-enone (82).

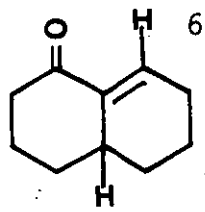
The minor product which may arise from dehydration of (111) or (112) had ν_{max} 1685 (C=O, enone), 1620 (C=C)cm^{-1} in its infrared spectrum and its ^1H n.m.r. spectrum had important signals at δ6.35 (t, RC<u>H</u>=CR-CO, J 3Hz) and 1.04 (s, Me). The chemical shifts of some related exocyclic enones are given below.[70]



6.43, t J 2.5Hz

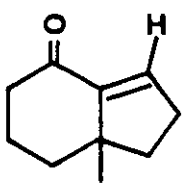
(123)

δ 1.04, s



6.65, m

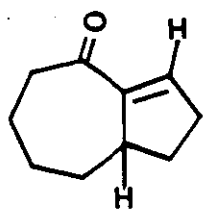
(124)



6.45, t, J 4Hz

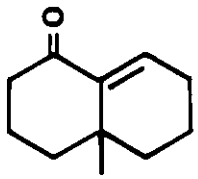
(125)

δ 1.10, s

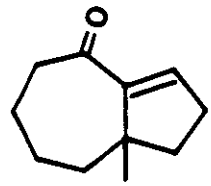


6.77, brd d, J 2Hz

Dehydration of (111) or (112) would be expected to give (123) or (126). The spectroscopic of the minor product (122) does not fit the reported date for (123).



(123)

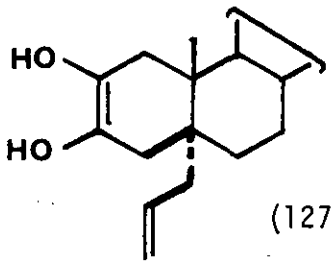


(126)

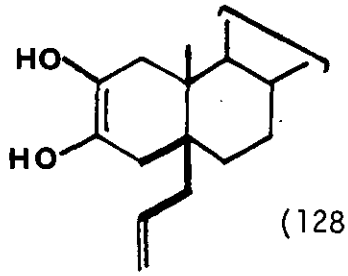
Part III Preparation and Reactions of 5-(2-propenyl)-5α and 5β-cholestane 2,3-acyloins

In Part I it was suggested that the ease of obtaining the reacting conformation was a major controlling factor in the ene reaction. This trend is seen in going from an intermolecular to an intramolecular reaction where the temperature required for reaction of an ene enophile pair decreases considerably. This is due to the less negative ΔS. We considered that restricting the motion of the alkene chain by constructing it nearer to the site of reaction would increase ΔS still further and therefore lower the reaction temperature.

In the 5-(2-propenyl)-cholestanes (127) and (128) the alkene chain is partially incorporated into the A-ring and hangs above or below the steroid plane.



(127)

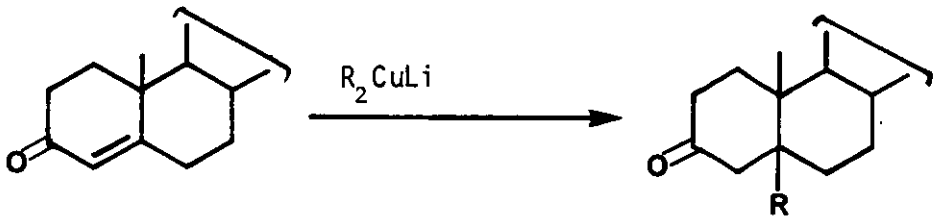


(128)

The most direct method of introducing the alkene chain is the conjugate addition of an allyl copper reagent to cholestenone (42). The additions of diethyl- and dimethyl- lithium cuprate to cholestenone, and vinyl lithium cuprate to 19-nor-cholestenone (129) have been reported[72,73] and give the 5β-stereochemistry (Scheme 55).

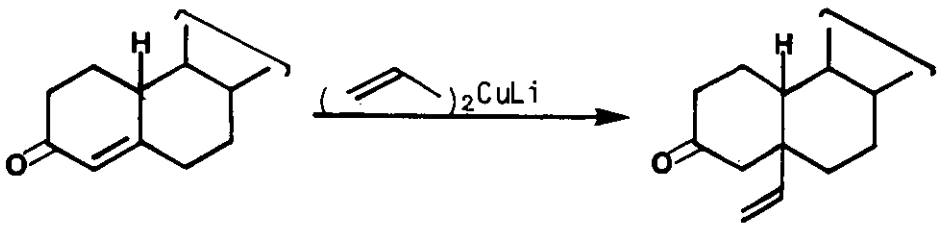
Scheme 55

(42)

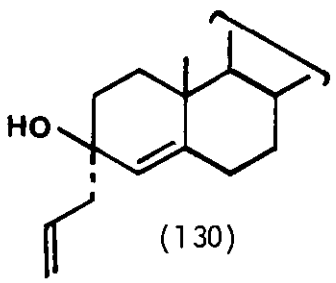


R = Me, Et

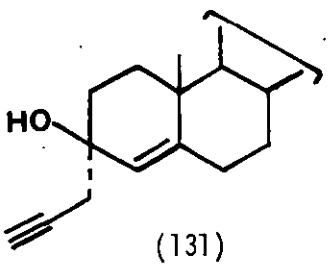
(129)



Attempted copper (I) iodide catalysed conjugate addition of allyl magnesium bromide and propargyl magnesium bromide failed, giving only the tertiary alcohols (130) and (131) respectively on mild work up.



(130)



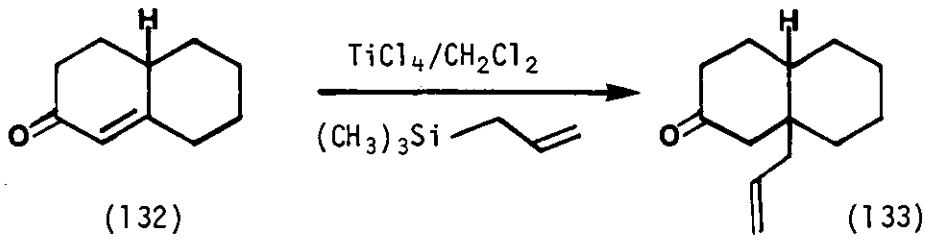
(131)

The assigned alcohol structure (130) was supported by its infrared ($\nu_{max.}$ 3300 (OH), 3075 and 1640 ($RCH{=}CH_2$)cm^{-1}) and ^1H n.m.r. (δ 5.27, s, C4-H) spectra. The alcohol (131) has similarly characteristic infrared ($\nu_{max.}$ 3310 (C≡C-H, OH) and 2125 (C≡C) cm^{-1}) and ^1H n.m.r. (δ 5.33, s, C4-H) spectra. The 3β-OH configuration was assigned by analogy with the reported[74] addition of methyl Grignard reagent to cholestenone which gave a 9:1 ratio of the β-alcohol over its epimer.

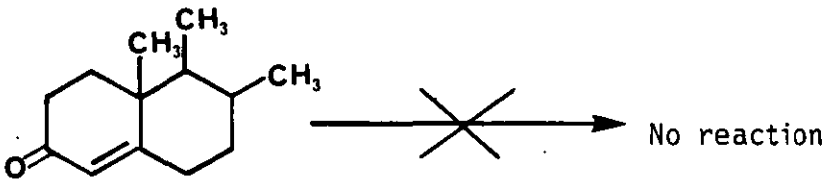
Allyl copper reagents have been shown[75] to prefer the 1,2-mode of addition with all but the least sterically hindered enones. In contrast Sakurai[76] has shown that trimethylallylsilane will selectively transfer

the allyl group in a 1,4 mode of addition, to hindered enones. Treatment of the decalenone (132) with trimethylallylsilane and titanium tetrachloride gave the allyldecalone (133) in good yield. However, decalenone (134) was reported[77] to be unreactive towards this system (Scheme 56).

Scheme 56



(132) (133)

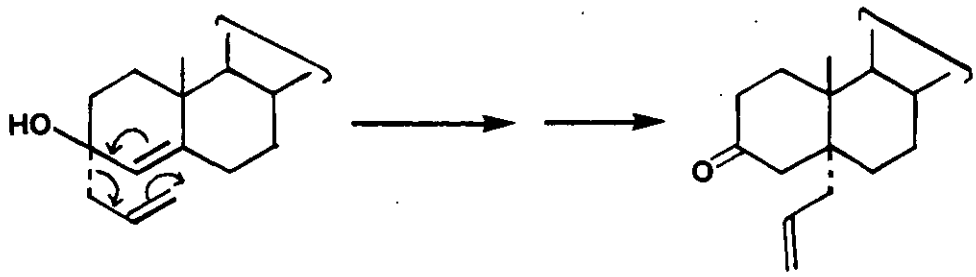


(134)

Cholestenone when treated with trimethylallylsilane/titanium tetrachloride in dichloromethane at room temperature for twenty four hours failed to react and only starting material was recovered.

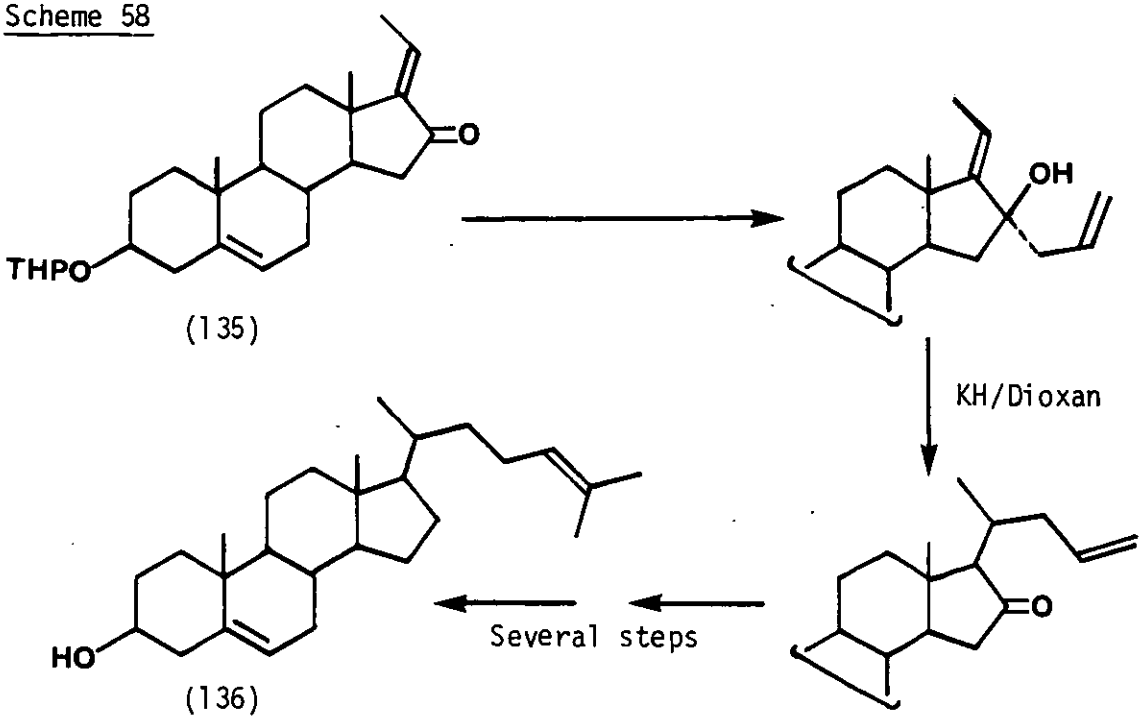
It was realised that the allyl-alcohol (130) had the correct substituent regiochemistry for an oxy-Cope reaction[78], i.e. a 3-hydroxy-1,5-diene (Scheme 57).

Scheme 57



This strategy has been used in the synthesis of desmosterol (136) from the pregn-17-en-16-one (135).[79]

Scheme 58



(135)

(136)

The allyl-alcohol (130) failed to undergo a Cope rearrangement with potassium hydride or sodium hydride in a variety of solvents, (Table I). The most forcing conditions gave cholestenone (42) arising from a β-hydroxy olefin cleavage (retro ene reaction), (Scheme 59).

Table I

Solvent	NaH	KH
Diethyl ether	-	No reaction
T.H.F.	No reaction	-
Dimethoxyethane	No reaction	Cholestenone
Dioxane	-	Cholestenone

Scheme 59

(130)

(42)

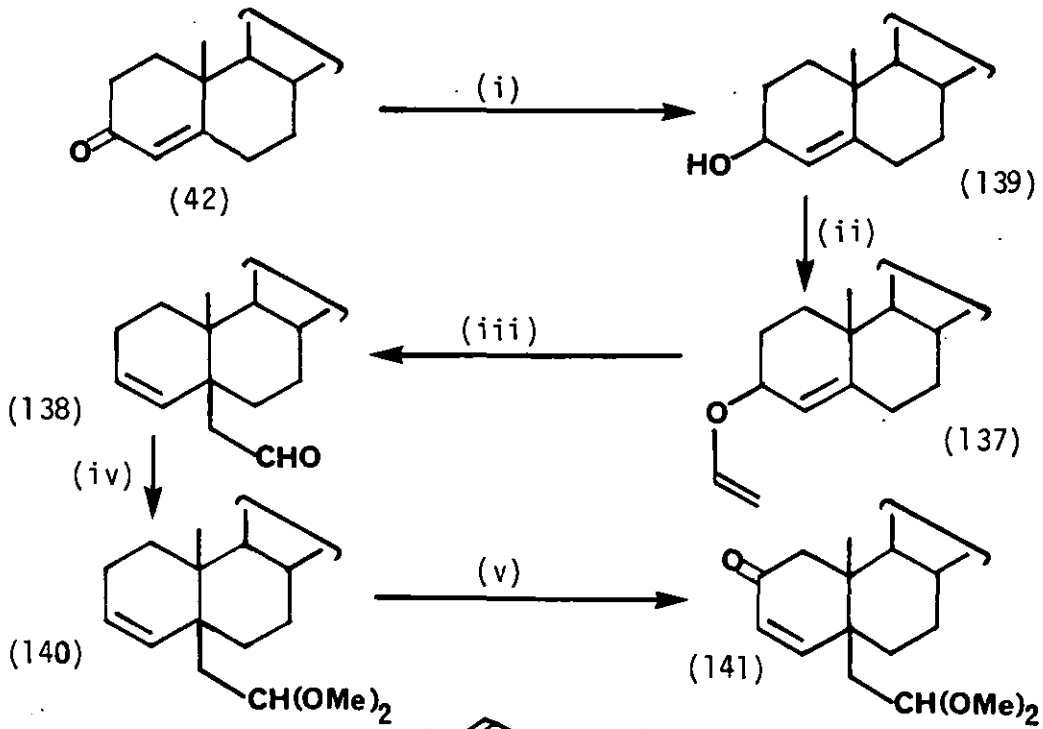
There are reports[80,81] of the synthetic utility of the oxy-Cope reaction being diminished by the competing retro-ene cleavage process. These generally involve cases where a quaternary centre is generated as a consequence of the Cope process.

The related Claisen rearrangement has been used for the angular functionalisation of terpene derivatives[82]. 3β-Vinyloxy-cholest-4-ene (137) was reported[82] to undergo a Claisen rearrangement (Scheme 60) at 200°C to give the 5β-acetaldehyde derivative (138) in good yield. It was envisaged that (138) could be modified to give the desired 5-(2-propenyl)-5β-cholestane-2,3-acyloin (128).

Scheme 60

Selective reduction of cholestenone (42) with sodium borohydride/cerium (III) chloride in methanol[83] gave the 3β-alcohol (139)[84]. Treatment of (139) with ethyl vinyl ether and mercury (II) acetate afforded the vinyl ether (137)[82] which underwent the Claisen rearrangement in refluxing decalin to give the aldehyde (138)[82]. The aldehyde was protected as the dimethoxy acetal (140) by treatment with trimethylorthoformate and p-toluenesulphonic acid in methanol. Allylic oxidation was achieved using chromium trioxide and dimethylpyrazole[85] in dichloromethane giving the enone (141) (Scheme 61).

Scheme 61



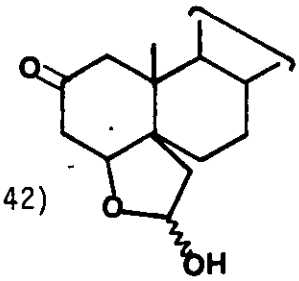
Reagents: $NaBH_4/CeCl_3/MeOH$; ii) ⟋OEt/$Hg(OAc)_2$; iii) Δ/decalin; iv) $(MeO)_3CH/MeOH/H^+$; v) CH_2Cl_2/CrO_3/Dimethylpyrazole.

The enone (141) had characteristic infrared ($\nu_{max.}$ 1680 (C=O)cm^{-1}) and 'H n.m.r. (δ 6.73 and 6.05, ABq, RC<u>H</u>=C<u>H</u>-C=O) spectra which confirmed the presence of an unsubstituted α,β-unsaturated ketone.

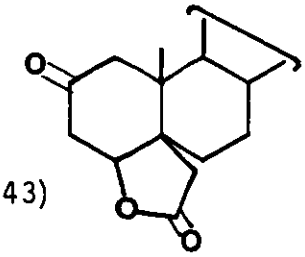
Hydrolysis of the dimethoxy acetal (140) with aqueous perchloric acid gave a quantitative return of the aldehyde (138). However, when the enone (141) was treated in the same way only the lactol (142) could be isolated. Assignment of the lactol structure was supported by its infrared ($\nu_{max.}$ 3400 (OH) and 1710 (C=O) cm^{-1}) and its 'H n.m.r. (δ 5.77, q, RC<u>H</u>(OH)OR and 4.52, t, C4α-H) spectra. The mass spectrum had a molecular ion at m/z 444 which fragmented with the loss of H_2O to give a peak at m/z 426.

Further evidence for the structure was obtained by oxidation of the lactol (142) with pyridinium chlorochromate in dichloromethane to give the lactone (143). The lactone had a characteristic δ-lactone carbonyl stretching frequency (1780 cm^{-1}) in its infrared spectrum and the C4α-H signal in the 'H n.m.r. spectrum (δ 5.0) was downfield by 0.48 ppm from that in (142).

(142)

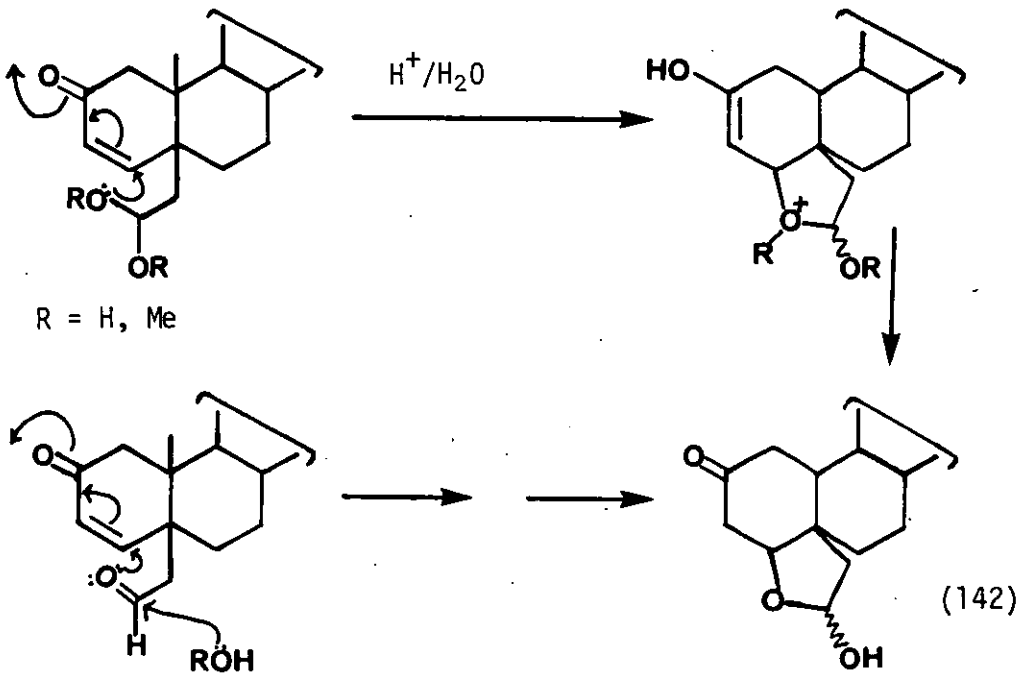


(143)



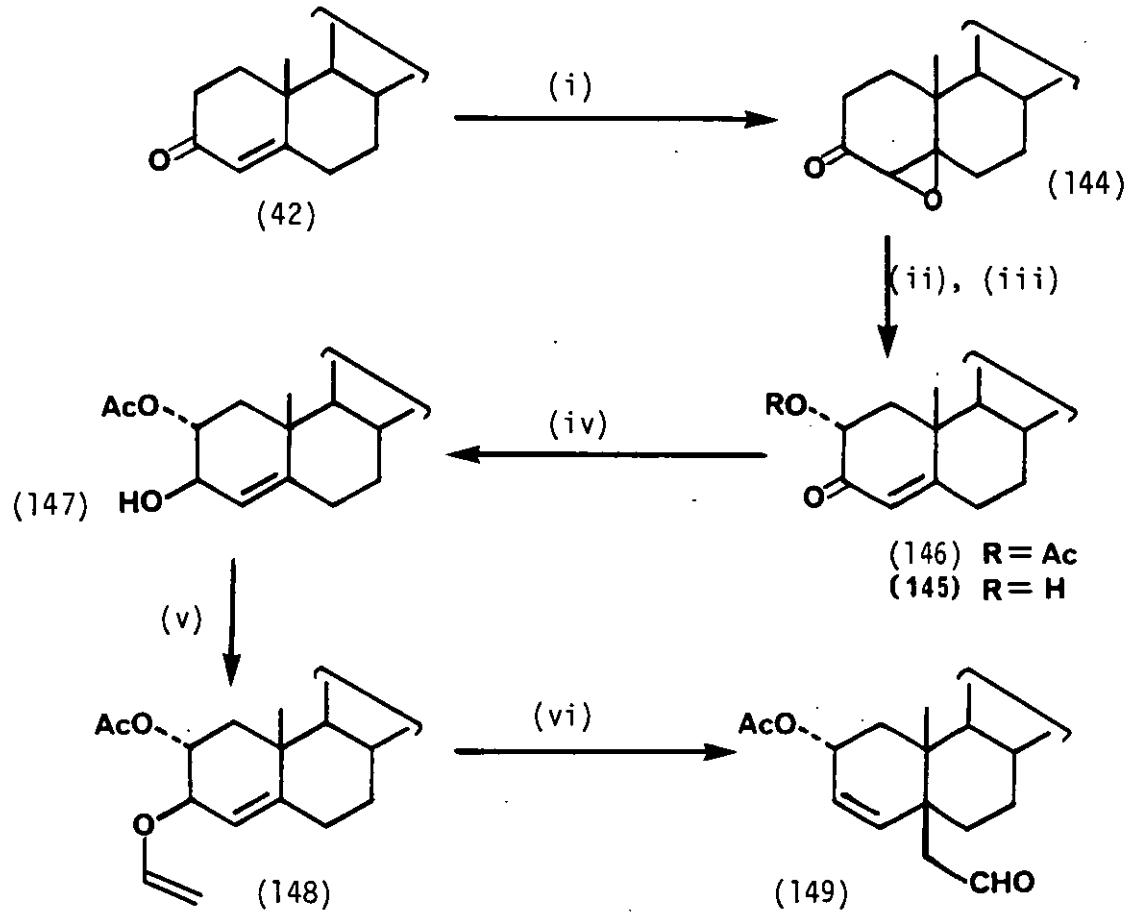
It is thought that the lactol (142) arises from an acid-catalysed intramolecular Michael addition of either the acetal or the aldehyde to the enone (Scheme 62).

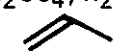
Scheme 62



An alternative synthetic strategy to (128) has been investigated in which the 2-oxygen function is introduced before the 5β-allyl group (Scheme 63).

Scheme 63

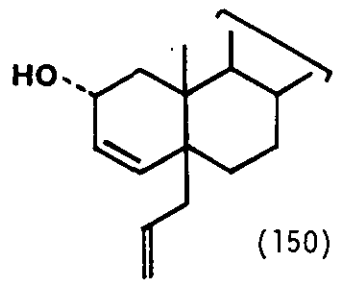


Reagents: i) H_2O_2/NaOH/MeOH, ii) $H_2SO_4/H_2O/CH_3COCH_3$; iii) Ac_2O/Py; iv) $NaBH_4/CeCl_3$/MeOH; v)  OEt/$Hg(OAc)_2$; vi) Δ/decalin

Cholestenone (42) was epoxidised with alkaline hydrogen peroxide in methanol to give the β-epoxide (144)[86]. Acid-catalysed rearrangement gave the hydroxy-enone (145)[86] which was acetylated with acetic anhydride in pyridine to give the acetoxy-enone (146)[86]. Selective reduction with sodium borohydride/cerium (III) chloride in methanol[83] to the allylic alcohol (147)[87] and treatment with mercury (II) acetate in ethyl vinyl ether gave the acetoxy vinyl ether (148) in good yield. The Claisen rearrangement was achieved by heating (148) under reflux in a decalin solution for 6 hours giving the acetoxy aldehyde (149).

The infrared spectrum of (149) had ν_{max} 1720 (C=O)cm^{-1} and its 'H n.m.r. spectrum had important signals at δ 9.92 (t, RCHO, J 3Hz) 5.96 (s, C3-H and C4-H), 5.45 (brd d, C2β-H) and 2.08 (s, OAc) which confirmed the assigned structure. The mass spectrum did not show a molecular ion but had peaks for the loss of acetaldehyde (m/z 426) and the loss of acetic acid (m/z 410) from the molecular ion.

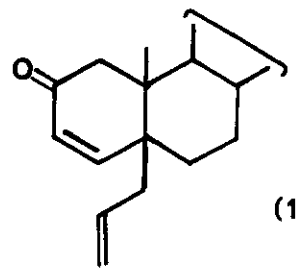
Treatment of the aldehyde (149) with $Ph_3P=CH_2$ in T.H.F. at room temperature and hydrolysis of the crude product in refluxing methanolic sodium hydroxide gave the allylic alcohol (150).



(150)

The alcohol (150) had infrared ($\nu_{max.}$ 3300 (OH), 1680, 1640, (RCH=CH_2) cm^{-1}) and 'H n.m.r. (δ 5.4-6.1, m and 5.06, m, olefinic protons, 4.20, brd s, C2β-H) spectra which confirmed the presence of the 5-propenyl group and the allylic alcohol. Its mass spectrum had a low intensity molecular ion at m/z 426 which fragmented with the loss of H_2O to give a peak at m/z 408. Further loss of C_3H_5 gave a peak at m/z 367.

