APPROACHES TO THE SYNTHESIS OF STEROIDAL α-METHYLENE LACTONES

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by

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Lameck S. Chagonda.

Loughborough University

1982.

CONTENTS

SUMMARY

A brief review of the biological properties and the synthesis of α-methylene-γ- and δ-lactones is presented.

Estrone 69 was converted to estrololactone-methyl ether 71 which was α-formylated with ethyl formate, diethylaminated, hydrogenated and underwent β-elimination to the 3-methoxy-16-methylene-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)-triene 75 which was reduced to the 16-methyl lactone 77 and thiolated to the thiol-adduct 76. The estrololactone 70a was α-formylated, acetylated, diethylaminated, hydrogenated and underwent β-elimination to the 3-acetoxy-16-methylene-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)-triene 99 which was hydrolysed to the 3-hydroxy-16-methylene lactone 78. The reaction of the estrololactone methyl ether 71 with triphenylphosphonium ethyl bromide gave 3-methoxy-16-isopropylidene--17-oxo-17a-oxa-D-homo-estra-1,3,5(10)-triene 100.

Cholesterol 109 was first converted to 3-oxo-4-oxa-5α-cholestane 119 and eventually to 2-methylene-4-oxa-3-oxo-5α-cholestane 122 through similar procedures. The lactone 122 was thiolated to the ethyl and phenyl thiol-adducts 123 and 124 respectively.

Baeyer-Villiger oxidation of the steroidal arylidene 17-ketones 128 (a, b and c) and alkylidene 17-ketones 129 (a and b) with trifluoro-peracetic acid gave isomeric 16α- and β-epoxides 130 and 152 respectively. Similar oxidation of the p-methoxybenzylidene ketone 128d gave the epoxy-enol lactone 145 and β-diketones 142 and 148.

Baeyer-Villiger oxidation of the arylidene ketones 128 (a, b, c and d) with 40-45% peracetic acid gave α-acetoxyketo-acids 153. The α-acetoxyketo-acid 153d was esterified with diazomethane to the methyl ester 154d.

Reduction of the benzylidene ketones 128 (a and d) gave reduced mixtures which were oxidised with Jones' reagent to the ketones 163.

The benzylidene ketone 163a was oxidised with 45% peracetic acid to the lactone 166a, which was brominated and dehydrobrominated to the benzylidene lactone 170 which was hydrolysed to 3β-hydroxy-16-benzylidene-17--oxo-17a-oxa-D-homo-5α-androstane 171. The reduced ketone 163d was oxidised with 40-45% peracetic acid to the lactone 166d which was not treated further. The oxidation of the 16-isopropyl ketone 161 with peracetic acid was unsuccessful.

Reaction of 3-hydroxybenzylidene ketone 127a with thiophenol gave the thiol-adduct 174 but trifluoroperacetic acid oxidation of it did not give the expected benzylidene lactone 176. The 3β-hydroxy-5α-androstan-17-one 126a was o-silylated with trimethylchlorosilane to the silyl enol ether 178 but condensation with butyraldehyde in the presence of titanium chloride did not give the desired β-hydroxylactone 181. The lithium enolate 189 of the 3β-hydroxy-17-oxo-17a-oxa-D-homo-5α-androstane 188 with butyraldehyde and zinc chloride did not give the 3β-hydroxylactone 190. The lithium enolate of the 3-methoxy-17-oxo-17a-oxa-D-homo-estra--1,3,5(10)-triene 71 was however deuterated to the lactone 191.

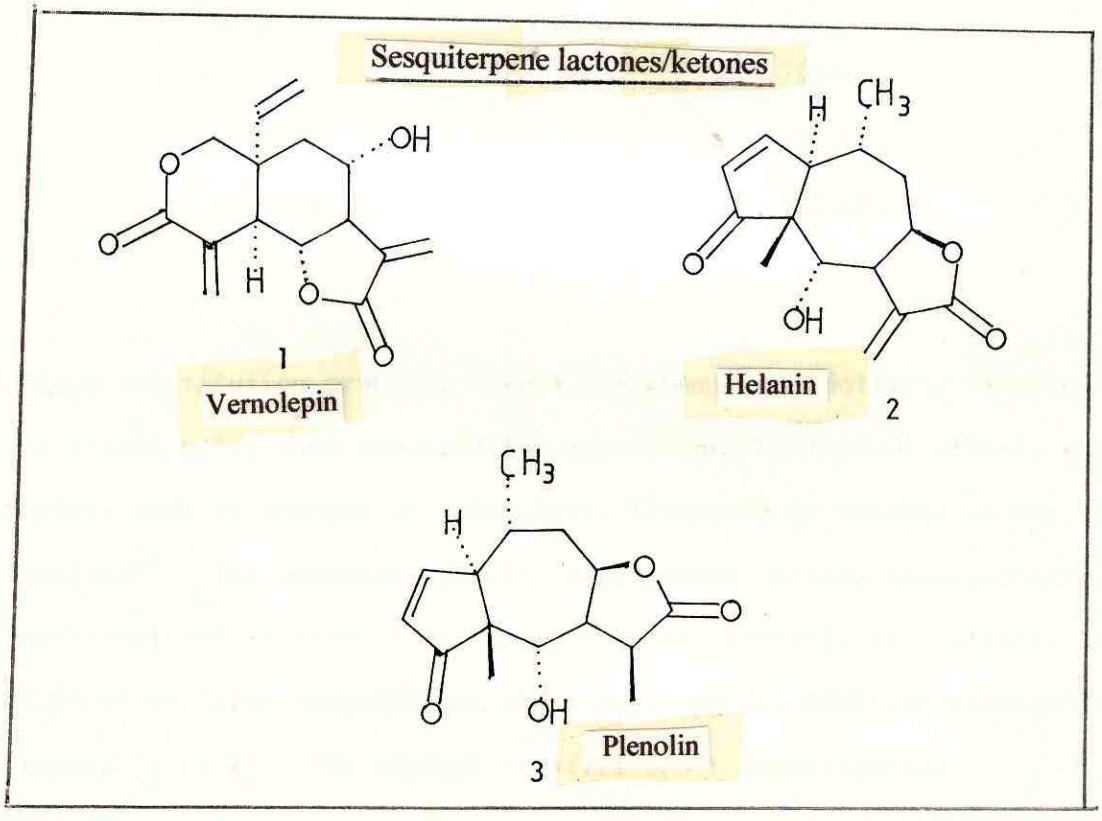
The cytotoxic activity (LD_{50}) was determined by a tissue culture technique on HeLa S_3 cells and preliminary results show considerable activity for the 3-acetoxy-16-methylene lactone 99 (0.14 μg/ml), the 3-methoxy-16-methylene lactone 75 and its thiol-adduct 76 (0.24 μg/ml) and the 3-hydroxy-16-methylene-lactone 78 (0.50 μg/ml); the 3-acetoxy--16-acyloxy-methylene lactone 94, the 3-methoxy-16-methyl lactone 77, the 3-methoxy-16-isopropylidene lactone 100 and the benzylidene lactones 170 and 171 are inactive (> 10.00 μg/ml).

I

INTRODUCTION
(i)

BIOLOGICAL BACKGROUND:

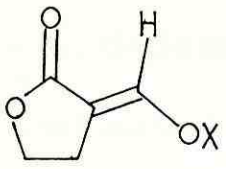
Alkylating agents were the first anti-cancer agents, and amongst the most common in clinical use, today.[1] Recently, some sesquiterpene lactones and/or ketones having the $O{=}CC{=}CH_2$ moiety have been found to have cytotoxic effects against animal tumour systems in vivo and in vitro against a wide range of neoplasias. Vernolepin 1[2], helenalin 2[3] and plenolin 3[3] all alkylate L-cysteine.



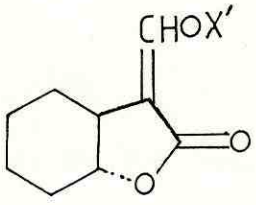
Their alkylating nature and hence anti-tumour inhibition is due to a Michael-type interaction of α,β-unsaturated lactones or ketones with biological nucleophiles, that is, thiol-bearing enzymes such as phosphofructokinase[4], glycogen synthetase[5] or thymidine kinase[6]. The structure-activity relationships have been well elucidated by Hall et al[3]; activity is credited

to the inaction of sulfhydryl-bearing enzymes necessary for DNA replication and not the alkylation of purine bases.

Most natural sesquiterpenes are considered to be too toxic for clinical use[7], and efforts are in progress to synthesise simpler analogues with improved therapeutic indices. Functionalised α-methylene butyrolactones 4[7a] apparently show no activity whilst the lactones 5[8] show enhanced activity over the parent α-methylene lactones.

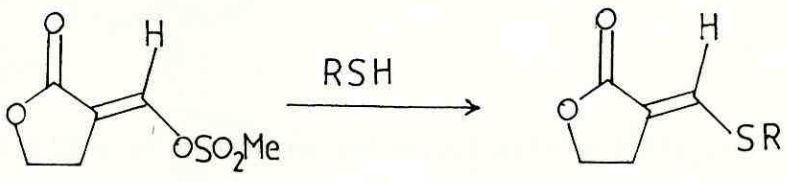


4 X =-Ts,
-COPh
-$COCH_2Ph$



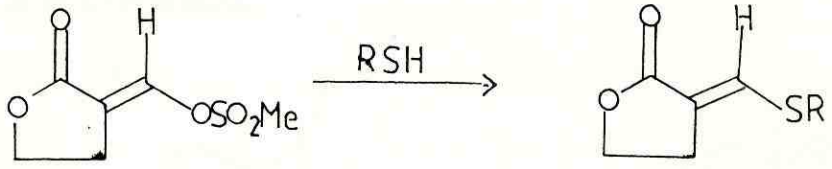
5 X' =-$SiMe_3$
-SO_2CH_3
-SO_2CF_3

Acyloxy-substitution probably lowers the chemical reactivity of α-methylene-γ-lactones below that required for significant biological effects whilst factors such as changes in solubility, transport or metabolism may also be involved[7a]. The enhanced activity over parent lactone observed with functionalised lactones 5 is ascribed to the possible irreversible alkylation of cellular nucleophiles via a nucleophilic addition-elimination process [6 to 7]. The concept is still under investigation.



6 7

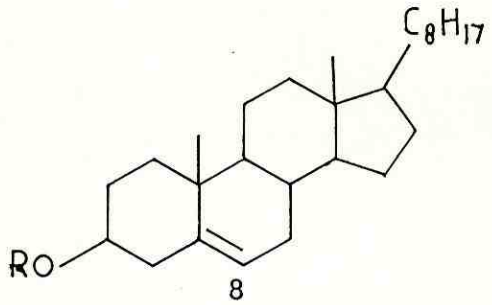
R = Ph, t-Bu, $CH_2CH(NH_2)COOH$



6 7

R = Ph, t - Bu, $CH_2CH(NH_2)COOH$

Some steroidal mustard alkylating agents 8[9], 9[10] and steroidal α-methylene lactones 10[11] have been found to have considerable cytotoxicity against various experimental tumours and clinical trials on some of them are under way[12].



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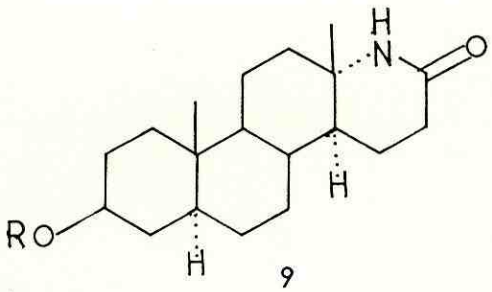

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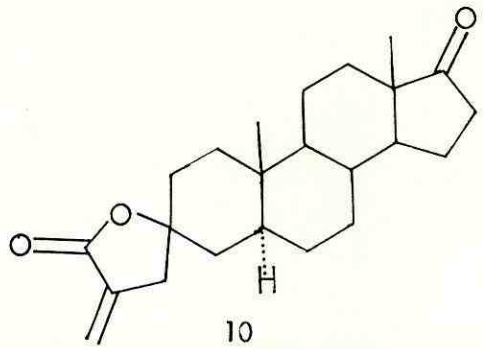
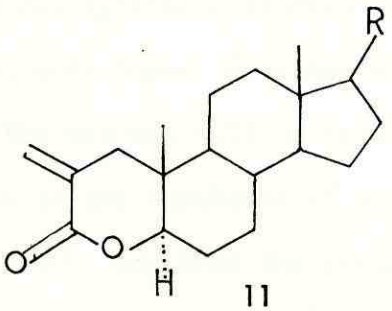
R = -CO CH_2Ar N $(CH_2CH_2Cl)_2$



10

The possibility of combining potential cytotoxicity and target specificity, for example against breast or prostatic cancer, is an attractive one, since selectivity is often a major problem. Potential target specific alkylating agents, steroidal lactones bearing α-methylene functions in the A and D rings

have been synthesised[13]. The lactones 11 and 12 are active against human nasopharyngeal carcinoma (KB) cells in culture, and the former also forms an adduct with L-cysteine.



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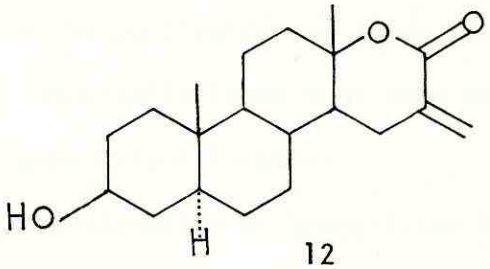


12

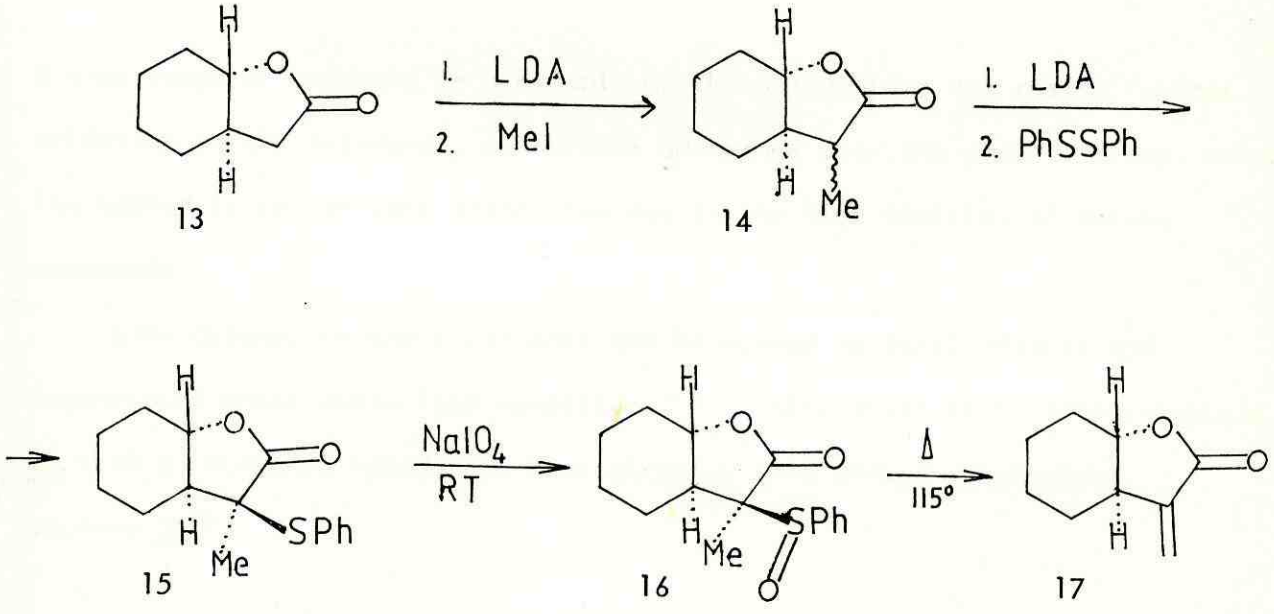
R = OH, OAc, C_8H_{17}.

(ii)

SYNTHETIC APPROACHES

Due to their proven cytotoxic effects, the synthesis of α-methylene-γ-butyrolactones has attracted considerable attention and made them prime targets for numerous synthetic studies including several excellent reviews[14-17]. In addition, many papers have appeared since the publication of these reviews. Only some of the methods will be highlighted, especially those that seem easily adaptable to the synthesis of steroidal α-methylene lactones.

