SYNTHESIS OF DELTA-1(9)-OCTALINOLS AND THEIR ANALOGUES

A thesis submitted to the UNIVERSITY OF CAPE TOWN

in fulfilment of the requirements of the

degree of

MASTER OF SCIENCE

by

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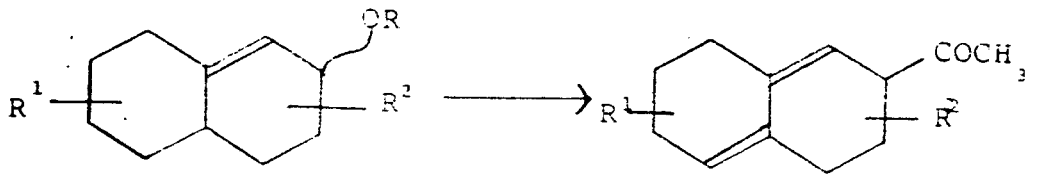
Sincere thanks are expressed to Miss B K Williamson for her contribution by running GC-Mass Spectra, Mr Z Brown for running the ^{1}H-n.m.r. spectra, and Mr W R T Hemsted, for all micro-analyses. I am very grateful to the staff of the Department of Organic Chemistry for providing such a warm and friendly atmosphere in which I was able to finish my work.

Thanks are also extended to the University of Cape Town for providing a Scholarship which enabled me to finish my work.

SUMMARY

This project was initiated by the observation that a natural glycoside of a triterpene, which incorporated the allylic alcoholic moiety 1, gave the novel ketone diene 2 when it was subjected to acetolysis.

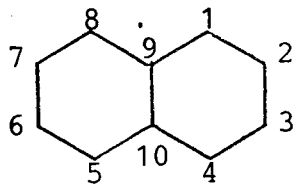


1 2

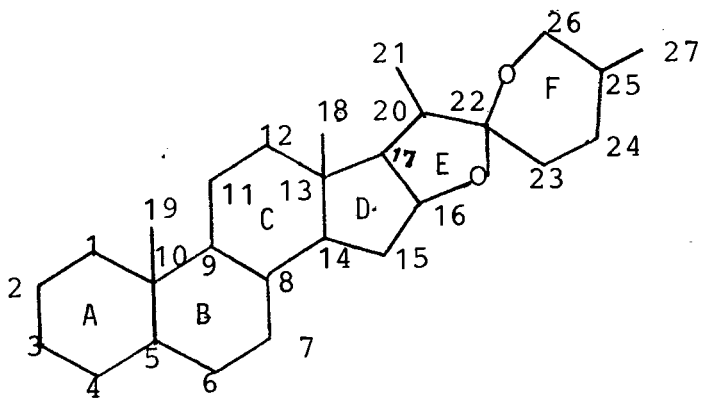
A number of octahydronaphthalinols (1, R=H) ($\Delta^{1(9)}$ - octalinols), were prepared by reduction of the α,β - unsaturated octalones obtained from cyclohexanones condensed with α,β-unsaturated ketones. These octalinols were characterised as their acetates (1, R=Ac). The attempts to convert these to the desired ketone dienes 2 by reaction with mixtures of acetic anhydride-acetic acid-boron trifluoride proved unsuccessful. Two model compounds derived from hecogenin and incorporating the octalinol residue 1 were also prepared in the hope that the analogous ketone 2 might be obtained. This reaction, too, was unsuccessful.

NUMBERING OF FORMULAS

The numbering system for naphthalene will follow that used in Chemical Abstracts, namely:



and for hecogenin and its derivatives:



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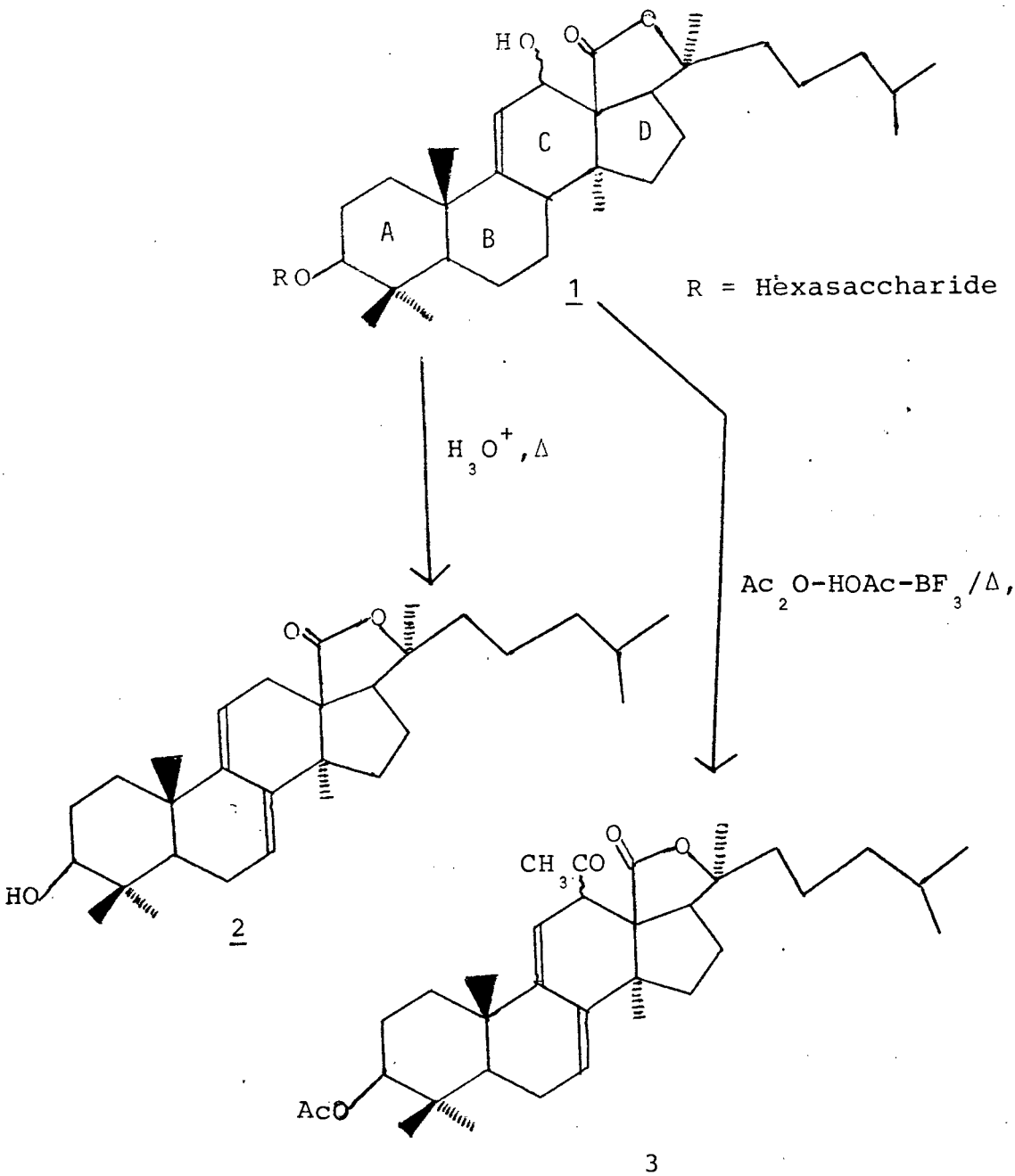
INTRODUCTION

CHAPTER 1

INTRODUCTION



The saponins of sea cucumbers (Holothurians, Echinodermata) are secondary metabolites shown to be glycosides of novel triterpenes which incorporate a γ-lactone ring, and frequently possess a C 9(11)-double bond.[1] One such saponin, (1) is seen to possess an allylic alcohol function.[2] When saponin (1) was subjected to acid hydrolysis, the diene (2) was obtained. Acetolysis, however, of saponin (1), by heating with a mixture of acetic anhydride-acetic acid and boron trifluoride in a sealed tube at 100° gave the diene ketone (3) unexpectedly. This appeared to be the first report of this type of C-acylation.[2] It was therefore of interest to discover whether the reaction is general for allylic alcohols.

A brief study of the chemistry of allylic alcohols and their acetates showed that they are easily hydrolysed to form carbonium ions which are stabilised by delocalisation.[3] For example, S_N1 solvolysis of 3-hydroxybut-1-ene in ethanol containing dry hydrochloric acid (eq. i) gives the carbonium ion (4).

$$Me\text{-}CH(OH)CH{=}CH_2 \xrightarrow{H^+,EtOH} [Me\overset{+}{C}H\text{-}CH{=}CH_2 \leftrightarrow MeCH{=}CH\overset{+}{C}H_2]$$

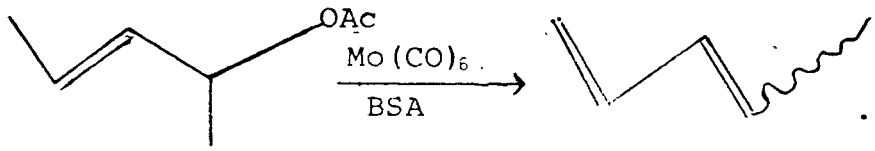
$$\underline{4} \downarrow EtOH$$

$$Me\text{-}CH(OEt)CH{=}CH_2 + Me\text{-}CH{=}CH\text{-}CH_2OEt$$

.....(eq. i)

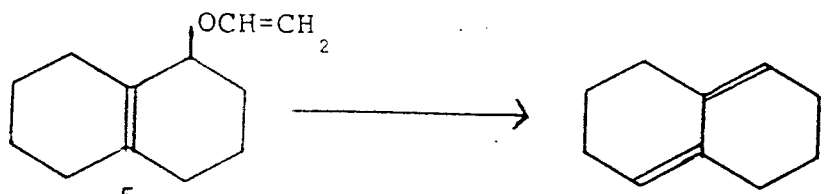
Nucleophilic attack by ethanol can occur at either C_1 or C_3 to yield a mixture of the two possible ethers, and these are indeed obtained. If, however, the reaction is carried out in an ethanolic solution of sodium ethoxide, a straightforward S_N2 displacement reaction occurs to form only one product, namely Me-CH(OEt).$CH=CH_2$.

Lautens and Trost[4] have shown that allylic acetates smoothly eliminate the elements of acetic acid in the presence of O,N-bis-(trimethylsilyl)acetamide (BSA) and molybdenum hexacarbonyl, thus providing a simple and practical approach for the synthesis of dienes (eq. ii).



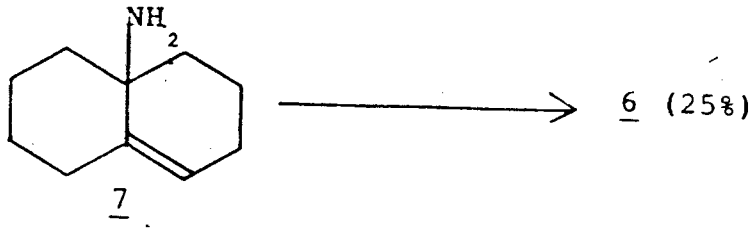
...(eq. ii)

Relevant to the observed formation of the conjugated heteroannular diene (2), the allylic vinyl ether (5) was shown to give, after heating in a sealed tube the conjugated diene (6) as a minor product.[5] The hexalin (6), however, was



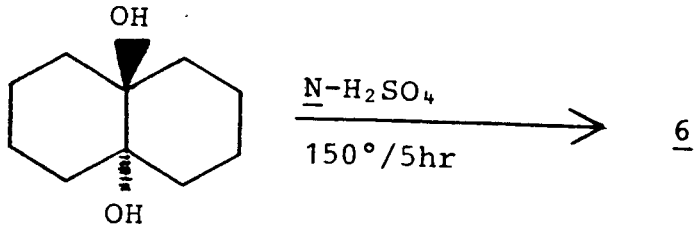
5 6

not characterised. The amino octalin (7) gave the diene (6) among other products when heated at 50° with concentrated sodium nitrite in 10% acetic acid.[6]



7

The 9,10-diol of trans decalin (8), clearly a precursor of an allylic alcohol system, also gave the diene (6) when heated under the conditions shown.[7]



8

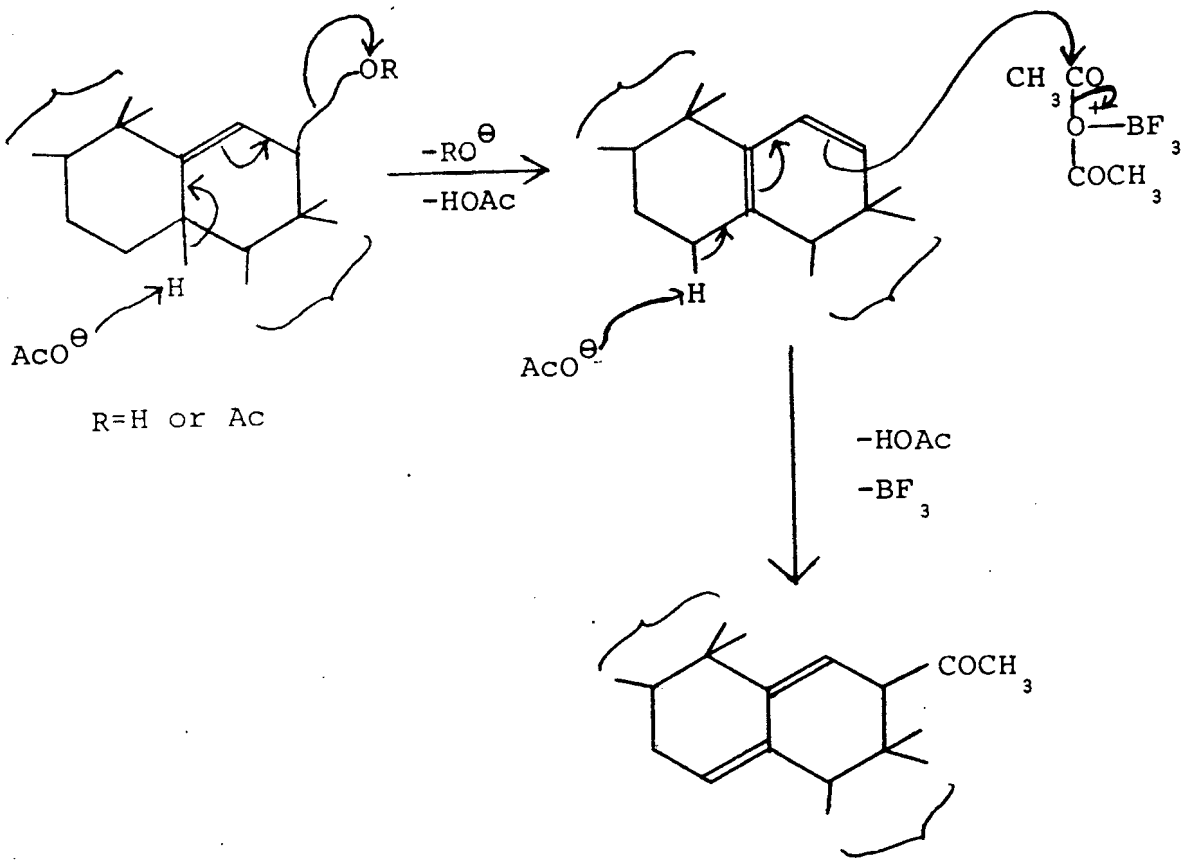
Although other hexalin isomers of the diene (6) can be formed in the above reactions, Bates et al. have demonstrated that the isomer (6) is thermodynamically the most stable.[8]

A search of the literature fails to show any reactions of 2-hydroxy-$\Delta^{1(9)}$-octalins or their acetates or any analogues on treatment either with hot acids or upon acetolysis. One

might postulate a mechanism for the formation of the diene ketone (3) as depicted in scheme 1.1.

The main objective of the present project was to synthesise model allylic alcohols or acetates incorporating rings B and C of the triterpenoid glycoside (1) and then to observe their behaviour under the experimental conditions described earlier.