The alcohol (150) when stirred with a suspension of manganese dioxide in dichloromethane[88] was oxidised to the enone (151) quantitatively.

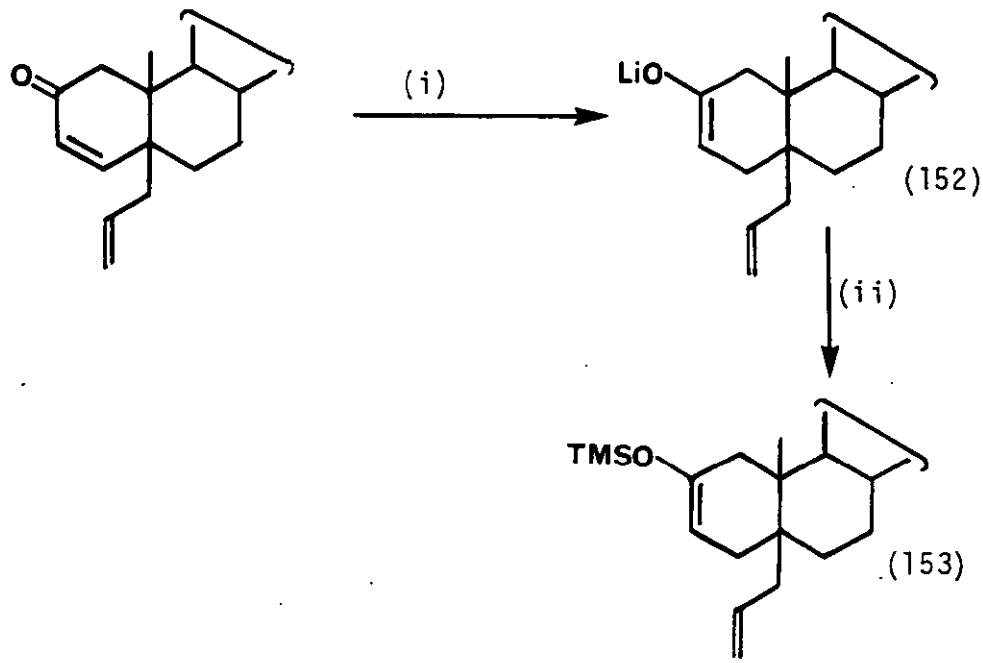


(151)

The presence of the enone was confirmed by its infrared ($\nu_{max.}$ 1680 (C=O) cm^{-1}) and ^1H n.m.r. (δ 6.65 and 6.14, ABq, RCH=CH-C=O) spectra which compared well with those of the enone (141).

The enone (151) was reduced with lithium in liquid ammonia to give the lithium enolate (152) which was treated with trimethylsilyl chloride in triethylamine[89] to give the silylenolether (153) (Scheme 64).

Scheme 64

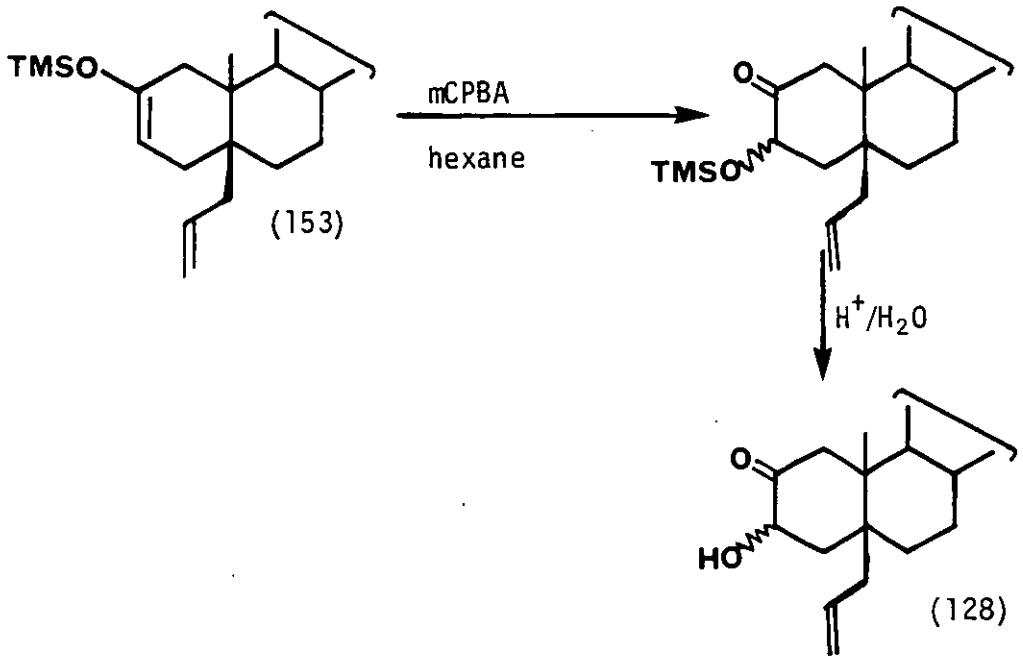


Reagents: i) $Li/NH_3/THF/t$-BuOH; ii) $(CH_3)_3SiCl/Et_3N$

The silylenolether (153) had $\nu_{max.}$ 1680 (C=C-OSiMe$_3$)cm^{-1} in its infrared spectrum and a signal at δ 4.65 (brd s, RCH=CR-OSiMe$_3$) in its ^1H n.m.r. spectrum. The enol ether regiochemistry was assigned on the basis of the mechanism. The mass spectrum had a molecular ion at m/z 498.

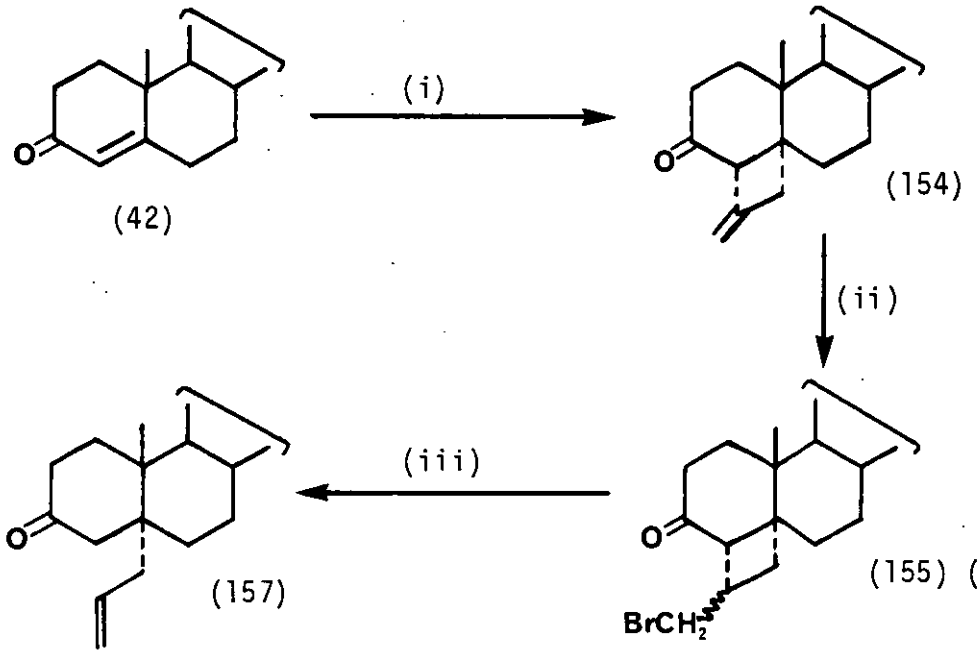
It was intended to oxidise the silylenolether (153) with m-chloroperbenzoic acid by the method of Rubottom et al[90] to give, after hydrolysis, the acyloin (128) (Scheme 65). Unfortunately, a lack of time prevented the completion of this synthesis.

Scheme 65 Proposed Synthesis



A recent publication by Funk et al[77] describes the indirect introduction of an angular propenyl group into a decalenone system in 3 steps. We applied this strategy to cholestenone (Scheme 66).

Scheme 66

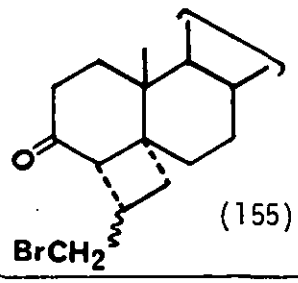


Reagents: i) hν/hexane/=·=; ii) HBr/hν/hexane; iii) Li/NH_3/T.H.F.

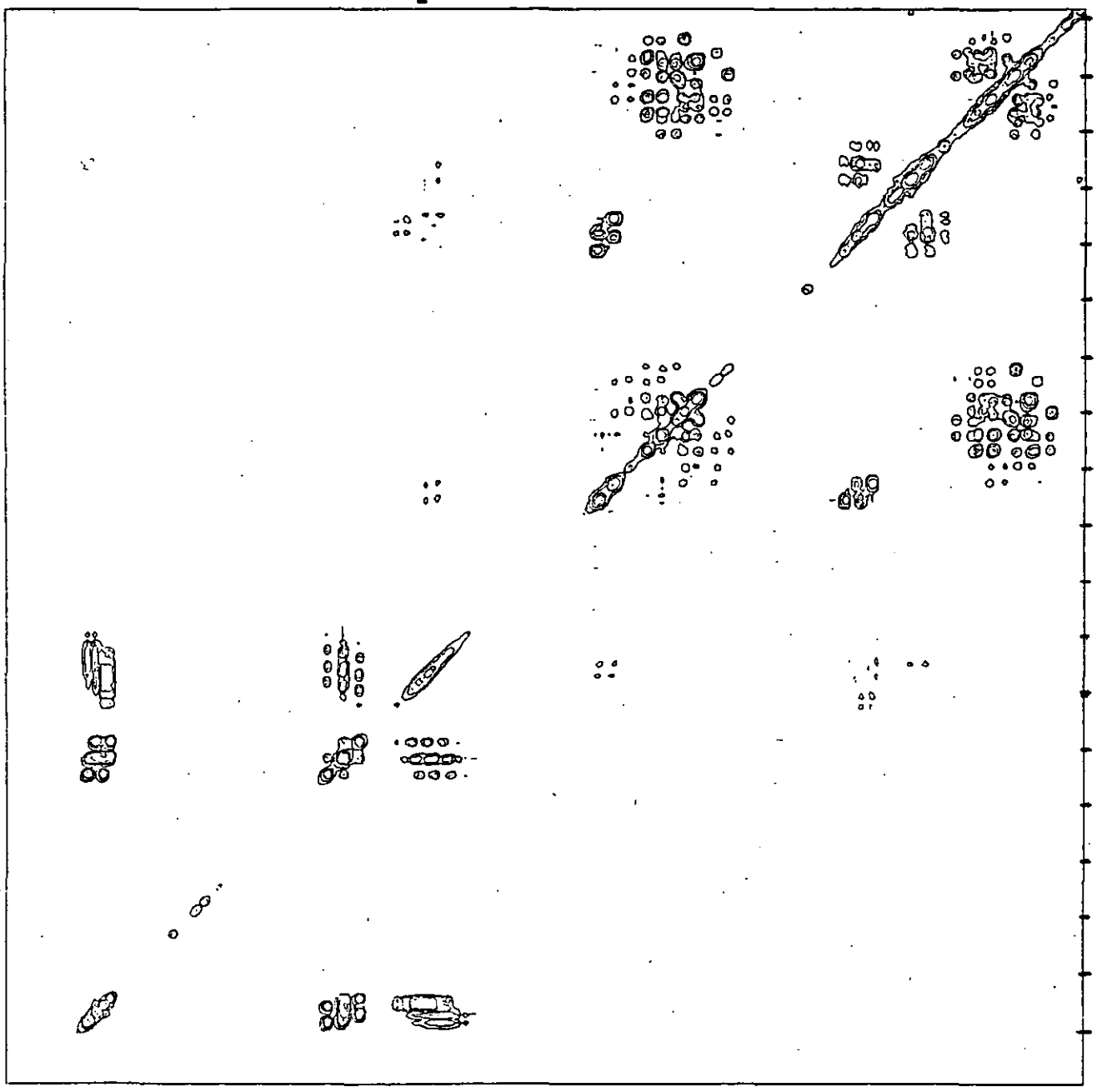
Cholestenone (42) was irradiated in the presence of allene in hexane solution at -60°C to afford the photo-adduct (154). A signal at δ 5.07 (m, $W_{\frac{1}{2}}$ 8Hz) in the ^{1}H n.m.r. spectrum confirmed the presence of an exo-methylene group. The 4α,5α-stereochemistry and methylene regiochemistry were assigned by comparison with similar known steroid photo-adducts[91] The photochemically initiated anti-Markovnikov addition of hydrogen bromide to the photo-adduct (154) gave a mixture of the isomeric bromides (155) and (156). The bromides were usually used as a mixture but could be separated by flash column chromatography.

The least polar isomer (155) had important signals in its 360 MHz ^{1}H n.m.r. spectrum at δ 3.45 (q, RCH_2Br, J 3.6 and 9Hz), 3.01 (q, RCH_2Br, J 9 and 10.8 Hz) and 2.85 (m, $R_2\underline{C}H\text{-}CH_2Br$). Double irradiation of the signal at δ 3.45 causes the signal at δ 3.01 to collapse to a doublet (J 10.8 Hz) illustrating the vicinal coupling between the cyclobutane ring methine proton and one of the bromomethyl group protons. Double irradiation of the ring methine signal at δ 2.85 causes the signal at δ 3.45 to collapse to a doublet (J 9Hz) illustrating the geminal coupling of the bromomethyl protons. The two dimensional ^{1}H n.m.r. spectra (page 75) clearly shows the coupling of these protons to each other.

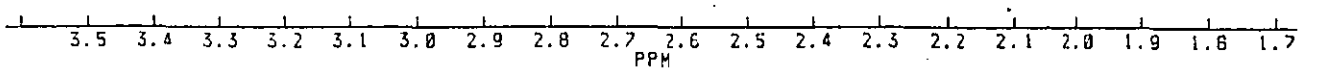
The more polar isomer (156) had important signals in its 360 MHz ^{1}H n.m.r. spectrum at δ 3.55 (q, RCH_2Br, J 6.3 and 9.9 Hz) 3.40 (t, RCH_2Br, J 9.9 Hz) and 2.46 (m $R_2\underline{C}H\text{-}CH_2Br$). Double irradiation of the signal at δ 2.46 caused the signals at δ 3.55 and 3.40 to collapse to doublets (J 9.9 Hz) illustrating the geminal coupling between the bromomethyl protons. The coupling between these protons was clearly visible in the two dimensional ^{1}H n.m.r. spectrum (page 76).

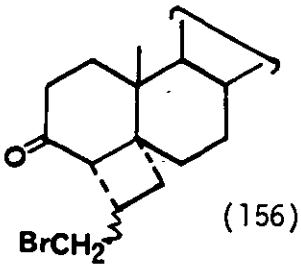


(155)

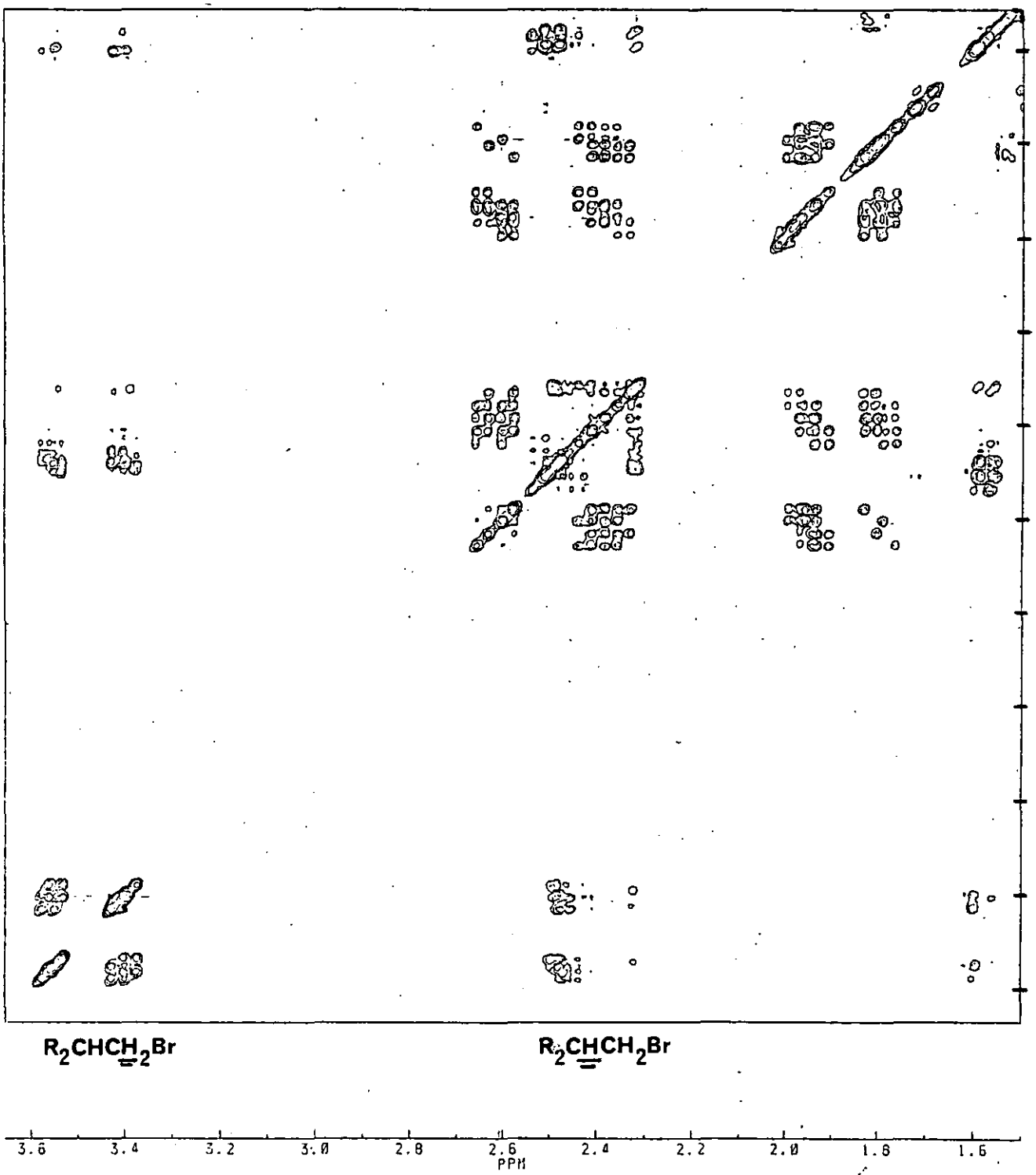


R_2CHCH_2Br R_2CHCH_2Br





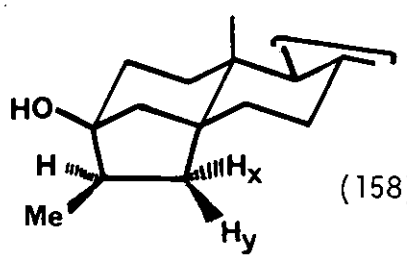
(156)



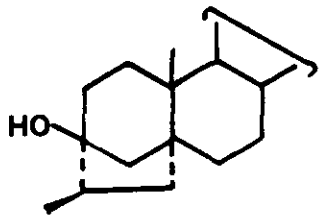
The bromides (155) and (156) were reductively cleaved with lithium in liquid ammonia and T.H.F. to give the required allyl-ketone (157) (75%). A by-product of this reaction was an alcohol (158), the yield of which could be reduced by the use of a minimum amount of lithium and a short reaction time.

The allyl-ketone (157) had infrared ($\nu_{max.}$ 3080, 1640 ($RCH=CH_2$), 1710 (C=O) cm^{-1}) and ^1H n.m.r. (δ 5.4 - 6.1, m and 5.1, m, $RCH=CH_2$) spectra which confirmed the presence of the allyl and ketone groups. The mass spectrum had a molecular ion at m/z 426 which fragmented with loss of C_3H_5 to give a ion at m/z 385.

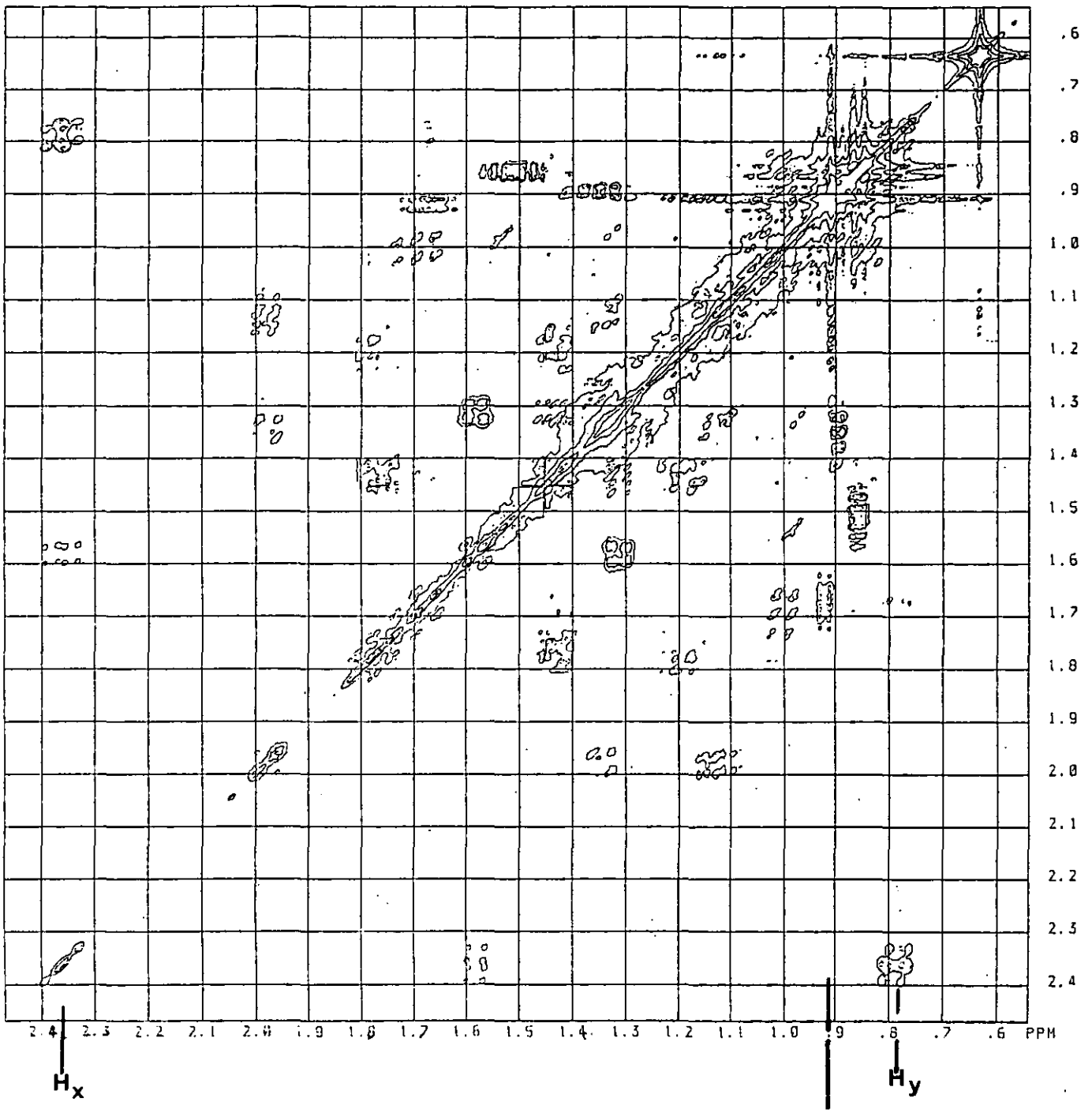
The alcohol (158) was identified from its infrared spectrum which had $\nu_{max.}$ 3500 (OH) cm^{-1}. The 360 MHz ^1H n.m.r. spectrum had a signal at δ 0.92 (d, J 7Hz) for the bridge methyl and a signal at δ 2.36 (m) which was assigned to the bridge methylene proton, H_x. The two-dimensional ^1H n.m.r. spectrum (page **78**) shows the spin-spin coupling of the bridge methylene proton, H_x (δ 2.36) to the bridge methylene proton H_y (δ 0.79, dd, J 5 and 14 Hz). The lowfield position of the signal for H_x is presumed to be due to the steric crowding it suffers from the 7α- and 9α- protons. The mass spectrum had a molecular ion at m/z 428 which fragmented with loss of methyl to give an ion at m/z 413 and with loss of C_3H_7 to give an ion at m/z 385. It is assumed that the methyl will take up the least sterically hindered position.



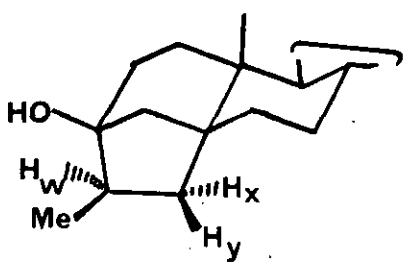
(158)



(158)

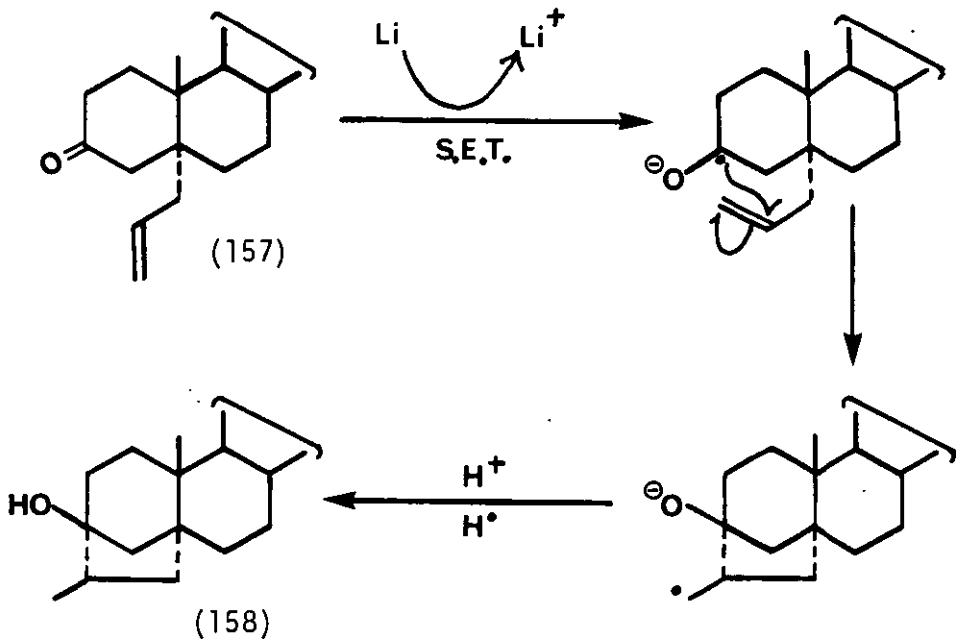


Bridge methyl



It is proposed that the alcohol (158) arises from a reductive radical cyclisation of the allyl-ketone (157) (Scheme 67). Evidence for this was gained by treating the allyl-ketone with lithium in liquid ammonia which resulted in the isolation of the alcohol in 46% yield, and unchanged starting material.