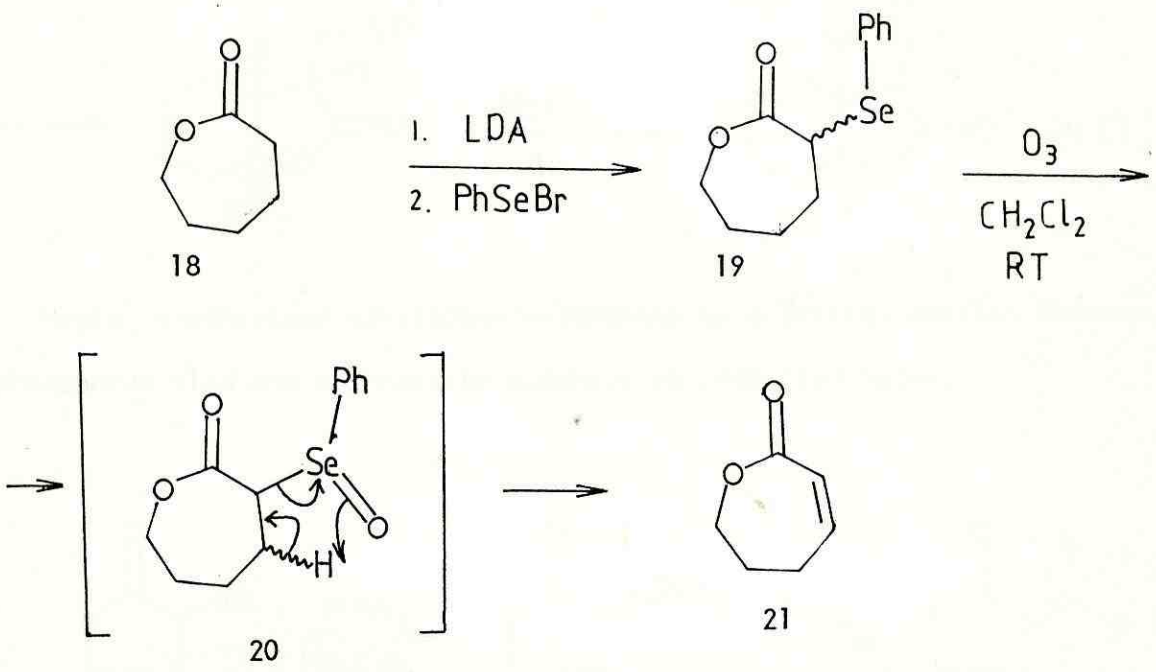
Grieco[18] achieved the exclusive α-methylenation of trans-fused bicyclic γ-butyrolactones via the pyrolysis of α-phenylsulfinyl lactones. His approach required stereospecific introduction of α-phenylsulfinyl substituent to establish the anti-relationship between the leaving α-phenylsulfinyl group and the adjacent methine proton at the ring junction in the bicyclic lactone 16. Oxidative elimination gave the bicyclic lactone 17 which contains the exo-cyclic double bond.



A similar high yield "α-methylenation sequence" has been achieved using alkylselenoxides,[19]. The selenoxides with the proper stereochemistry, undergo facile elimination at low temperature with exclusive formation of

exocyclic olefin.

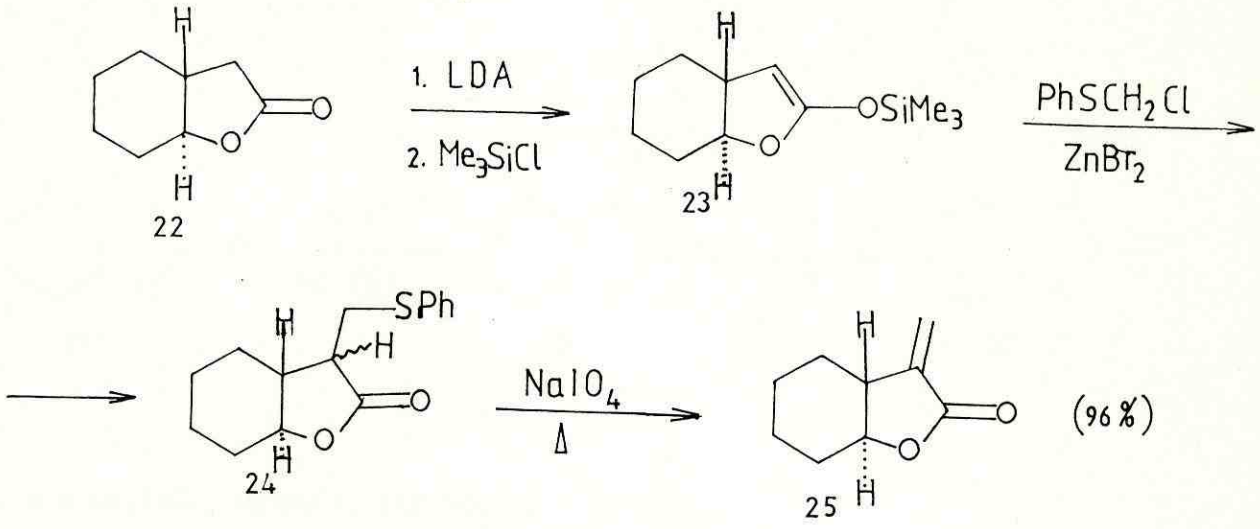
The syn-elimination at room temperature of α-phenylselenoxide to give endocyclic methylene lactones was achieved by Reich[20]. The elimination proceeds under mild conditions to the endocyclic lactone 21.



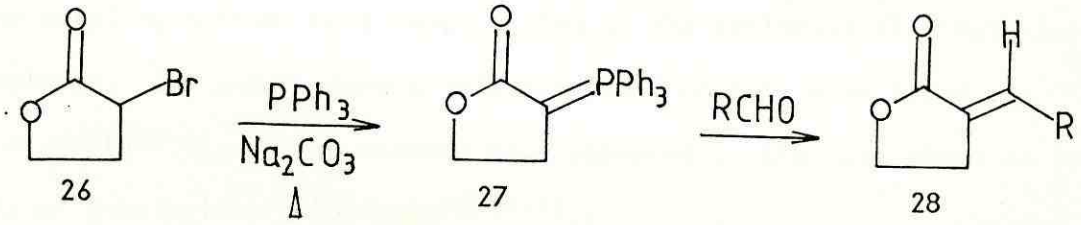
18 19 20 21

A wide range of oxidants is available as the selenoxides can resist further oxidation to the selenones, an obvious advantage over the phenylsulfinyl method. The method is rather less attractive due to the high toxicity of seleno-compounds.

α-Methylene, γ- and δ-lactones can be masked as thiol-adducts and regenerated under controlled conditions[2,21]. Alkylation of a lactone enolate 23 with α-thioalkyl halide can lead directly to a masked α-methylene lactone 24[22].

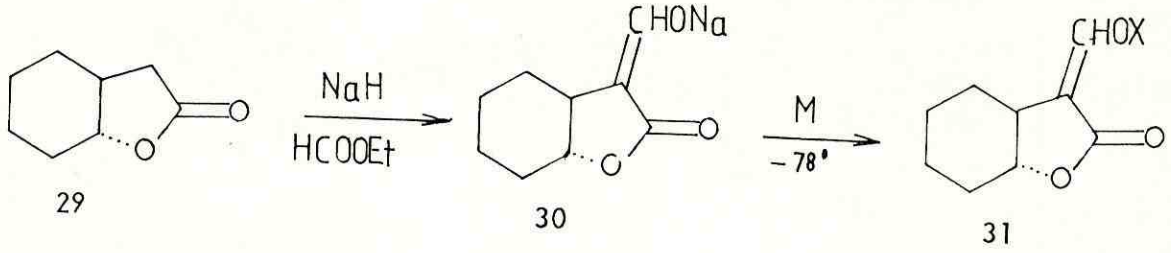


Howie[7] synthesised alkylidene-γ-lactones by a Wittig-reaction between a phosphorus ylid and appropriate aldehyde as indicated below.



R = H, Me, Ethyl, etc.

Stang and Treptow[23] synthesised simple vinyl and α-methylene-γ-butyrolactone sulphonate esters and silyl enol ethers. This class of compounds was made by reacting the bicyclic lactone sodium enolate 30 with trifluoromethane sulphonyl anhydride [$(CF_3SO_2)_2O$], mesyl chloride (CH_3SO_2Cl) or with chloro-trimethyl silane (Me_3SiCl) at -78° in an appropriate solvent, usually ether or glyme. The functionalised methylene lactones 31 were produced in high yields (over 70%).



29 30 31

M = Me_3SiCl, $MeSO_2Cl$, $(CF_3SO_2)_2O$

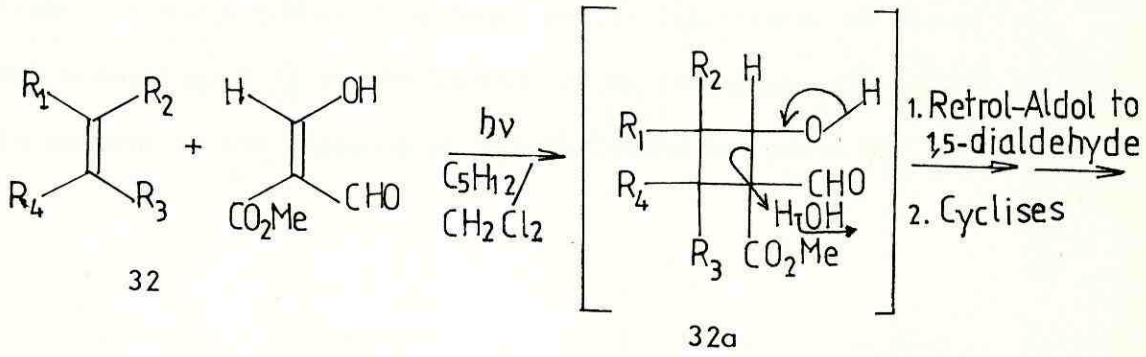
X = $SiMe_3$, SO_2CH_3, SO_2CF_3.

Total synthesis of racemic frullanolide[24] dl-helenalin[25], dl-confertin[26] and dl-damsin[26] are reported in the literature.

Many existing methods have concentrated on the synthesis of α-methylene-γ-butyrolactones. The α-methylene-δ-valerolactone group is also found in natural products[27,28]. A few methods have appeared in the literature on the synthesis of α-methylene-δ-lactones[16,29-31].

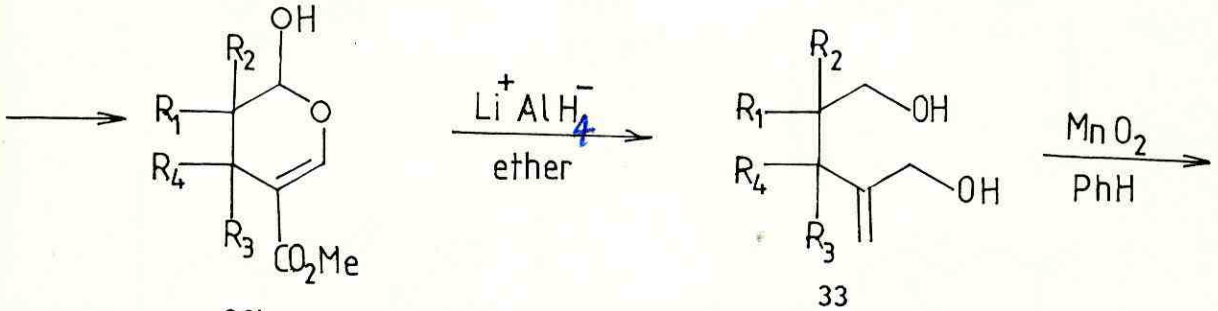
Baldwin[30] describes a convenient preparation of α-methylene-δ-valerolactone which starts with a photochemical addition to give a photo-adduct 32b, in 80-90% yield. The substituted olefin reacts with methyl diformylacetate[30a] in its enol form 32 to give a cyclobutane derivative 32a by a cis[2 + 2] addition. This undergoes retro-aldol cleavage to form the corresponding 1,5 dialdehyde derivative which cyclises to the hemiacetal 32b. The reduction of the adduct 32b with lithium tetrahydroaluminate to the alkenediol 33 and subsequent oxidation with manganese dioxide gave α-methylene-δ-valerolactone 34. This method looks attractive as the olefinic intermediates could be procured easily.

Semmelhack[31] studies on transition-metal mediated methods have developed an intramolecular carbonylation procedure which is considered general. A two-step cyclisation carbonylation with a convenient nickel reagent leads to