SCHEME 1.1 - A possible mechanism for the formation of the diene ketone



CHAPTER 2

RESULTS AND DISCUSSION

CHAPTER 2

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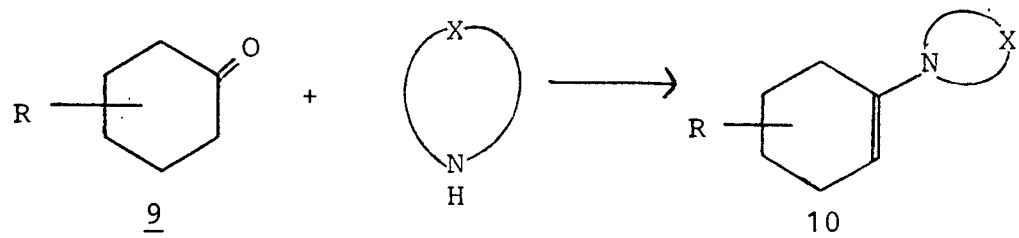
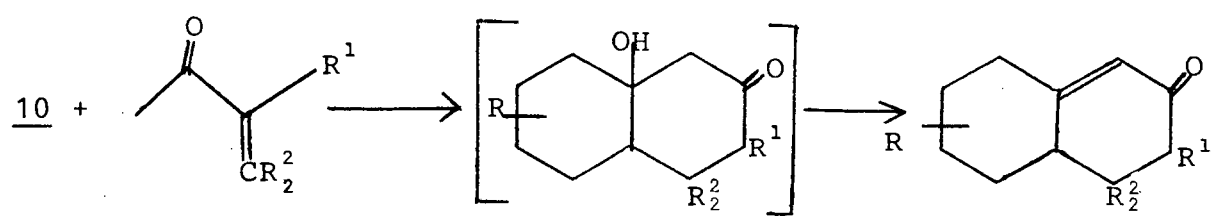
2.1 Synthesis of octalinols and their acetates



9 10

	R	X
a	H	$-(CH_2)_2O-(CH_2)_2-$
b	H	$-(CH_2)_4-$
c	4-Me	$-(CH_2)_4-$
d	4-Me	$-(CH_2)_2O-(CH_2)_2-$

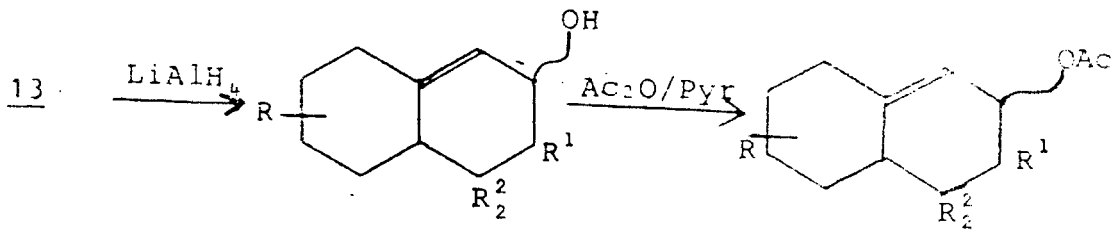
SCHEME 2.1 Formation of the enamines (10)



11 12 13

	R	R^1	R^2
a	H	H	H
b	H	Me	H
c	6-Me	Me	H
d	H	H	Me

SCHEME 2.2 Annelation of the enamines (10) to form the octalones (13)



14 15

	R	R^1	R^2
a	H	H	H
b	H	Me	H
c	6-Me	Me	H
d	H	H	Me

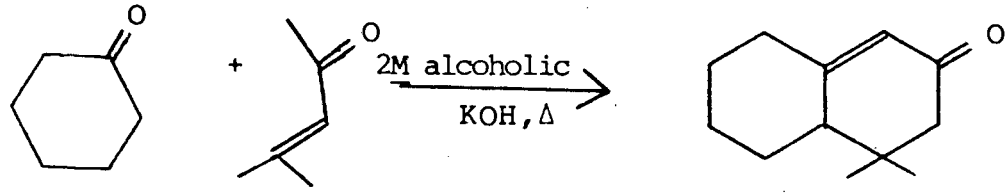
SCHEME 2.3 Reduction of the octalones (13) to the octalinols (14)

The octalones (13a-d) (Scheme 2.2) were synthesised by alkylating the enamines of morpholine or pyrrolidine (10a-c) with the α,β-unsaturated carbonyl compounds (11a-c) and cyclising the product.[10] The boiling points and percentage yields of octalones (13a-c) are given in Table 2.1. The ^{1}H-n.m.r. spectra of the octalones included a signal at δ5,18-5,80 ppm characteristic of α,β-unsaturated ketones (Table 2.3). The presence of this chromophore in the octalones (13a-c) was also established by infrared spectroscopy which showed, among others, appropriate absorptions at 3020 (C=CH stretch), 1666 and 1624 cm^{-1} (α, β-unsaturated ketones).[11]

TABLE 2.1 Octalones prepared by Michael-type condensations

Enamines	Octalones	% yield	b.p. (°/mm) observed	Lit
10a	13a	34	79-82/0,6	68-69/1,0[10]
10b	13b	42	80-82/0,7	100-105/0,5[10]
10c	13c	57	76-78/0,4	112-116/2,5[12]
-	13d	57	73-91/0,2-0,4	-

All attempts to alkylate the enamines with mesityl oxide (11d) failed to give the expected product. However, when an excess of cyclohexanone (9a, R = H) was reacted with mesityl oxide (11d) in alcoholic potassium hydroxide, octalone (13d) was obtained but proved difficult to purify.



9a 11d 13d

The cyclohexanone-morpholine enamine (10a) on alkylation with methyl vinyl ketone (11a), followed by cyclisation, gave the intermediate ketol (12a), (m.p. 142-143°) in only 3-4% yield. Similarly, 4-methylcyclohexanone-morpholine enamine (10d) on alkylation with methyl isopropenyl ketone (11b), followed by cyclisation, gave the intermediate ketol (12c), (m.p. 135-137°) in only 3-4% yield. The desired octalone (13c) was not present. It was readily obtained

however, by dehydrating the ketol (12c) with trifluoroacetic acid under reflux. The 4-methylcyclohexanone-pyrrolidine enamine (10c) underwent ready alkylation with methyl isopropenyl ketone (11b) followed by cyclisation to give directly a better yield (57%) of octalone (13c). (Table 2.1)

These octalones (13a-d) were each reduced with lithium aluminium hydride to the octalinols (14a-d) (Table 2.2). These octalinols were each characterised as their respective acetates (15a-d) prepared by reaction with acetic anhydride-pyridine at room temperature overnight (Table 2.2). These acetates were oils. Satisfactory elemental analyses were obtained for compounds (15b) and (15c).

TABLE 2.2 Data on octalinols and their acetates

Octalinol	Acetate	b.p. (°/mm)		Elemental Composition			
				%C		%H	
		observed	Lit	Calc.	Found	Calc.	Found
14a		82-84/1,5	-	78,79	78,7	10,6	10,6
	15a	-	-	-		-	
14b		74-76/0,5	-	79,4	79,3	10,9	10,6
	15b	-	-	75,0	75,1	9,68	9,5
14c		78-80/0,6	105-107/2,5[13]	79,9	79,8	11,18	11,0
	15c	-	-	75,63	75,6	9,98	9,7
14d		84-85/ 3,2	-	79,9	79,1	11,2	11,1
	15d	-	-	-		-	

TABLE 2.3 Significant signals in the ^{1}H-n.m.r. spectra of the octalones (13), octalinols (14) and their acetates (15)

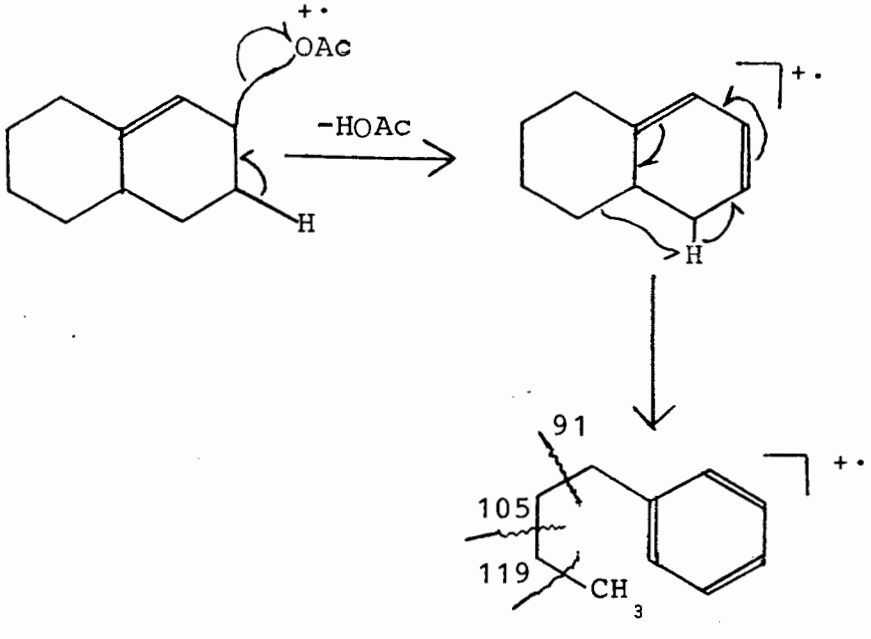
Assignment	Multiplicity	Signals (range) δ/ppm
-C=C<u>H</u>-C(=O)-	broad/singlet	5,18-5,80
>C<u>H</u>-O-	multiplet/broad	4,94-5,14
-OC(=O)-C<u>H</u>$_3$	singlet	2,04-2,06
>CH-C<u>H</u>$_3$	doublet	0,91-0,95

The acetates (15b) and (15c) each showed a very strong infrared absorption band at ca 1240cm^{-1} characteristic of α,β-unsaturated acetates (C-O-C), (Fig. 2.1).[11]

The mass spectra of the α,β-unsaturated acetates (15a-c) (Table 2.4) showed base peaks at m/z 134, 148 and 162 respectively which correspond to the loss of acetic acid. Further significant peaks which are common to all three spectra are those due to the loss of CH_3CO^+ (M^+-43) and the formation of tropylium ion ($C_7H_7^+$) at m/z 91 due to aromatisation as shown in Scheme 2.4. Other peaks are observed at m/z 105 and m/z 119 (Scheme 2.4, Table 2.4).

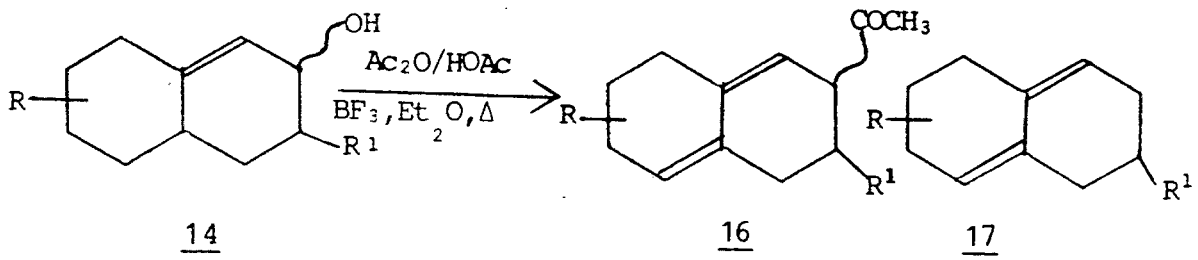
TABLE 2.4 Significant peaks in the mass spectra of the acetates of $\Delta^{1(9)}$-octalin-2-ols

	Compound (m/z (I/Base %))		
Peak	15a	15b	15c
M^+	194(2)	208(3)	222(8)
M^++H-CH_3CO	152(18)	166(18)	180(32)
M^+-HOAc	134(100)	148(100)	162(100)
M^+-HOAc-Me	-	133(44)	147(51)
M^+-HOAc-2Me	-	-	133(41)
	119(27)	119(42)	119(40)
	105(31)	105(46)	105(64)
$C_7H_7^+$	91(57)	91(39)	91(75)
CH_3CO^+	43(35)	43(25)	43(63)



SCHEME 2.4 A possible mode of fragmentation of the acetates of $\Delta^{1(9)}$-octalin-2-ols

Attempts to form the desired diene ketones (16) from octalinols (14a-c) were unsuccessful.

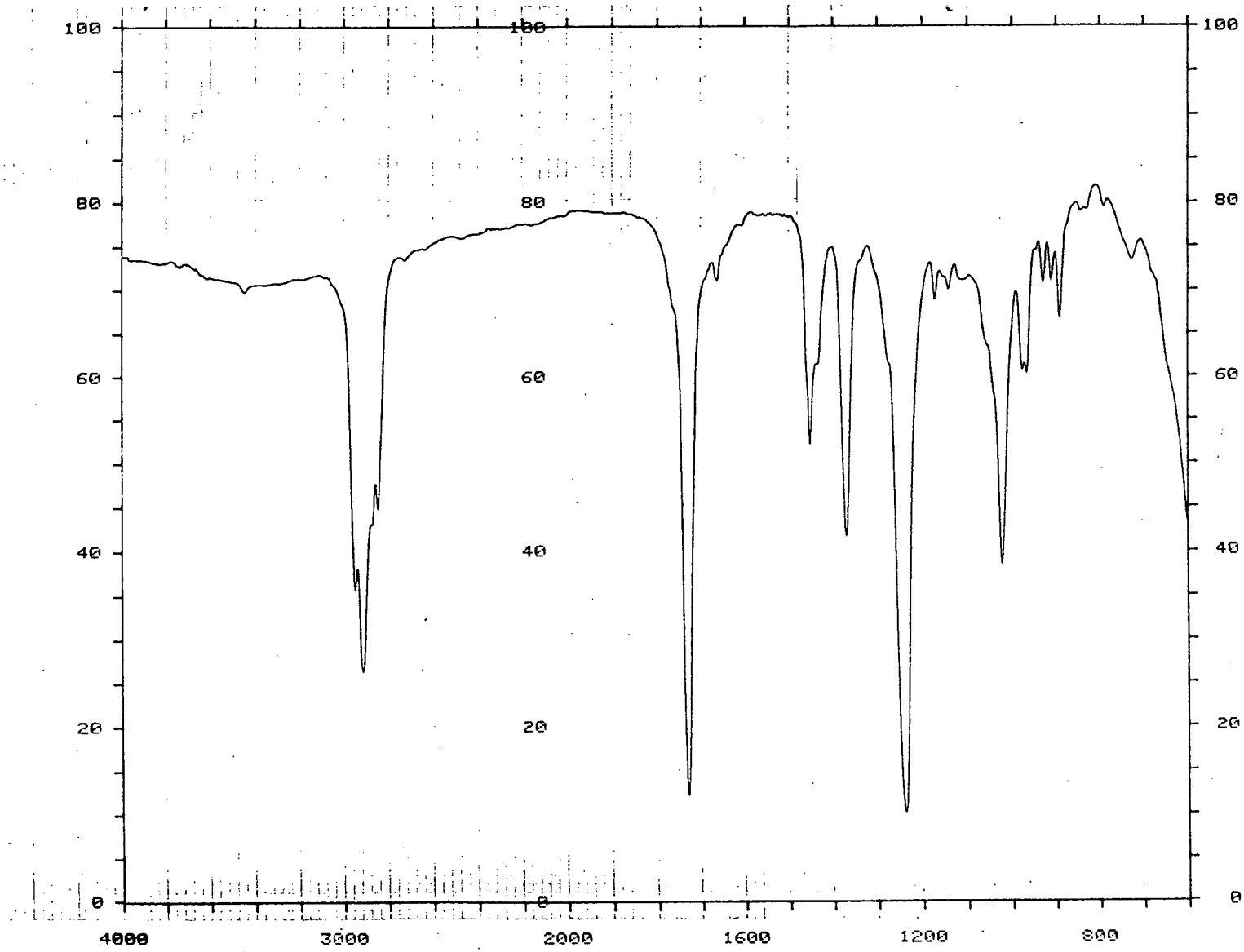


14 16 17

The octalinols (14a-c) were each heated with a mixture of acetic anhydride, acetic acid, and boron trifluoride ethereate. Work-up gave a dark, viscous gum which was tentatively examined by GC-Mass spectra to determine whether the reaction had been successful. The results are summarised in Table 3.2 (p.55). The intensities of the peaks for the desired products (16) from the respective starting compounds (14a), (14b) and (14c) were low, viz., m/z 176 (2%), 190 (4%) and 204 (10%). There was also evidence that the dienes (17) had formed and undergone varying degrees of di-and trimerisation. Thus the product from the octalinol (14a: $R=R^1=H$) showed a base peak at m/z 268, corresponding to $C_{20}H_{28}$, i.e. the dimer of hexalin (17a: $R^1 = R = H$), and a weaker peak at m/z 403, $C_{30}H_{43}$, i.e. the trimer of the same hexalin + H. The product from compound (14b: R^1= Me; R = H) however, had a base peak at m/z 147, corresponding to $C_{11}H_{16}$-H, i.e. the hexalin (17b: R = H; R^1= Me), with only a weak peak at m/z 296 which would correspond to the dimer of the same hexalin.

The product from the octalinol (14c: R = 6-Me; R^1= Me) showed a peak at m/z 162, corresponding to $C_{12}H_{18}$, i.e. the hexalin (17c: R = 6-Me; R^1= Me), with a medium weak peak at m/z 323, $C_{24}H_{36}$-H, i.e. the dimer of the same hexalin.

In an attempt to prevent polymerisation a trace of hydroquinone was added to each acetate before reaction. GC-Mass spectral analysis of the gums then showed some improvement in the relative intensities of the peaks which correspond to the desired products (16a-c) viz., 176 (7%), 190 (0,6%) and 204 (22%) respectively but the low yields of the crude products (less than 3%) were disappointing. No attempt was made to isolate the compounds (16) and (17) on account of these results. One can only conclude that these experiments had been unsuccessful.



PERKIN-ELMER 983

DATE

SAMPLE

OPERATOR

SCAN MODE	2
NOISE FILTER	1
RESOLUTION	7.0
ORDINATE MODE	%T
RANGE	4000.0- 600.0
ABSC. SCALE	0.50

PEAK THRESHOLD 1 %T

CM-1	%T
3448.0	69.72
2949.0	35.54
2915.0	26.25
2846.0	44.77
1732.0	12.03
1664.0	70.94
1452.0	52.14
1370.0	41.62
1239.0	9.99
1171.0	68.75
1141.0	69.96
1023.0	38.32
966.0	60.31
929.0	70.66
910.0	70.92
891.0	66.63
844.0	78.84
728.0	73.36

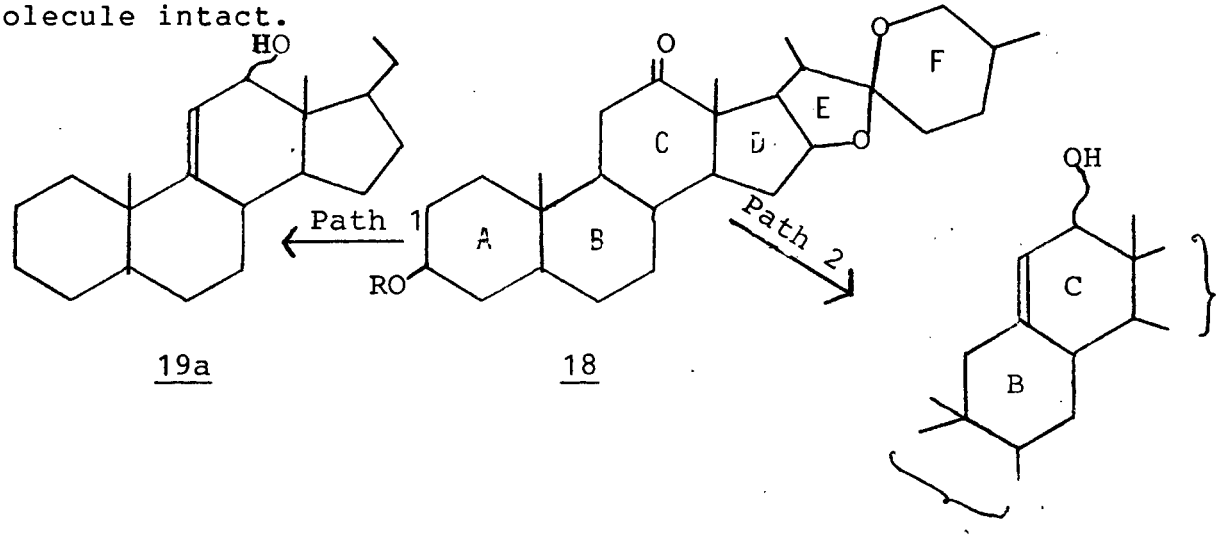
FIGURE 2.1 Infrared spectrum of 3,6-dimethyl-$\Delta^{1(9)}$-octalin-2-ol acetate