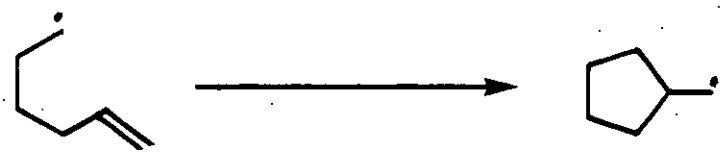
Scheme 67



This cyclisation is particularly efficient when compared to the cyclisation of 4,5-secocholest-3-en-5-one reported by Pradhan[62,63] since no secondary alcohol is isolated. This may be due to the close proximity of the allyl chain to the reacting centre. A similar effect is reported[92] with the norbornene system (159) (Scheme 68) which cyclises much more rapidly than the hexenyl radical.

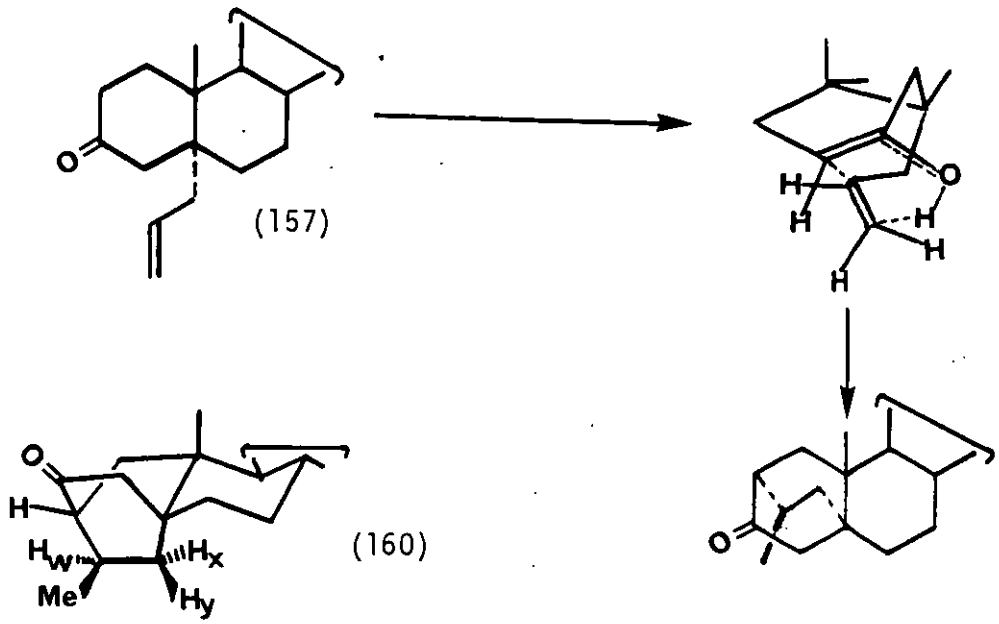
Scheme 68

faster than

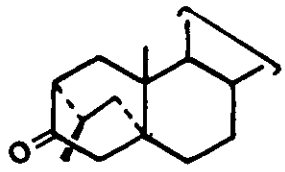


The allyl-ketone (157), when heated in decalin solution in a sealed tube at 330°C, underwent an ene reaction (Scheme 69) giving the ketone (160) (79%). Cyclisation could also be achieved at temperatures as low as 250°C although the conversion was reduced to 57% (4 hours).

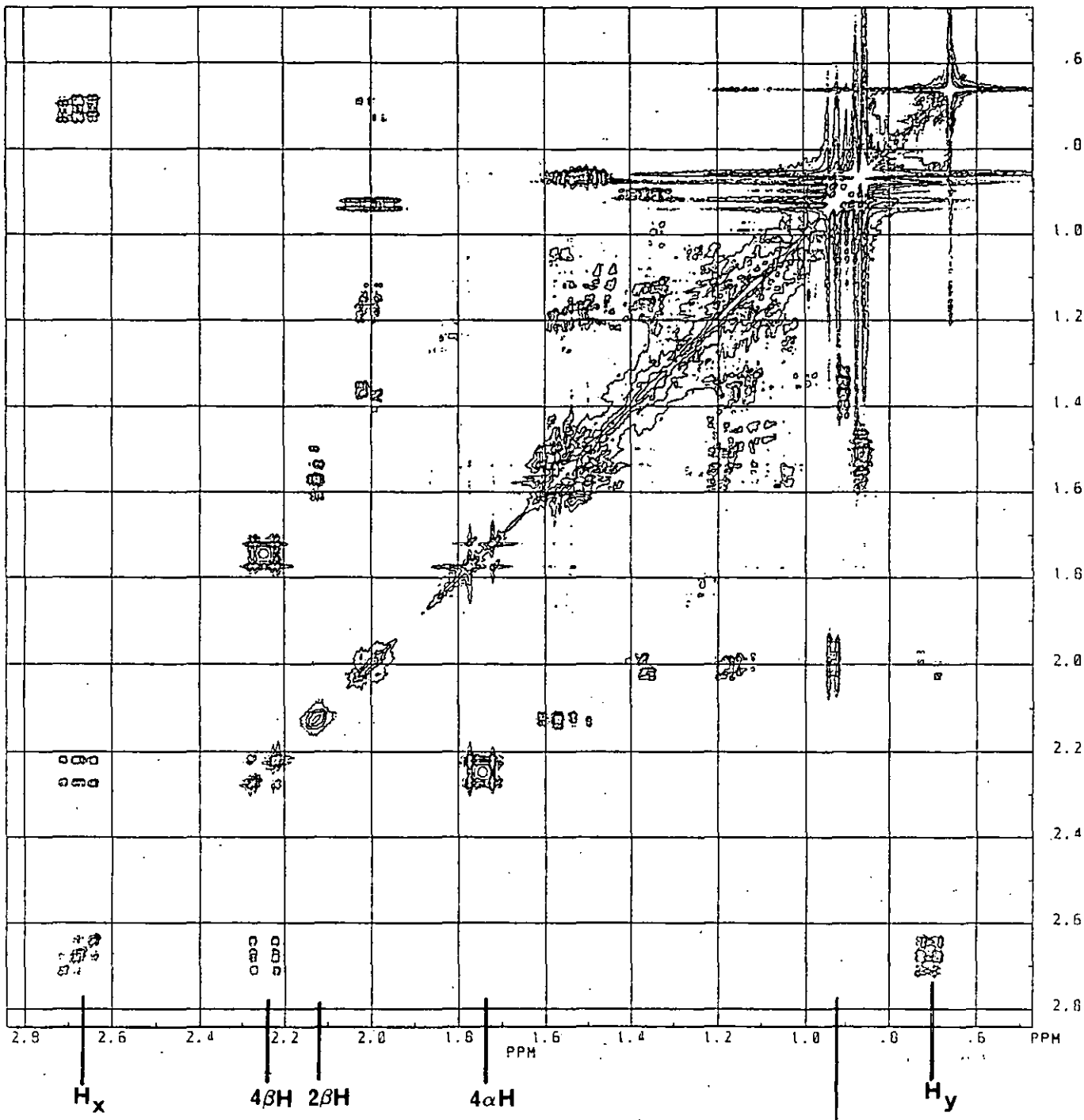
Scheme 69



The ketone (160) had $\nu_{max.}$ 1728 (C=O) cm^{-1} in its infrared spectrum and the 360 MHz 'H n.m.r. spectrum had a signal at δ0.93 (d, J 7Hz) for the bridge methyl. The 4-methylene group gave a double doublet at δ2.25 [$J_{(gem)}$ 19Hz and 3Hz] and a doublet at δ1.74 [$J_{(gem)}$ 19Hz]. The lower field signal is assigned to the 4β- proton which suffers long range(W) spin-spin coupling with the bridge methylene proton H_X (δ 2.67, m). The two-dimensional 'H n.m.r. spectrum (page **81**) shows the spin-spin coupling of H_X (δ 2.67) to the 4β-H and to H_y (δ 0.71, dd, J 14 and 3 Hz). A signal at δ 2.13 (brd s, $W_{\frac{1}{2}}$ 7 Hz) was assigned to the 2β- proton. The mass spectrum had a molecular ion at m/z 426 which fragmented with the loss of methyl to give an ion at m/z 411. The regiochemistry and methyl stereochemistry were assigned on the basis of the proposed mechanism and by comparison with the similar reaction of 5-vinyl-5α-cholestan-3-one (161) (Scheme 70).[73]



(160)


.6
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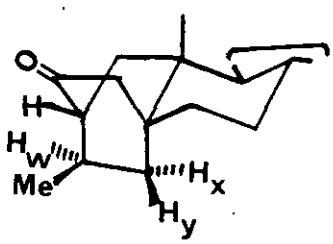
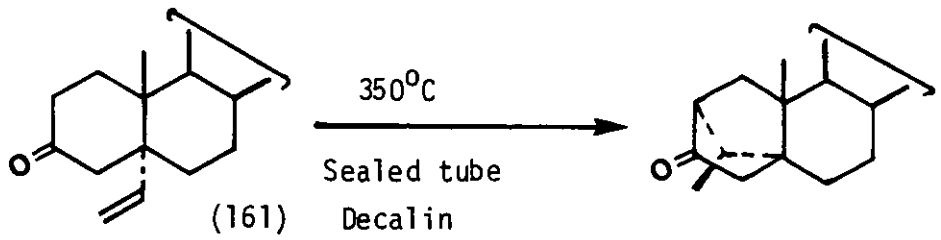
1.6
1.8
2.0
2.2
2.4
2.6
2.8
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
.8
.6
PPM
PPM
H_x
4βH
2βH
4αH
H_y
Bridge methyl

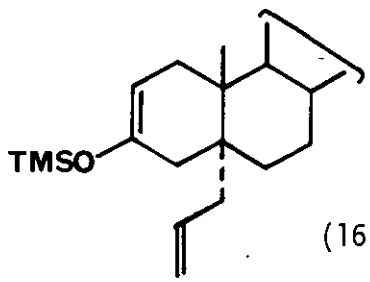

O
H
H_w
Me
H_x
H_y

Scheme 70



(161)

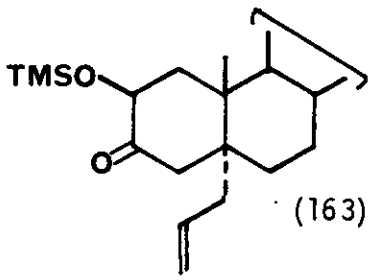
The allyl-ketone (157) was converted to the silylenolether (162) by treatment with trimethylsilyl chloride and triethylamine in refluxing dimethylformamide.[93] It was assumed to be the 2-enol ether on the basis of thermodynamic stability. The infrared ($\nu_{max.}$ 1665 (RCH=CR-OSiMe) cm^{-1}) and the 'H n.m.r. (δ 4.7, brd s) spectra confirmed the presence of an enol ether.



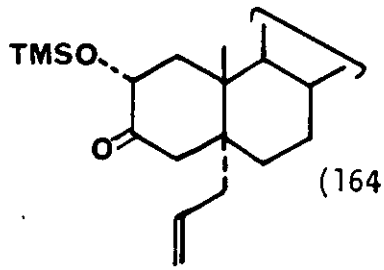
(162)

Oxidation with m-chloroperbenzoic acid in anhydrous hexane[90] and non-aqueous work up gave a mixture of the silyloxy ketones (163) and (164). Careful flash column chromatography gave the least polar epimer, 2β-(trimethylsilyloxy)-5-(2-propenyl)-5α-cholestan-3-one (163) as an oil, and the more polar epimer 2α-(trimethylsilyloxy)-5-(2-propenyl)-5α-cholestan-3-one (164) which was crystalline. The C2-stereochemistry was assigned on the basis of the spin-spin coupling constants for the C2-H in the 'H n.m.r.

spectra. Compound (163) has a signal at δ 4.10 (q, C2α-H, J 7 and 3 Hz) whereas compound (164) had a signal at δ 4.15 (q, C2β-H, J 11 and 7 Hz), the larger coupling constant being attributed to an axial-axial coupling.



(163)

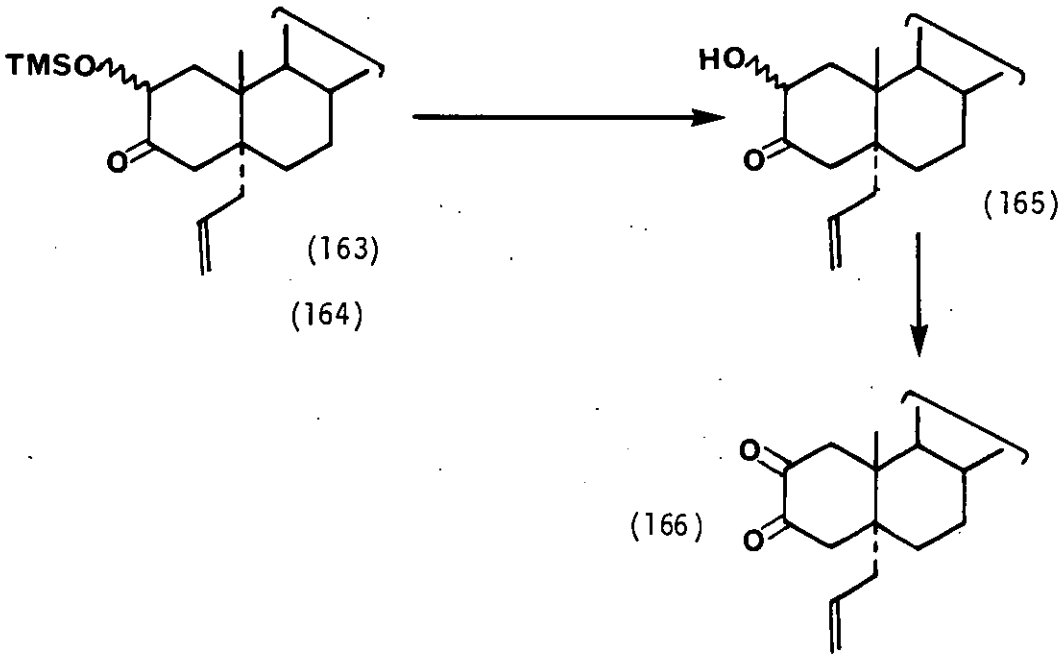


(164)

The 2β-silyloxy-ketone (163) hydrolysed on standing, but the 2α-silyloxy-ketone (164), when pure, appeared quite stable.

Deprotection of the mixed epimers with tetrabutylammonium fluoride/silica in chloroform gave initially the acyloins (165) which were converted very quickly in the presence of air into the disophenol (166) (Scheme 71).

Scheme 71



(163)

(164)

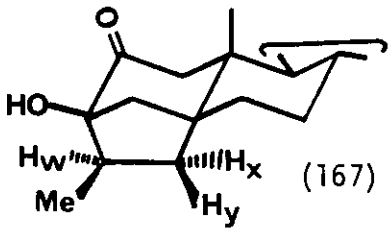
(165)

(166)

The diosphenol (166) had $\nu_{max.}$ 3400, (OH) 1710 (C=O) and 1665 (C=C(OH)-C=O) cm^{-1} in its infrared spectrum. The ^1H n.m.r. spectrum had important signals at δ 6.1 (s, C1-H) and 5.7 (s, C4-H). The mass spectrum had a molecular ion at m/z 440.

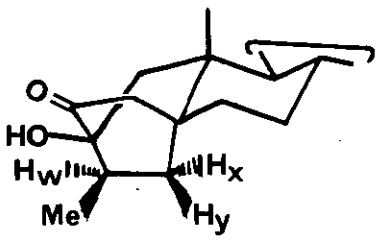
The analogous oxidation of 2α-hydroxy-cholestan-3-one in alkaline solution has been reported.[43] It is unusual that this autoxidation occurs rapidly and without base catalysis.

Deprotection of the silyloxy-ketones with $Bu_4N^+F^-/SiO_2$ in a refluxing solution of deoxygenated toluene under an atmosphere of argon (18 hours) afforded two products. Separation by preparative thin layer chromatography gave the 3α,5α-ethano-compound (167) (6%) and the 2α,5α-ethano-compound (168) (33%). Similar yields of (167) (7%) and (168) 27%) were obtained by heating a solution of the silyloxy-ketones (163) and (164) in decalin with $Bu_4N^+F^-/SiO_2$ in a sealed tube at 200°C (4 hours).



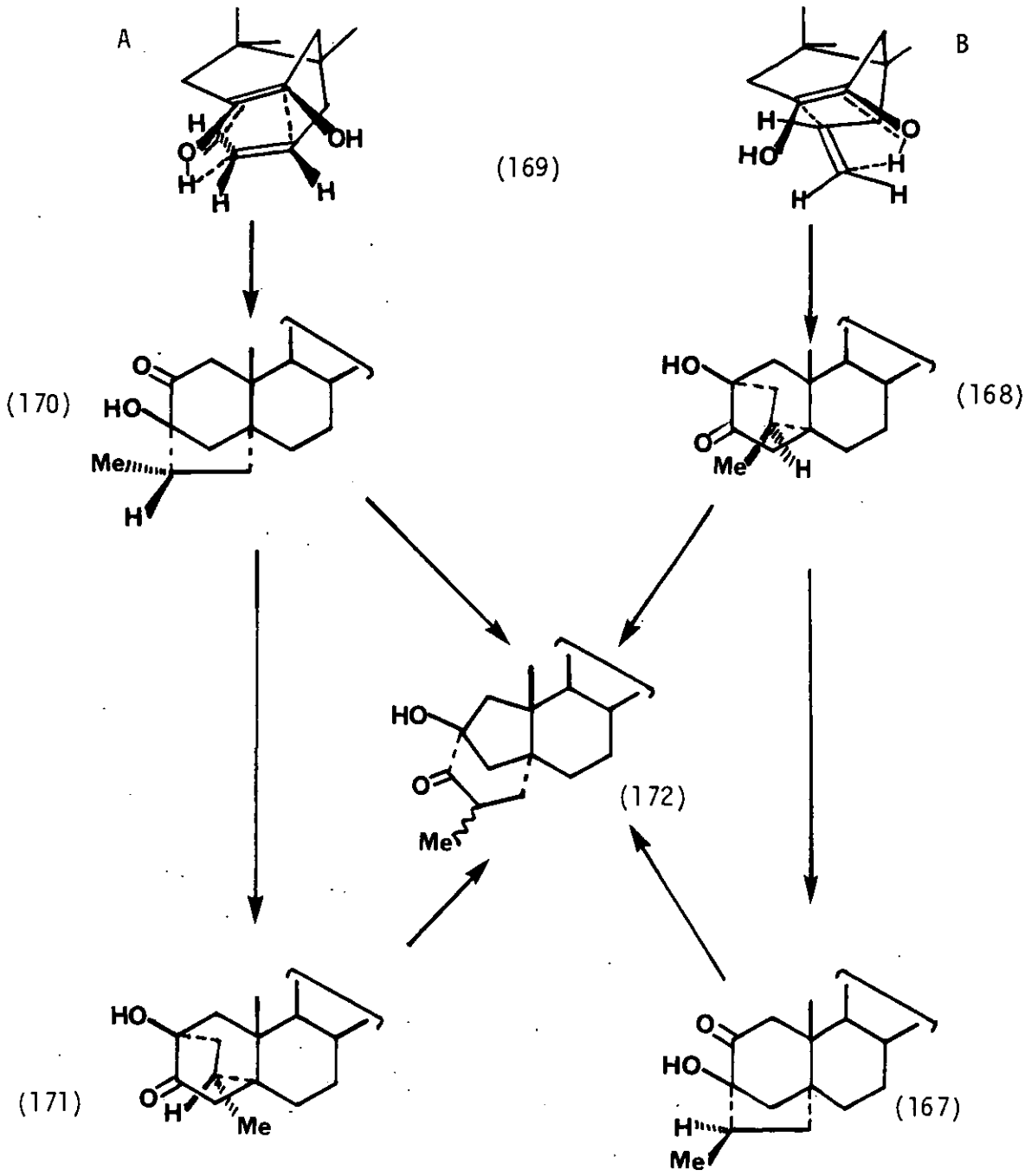
(167)

(168)



Ene reaction of the dienediol (169) in conformations A and B would give rise to the primary products (168) and (170); these could undergo further rearrangement to the related products (167) and (171) or by shift of the alternative bonds to the compounds (172) (Scheme 72).

Scheme 72

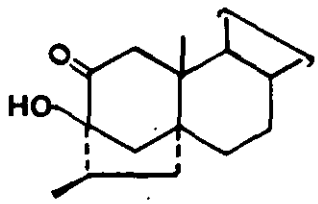


The assigned structures were supported by the spectroscopic evidence. In particular, the infrared spectrum of the minor isomer (167) [$\nu_{max.}$ 3495 (OH), 1705 (C=O)cm^{-1}] differed from that of the major isomer (168) [$\nu_{max.}$ 3500 (OH), 1725 (C=O)cm^{-1}] suggesting a different carbon skeleton rather than simply a difference in the configuration of the 1-methyl (bridge).

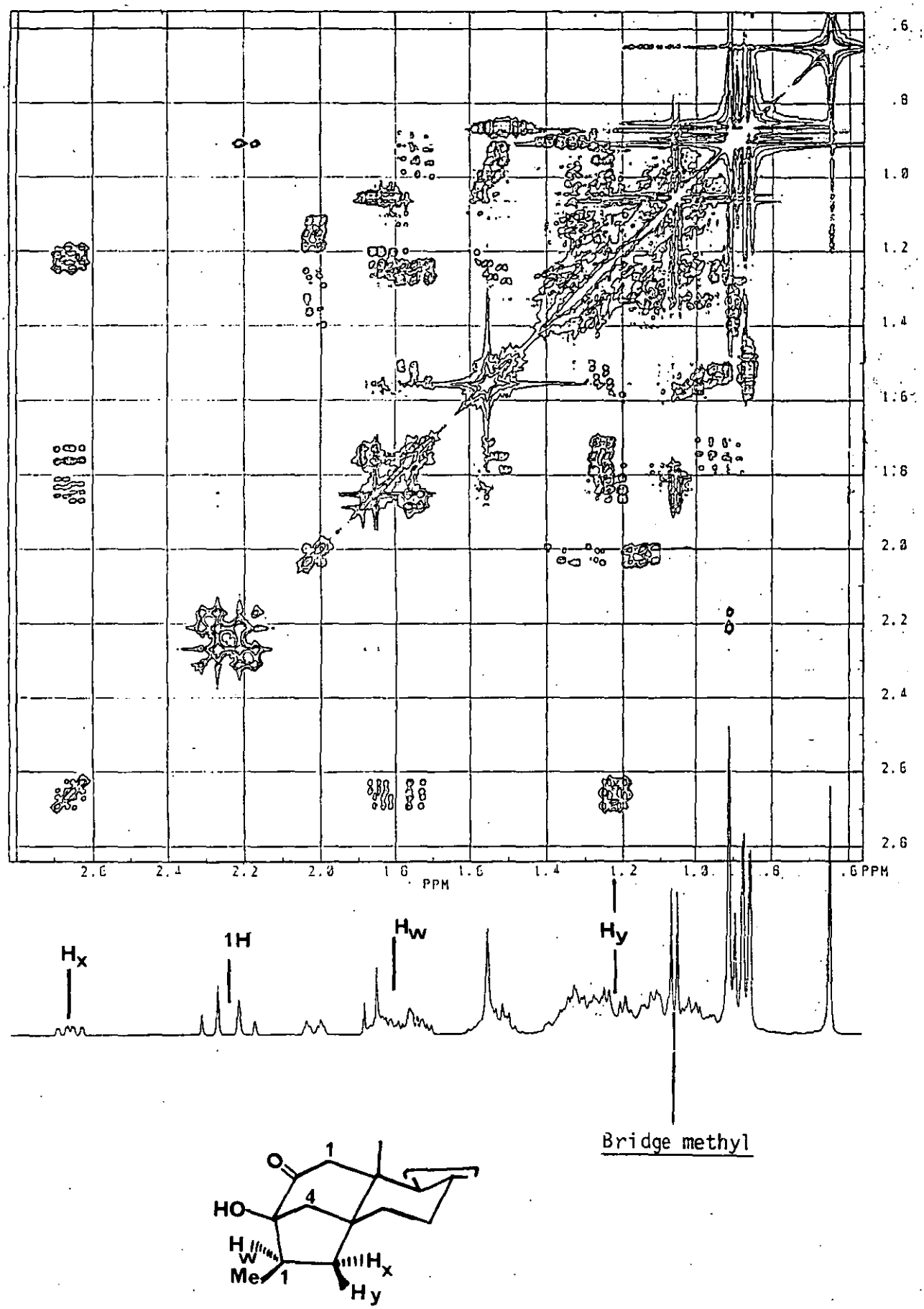
The 360 MHz 'H n.m.r. spectrum of the minor isomer (167) had a signal at δ 1.05 (d, J 7 Hz) for the bridge methyl. The C1 methylene protons gave an AB quartet at δ 2.25 [$J_{(gem)}$ 15 Hz] in which the upfield branch was slightly broadened. The bridge methylene proton, H_X again appeared at low field (δ 2.64, quartet d, J 14, 9 and 3 Hz). The general splitting pattern compared with that of the bridge methylene proton, H_X in alcohol (158). The two dimensional 'H n.m.r. spectrum showed the spin-spin coupling of H_X to the C1-proton Hw (δ 1.8, m) and the other bridge methylene proton, H_y (δ 1.22). A sharp singlet at δ 3.6 was assigned to the hydroxyl proton. The absence of any N.O.E. of the 1-methylene on double irradiation of the bridge methyl resonance (δ 1.05) confirmed the assigned methyl configuration. In the alternative configuration (170) a significant N.O.E. between the C1α-H and the bridge methyl would be expected. That the 3,5-ethano-compound (167) may be formed from the 2,5-ethano compound (168) was demonstrated by t.l.c. of the product of heating (168) in decalin at 200°C for 4 hours in a sealed tube. The mass spectrum of compound (167) had a molecular ion at m/z 442 which fragmented with loss of CH_3CHO to give an ion at m/z 398.