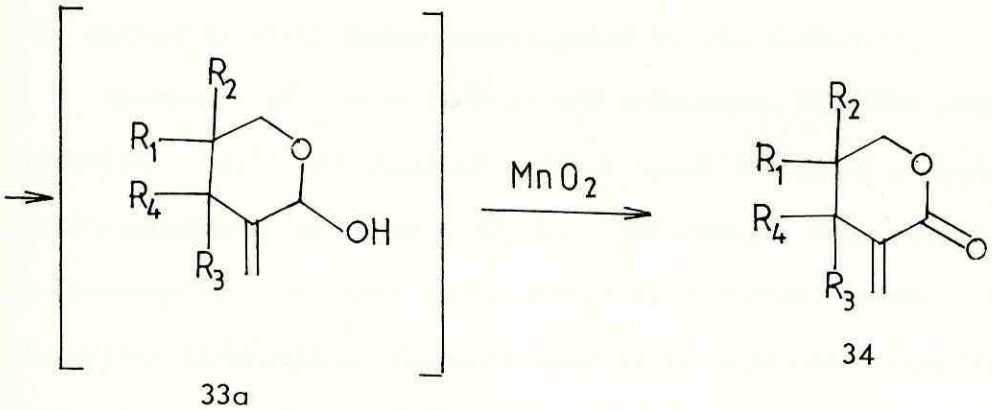
32

32a



32b

33

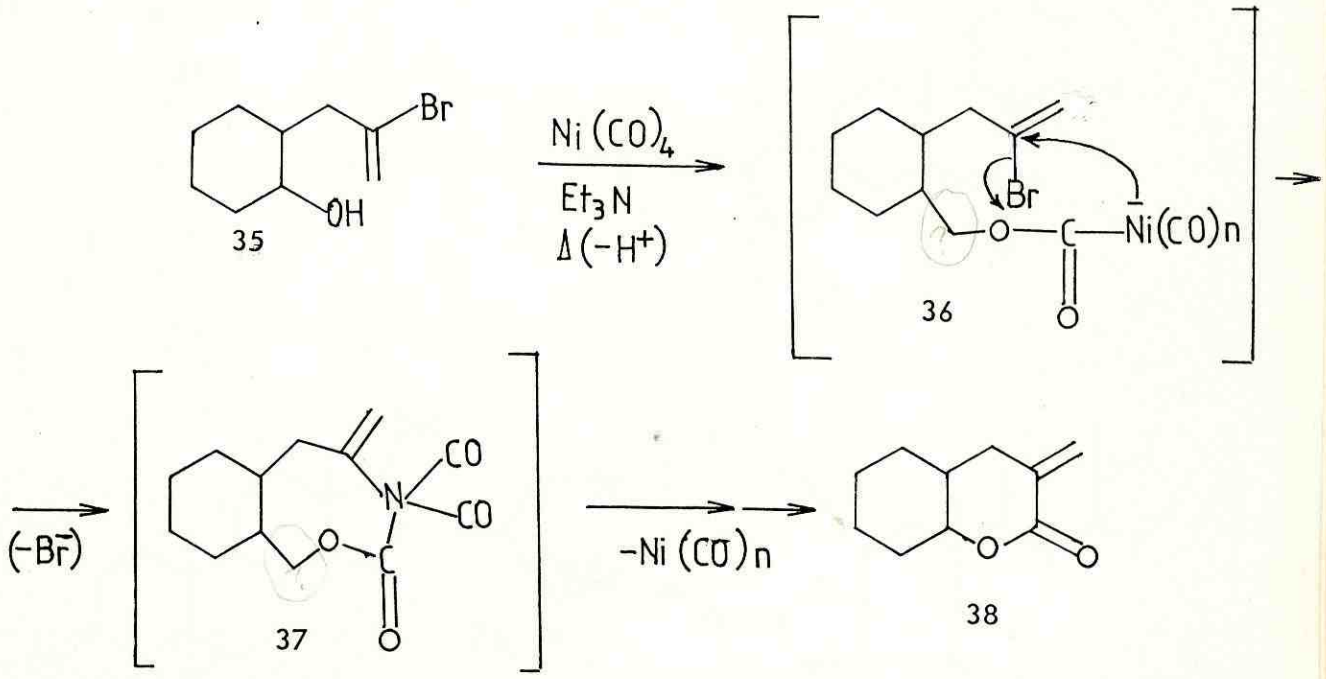


33a

34

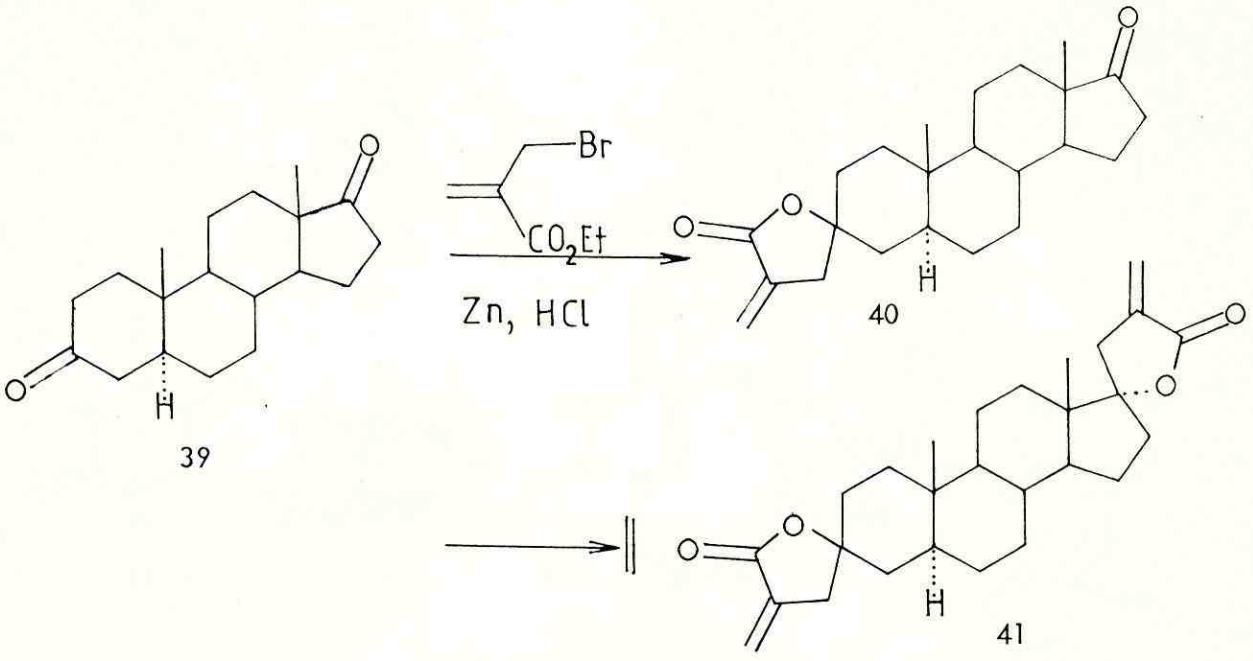
$R^1 - R^4$ = H or alkyl.

the formation of 5 and 6-membered lactones and is illustrated by conversion of the vinyl bromoalcohol 35 to the lactone 38 by treatment with nickel carbonyl in benzene in the presence of triethylamine to remove HBr.

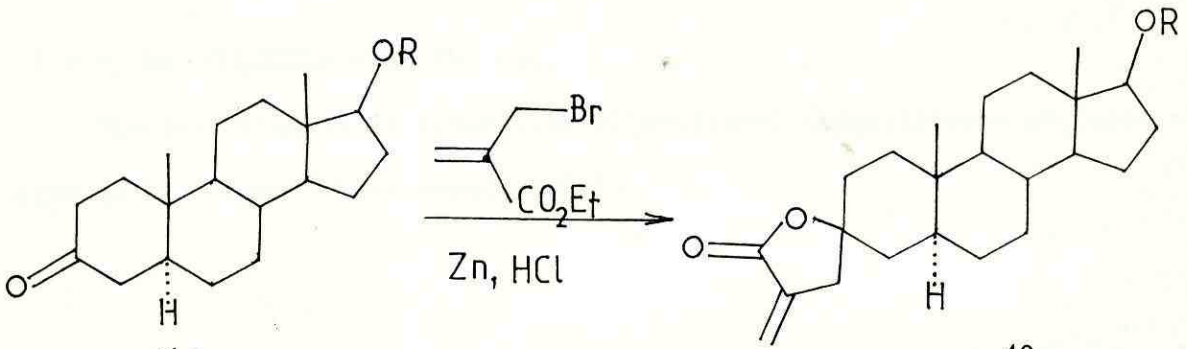


The method is still being investigated by the authors[31].

Synthesis of α-methylene γ- and δ-lactones has also been applied to steroids. Lee[11] synthesised several novel steroidal α-methylene-γ-spiranolactones for example 40, by a Reformatsky-type reaction between ethyl α-(bromomethyl)-acrylate and appropriate steroidal ketone. Initial objectives to obtain bifunctional lactones such as 41 were not accomplished though bifunctional analogues for example 42, were successfully synthesised.



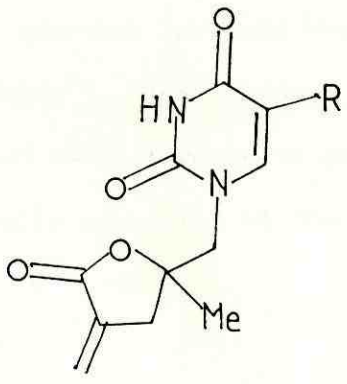
39 40 41



41a 42

R = H, COCH = CH - Ph.

Lee[11a] extended this approach for the synthesis of uracil and thymine α-methylene γ-lactones 44.



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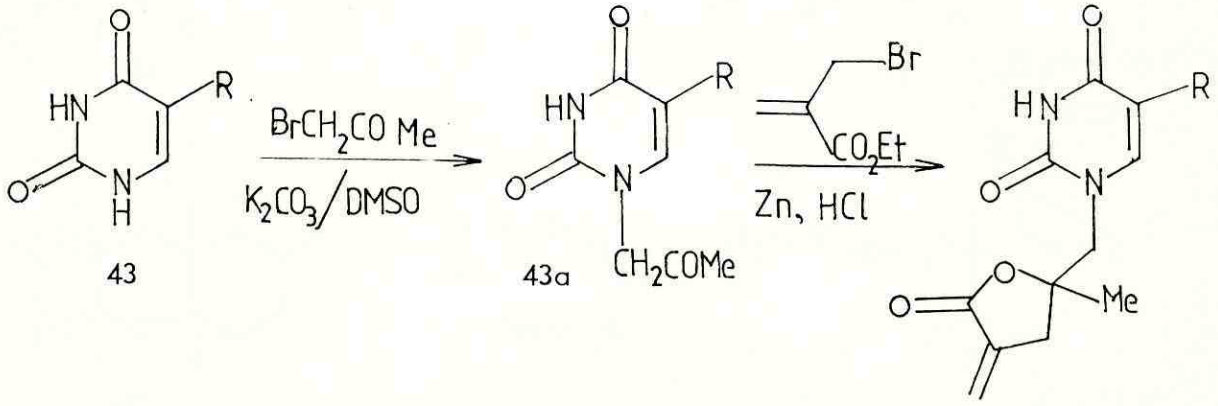
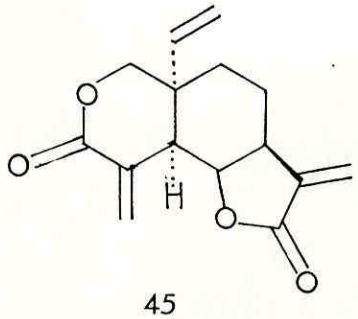


43 43a 44

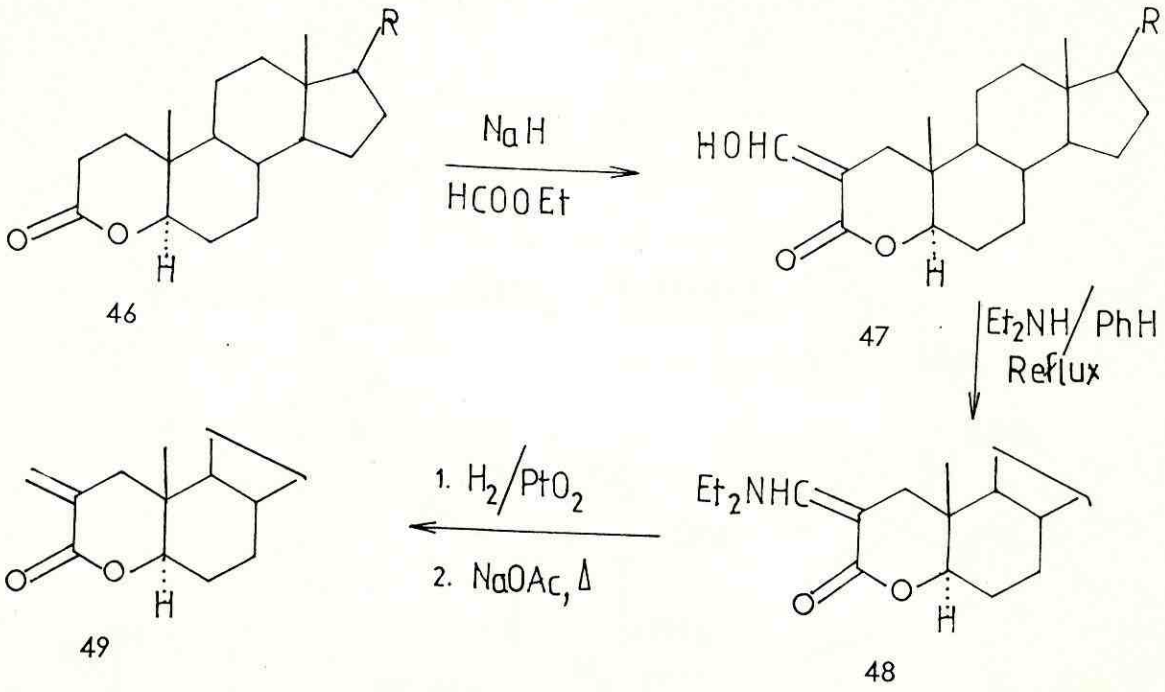
R = H, Me, CH_2OCOCH = CH Ph, etc.

Similar attempts to synthesise bifunctional sesquiterpene lactones of the type 45 by Grieco[35] were unsuccessful.

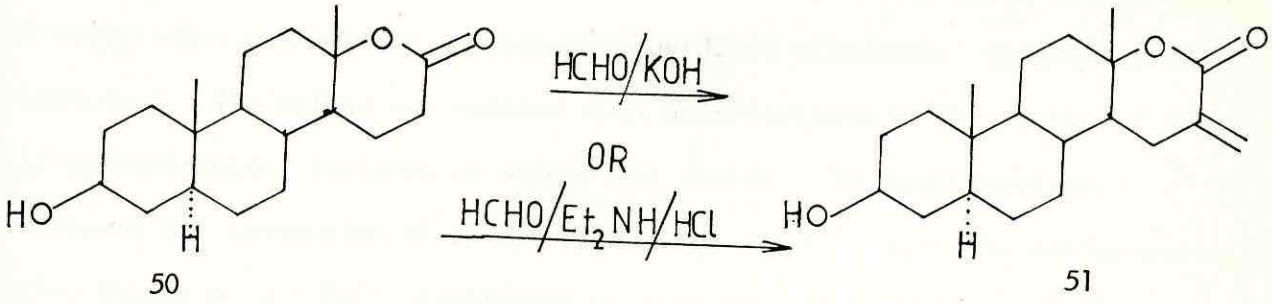


45

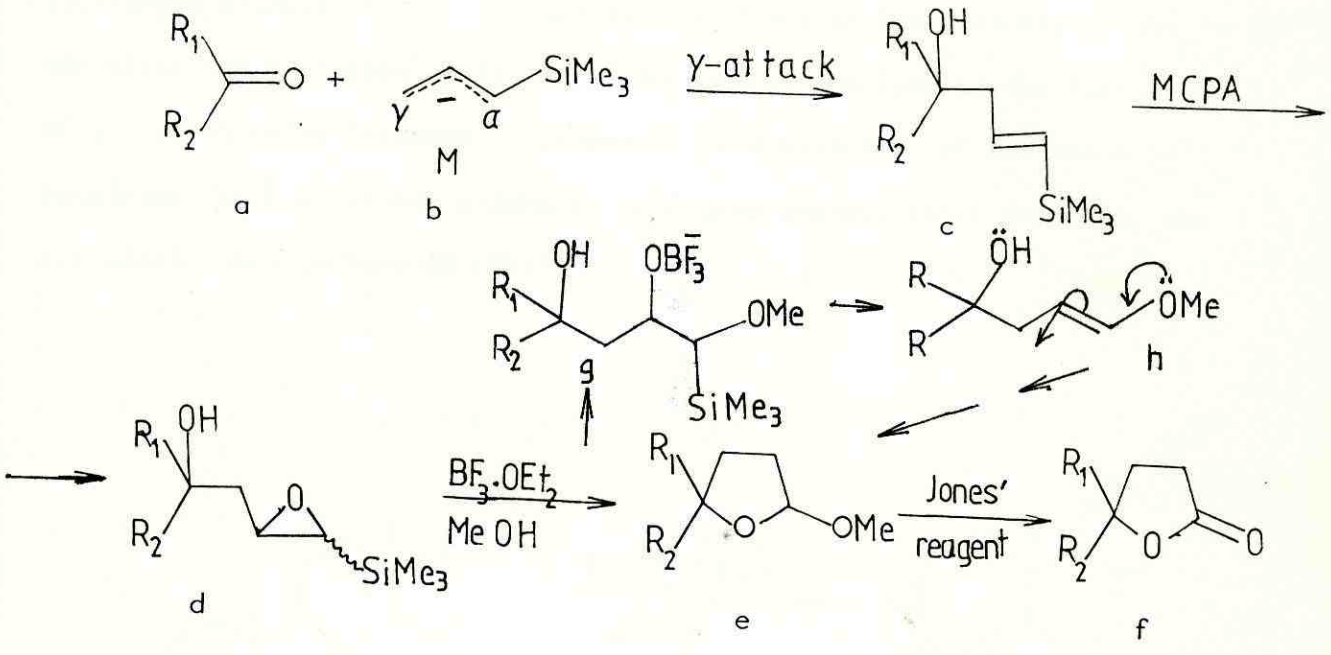
The synthesis of some steroidal α-methylene-δ-lactones was achieved by Dehal[13,16]. His approach involved known α-methylenation procedures of Yamada and coworkers[32]. The lactones were first allowed to react with sodium hydride and ethyl formate to give the hydroxymethylene lactone 47 which was eventually converted to the lactone 49 by the series of steps indicated below.



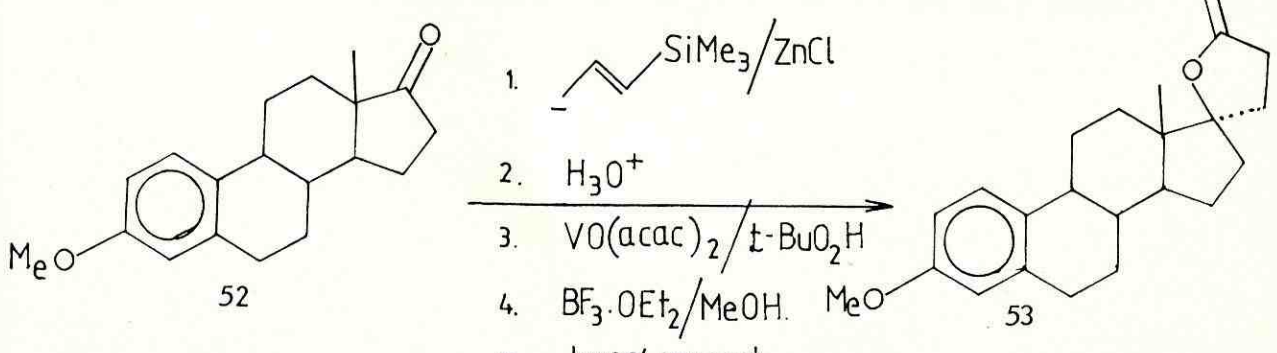
Attempts to α-methylenate the D-ring lactone by the same method were unsuccessful. Direct α-methylenation of the D-ring lactone[33] was, however, achieved by an aldol-type reaction with formaldehyde and by a Mannich-type reaction with $HCHO/Et_2NH/Et_2NH{:}HCl$[15] to give α-methylene-δ-valerolactone 51 in 27% yield.