2.2 Synthesis of an allylic alcohol (19a: R = H) and its acetate from hecogenin (Path 1)

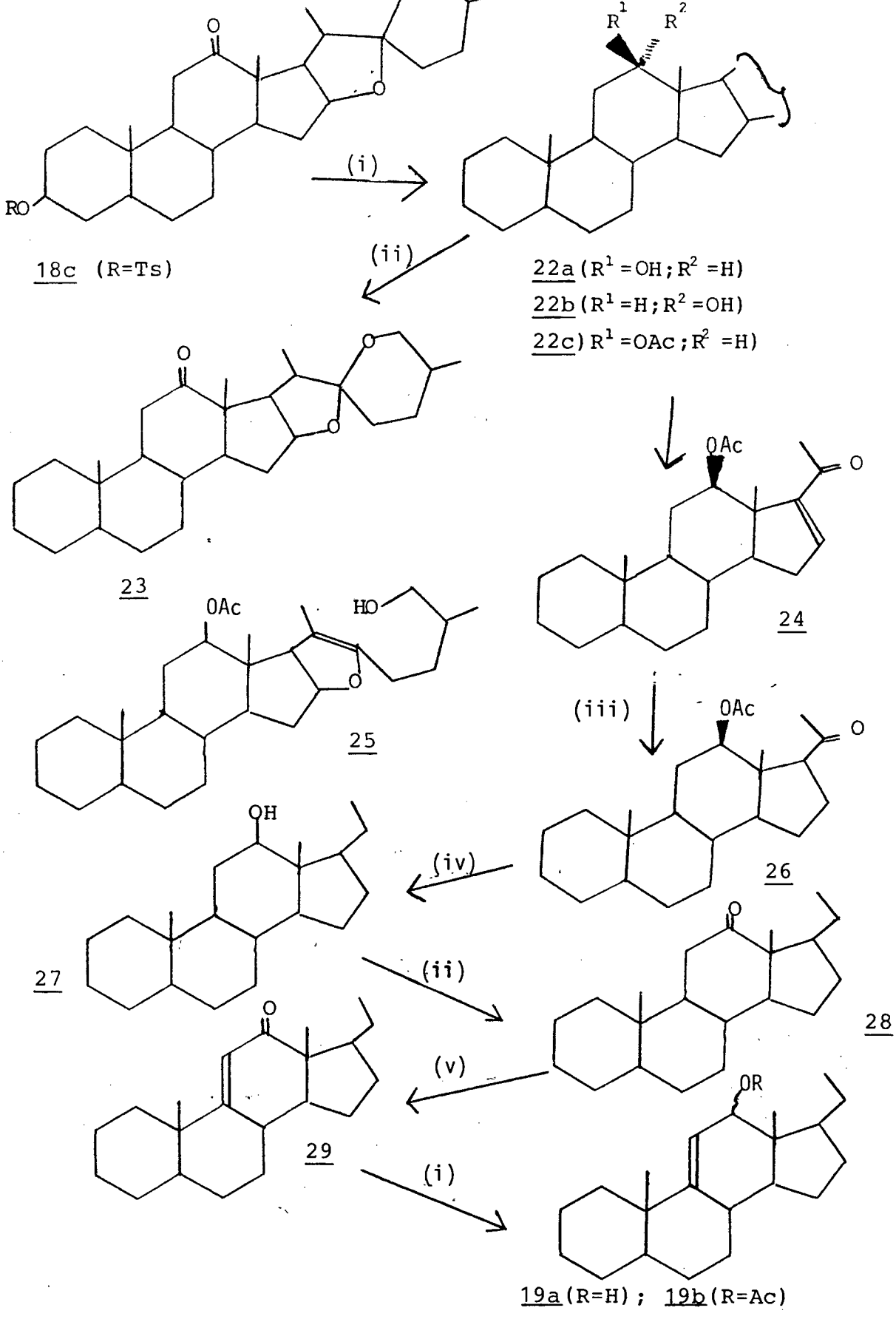
Owing to the failure of the octalin-2-ols and their acetates to form the diene ketones (16) under the acylating conditions described, it was decided to modify an existing triterpenoid molecule and introduce an allylic alcohol moiety into the ring. It was considered that such a compound would have less tendency to dimerise under the acetylation conditions and might be more favourably structured to form the analogue of the diene ketone (16). It was decided to start with the readily available hecogenin (18a: R = H) and its acetate (18b: R = Ac).

Two routes were followed. Path 1 leads to the compound (19a) possessing only the allylic alcohol moiety with all other functional groups removed.

Path 2 aims to convert the keto function at C-12 to the allylic alcohol (20), while keeping the remainder of the molecule intact.



19a 18 20



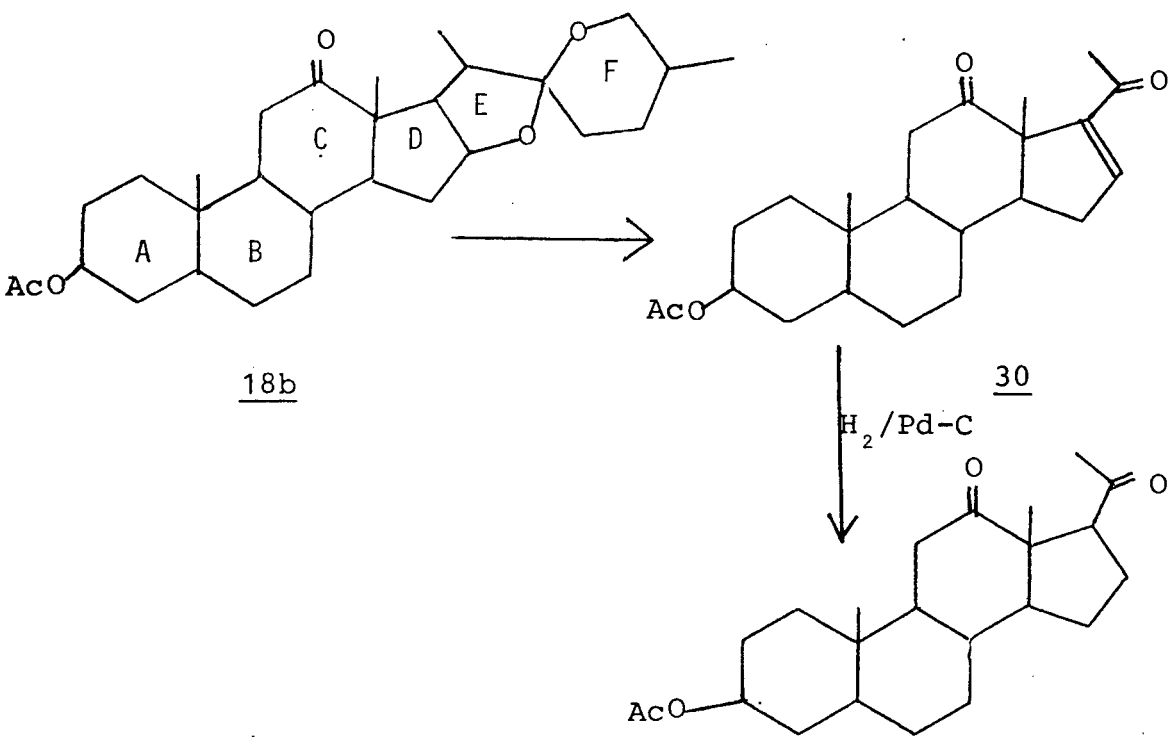
SCHEME 2.5 Synthesis of the allylic alcohol (19a: R = H)

(Path 1)

Reagents: (i) $LiAlH_4$-THF; (ii) CrO_3-Me_2CO; (iii) H_2/Pd-C; (iv) N_2H_4, n-BuOH, KOH, Δ ; (v) SeO_2 .

Path 1 is feasible by utilising the series of transformations of hecogenin (18a) to the allylic ketone (29) described in a comprehensive paper by Djerassi and Tökes[14] and summarised in scheme 2.5.

A series of exploratory experiments were performed on hecogenin acetate (18b) to establish the procedure for cleaving the spiroketal ring followed by catalytic reduction to give the diketone (31).



18b 30 31

Compound (30), $C_{23}H_{32}O_4$, m.p. 178-181°, was obtained in an overall yield of 28% from hecogenin acetate (18b). The hexanoic anhydride modification[15] was used to cleave off rings E and F without purifying the intermediate compounds.

Catalytic hydrogenation of compound (30) over palladised charcoal yielded the diketone (31), $C_{23}H_{34}O_4$, m.p. 188-190°, in 49% yield. Both compounds (30) and (31) gave similar mass spectra (Table 2.5) with corresponding molecular ions at m/z 372 and 374 respectively, and ions at m/z 357 and 359, equivalent to the loss of a methyl group from each, and at m/z 329 and 331, corresponding to the loss of CH_3CO^+ (M^+-CH_3CO). They both showed base peaks at m/z 43 ($C_2H_3O^+$). Clearly compound (31) cannot be converted to an allylic alcohol at C-12 without affecting the methyl ketone at the same time, but this method of cleaving the spiroketal ring was successful and will be used subsequently.

Hecogenin was converted to the tosylate (18c : R = Ts) which, on reduction with lithium aluminium hydride,[16] yielded the epimeric 3-deoxy spiroketal alcohols (22a) and (22b). These could be readily separated by column chromatography on neutral alumina (activity II) into the 12α-epimer (22b) and the 12β-epimer (22a)[17] which was the major product. After recrystallisation from methanol, each epimer was identified by its melting point, viz. m.p. 185-186° and 199-200° for compounds (22a) and (22b) respectively. (Lit.[14] 191,5-192,5° for (22a) and 203-204° for (22b)).

A sample of the mixture of epimeric alcohols was oxidised by chromium trioxide to the ketone (23), m.p. 196-198°, in 74%

yield. The mass spectrum (Table 2.6) showed peaks at m/z 414 (M^+), 342 ($M^+ - C_4H_8O$) and 300 ($M^+ - C_6H_{10}O_2$) with a base peak at m/z 139 ($C_9H_{15}O^+$). These peaks confirm that the spiroketal moiety remains intact in compound (23) under the above reaction conditions. [A fuller discussion of the fragmentation of the spiroketal system under electron impact mass spectrometry is discussed in Section 2.3].

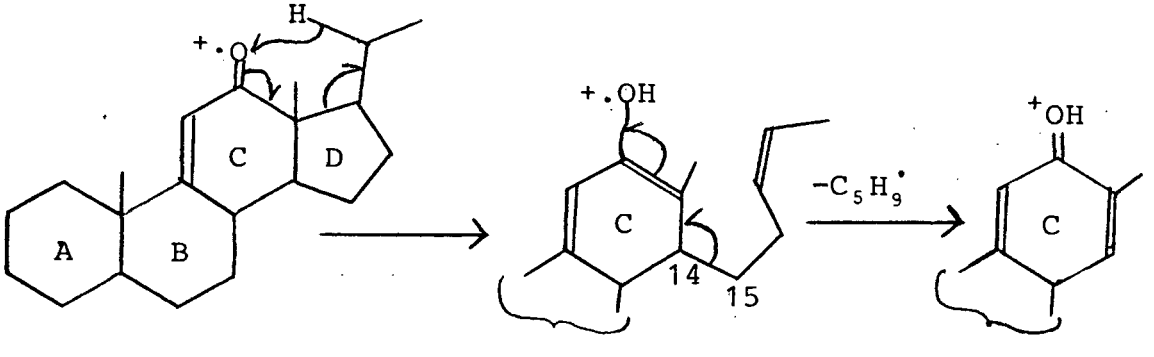
The 12 β-epimeric alcohol was acetylated using pyridine-acetic anhydride and the acetate (22c) was then subjected to Marker side-chain degradation to cleave rings E and F[15] using initially hexanoic anhydride instead of octanoic anhydride. The keto-acetate (24), $C_{23}H_{34}O_3$, m.p. 167-169°, was obtained in 30% yield by column chromatography of the product. A better yield (44%) was obtained using octanoic anhydride in the degradation procedure.[15] The ^{1}H-n.m.r. spectrum included a signal at δ6,62 ppm (1H,t J 4 Hz), for the -CH=C-CO- at C-16. The mass spectrum (Table 2.5) showed peaks at m/z 358 (M^+), 298 (M^+-CH_3COOH), 283 ($M^+-CH_3CO_2H-CH_3$) and the base peak at m/z 43 (CH_3CO^+).

In addition to compound (24), a second product, m.p. 163-165°, analysing for $C_{29}H_{46}O_4$, was obtained in 5% yield. The mass spectrum (Table 2.6) together with the analytical data tentatively suggests this compound has the structure (25).

The keto-acetate (24) was catalytically hydrogenated to 5β-pregnan-12β-acetoxy-20-one (26). Wolf-Kishner reduction[14] gave the alcohol (27), $C_{21}H_{36}O$, m.p. 138-140°, in 47% yield. The infrared spectrum of (27) showed an absorption at 3351cm^{-1} (-OH stretch) and this structure was supported by the ^{1}H- n.m.r. spectrum which included a signal at δ1,55 ppm (1H, s), for -OH at C-12. The mass spectrum (Table 2.5) showed peaks at m/z 304 (M^+), 286 (M^+-H_2O), 271 ($M^+-H_2O-CH_3$), and 257 ($M^+-H_2O-C_2H_5$).

Compound (27) on oxidation with chromium trioxide gave the known 5α-pregnan-12-one (28).

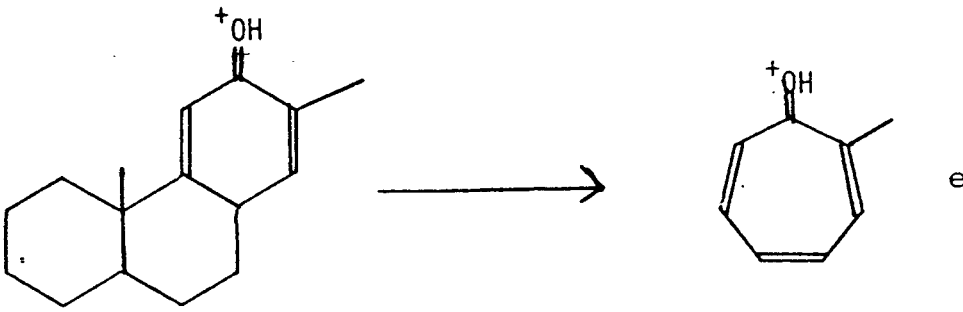
Selenium dioxide oxidation[18] of the pregnanone (28) led to Δ$^{9(11)}$ -5α -pregnen-12-one (29). The mass spectrum of compound (29) (Table 2.5) showed the molecular ion at m/z 300. The peak at m/z 285 can be assigned to the expulsion of an angular methyl group (characteristic of 12-keto pregnanes).[19] The formation of the ion at m/z 231 can arise by a McLafferty rearrangement[20,21] with a transfer of a hydrogen atom from C-20 (29 → a) and



eq. 2.1

29 a b

homolytic fission of the C14-C15 bond to yield the oxonium ion b, m/z 231 (eq. 2.1). The ion b undergoes complex rearrangement to c (eq. 2.2), m/z 121 which is reported to be the most intense peak and is characteristic of 12-keto steroids.[19]



b

c
m/z 121

eq. 2.2

Lithium aluminium hydride reduction of the compound (29) led to the desired allylic alcohol (19a), $C_{21}H_{34}O$, m.p. 118-121°, in 76% yield. The ^{1}H-n.m.r spectrum included a signal at δ5,03 ppm (1H, broad), for -C=CH-CH-O at C-11, and another signal at δ4,02 ppm (1H, broad), for -C=CH-CH-O at C-12. The mass spectrum (Table 2.5) showed that the base peak was the molecular ion, m/z 302, with the expected peaks at m/z 284 ($M^+ - H_2O$), 269 ($M^+ - H_2O - CH_3$), and 255 ($M^+ - H_2O - C_2H_5$). The epimers of the allylic alcohol (19a) were not separated but were further converted to the acetate (19b: R = Ac), m.p. 136-138°. The ^{1}H-n.m.r. spectrum of the acetate included a signal at δ2,04 ppm (s, CH_3COO-). The mass spectrum (Table 2.5) showed the molecular ion at m/z 344 and further peaks at m/z 302 ($M^+ + H - CH_3CO$), 284 ($M^+ - CH_3CO_2H$) and with the base peak at m/z 255 due to the loss of ($CH_3CO_2H + C_2H_5$).