The major isomer (168) had a signal in the 360 MHz 'H n.m.r. spectrum at δ 0.85 (d, 7 Hz) for the bridge methyl. The C4-methylene gave a double doublet at δ 2.45 [$J_{(gem)}$ 19 Hz and 3 Hz] and a doublet at δ1.92 [$J_{(gem)}$ 19Hz] The lower field signals were assigned to the 4β-H which suffers long range spin-spin coupling (W) with the bridge methylene proton, H_X (δ2.91) [cf. ketone (160)]. The two-dimensional 'H n.m.r. (page 90) shows the spin-spin coupling

of proton H_X (δ 2.91, m, J 3, 10 and 15 Hz) to the 4β-H, the proton, H_W, (δ 2.03, m) and the other bridge methylene proton, H_Y (δ 0.90). The spin-spin coupling between proton H_W and the bridge methyl is also visible. The signal for the hydroxyl proton appeared as a sharp singlet at δ3.50. The mass spectrum had a molecular ion at m/z 442 which fragmented with loss of CH_3CHO to give an ion at m/z 398.


O
HO

(167)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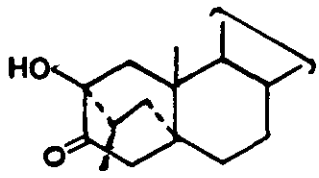
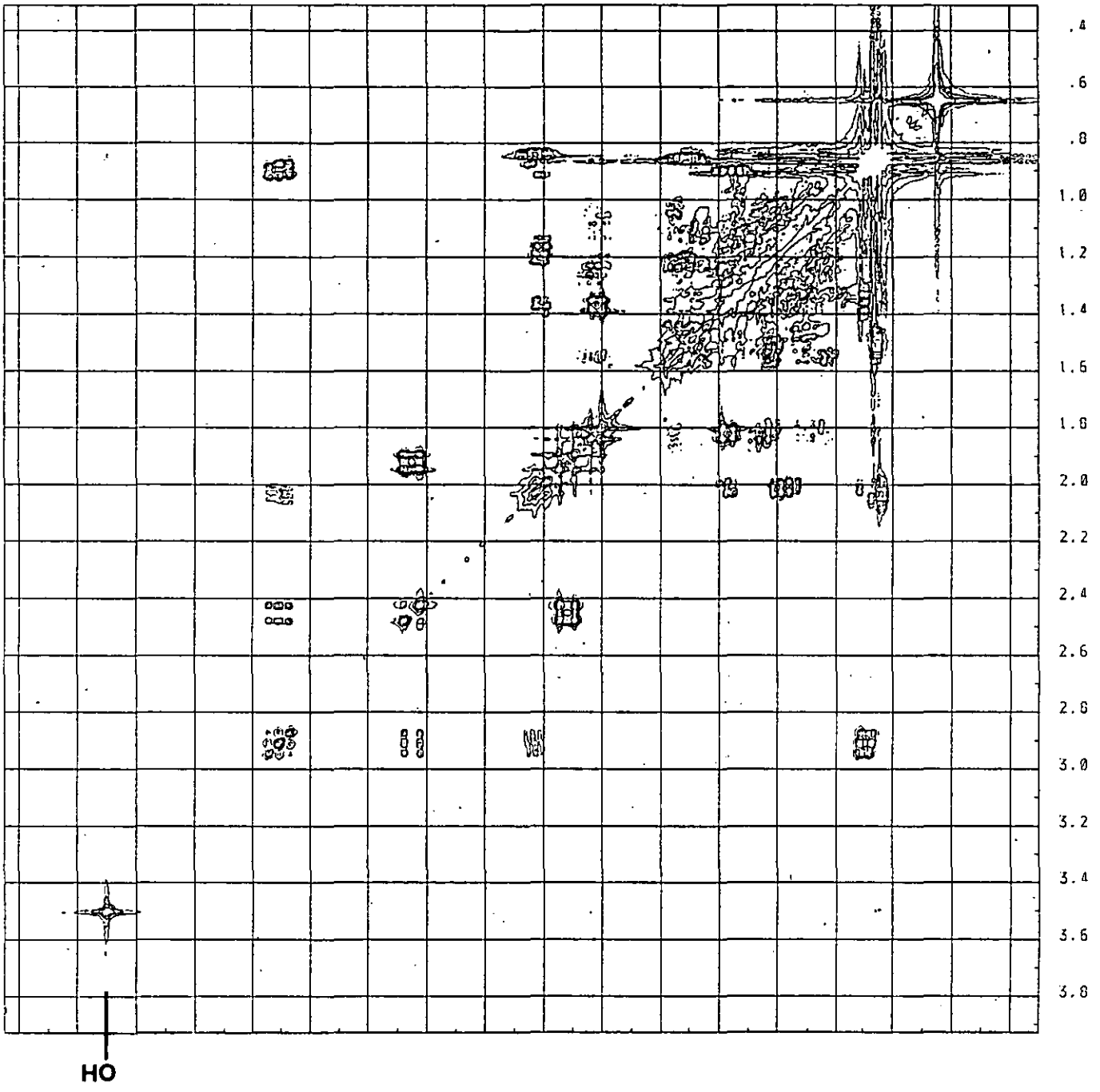
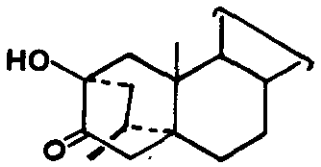
2.4
2.6
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
.8
.6 PPM
PPM
Hx
1H
Hw
Hy
Bridge methyl

O
1
4
HO
Hw
Me
1
Hx
Hy

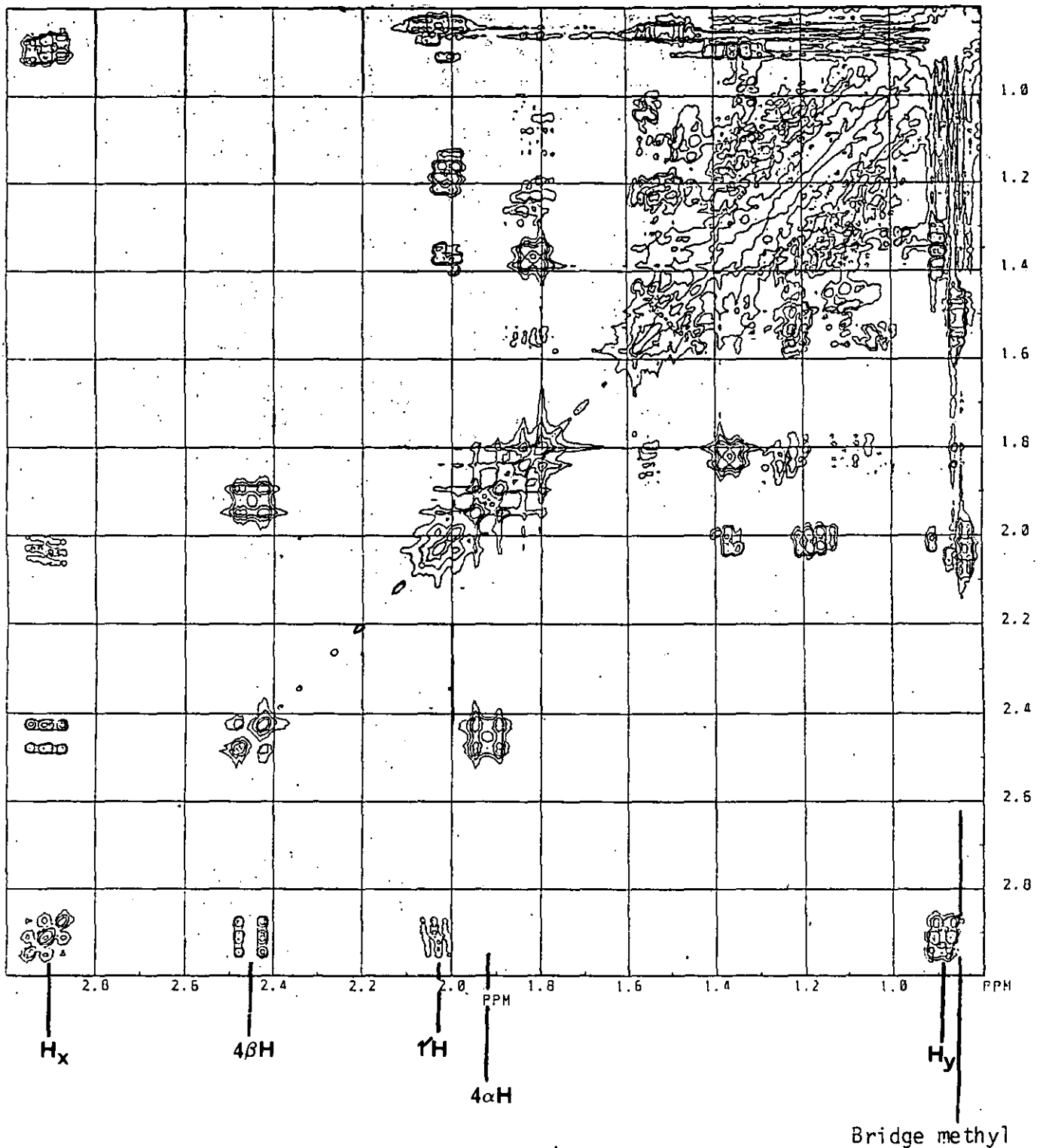


(168)




HO
O

(168)


1.0
1.2
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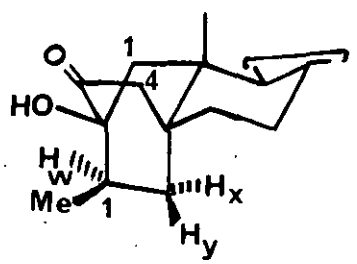
1.6
1.8
2.0
2.2
2.4
2.6
2.8
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
PPM
PPM
Hx
4βH
γH
4αH
Hy
Bridge methyl

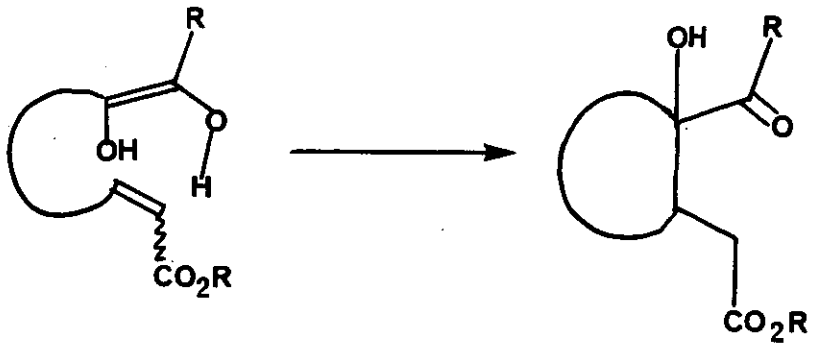

O
1
4
HO
Hw
Me
1
Hx
Hy

The ene reaction of acyloins (165) is a further example of the increased reactivity of acyloins compared to ketones ($110^{o}C$ vs $250^{o}C$). This enhanced reactivity is believed to be due to the extra oxygen in the dienediol increasing the ene electron density.

The decrease in reaction temperature compared to that of acyloin (48) is probably due to the lower mobility of the alkene (enophile) chain.

Future developments include coupling of an acyloin with an electron deficient enophile (Scheme 73). Ths should allow the reaction to proceed at even lower temperatures.

Scheme 73



EXPERIMENTAL

Solvents were dried and distilled by conventional methods. Solutions were dried over anhydrous magnesium sulphate and solvents removed *in vacuo* on a rotary evaporator.

Preparative thin layer chromatography (t.l.c.) was performed using a Merck Kieselgel 60 PF_{254} and $_{360}$. Flash chromatography was accomplished using Merck silica gel 230-400 mesh according to the method of Still *et al.*[94]

Infrared spectra were recorded as Nujol mulls (solids) or thin films (oils, liquids) on a Perkin-Elmer 177 spectrometer.

^1H nuclear magnetic resonance spectra were determined in deuterochloroform using tetramethylsilane (T.M.S.) as internal standard. 60 MHz spectra were recorded on a Varian EM 360 A spectrometer and 90 MHz spectra were recorded on a Perkin-Elmer R32 spectrometer. 360 MHz and 2d ^1H n.m.r. spectra were run at Fisons p.l.c. Loughborough on a Bruker spectrometer.

^{13}C nuclear magnetic resonance spectra were determined in deuterochloroform with tetramethylsilane as internal standard on a Bruker WP-80 spectrometer.

Mass spectra were recorded using a Kratos MS80 spectrometer linked to a DS-55 data system.

Elemental analyses were performed by the Microanalytical Department, University of Manchester.

Optical rotations were measured for solutions in chloroform with an Automatic Digital Polarimeter AA-10.

Melting points were determined on a Kofler block and are uncorrected.

Ether refers to diethyl ether and petrol to petroleum ether 40-60°C boiling fraction.

Organometallic reagents in solution were transferred by glass syringe and handled under argon.

Deoxygenation of *t*-butanol solutions was achieved by refluxing while argon was bubbled through for at least four hours.

Experiment Number

1) 3β-Tosyloxycholest-5-ene

2) 3β-Tosyloxy-5,6α-epoxy-5α-cholestane

3) 3β-Tosyloxy-6β-methoxy-5α-cholestan-5-ol

4) Reaction of 3β-tosyloxy-6β-methoxy-5α-cholestan-5-ol with potassium t-butoxide in t-butanol

5) Cholest-4-en-3-one

6) 3-Ethoxycholesta-3,5-diene

7) 6β-Hydroxycholest-4-en-3-one

8) 5,6α-Epoxy-5α-cholestan-3β-ol

9) 6α-Hydroxycholest-4-en-3-one

10) 6β-Hydroxy-4β,5-epoxy-5β-cholestan-3-one

11) 6α-Hydroxy-4β,5-epoxy-5β-cholestan-3-one

12) 6β-Acetoxy-4β,5-epoxy-5β-cholestan-3-one

13) 6α-Acetoxy-4β,5-epoxy-5β-cholestan-3-one

14) 6β-Acetoxy-4,5-secocholest-3-yn-5-one

15) 6α-Acetoxy-4,5-secocholest-3-yn-5-one

16) 6β-Acetoxy-4,5-secocholest-3-en-5-one

17) 6α-Acetoxy-4,5-secocholest-3-en-5-one

18) 5β-Hydroxy-4,5-secocholest-3-yn-6-one

19) Hydrolysis of 6β-acetoxy-4,5-secocholest-3-en-5-one

a) with methanol/concentrated hydrochloric acid
b) with 90% aqueous ethanol/concentrated hydrochloric acid
c) with ethanol/dilute hydrochloric acid
d) with ethanolic potassium hydroxide/inert atmosphere
e) with ethanolic potassium hydroxide/air

20) Reaction of 5β-hydroxy-4,5-secocholest-3-en-6-one with potassium t-butoxide in t-butanol

a) under an inert atmosphere
b) in the presence of air

21) 6-Hydroxy-4,5-secocholesta-3,6-dien-5-one

22) 3β-Tosyloxy-5α-cholestane-5,6β-diol

23) Reaction of 3β-tosyloxy-5α-cholestane-5,6β-diol with potassium t-butoxide in t-butanol

a) under an inert atmosphere
b) in the presence of air

24) 3β-Tosyloxy-5α-cholestan-5-ol-6-one

25) 3β-Tosyloxy-[6α-^{2}H]-5α-cholestane-5,6β-diol

26) Reaction of 3β-tosyloxy-[6α-^{2}H]-5α-cholestane-5,6β-diol with potassium t-butoxide in t-butanol

27) 3β-Mesyloxycholest-5-ene

28) 3β-Mesyloxy-5,6α-epoxy-5α-cholestane

29) 3β-Mesyloxy-5α-cholestane-5,6β-diol

30) Reaction of 3β-mesyloxy-5α-cholestane-5,6β-diol with potassium t-butoxide in t-butanol

31) 3β-Chlorocholest-5-ene

32) 3β-Chloro-5,6α-epoxy-5α-cholestane

33) 3β-Chloro-5α-cholestane-5,6β-diol

34) Reaction of 3β-chloro-5α-cholestane-5,6β-diol with potassium t-butoxide in t-butanol

35) 5α-Cholestane-3α,5,6β-triol

36) 5α-Cholestane-3β,5-diol-6-one

37) 5β-Cholestane-3β,5-diol-6-one

38) 3β-Tosyloxy-5β-cholestan-5-ol-6-one

39) 3β-Tosyloxy-5β-cholestane-5,6β-diol

40) Reaction of 3β-tosyloxy-5β-cholestane-5,6β-diol with potassium t-butoxide in t-butanol

41) 3β-Tosyloxy-[6α-^{2}H]-5β-cholestane-5,6β-diol

42) Reaction of 3β-tosyloxy-[6α-^{2}H]-5β-cholestane-5,6β-diol with potassium t-butoxide in t-butanol

43) Cyclisation of 5β-hydroxy-4,5-secocholest-3-en-5-one

44) Thermal rearrangement of 3β-methyl-A-nor-5β-cholestan-5-ol-6-one

45) Acid catalysed rearrangement of 3β-methyl-A-nor-5β-cholestan-5-ol-6-one

46) Deuteration of 3-Methyl-B-nor-5β-cholest-2-en-4-one

47) 5α-Cholestan-5-ol-6-one

48) 5β-Cholestan-5-ol-6-one

49) Attempted reductive cyclisation of 6-hydroxy-4,5-secocholesta-3,6-dien-5-one

50) 6β-Acetoxy-4,5-secocholest-3-en-5ξ-ol

51) 5ξ-Mesyloxy-6β-acetoxy-4,5-secocholest-3-ene

52) Attempted reductive radical cyclisation of 5ξ-mesyloxy-6β-acetoxy-4,5-secocholest-3-ene

53) 1-(Trimethylsilyloxy)-3-methyl-3-(3-butenyl)-cyclohex-1-ene

54) 3-Methyl-3-(3-butenyl)-2-hydroxy-cyclohexan-1-one

55) Attempted cyclisation of 3-methyl-3-(3-butenyl)-2-hydroxy-cyclohexan-1-one with potassium t-butoxide in t-butanol

56) Cyclisation of 3-methyl-3-(3-butenyl)-2-hydroxy-cyclohexan-1-one in decalin

57) 3β,7aβ-Dimethyl-3aβ,4β-dihydroxy-octahydro-4H-indene

58) 5β,7aβ-Dimethyl-3aβ,4β-dihydroxy-octahydro-4H-indene

59) Cyclisation of 3-methyl-3-(3-butenyl)-2-hydroxy-cyclohexan-1-one in decalin with product dehydration

60) Attempted conjugate addition of allyl magnesium bromide to cholestenone

61) Attempted conjugate addition of propargyl magnesium bromide to cholestenone

62) Attempted conjugate addition of trimethylallylsilane to cholestenone

63) 3α-(2-Propenyl)-3β-hydroxy-cholest-4-ene

64) Attempted oxy-Cope rearrangement

65) Cholest-4-en-3β-ol

66) 3β-Vinyloxy-cholest-4-ene

67) Δ^3,5β-Cholestenylacetaldehyde

68) 5-(2,2-Dimethoxy-ethyl)-5β-cholest-3-one

69) 5-(2,2-Dimethoxy-ethyl)-5β-cholest-3-en-2-one

70) Hydrolysis of 5-(2,2-dimethoxy-ethyl)-5β-cholest-3-ene

71) Attempted hydrolysis of 5-(2,2-dimethoxy-ethyl)-5β-cholest-3-en-2-one

72) 4β,5-Epoxy-5β-cholestan-3-one

73) 2α-Hydroxy-cholest-4-en-3-one

74) 2α-Acetoxy-cholest-4-en-3-one

75) 2α-Acetoxy-cholest-4-en-3β-ol

76) 3β-Vinyloxy-2α-acetoxy-cholest-4-ene

77) 2α-Acetoxy-Δ^3-5β-cholestenylacetaldehyde

78) 5-(2-Propenyl)-5β-cholest-3-en-2α-ol

79) 5-(2-Propenyl)-5β-cholest-3-en-2-one

80) 2-(Trimethylsilyloxy)-5-(2-propenyl)-5β-cholest-2-ene

81) 4α,5-(1-Methylene-ethano)-5α-cholestan-3-one

82) 4α,5-(1-Bromomethylethano)-5α-cholestan-3-one

83) 5-(2-propenyl)-5α-cholestan-3-one

84) Reductive cyclisation of 5-(2-propenyl)-5α-cholestan-3-one

85) Thermal cyclisation of 5-(2-propenyl)-5α-cholestan-3-one

86) 3-(Trimethylsilyloxy)-5-(2-propenyl)-5α-cholest-2-ene

87) 2ξ-(Trimethylsilyloxy)-5-(2-propenyl)-5α-cholestan-3-one

88) Attempted hydrolysis of 2ξ-(trimethylsilyloxy)-5-(2-propenyl)-5α-cholestan-3-one

89) Hydrolysis and thermal cyclisation of 2ξ-(trimethylsilyloxy)-5-(2-propenyl)-5α-cholestan-3-one

a) in a sealed tube
b) in refluxing toluene

Part 1

1. 3ß-Tosyloxycholest-5-ene (29)

Cholesterol (10g) and p-toluenesulphonyl chloride (20g) were dissolved in pyridine (120 ml) and allowed to stand at room temperature overnight. The solution was poured over ice and the resulting solid product filtered off. Recrystallisation from acetone gave the pure tosylate (29) (15.3g, 98%), m.p. 130-132°C, (lit.[32] m.p. 131.5-132.5°C).

2. 3ß-Tos yloxy-5,6α-epoxy-5α-cholestane (30)

3ß-Tosyloxycholest-5-ene (15.4g) was dissolved in dry ether (400 ml) and dry chloroform (40 ml). m-Chloroperbenzoic acid (9.8g, 2 mol. equiv.) was added and the solution was stirred at room temperature overnight. The ether solution was washed with aqueous sodium sulphite until neutral (Starch/Iodide paper), aqueous sodium bicarbonate (100 ml) and water (100 ml), dried and evaporated in vacuo to give the epoxide (30) (15.8g, 99%) which was used without further purification (lit.[33] m.p. 124°C).

3. 3ß-Tosyloxy-6ß-methoxy-5α-cholestan-5-ol (31)

3ß-Tosyloxy-5,6α-epoxy-5α-cholestane (2.0g) was dissolved in dry methanol (80 ml) and ether (10 ml). Boron trifluoride etherate (2 ml) was added and the solution allowed to stand at room temperature for four hours.

The solution was diluted with water (200 ml) and extracted with ether (3 x 75ml). The combined ether extracts were washed with aqueous sodium bicarbonate (50 ml) and water (50 ml), dried and evaporated in vacuo to give a sticky white solid (2.1g). Recrystallisation from methanol gave the methoxy tosylate (31) (1.7g, 72%) as white needles. m.p. 120-123°C (lit.[31] m.p. 123-125°C) ν_{max} 3550 (sharp, OH), 1600 (C=C aromatic) cm^{-1}, δ 7.85 and 7.37 (ABq, 4H, tosyl aromatic protons), 5.0 (m, 1H, C3α-H, $W_{\frac{1}{2}}$ 18Hz), 3.38 (s, 3H, OMe), 2.95 (brd s, 1H, C6α-H, $W_{\frac{1}{2}}$ 6 Hz), 2.47 (s, 3H, tosyl- Me), 1.06 (s, 3H C10ß-Me), 0.66 (s, 3H, C13ß-Me).

4. Reaction of 3ß-Tosyloxy-6ß-methoxy-5α-cholestan-5-ol with potassium t-butoxide in t-butanol

A solution of potassium t-butoxide (0.45g, 2 mol. equiv.) in t-butanol (30 ml) was added to a solution of 3ß-tosyloxy-6ß-methoxy-5α-cholestan-5-ol (1.2g) in t-butanol (70 ml) under argon. The mixture was stirred for two and a half hours at 55°C, then poured into water (200 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with water (2 x 25 ml), dried and evaporated in vacuo to give an oil. Preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave 6ß-methoxy-4,5-secocholest-3-en-5-one (32) (0.024g, 2%), an oil, ν_{max} 1720 (C=C) cm^{-1}, δ 5.5-5.9 (m, 1H, RC<u>H</u>=CH_2), 4.9-5.2 (m, 2H, RCH=C<u>H</u>$_2$), 3.64 (brd t, 1H, C6α-H, J (apparent) 4Hz), 3.34 (s, 3H, OMe), 1.20 (s, 3H, C10ß-Me) and 0.75 (s, 3H, C13ß-Me). (Found: m/z 416.3657 ($M^{+\cdot}$). $C_{28}H_{48}O_2$ requires $M^{+\cdot}$ 416.3654). A second fraction containing a mixture (55%) of 6ß-methoxy-5α-cholestan-3α,5-epoxide (34), an oil $[\alpha]_D$ + 21° (c=0.01349 gl^{-1}), δ 4.5 (m, 1H, C3ß-H), 3.40 (m, 1H, C6α-H), 3.32 (s, 3H, OMe), 2.6 (q, 1H, C4α-H, J 9 and 7Hz) 2.06 (d, 1H, C4ß-H J 9Hz), 1.14 (s, 3H, C10ß-Me) and 0.69 (s, 3H, C13ß-Me), (ref.[31]) and 6α-methoxy-4,5-seco-cholest-3-ene-5-one (33), an oil, ν_{max} 3080 (RCH=CH_2), 1720 (C=C), 1640 (RCH=CH_2) cm^{-1}, δ 5.6-6.1 (m, 1H, RC<u>H</u>=CH_2), 4.85-5.20 (m, 2H, RCH=C<u>H</u>$_2$), 4.0 (q, 1H, C6ß-H, J 6 & 11 Hz), 3.46 (s, 3H, OMe), 1.10 (s, 3H, C10ß-Me) and 0.73 (s, 3H, C13ß-Me). (Found: m/z 416.3654 ($M^{+\cdot}$). $C_{28}H_{48}O_2$ requires $M^{+\cdot}$ 416.3654).

The mixture was dissolved in methanol (20 ml) and reduced with an excess of sodium borohydride. Work up and preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave 6ß-methoxy-4,5-secocholest-3-en-5ξ-ol (2%) (35) an oil, ν_{max} 3580, 3470 (OH), 3070, 1640 (RCH=CH_2] cm^{-1}, δ 5.6-6.0 (m, 1H, RC<u>H</u>=CH_2), 4.8-5.2 (m, 2H, RCH=C<u>H</u>$_2$), 3.42 and 3.35 (s, OMe), 3.25 (m, C5-H & C6-H), 0.95 & 0.90 (s, C10ß-Me) and 0.60 & 0.65 (s, C13ß-Me). (Found: m/z 418.3800 ($M^{+\cdot}$). $C_{28}H_{50}O_2$ requires $M^{+\cdot}$ 418.3810) and 6ß-methoxy-5α-cholestan-3α,5-epoxide (34).