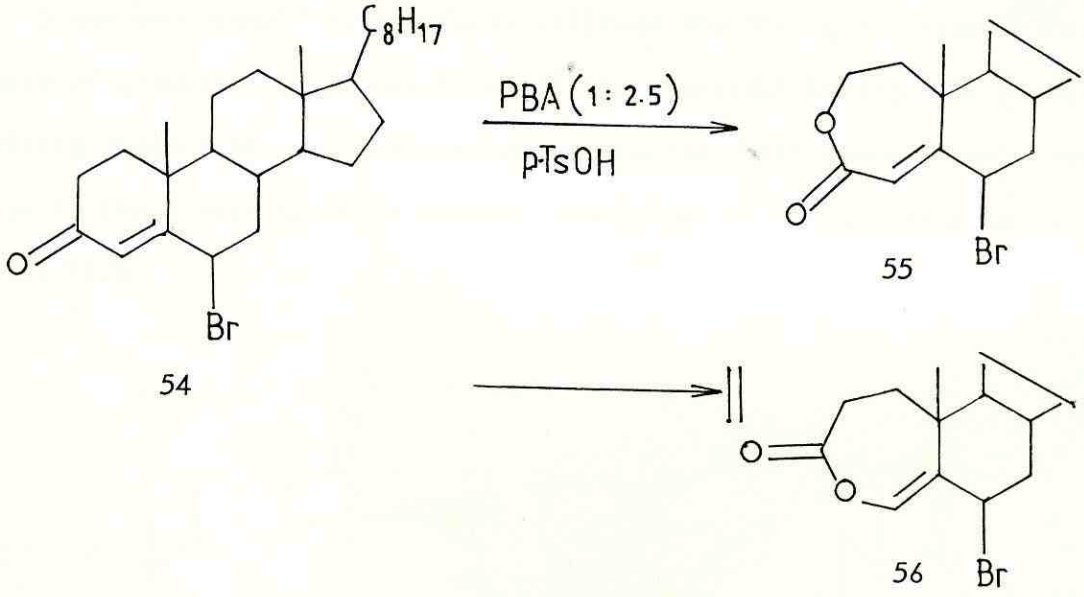
Ehlinger and Magnus[34] studied the reaction of (trimethylsilyl) allyl anion with ketones and aldehydes to give γ-lactones. As a general approach allyltrimethylsilane was deprotonated with sec-butyllithium to give the ambident anion b, M = Li^+ which reacted with ketones a to form δ-hydroxy vinylsilanes c. The vinylsilanes were oxidised with peracids to the α,β-epoxysilanes d,



which rearranges with boron trifluoride etherate in methanol to the lactol O-methylether e which was subsequently oxidised with Jones' reagent to the lactone f. The method was applied with modifications to the synthesis of 17-spirosteroidal lactones in rather low yields. The modifications involved the conversion of lithio species b, M = Li^+, with the corresponding zinc chloro b, M = ZnCl, counterion by treatment of b, M = Li^+, with zinc chloride and the use of vanadyl acetate with tert-BuOOH for the peroxidation. Through a series of reactions, estrone methyl ether 52 was converted to the spirolactone 53 in 25% yield.

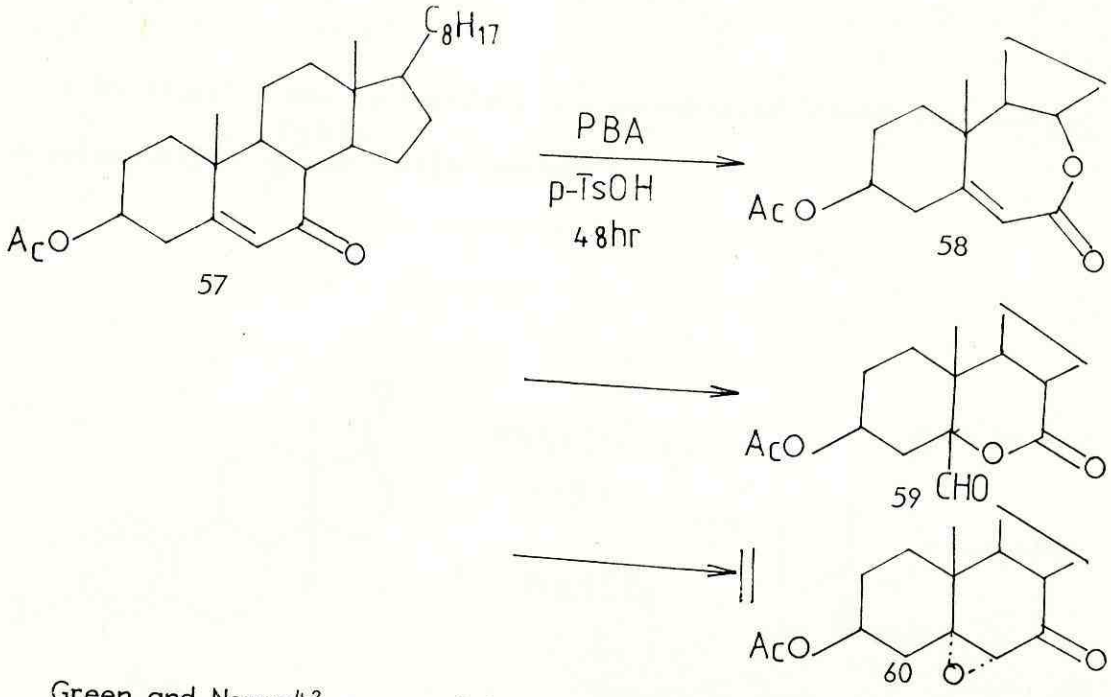


Peracid oxidation of α,β-unsaturated ketones can lead to enol lactones, α,β-unsaturated lactones, epoxyketones or lactones and a variety of rearranged products[36-41]. Substitution patterns in the vicinity of the ketone can alter the migratory aptitudes of the groups and lead to the formation of α,β-unsaturated lactones. Perbenzoic acid oxidation of the enone 54 catalysed with p-toluene sulphonic acid gave amongst other products, the α,β-unsaturated lactone 55 (8%)[39].

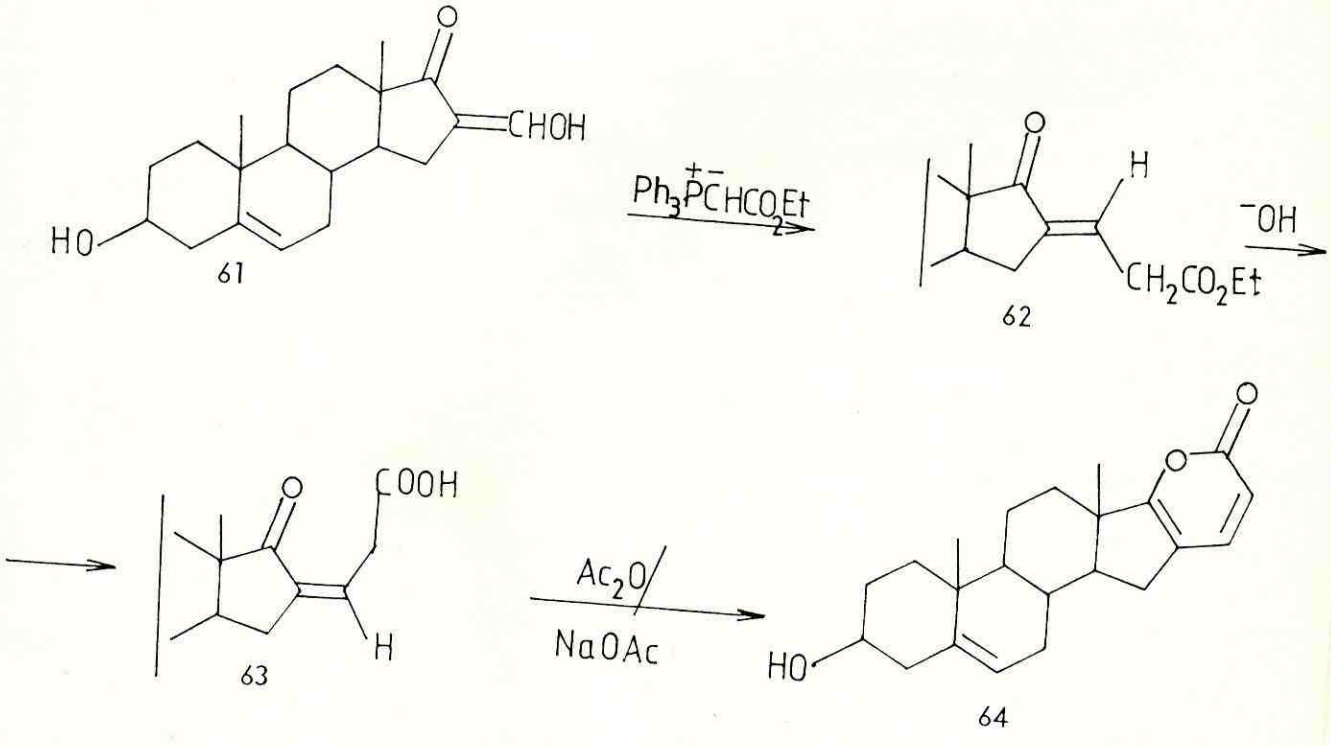


The formation of the lactone 55, indicates that a methylene group can have a greater migratory aptitude than a vinylic group.

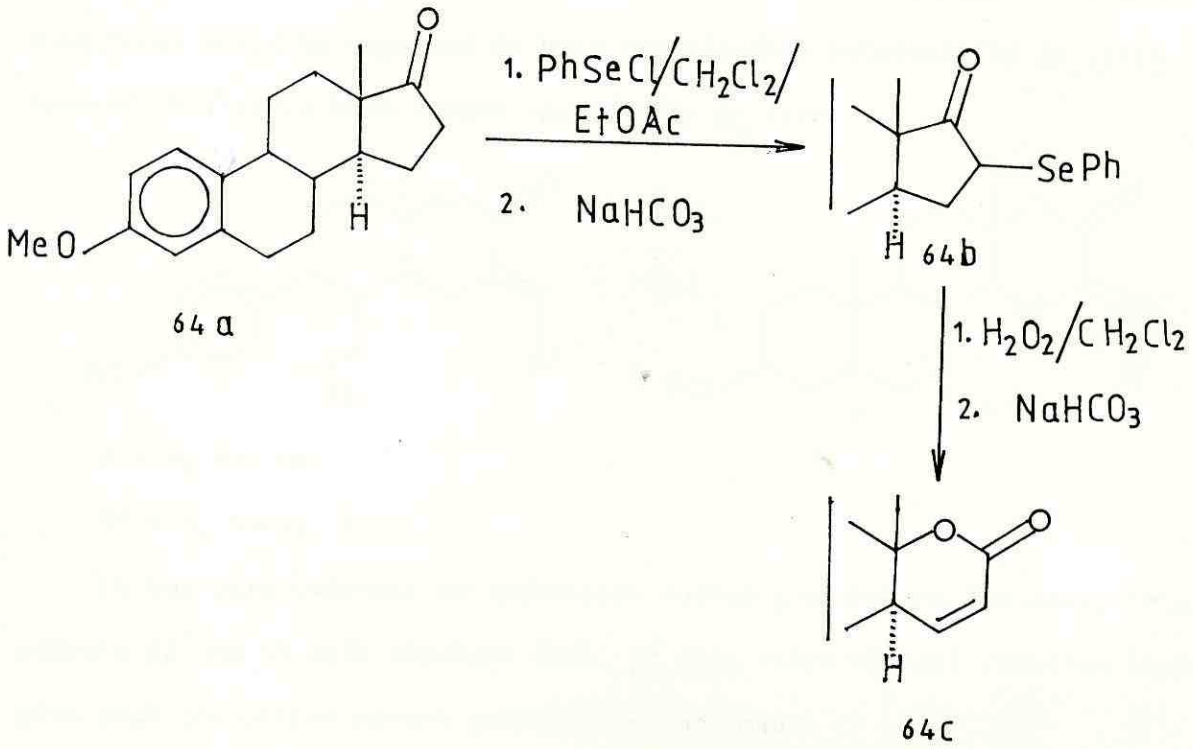
The oxidation of the enone 57 gave the lactones 58 and 59 as the only identifiable products both in less than 5% yield. Prolonged oxidation periods, about 90 hours, gave the 5β-formyl lactone 59 (~ 5%)[38] as the only product.



Green and Newaz[42] successfully utilised the Wittig reaction[43] in the course of preparing α-pyrones fused to the steroidal D-ring. Only the E-Wittig product 62, was obtained and hydrolysed with concomittant isomerisation to the Z-acid 63 which readily lactonised to the α-pyrone 64, in modest yields (37%).



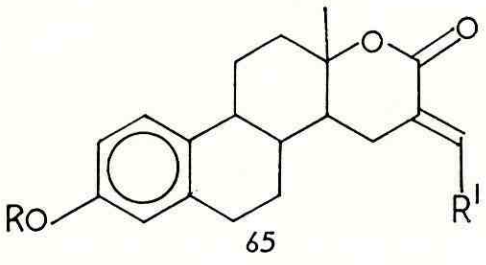
Williams[87] has synthesised α, β-unsaturated D-homo lactones 64C by a selenylation-dehydroselenylation method[20].



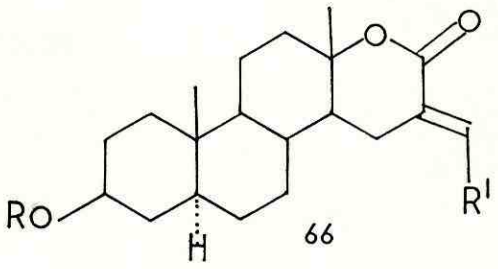
(iii)

OBJECTIVES:

The main object of the research was to synthesise potential anti-tumour steroidal α-methylene, α-alkylidene and α-arylidene-δ-lactones 65 and 66 for hormonally related cancers such as breast or prostatic cancer. The α-methylene-δ-lactones would be expected to have considerable cytotoxicity in vitro, and some of them could have target specificity in vivo.



65



66

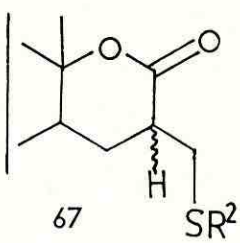
R = H, Ac, Me.

R^1 = H, Alkyl, Aryl.

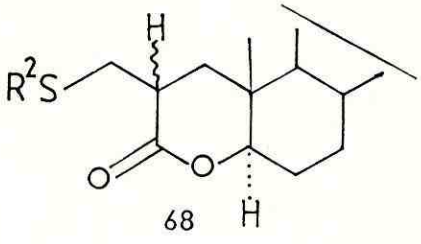
It was also intended to synthesise masked α-methylene lactones, thiol adducts 67 and 68 with the hope that, in vivo retro-Michael reaction could give back the active parent α-methylene lactones.

Peracid oxidations on α,β-unsaturated steroidal 17-ketones would also be considered as part of the general synthetic programme since these could, in principle, lead to α,β- unsaturated lactones if the migration of C-13 versus C-16 could be induced.

The biological activity of the α-methylene lactones and their masked derivatives as well as receptor binding studies would be investigated by colleagues in these laboratories.



67



68

R^2 = Et, Ph.