Compounds	m/z (Intensity/base %)										
	M^+	$M-CH_3$	$M-H_2O$	$M-CH_3CO$	$M-CH_3CO_2H$	$M-(H_2O+CH_3)$	$M-(H_2O+C_2H_5)$	$M-(CH_3CO_2H+CH_3$ or $C_2H_5)$	$M-C_5H_{11}$	$C_7H_7O^+$	CH_3CO^+
24	358 (2%)			315 (33%)	298 (79%)			283 (36%)			43 (100%)
26	360 (0)			317 (0,7%)	300 (57%)			285 (23%)			43 (100%)
27	304 (7%)		286 (87%)			271 (34%)	257 (74%)		233 (53%)		
29	300 (49%)	285 (8%)							231 (61%)	121 (100%)	
19a	302 (100%)		284 (9%)			269 (20%)	255 (20%)				
19b	344 (3%)			302 (27%)	284 (24%)			255 (100%)			
30	372 (24%)	357 (10%)		329 (8%)							43 (100%)
31	374 (51%)	359 (28%)		331 (6%)	314 (9%)						43 (100%)

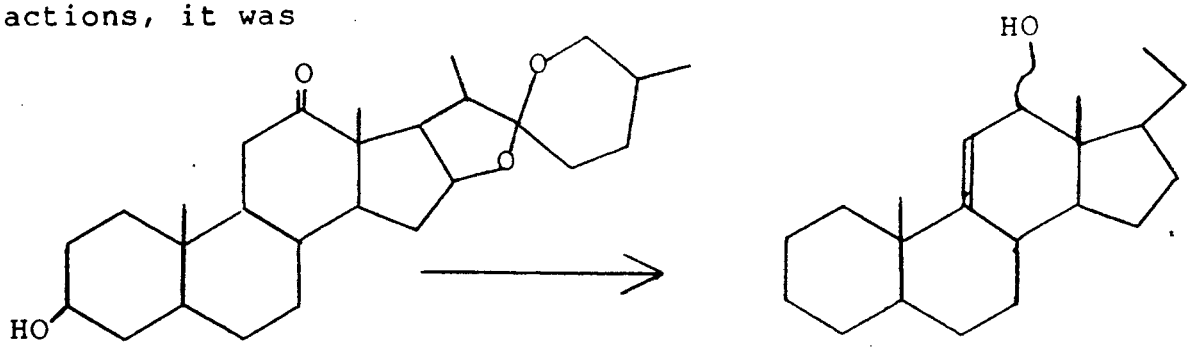
TABLE 2.5: Principal mass spectral peaks of non-spiroketal compounds with relative intensities

Compounds	m/z (Intensity/base, %)								
	$M^+ + H$	M^+	$M - C_4H_8O$	$M - (C_4H_8O + CH_3)$	$M - (C_6H_{10}O_2)$	$-(C_6H_{10}\underline{M}O_2 + CH_3)$	$-(C_6H_{10}\underline{M}O_2 + CH_3CO)$	$-(C_6H_{10}\underline{M}O_2 + CH_3CO_2H$ or $H_2O)$	$C_9H_{15}O^+$
18b (R=Ac)	473 (10%)	472 (0)	400 (10%)		358 (16%)		315 (13%)		139 (100%)
22a		416 (12%)	344 (17%)	329 (15%)	302 (30%)			284 (46%)	139 (100%)
22b		416 (13%)	344 (21%)	329 (8%)	302 (24%)			284 (38%)	139 (100%)
23		414 (11%)	342 (8%)		300 (19%)		257 (17%)		139 (100%)
22c		458 (10%)	386 (13%)		344 (4%)	329 (21%)		284 (77%)	139 (100%)
32		470 (4%)	398 (6%)		356 (18%)				139 (100%)
33b		514 (18%)	442 (9%)		400 (9%)			340 (52%)	139 (100%)
25		458 (11%)	386 (12%)			329 (11%)		284 (59%)	139 (100%)

TABLE 2.6: Principal mass spectral peaks of steroidal sapogenins and their derivatives with relative intensities

2.3 Synthesis of the spirostendiol (33a) and its diacetate (33b) from hecogenin (Path 2)

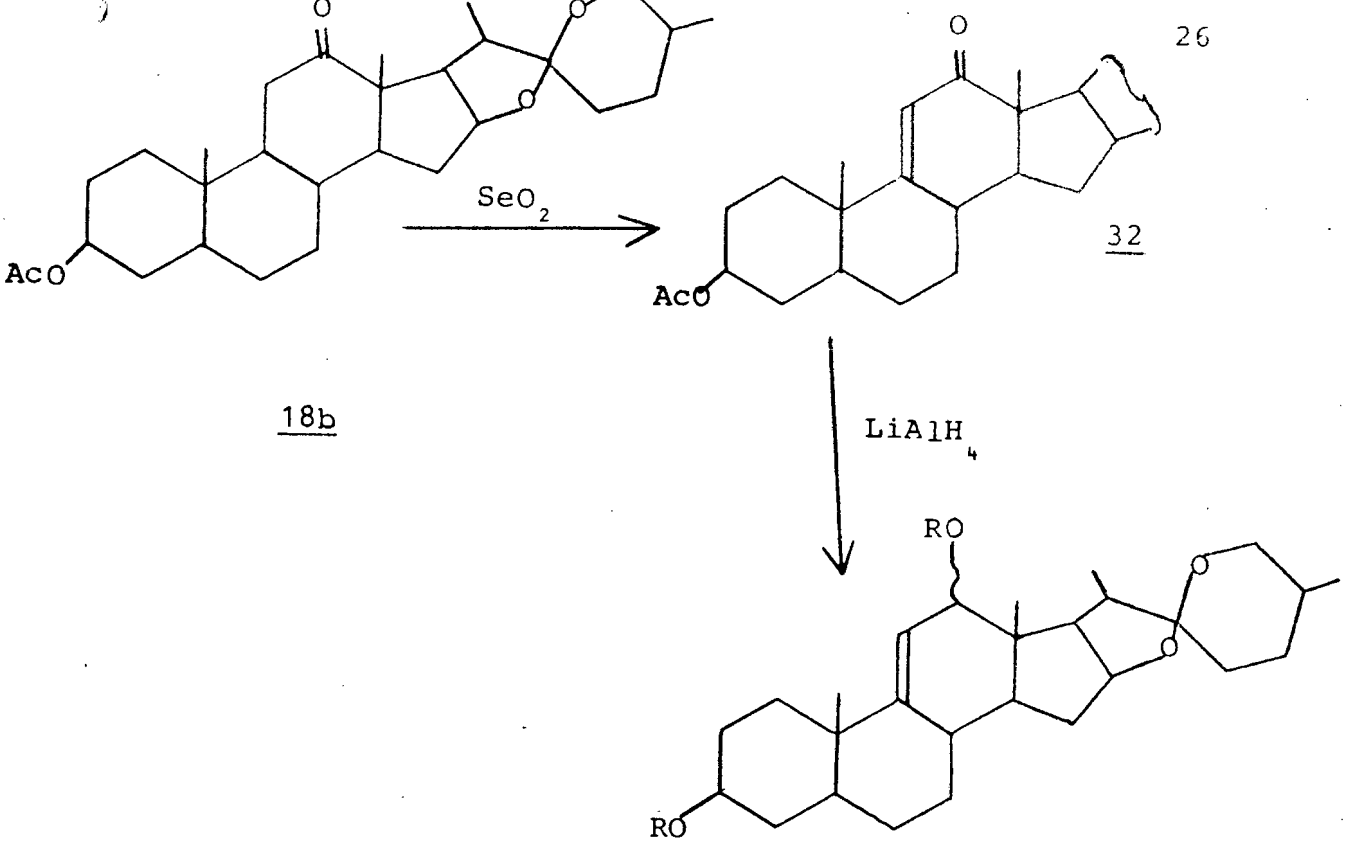
Since the final yield of the allylic alcohol (19a) from hecogenin (18a) was low, because of the many transforming reactions, it was



18a 19a

decided to follow a shorter route, namely path 2, and modify the intact hecogenin structure as shown in Scheme 2.6.

The double bond was introduced by selenium dioxide oxidation[18] of hecogenin acetate (18b) which consistently gave low yields (10%) of the α,β-unsaturated ketone (32), $C_{29}H_{42}O_5$, m.p. 217-219°. The ^{1}H-n.m.r. spectrum of the conjugated ketone (32) included signals at δ5,67 ppm (1H, s) for -C=CH-CO at C-11 and δ2,01 ppm (3H, s) for CH_3COO- at C-3. The chromophore in the compound (32) was also established by infrared spectroscopy which showed, amongst others, appropriate absorptions at 3010 (C=CH stretch), 1737 and 1251 cm^{-1} (CH_3COO stretch), and 1669 and 1595 cm^{-1} (α,β-unsaturated ketone).[11]



33a (R=H)
33b (R=Ac)

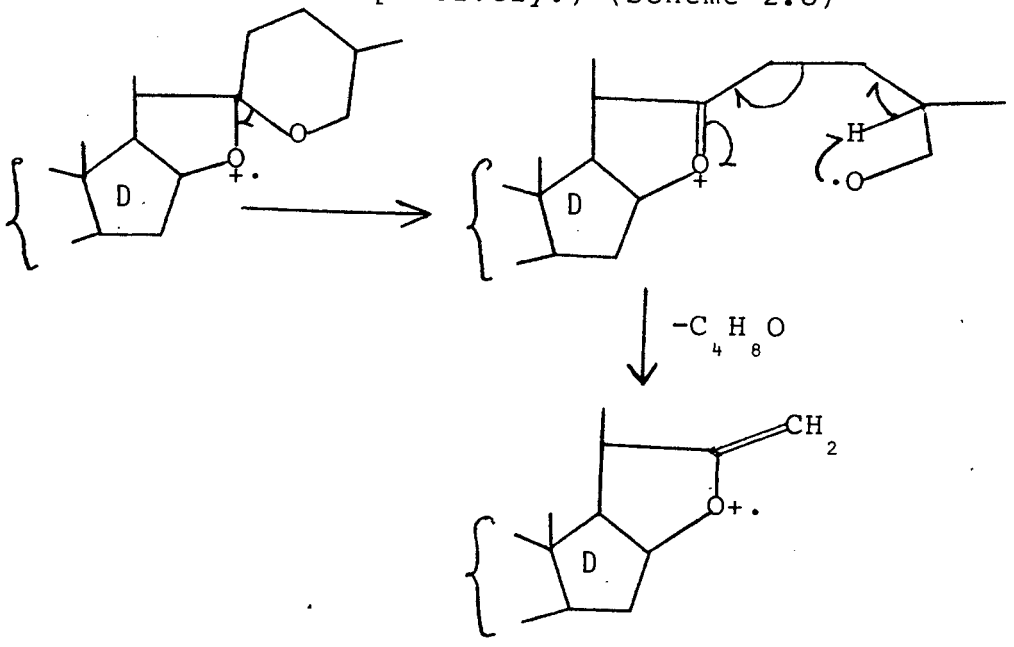
SCHEME 2.6 Showing the transformation of hecogenin acetate (18b) to the allylic alcohol (33a) (Path 2)

Lithium aluminium hydride reduced compound (32) to the diol (33a) (32% yield), which was characterised as the diacetate (33b), m.p. 140-142°. The epimers of (33a) and (33b) were not separated.

The mass spectra of compounds (18b), (32) and (33b) are summarised in Table 2.6. These confirm their molecular formulas with peaks for M^+ at m/z 473 ($M^+ + H$), 470 (M^+), and 514 (M^+) respectively. All the compounds show the loss of C_4H_8O which confirms that the spiroketal residue is intact

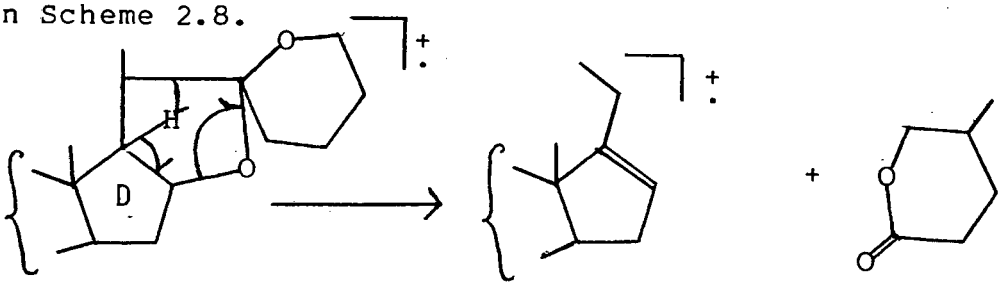
in both (32) and (33b). The fragmentation of the molecular ions resulting in the expulsion of this residue may be the result of a concerted mechanism shown in Scheme 2.7.

Another cleavage which is apparently common to the compounds under review is the loss of $C_6H_{10}O_2$ (fragment ions at m/z 358, 356 and 400 respectively.) (Scheme 2.8)



SCHEME 2.7 A possible mechanism for cleavage of the spiroketal system

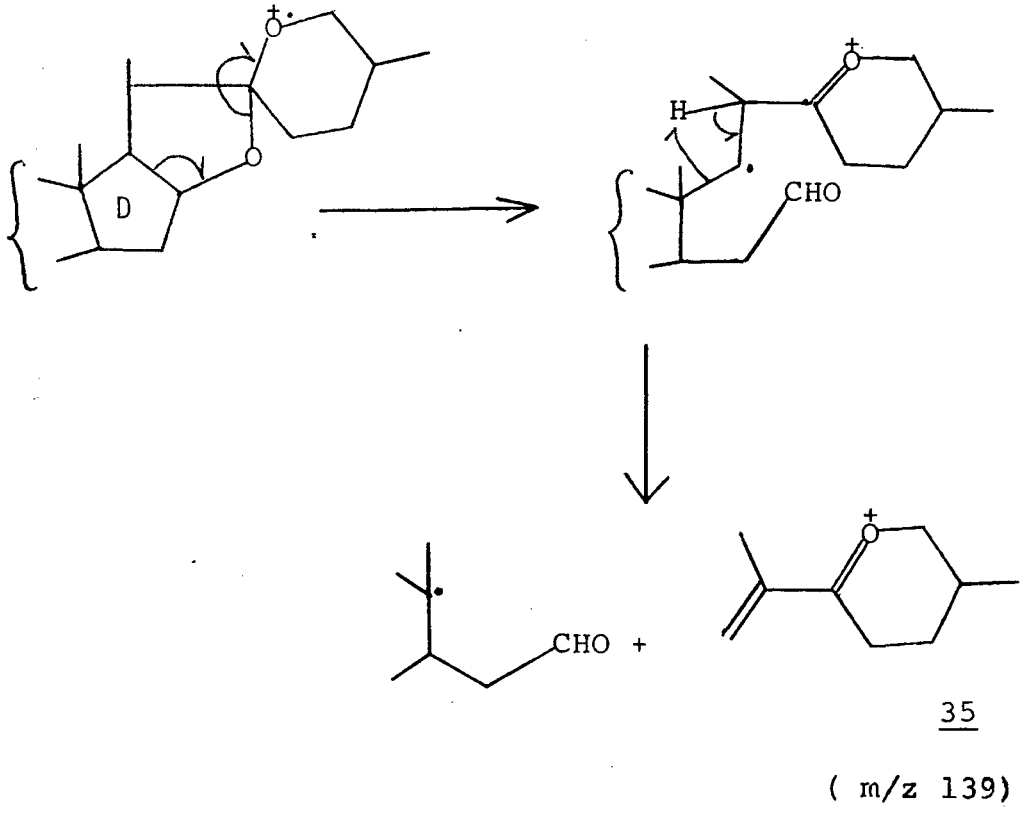
This may be explained by expulsion of the lactone (34) shown in Scheme 2.8.



34

SCHEME 2.8 Elimination of the lactone (34) from the spiroketal residue

The base peak in the mass spectra of all three of the above compounds occurred at m/z 139, equivalent to the ion, $C_9H_{15}O^+$ (Table 2.6). A plausible explanation for the formation of this ion, for which structure (35) is proposed, is presented in Scheme 2.9



35

(m/z 139)

SCHEME 2.9 A mechanism for the formation of the base peak ion, $C_9H_{15}O^+$ (35)

The ^{1}H-n.m.r. spectrum of the diol (33a) had features in common with the allylic alcohol (19a) as expected. These are summarised in Table 2.7.

Compound (33a)	Compound (19a)	Assignment
δ/ppm	δ/ppm	
5.12[a]	5.03[a]	>C=C<u>H</u>-CH(OH)-
4.0-4.6m	4.02m	>C<u>H</u>(OH)-
3.44m	-	-C(26)<u>H</u> -O-

a = an unresolved doublet

TABLE 2.7 Significant signals in the ^{1}H-n.m.r. spectra of the allylic alcohols (19a) and (33a)

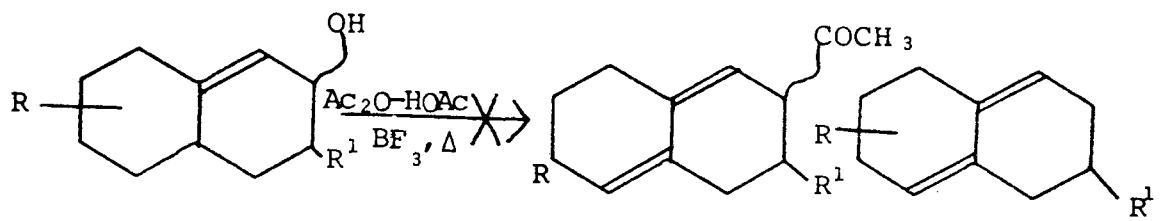
A significant difference was the broad signal at δ3,44 ppm for compound (33a), attributed to the methylene protons adjoining the oxygen atom in the tetrahydropyran ring, thus further confirming that the spiroketal system was intact. As was to be expected, the reduction step (32) ⟶ (33a) removed the C3-acetate residue. The absence of a signal at δ2,00 ppm confirmed this.

Acetylation of the diol (33a) with acetic anhydride-pyridine gave the diacetate (33b), m.p. 140-142° in 53% yield, which analysed satisfactorily for $C_{31}H_{46}O_6$, M^+ 514. The electron impact mass spectrum of the diacetate (33b) (Table 2.6) showed expected peaks at m/z 442 ($M^+-C_4H_8O$), 400 ($M^+-C_6H_{10}O_2$), 340 ($M^+-C_6H_{10}O_2-CH_3CO_2H$), and the base peak at m/z 139 ($C_9H_{15}O^+$). These are in accord with schemes 2.7, 2.8 and 2.9. On comparing the mass spectra of the allylic acetates (33b, Table 2.6) and (19b, Table 2.5), one

must conclude that the peaks at m/z 442, 440 and 139 in the mass spectrum of the allylic diacetate (33b) must be associated with the spiroketal residue, since this is absent in compound (19b). Two other peaks in the mass spectrum of compound (19b) occur at m/z 302 (M^+-$CH_2C{=}O$ from the acetate) and 255 which was also the base peak. This latter peak corresponds to the loss of ($CH_3COOH + C_2H_5$). Whether the cleavage of the ethyl group at C17 occurs in concert with the loss of acetic acid residue, or by a two step process was not determined.

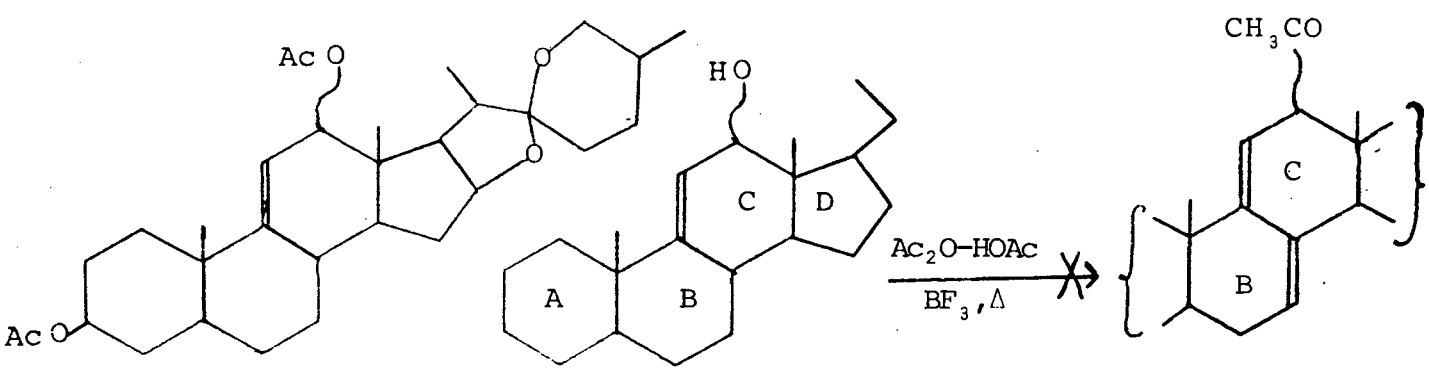
2.4 Attempts to convert the allylic alcohols and their acetates to diene ketones

Earlier it was reported that the attempts to convert the octalinols (14a-c) and their acetates (15a-c) to the desired diene ketones (16) by heating with a mixture of acetic anhydride, acetic acid and boron trifluoroethereate were unsuccessful.