5. Cholest-4-en-3-one (42)

A solution of aluminium isopropoxide (13.4g, 1.6 mol. equiv.) in toluene (70 ml) was added to a refluxing solution of cholesterol (40g) in toluene (400 ml) and cyclohexanone (200 ml) over thirty minutes. During the addition toluene was distilled off via a Dean-Stark trap.

The solution was cooled to room temperature and saturated aqueous sodium-potassium tartrate (160 ml) was added. The mixture was steam distilled until 1200 ml of distillate had been collected. The residual mixture was cooled and extracted with chloroform (3 x 100 ml). The combined chloroform extracts were washed with water (100 ml), dried and evaporated in vacuo. Recrystallisation of the oily product from methanol at 0°C gave cholest-4-en-3-one (32g, 80%), m.p. 79-81°C (lit.[34] m.p. 79-81°C).

6. 3-Ethoxycholesta-3,5-diene (43)

Cholestenone (6.2g) was dissolved in absolute ethanol (20 ml) and triethylorthoformate (6 ml) with warming. A few drops of ethanolic hydrogen chloride [acetyl chloride (1 ml) in ethanol (10 ml)] were added and the mixture allowed to stand at room temperature for two minutes. Pyridine (2 ml) was added and the solution cooled to 0°C. The crude product was filtered off and recrystallised from acetone to give 3-ethoxycholesta-3,5-diene (4.2g, 65%) m.p. 83-85°C (lit.[35] m.p. 83.5-85°C), ν_{max} 1625, 1650 (C=C) cm^{-1}.

7. 6ß-Hydroxycholest-4-en-3-one (36)

3-Ethoxycholesta-3,5-diene (2.0g) was dissolved in 95% ethanol (200 ml). The solution was irradiated (4 x 100 watt tungsten filament lamps) while air was bubbled through for 5 hours (t.l.c.). The solvent was removed in vacuo and the crude product recrystallised from acetone-hexane to give 6ß-hydroxycholest-4-en-3-one (1.1g, 58%), m.p. 192-194°C (lit.[37] m.p. 192-194°C), ν_{max} 3400 (OH), 1680 (C=O), 1615 (C=C) cm^{-1}.

8. 5,6α-Epoxy-5α-cholestan-3ß-ol (44)

To a solution of cholesterol (10g) in dry ether (100 ml) at 0°C was added sodium bicarbonate (3.0g) and m-chloroperbenzoic acid (6.2g, 1.5 mol. equiv.). The solution was stirred at room temperature for twenty hours, then washed with aqueous sodium sulphite (50 ml), aqueous sodium bicarbonate (50 ml) and water (50 ml), dried and evaporated in vacuo. Recrystallisation from 88% aqueous acetone gave pure 5,6α-epoxy-5α-cholestan-3ß-ol (8.3g, 80%), m.p. 139-142°C (lit.[38] m.p. 141-143°C).

9. 6α-Hydroxycholest-4-en-3-one (23)

Pyridinium chlorochromate (8.6g, 2 mol. equiv.) was added to a solution of 5,6α-epoxy-5α-cholestan-3ß-ol (8.2g) in dichloromethane (150 ml). The solution was stirred at room temperature overnight then filtered. The filtrate was washed with dilute hydrochloric acid (50 ml), aqueous sodium bicarbonate (50 ml) and water (50 ml), dried and evaporated in vacuo to yield the epoxy-ketone (45) (6.2g, 76%) as a brown foam (one-spot by t.l.c.).

The crude epoxy-ketone (45) was dissolved in ethanol (100 ml) and triethylamine (50 ml) then heated under reflux for four hours. The solution was concentrated in vacuo, then diluted with ether (100 ml). The ether was washed with dilute hydrochloric acid (25 ml), aqueous sodium bicarbonate (25 ml) and water (25 ml), dried and evaporated in vacuo to give an off-white foam. Flash column chromatography [SiO_2, petrol:ether, 6:1, (v/v)] gave 6α-hydroxycholest-4-en-3-one (4.1g, 60%), m.p. 154-155°C (methanol) (lit.[39] m.p. 156°C).

10. 6ß-Hydroxy-4ß,5-epoxy-5ß-cholestan-3-one (37)

A solution of hydrogen peroxide (30%, 1.5 ml) in aqueous sodium hydroxide (2 M, 10 ml) was added to 6ß-hydroxycholest-4-en-3-one (1.0g) in methanol (80 ml). The mixture was stirred at room temperature for 3 hours, then diluted with water (200 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with brine (2 x 50 ml) dried and

evaporated in vacuo to give 6ß-hydroxy-4ß,5-epoxy-5ß-cholestan-3-one (0.67g, 64%), m.p. 174-76°C (methanol), $[\alpha]_D$ + 85° (c= 0.017 gl^{-1}), ν_{max} 3520 (sharp, OH), 1710 (C=O) cm^{-1}, δ 3.48 (brd. s, 1H, C6α-H, $W_{\frac{1}{2}}$ 6Hz), 3.02 (s, 1H, C4α-H), 1.36 (s, 3H, C10ß-Me) 0.74 (s, 3H, C13ß-Me). (Found: m/z 416.3268 ($M^{+\cdot}$). $C_{27}H_{44}O_3$ requires $M^{+\cdot}$ 416.3290. (Found: C,77.8; H, 11.0. $C_{27}H_{44}O_3$ requires C, 77.8; H, 10.6%).

11. 6α-Hydroxy-4ß,5-epoxy-5ß-cholestan-3-one (24)

6α-Hydroxycholest-4-en-3-one (2.2g) was treated as above with hydrogen peroxide (30%, 4 ml) and sodium hydroxide (4N, 10 ml) in methanol (200 ml) to give 6α-hydroxy-4ξ,5-epoxy-5ξ-cholestan-3-one (1.4g, 61%) an oil, $[\alpha]_D$ + 42° (C = 0.00979 gl^{-1}) (ref[31]). Recrystallisation from methanol gave the pure 4ß,5ß-epoxide (24) m.p. 138°C, $[\alpha]_D$ + 58° (c = 0.02534 gl^{-1}), ν_{max} 3440 (brd, OH), 1710 (C=O) cm^{-1}, δ 4.14 (q, 1H, C6ß-H J 5 and 11Hz),3.46 (s, 1H, C4α-H), 1.14 (s, 3H, C10ß-Me) and 0.69 (s, 3H, C13ß-Me). (Found: m/z 416.3294 ($M^{+\cdot}$). $C_{27}H_{44}O_3$ requires $M^{+\cdot}$ 416.3290). (Found: C, 77.5; H, 10.8. $C_{27}H_{44}O_3$ requires C, 77.8; H, 10.6%).

12. 6ß-Acetoxy-4ß,5-epoxy-5ß-cholestan-3-one (38)

6ß-Hydroxy-4ß,5-epoxy-5ß-cholestan-3-one (0.5g) was dissolved in pyridine (20 ml) and acetic anhydride (5 ml) and allowed to stand at room temperature overnight. The reaction mixture was poured over ice and extracted with ether (3 x 50 ml). The combined ether extracts were washed with dilute hydrochloric acid (2 x 25 ml), aqueous sodium bicarbonate (25 ml) and water (25 ml), dried and evaporated in vacuo to give the acetate (38) (0.343g, 78%) m.p. 106-107°C (methanol) $[\alpha]_D$ + 45° (c=0.0119gl^{-1}) ν_{max}. 1740 (C=O, ester), 1720 (shoulder, C=O, ketone) cm^{-1}, δ 4.60 (brd s, 1H, C6α-H, $W_{\frac{1}{2}}$ 6Hz), 3.06 (s, 1H, C4α-H), 2.11 (s, 3H,OAc). 1.30 (s, 3H, C10ß-Me) and 0.72 (s, 3H, C13ß-Me). (Found: m/z 458.3428 ($M^{+\cdot}$) $C_{29}H_{46}O_4$ requires $M^{+\cdot}$ 458.3396) (Found: C, 75.8; H, 10.2. $C_{29}H_{46}O_4$ requires C, 75.9; H, 10.1%).

13. 6α-Acetoxy-4ß,5-epoxy-5ß-cholestan-3-one (39)

6α-Hydroxy-4ß,5-epoxy-5ß-cholestan-3-one (0.82g) was acetylated with acetic anhydride in pyridine as above. Preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave the acetate (39) (0.57g, 63%), an oil, $[\alpha]_D$ + 53° (c=0.01553gl^{-1}), ν_{max}. 1745 (C=O, ester), 1710 (C=O, ketone) cm^{-1}, δ 5.43 (q, 1H, C6ß-H, J5 and 11 Hz), 3.40 (s, 1H, C4α-H), 2.05 (s, 3H, OAc), 1.22 (s, 3H, C10ß-Me) and 0.72 (s, 3H, C13ß-Me). (Found: m/z 458.3393 ($M^{+\cdot}$) $C_{29}H_{46}O_4$ requires $M^{+\cdot}$ 458.3396).

14. 6ß-Acetoxy-4,5-secocholest-3-yn-5-one (40)

p-toluenesulphonhydrazide (0.94g, 1.1 mol. equiv.) was added to a solution of 6ß-acetoxy-4ß,5-epoxy-5ß-cholestan-3-one (2.3g) in absolute ethanol (80 ml). The solution was stirred at 50°C for two and a half hours, then diluted with water (200 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with dilute hydrochloric acid (25 ml), aqueous sodium bicarbonate (25 ml) and water (25 ml), dried and evaporated in vacuo to give an orange oil. Preparative thin layer chromatography [SiO_2, petrol:ether, 3:2 (v/v)] gave the pure acetylene (40) (0.89g, 40%), an oil $[\alpha]_D$ -42°C (c=0.012 gl^{-1}), ν_{max}. 3300 (C≡C-H) 2120 (C≡C) 1745 (C=O, acetate) 1728 (C=O, ketone); δ 5.39 (brd t, 1H, C6α-H, J (apparent) 9Hz), 2.12 (s, 3H, OAc), 1.08 (s, 3H, C10ß-Me), 0.70 (s, 3H, C13ß-Me). (Found: m/z 442.3443 ($M^{+\cdot}$). $C_{29}H_{46}O_3$ requires $M^{+\cdot}$ 442.3447).

15. 6α-Acetoxy-4,5-secocholest-3-yn-5-one (25)

6α-Acetoxy-4ß,5-epoxy-5ß-cholestan-3-one (0.59g) was treated as above with p-toluenesulphonnhydrazide (0.25g) in ethanol (40 ml). Preparative thin layer chromatography gave 6α-acetoxy-4,5-secocholest-3-yn-5-one (0.241g, 42%), an oil, $[\alpha]_D$ -12° (c=0.00971 gl^{-1}), ν_{max} 3315 (C≡C-H), 2120 (C≡C), 1745 (C=O, ester), 1728 (C=O, ketone) cm^{-1}, δ 5.46 (q, 1H, C6ß-H, J6 and 11 Hz), 2.18 (s, 3H, OAc), 1.20 (s, 3H, C10ß-Me) and 0.77 (s, 3H, C13ß-Me). (Found: m/z 442.3444 ($M^{+\cdot}$). $C_{29}H_{46}O_3$ requires $M^{+\cdot}$ 442.3447).

16. 6ß-Acetoxy-4,5-secocholest-3-en-5-one (41)

6ß-Acetoxy-4,5-secocholest-3-yn-5-one (0.73g) in ethyl acetate (20 ml) was added to a pre-hydrogenated suspension of 5% palladium on barium sulphate (~200 mgs) in ethyl acetate (20 ml) poisoned with quinoline (4 drops 20% solution). The suspension was stirred vigorously until 1 mole of hydrogen had been consumed. The catalyst was filtered off and the resulting solution washed with dilute hydrochloric acid (10 ml) and water (10 ml) dried and evaporated in vacuo. Preparative thin layer chromatography [SiO_2, petrol:ether, 3:2 (v/v)] gave the pure olefin (41) (0.571g, 78%), an oil $[\alpha]_D$ -31° (c=0.01079gl^{-1}), ν_{max}. 3080 (RCH=CH_2), 1745 (C=O, acetate), 1728 (C=O, ketone), 1640 (RCH=CH_2)cm^{-1}; δ 5.6-6.0 (m, 1H, RC<u>H</u>=-CH_2), 5.42 (brd t, 1H, C6α-H $J_{(apparent)}$ 9Hz), 4.85-5.15 (m, 2H, RCH=CH_2), 2.14 (s, 3H, OAc), 1.08 (s, 3H, C10ß-Me); 0.69 (s, 3H, C13ß-Me). (Found: m/z 444.3607 ($M^{+\cdot}$). $C_{29}H_{48}O_3$ requires $M^{+\cdot}$ 444.3603).

17. 6α-Acetoxy-4,5-secocholest-3-en-5-one (26)

6α-Acetoxy-4,5-secocholest-3-yn-5-one (0.188g) was hydrogenated as above. Preparative thin layer chromatography [SiO_2, petrol:ether, 3:1 (v/v)] gave the olefin (26) (0.106g, 56%), an oil, [α] -4.5° (c=0.01099 gl^{-1}) ν_{max} 3075 (RCH=CH_2) 1750 (C=O, ester), 1728 (C=O, ketone), 1640 (RCH=CH_2) cm^{-1}, δ 5.6-6.1 (m, 1H, RC<u>H</u>=CH_2), 5.48 (q, 1H, C6ß-H, J 6 and 11 Hz), 4.85-5.20 (m, 2H, RCH=C<u>H</u>$_2$), 2.17 (s, 3H, OAc), 1.19 (s, 3H, C10ß-Me) and 0.76 (s, 3H, C13ß-Me). (Found: m/z 444.3586 ($M^{+\cdot}$). $C_{29}H_{48}O_3$ requires $M^{+\cdot}$ 444.3603).

18. 5ß-Hydroxy-4,5-secocholest-3-yn-6-one (47)

6ß-Hydroxy-4ß,5-epoxy-5ß-cholestan-3-one (0.99g) was dissolved in ethanol (60 ml) and <u>p</u>-toluenesulphonhydrazide (0.461g, 1 mol. equiv.) was added. The solution was stirred at 50°C for two hours, then diluted with water (200 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with dilute hydrochloric acid (25 ml), aqueous

sodium bicarbonate (25 ml) and water (25 ml), dried and evaporated in vacuo to give an oil (0. 839g). Preparative thin layer chromatography twice [SiO_2, petrol:ether, 2:1 (v/v)] gave 5ß-hydroxy-4,5-secocholest-3-yn-6-one (0.3g, 31%), an oil, ν_{max}. 3520 (OH), 3280 (C≡C-H), 2110 (C≡C), 1715 (C=O) cm^{-1}, δ 4.08 (s, 1H, C5α-H), 3.55 (brd s, 1H, OH, D_2O exchangeable), 0.70 (s, 3H, C10ß-Me) and 0.68 (s, 3H, C13ß-Me). (Found: m/z 400.3346 ($M^{+\cdot}$). $C_{27}H_{44}O_2$ requires $M^{+\cdot}$ 400.3341).

19. Hydrolysis of 6ß-Acetoxy-4,5-secocholest-3-en-5-one

(a) With methanol and concentrated hydrochloric acid:-

6ß-Acetoxy-4,5-secocholest-3-en-5-one (0.43g) was dissolved in methanol (35 ml) and concentrated hydrochloric acid (5 ml) and heated under reflux overnight. The solution was diluted with water (150 ml) extracted with ether (3 x 25 ml). The combined ether extracts were washed with aqueous sodium bicarbonate (25 ml) and water (25 ml), dried and evaporated in vacuo. Preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave 6ß-methoxy-4,5-secocholest-3-en-5-one (33) (0.097g, 24%)

(b) With ethanol and concentrated hydrochloric acid:-

A solution of 6ß-acetoxy-4,5-secocholest-3-en-5-one (0.52g) in ethanol (50 ml), water (5 ml) and concentrated hydrochloric acid (5 ml) was heated under reflux refluxed for one and a half hours. The solution was diluted with water (200 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with aqueous sodium bicarbonate (25 ml) and water (25 ml), dried and evaporated in vacuo to give 5ß-hydroxy-4,5-seco-cholest-3-en-6-one (0.41g, 88%), an oil, $[\alpha]_D$ + 12° (c=0.012 gl^{-1}), ν_{max}. 3470 (OH), 3070 (RCH=CH_2), 1710 (C=O), 1640 (RCH=CH_2) cm^{-1}, δ 5.55-6.10 (m, 1H, RC<u>H</u>=CH_2), 4.9-5.25 (m, 2H, RCH=C<u>H</u>$_2$), 4.25 (brd s, 1H, OH, D_2O exchangeable), 4.08 (s, 1H, C5α-H), 0.69 (s, 6H, C10ß-Me and C13ß-Me). (Found: m/z 402.3506 ($M^{+\cdot}$). $C_{27}H_{46}O_2$ requires $M^{+\cdot}$ 402.3498).

(c) With ethanol and dilute hydrochloric acid :-

6ß-Acetoxy-4,5-secocholest-3-ene-5-one (1.3g) was dissolved in ethanol (50 ml) and dilute hydrochloric acid (2M, 10 ml). The solution was heated under reflux for five hours (t.l.c.) then diluted with water (200 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with aqueous sodium bicarbonate (25 ml) and water (25 ml), dried and evaporated in vacuo. Preparative thin layer chromatography [SiO_2, petrol: ether, 2:1 (v/v)] gave 5ß-hydroxy-4,5-secocholest-3-en-6-one (48) (0.36g, 30%) and 6α-hydroxy-4,5-secocholest-3-en-5-one (49) (0.294g, 24%), an oil, $[\alpha]_D$ +17° (c=0.00929 gl^{-1}); ν_{max}. 3470 (OH), 3070 ($RCH=CH_2$), 1700 (C=O), 1640 ($RCH=CH_2$) cm^{-1}, δ 5.5-6.2 (m, 1H, $RC\underline{H}=CH_2$), 4.9-5.2 (m, 2H, $RCH=C\underline{H}_2$), 4.38 (q, 1H, C6ß-H, J7 and 11Hz), 3.9 (brd s, 1H, OH), 1.10 (s, 3H, C10ß-Me) and 0.65 (s, 3H, C13ß-Me). (Found: m/z 402.3498 ($M^{+\cdot}$). $C_{27}H_{46}O_2$ requires $M^{+\cdot}$ 402.3498).

(d) With ethanolic potassium hydroxide under an inert atmosphere:-

6ß-Acetoxy-4,5-secocholest-3-en-5-one (0.385g) was added to a solution of potassium hydroxide in thoroughly deoxygenated ethanol (30%, 30 ml) under argon. The solution was heated under reflux for one hour, then acidified with dilute hydrochloric, diluted with water (150 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with water (50 ml), dried and evaporated in vacuo to give 5ß-hydroxy-4,5-secocholest-3-en-6-one (48) (0.285g, 90%).

(e) With ethanolic potassium hydroxide in the presence of air:-

6ß-Acetoxy-4,5-secocholest-3-ene-5-one (0.45g) was added to ethanolic potassium hydroxide (5%, 30 ml) and stirred for one hour at room temperature. The solution was diluted with water (150 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with water (50 ml), dried and evaporated in vacuo to 6-hydroxy-4,5-secocholesta-3,5-dien-5-one (27) (0.36g, 80%), m.p. 125-127°C (methanol), $[\alpha]_D$ -66° (c=0.0143

gl^{-1}), ν_{max} 3430 (sharp, OH), 3080 ($RCH=CH_2$), 1670 (C=O), 1650 (C=C) cm^{-1}, δ 6.09 (s, 1H, OH, D_2O exchangeable), 6.01 (d, 1H, C7-H, J2 Hz), 5.5-6.0 (m, 1H, $RC\underline{H}=CH_2$), 4.9-5.2 (m, 1H, $RCH=C\underline{H}_2$), 1.06 (s, 3H, C10ß-Me) and 0.78 (s, 3H, C13ß-Me). (Found: m/z 400.3334 ($M^{+\cdot}$). $C_{27}H_{44}O_2$ requires $M^{+\cdot}$ 400.3341). (Found: C, 80.7; H, 11.5. $C_{27}H_{44}O_2$ requires C, 80.9; H, 11.1%).

The diosphenol (27) was acetylated with acetic anhydride in pyridine at room temperature overnight to give the disophenol acetate (51), an oil, 3080 ($RCH=CH_2$), 1765 (C=O, ester), 1690 (C=O), 1640 ($RCH=CH_2$) cm^{-1}, δ 6.47 (d, 1H C7- H, J 2Hz), 5.6-6.2 (m, 1H, $RC\underline{H}=CH_2$), 4.85-5.2 (m, 2H, $RCH=C\underline{H}_2$), 2.22 (s, 3H, OAc), 1.08 (s, 3H, C10ß-Me) and 0.79 (s, 3H, C13ß-Me). (Found: m/z 442.3451 ($M^{+\cdot}$). $C_{29}H_{44}O_3$ requires $M^{+\cdot}$ 442.3448).

20. Reaction of 5ß-hydroxy-4,5-secocholest-3-en-6-one with potassium t-butoxide in t-butanol

(a) Under an inert atmosphere:-

To a thoroughly deoxygenated solution of the 5ß-acyloin (48) (0.412g) in t-butanol (30 ml) at 78°C was added a deoxygenated solution of potassium t-butoxide (0.23g, 2 mol. equiv.) in t-butanol (10 ml). The solution was stirred for two hours under argon at 78°C, then acidified with dilute hydrochloric acid, diluted with water (100 ml) and extracted with ether (3 x 25 ml). The combined ether extracts were washed with water (3 x 25 ml), dried and evaporated in vacuo to give unchanged starting material (0.369g).

(b) In the presence of air:-

A solution of the 5ß-acyloin (48) (0.18g) in t-butanol (10 ml) was added to a solution of potassium t-butoxide (0.11g, 2 mol. equiv.) in t-butanol (10 ml) and stirred at 55°C for four hours. The solution was diluted with water (100 ml) and extracted with ether (3 x 25 ml). The combined ether extracts were washed with dilute hydrochloric acid (25 ml), aqueous sodium bicarbonate (25 ml) and water (25 ml), dried and evaporated in vacuo to give the diosphenol (27) (0.15g, 83%).

21. 6-Hydroxy-4,5-secocholesta-3,6-dien-5-one (27)

The 5ß-acyloin (48) (0.314g) was added to ethanolic potassium hydroxide (5%, 30 ml) and stirred at room temperature for one hour. The solution was diluted with water (100 ml) and extracted with ether (3 x 25 ml). The combined ether extracts were washed with water (25 ml), dried and evaporated in vacuo to give the disophenol (27) (0.285g, 91%).

22. 3ß-Tosyloxy-5α-cholestane-5α,6ß-diol (17)

3ß-Tosyloy-5,6α-epoxy-5α-cholestane (3.85g) was dissolved in methyl ethyl ketone (120 ml). To this rapidly stirring solution was added perchloric acid (60%, 1 ml). Stirring was continued for fifteen minutes then the solution was diluted with ether (80 ml), washed with aqueous sodium bicarbonate (50 ml) and water (50 ml), dried and evaporated in vacuo to give the tosyloxy diol (17) (3.5g, 89%), m.p. 148°C dec. (acetone, petrol) (lit.[46] m.p. 148-150°C dec.).

23. Reaction of 3ß-tosyloxy-5α-cholestane-5,6ß-diol with potassium t-butoxide in t-butanol

(a) Under an inert temperature:-

A deoxygenated solution of potassium t-butoxide (0.46g, 2 mol. equiv.) in t-butanol was added to a deoxygenated solution of 3ß-tosyloxy-5α-cholestane-5,6ß-diol (1.2g) in t-butanol (90 ml). The mixture was stirred at 50°C for two hours under argon then diluted with water (150 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with water (2 x 50 ml), dried and evaporated in vacuo. Preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave 3ß-methyl-A-nor-5ß-cholestan-5-ol-6-one (0.096g, 11%), (lit.[29] m.p. 116-118°C), a second fraction 5ß-hydroxy-4,5-secocholest-3-en-6-one (48), (0.034g, 4%) and a further polar fraction 6ß-hydroxy-5α-cholestan-3α,5-epoxide (58) (0.41g, 49%.), (lit.[47] m.p. 121-123°C).

(b) In the presence of air:-

3ß-Tosyloxy-5α-cholestane-5,6ß-diol (1.2g) was treated as above in the presence of air. Preparative thin layer chromatography [SiO_2, petrol: ether, 2:1 (v/v)] gave 6-hydroxy-4,5-secocholesta-3 ,6-dien-5-one (27) (0.140g, 17%) (m.p. 125-127°C) and 6ß-hydroxy-5α-cholestan-3α,5-epoxide (58) (0.449g, 53%).

24. 3ß-Tosyloxy-5α-cholestan-5-ol-6-one (59)

A solution of 3ß-tosyloxy-5α-cholestan-5,6ß-diol (2.0g) and pyridinium chlorochromate (2.25g, 2 mol. equiv.) in dichloromethane (60 ml) was stirred at room temperature for two hours. The solution was washed with dilute acetic acid (2 x 25 ml), aqueous sodium bicarbonate (2 x 25 ml) and water (25 ml), dried and evaporated in vacuo. Recrystallisation from methanol gave 3ß-tosyloxy-5α-cholestan-5-ol-6-one (1.6g, 78%), m.p. 161-163°C, (lit.[48] m.p. 161-163°C).

25. 3ß-Tosyloxy-[6α-^{2}H]-5α-cholestane-5,6ß-diol (60)

Sodium borodeuteride (0.209g, 2 mol. equiv.) was added to a rapidly stirring solution of 3ß-tosyloxy-5α-cholestan-5-ol-6-one (1.42g) in methanol (80 ml). Stirring was continued for ten minutes, then the solution was diluted with water (150 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with dilute hydrochloric acid (25 ml), aqueous sodium bicarbonate (25 ml) and water (25 ml), dried and evaporated in vacuo. Recrystallisation from acetone, petrol gave 3ß-tosyloxy-[6α-^{2}H]-5α-cholestane-5,6ß-diol (1.06g, 74%), m.p. 148-150°C dec., ^{1}H n.m.r. absence of signal at δ 3.58 (C6α-H).

26. Reaction of 3ß-tosyloxy-[6α-^{2}H]-5α-cholestane-5,6ß-diol with potassium t-butoxide in t-butanol

A solution of potassium t-butoxide (0.43g, 2 mol. equiv.) in deoxygenated t-butanol (30 ml) was added to a solution of 3ß-tosyloxy-[6α-^{2}H]-5α-cholestane-5,6ß-diol (1.06g) in deoxygenated t-butanol (80 ml). The

solution was stirred at 50°C for two and a half hours under argon. Work up as for Expt. 23, followed by preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave 3ß-methyl-A-nor-5ß-cholestan-5-ol-6-one (19) (0.022g, 2%). (Found: m/z 402 ($M^{+\bullet}$). $C_{27}H_{46}O_2$ requires $M^{+\bullet}$ 402), no deuterium retention, the unsaturated acyloin (48) (0.070g, 9%), no deuterium retention and the 6ß-hydroxy-[6α-^{2}H]-5α-cholestan-3α,5-epoxide (0.42g, 57%).