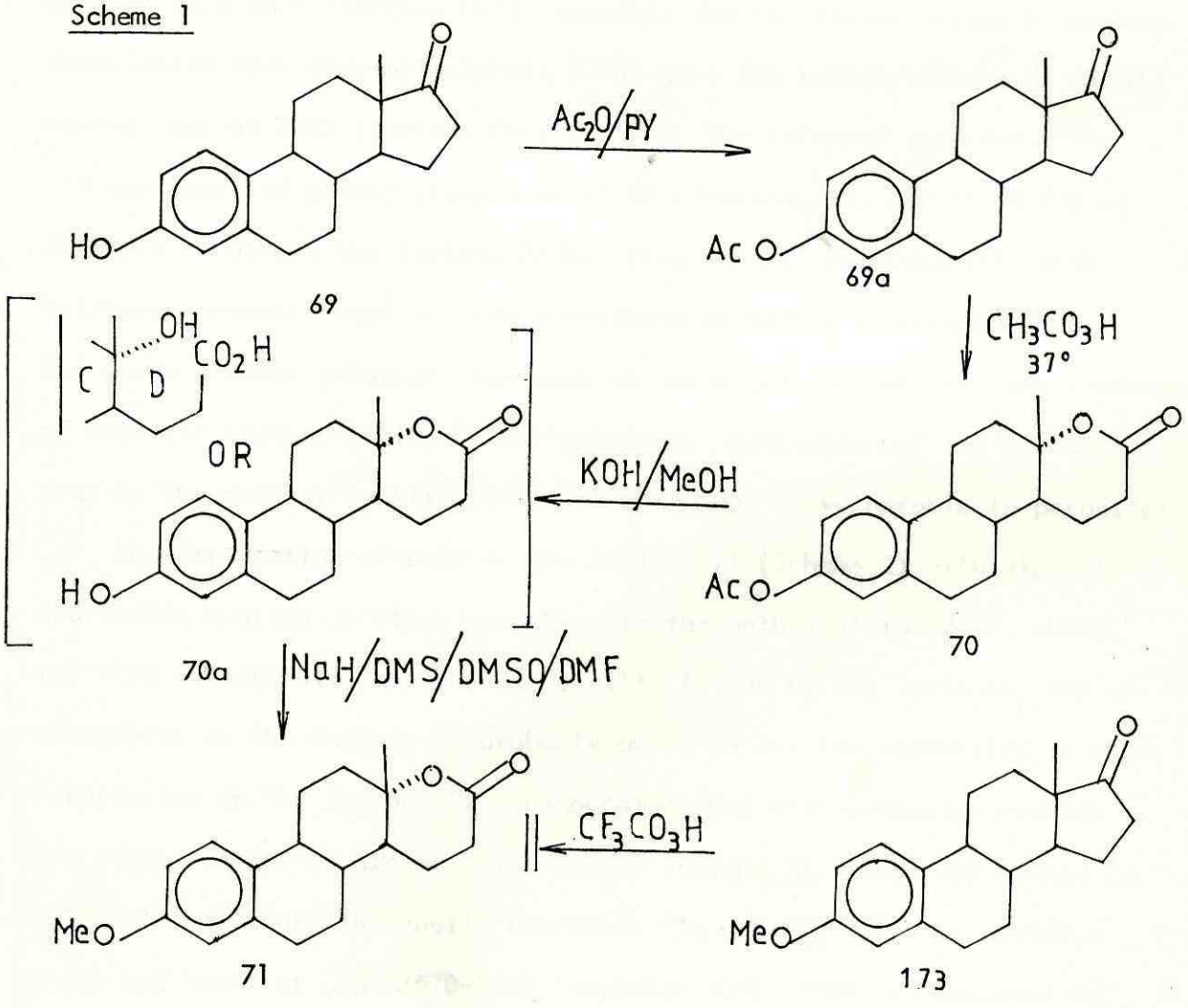
DISCUSSION

DISCUSSION

II

The methylene lactones were synthesised from preformed lactones by extension of the method developed by Yamada[32]. The estrone lactone 71 was formed by the series of reactions given in Scheme 1, which started with the acetylation of estrone 69 with acetic anhydride in pyridine to estrone acetate 69a (89%).

Scheme 1



Baeyer-Villiger oxidation of the estrone acetate with glacial acetic acid and 86% hydrogen peroxide proceeded with C-13 migration to form 3-acetoxy-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)triene 70. The infrared spectrum

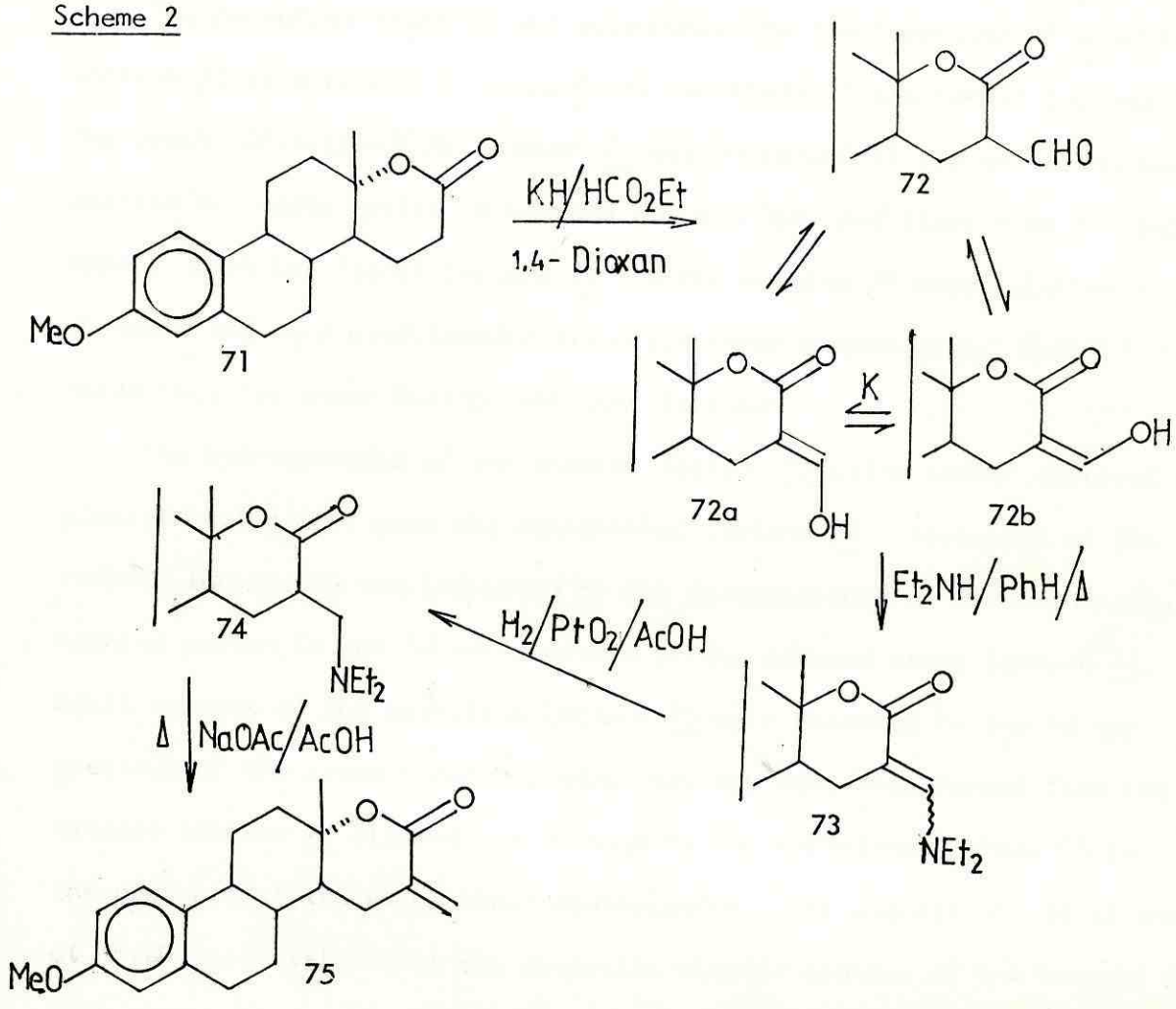
showed a band at νmax 1750 cm^{-1} for the acetate carbonyl and another at 1715 cm^{-1} which was assigned to the lactone C=O. The ^1H nmr spectrum showed signals at δ2.30 (acetate H) and δ1.36 (18-H)[78] which was evidence for the formation of the lactone 70. Yields of 55-60% were obtained with 86% hydrogen peroxide[44] over which it showed no obvious advantages.

The hydrolysis of the lactone 70 with potassium hydroxide gave the hydrolysed lactone 70a whose ir spectrum showed a low carbonyl frequency at νmax 1676 cm^{-1} (lactone C=O), possibly due to intermolecular H-bonding. Methylation with dimethylsulphate (DMS) gave the methoxylactone 71 (97%) having νmax at 1725 (lactone C=0) cm^{-1} in the infrared spectrum. The ^1H nmr spectrum showed signals at δ3.80 (3-methoxy H) and δ1.38 (18-H). Attempts to obtain the lactone 71 by using Emmons' conditions[45] with trifluoroperacetic acid in dichloromethane on methyl estrone 173 failed. The crude product obtained from such an oxidation did not show any evidence of aromatic protons in the ^1H nmr spectrum. Activation of the aromatic ring by the methoxy substituent could have made it vulnerable to peroxidation.

The formylation attempt on the lactone 71 (Scheme 2) with ethyl formate and sodium hydride in ether according to the method of Yamada[32] which was also successfully applied by Dehal[13] to the A-ring lactones, was unsuccessful on the lactone 71 probably owing to its low solubility in ether. Formylation to the lactone 72, was accomplished with potassium hydride and ethyl formate in dioxan. The formyl lactone 72, which was formed in 95% yield, may form two enolic tautomers 72a and 72b. The ir spectrum which had bands at νmax 3500-2500 (chelated -OH), 2700 (m, chelated OH), 1680 and 1621 (formyl lactone) cm^{-1}, indicated the hydroxymethylene lactones were largely present although the equilibrium system could not be studied by ^1H nmr spectroscopy owing to its low solubility in most suitable solvents.

* could be 13-hydroxy acid.

Scheme 2



The amination of the formyl lactone 72 with diethylamine in benzene at 65-70° gave the enamine 73. The ^{1}H nmr spectrum of the crude enamine 73 showed an aminomethylene methine proton at δ7.68 as a narrow triplet ($J \sim 1.5$ Hz) due to trans-allylic coupling with the C-15 protons, and signals at δ3.38 (q, J = 7Hz, N $\underline{CH_2}CH_3$) and δ1.21 (t, J = 7Hz, N $CH_2\underline{CH_3}$). Due to the low field signal at δ7.68, the lactone 73 was assigned the E-configuration. No evidence for the Z-isomer of the enamine lactone 73 was observed. Dehal[16] synthesised A-ring enamine lactones which he obtained as a mixture of E- and Z-isomers and assigned the E-configuration to the enamine with the singlet signal at δ7.70 and the Z-configuration to the isomer having the singlet signal at δ7.18.

The amination reaction was accompanied by the formation of unsubstituted lactone 71 as a result of retro-Aldol reactions of the formyl lactone 72. The amount of retro-Aldol product 71 was increased if the amination was carried out under reflux in benzene using a Dean and Stark trap to remove water. Both the formyl lactone 72 and the enamine 73 were relatively unstable and were used immediately after their preparation. Dehal[16], had noted this for other D-ring methylene lactones.

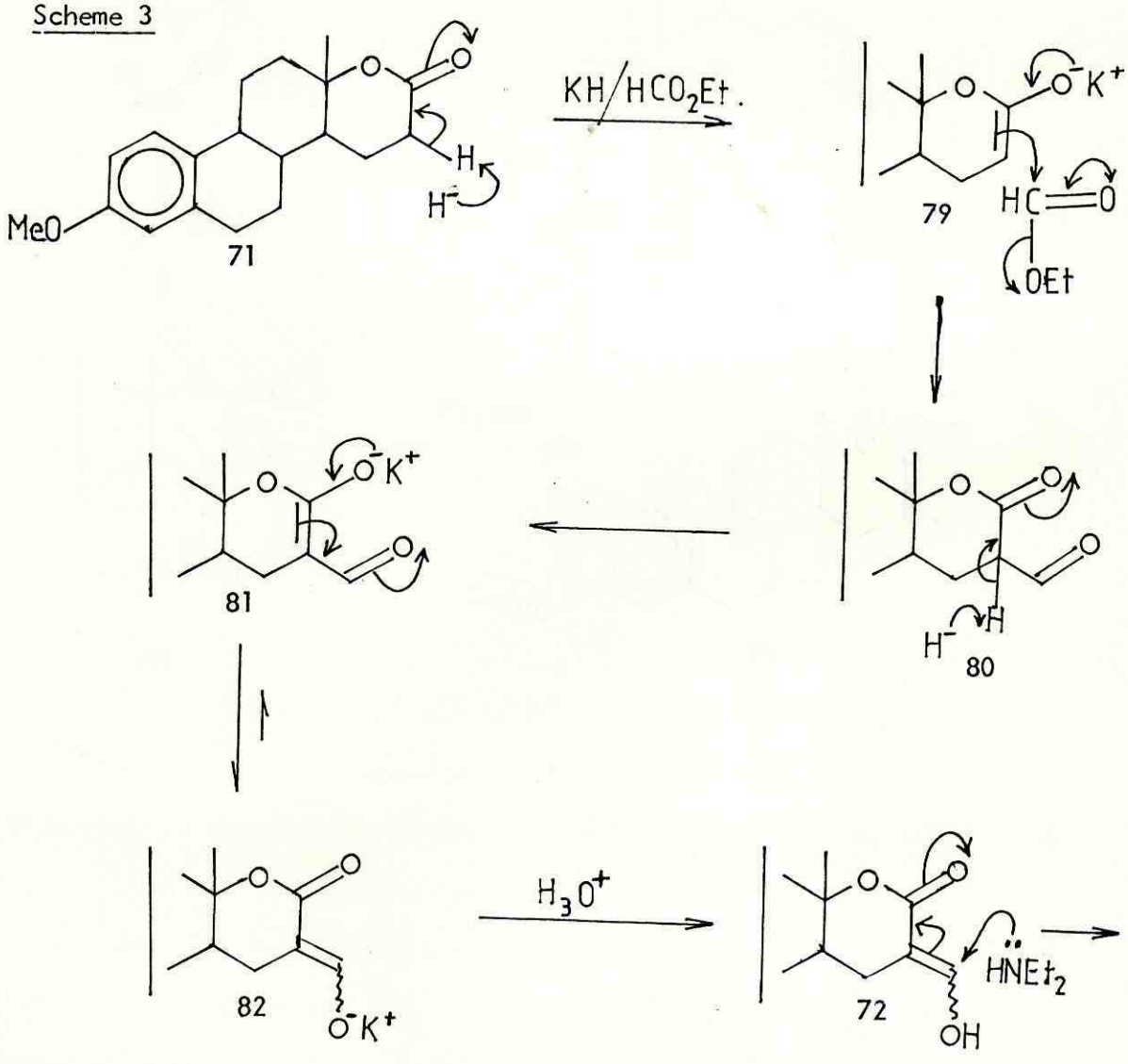
The hydrogenation of the enamine lactone 73 using Adams' catalyst in glacial acetic acid gave the aminomethyl lactone 74. Formation of the reduced lactone 74 was indicated by the disappearance of the aminomethylene methine proton in the ^1H nmr spectrum of the reduced crude lactone 74. Small amounts of the methylene lactone 75 were observed in the ^1H nmr spectrum of the crude reduced product and may have been formed from the reduced lactone 74 eliminating through to the methylene lactone 75 in the presence of traces of basic diethylamine. The signals at δ6.45 and at δ5.60 were assigned to the exocyclic vinylic protons of the lactone 75. Such observations were consistent with those made by Dehal[16] on analogous reductions of 2-(N,N-diethylamino)-methylene-3-oxo-4-oxa-5α-cholestane 121.