14 16 17

These results, based on the evidence from GC-mass spectral studies that the heteroannular dienes (17) appeared to polymerise, led to the decision to synthesise the allylic alcohol (19a) (Section 2.2). The product was considered to have less tendency to polymerise and hence there was a greater possibility of obtaining the desired diene ketone (36).

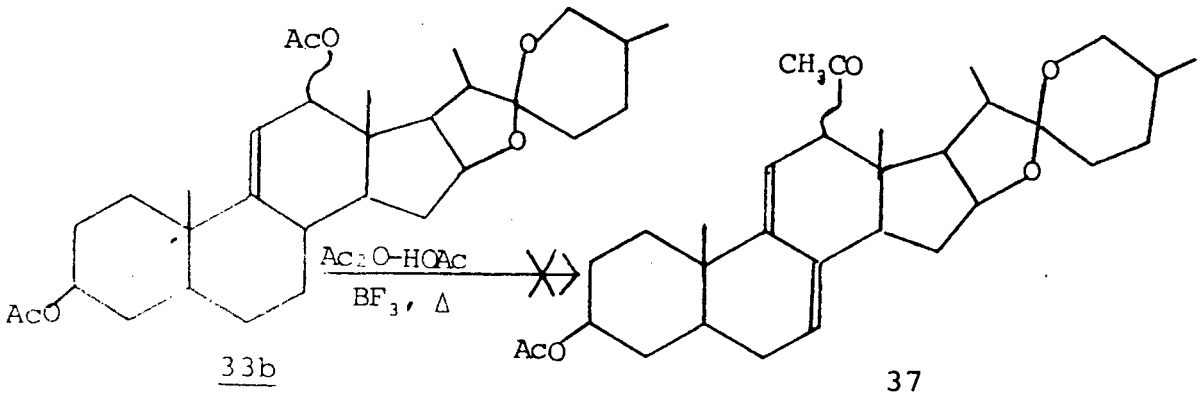


33b 19a 36

Due to the many transforming reactions which resulted in a low yield of compound (19a), it was decided to synthesise the diacetate (33b) (Section 2.3) as well.

The tetracyclic allylic alcohol (19a) was heated with the boron trifluoride-acetic anhydride-acetic acid mixture and the oily product obtained after both column and preparative layer chromatography on silica gel was shown to be homogenous by thin layer chromatography. GC-MS of the product failed to reveal a peak at m/z 326 for the expected compound (36). Instead the highest peak in the mass spectrum of the product appeared at m/z 374 (42%)and was assumed to be that of the molecular ion. The base peak occured at m/z 331 (M^+-CH_3CO), with a complementary peak at m/z 43 (CH_3CO^+). The infrared spectrum showed a strong absorption at 1705cm^{-1} (C=O stretch) but no absorption in the C=C region. A singlet at δ2,20 ppm in the ^{1}H-n.m.r. spectrum confirmed the presence of an acetyl group. No conclusions can be drawn from these results and the reaction was not examined further.

In the same way, the allylic acetate (33b) was subjected to the reaction with acetic anhydride-acetic acid and boron trifluoride in the hope of forming compound (37).



33b 37

Although a weak peak at m/z 496 (3%) may be the molecular ion for the desired diene ketone (37), in the absence of peaks at m/z 424, 382 and 139, which are indicative of the spiroketal system as discussed earlier (Section 2.3), one must conclude that the diene ketone (37) was not formed. The highest peak observed at m/z 575 (5%) suggests that the spiroketal system had been opened and the resulting diol fully acetylated. However, this reaction was not investigated further.

CHAPTER 3

EXPERIMENTAL

CHAPTER 3

EXPERIMENTAL

Unless otherwise stated, melting points were measured on a Fischer-Johns apparatus. Infrared spectra were recorded on a Perkin-Elmer Infrared Spectrometer, Model 983. ^{1}H-n.m.r. spectra were measured for solutions in [^{2}H]-chloroform, with tetramethylsilane as internal reference and recorded on a Perkin-Elmer WH90 n.m.r. spectrometer. Mass spectra were recorded on a VG Micromass 16F Mass Spectrometer coupled with a Carlo Erba Gas Chromatograph. Preparative layer chromatography was performed on glass plates coated with Merck silica gel $60F_{254}$. Column chromatography refers to dry-packed columns using silica gel (70-230 mesh). Neutral alumina columns (activity II) were also used. Neutral alumina (50g) was heated at 350° in the oven overnight in a stoppered conical flask, cooled, then 1-1,5mL of water was added and the flask was shaken well to give activity II.

Petroleum ether b.p. 60-80° was washed repeatedly with 10% of its volume of concentrated sulphuric acid, then washed with successive portions of potassium permanganate in 10% sulphuric acid until the colour of the permanganate remained unchanged. The solvent was then thoroughly washed with water, dried (anhyd. $CaCl_2$), and distilled.

Commercial diethyl ether was shaken with a concentrated solution of ferrous salt (5-10 g) to 1 litre of ether, dried (anhyd. $CaCl_2$), filtered, and then dried over sodium.

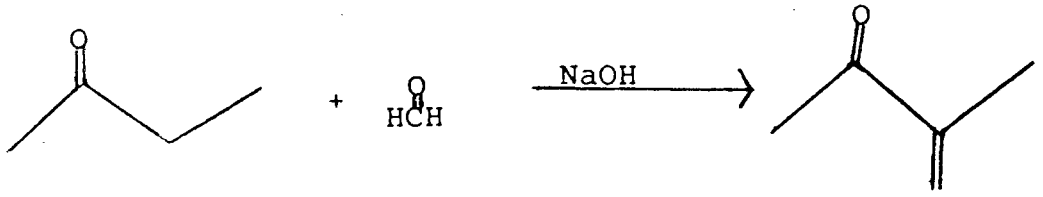
Dioxan (99-100°) and tetrahydrofuran were each refluxed over an excess of lithium aluminium hydride for 30 minutes before distillation. Boron trifluoroethereate was distilled from sodium hydride at 50°/16 mm.

Ceric sulphate reagent for spraying TLC plates was made by dissolving $Ce(SO_4)_2$ (6 g) in 1,5M H_2SO_4 (200 mL) with warming. The plates were heated to reveal the spots.

Selenium dioxide was purified by the following procedure:[22] Crude SeO_2 was placed in a large porcelain crucible, which was supported in a hole made in a stout asbestos board. Two nested funnels were inverted over the crucible, the larger funnel having a plug of glass wool in the neck. The crucible was heated in the hood until sublimation was complete (ca 25 minutes). When the crucible had cooled, the sublimed selenium dioxide (as long needle-like crystals) was removed and stored in a tightly stoppered bottle because of its poisonous properties.

All ketones were purified by redistillation before use.

Methyl isopropenyl ketone (11b) was prepared by the following procedure:[9]



11b

Methyl ethyl ketone (500 mL; 5,5 moles), 40% formalin (375 mL;5,0 moles), and 2M sodium hydroxide (10 mL) were stirred in a 1L round-bottomed flask. The mixture was warmed to start the reaction, then cooled in ice as the reaction was exothermic. (To keep the reaction alkaline, sodium hydroxide was added at intervals since formic acid was formed via Cannizzaro reaction). The mixture was then left at room temperature overnight. Acetic acid was added to neutralise the excess sodium hydroxide. The unchanged ketone and water were distilled up to 105°/760 mm i.e. approximately 450 g. Oxalic acid (anhydrous) (1% by weight of the residue) and a trace of quinol to prevent polymerisation were added and the mixture was distilled at 82° (methyl isopropenyl ketone formed an azeotropic mixture with water). The distillate was dried (anhyd. Na_2SO_4) and redistilled, b.p. 96,5-98°, $\delta(CDCl_3)$ 1,84 (3H,s,$-CH_3$), 2,30 (3H,s,$-CH_3CO$), and 5,86 (2H,d,J 16 Hz, geminal protons of conjugated alkene, $-CH_2=C-CO$); m/z 84(M^+), 69(M^+-CH_3), and 43 (CH_3CO^+).

3.1 Preparation of enamines of cyclic ketones

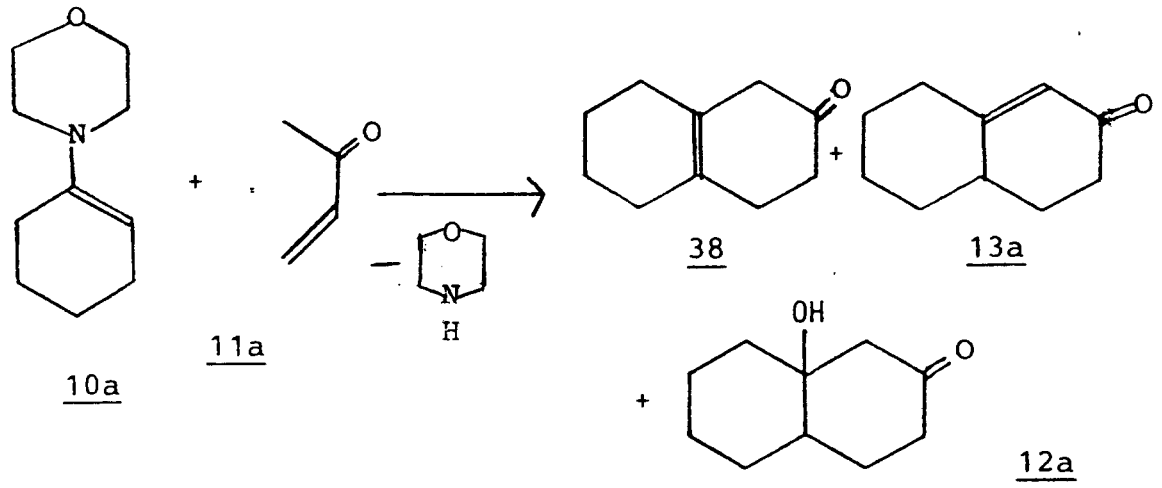
The following general procedure was adopted.[10] One equivalent of the ketone was heated with 1,5-2 equivalents of pyrrolidine or morpholine using about 300 mL of dry toluene per mole of ketone. The mixture was refluxed under a water separator until no further separation of water was observed. This usually required 5 to 8 hours with cyclohexanones. To improve the rate of reaction, p-toluenesulphonic acid (0,6 g) was added to the mixture. The enamines were used immediately without being fully characterised because of their instability. The data on the enamines is shown in Table 3.1.

Ketones	Enamines of cyclic amines	b.p.(°/mm)		% yield
		Product	Lit.[10]	
Cyclohexanone (9a)	morpholine (10a)	76-77/1,8	104-106/12	72-80
Cyclohexanone	pyrrolidine (10b)	55-57/0,4	88-92/15	65-77
4-Methylcyclo-hexanone (9c)	pyrrolidine (10c)	52-54/0,4		63-64
4-Methylcyclo-hexanone (9c)	morpholine (10d)	62-64/0,2	138-140/17	53-54

TABLE 3.1 Boiling points and percentage yields of enamines of cyclic amines (10a-d)

3.2 Cyclizations of enamines of cyclohexanones to 4,5,6,7,8,10-hexahydro-[3H]-naphthalenones ($\Delta^{1(9)}$-octal-2-ones)

3.2.1 Preparation of 4,5,6,7,8,10-hexahydro-2(3H)-naphthalenone ($\Delta^{1(9)}$-octal-2-one) (13a)[10]



10a + 11a → 38 + 13a + 12a

A solution of (10a) (9,26 g; 0,055 moles) in dioxan (60 mL) was placed in a 250 mL round-bottomed flask equipped with a bar magnetic stirrer. To this stirred solution was added freshly distilled methyl vinyl ketone (11a) (4,09 g; 0,058 moles) over a period of approximately 10 minutes. The resulting solution was heated under reflux for 4 hours, after which time 70 mL of water was added, and the mixture was heated for a further 10 hours. The solution was cooled to room temperature, poured into 100 mL of water and extracted with ether (4 x 50 mL). The ethereal extract was washed sequentially with 3M HCl (3 x 25 mL), saturated aqueous $NaHCO_3$ (2 x 10 mL), water (25 mL) and finally with saturated aqueous NaCl (20 mL), and then dried (anhyd.

Na_2SO_4), and filtered. The solvent was evaporated and the residual octalones were distilled through a short column at 68-70°/0,5 mm (lit.[10] b.p. 66°/0,05 mm). The product (3,58 g; 44%) was a mixture of the octalones (38) and (13a).

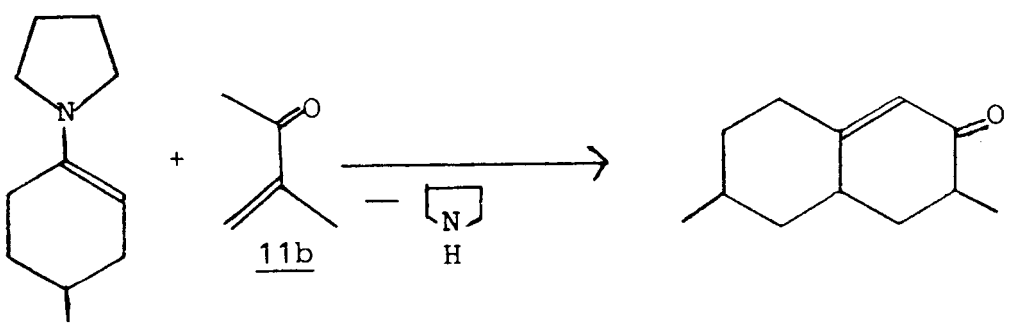
The mixture of octalones (38) and (13a) was dissolved in petroleum ether (60-110°) (20 mL) and the solution was cooled in acetone-dry ice with stirring until $\Delta^{1(9)}$-octal-2-one (13a) crystallised out. The petroleum ether was removed by suction through a fritted pipette while keeping the solution chilled to prevent the crystalline compound (13a) from melting and dissolving. The crystalline $\Delta^{1(9)}$-octal-2-one was again dissolved in 15 mL of petroleum ether and the same procedure followed. The purified $\Delta^{1(9)}$-octal-2-one crystals were allowed to melt and the petroleum ether was evaporated and completely removed under high vacuum. The final yield of (13a) was 2,77 g (34%), b.p. 79-82/0,6 mm (lit.[10] b.p. 68-69°/1,0 mm); ν_{max}(film) 3060, 1690, and 1635 cm^{-1} ; δ($CDCl_3$) 5,76 (1H,s,1-H); m/z 150(M^+), 122(M^+-28), 108, 94 and 79.

The ketol (12a) was a by-product of the reaction. When the mixture of (38) and (13a) was distilled off, a crude crystalline material remained. Recrystallisation from petroleum ether containing a little ethyl acetate gave the ketol (12a) (3-4%), m.p. 142-143°; ν_{max}(KCl) 3356 and 1712 cm^{-1} ; δ($CDCl_3$) 2,33 (4H,m,1- and 3-H_2); m/z 168(M^+), 150

($M^+ - H_2O$), 98 ($M^+ - C_4H_6O$); (Found: C, 71,6; H, 9,5. $C_{10}H_{16}O_2$ requires C, 71,4; H, 9,6%).

A mixture of the ketol (12a) (90 mg; 0,536 mmole), ethanol (5 mL), and 2M trifluoroacetic acid (1 mL) was refluxed for 1 hour in on a steam-bath. The mixture was cooled, and extracted with ether (3 x 15 mL). The combined ethereal extracts were dried (anhyd. Na_2SO_4) and filtered. The solvent was evaporated and the crude product chromatographed (Si-gel column, 70-230 mesh, (10 g); eluent 20% ethyl acetate-light petroleum ether), to yield 17,9 mg (22%) of the compound (13a).

3.2.2 3,6-Dimethyl-$\Delta^{1(9)}$-octal-2-one (13c)



10c 11b 13c

A solution of enamine (10c) (15,26 g; 0,0872 moles) and methyl isopropenyl ketone[9] (11b) (8,4 g; 0,1 moles) in dioxan (75 mL) was refluxed for 12 hours. A buffer solution (acetic acid (9 mL), water (9 mL), and sodium acetate (4,1 g)) was then added and refluxing was continued for 4 hours. After cooling, the organic layer was separated off and the aqueous layer was extracted with toluene. The combined

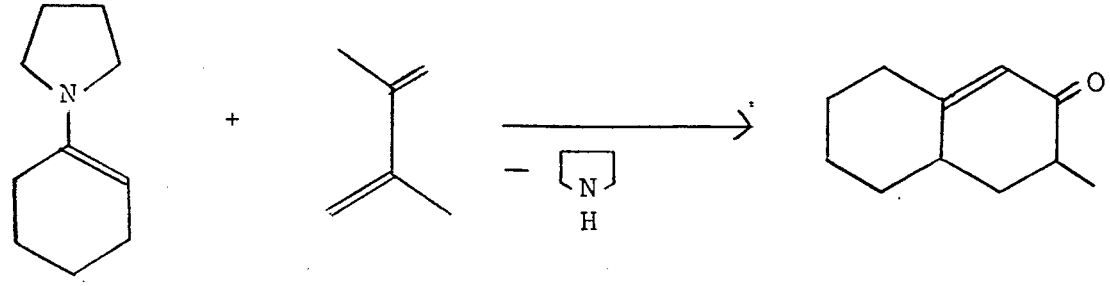
organic extracts were washed successively with 10% hydrochloric acid and saturated aqueous sodium bicarbonate, and dried (anhyd. Na_2SO_4). Removal of the solvent at room temperature gave a product which, on distillation, gave the octalone (13c), (8,60 g; 57%), b.p. 76-78°/0,4 mm (lit.[12] 112-116°/2,5 mm); ν_{max} (KCl) 3020, 1670, and 1624 cm^{-1}; $\delta(CDCl_3)$ 5,65 (1H, s, 1-H), 1,08 (3H, d, J 7 Hz, 3-CH_3), and 0,92 (3H, d, J 7 Hz, 6-CH_3); m/z 178 (M^+), 163 (M^+-CH_3), 150, 107, 93, and 79; (Found: C, 80,5; H, 9,8. Calc. for $C_{12}H_{12}O$: C, 80,85; H, 10,18%).