27. 3ß-Mesyloxycholest-5-ene (62)

Cholesterol (3.0g) and methanesulphonyl chloride (3 ml) were dissolved in pyridine (60 ml) and allowed to stand at room temperature overnight. The solution was poured over ice and the resulting solid filtered off. Recrystallisation from acetone gave 3ß-mesyloxycholest-5-ene (3.5g, 98%), m.p. 121-124°C (lit.[50] m.p. 115-116°C).

28. 3ß-Mesyloxy-5,6α-epoxy-5α-cholestane (64)

3ß-Mesyloxycholest-5-ene (3.0g) was dissolved in ether (150 ml) and chloroform (20 ml). m-Chloroperbenzoic acid (2.0g, 1.5 mol. equiv.) was added and the solution stirred at room temperature overnight. The solution was washed with aqueous sodium sulphite (50 ml), aqueous sodium bicarbonate (50 ml) and water (50 ml), dried and evaporated in vacuo to give a white solid. Recrystallisation from petrol gave 3ß-mesyloxy-5,6α-epoxy-5α-cholestane (2.4g, 73%), m.p. 140-146°C (lit.[46] m.p. 144-148°C).

29. 3ß-Mesyloxy-5α-cholestane-5,6α-diol (66)

3ß-Mesyloxy-5,6α-epoxy-5α-cholestane (2.4g) was dissolved in methyl ethyl ketone (150 ml) and to this rapidly stirring solution was added perchloric acid (60%, 2 ml) dropwise. The solution was stirred at room temperature for fifteen minutes, then diluted with ether (50 ml), washed with aqueous sodium bicarbonate (50 ml) and water (50 ml), dried and evaporated in vacuo to give an off-white solid. Recrystallisation from acetone:

petrol gave 3ß-mesyloxy-5α-cholestane-5,6ß-diol (1.7g, 67%), m.p. 153-154°C dec, $[\alpha]_D$ -8° (c=0.015 gl^{-1}), ν_{max} 3530, 3550 (OH) cm^{-1}, δ 5.15 (m, 1H, C3α-H), 3.58 (brd s, 1H, C6α-H, $W_{\frac{1}{2}}$ 6Hz), 3.2 (s, 3H, $-O_2S-Me$), 1.19 (s, 3H, C10ß-Me) and 0.68 (s, 3H, C13ß-Me) (Found: C, 67.1; H, 10.1, $C_{28}H_{50}O_5S$ requires C, 67.4; H, 10.1%).

30. Reaction of 3ß-mesyloxy-5α-cholestane-5,6ß-diol with potassium t-butoxide in t-butanol

A solution of potassium-t-butoxide (0.46g, 2 mol. equiv.) in deoxygenated t-butanol (30 ml) was added to a solution of 3ß-mesyloxy-5α-cholestane-5,6ß-diol (1.0g) in deoxygenated t-butanol (80 ml). The solution was stirred for two and a half hours under argon at 55-65°C. Work up as for Expt. 23 and preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave 3ß-methyl-A-nor-5ß-cholestan-5-ol-6-one (0.021g, 2.6%), 5ß-hydroxy-4,5-secocholest-3-en-6-one (48) (0.084g, 10%) and 6ß-hydroxy-5α-cholestan-3α,5-epoxide (58) (0.44g, 54%).

31. Chlorocholest-5-ene (61)

Thionyl chloride (10 ml) was added to cholesterol at 0°C. The solution was heated under reflux for one hour then poured over ice. The product was filtered off and recrystallised from acetone to give 3ß-chlorocholest-5-ene (4.1g, 78%), m.p. 93-95°C (lit.[49] m.p. 95-96°C).

32. 3ß-Chloro-5,6α-epoxy-5α-cholestane (63)

m-Chloroperbenzoic acid (2.4g, 1.5 mol. equiv.) was added to a solution of 3ß-chlorocholest-5-ene (3.8g) in ether (40 ml). The solution was stirred overnight at room temperature, then washed with aqueous sodium sulphite (25 ml), aqueous sodium bicarbonate (25 ml), and water (25 ml), dried and evaporated in vacuo. Recrystallisation from acetone gave 3ß-chloro-5,6α-epoxy-5α-cholestane (2.65g, 68%), m.p. 89-90°C (lit.[51] m.p. 89.5-90.5°C).

33. 3ß-Chloro-5α-cholestane-5,6β-diol(65)

To a rapidly stirring solution of 3ß-chloro-5,6α-epoxy-5α-cholestane (2.3g) in methyl ethyl ketone (60 ml) was added perchloric acid (60%, 1 ml)) dropwise. After fifteen minutes the solution was diluted with ether (40 ml) and washed with aqueous sodium bicarbonate (25 ml) and water (25 ml), dried and evaporated in vacuo. Recrystallisation from acetone, petrol gave 3ß-chloro-5α-cholestane-5,6β-diol(2.3g, 95%) m.p. 124-126°C (lit.[51] m.p. 126°C).

34. Reaction of 3ß-chloro-5α-cholestane-5,6ß-diol with potassium t-butoxide in t-butanol

A solution of potassium t-butoxide (0.69g, 3 mol. equiv.) in deoxygenated t-butanol (30 ml) was added to a solution of 3ß-chloro-5α-cholestane-5,6ß-diol (0.91g) in deoxygenated t-butanol (100 ml). The solution was stirred for twenty four hours at 65°C under argon. Work up as for Expt. 23 and preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave unchanged starting material (0.233g, 30%) and 6ß-hydroxy-5α-cholestan-3α,5-epoxide (58) (0.281g, 35%).

35. 5α-Cholestane-3ß,5,6ß-triol

Cholesterol (10.4g) was suspended in 90% formic acid (100 ml) and warmed to 80°C for fifteen minutes where upon an oily upper layer separated. The mixture was allowed to cool then hydrogen peroxide (30%, 10 ml) was added. The reaction mixture was stirred overnight and then diluted with boiling water (150 ml). The solution was allowed to cool and the resulting solid was filtered off. The solid was washed several times with water then dissolved in methanol (300 ml). The methanolic solution was made alkaline with an excess of aqueous sodium hydroxide (25%) and heated on a steam bath for thirty minutes. The mixture was acidified with dilute hydrochloric acid and cooled to 0°C. The crude product was filtered off and recrystallised from methanol to give 5α-cholestane-3ß,5,5ß-triol (8.7g, 77%) m.p. 237-239°C (lit.[53] m.p. 237-239°C).

36. 5α-Cholestane-3ß,5-diol-6-one (72)

5α-Cholestane-3ß,5,6ß-triol (4.1g) was dissolved in dioxane (40 ml) and water (4 ml). N-bromosuccinimide (2.2g, 1.05 mol. equiv.) was added and the solution stirred at room temperature for ten minutes. Aqueous sodium metabisulphite solution was added until the yellow bromine colour disappeared. Water (20 ml) was added and the solution cooled to 0°C. The resulting precipitate was filtered off and recrystallised from methanol to give 5α-cholestane-3ß,5-diol-6-one (1.82g, 91%), m.p. 230-232°C (lit.[53] m.p. 231-232°C).

37. 5ß-Cholestane-3ß,5-diol-6-one (73)

A solution of 5α-cholestane-3ß,5-diol-6-one (6.9g) in methanolic sodium hydroxide (10%, 300ml) was heated under reflux for two hours. The solution was concentrated in vacuo, diluted with water (200 ml) and extracted with ether (3 x 50 ml). The ether was dried and evaporated in vacuo. Flash column chromatography [SiO_2, ether] gave 5ß-cholestane-3ß,5-diol-6-one (5.3g, 77%) (lit.[54] 62°C) and unchanged starting material (1.0g, 14%).

38. 3ß-Tosyloxy-5ß-cholestan-5-ol-6-one (74)

5ß-Cholestan-5-ol-6-one (4.9g) and p-toluenesulphonyl chloride (10g) were dissolved in pyridine (60 ml) and allowed to stand at room temperature for three days. The solution was poured over ice and extracted with ether (3 x 50 ml). The combined ether extracts were washed with dilute hydrochloric acid (50 ml) and water (50 ml), dried and evaporated in vacuo to give an oil. Crystallisation from petrol gave 3ß-tosyloxy-5ß-cholestan-5-ol-6-one (4.1g, 61%), m.p. 144-145°C (lit.[55] 144-145°C).

39. 3ß-Tosyloxy-5ß-cholestane-5,6ß-diol (75)

Sodium borohydride (0.25g, 3 mol. equiv.) was added to a rapidly stirred suspension of 3ß-tosyloxy-5ß-cholestan-5-ol-6-one (1.0g) in methanol (50 ml) and ether (5 ml). Stirring was continued for thirty minutes, then the solution was diluted with water (200 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with dilute hydrochloric

acid (50 ml), aqueous sodium bicarbonate (50 ml) and water (50 ml), dried and evaporated *in vacuo*. Recrystallisation from methanol gave 3ß-tosyloxy-5ß-cholestane-5,6ß-diol (0.86g, 85%) m.p. 88°C, $[\alpha]_D$ + 19° (c=0.011 gl^{-1}), ν_{max} 3530 (OH), 1600 (C=C aromatic) cm^{-1}, δ 7.88 and 7.42 (ABq, 4H, tosyl aromatics), 4.97 (brd s, 1H, C3α-H, $W_{\frac{1}{2}}$ 7Hz), 3.53 (brd s, 1H, C6α-H, $W_{\frac{1}{2}}$ 6Hz), 2.64 (s, 2H,OH), 2.47 (s, 3H, tosyl methyl), 1.11 (s, 3H, C10ß-Me) and 0.68 (s, 3H, C13ß-Me).

The tosyloxy diol (75) was acetylated with acetic anhydride in pyridine overnight at room temperature to give 3ß-tosyloxy-6ß-acetoxy-5ß-cholestan-5-ol (76) m.p. 119-120°C dec. (methanol), ν_{max} 3620 (OH), 1630 (C=O, ester), 1600 (C=C, aromatic) cm^{-1}, and 1730 (C=O) cm^{-1}, 7.84 and 7.38 (ABq, 4H, tosyl aromatics), 4.94 (brd s, 1H, C3β-H), 4.76 (brd s, 1H, C6 -H), 2.47 (s, 3H tosyl methyl), 2.10 (s, 3H, OAc), 1.07 (s, 3H, C10β-Me), and 0.68 (s, 3H, C13β-Me). (Found: C, 69.9; H, 9.4. $C_{36}H_{56}O_6$ requires C, 70.1; H,9.1%).

40. Reaction of 3ß-tosyloxy-5ß-cholestane-5,6ß-diol with potassium t-butoxide in t-butanol

A solution of potassium t-butoxide (0.31g, 2 mol. equiv.) in deoxygenated t-butanol (30 ml) was added to a solution of 3ß-tosyloxy-5ß-cholestane-5,6ß-diol (0.8g) in deoxygenated t-butanol (80 ml). The solution was stirred at 55°C for sixteen hours under argon. Work up and preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave 3ß-methyl-A-nor-5ß-cholestan-5-ol-6-one (19) (0.23g, 45%), 6-hydroxy-4,5-secocholesta-3,6-dien-5-one (27) (0.019g, 3%), 5ß-hydroxy-4,5-secocholest-3-en -5-one (48) (0.031g, 5%), and a mixture of Δ^2 and Δ^3-5ß-cholestene-5,6ß-diol (77), (0.099g, 18%), a gum, ν_{max} 3450 (brd, OH), 1670 (C=C) cm^{-1}, δ 5.2-6.0 (m, olefinic protons), 3.69 (s, 1H C6α-H), 1.09 (s, 3H, C10ß-Me) and 0.68 (s, 3H, C13ß-Me). (Found: m/z 402.3484 ($M^{+\cdot}$). $C_{27}H_{46}O_2$ requires $M^{+\cdot}$ 402.3498).

Acetylation with acetic anhydride in pyridine gave Δ^2 and Δ^3-6ß-acetoxy-5ß-cholesten-5-ol (78), a gum, ν_{max} 3450 (brd OH), 1725 (C=O, ester) cm^{-1}, δ 5.2-6.0 (m, olefinic protons), 4.87 (s, 3H, C6α-H), 2.12 (s, 3H, OAc), 1.05 (s, 3H, C10ß-Me) and 0.68 (s, 3H, C13ß-Me).

41. 3ß-Tosyloxy-[6α-^{2}H]-5ß-cholestane-5,6ß-diol (79)

Sodium borodeuteride (0.21g, 2 mol. equiv.) was added to a solution of 3ß-tosyloxy-5ß-cholestan-5-ol-6-one (1.5g) in methanol (40 ml) and ether (10 ml). The solution was stirred for thirty minutes and worked up as before. Recrystallisation from methanol gave 3ß-tosyloxy-[6α-^{2}H]-5ß-cholestane-5,6ß-diol (1.2g 88%), m.p. 87-88°C

42. Reaction of 3ß-tosyloxy-[6α-^{2}H]-5ß-cholestane-5,6ß-diol with potassium t-butoxide in t-butanol

A solution of potassium t-butoxide (0.39g, 2 mol. equiv.) in deoxygenated t-butanol (30 ml) was added to a solution of 3ß-tosyloxy-[6α-^{2}H]-5ß-cholestane-5,6ß-diol (1.0g) in deoxygenated t-butanol (100 ml). The solution was stirred for sixteen hours at 55-65°C under argon. Work up and preparative thin layer chromatography [SiO_2, petrol:ether, 2:1, (v/v)] gave a band containing a mixture 3ß-methyl-A-nor-5ß-cholestan-5-ol-6-one(19) and 6-hydroxy-4,5-secocholesta-3,6-dien-5-one (27) (0.33g, 47%), 5ß-hydroxy-4,5-secocholest-3-en-5-one (48) (0.034g, 5%) and Δ^2 and Δ^3-[6α-^{2}H]-5ß-cholestene-5,6ß-diol (77) (0.092g, 13%).

Acetylation of the mixed band and preparative thin layer chromatography [SiO_2, petrol:ether, 3:1 (v/v)] gave 3ß-methyl-A-nor-5ß-cholestan-5-ol-6-one (19) (0.187g, 26%) and 6-acetoxy-4,5-secocholesta-3,6-dien-5-one (51) (0.093g, 12%).

43. Cyclisation of 5ß-hydroxy-4,5-secocholest-3-en-5-one

A solution of 5ß-hydroxy-4,5-secocholest-3-en-5-one (0.40g) in decalin (5 ml) was heated under argon in a sealed tube for five and a half hours at 200°C. The decalin was removed in vacuo. Preparative thin layer chromato-

graphy [SiO_2, petrol:ether, 2:1 (v/v)] gave 5ß-cholestan-5-ol-6-one (0.0528g 13%), m.p. 104-105°C (methanol) (lit.[56] m.p. 102-103°C) and 3-methyl-B-nor-5ß-cholest-2-en-4-one (0.102g, 26%) m.p. 83-84°C (methanol), $[\alpha]_D$ + 146° (c=0.00626 gl^{-1}), ν_{max} 1665 (C=O) cm^{-1}, λ_{max} 240 nm (ε 9820), δ 6.50 (m, 1H, RC<u>H</u>=CMe-C=O, $W_{\frac{1}{2}}$ 10 Hz, collapses to quartet, J 3 and 6 Hz on irradiating at δ 1.80 ppm), 1.80 (brd s, 3H, RCH=C<u>Me</u>-C=O, collapses to double doublet J 1.2 & 2.4Hz, on irradiating at δ 6.50), 0.96 (s, 3H, C10ß-Me) and 0.65 (s, 3H, C13ß-Me). (Found: m/z 384.3363 ($M^{+\cdot}$) $C_{27}H_{44}O$ requires $M^{+\cdot}$ 384.3392). (Found: C, 84.3; H, 11.9. $C_{27}H_{44}O$ requires C, 84.3; H, 11.5%).

44. <u>Thermal rearrangement of 3ß-methyl-A-nor-5ß-cholestan-5-ol-6-one</u>

A solution of 3ß-methyl-A-nor-5ß-cholestan-5-ol-6-one (0.188g) in decalin (5 ml) was heated in a sealed tube under argon at 200°C for five and a half hours. The decalin was removed <u>in vacuo</u> and preaparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave unchanged starting material (0.097g, 57%) and 3-methyl-B-nor-5ß-cholest-2-en-4-one (82) (0.025g, 15%).

45. <u>Acid catalysed rearrangement of 3ß-methyl-A-nor-5ß-cholestan-5-ol-6-one</u>

<u>p</u>-Toluene sulphonic acid (0.01g) was added to a solution of 3ß-methyl-A-nor-5ß-cholestan-5-ol-6-one (0.180g) in benzene (30 ml). The solution was heated at reflux overnight then washed with aqueous sodium bicarbonate (5 ml) and water (5 ml), dried and evaporated <u>in vacuo</u>. Preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave 3-methyl-A-nor-cholest-3-en-6-one (0.058g, 32%), m.p. 80-81°C (methanol), $[\alpha]_D$ + 56° (c=0.00745 gl^{-1}), ν_{max} 1680 (C=O), 1625 (C=C) cm^{-1}, λ_{max} 260 nm (ε 11,500), δ 2.04 (s, 3H, C3-Me), 0.98 (s, 3H, C10ß-Me) and 0.71 (s, 3H, C13ß-Me). (Found: m/z 384.3390 ($M^{+\cdot}$). $C_{27}H_{44}O$ requires $M^{+\cdot}$ 384.3391) (Found: C, 84.4; H, 11.5. $C_{27}H_{44}O$ requires C, 84.3; H, 11.5%). and 3-methyl-B- nor-5ß-cholest-2 -en-4-one (82) (0.089g, 49%).

46. Deuteration of 3-methyl-B-nor-5ß-cholest-2-en-4-one

A solution of 3-methyl-B-nor-5ß-cholest-2-en-4-one (0.0364g) in dioxane (2 ml) was added to a solution of sodium (0.07g) in deuterium oxide (3 ml) and dioxane (4 ml). The solution was heated under reflux for twenty seven hours under nitrogen, then diluted with ether (50 ml) and washed with water (15 ml). The ether was dried and evaporated in vacuo to give an oil which, on crystallisation from methanol, gave [1α,1ß,5ß,-^{2}H]-3-methyl-B-nor-cholest-2-en-4-one, δ 6.50 (m, 1H, RC<u>H</u>=CMe-C=O, $W_{\frac{1}{2}}$ 5Hz, collapses to singlet on irradiating at δ 1.80), 1.80 (d, 3H, RCH=C<u>M</u>e-C=O, collapses to singlet on irradiating at δ 6.50). (Found: m/z 387.3583 ($M^{+\cdot}$). $C_{27}H_{41}D_3O$ requires $M^{+\cdot}$ 387.355).

47. 5α-Cholestan-5-ol-6-one (83)

Zinc (3.4g, 10 mol. equiv.) and sodium iodide (3.5g, 5 mol. equiv.) were added to a solution of 3ß-tosyloxy-5α-cholestan-5-ol-6-one (3.0g) in dimethoxyethane (40 ml). The mixture was heated under reflux for two and a half hours, then diluted with ether (50 ml) washed with dilute hydrochloric (25 ml), aqueous sodium bicarbonate (25 ml) and water (25 ml), dried and evaporated in vacuo. Recrystallisation (x2) from methanol gave 5α-cholestan-5-ol-6-one (1.4g, 66%), m.p. 151-153°C (lit.[56] m.p. 153°C).

48. 5ß-Cholestan-5-ol-6-one (81)

A solution of 5α-cholestan-5-ol-6-one (0.2g) in methanolic potassium hydroxide (10%, 30 ml) was heated under reflux for ten hours. The solution was diluted with water (100 ml) and extracted with ether (3 x 25 ml). The combined extracts were washed with dilute hydrochloric acid (25 ml) and water (25 ml), dried and evaporated in vacuo to give an oil. Flash column chromatography [SiO_2, petrol:ether, 9:1 (v/v)] gave 5ß-cholestan-5-ol-6-one (0.18g, 90%) m.p. 104-105°C (methanol, acetone) (lit.[56] m.p. 102-103°C).

49. Attempted reductive radical cyclisation of 6-hydroxy-4,5-secocholesta-3,6-dien-5-one

A solution of 6-hydroxy-4,5-secocholesta-3,6-dien-5-one (0.075g) in THF (25 ml) was stirred with sodium (0.043g) under nitrogen for three days. The solution was filtered and diluted with ether (50 ml). The etheral solution was washed with dilute hydrochloric acid (25 ml), aqueous sodium bicarbonate (25 ml) and water (25 ml), dried and evaporated in vacuo to unchanged starting material (0.059g, 79%).

50. 6ß-Acetoxy-4,5-secocholest-3-en-5ξ-ol (99)

Sodium borohydride (0.24g, 4 mol. equiv.) was added to a solution of 6ß-acetoxy-4,5-secocholest-3-en-5-one (0.74g) in ethanol (40 ml) and ether (5 ml) at 0°C. Stirring was continued for ten minutes then the solution was diluted with water (100 ml) and extracted with ether (3 x 50ml). The combined ether extracts were washed with dilute hydrochloric acid (50 ml) and brine (50 ml), dried and evaporated in vacuo. Preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave 6ß-acetoxy-4,5-seco-cholest-3-en- 5ξ-ol (0.61g, 82%), an oil, $[\alpha]_D$ -1.9° (c=0.01068 gl^{-1}), ν_{max} 3480 (OH), 3080 ($RCH=CH_2$), 1720 (C=O, ester) 1640 ($RCH=CH_2$) cm^{-1}, δ 5.6-6.1 (m, 1 $RC\underline{H}=CH_2$), 5.25 (m, 1H, C6α-H, $W_{\frac{1}{2}}$, 8 Hz), 4.85-5.2 (m, 2H, $RCH=C\underline{H}_2$), 3.55 (d, 1H, C5-H, J 4Hz), 2.12 (s, 3H, OAc), 0.97 (s, 3H, C10ß-Me) and 0.72 (s, 3H, C13ß-Me) (Found: m/z 386.3537 ($M^+ - CH_3CO_2H$) requires 386.3548).

51. 5ξ-Mesyloxy-6ß-acetoxy-4,5-secocholest-3-ene (100)

6ß-Acetoxy-4,5-secocholest-3-en-5ξ-ol (0.6g) and methane sulphonyl chloride (0.7g) were dissolved in pyridine (30 ml) and allowed to stand at room temperature overnight. The reaction mixture was poured over ice and extracted with ether (3 x 25 ml). The combined ether extracts were washed with dilute hydrochloric acid (25 ml), aqueous sodium bicarbonate (25 ml) and water (25 ml), dried and evaporated in vacuo to give an oil. Prepara-

tive thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave 5ξ-mesyloxy-6ß-acetoxy-4,5-secocholest-3-ene (0.466g, 66%), an oil, $[\alpha]_D$ -0.2° (c=0.01267 gl^{-1}) ν_{max} 3080 ($RCH=CH_2$), 1730 (C=O, acetate), 1640 ($RCH=CH_2$) cm^{-1}, δ 5.6-6.1 (m, 1H, $RC\underline{H}=CH_2$), 5.65 (m, H, 6α-H, $W_{\frac{1}{2}}$ 9Hz), 4.85-5.2 (m, 2H, $RCH=C\underline{H}_2$), 4.65 (d, 1H, C5-H, J 4Hz), 3.05 (s, 3H, $-SO_2$-Me), 2.14 (s, 3H, OAc), 1.05 (s, 3H, C10ß-Me) and 0.70 (s, 3H, C13ß-Me) (Found: m/z 428.3671 (M $-CH_3SO_3H$) requires 428.365).

52. Attempted reductive radical cyclisation of 5ξ-mesyloxy-6ß-acetoxy-4,5-secocholest-3-ene

Zinc (0.48g, 10 mol. equiv.) and sodium iodide (0.57g, 5 mol. equiv.) were added to a solution of 5ξ-mesyloxy-6ß-acetoxy-4,5-secocholest-3-ene (0.4g) in dimethoxyethane (25 ml). The mixture was heated under reflux for two hours, then filtered and diluted with ether (25 ml). The ether solution was washed with dilute hydrochloric acid (25 ml), aqueous sodium bicarbonate (25 ml) and water (25 ml), dried and evaporated in vacuo to yield unchanged starting material (0.230g).

Treatment of the recovered material, as above, for two weeks gave an oil (0.0538g) containing several components (t.l.c.).

Part II

53. 1-(Trimethylsilyloxy)-3-methyl-3-(3-butenyl)-cyclohex-1-ene (103)

To a stirred suspension of copper (I) iodide (0.6 mol. equiv.) in T.H.F. (50 ml) at -40°C under an argon atmosphere was added a solution of methyl lithium (17.8 ml, 0.55 mol. equiv.) in ether. The yellow suspension of methyl copper was allowed to warm to 0°C (∿ 15 minutes), it was then cooled to -40°C and a solution of 3-butenyl magnesium bromide* (1.2 mol. equiv.) in ether was added. The solution was stirred for a further thirty minutes, at which time 3-methyl-2-cyclohexen-1-one (6.0g, 1.0 mol. equiv.) in T.H.F. (20 ml) was added. The solution was allowed to warm to room temperature and stirring continued for a further two hours.

Trimethylsilyl chloride (12.6g, 2.2 mol. equiv.) in triethylamine (40 ml) was added and the solution stirred for sixty minutes. The reaction mixture was diluted with petrol (100 ml) and washed with aqueous ammonium chloride (2 x 50 ml), aqueous sodium bicarbonate (50 ml), dried and evaporated in vacuo to give a green liquid (14.3g). Distillation gave the pure silylenolether (103) (10.6g, 82%) b.p. 110-115°C (1.5 mm Hg), $\nu_{max.}$ 3080 ($RCH=CH_2$), 1660 ($C=C-OSiMe_3$), 1640 ($RCH=CH_2$) cm^{-1}, δ 5.4-5.9 (m, 1H, $RC\underline{H}=CH_2$) 4.85-5.0 (m, 2H, $RCH=C\underline{H_2}$) 4.50 (s, 1H, $C\underline{H}=CR-OSiMe_3$) 0.95 (s, 3H, Me) 0.18 (s, 9H, $OSiMe_3$). (Found: m/z 238.1768 ($M^{+\cdot}$). $C_{14}H_{26}OSi$ requires $M^{+\cdot}$ 238.1753).

* 3-butenyl bromide (8.8g, 1.2 mol. equiv.) in ether (20 ml) was added dropwise to a suspension of magnesium (1.6g, 1.2 mol. equiv.) at a rate maintaining a gentle reflux. Stirring was continued for a further one hour to ensure complete reaction.