The elimination was completed on refluxing with sodium acetate in acetic acid. Chromatographic separation gave 3-methoxy-16-methylene-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)-triene 75 (32%). The ir spectrum showed frequencies at νmax 1712 and 1622 cm^{-1} which were assigned to the α,β-unsaturated lactone. The UV spectrum showed λmax at 218 nm (ε = 4,530) and λmax at 277 nm (ε = 5,779). The ^1H nmr spectrum showed vinylic proton singlets at δ6.45 and at δ5.60. The vinylic proton at δ6.45 was assigned to the cis-H due to the possible anisotropic effect of the C=O and that at δ5.60, was assigned to the trans-H. Vinylic proton signals at δ6.50 and at δ5.57 were recorded for the A-ring

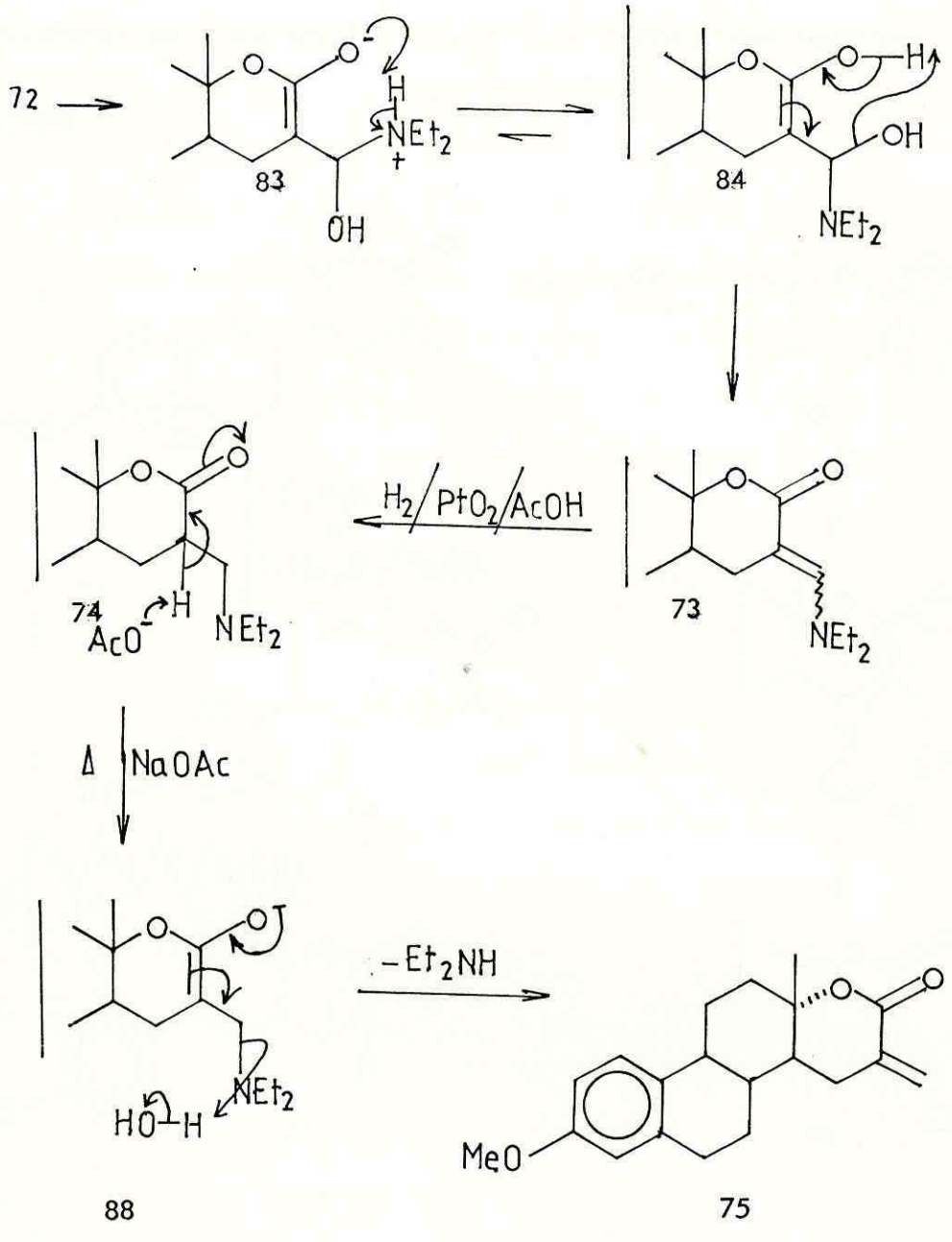
α,β-unsaturated methylene lactone by Dehal[16]. The mass spectrum showed a base peak at m/e 312 corresponding to the molecular ion.

The mechanism for the formation of the lactone 75 involves initial proton abstraction with the strong base, potassium hydride (71, Scheme 3). A Claisen-Schmidt condensation with ethyl formate and subsequent acidification of the alkoxide 82 gives the hydroxymethylene lactone 72. A Michael addition of diethylamine with the lactone 72 follows leading to the enamine 73 which is hydrogenated to the amine 74 which undergoes β-elimination to give the methylene lactone 75.

Scheme 3

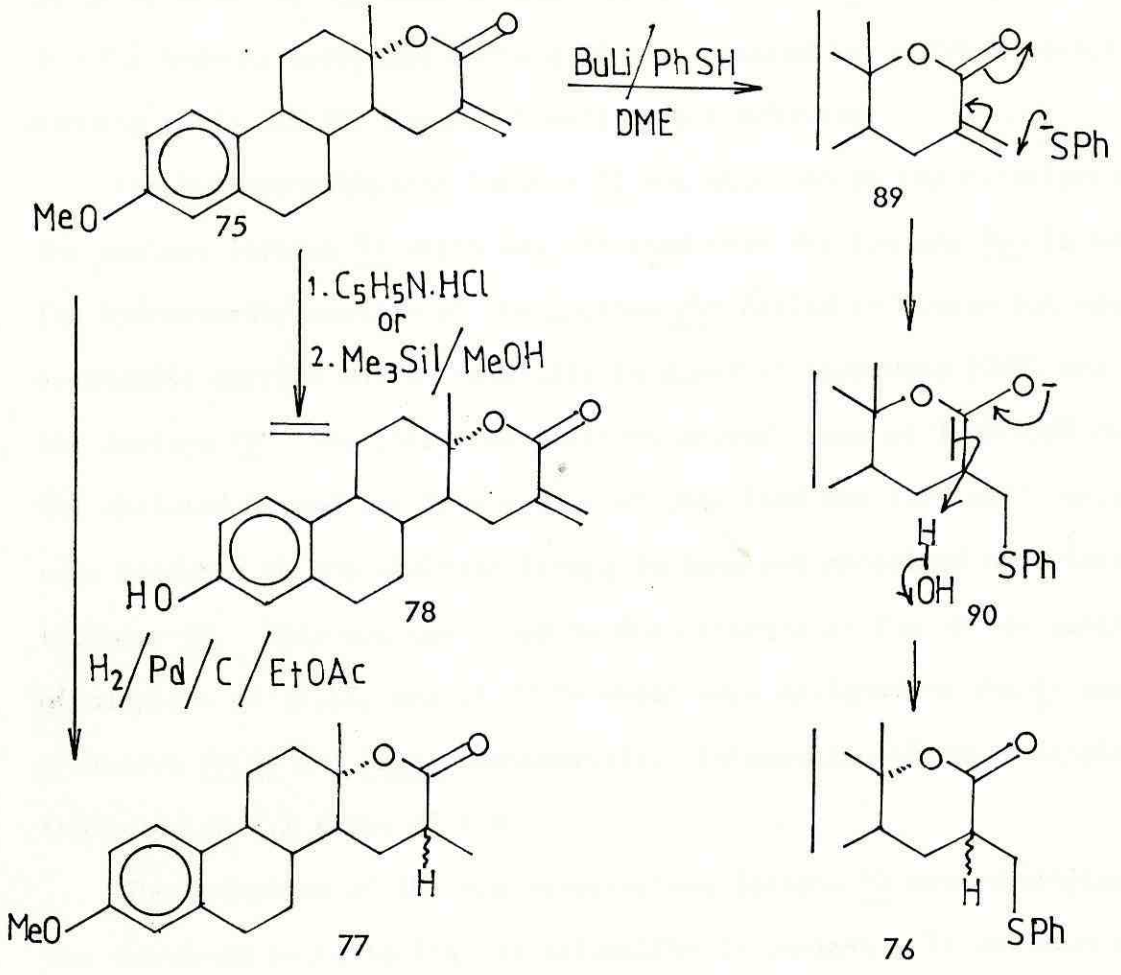


Scheme 3 (continued)



The treatment of the methylene lactone 75 with n-butyl-lithium and thiophenol gave the thiol-adduct 76 in a Michael-type reaction, Scheme 4.

Scheme 4



The reduction of the methylene lactone 75 gave the reduced lactone 77 with the ir spectrum showing a carbonyl frequency at νmax 1730 cm^{-1} which was assigned to the lactone. The mass spectrum showed the base peak corresponding to the molecular ion at m/e 314 . Attempts to demethylate the methylene lactone 75 to the hydroxy lactone 78 by heating with pyridinium hydrochloride at 200-220° or by treatment with trimethylsilyl iodide[79] at 60° in carbon tetrachloride, did not succeed.

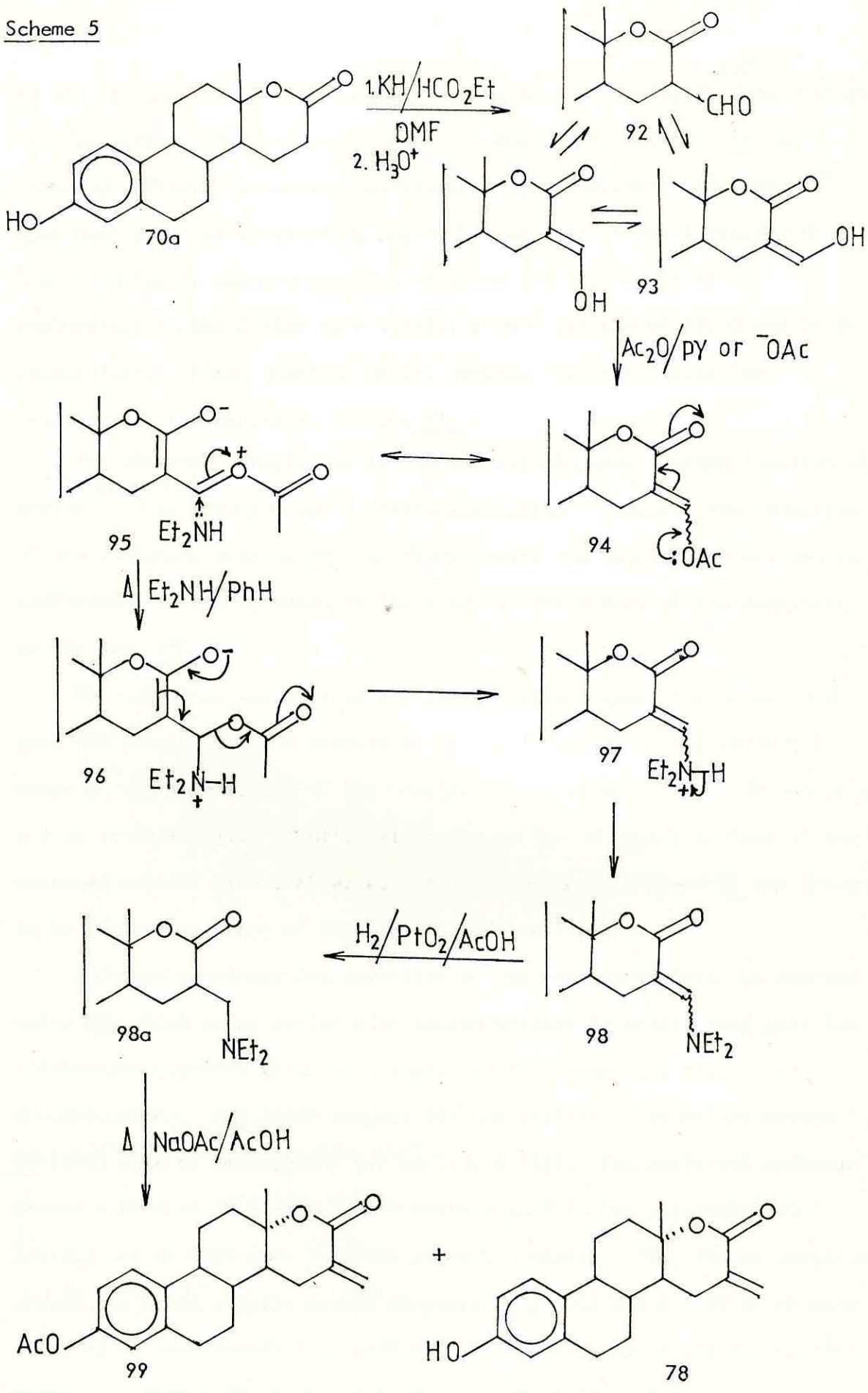
Aluminium bromide-ethane thiol at 0° has been used successfully by Node[80] for the demethylation of 3,17-dimethoxy-estra-1,3,5(10)triene to estradiol but it was not attempted with the methylene lactone 75 as an alternative approach to the hydroxy lactone 78 was adopted, Scheme 5. The hydroxy methylene lactone 78 was required for estrone-receptor binding tests and for potential anti-tumour activity.

The hydroxy-methylene lactone 78 was obtained by the hydrolysis of the acetoxy lactone 99 which was obtained from the lactone 70a (Scheme 5). The hydroxymethylenation of the lactone 70a failed in dioxan but was eventually carried out successfully in dimethyl-formamide (DMF) and gave the lactone 93. The infra-red spectrum showed νmax at 3600-2500 cm^{-1} for the chelated OH and two frequencies at νmax 1685 and 1610 cm^{-1} which were assigned to the enolised formyl lactone and contained no detectable tautomer 92. This was confirmed by the presence in the ^1H nmr spectrum of singlets at δ7.82, and at δ7.20 which were assigned to the E- and Z-isomers 93(a) and 93(b) respectively. Integration of these singlets indicated an E:Z ratio of 6:4.

The amination of the hydroxymethylene lactone 93 with diethylamine was abandoned owing to its low solubility in benzene. It was then decided to acetylate the hydroxymethylene lactone 93 in an attempt to improve its solubility. The acetylation was carried out with acetic anhydride in pyridine and gave the diacetate lactone 94 in 72% yield. The ir spectrum of the lactone 94 showed a carbonyl band at νmax 1768 cm^{-1} which was assigned to the 3-acetoxy group and the enol acetate. A further carbonyl band at 1706 cm^{-1} was assigned to the D-ring lactone and a band at 1640 cm^{-1} suggested the presence of the exocyclic double bond.

The ^1H nmr spectrum of the lactone 94 showed a vinylic proton signal at δ8.42 as a narrow triplet ($J \sim 1.5$Hz) and a singlet at δ2.29 was assigned to the protons of the two acetate groups. The diacetate lactone

Scheme 5


1. KH/HCO2Et
DMF
2. H3O+
HO
70a
CHO
92
OH
93
OH
Ac2O/PY or ⁻OAc
95
Et2NH
94
:OAc
Δ Et2NH/PhH
96
Et2N–H
97
Et2N–H
H2/PtO2/AcOH
98a
NEt2
98
NEt2
Δ NaOAc/AcOH
AcO
99
+
HO
78

94 was assigned the E-configuration owing to the low field signal for the vinylic proton. No evidence for the Z-isomer of the lactone 94 was observed. Previously acyloxy-substituted α-methylene-γ- lactones 47a have been prepared by reacting the sodium enolate of the lactone with benzoyl chloride and phenylacetyl chloride and were found to be exclusively in the E-form with vinylic proton signals at δ8.55 and δ8.20 respectively. These chemical shifts compare favourably with that observed for the diacetate lactone 94.

The observed acetylation of the hydroxymethylene lactone function with acetic anhydride in pyridine was a little unexpected. However, the amination of the diacetate lactone 94 with diethylamine was expected to proceed as indicated in Scheme 5, owing to the electron deficiency of the exocyclic carbon (see 95).

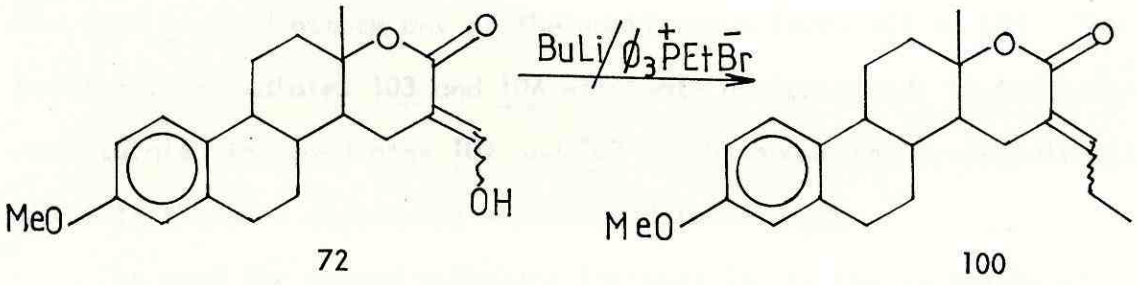
The amination was carried out in refluxing benzene for 30 hr. and gave the enamine 98 as a mixture of E- and Z-isomers in the ratio 5:4 based on the integration of the vinylic proton signals at δ 7.60 and at δ 6.55 respectively. A multiplet at δ 3.28 for $-N\underline{CH_2CH_3}$ instead of the expected quartet as was observed for the enamine 73 (Scheme 2) was thought to be further evidence of the presence of two isomers.