4-methylcyclohexanone-morpholine enamine (10d) (12,0 g; 66,3 mmole) and methyl isopropenyl ketone (11b) (5,50 g; 63,1 mmole) were treated according to the procedure described in section 3.2.1. After working up, removal of the solvent by vacuum evaporation gave a solid which, on recrystallisation from petroleum ether gave in low yield 3,6-dimethyl-decal-2-on-9-ol (12c) (0,41 g; 3%), m.p. 135-137° (lit.[12] 165°); ν_{max} (Nujol) 3420 and 1710 cm^{-1}; $\delta(CDCl_3)$ 2,36 (3H, m, 1—H_2 and 3-H), 1,04 (3H, d, J 7 Hz, 3-CH_3), and 0,93 (3H, d, J 6 Hz, 6-CH_3); m/z 196 (M^+), 179 (M^+-OH), 125 (M^+-C_4H_7O), 112 (M^+-C_5H_8O), and 97; (Found: C, 73,2; H, 10,4. Calc. for $C_{12}H_{20}O_2$: C, 73,5; H, 10,2%).

The decalonol (12c) (100 mg; 0,510 mmole), ethanol (5 mL), and 2M trifluoroacetic acid (1 mL) were reacted according to the procedure described in section 3.2.1.

After working up, removal of the solvent by vacuum evaporation gave a crude product (88,2 mg) that was chromatographed (Si-gel column, 70-230 mesh, (10 g); eluent petroleum ether-ethyl acetate (8 : 1)), to yield 30,3mg, (34%) of the compound (13c).

3.2.3 3-Methyl-$\Delta^{1(9)}$-octal-2-one (13b)

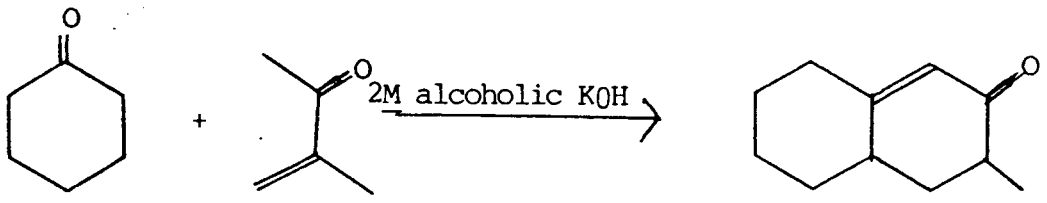


10a 11b 13b

When cyclohexanone-pyrrolidine enamine (10a) (17,5 g; 0,116 mole) was reacted with the methyl isopropenyl ketone (11b) (10,1 g; 0,12 mole) according to the procedure described in the previous secton 3.2.2, the octalone (13b), b.p. 80-82°/0,7 mm (lit.[10] 100-105°/0,5 mm) was obtained in 42% yield, ν_{max} (film) 3010, 1666, and 1624 cm^{-1}; $\delta(CDCl_3)$ 5,74 (s, 1-H) and 1,09 (3H, d, J 6 Hz, 3-CH_3); m/z 164 (M^+), 122 ($M^+ - C_3H_6$), 94 ($M^+ - C_4H_6O$), and 79; (Found: C, 79,1 ; H, 9,8 . Calc. for $C_{11}H_{16}O$: 80,4; H, 9,8%)

3.3 Alternative preparation of octal-2-ones via Michael-type condensation of cyclohexanone with α,β-unsaturated ketones

3.3.1 3-Methyl-$\Delta^{1(9)}$-octal-2-one (13b)



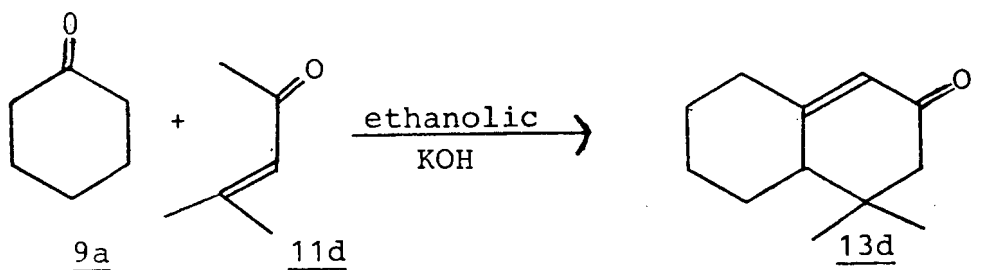
9a 11b 13b

To a mixture of cyclohexanone (9a) (100,0 g; 1,02 mole) and methyl isopropenyl ketone (11b) (12,0 g; 0,143 mole) was added 2M ethanolic potassium hydroxide (7,5 mL). The reaction mixture was refluxed for 10 minutes, cooled to room temperature, neutralised (5M hydrochloric acid), and extracted with ether (3 x 70 mL). The combined ethereal extracts were dried (anhyd. potassium carbonate), filtered, and the solvent was evaporated off to yield crude product (96,2 g) which was distilled to yield the octal-2-one (13b) (13,3 g; 57%), b.p. 82-86°/0,7 mm. The distillate (9,19 g) was applied to a column of silica gel (70-230 mesh, 400 g) and eluted with chloroform, collecting 100 mL fractions. The fractions were monitored by TLC (eluent chloroform-methanol (97 : 3)). Fraction numbers 26 to 29 were combined, evaporated to yield an oil which on distillation gave pure compound (13b) (2,3 g; 25% overall yield), b.p.

80-82°/0,4 mm. The infrared spectrum was identical with that found in 3.2.3.

The compound (13b) gave a semicarbazone, (m.p. 203-206° (from little ethanol-water) (Found: C, 65,1 ; H, 8,8; N, 19,0 . Calc. for $C_{12}H_{19}ON_3$: C, 65,1; H, 8,7; N, 19,0%) and a 2,4-dinitrophenylhydrazone, m.p. 145-147° (from ethanol) (Found: C, 59,0; H, 5,5 ; N, 16,2 . Calc. for $C_{17}H_{20}O_4N_4$: C, 59,3; H, 5,9; N, 16,3%).

3.3.2 4,4-Dimethyl-$\Delta^{1(9)}$-octal-2-one (13d)



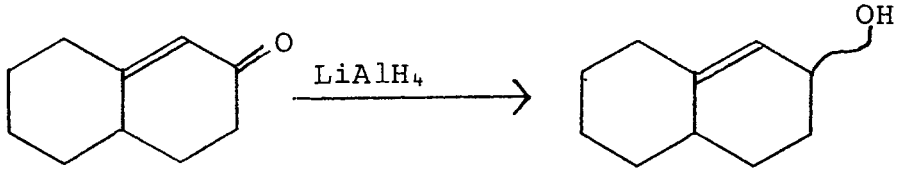
9a 11d 13d

The procedure was the same as that described for the synthesis of compound (13b) (Section 3.3.1). From cyclohexanone (9a) (100,0 g; 1,02 mole) and mesityl oxide (11d) (12,0 g; 0,122 mole) was obtained the desired octalone (13d) as a new compound (12,4 g; 57%), b.p. 73-91°/0,2-0,4 mm; δ($CDCl_3$) 5,79 (1H, s, 1-H), 3,67 (2H, s, 3—H_2), 1,04 (3H, s, 4-CH_3), and 0,95 (3H, s, 4-CH_3); m/z 178 (M^+), 163 (M^+-CH_3), 150 (M^+-CO), 122 ($M^+-C_4H_8$), and 79; (Found: C, 78,2; H, 10,3. $C_{12}H_{18}O$ requires C, 80,9; H, 10,2%).

3.4 Reductions of the $\Delta^{1(9)}$-octal-2-ones to 2,3,4,5,6,7,8,10-octahydronaphthalin-2-ols ($\Delta^{1(9)}$-octalin-2-ols)

General procedure: The octalone was dissolved in dry ether (1 L per mole of compound). A slurry of excess lithium aluminium hydride (ca 60,0 g per mole of octalone in 5 L of dry ether) was added drop-wise to the ice-cold solution with stirring. After the addition of the slurry, the mixture was stirred for a further 40-60 minutes. A saturated aqueous solution of ammonium chloride was cautiously added drop-wise to destroy the excess lithium aluminium hydride followed by anhydrous magnesium sulphate and the ether layer was separated from the solids by filtration and dried (anhyd. Na_2SO_4). The filtered ethereal extract was evaporated and the residue was distilled under high vacuum.

3.4.1 2-Hydroxy-2,3,4,5,6,7,8,10-octahydronaphthalene (14a)



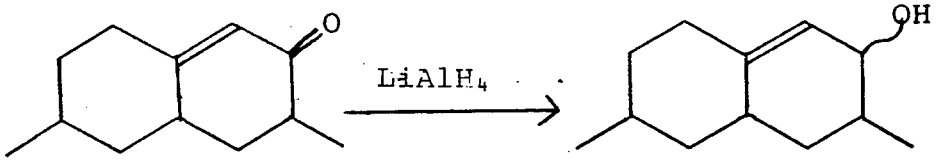
13a 14a

Reduction of the 2-octalone (13a) (3,0 g; 20 mmole) following the above procedure gave the octalinol (14a) (1,5 g; 50% yield), b.p. 82-84°/1,5 mm; ν_{max} (film) 3340, 3020, and 1665cm^{-1} ;δ($CDCl_3$) 5,44 (1H, d, J 7 Hz, 1-H) and 4,18 (1H,

broad, -C<u>H</u>(OH)-); m/z 152 (M^+), 134 (M^+-H_2O), 109, 91 and 79; (Found: C, 78,7; H, 10,6 . $C_{10}H_{16}O$ requires C, 78,9; H, 10,6%).

A comparison of compounds (<u>38</u>), <u>13a</u>) and (<u>14a</u>) by TLC on silica gel in $CHCl_3$-MeOH (97 : 3) gave spots, revealed by iodine and U.V. at R_F 0,35, 0,62 and 0,49 respectively.

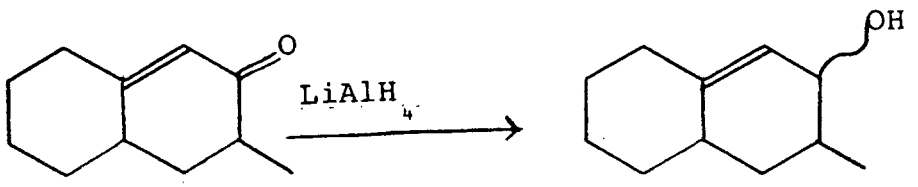
3.4.2 <u>2-Hydroxy-3,6-dimethyl-2,3,4,5,6,7,8,10-octahydro-naphthalene (14c)</u>



<u>13c</u> <u>14c</u>

Reduction of the 2-octalone (<u>13c</u>) (3,0 g; 16,9 mmole) gave the octalinol (<u>14c</u>) (1,7 g; 55% yield), b.p. 78-80°/0,6 mm (105-107°/2,5 mm)[13] ; ν_{max} (film) 3333, 2945, and 1664 cm^{-1}; $\delta(CDCl_3)$ 5,34 (1H, broad, 1-H), 3,75 (1H, broad, -C<u>H</u>(OH)-), 1,05 (3H, d, J 6 Hz, 3-CH_3), and 0,89 (3H, d, J 6 Hz, 6-CH_3); m/z 180 (M^+), 162 (M^+-H_2O), 147, 138, 123 (M^+ + $H-C_3H_6O$), 108, 91, and 79; (Found: C, 79,8 ; H, 11,0 . Calc. for $C_{12}H_{20}O$: C, 79,9; H, 11,2%).

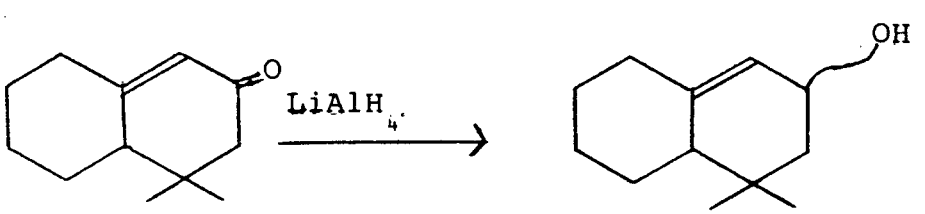
3.4.3 2-Hydroxy-3-methyl-2,3,4,5,6,7,8,10-octahydronaphthalene (14b)



13b 14b

The 2-octalone (13b) (3,0 g; 18,3 mmole) on reduction gave the methyloctalinol (14b) (1,6 g; 54% yield), b.p. 74-76°/0,5 mm; ν_{max} 3332, 2920, and 1662 cm^{-1}; $\delta(CDCl_3)$ 5,34 (1H, broad, 1-H), 3,78 (1H, broad, -CH(OH)-), and 1,07 (3H, d, J 6 Hz, 3-CH_3); m/z 166 (M^+), 148 (M^+-H_2O), 133, 123 ($M^+ + H - C_2H_4O$), 109 ($M^+ + H - C_3H_6O$), 95 ($M^+ + H - C_4H_8O$), and 81; (Found: C, 79,3 ; H, 10,6 . $C_{11}H_{18}O$ requires C, 79,4 ; H, 10,9%).

3.4.4 2-Hydroxy-4,4-dimethyl-2,3,4,5,6,7,8,10-octahydronaphthalene (14d)



13d 14d

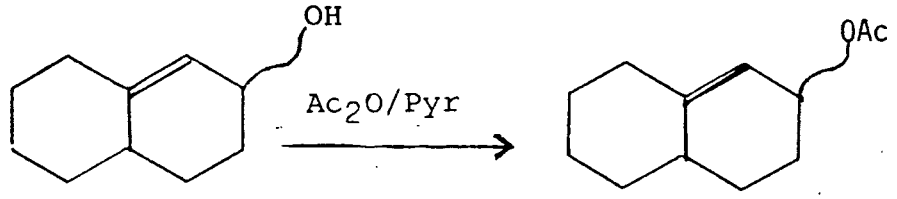
Reduction of 2-octalone (13d) (3,56 g; 20 mmole) gave the previously unreported octalinol (14d) (1,1 g; 31% yield), b.p. 84-85°/3,2 mm; ν_{max} 3347, 2919, and 1663 cm^{-1}; $\delta(CDCl_3)$ 5,34 (1H, s, 1-H), 4,0 (2H, broad, 3—H_2), 3,38 (1H, broad,

-C<u>H</u>(OH)-), and 0,88 (6H, s, $>CMe_2$); m/z 180 (M^+), 162 (M^+-H_2O), 147, 119, 105, 91 and 77; (Found: C, 79,9; H, 11,2. $C_{12}H_{20}O$ requires C, 80,0; H, 11,1%).

3.5 Acetylation of $\Delta^{1(9)}$-octalin-2-ols

General procedure: The octalinols (1,0 mmole) were acetylated with acetic anhydride (2 mL) and pyridine (3 mL) at 100°/1 hr and then kept at room temperature overnight, the mixture poured into ice (10 g per 1,0 mmole of compound), and extracted with chloroform (3 x 10 mL). The combined chloroform extracts were washed successively with 5% $NaHCO_3$ solution and water, then dried (anhyd. Na_2SO_4), filtered and the solvent evaporated. The yields were almost quantitative, and the products were oils.

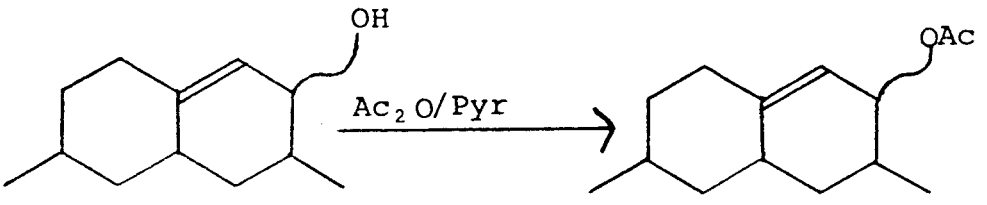
3.5.1 2-Acetoxy-2,3,4,5,6,7,8,10-octahydronaphthalene (15a)



14a 15a

The impure 2-acetoxyoctalin (15a) was obtained as an oil, $\delta(CDCl_3)$ 5,80 (1H, broad, 1-H), 5, 14 (1H, m, -CH(OAc)), and 2,02 (3H, s, 2-$OCOCH_3$); m/z 194 (M^+), 152 (M^+ + H-$COCH_3$), 134 (M^+-CH_3CO_2H), 119, 105, 91, and 79.

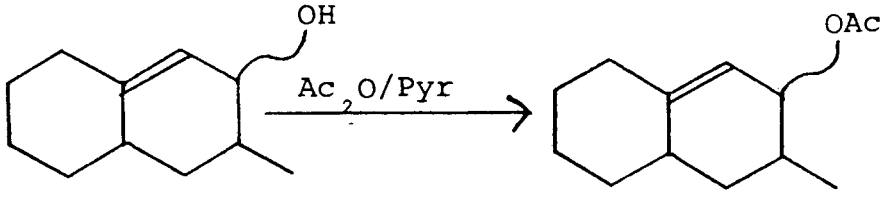
3.5.2 2-Acetoxy-3,6-dimethyl-2,3,4,5,6,7,8,10-octahydro-naphthalene (15c)



14c 15c

The 2-acetoxyoctalin (15c) showed, ν_{max} (film) 2949, 1732, 1664, and 1239 cm^{-1} ; $\delta(CDCl_3)$ 5,18 (1H, broad, 1-H), 4,94 (1H, broad, -CH(OAc)-), 2,04 (3H, s, 2-$OCOCH_3$), and 0,91 (6H, d, J 6 Hz, 6-Me and 3-Me); m/z 222 (M^+), 180 (M^+ + H-$COCH_3$), 162 (M^+-CH_3CO_2H), 147, 120, 105, 91 and 79; (Found: C, 75,6; H, 9,7. $C_{14}H_{22}O_2$ requires C, 75,6 ; H, 10.0%).