54. Cis and trans 3-methyl-3-(3-butenyl)-2-hydroxy-cyclohexan-1-one (105) (106)

To a solution of 1-(trimethylsilyloxy)-3-methyl-3-(3-butenyl)-cyclohex-1-ene (13.4g) in ether (150 ml) was added sodium hydrogen carbonate (7.2g, 2 mol. equiv.) and m-chloroperbenzoic acid (12.8g, 1 mol. equiv.). The mixture was stirred for five hours and then filtered. The filtrate was washed with aqueous sodium sulphite (50 ml), aqueous sodium bicarbonate (50 ml) and water (50 ml), dried and evaporated in vacuo to give a white solid (17.4g).

The solid was dissolved in hot hexane (60 ml), then the hexane solution was cooled to 0°C. The crystallised m-chlorobenzoate ester (115) was filtered off and the filtrate evaporated in vacuo to give the crude α-silyloxy ketones (11.5g, 80%).

The α-silyloxy ketones were dissolved in ethanol (90 ml) and hydrochloric acid (2M, 20 ml) and stirred at room temperature for forty minutes. The solution was diluted with brine (200 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with aqueous sodium bicarbonate (50 ml) and water (50 ml), dried and evaporated in vacuo. Distillation under reduced pressure gave the isomeric acyloins (6.5g, 63%) (100-145°C, 2mm Hg).

Flash column chromatography [SiO_2, petrol:ether, 8:1 (v/v)] gave 3-methyl-3-(3-butenyl)-cyclohexan-1-one (102) (0.86g, 8%), $\nu_{max.}$ 3080 ($RCH=CH_2$) 1715 (C=O) 1640 ($RCH=CH_2$) cm^{-1} (lit. ref.[65]).

Trans-3-methyl-r-3-(3-butenyl)-2-hydroxy-cyclohexan-1-one (105)(1.18g, 12%), $\nu_{max.}$ 3485 (OH), 3075 (RCH=CH), 1710 (C=O), 1640 ($R\underline{C}H=CH_2$) cm^{-1}, 5.65-6.13 (m,1H,$R\underline{C}H=CH_2$), 4.9-5.2 (m,2H,$RCH=C\underline{H}_2$) 4.0 (s,1H, C2-H) 3.60 (brd s, 1H,OH, D_2O exchangeable) 0.74 (s,3H,Me). (Found: m/z 182.1306 ($M^{+\cdot}$) $C_{11}H_{18}O_2$ requires $M^{+\cdot}$ 182.1307), Oxime m.p. 132-134°C (petrol, ether). (Found: C, 67.0; H, 9.9; N, 7.1. $C_{11}H_{19}NO_2$ requires C, 67.0; H, 9.7; N, 7.1%).

A fraction containing a mixture of isomers (1.38g, 13%) and cis-3-methyl-r-3-(butenyl)-2-hydroxy-cyclohex-1-one (106) (0.96g, 9%), $\nu_{max.}$ 3490 (OH), 3075 ($RCH=CH_2$), 1708 (C=O), 1640 ($RCH=CH_2$) cm^{-1}, δ 5.59 - 6.05(m, 1H, $RCH=CH_2$), 4.85 - 5.2 (m, 2H, $RCH=CH_2$), 3.95 (s, 1H, C2-H), 3.78 (brd s, 1H, OH, D_2O exchangeable), 1.14 (s, 3H, Me). (Found: m/z 182.1304 ($M^{+}\cdot$). $C_{11}H_{18}O_2$ requires $M^{+}\cdot$ 182.1307). Oxime m.p. 135-136°C (petrol, ether). (Found: C, 67.1; H, 9.98; N, 7.0. $C_{11}H_{19}NO_2$ requires C, 67.0; H, 9.7; N, 7.1%). 2,4-dinitrophenylosazone m.p. 193-194°C (methanol). (Found: C, 51.3; H, 4.3; N, 20.9. $C_{23}H_{24}O_8N_8$ requires C, 51.1; H, 4.5; N, 20.7%).

55. Attempted cyclisation of 3-methyl-3-(3-butenyl)-2-hydroxy-cyclohexan-1-one with potassium t-butoxide in t-butanol

The acyloins (105),(106) (0.4g) were added to a deoxygenated solution of potassium t-butoxide (2 mol. equiv.) in t-butanol (40 ml).

The solution was stirred at 50°C under an argon atmosphere for 4 hours, then diluted water (100 ml), neutralised with hydrochloric acid (2M) and extracted with ether (3 x 25 ml). The combined ether extracts were washed with water (2 x 25 ml), dried and evaporated in vacuo to give unchanged starting material (0.39g).

56. Cyclisation of 3-methyl-3-(3-butenyl)-2-hydroxy-cyclohexan-1-one in decalin

A solution of the acyloins (105),(106) (1.7g) in decalin (15 ml) was heated under reflux for 24 hours under an argon atmosphere. The solution was flash chromatographed [SiO_2, petrol to remove the decalin, then petrol: ether, 8:1 (v/v)] to give 3β,7aβ-dimethyl-3aβ-hydroxy-octahydro-4H-inden-4-one (109) (0.32g, 19%). Further purification by preparative thin layer chromatography [SiO_2, petrol:ether, 3:1 (v/v)] gave pure (109) (0.150g, 9%), $\nu_{max.}$ 3495 (OH), 1700 (C=O) cm^{-1}, δ 3.7 (s, 1H, OH, D_2O exchangeable), 0.99 (s, 3H, C7a-Me), 0.81 (d, 3H, C3-Me, J 7Hz).

(Found: m/z 182.1307 ($M^{+}\cdot$). $C_{11}H_{18}O_2$ requires $M^{+}\cdot$ 182.1307). Oxime m.p. 103-104°C (petrol:ether). (Found: C, 66.7; H, 9.8; N, 7.0. $C_{11}H_{19}NO_2$ requires C, 67.0; H, 9.7; N, 7.1%).

A second column fraction, 5β,7aβ-dimethyl-3aβ-hydroxy-octahydro-4H-inden-4-one (110) (0.55g, 32%). Further purification by preparative thin layer chromatography [SiO_2, petrol:ether 3:1 (v/v)] gave pure (110) (0.318g, 19%), $\nu_{max.}$ 3495 (OH), 1695 (C=O)cm^{-1}, δ 4.02 (s, 1H, OH, D_2O exchangeable), 1.05 (d, 3H, C5-Me, J 7Hz) and 0.92 (s, 3H, C7a-Me). (Found: m/z 182.1303 ($M^{+}\cdot$). $C_{11}H_{18}O_2$ requires $M^{+}\cdot$ 182.1307). Oxime, m.p. 175-176°C (petrol;ether) (Found: C, 67.0; H, 10.0; N, 7.2%. $C_{11}H_{19}NO_2$ requires C, 67.0; H, 9.7; N, 7.1%).

The final column fraction (0.44g, 26%) contained a mixture. Preparative thin layer chromatography [SiO_2, petrol:ether, 3:1 (v/v)] gave an unidentified cyclisation product (111) (0.08g, 5%) $\nu_{max.}$ 3495 (OH), 1712 (C=O) cm^{-1}, δ 3.88 (s, OH) and 1.07 (s, 3H, Me). (Found: m/z 182.1307($M^{+}\cdot$). $C_{11}H_{18}O_2$ requires $M^{+}\cdot$182.1307) and unchanged starting material (0.138g, 8%).

57. 3β,7âβ-Dimethyl-3aβ,4β-dihydroxy-octahydro-4H-indene (119)

The ketol (109) (140 mg) was dissolved in methanol (10 ml) and sodium borohydride (3 mol. equiv.) was added at with stirring. After ten minutes at room temperature the solution was diluted with water (75 ml) and extracted with ether (3 x 25 ml). The combined ether extracts were washed with water (25 ml), dried and evaporated in vacuo to give a semi-crystalline gum (0.118g, 84%). Flash chromatography [SiO_2, petrol:ether, 8:1 (v/v)] gave the diol (119) (0.70g, 50%), m.p. 94-96°C (hexane), $\nu_{max.}$ 3350 (brd, OH) cm^{-1}, δ 3.74 (m, 1H, C4β-H, $W_{\frac{1}{2}}$ 10Hz), 1.08 (d, 3H, C3β-Me, J 7Hz) 1.0 (s, 3H, C7aβ-Me). (Found: m/z 184.1470 ($M^{+}\cdot$). $C_{11}H_{20}O_2$ requires $M^{+}\cdot$ 184.1463).

58. 5β,7aβ-Dimethyl-3aβ,4β-dihydroxy-octahydro-4H-indene (120)

The ketol (110) (0.170g) was treated as above to give the crude diol (0.140g) (82%). Flash chromatography [SiO_2, petrol:ether, 8:1 (v/v)] gave the diol (120) (0.097g, 57%), m.p. 95-96°C (hexane), $\nu_{max.}$ 3500, 3460 (OH) cm^{-1}, 3.58 (brd s, 1H, C4α-H, $W_{\frac{1}{2}}$, 4Hz), 2.54 (brd s, 1H, OH, D_2O exchangeable), 2.31 (brd s, 1H, OH, D_2O exchangeable), 1.07 (s, 3H, C7aβ-Me), 1.0 (d, 3H, C5β-Me, J 6.5 Hz). (Found: m/z 184.1455 ($M^{+\cdot}$). $C_{11}H_{20}O_2$ requires $M^{+\cdot}$ 184.1463). (Found: C, 72.1; H, 11.2. $C_{11}H_{20}O_2$ requires C, 71.7; H, 10.9%).

59. Cyclisation of 3-methyl-3-(3-butenyl)-2-hydroxy-cyclohexan-1-one in decalin with product dehydration

A solution of the acyloins (105), (106) (3.0g) in decalin (15 ml) was heated under reflux for twentyfour hours under argon. The solution became cloudy and water droplets appeared in the condenser. Flash column chromatography [SiO_2, petrol to remove the decalin, then petrol:ether, 8:1 (v/v)] gave a fraction containing a mixture of enones (121) and (122) (1.25g, 46%) and starting material (1.1g, 37%).

The enones were purified by preparative thin layer chromatography [SiO_2, petrol:ether, 3:1 (v/v)] to give 5,7a-dimethyl-1,2,3,3a,7,7a-hexahydro-4H-inden-4-one (121) (0.540g, 20%), $\nu_{max.}$ 1665 (C=O) cm^{-1}, δ 6.47 (m, 1H, RCH=CMe-C=O), 1.78 (brd s, 3H, RCH=CMeC=O), 1.10 (s, 3H, C7a-Me). (Found: m/z 164.1202 ($M^{+\cdot}$). $C_{11}H_{16}O$ requires $M^{+\cdot}$ 164.1201) and an unidentified enone (122) (0.131g, 5%), $\nu_{max.}$ 1685 (C=O), 1620 (C=C) cm^{-1}, δ 6.35 (t, RCH=CR-C=O, J 3Hz), 1.04 (s, 3H, methyl).

Part III

60. Attempted conjugate addition of allyl magnesium bromide to cholest-4-ene-3-one

To a suspension of magnesium (0.34g, 3 mol. equiv.) in ether (50 ml) was added a solution of allyl bromide (1.7g, 3 mol. equiv.) in ether (20 ml) at a rate maintaining a steady reflux. After addition was complete, the solution was stirred for a further hour then cooled to -30°C. Copper (I) iodide (0.53g, 0.6 mol. equiv.) was added. Stirring was continued for a further fifteen minutes and then a solution of cholestenone (2.0g) in ether (20 m l) was added. The solution was allowed to warm to room temperature and stir for eighteen hours, it was then washed with aqueous ammonium chloride (25 ml), aqueous sodium bicarbonate (25 ml) and water (25 ml), dried and evaporated in vacuo. Recrystallisation from methanol gave 3α-(2-propenyl)-3ß-hydroxy-cholest-4-ene (130)(1.12g, 56%) m.p. 67-68°C, $[\alpha]_D$ + 82° (c=0.01296 gl^{-1}); ν_{max} 3300 (OH, broad), 3075 ($RCH=CH_2$), 1640 ($RCH=CH_2$) cm^{-1}, δ 5.75-6.25 (m, 1H,$RC\underline{H}=CH_2$) 5.27 (s, 1H, C4-H), 5.24 (m, 2H, $RCH=C\underline{H}_2$), 1.06 (s, 3H, C10ß-Me) 0.69 (s, 3H,C13ß-Me) (Found: m/z 408.3764 ($M-H_2O$) requires 408.3756) (Found: C, 84.5; H, 12.2. $C_{30}H_{50}O$ requires C, 84.4; H, 11.8%).

61. Attempted conjugate addition of propargyl magnesium bromide to cholest-4-en-3-one

To a suspension of magnesium (0.42g, 4.2 mol. equiv.) in ether (20 ml) activated with a catalytic quantity of mercuric chloride, was added propargyl bromide (2.6g, 80% toluene solution, 4 mol. equiv.) in ether (30 ml) at a rate maintaining a steady reflux. Stirring was continued for a further hour, then the solution was cooled to -30°C and copper iodide (0.32g, 0.4 mol. equiv.) was added. Stirring was continued for a further fifteen minutes then a solution of cholestenone (1.6g) in ether (30 ml) was

added dropwise. The solution was allowed to warm to room temperature and then it was stirred overnight. Work-up as above gave 3α-(2-propynyl)-3ß-hydroxy-cholest-4-ene (131) (1.34g, 74%), m.p. 84-85°C (methanol), $[\alpha]_D$ + 73° (c=0.0614 g^{-1}), ν_{max} 3310 (brd, OH, RC≡CH), 2125 (C≡C), 1630 (C=C) cm^{-1}, δ 5.33 (s, 1H, C4-H), 2.49 (d, 2H, $RC\underline{H}_2C{\equiv}CH$ J 3Hz) 2.11 (t, 1H, $RCH_2C{\equiv}C\underline{H}$), 1.09 (s, 3H, C10ß-Me) 0.61 (s, 3H, C13ß-Me) (Found: m/z 424.3647 ($M^{+\cdot}$). $C_{30}H_{48}O$ requires $M^{+\cdot}$ 424.3705. (Found: C,84.9; H 11.9. $C_{30}H_{48}O$ requires C, 84.4; H, 11.4%).

62. Attempted conjugate addition of trimethylallylsilane to cholestenone

Titanium tetrachloride (0.55g,0.95 ml,1.1 mol. equiv.) was added to a solution of cholestenone (1.0g) and trimethylallylsilane (0.39g, 1.4 mol. equiv.) in dichloromethane (30 ml) at -78°C. The solution was allowed to warm to room temperature and then stir for twentyfour hours. The dichloromethane was washed with water (10 ml), aqueous sodium bicarbonate (10 ml) and water (10 ml), dried and evaporated in vacuo to give unchanged starting material (1.1g).

63. 3α-(2-Propenyl)-3ß-hydroxy-cholest-4-ene (130)

A solution of allyl bromide (1.89g, 3 mol. equiv.) in ether (10 ml) was added dropwise to a suspension of magnesium (1.25g, 10 mol. equiv.) in ether (40 ml) at a rate maintaining a gentle reflux. Stirring was continued for a further one hour, then a solution of cholestenone (2.0g) in ether (20 ml) was added. The mixture was left stirring overnight and then filtered. The filtrate was washed with aqueous ammonium chloride (15 ml), aqueous sodium bicarbonate (15 ml) and water (15 ml), dried and evaporated in vacuo. Recrystallisation from methanol gave 3α-(2-propenyl)-3ß-hydroxy-cholest-4-ene (130) (1.52g, 68.%).

64. General method for the attempted oxy-Cope rearrangement of 3α-(2-propenyl)-3ß-hydroxy-cholest-4-ene

The allyl-alcohol (130) (0.5g) was added to a suspension of sodium hydride (0.28g, 50% oil dispersion, 5 mol. equiv.) in dry T.H.F. (30 ml). The mixture was heated under reflux (followed by t.l.c.), then diluted with ether (50 ml) and washed with hydrochloric acid (0.5M, 20 ml), aqueous sodium bicarbonate (20 ml) and water (20 ml), dried and evaporated in vacuo to give an oil (0.48g). The product was identified by its ^{1}H n.m.r. and infrared spectra.

65. Cholest-4-en-3ß-ol (139)

Sodium borohydride (0.6g, 1 mol. equiv.) was added to a solution of cholestenone (6.0g) and cerium (III) chloride (3.8g, 1 mol. equiv.) in methanol (150 ml) in small portions. The solution was stirred for thirty minutes at room temperature and then diluted with water (300 ml) and extracted with ether (3 x 100 ml). The combined ether extracts were washed with water (2 x 75 ml), dried and evaporated in vacuo. Recrystallisation from methanol gave cholest-4-en-3ß-ol (139) (4.4g, 73%), m.p. 131-132°C, (lit.[84] m.p. 131-132°C).

66. 3ß-Vinyloxy-cholest-4-ene (137)

To a refluxing solution of cholest-4-en-3ß-ol (5.6g) in ethyl vinyl ether (60 ml) was added mercury (II) acetate (~2.0g) in portions over twentyfour hours. The solution was diluted with ether (40 ml) and washed with aqueous sodium carbonate (25 ml) and water (25 ml), dried and evaporated in vacuo to give an oil. Flash chromatography [SiO_2, petrol] and recrystallisation from ethanol gave 3ß-vinyloxy-cholest-4-ene (137) (3.8g, 64%), m.p. 56-57%, (lit.[82] m.p. 56-57°C).

67. Δ^3,5ß-Cholestenylacetaldehyde (138)

3ß-Vinyloxy-cholest-4-ene (3.6g) was dissolved in decalin (30 ml) and heated under reflux under argon for four hours. The decalin was removed in vacuo and the product recrystallised from ethanol to give the aldehyde (138) (2.2g, 61%), m.p. 64-67°C (lit. m.p.[82] 66-69°C).

68. 5-(2,2-Dimethoxy-ethyl)-5β-cholest-3-ene (140)

The aldehyde (138) (1.7g) and trimethylorthoformate (1 .7g) were dissolved in methanol (100 ml). A catalytic amount of p-toluenesulphonic acid was added and the solution stirred for one and a quarter hours at room temperature. The reaction mixture was diluted with water (200 ml) and extracted with ether (3 x 75 ml). The combined ether extracts were washed with water (75 ml), dried and evaporated in vacuo to give a white solid (1.8g). Recrystallisation from acetone gave the dimethylacetal (140) (1.3g, 68%), m.p. 118-119°C, $[\alpha]_D$ + 85° (c=0.01135 gl^{-1}), δ 5.30-5.85 (m, 2H, C3-H & C4-H), 4.55 (q, 1H, $RCH_2\underline{CH}(OMe)_2$ J 4Hz) 3.29 (d, 6H, OMe) 0.84 (s, 3H, C10ß-Me) 0.65 (s, 3H, C13ß-Me). (Found: m/z 458.4149 ($M^{+\cdot}$). $C_{31}H_{54}O_2$ requires $M^{+\cdot}$ 458.4123). (Found: C, 81.0; H, 11.8. $C_{31}H_{54}O_2$ requires C, 81.2; H, 11.7%).

69. 5-(2,2-Dimethoxy-ethyl)-5β-cholest-3-en-2-one (141)

3,5-Dimethyl-pyrazole (15.4g, 21 mol. equiv.) was added to a solution of chromium trioxide (15.3g, 20 mol. equiv.) in dry dichloromethane at -20°C. The complex was allowed to form over fifteen minutes and then the acetal (140) (3.5g) was added. Stirring was continued for a further 6 hours keeping the temperature at -20°C. Sodium hydroxide (4N, 200 ml) was added and the solution was allowed to warm to room temperature over fifty minutes. The layers were separated and the aqueous layer was re-extracted with dichloromethane (100 ml). The combined dichloromethane extracts were washed with dilute hydrochloric acid (2M, 2 x 100 ml) and water (100 ml), dried and evaporated in vacuo to give off a white oily solid. Flash chromatography [SiO_2, petrol:ether 6:1 (v/v)] gave the enone (1.8g, 50%), m.p. 110°C (methanol), $[\alpha]_D$ + 53° (c=0.00824 gl^{-1}), ν_{max} 1680 (C=O) cm^{-1}, δ 6.73 and 6.05 (ABq, 2H, C3-H and C4-H, J 10Hz), 4.57 (t, 1H, $RCH_2\underline{CH}(OMe)_2$, J 6Hz), 3.32 (d, 6H, OMe), 2.49 (brd s, 2H, C1-H), 1.01 (s, 3H, C10ß-Me), 0.65 (s, 3H, C13ß-Me). (Found: m/z 440.3657 ($M-CH_3OH$) requires 440.3654). (Found: C,78.9; H, 11.1. $C_{31}H_{52}O_3$ requires C 78.8; H, 11.0%).

70. Hydrolysis of 5-(2,2-dimethoxy-ethyl)-5β-cholest-3-ene

The acetal (140) (0.098g) was dissolved in T.H.F. (30 ml) and perchloric acid (5 ml, 30%) and stirred for five hours under argon. The solution was diluted with ether (60 ml) and washed with aqueous sodium bicarbonate (30 ml) and water (30 ml) dried and evaporated in vacuo to give the aldehyde (138) (0.72g).

71. Attempted hydrolysis of 5-(2,2-dimethoxy-ethyl)cholest-3-en-2-one

The enone acetal (141) (0.23g) was dissolved in T.H.F. (30 ml) and perchloric acid (5 ml, 30.%) and stirred for two hours under argon. The solution was diluted with ether (60 ml), washed with aqueous sodium bicarbonate (30 ml) and water (30 ml), dried and evaporated in vacuo to give an oil (0.22g). Preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave the lactol (142) (0.102g, 46%) m.p. 122-124°C (methanol) $[\alpha]_D$ + 51° (c=0.0038gl^{-1}), ν_{max} (KBr) 3400 (brd, OH) 1710 (brd, C=O) cm^{-1}, δ 5.77 (q, 1H, $RCH_2\underline{C}H(OH)(OR)$, J 6Hz), 4.52 (t, 1H, C4α-H, J 8Hz), 1.05 (s, 3H, C10ß-Me), 0.65 (s, 3H, C13ß-Me). (Found: m/z 444.3598 ($M^{+\cdot}$). $C_{29}H_{48}O_3$ requires $M^{+\cdot}$ 444.3603.).

The lactol (0.3g) was dissolved in dichloromethane (50 ml) and pyridinium chlorochromate (0.3g, 2 mol. equiv.) was added. The solution was stirred at room temperature for two and a quarter hours, then washed with dilute hydrochloric acid (2M, 20 ml), aqueous sodium bicarbonate (20 ml) and water (20 ml), dried and evaporated in vacuo to give a brown oil (0.26g). Preparative thin layer chromatography [SiO_2, petrol:ether, 3:1 (v/v)] gave the lactone (143) (0.05g, 17%), m.p. 165-166°C (methanol), $[\alpha]_D$ + 92° (c=0.00789 gl^{-1}), ν_{max} 1780 (C=O, lactone), 1720 (C=O, ketone) cm^{-1}, δ 5.00 (t, 1H, C4α-H, J 8Hz), 1.07 (s, 3H, C10ß-Me), 0.67 (s, 3H, C13ß-Me). (Found: m/z 442.3442 ($M^{+\cdot}$). $C_{29}H_{46}O_3$ requires $M^{+\cdot}$ 442.3447). (Found: C, 79.1; H, 10.4. $C_{29}H_{46}O_3$ requires C, 78.7; H, 10.5%).

72. 4ß,5-Epoxy-5ß-cholestan-3-one (144)

To a solution of cholestenone (5.0g) in methanol (250 ml) and ether (80 ml) at 0°C was added hydrogen peroxide (30%, 15 ml) and sodium hydroxide (4N, 10 ml). The solution was allowed to warm to room temperature and stir for five hours. It was then diluted with brine (300 ml) and extracted with ether (3 x 100 ml). The combined ether extracts were washed with water (2 x 100 ml), dried and evaporated in vacuo. Recrystallisation from methanol-chloroform gave the epoxy-ketone (144) (3.1g, 60%), m.p. 115-117°C (lit.[86] 115-117°C).

73. 2α-Hydroxy-cholest-4-en-3-one (145)

4ß,5-epoxy-5ß-cholestan-3-one (3.1g) was dissolved in acetone (120 ml), water (6 ml) and concentrated sulphuric acid (2 ml) and heated under reflux for five hours. The reaction mixture was poured over ice and the precipitated product filtered off. The damp product was taken up into ether (100 ml) and washed with water (50 ml). The ether was dried and evaporated in vacuo to give an off white crystalline solid. Flash chromatography [SiO_2, petrol: ether, 4:1 (v/v)] gave 2α-hydroxy-cholest-4-en-3-one (145) (2.1g, 68%).

74. 2α-Acetoxy-cholest-4-en-3-one (146)

2α-Hydroxy-cholest-4-en-3-one (2.1g) was acetylated overnight with acetic anhydride (5 ml) in pyridine (20 ml). The usual work up and recrystallisation from methanol gave 2α-acetoxy-cholest-4-en-3-one (146) (1.7g, 81%), m.p. 139-141°C (lit.[86b] m.p. 140-141°C).

75. 2α-Acetoxy-cholest-4-en-3ß-ol (147)

2α-Acetoxy-cholest-4-en-3-one (2.0g) and cerium (III) chloride heptahydrate (1.7g, 1 mol. equiv.) were dissolved in methanol (80 ml). Sodium borohydride (0.35g, 2 mol. equiv.) was added with rapid stirring at 0°C. The solution was stirred for a further three minutes then diluted with water (150 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with water (50 ml) and evaporated in vacuo to give a white solid (2.0g). Recrystallisation from methanol gave 2α-acetoxy-cholest-4-en-3ß-ol (147) (1.5g, 75%), m.p. 105-107°C (lit.[87] m.p. 106-108°C).

76. 3ß-Vinyloxy-2α-acetoxy-cholest-4-ene (148)

To a refluxing solution of 2α-acetoxy-cholest-4-en-3ß-ol (1.0g) in ethyl vinyl ether (40 ml) was added mercury (II) acetate (0.5g) in small portions over eighteen hours. The reaction mixture was diluted with ether (60 ml), washed with aqueous sodium carbonate (25 ml) and water (25 ml), dried and evaporated in vacuo to give an oil. Flash column chromatography [SiO_2, petrol:ether, 10:1 (v/v)] gave 3ß-vinyloxy-2α-acetoxy-cholest-4-ene (148) (0.65g, 61%), m.p. 98-99°C (methanol) $[\alpha]_D$ -67° (c=0.01185 gl^{-1}), ν_{max} 1740 (C=O), 1630 (C=C) cm^{-1}, δ 6.41 (q, 1H, ROC<u>H</u>=CH_2 J 7Hz), 5.25 (brd s, 1H, C4-H), 5.1 (m, 1H, C2ß-H), 3.95-4.45 (m, 3H, ROCH=C<u>H</u>$_2$ and C3α-H), 1.18 (s, 3H, C10ß-Me), 0.70 (s, 3H, C13ß-Me). (Found: m/z 410.3631 (M-CH_3COOH) requires 410.3548). (Found: C, 79.3,; H, 10.6. $C_{31}H_{50}O_3$ requires C, 79.1; H, 10.7%).