Platinum-catalysed hydrogenation of the enamine 98 gave the reduced amine 98a which under reflux with sodium acetate in acetic acid gave two elimination products which were separated by preparative thin layer chromatography. The major product was the acetate 16-methylenelactone 99 (29%) with UV λmax (EtOH) 217 nm (ε = 6,928). The infra-red spectrum showed a band at 1718 cm^{-1} which was assigned to the α,β-unsaturated lactone and at 1625 cm^{-1} for the exocyclic olefin. The ^1H nmr spectrum showed two broad vinylic proton singlets at δ 6.41 and δ 5.52 which were assigned to the 16-methylene protons. The other product was the hydroxymethylene lactone 78 which was formed in 13% yield. The hydroxymethylene lactone 78 must have been formed during reflux by either the action of

sodium acetate or glacial acetic acid on the 3-acetoxy group and was identical to the product obtained by the hydrolysis of acetoxymethylene lactone 99 with potassium hydroxide. The ir spectrum of the lactone 78 showed bands at 1681 cm^{-1} and 1622 cm^{-1} which were ascribed to the α,β-unsaturated lactone. The ^1H nmr spectrum showed two broad vinylic proton singlets at δ 6.48 and at δ 5.60 which were assigned to the 16-methylene protons.

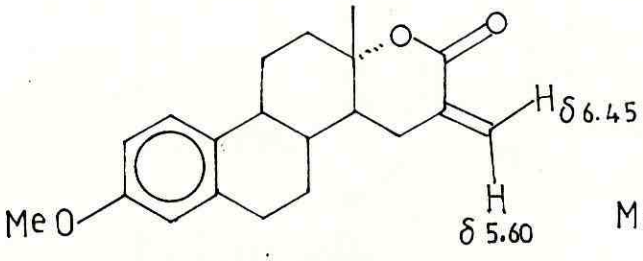
Wittig-reactions between hydroxy-methylene ketones and phosphorus ylids have been used for the synthesis of steroidal α-pyrones 64[42] and of prostaglandins[43]. It was anticipated that a reaction between the hydroxymethylene lactone 72 and ethyltriphenyl phosphonium bromide in the presence of butyl-lithium might give the alkylidene lactone 100 (Scheme 6).

Scheme 6

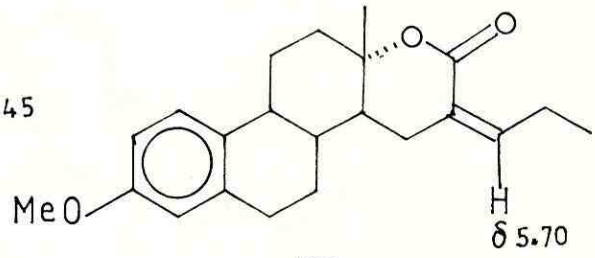


72 100

In the event, the lactone 100 was obtained in 19% yield after chromatographic separation. The ir spectrum showed a carbonyl frequency at νmax 1725 cm^{-1} for the α,β-unsaturated lactone. The ^1H nmr spectrum showed a vinylic proton multiplet at δ 5.70. The Z-configuration was assigned to the lactone 100 on the basis of its ^1H nmr spectrum compared to that of the lactone 75 where the low field proton signal at δ 6.45



75



100

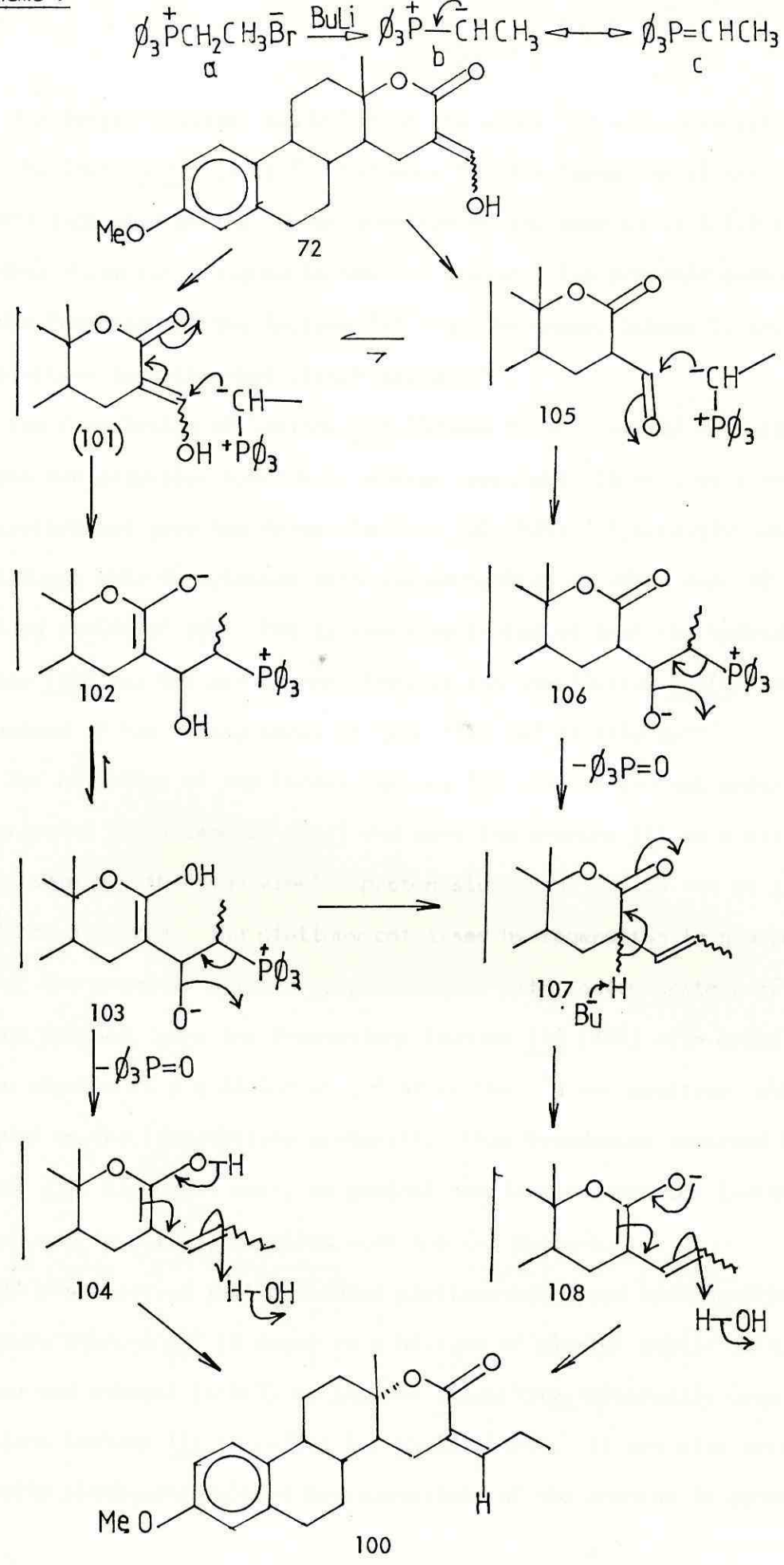
was assigned to the cis-H which is under considerable carbonyl anisotropic effect and that at δ 5.60 to the trans-H. Examination of a molecular model of the lactone 100 indicates that the Z-product is the more thermodynamically stable isomer, having the minimum interaction between the C-15 protons and the isopropylidene group.

Scheme 7 shows the possible synthetic route for the lactone 100. The ylid b could attack any of the equilibrium forms 101 or 105. The betaine intermediates 103 and 106 eliminate phosphinoxide to the β,γ--unsaturated intermediates 104 and 107 which isomerises by prototropic shift to the more stable α,β-unsaturated lactone 100.

The need for masked methylene lactones led to the synthesis of 2-methylene-3-oxo-4-oxa-5α-cholestane 122. The lactone 122 was previously synthesised by Dehal[16] from the preformed lactone 119 using Yamada's procedure[32].

The Oppenauer oxidation of cholesterol[46] with aluminium isopropoxide/cyclohexanone was accompanied by a prototropic shift and gave cholestenone 113 (Scheme 8) whose vinylic proton appeared at δ 5.67 in the ^{1}H nmr spectrum. The ir spectrum showed two bands at νmax 1680 cm^{-1} and 1615 cm^{-1} which were assigned to the conjugated C=O and olefin respectively.

Scheme 7



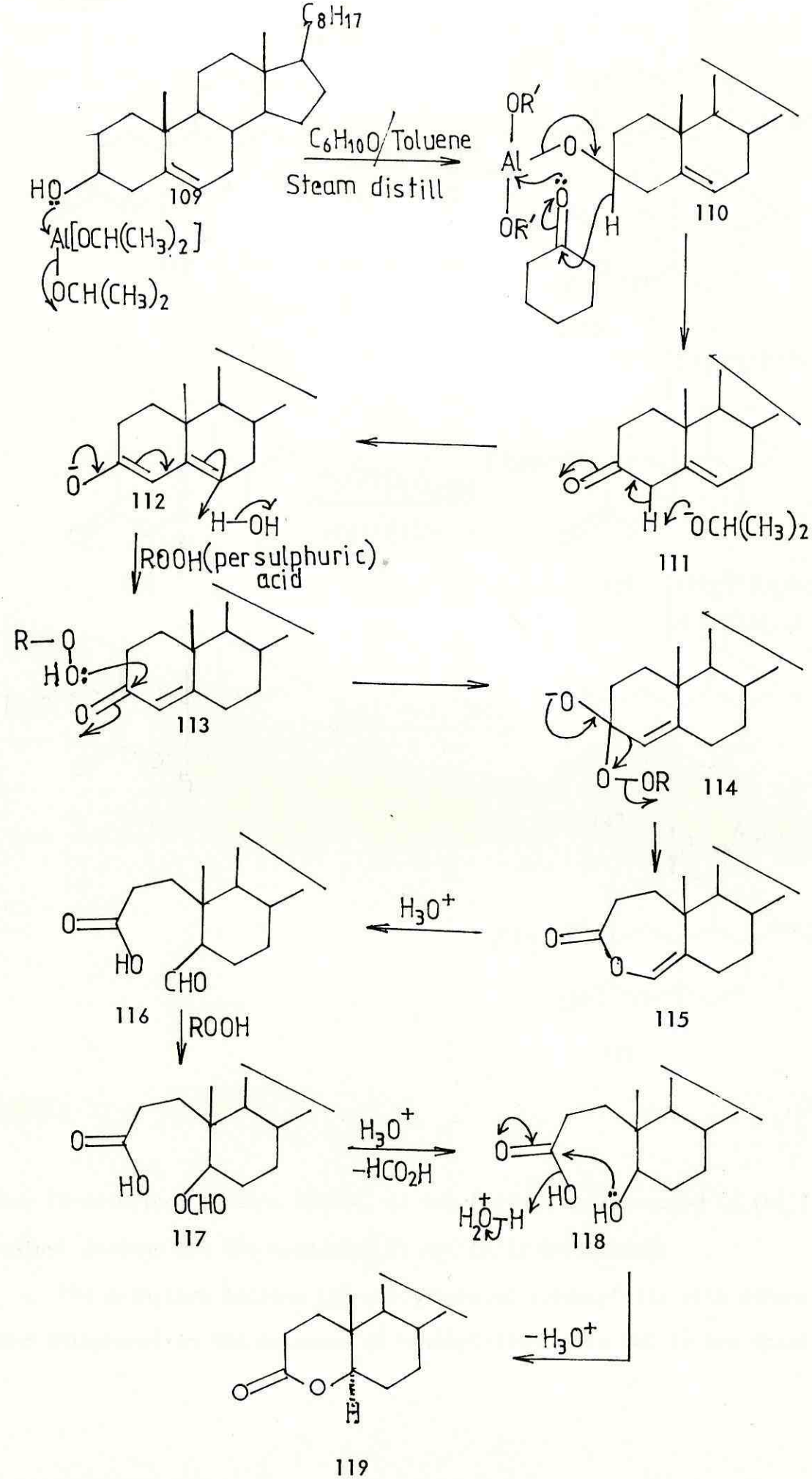
The Baeyer-Villiger oxidation of the enone 113 with persulphuric acid gave the lactone 119 (26%)[47]. Evidence for the formation of the lactone 119 was indicated in the ^{1}H nmr spectrum by the quartet at δ 3.9 (J= 10 and 4Hz) which was assigned to the C-5 proton. The probable mechanism for the formation of the lactone 119 from the enone, Scheme 8, involves a repetitive insertion-hydrolysis sequence[81].

The formylation of lactone 119 (Scheme 9) was carried out with ethyl formate and potassium hydride in dioxan overnight (18 hr.) at room temperature and gave the formyl lactone 120 (96%). Previously, Dehal[16] carried out this formylation with sodium hydride in ether over 70 hr. and obtained yields of 84%. The ir spectrum indicated that the hydroxymethylene lactone 120b was the predominant form in the equilibrium 120(a) and (b) by the appearance of two strong bands at Vmax 1702 and at 1610 cm^{-1}.

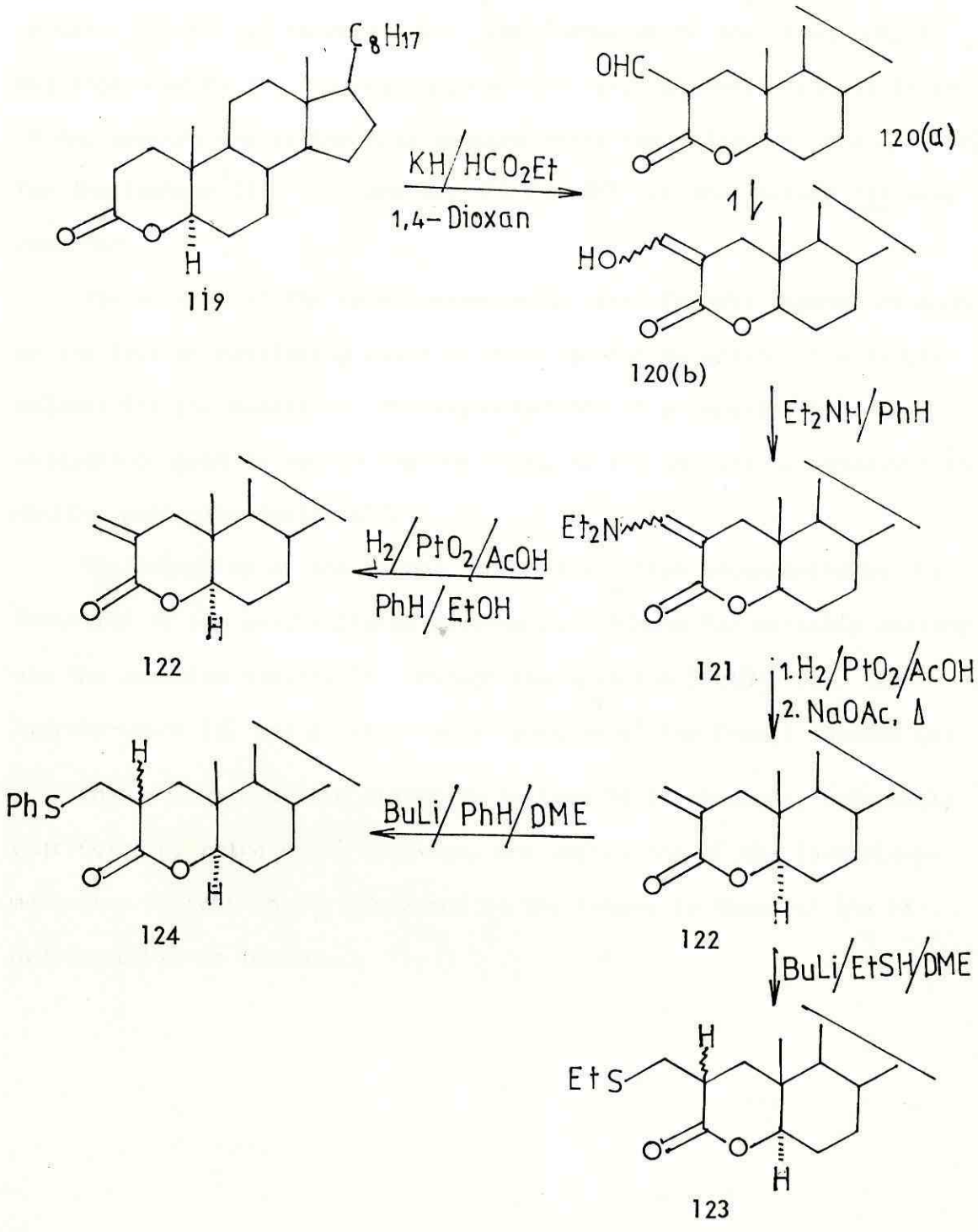
The amination of the formyl lactone 120 was carried out under reflux with diethylamine in benzene (3 days) and gave the enamine 121 as a mixture of E- and Z-isomers with broad vinylic proton signals at δ 7.58 and at δ 7.24 in the ^{1}H nmr spectrum. The platinum-catalysed hydrogenation in glacial acetic acid of the enamine followed by elimination with sodium acetate of the reduced product, gave the 2-methylene lactone 122 (63%) with broad vinylic proton signals at δ 6.45 and at δ 5.52 in the ^{1}H nmr spectrum which were assigned to the 16-methylene protons[16]. This broadening observed for the lactone 122, is due in part, to geminal coupling between the 2-methylene protons and to allylic coupling with the C-1 protons.