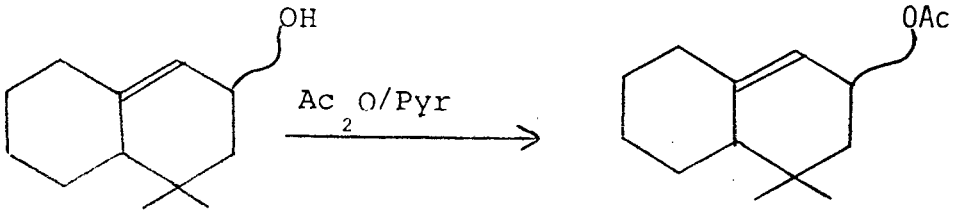
3.5.3 2-Acetoxy-3-methyl-2,3,4,5,6,7,8,10-octahydronaphth-alene (15b)



14b 15b

The 2-acetoxyoctalin (15b) showed, ν_{max} (film) 2925, 1731, 1665, and 1239 cm^{-1} ; $\delta(CDCl_3)$ 5,20 (1H, s, 1-H), 4,97 (1H, broad, -CH(OAc)), 2,06 (3H, s, 2-$OCOCH_3$), and 0,95 (3H, d, J 6 Hz, 3-Me); m/z 208 (M^+), 166 (M^+ + H -$COCH_3$), 148 (M^+-CH_3CO_2H), 133, 119, 105, 91 and 79; (Found: C, 74,9; H, 9,6. $C_{13}H_{20}O_2$ requires C, 75,0; H, 9,7%).

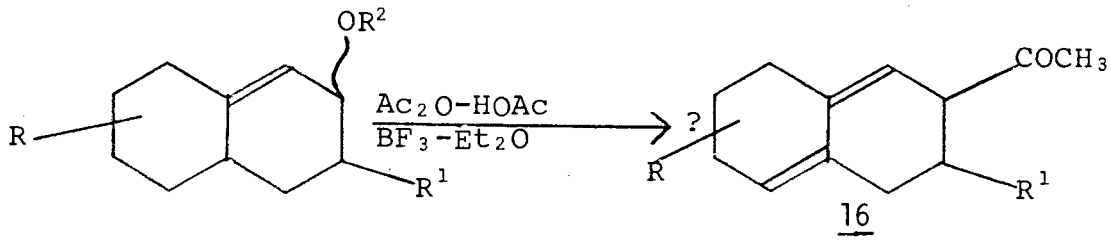
3.5.4 2-Acetoxy-4,4-dimethyl-2,3,4,5,6,7,8,10-octahydro-naphthalene (15d)



14d 15d

The impure 2-acetoxyoctalin (15d) was obtained, m/z 222 (M^+), 180, 163 (M^+-CH_3CO_2), 137, 109 and 44.

3.6 Attempts to prepare 2,3,4,6,7,8-hexahydronaphthalin-2-yl- ethanones



Starting compounds	R	R¹	R²
14a	H	H	H
15a	H	H	Ac
14c	6-Me	Me	H
15c	6-Me	Me	Ac
14b	H	Me	H
15b	H	Me	Ac

General procedure: The octalinols (or their acetates) were dissolved in glacial acetic acid (2 mL) per 100 mg of the octalinol) in a glass tube. Acetic anhydride (1mL) and boron trifluoroethereate (4 drops) were added and the tube was sealed immediately. The tube was heated in a water-bath at 100°. The time was varied, (between 5 and 60 minutes), to determine the best conditions for the acylation. The reaction mixture was poured onto ice (10,0 g) and extracted with chloroform (3 x 20 mL). The combined chloroform extracts were washed successively with 5% $NaHCO_3$ solution (20 mL), water (20 mL), then dried (anhyd. Na_2SO_4), filtered, and the solvent evaporated off. The GC-MS studies

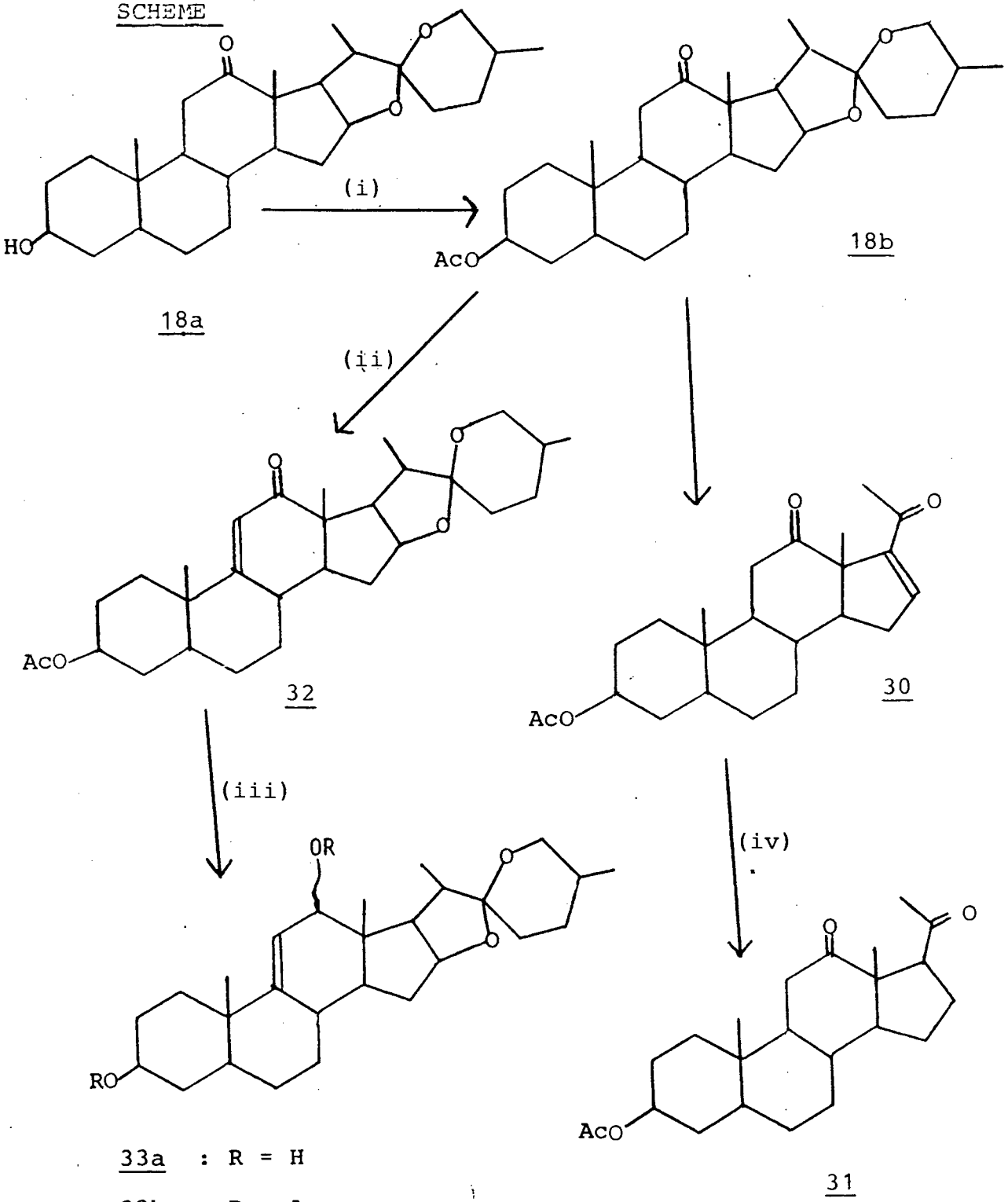
(Table 3.2) generally showed that a polymeric mass was obtained from each reaction, and that the desired acetylhexalins (16), if present, were not formed in significant amounts. Generally the results were disappointing.

TABLE 3.2 GC-MS of the C-acylation reactions of octalinols (14a-c) and their acetates. In reactions involving the compounds (15a-c) traces of hydroquinone (to stop polymerisation) were added. The reaction of compound (15c) was promising but the yield of crude product was very low (3-4%).

Starting compounds	Products (16) m/z (Rel. Int. %)
14a	403 (16%), 268 (100%), 176 (2%), 158 (71%), 135 (34%), 57 (75%), and 43 (56%). ($C_{12}H_{16}O$ requires 176).
15a	176 (7%), 150 (40%), 122 (100%), 108 (22%), 94 (33%), 79 (24%), and 41 (9%)
14c	366 (8%), 352 (15%), 338 (23%), 323 (30%), 204 (10%), 201 (42%), 162 (27%), 149 (40%), 81 (47%), 55 (61%), 43 (100%), and 41 (64%). ($C_{14}H_{20}O$ requires 204).
15c	204 (22%), 203 (100%), 187 (21%), 159 (22%), 142 (10%), 71 (7%), and 53 (9%)
14b	296 (7%), 214 (42%), 199 (48%), 190 (4%), 184 (36%), 169 (82%), 147 (100%), 141 (36%), 133 (11%), 119 (12%), 105 (18%), and 91 (15%). ($C_{13}H_{18}O$ requires 190).
15b	201 (0,6%), 190 (0,6%), 148 (100%), 79 (12%), 43 (28%), and 41 (10%)

3.7 Experiments to prepare the spirostenediol (33a) and its diacetate (33b) from hecogenin (18a)

SCHEME



33a : R = H

33b : R = Ac

Reagents : (i) Ac_2O-Pyr; (ii) SeO_2/HCl-HOAc; (iii) $LiAlH_4$

(iv) H_2/Pd-C

3.7.1 Preparation of hecogenin acetate (18b)

Hecogenin (18a) (744 mg; 1,731 mmole) was acetylated according to the procedure described in Section 3.5. The product was recrystallised (methanol) to yield compound (18b) (628 mg; 77%), m.p. 243(249°) (lit.[2,3] 243(252°), δ($CDCl_3$) 4,66 (1H, m, 3-H), 4,30 (1H, m, 16-H), 3,40 (2H, broad, C(26)H_2-O), 2,00 (3H,s, 3-$OCOCH_3$), 1,07 (3H, d, J 6 Hz, CHMe), 1,0 (3H, s, CMe), 0,92 (3H, s, CHMe), and 0,80 (3H, d, J 6 Hz, CHMe); m/z 473 (M^+ + H),413 (M^+-CH_3CO_2), 400, 358, 315, 139, and 126.

3.7.2 Dehydrogenation of hecogenin acetate (18b) to the unsaturated ketone (32)

Hecogenin acetate (18b) (321 mg; 0,684 mmole) was dissolved in 0,0006 M HCl in acetic acid (15 mL), and an excess of selenium dioxide (288 mg; 2,6 mmoles) was added. The mixture was refluxed overnight, filtered through a sintered glass funnel, concentrated to low volume using a rotavacuum evaporator, and extracted with ether (4 x20 mL). The dried (anhyd. Na_2SO_4) ethereal extract was filtered and the solvent was evaporated off. The crude product (452 mg) was dissolved in chlorobenzene-acetic acid (4:1 ; 8 mL)and chromium trioxide (0,3 g) in water (0,3 mL) was added. The mixture was vigorously stirred for 2 hours. The chlorobenzene solution was decanted and again stirred for 2 hours

with chromium trioxide (0,15 g) in water (0,15 mL). The organic phase was separated and washed with water (4 x 20 mL). After drying (anhyd. Na_2SO_4), the chlorobenzene was removed under reduced pressure and the crude product (377 mg) was chromatographed on a column of Si-gel (70-230 mesh, 13,0 g) using petroleum ether-ethyl acetate (6 : 1) as eluent. 10 mL - Fractions were collected and these were monitored by TLC (ceric sulphate spray and warming on a hot-plate). Fractions 11 to 13 were combined and evaporated to yield compound (32) (33 mg; 10%); m.p. 217-219° (from methanol); ν_{max} (KCl) 3010, 1737, 1669, 1595, and 1251 cm^{-1}; $\delta(CDCl_3)$ 5,68 (1H, s, -C=CH-), 4,65 (1H, broad, 3-H), 4,38 (1H, m, 16-H), 3,43 (2H, broad, $C(26)H_2$-O), 2,01 (3H, s, 3-$OCOCH_3$), 1,11 (6H, d, J 6 Hz, 2 x CMe), 0,91 (3H, s, CMe), and 0,78 (3H, d, J 6 Hz, CHMe); m/z 470 (M^+), 411 ($M^+-CH_3CO_2$), 398, 356, 139, and 121; (Found: C, 74,0; H, 9,0. $C_{29}H_{42}O_5$ requires C, 74,0; H, 8,9%).

3.7.3 Preparation of the spirostendiol (33a)

Reduction of compound (32) (51 mg; 0,108 mmole) with lithium aluminium hydride (1,0 g) was performed according to the procedure described in Section 3.4. The crude product was chromatographed on a column of Si-gel (70-230 mesh, 8,0 g) using petroleum ether-ethyl acetate (1 : 1) as eluent. 3 mL - Fractions were collected and these were monitored by TLC (ceric sulphate spray and warming on a hot-plate).

Fractions 18 to 28 were combined and evaporated to yield compound (33a) (16 mg; 32%), $\delta(CDCl_3)$ 5,12 (1H, s, =C(11)H-), 4,6-4,0 (3H, m, -CH(O)- at C3-, C12 and C16), 3,44 (2H, broad, $C(26)H_2$-O), 1,9 (2H, s, 3- and 12-OH disappears in D_2O), 0,96 (6H, s, 2 x CMe), and 0,74 (6H, dd, J 7 Hz, 2 x CHMe).

3.7.4 Preparation of the diacetoxyspirostene (33b)

Compound (33a) (26 mg; 0,055 mmole) was acetylated according to the procedure described in Section 3.5. The crude product was chromatographed on a Si-gel column (70-230 mesh, 10,0 g) using petroleum ether-ethyl acetate (4 : 1) as eluent. 3mL fractions were collected and these were monitored by TLC (ceric sulphate spray and warming on a hot-plate). Fractions 12 to 20 were combined and evaporated to yield compound (33b) (15 mg; 53%), m.p. 140-142° (from methanol), ν_{max} (KCl) 2928, 1734, 1636, and 1241 cm^{-1}; $\delta(CDCl_3)$ 5,26 (1H, d, J 8 Hz, =C(11)H-), 4,62-4,32 (3H, m, -CH(O)- at C3, C12 and C16), 3,42 (2H, broad, $C(26)H_2$-O), 2,07-2,01 (6H , s, 3- and 12-$OCOCH_3$), and 1,02-0,78 (12H, m, 2 x CMe , and 2 x CHMe); m/z 514 (M^+), 455 ($M^+-CH_3CO_2$), 442, 400, 358, 340, 139, and 108; (Found: C, 72,4; H, 8,9. $C_{31}H_{46}O_6$ requires C, 72,4; H, 8,9%).

3.7.5 Cleavage of the spiroketal of hecogenin acetate (18b) to the diketoacetate (30)

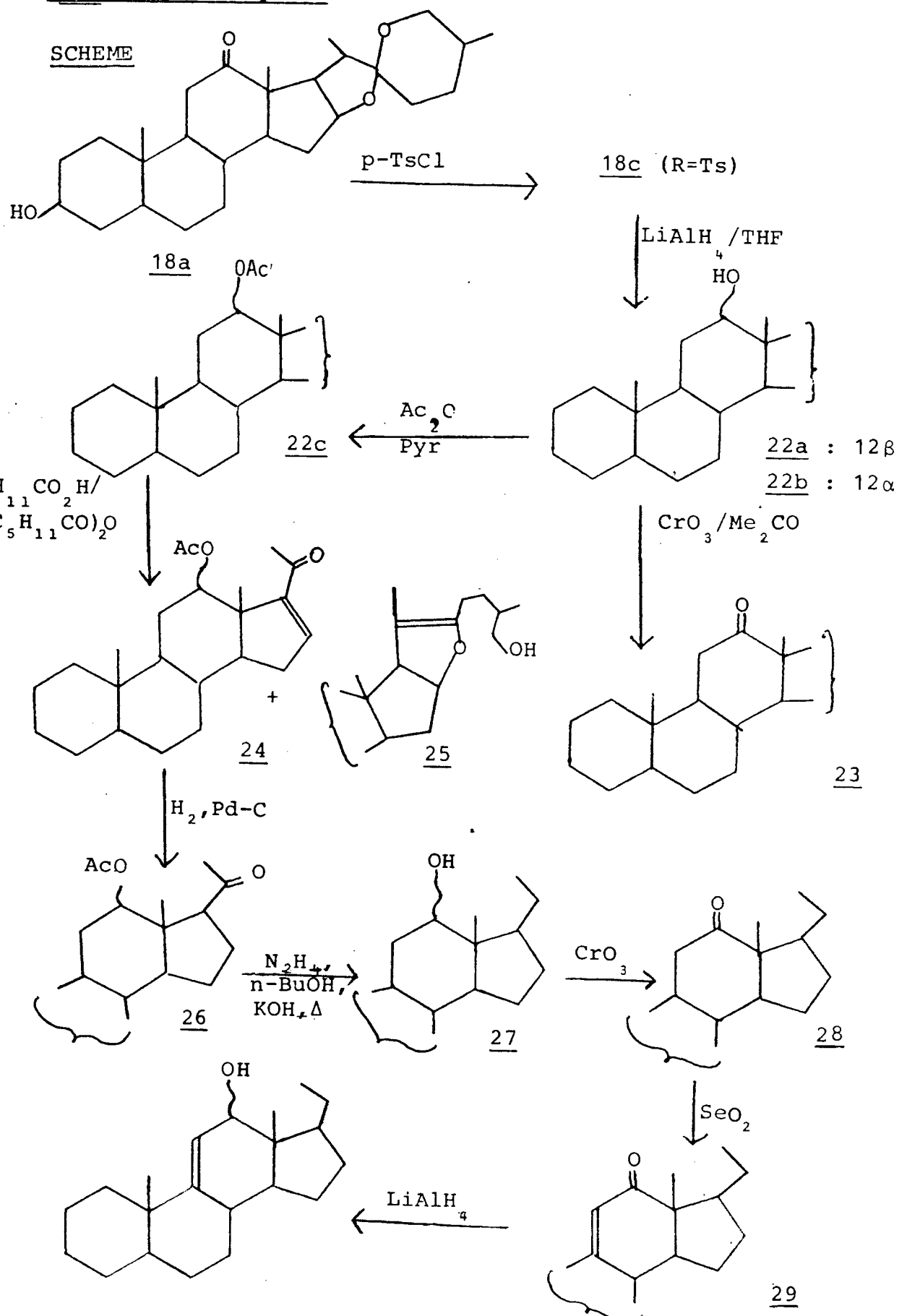
The procedure for cleaving the spiroketal of hecogenin acetate (18b) (3,0 g; 6,35 mmole) was the same as that described in Section 3.8.5. Work up gave compound (30) (0,648 g; 28%), m.p. 178-180° (from ether, lit.[15] 178-181°), $\delta(CDCl_3)$ 6,60 (1H, t, J 3 Hz, -C=C(16)H-), 4,68 (1H, m, 3-H), 2,30 (3H, s, 17-$COCH_3$), 2,00 (3H, s, 3-$OCOCH_3$), 1,3 (3H, s, CMe), and 0,94 (3H, s, CMe); m/z 372 (M^+), 357 (M^+-CH_3), 329 (M^+-CH_3CO), 149, 123, 105, 79, 67, 55, and 43; (Found: C, 72,3 ; H, 8,4. Calc. for $C_{23}H_{32}O_4$: C, 74,2; H, 8,6%).