77. 2α-Acetoxy-Δ^3-5ß-cholestenylacetaldehyde (149)

3ß-Vinyloxy-2α-acetoxy-cholest-4-ene (2.2g) was dissolved in dealin (30 ml) and heated under reflux for six hours under argon. The decalin was removed in vacuo and the crude product crystallised from methanol to give the aldehyde (149) (1.1g, 50%), ν_{max} 1720 (C=O) cm^{-1}, δ 9.92 (t, 1H, RC<u>H</u>O, J 3Hz), 5.96 (s, 2H, C3-H and C4-H), 5.45 (brd d, 1H, C2ß-H), 2.08 (s, 3H, OAc), 0.93 (s, 9H, C10ß-Me, 26 & 27 Me), 0.69 (s, 3H, C13ß-Me). (Found: m/z 410.3561 (M - CH_3COOH) requires 410.3545.).

2,4-dinitrophenylhydrazone, m.p. 177-179°C (methanol), ν_{max} 2280 (NH), 1730 (C=O) cm^{-1} $[\alpha]_D$ -221° (c=0.00407 gl^{-1}). (Found: C, 68.3; H, 8.4; N, 8.3. $C_{37}H_{54}N_4O_6$ requires C, 68.3; H, 8.4; N, 8.6%).

78. 5-(2-Propenyl)-5ß-cholest-3-en-2α-ol (150)

n-Butyl lithium (6.4 ml, 30% w/v in hexane) was added to a stirred suspension of methyl triphenyl phosphonium iodide (6.1g, 3 mol. equiv.) in T.H.F. (100 ml) at room temperature under argon. The red solution was stirred for thirty minutes to allow complete formation of the ylid and then

a solution of the aldehyde (149) (2.36g) in T.H.F. (20 ml) was added. The reaction mixture was stirred for eighteen hours at room temperature then diluted with petrol (100 ml) and filtered. The filtrate was washed with dil. hydrochloric acid (40 ml), aqueous sodium bicarbonate (40 ml) and water (40 ml), dried and evaporated in vacuo to give an oil. The crude product was hydrolysed in a refluxing solution of methanolic potassium hydroxide (5% 50 ml) for eighteen hours. The solution was diluted with brine (150 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with dilute hydrochloric acid (2M, 50 ml) aqueous sodium bicarbonate (50 ml) and water (50 ml), dried and evaporated in vacuo. Flash column chromatography [SiO_2, petrol:ether, 6:1, (v/v)] gave 5-(2-propenyl)-5ß-cholest-3-en-2α-ol (150) (0.88g, 41%), m.p. 127-128°C (methanol), $[\alpha]_D$ +143° (c=0.00554 gl^{-1}), ν_{max}, 3300 (brd, OH), 3080, 1640 ($RCH=CH_2$), δ 5.4-6.1 (m, 3H, $RC\underline{H}=CH_2$, C3-H and C4-H), 5.06 (m, 2H, $RCH=C\underline{H}_2$), 4.20 (brd s, 1H, C2ß-H, $W_{\frac{1}{2}}$ 10Hz), 0.83 (s, 3H, C10ß-Me), 0.60 (s, 3H, C13ß-Me), (Found: m/z 426.3869 ($M^{+\cdot}$). $C_{30}H_{50}O$ requires $M^{+\cdot}$ 426.3861). (Found: C, 84.4; H, 11.8. $C_{30}H_{50}O$ requires C, 84.8; H, 11.7%).

79. 5-(2-Propenyl)-5ß-cholest-3-en-2-one (151)

The alcohol (150) (0.88g) was added to a suspension of manganese dioxide (4.0g) in dichloromethane and stirred at room temperature for twelve hours. The suspension was filtered and the filtrate was evaporated in vacuo to give 5-(2-propenyl)-5ß-cholest-3-en-2-one (151) (0.87g, 99%), m.p. 58-60°C (methanol), $[\alpha]_D$ +77° (c=0.00323 gl^{-1}), ν_{max} 3080 ($RCH=CH_2$), 1680 (C=O), 1640 (C=C) cm^{-1}, δ 6.65 and 6.14 (ABq, 2H, C3-H and C4-H, J 9Hz), 5.6-6.2 (m, 1H, $RC\underline{H}=CH_2$), 5.2 (m, 2H, $RCH=C\underline{H}_2$), 1.04 (s, 3H, C10ß-Me), 0.67 (s, 3H, C13ß-Me). (Found: m/z 424.3705 ($M^{+\cdot}$). $C_{30}H_{48}O$ requires $M^{+\cdot}$ 424.3705). (Found: C, 85.2; H, 11.6. $C_{30}H_{48}O$ requires C, 84.8; H, 11.4%).

80. 2-(Trimethylsilyloxy)-5-(2-propenyl)-5ß-cholest-2-ene (153)

A solution of the enone (151) (0.5g) in T.H.F. (15 ml) and t-butanol (0.07 g , 0.8 mol. equiv.) was added dropwise with stirring to a solution of lithium (0.033g, 4 mol. equiv.) in liquid ammonia (25 ml). Stirring was continued for a further fifteen minutes, then the excess lithium was destroyed by the addition of isoprene (2 ml) and the ammonia removed under a stream of dry nitrogen. The solid residue was redissolved in anhydrous T.H.F. and a solution of trimethylsilyl chloride (0.25g, 2 mol. equiv.) in triethylamine (20 ml) was added. The solution was stirred for two hours, then diluted with petrol (100 ml) and washed with aqueous sodium bicarbonate (25 ml), dilute hydrochloric acid (0.5M, 25 ml), aqueous sodium bicarbonate (2 x 25 ml) and water (25 ml), dried and evaporated in vacuo. Recrystallisation from acetone gave the silylenolether (152) (0.33g, 56%) m.p. 104-105°C, $[\alpha]_D$ +23° (c=0.01479 gl^{-1}), ν_{max} 3080 ($RCH_2{=}CH_2$), 1680 ($C{=}COSiMe_3$) 1640 ($RCH{=}CH_2$) cm^{-1}, δ 5.5-6.1 (m, 1H, $RC\underline{H}{=}CH_2$) 4.8-5.1 (m, 2H, $RCH{=}C\underline{H}_2$), 4.65 (brd s, 1H, C3-H), 0.91 (s, 3H, C10ß-Me), 0.66 (s, 3H, C13ß-Me) and 0.19 (s, 9H, $OSiMe_3$). (Found: m/z 498.4250 ($M^{+\bullet}$). $C_{33}H_{58}OSi$ requires $M^{+\bullet}$ 498.4257). (Found: C, 79.6; H, 12.1. $C_{33}H_{58}OSi$ requires C, 79.4; H, 11.7%).

81. 4α,5-(1-Methylene-ethano)-5α-cholestan-3-one (154)

A solution of cholestenone (6.0g) and allene (14g, 20 mol. equiv.) in n-hexane (H.P.L.C. grade, 300 ml) was irradiated (Hanovia, 100W medium pressure mercury arc lamp) for approximately three hours at -60°C. The solvent was evaporated in vacuo and the crude product recrystallised from dichloromethane/methanol to give the adduct (4.3g, 65%), m.p. 158-159°C, $[\alpha]_D$ +62° (c=0.01315 gl^{-1}), ν_{max} 1695 (C=O), 1675 (C=C) cm^{-1}, δ 5.07 (m, 2H, $R_2C{=}C\underline{H}_2$, $W_{\frac{1}{2}}$ 8Hz), 0.84 (s, C10ß-Me) and 0.68 (s, 3H, C13ß-Me). (Found: m/z 424.3699 ($M^{+\bullet}$). $C_{30}H_{48}O$ requires $M^{+\bullet}$ 424.3705). (Found: C, 85.1; H, 11.4. $C_{30}H_{48}O$ requires C, 84.8; H, 11.4%).

82. 4α-(1-Bromomethyl.ethano)-5α-cholestan-3-one (155) (156)

Anhydrous hydrogen bromide was bubbled through an irradiated (Hanovia 100W medium pressure mercury arc lamp) solution of the allene photoadduct (154) (3.0g) in hexane (300 ml) for two hours. The solution was washed with aqueous sodium bicarbonate (100 ml), sodium thiosulphate (100 ml) and water (100 ml) dried and evaporated in vacuo. Recrystallisation from dichloromethane methanol, gave an isomeric mixture bromides (155) and (156) (3.4g, 95%). The product was usually used as a mixture but could be separated. Flash chromatography [SiO_2, petrol:ether, 4:1, (v/v)] gave as the least polar isomer (155) m.p. 128-130°C (dichloromethane, methanol) $[\alpha]_D$ +98° (c=0.00416 gl^{-1}), ν_{max} 1690 (C=O) cm^{-1}, δ 3.45 and 3.01 (m, 2H, $RC\underline{H}_2Br$), 0.81 (s, 3H, C10ß-Me) and 0.66 (s, 3H, C13ß-Me). (Found: m/z 506.2929/504.2944 ($M^{+\cdot}$) $C_{30}H_{49}OBr$ requires $M^{+\cdot}$ 506.2947/504.2967) (Found: C, 71.2; H, 9.9. $C_{30}H_{49}OBr$ requires C, 71.1; H 9.9%). and as the most polar isomer (156) m.p. 156-158°C (dichloromethane, methanol) $[\alpha]_D$ +24° (c=0.0058 gl^{-1}), ν_{max} 1695 (C=O) cm^{-1}, δ 3.55 and 3.40 (m, 2H, $RC\underline{H}_2Br$), 0.77 (s, 3H, C10ß-Me) and 0.65 (s, 3H, C13ß-Me) (Found: m/z 506.2941/504.2961 ($M^{+\cdot}$). $C_{30}H_{49}OBr$ requires $M^{+\cdot}$ 506.2947/504.2967) (Found: C, 71.5; H, 9.9. $C_{30}H_{49}OBr$ requires C, 71.1; H, 9.9%).

83. 5-(2-propenyl)-5α-cholestan-3-one (157)

A solution of the bromides (155) (156) (6.8g) in T.H.F. (60 ml) was added dropwise to a solution of lithium (0.56g, 6 mol. equiv.) in liquid ammonia (150 ml) and T.H.F. (60 ml) over ten minutes with stirring. Stirring was continued for a further fifteen minutes then the excess lithium was destroyed by the addition of ammonium chloride. The ammonia was removed under stream of nitrogen and the reaction mixture diluted with ether (150 ml). The ether solution was washed with aqueous sodium bicarbonate (50 ml) and water (50 ml), dried and evaporated in vacuo. Flash column chromatography [SiO_2, petrol:ether, 6:1 (v/v)] gave 5-(2-propenyl)-5α-cholestan-3-

one (157) (4.3g, 75%), m.p. 124-125°C (acetone), $[\alpha]_D$ +50° (c=0.00539 gl^{-1}) ν_{max} 3080 ($RCH=CH_2$), 1710 (C=O), 1640 ($RCH=CH_2$) cm^{-1}, δ 5.4-6.1 (m, 1H, $RCH=CH_2$), 5.1 (m, 2H, $RCH=CH_2$), 1.21 (s, 3H, C10ß-Me) 0.69 (s, 3H, C13ß-Me) (Found: m/z 426.3852 ($M^{+\cdot}$). $C_{30}H_{50}O$ requires $M^{+\cdot}$ 426.3861) (Found: C, 84.1; H, 11.8. $C_{30}H_{50}O$ requires C, 84.4; H, 11.8%). and 3α,5-(1-methylethano)-5α-cholestan-3ß-ol (158) (1.15g, 20%) m.p. 184°C (ethylacetate), $[\alpha]_D$ +21° (c=0.00771 gl^{-1}), ν_{max} 3500 (cm^{-1}), δ 0.92 (d, 3H, bridge methyl, J 7Hz) 0.91 (s, 3H, C10ß-Me) and 0.64 (s, 3H, C13ß-Me) (Found: m/z 428.4026 ($M^{+\cdot}$). $C_{30}H_{52}O$ $M^{+\cdot}$ 428.4018 (Found: C, 83.7; H, 12.2. $C_{30}H_{52}O$ requires C, 84.1; H, 12.2%).

84. Reductive cyclisation of 5-(2-propenyl)-5α-cholestan-3-one

A solution of the allyl ketone (157) (0.3g) in T.H.F. (10 ml) was added dropwise with stirring to a solution of lithium (0.019g, 4 mol. equiv.) in liquid ammonia (30 ml). Stirring continued for thirty minutes then the excess lithium was destroyed by the addition of ammonium chloride. The ammonia was removed under a stream of nitrogen and the resulting reaction mixture diluted with ether (50 ml). The ether solution was washed with aqueous sodium bicarbonate (15 ml) and water (15 ml), dried and evaporated in vacuo. Flash column chromatography [SiO_2, petrol:ether, 6:1, (v/v)] gave the allyl ketone (157) (0.115g, 38%) and 3α,5-(1-methylethano)5α- cholestan-3ß-ol (158) (0.139g, 46%).

85. Thermal cyclisation of 5-(2-propenyl)-5α-cholestan-3-one

5-(2-propenyl-)-5α-cholestan-3-one (0.25g) in decalin (2 ml) was heated in a sealed tube at 330°C for fours hours. The decalin was evaporated in vacuo. Flash column chromatography [SiO_2, petrol:ether, 6:1 (v/v)] gave 2α,5-(1-methylethano)-5α-cholestan-3-one (160) (0.198g, 79%), m.p. 92-94°C (methanol) $[\alpha]_D$ +52° (c =0.00765 gl^{-1}), ν_{max} 1725 (C=O) cm^{-1}, δ 0.93 (d, 3H, bridge methyl, J 7Hz), 0.86 (s, 3H, C10ß-Me) and 0.67 (s, 3H, C13ß-Me) (Found: m/z 426.3871 ($M^{+\cdot}$) $C_{30}H_{50}O$ requires $M^{+\cdot}$ 426.3861). (Found: C, 84.6; H, 12.2. $C_{30}H_{50}O$ requires C, 84.4; H, 12.2%).

86. 3-(Trimethylsilyloxy)-5-(2-propenyl)-5α-cholest-2-ene (162)

5-(2-propenyl)-5α-cholestan-3-one (2.5g) was dissolved in dimethylformamide (60 ml), triethylamine (5 ml) and trimethylsilyl chloride (5 ml), and heated at reflux under nitrogen for twentyfour hours. The cooled solution was diluted with petrol (100 ml) and washed with aqueous sodium bicarbonate (50 ml). The aqueous layer was re-extracted with petrol (50 ml) and the combined petrol extracts were washed with aqueous sodium bicarbonate (50 ml), dilute hydrochloric acid (1M, 50 ml), aqueous sodium bicarbonate (2 x 50 ml) and water (50 ml), dried and evaporated in vacuo. Recrystallisation from acetone gave the silylenolether (162) (2.0g, 68%), m.p. 103-118°C (acetone), $[\alpha]_D$ +38° (c=0.0577 gl^{-1}), ν_{max} 3080 ($RCH=CH_2$), 1665 ($C=C-OSiMe_3$) 1640 ($RCH=CH_2$) cm^{-1}, δ 5.5-6.1 (m, 1H, $RC\underline{H}=CH_2$) 4.7-5.2 (m, 3H, $RCH=C\underline{H}_2$ and C2-H), 0.81 (s, 9H, C10ß-Me, 26 & 27 Me), 0.67 (s, 3H, C13ß-Me) and 0.18 (s, 9H, $OSiMe_3$) (Found: m/z 498.4248 ($M^{+\cdot}$). $C_{33}H_{58}OSi$ requires $M^{+\cdot}$ 498.4258).

87. 2ξ-(Trimethylsilyoxy)-5-(2-propenyl)-5α-cholestan-3-one (163) (164)

A solution of the silylenolether (162) (2.0g) in hexane (20 ml) was added dropwise to a suspension of m-chloroperbenzoic acid (1.04g, 1.2 mol. equiv.) in hexane (50 ml) at 0°C. The solution was allowed to warm to room temperature and then stirred for a further five hours. The m-chloroperbenzoic acid was removed by filtration and the filtrate was evaporated in vacuo. Flash column chromatography [SiO_2, petrol:ether, 10:1 (v/v)] gave 2ξ-(trimethylsilyloxy)-5-(2-propenyl)-5α-cholestan-3-one (1.3g, 62%), an oil, $[\alpha]_D$ +43° (c=0.01158 gl^{-1}), ν_{max} 1728 cm^{-1}, Further careful chromatography allowed the separation of the isomers, giving 2ß-(trimethylsilyloxy)-5-(2-propenyl)-5α-cholestan-3-one (163), an oil, ν_{max} 1728 (C=O) cm^{-1}, δ 5.5-6.0 (m, 1H, $RC\underline{H}=CH_2$), 5.85-5.1 (m, 2H, $RCH=C\underline{H}_2$) 4.10 (brd q, 1H, C2ß-H, J 3 and 7Hz), 1.17 (s, 3H, C10ß-Me) and 2α-(trimethylsilyloxy)-5-(2-propenyl)-5α-cholestan-3-one (164), m.p. 131-133°C (methanol),

$[\alpha]_D$ +36° (c=0.00223 gl^{-1}) ν_{max} 1728 (C=O) cm^{-1}, δ 5.5-6.0 (m, 1H, RC<u>H</u>=CH_2), 4.85-5.1 (m, 2H, RCH=C<u>H</u>$_2$), 4.15 (q, 1H, C2ß-H, J 7 and 11Hz), 0.90 (s, 3H, C10ß-Me), 0.69 (s, 3H, C13ß-Me) and 0.13 (s, 9H, $OSiMe_3$). (Found: m/z 514.4197 ($M^{+\bullet}$). $C_{33}H_{58}O_2Si$ requires $M^{+\bullet}$ 514.4206) (Found: C, 77.0; H, 11.3. $C_{33}H_{58}O_2Si$ C, 77.0; H, 11.6%).

88. <u>Attempted hydrolysis of 2ξ-(trimethylsilyloxy)-5-(2-propenyl)-5α-cholestan-3-one</u>

Tetrabutyl ammonium fluoride on silica (0.8g, 2 mol. equiv. F^-) was added to a solution of the silyloxy ketones (0.37g) in chloroform (20 ml). The suspension was stirred for two hours and then filtered. The filtrate was washed with hydrochloric acid (2M, 5 ml), aqueous sodium bicarbonate (5 ml) and water (5 ml), dried and evaporated <u>in vacuo</u> (0.28g, 88%). Preparative thin layer chromatography [SiO_2, petrol: ether, 3:1 (v/v)] gave the diosphenol (166) (0.056g, 17%), an oil, ν_{max} 1710 (C=O, ketone), 1665 (C=O, enene) cm^{-1} δ 6.1 (s,C1-H), 5.7 (s, C4-H), 5.1 (m, RCH_2=C<u>H</u>$_2$). (Found m/z 440.3648 ($M^{+\bullet}$). $C_{30}H_{48}O_2$ requires $M^{+\bullet}$ 440.3654).

89. <u>Hydrolysis and thermal cyclisation of 2ξ-(trimethylsilyloxy)-5-(2-propenyl)-5α-cholestan-3-one</u>

a) In a sealed tube:-

A solution of the α-silyloxy-ketone (163, 164)(1.1g) in deoxygenated decalin (20 ml) was sealed in a tube containing tetrabutylammonium fluoride on silica (2 mol. equiv. F^-) and heated at 200°C for four hours. The suspension was filtered and the filtrate washed with water (2 ml), dried and evaporated <u>in vacuo</u>. Preparative thin layer chromatography [SiO_2, petrol: ether, 3:1 (v/v)] gave 3α,5-(1-methylethano)-3ß-hydroxy-5α-cholestan-2-one (167) (0.59g, 7%) m.p. 139-141°C (methanol), $[\alpha]_D$ +48° (c=0.00682 gl^{-1}), ν_{max} 3495 (OH), 1705 (C=O) cm^{-1}, δ 3.6 (s, OH), 2.64 (quartet d, C2 -H, J 14, 9 and 3Hz), 2.25 (ABq, C2-H, $J_{(gem)}$ 15Hz), 1.05 (d, C1 -Me, J 7Hz), 0.91 (s, C10ß-Me) and 0.65 (s, C13ß-Me). (Found: m/z

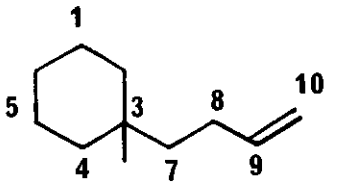
442.3824 ($M^{+\bullet}$). $C_{30}H_{50}O_2$ requires $M^{+\bullet}$ 442.3811) and 2α,5 (1-methylethano)-2ß-hydroxy-5α-cholestan-3-one (168) (0.230g, 27%), m.p. 110-112°C (methanol), ν_{max} 3500 (OH), 1725 (C=O) cm^{-1}, δ 3.50 (s, OH), 2.91 (m, C2-H), 2.45 (dd, C4ß-H, $J_{(gem)}$ 19Hz and 3Hz), 1.92 (d, C4α-H, $J_{(gem)}$ 19Hz), 0.90 (s, C10ß-Me), 0.85 (d, C1-Me, J 7Hz) and 0.66 (s, C13ß-Me). (Found: m/z 442.3819 ($M^{+\bullet}$). $C_{30}H_{50}O_2$ requires $M^{+\bullet}$ 442.3811). (Found: C, 81.6; H, 11.4. $C_{30}H_{50}O_2$ requires C, 81.4; H 11.4%).

b) In refluxing toluene:-

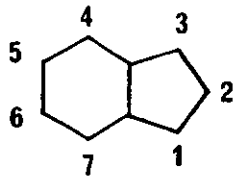
Tetrabutylammonium fluoride on silica (2 mol. equiv. F^-) was added to a solution of the α-silyloxy-ketone (163, 164)(0.20g) in deoxygenated toluene (25 ml). The solution was heated under reflux for eighteen hours under argon, then filterd, washed with water (10 ml), dried and evaporated in vacuo. Preparative thin layer chromatography [SiO_2, petrol:ether, 3:1 (v/v)] gave 3α,5-(1-methylethano)-3ß-hydroxy-5α-cholestan-2-one (167) (0.006g, 3%) and 2α,5-(1-methylethano)-2ß-hydroxy-5α-cholestan-3-one (168) (0.057g, 33%).

APPENDIX I

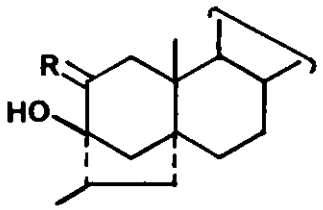
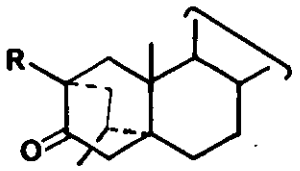
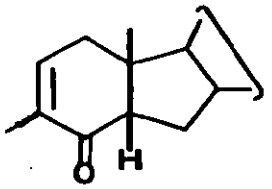
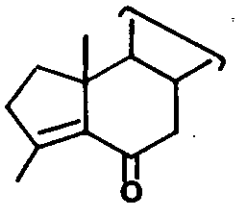
^{13}C n.m.r. DATA



Compound	Carbon No.											
	1	2	3	4	5	6	7	8	9	10	Me	$SiMe_3$
Ketone (102)	211.5	53.7	38.5	35.7	22.1	40.9	40.9	27.9	138.8	114.5	24.9	-
Silylenolether (103)	149.5	114.2	42.6	34.5	19.5	29.8	34.5	28.7	139.6	113.7	27.9	0.2
Acyloin isomer (1) (105)	211.8	80.9	44.2	34.0	22.1	40.1	38.7	27.4	139.1	114.4	17.0	-
Acyloin isomer (2) (106)	211.3	83.7	43.8	33.5	21.8	38.8	29.1	28.1	138.9	114.5	24.6	-



Compound	Carbon No.											
	1	2	3	3a	4	5	6	7	7a	7aMe	3Me	5Me
Hydrindanolone 1 (109)	36.7	30.6	42.6	89.3	215.0	38.9	23.9	36.7	54.2	19.3	13.0	-
Hydrindanolone 2 (110)	34.8	21.3	39.2	88.2	214.3	39.7	33.2	39.0	54.9	18.2	-	14.5
Enone (121)	34.5	22.4	28.9	57.2	201.7	133.2	142.6	39.4	44.9	26.2	-	15.9

Compound / Carbon No.						
	$R=H_2$ (158)	R=O (167)	R=OH (168)	R=H (160)	(82)	(85)
1	37.3	47.6	47.6	42.8	55.7	47.3
2	42.3	213.7	79.6	51.0	142.0	Unassigned
3	79.0	84.4	216.0	217.8	134.6	148.9
4	43.9	43.6	50.3	49.0	203.1	-
5	41.2	43.6	38.4	35.1	55.8	141.9
6	28.8	28.0	28.2	26.6	-	201.3
7	33.3	33.7	31.7	32.3	34.6	52.4
8	35.6	35.1	35.6	35.7	35.4	37.1
9	48.1	47.7	49.0	48.9	55.7	Unassigned
10	44.9	44.2	38.6	39.2	44.2	51.7
11	21.6	22.7	22.1	22.0	21.4	22.2
12	40.2	39.9	40.1	40.2	39.6	39.1
13	42.6	42.6	42.9	42.9	41.5	42.9
14	56.3	56.2	56.2	56.3	56.3	56.7

...Contd.

15	24.2	24.1	24.0	24.0	24.4	24.2
16	28.2	28.2	28.3	28.3	28.6	28.1
17	56.4	56.2	56.4	56.5	56.4	56.7
18	12.0	12.0	12.5	12.6	12.3	12.0
19	18.7	18.5	18.7	18.0	25.7	16.0
20	35.6	35.6	35.7	35.8	35.7	35.7
21	18.7	18.7	18.7	18.7	18.8	18.8
22	36.2	36.1	36.1	36.1	36.3	36.2
23	23.8	23.8	23.8	23.8	23.9	23.9
24	39.5	39.5	39.5	39.5	39.6	39.6
25	27.0	27.0	27.0	27.0	28.0	28.1
26	22.5	22.5	22.5	22.5	22.6	22.6
27	22.8	22.8	22.8	22.8	22.8	22.8
1-Methyl (bridge)	14.6	15.7	18.7	23.0	-	-
1-Ethano	37.7	37.5	36.0	31.5	-	-
2-Ethano	35.3	39.5	37.1	35.8	-	-
3-Methyl	-	-	-	-	16.4	19.4

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