3.7.6 Catalytic hydrogenation of compound (30) to the diketone (31)

Compound (30) (583 mg; 1,56 mmole) was hydrogenated as described in Section 3.8.6 to yield compound (31) (288 mg; 49%), m.p. 188-190° (from ethyl acetate, lit.[15] 188-190°); $\delta(CDCl_3)$ 4,68 (1H, m, 3—H), 3,30 (1H, t, J 10 Hz, 17—H), 2,24 (3H, s, 17-$COCH_3$), 2,00 (3H, s, 3-$OCOCH_3$), 0,94 (3H, s, CMe), and 0,90 (3H, s, CMe); m/z 374 (M^+), 359 (M^+-CH_3), 331 (M^+-CH_3CO), 314, 213, 253, 147, 107, 81, 67 and 43; (Found: C, 73,6; H, 9,1. Calc. for $C_{23}H_{34}O_4$: C, 73,8; H, 9,1%).

3.8 Experiments to prepare a stenol (19a) and its acetate (19b) from hecogenin

SCHEME



3.8.1 Preparation of hecogenin tosylate (18c : R = Ts)

Hecogenin (18a) (200 mg, 0,465 mmole) was dissolved in warm dry pyridine (3 mL). After cooling to room temperature, p-toluenesulphonyl chloride (200 mg) added with shaking until all the solids had dissolved. After standing overnight at room temperature, excess tosyl chloride was decomposed by addition of water. The product was extracted in chloroform. The chloroform extracts were washed with saturated sodium bicarbonate (to remove tosic acid), water, dried (anhyd. Na_2So_4), filtered, and the solvent evaporated to yield compound (18c : R=Ts) (184,6 mg; 68%), m.p. 194-195° (from acetone) (lit.[16] 192-193°); $[\alpha]_D^{23}$ -19°; ν_{max} (KCl) 1705, 1599, 1357, and 1170 cm^{-1} ; $\delta(CDCl_3)$ 7,75 (2H, d, J 10 Hz, ortho H's), 7,29 (2H, d, J 10 Hz, meta H's), 4,31 (2H, m, 3—H and 16—H), 3,34 (2H, d, J 10 Hz, $C(26)H_2$-O), and 1,09-0,75 (15H, m, Tos-Me, 2 x CMe, and 2 x CHMe);
(Found: C, 70,1; H, 8,3 . Calc. for $C_{34}H_{45}O_6S$: C, 69,8; H, 8,3%).

3.8.2 Reduction of compound (18c: R = Ts) to the epimeric spirostanols (22a) and (22b)[14]

Hecogenin tosylate (18c : R = Ts) 202 mg; 0,343 mmole was dissolved in carefully dried tetrahydrofuran (15 mL). The solution was added drop-wise to a refluxing suspension of $LiAlH_4$ (2,5 g) in dry tetrahydrofuran 20 mL). The mixture was refluxed with vigorous stirring for a further 5 hours. The excess reductant was cautiously decomposed with water, then hydrochloric acid was added until the solution became clear. The solution was extracted with ether and the dried (Na_2SO_4) ethereal extract evaporated. The residue was chromatographed on a column of neutral alumina (activity II, 50 g) using benzene as eluent. 5 mL-Fractions were collected and were monitored by TLC (ceric sulphate spray and warming on a hot-plate). Fractions 6 to 11 were combined and evaporated to give 5α, 22α-O-spirostan-12β-ol (22a) in 54% yield, as needles (from methanol) m.p. 185-186° (lit.[14] 191,5-192,5°); m/z 416 (M^+), 344, 329, 302, 284, 232, 139, 109 and 81.

Further elution of the column with benzene-ether (9 : 1) gave 5α,22α-O-spirostan-12α-ol (22b) in 18% yield, m.p. 199-200° (from methanol, lit.[14] 203-204°); m/z 416 (M^+), 344, 329, 302, 284, 255, 139, 109, and 81; (Found: C, 77,5 ; H, 10,6. Calc. for $C_{27}H_{44}O_3$: C, 77,8; H:, 10,6%).

The compounds (18c : R =Ts), (22a), and (22b) were monitored by TLC on silica gel in benzene-ether (9 : 1) and visualised by spraying with ceric sulphate solution and warming the TLC plate on a hot-plate.

Compounds	R_F
(18c : R = Ts)	0,42
22a	0,32
22b	0,19

3.8.3 Oxidation of the spirostanol (22a) and (22b) to 5α, 22α-O-spirostan-12-one (23)[14]

A solution of chromium trioxide was first prepared as follows: CrO_3 (10,0 g; 100 mmole) in water (20 mL) and concentrated H_2SO_4 (8,5 mL) was diluted to 50 mL with water in a volumetric flask. This solution which contained 2 mmole CrO_3/mL, was used in these oxidations of compounds (22a), (22b) and compound (27).

A mixture of the epimeric 5α , 22α-O-spirostan-12-ols (22a and 22b) (106 mg; 0,26 mmole) was dissolved in AR acetone (3 mL) and the solution magnetically stirred with ice-cooling (5-10°). To this solution was added the prepared solution of the above chromium trioxide (0,25 mL; 0,5 mmole). The mixture was stirred for 60 minutes, then diluted with 3 mL of water and extracted with ether (4 x 20 mL). The ether

layer was dried (anhyd. Na_2SO_4), filtered through cotton wool and evaporated to dryness.

Recrystallisation of the residue (methanol) gave the spirostanone (23) (74 mg; 74%), m.p. 196-198°; δ($CDCl_3$) 4,32 (1H, q, J 8 Hz, 16—H), 3,35 (2H, d, J 10 Hz, $C(26)H_2$-O), and 1,1-0,74 (12H , m, 2 x CMe, 2 x CHMe); m/z 414 (M^+), 386 (M^+-CO) 342, 300, 257, 139, 126, 109, and 81.

3.8.4 Conversion of spirostanol (22a) to its acetate (22c)[14]

Spirostanol (22a) (1,37 g; 3,3 mmole) was acetylated according to the method described in Section 3.5. The product was recrystallised (ethanol) to yield compound (22c) (1,21 g; 80%), m.p. 170-172° (lit.[14] 170-172°); m/z 458 (M^+), 399 ($M^+ - CH_3CO_2$), 386 ($M^+ - C_4H_8O$), 344 ($M^+ - C_6H_{10}O_2$), 329, 284, 139, 108, and 69.

3.8.5 Degradation of spirostanol acetate (22c)[14]

The 12β-acetoxyspirostane (22c) (1,4 g; 3,05 mmole) was heated under reflux for 6 hours with a mixture of n-hexanoic acid (13,2 mL), n-hexanoic anhydride (6,8 mL), and acetic anhydride (5,2 mL). The reaction mixture was cooled and extracted with ether. The ethereal extract was washed with 2M sodium hydroxide, water, and dried (anhyd. Na_2SO_4). Evaporation of the ether left an oil which was saponified by heating for 30 minutes under reflux with methanol (20 mL)

containing potassium hydroxide (1,0 g). The mixture was extracted into methylene chloride, washed with water, dried (anhyd. Na_2SO_4), filtered, and the solvent evaporated. The crude product was acetylated overnight with a mixture containing equal volumes of AR pyridine (15 mL) and acetic anhydride (15 mL). The solution was poured onto ice (100 g) and extracted with chloroform. The chloroform extract was washed with 5% $NaHCO_3$ solution (40 mL), washed with water (40 mL), dried (anhyd. Na_2SO_4), filtered, and the solvent evaporated. The crude acetate (2,57 g) was dissolved in glacial acetic acid (21 mL) and 1,39 N CrO_3 in 90% acetic acid (27 mL, 30% excess) added. The temperature was kept below 30°C for 1½ hr and then methanol (30 mL) was added to destroy excess oxidant. The mixture was extracted with ether, the organic extract washed with saturated sodium bicarbonate solution and water, dried (anhyd. Na_2SO_4), filtered, and evaporated to yield an oil (2,5 g). This product was refluxed with glacial acetic acid for 2 hours. The solvent was then removed by rotary vacuum evaporation and the residue dissolved in methylene chloride. This solution was washed successively with saturated $NaHCO_3$ solution, then several times with water, dried (anhyd. Na_2SO_4), filtered,and evaporated to dryness to yield a product that was chromatographed on a column of Si-gel (70-230 mesh, 120 g), using petroleum ether-ethyl acetate (8 : 1) as eluent. Fractions of 20 mL were collected and these were monitored by TLC (ceric sulphate spray and warming on a

hot-plate). Fractions 10 to 13 were combined and the solvent evaporated to yield compound (25) (69 mg; 5%), m.p. 163-165° (from ethanol); δ($CDCl_3$) 4,88 (broad, 26-OH), 4,40 (m, -C<u>H</u>(OAc)- and -C(16)H-), 3,4 (broad, C<u>H</u>$_2$-OH), 2,00 (s, 12-$OCOCH_3$) 1,58 (s, CH_3-C=)and 0,92-0,78 (m, 2 x C<u>Me</u>, and CH<u>Me</u>); m/z 458 (M^+), 399 (M^+-CH_3CO_2), 386, 329, 284, 139, 120, and 95; (Found: C, 75,9 ; H, 10,0. $C_{29}H_{46}O_4$ requires C, 76,0; H, 10,0%).

Fractions 16 to 43 were combined and evaporated to yield compound (24) (332 mg; 30%), m.p. 167-169° (from ethanol, lit.[14] 182,5-183°); δ($CDCl_3$) 6,62 (1H, t, J 4 Hz, =C(16)H-), 2,30 (3H, s, 17-$COCH_3$), and 2,00 (3H, s, 12-$OCOCH_3$); m/z 358 (M^+), 315 (M^+-CH_3CO), 298 (M^+-CH_3CO_2H), 283, 255, 173, 149, 135, 109, and 43; (Found: C, 77,1 ; H, 9,4 . Calc. for $C_{23}H_{34}O_3$: C, 77,1; H, 9,6%).

When compound (22c) (933 mg; 2,0 mmole) was reacted with a mixture of n-octanoic acid and n-octanoic anhydride[14,15], a better yield of the desired degraded compound (24) (322 mg; 44%) was obtained.

3.8.6 Catalytic hydrogenation of compound (24)[14]

A solution of compound (24) (160 mg; 0,447 mmole) in AR ethyl acetate (10 mL) was shaken overnight at room temperature with hydrogen gas at 17 p.s.i. and 10% palladized charcoal (15 mg) as catalyst. TLC of the product on silica gel in benzene-ether (3 : 2)showed the presence of ketone (26), invisible under 254 nm light but revealed by spraying with cerium (IV) sulphate and heating, at R_F 0,62. The starting compound (24) R_F 0,55, usually visible under UV light, was absent. The solution was filtered through cotton wool to remove the catalyst and evaporated to dryness to give the ketone (26) (140 mg; 78%), m.p. 107-109° (from ethanol, lit.[14] 149-149,5°); m/z 317 (M^+-CH_3 CO), 300 (M^+-CH_3CO_2H), 285, 257, 242, 149, 133, 109, and 43.

3.8.7 Wolf-Kishner reduction of ketone (26)[14]

A mixture of compound (26) (200 mg; 0,556 mmole), ethylene glycol (8 mL), n-butyl alcohol (4 mL), and 95% hydrazine hydrate (3 mL) was heated under reflux for 1 hour. The temperature was reduced to 100°, potassium hydroxide (600 mg) was added and the mixture heated (without condenser) until the temperature reached 200°. Heating under reflux at 215° was continued and TLC on silica gel plates in benzene-ether (7 : 3) was used to monitor the progress of the

reaction. The TLC plates were sprayed with acidic cerium (IV) sulphate and heated. After four hours the ketone (R_F 0,44) was absent and a new spot at R_F 0,61 was present. The reaction mixture was cooled, poured into water and extracted with ether. The ethereal extract was washed with water, dried (anhyd. Na_2SO_4), filtered, and evaporated to yield crude compound (27) (194 mg). This was chromatographed on a column of silica gel (70-230 mesh, 10 g) which was eluted with petroleum ether-ethyl acetate (8 : 1). The fractions (2,5 mL) were monitored as above. Tubes 9 and 10 gave pure compound (27) (80 mg; 47%), m.p. 138-140° (from methanol); ν_{max} (KCl) 3351 cm^{-1}; $\delta(CDCl_3)$ 3,75 (1H, t, J 4 Hz, 12—H), 1,55 (1H, s, 12-OH), and 0,95-0,60 (9H, m, 2 x CMe, and CHMe); m/z 304 (M^+), 286 (M^+-H_2O), 271, 257, 233, 217, 203, 176, 149, 122, 109, 95, 81, 55, and 41; (Found: C, 81,1; H, 12,3. $C_{21}H_{36}O$ requires C, 82,9; H, 11,8%).

3.8.8 Chromium trioxide oxidation of compound (27)[14]

The procedure was that described in Section 3.8.3. The oxidation of alcohol (27) (198 mg; 0,651 mmole) was monitored by TLC, using chloroform-methanol (99 : 1) as eluting solvent and acidic cerium(IV) sulphate spray followed by heating to reveal the spots. The starting spot, R_F 0,68, gave place to a spot at R_F 0,75, for the ketone

(28). Work up gave the ketone (28) (179 mg; 90%), m.p. 138-140° (from methanol, lit.[14] 138-141°); ν_{max} (KCl) 1705 cm^{-1}.

3.8.9 Dehydrogenation of compound (28) with selenium dioxide[14]

The procedure was that described earlier for the synthesis of compound (32) [Section 3.7.2]. Dehydrogenation of compound (28) (150 mg; 0,497 mmole) with selenium dioxide gave a crude product which was chromatographed on a column of Si-gel (70-230 mesh, 10 g) using chloroform as eluent and yielded compound (29) (78 mg; 52%), m.p. 109-111° (from methanol, lit.[14] 132-134°); ν_{max} (KCl) 3058, 1663, and 1592 cm^{-1}; $\delta(CDCl_3)$ 5,61 (1H, s, =C(11)H-) and 1,02-0,8 (9H, m, 2 x CMe, and CHMe); m/z 300 (M^+), 285 (M^+-CH_3), 231, 175, 121, 95, and 81.

3.8.10 Reduction to the allylic alcohol (19a)

The procedure for the reduction of compound (29) (77 mg; 0,255 mmole) was the same as that described in Section 3.4. The reduction was monitored by TLC using petroleum ether-ethyl acetate (1 : 1) and visualising first under UV and then by spraying with acid cerium(IV) sulphate followed by heating. The original α,β-unsaturated ketone (29) was UV-active whereas the allylic alcohol (19a) was only revealed after spraying. The crude product was chromatographed on

silica gel (70-230 mesh) eluting with petroleum ether-ethyl acetate (1 : 1). The new compound (19a) was obtained in 76% yield, m.p. 118-121° (from methanol); λ_{max} (ethanol) 202nm (ε=1400); $\delta(CDCl_3)$ 5,03 (1H, broad, =C(11)H-), 4,02 (1H, broad, -C(12)H-), and 0,93-0,54 (9H, m, 2 x CMe, and CHMe); m/z 302 (M^+), 284 (M^+-H_2O), 269, 255, 191, 177, 159, 135, 121, 109, and 95; (Found: C, 82,2; H, 11,1 . $C_{21}H_{34}O$ requires C, 83,4; H, 11,3%).

3.8.11 Preparation of the allylic acetate (19b)

Acetylation of compound (19a) (23 mg; 0,078 mmole) by heating for 1 hour at 100° with acetic anhydride (1 mL) and pyridine (2 mL), then leaving overnight at room temperature, yielded the previously unprepared allylic acetate (19b) (21 mg; 80%), m.p. 136-138° (from methanol); $\delta(CDCl_3)$ 5,22 (1H, s, =C(11)H-), 4,94 (1H, s, -C(12)H-), 2,04 (3H, s, 12-$OCOCH_3$), and 0,94-0,02 (9H, m, 2 x CMe, and CHMe); m/z 344 (M^+), 302 (M^++H-CH_3CO), 284 ($M^+-CH_3CO_2H$), 269, 255, 159, 145, 105, 91, and 81.

3.9 Attempts to form the diene ketones from allylic alcohols and acetates

3.9.1 The attempted C-acylation of the diacetoxy-spirostene (33b)

Compound (33b) (18 mg; 0,035 mmole) was reacted with a mixture of acetic acid, acetic anhydride, and boron trifluoroethereate according to the procedure described in Section 3.6. After the work-up the crude yield was 3 mg. The GC-MS showed peaks at m/z 575(5%) (M^+), 496(3%), 461(10%), 421(27%), 367(14%), 339(20%), 311(51%), 277(39%), 251(31%), 175(22%), 121(33%), 95(39%), 69(47%), and 43(100%).

3.9.2 The attempted C-acylation of the allylic alcohol (19a)

Compound (19a) (26 mg; 0,086 mmole) was reacted with a mixture of acetic acid, acetic anhydride, and boron trifluoroethereate according to the procedure described in Section 3.6. After the work-up the crude product was washed through a column of Si-gel (70-230 mesh) with petroleum ether-ethyl acetate (1 : 1) to give a product (27,9 mg). Preparative TLC of this material (27,9 mg), eluting with petroleum ether-ethyl acetate (3 : 1), resulted in bands having the following R_F values: 0,79, 0,59, and 0,37 with

yields of 3,8 mg, 5,1 mg, and 8,6 mg respectively. The second band (R_F 0,59) showed, ν_{max} (KCl) 2923,1705,1350, 860 cm^{-1} ; $\delta(CDCl_3)$ 2,2 ($COCH_3$, s); m/z 374 (42%) (M^+), 359 (11%) (M^+-CH_3), 331 (100%) (M^+-COCH_3), 307 (24%), 235 (26%), 149 (24%), 121 (13%), and 43 (32%).

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