It was observed that prolonged platinum-catalysed hydrogenation of an impure enamine 121 (7 days) in a mixture of glacial acetic acid, benzene and ethanol (4:3:1) to improve solubility, eventually gave the methylene lactone 122 in rather low yields (40%). It was also observed that with platinum-catalysed hydrogenations of the enamine in general,

Scheme 8


C8H17
HO
109
Al[OCH(CH3)2]
OCH(CH3)2
C6H10O/Toluene
Steam distill
OR'
Al
OR'
O
H
110
O
112
H—OH
H
OCH(CH3)2
111
ROOH(persulphuric) acid
R—O
HO:
O
113
O
O
OR
114
O
115
H3O+
HO
CHO
116
ROOH
HO
OCHO
117
H3O+
-HCO2H
O
HO
H2O
H
HO
118
-H3O+
O
O
H
119

Scheme 9



any 16-methylene lactone formed, is not further hydrogenated to the 16-methyl lactone but the mechanism is not fully understood.

The methylene lactone 122 was thiolated successfully with ethane thiol and thiophenol in the presence of n-butyl-lithium in DME to the thiol

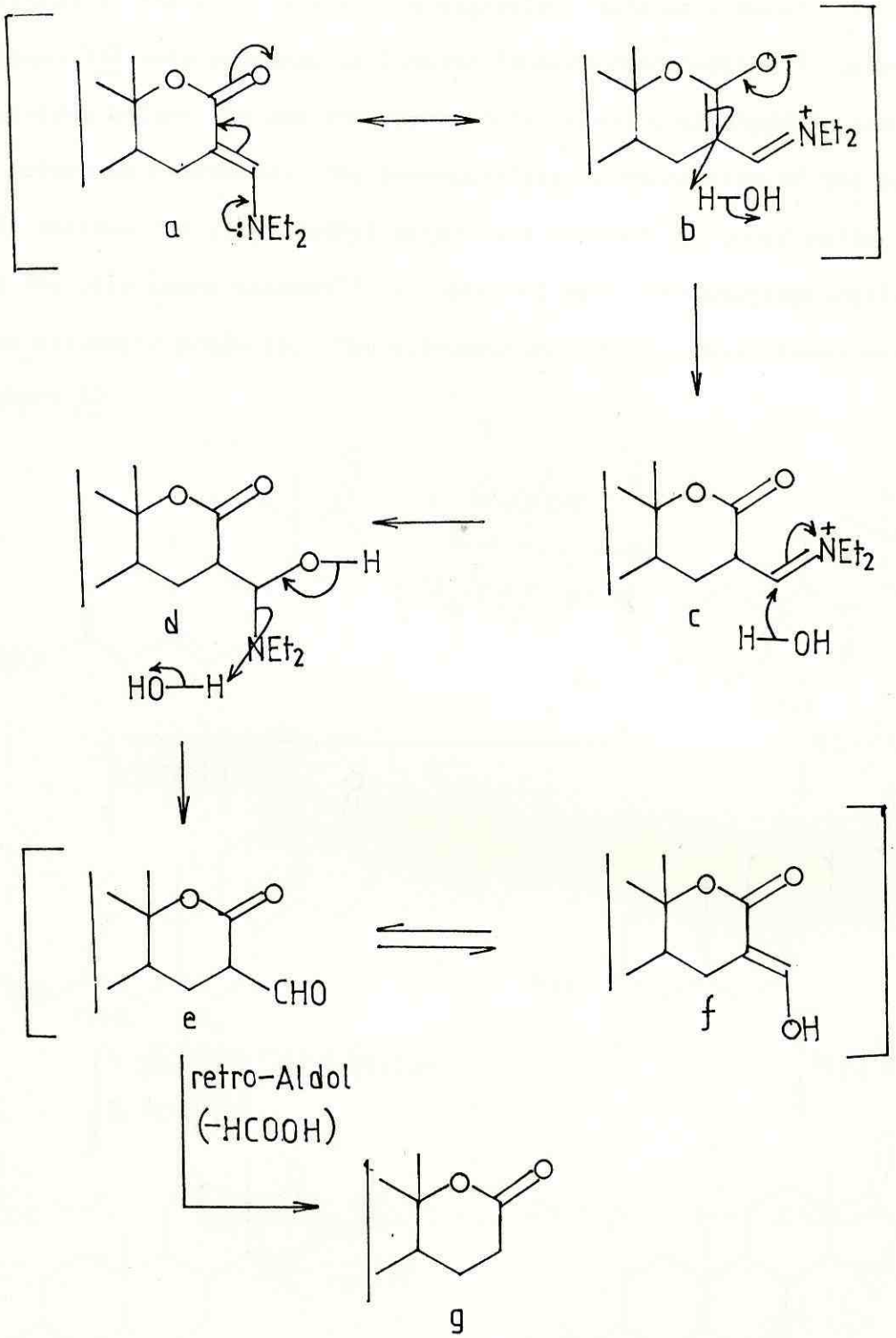
adducts 123 and 124 respectively. The formation of the thiol adducts was indicated by the disappearance of the vinylic proton signals in the ^1H nmr spectra and by the mass spectra where the molecular ions m/e 462(53%) for the lactone 123 and m/e 510 (14.5%) for the lactone 124 were recorded.

The success of the formylations with ethyl formate depends as much on the type of metalating agent as on a careful selection of suitable solvent for the reaction. Potassium hydride is a superior base and metalating agent to sodium hydride owing to its ability to rapidly form reactive potassium enolates[48].

The amination of the formyl lactones is often accompanied by the formation of the unsubstituted lactone (g) (Scheme 9a) possibly arising via the imminium enolate (b) through the imminium lactone (c), the hydroxy-amine (d) and a retro-Aldol reaction of the formyl lactone (e).

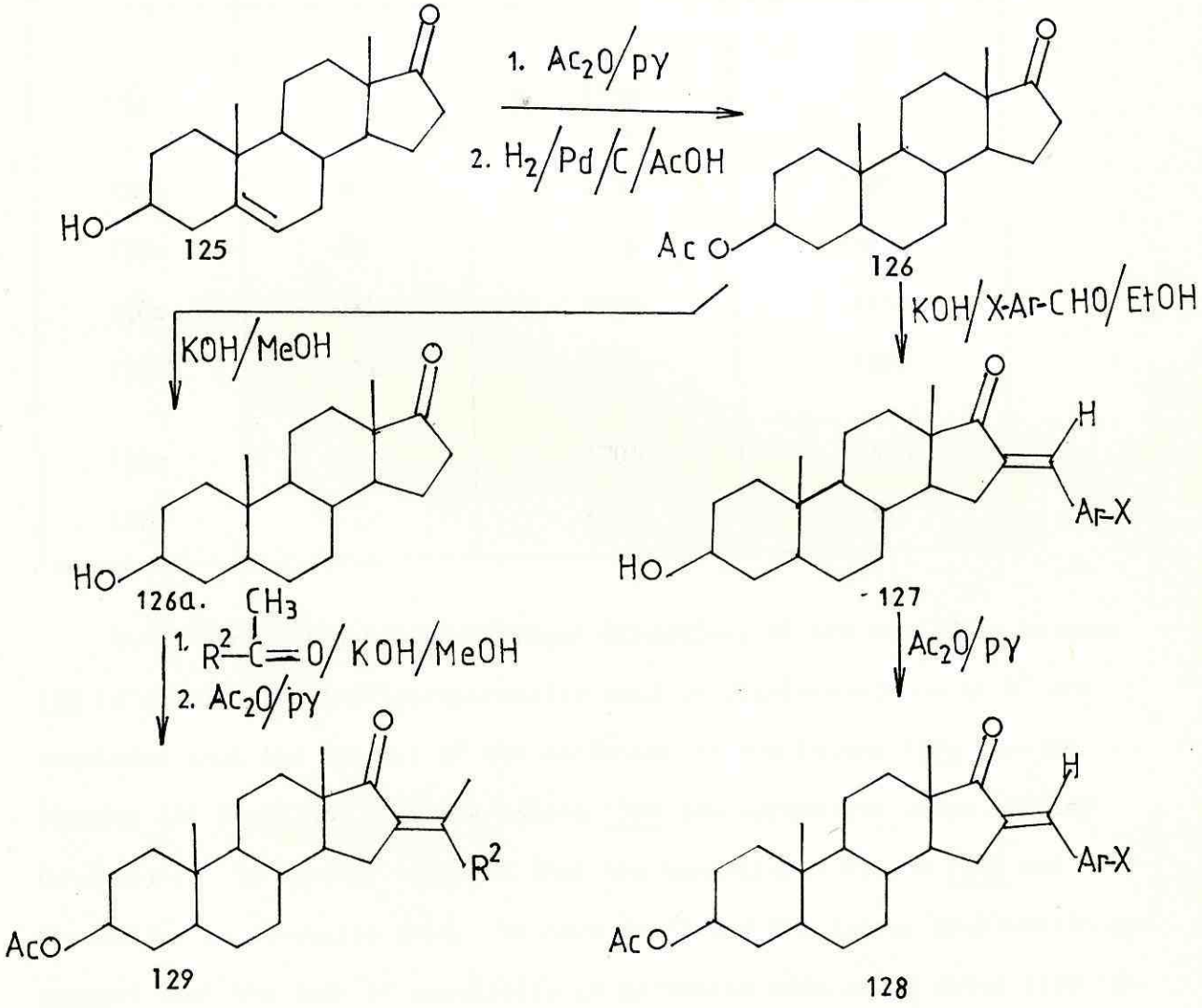
The amination of the diacetate lactone 94 is, however, relatively unaffected by retro-Aldol reactions and aminations of the 16-acyloxymethylene lactone may be preferred in the future to those of the 16-hydroxymethylene lactone.

Scheme 9a


a
:NEt2
b
+NEt2
H–OH
c
+NEt2
H–OH
d
H
NEt2
HO–H
e
CHO
f
OH
retro-Aldol
(-HCOOH)
g

It was intended to carry out Baeyer-Villiger oxidations on arylidene and alkylidene ketones as a possible route to arylidene and alkylidene lactones if the C-13 versus C-16 migration could be induced. The arylidene ketones 127 were prepared by Claisen-Schmidt condensation[49] between the steroidal ketone 126 and the appropriate aromatic aldehyde in the presence of potassium hydroxide. The base-catalysed condensation of the ketone 126a with acetone and ethyl methyl ketone was carried out under reflux in methanol and the alkylidene ketones[76] so obtained were chromatographically separated from polymeric products. The α,β-unsaturated-3-hydroxyketones were acetylated

Scheme 10



a; R^2=Me

b; R^2=Et

a; X=H , c; X=NO_2

b; X=Cl, d; X=OMe

with acetic anhydride in pyridine to the 3-acetoxy-α,β-unsaturated ketones 128 and 129 (Scheme 10) whose carbonyl and exocyclic olefinic bands in their ir spectra are given in Table I.

The ^1H nmr spectra of the α,β-unsaturated ketones 128 displayed singlets between δ 7.50 and δ 7.30 which were assigned to the benzylidene methine protons and confirmed the E-isomers were formed.

Table I

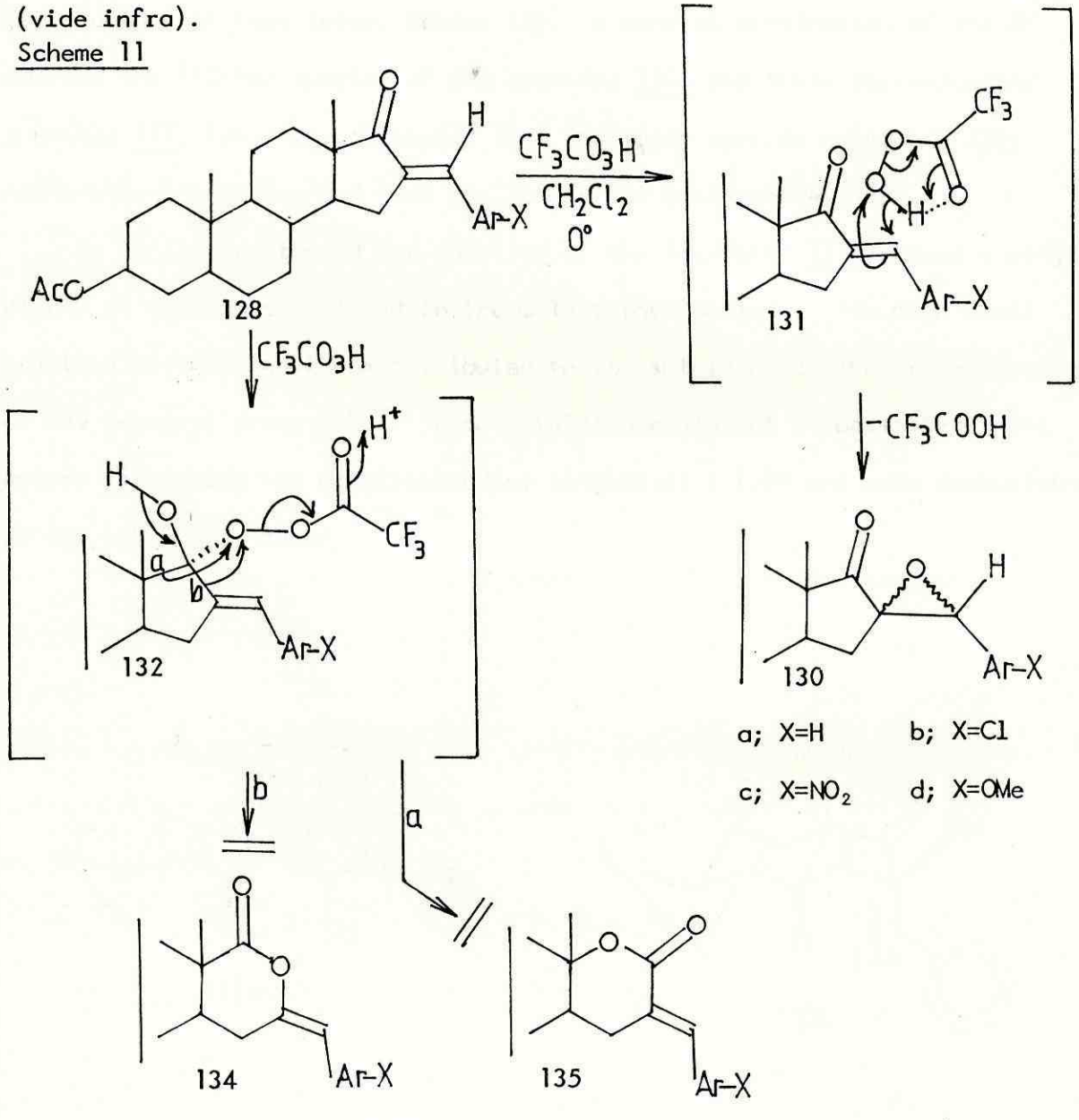
Ketone	(-Ar-X) X	IR Frequencies cm^{-1} 17-νC=O	νC=C
126	-	1750	-
128a	-H	1720	1640
128b	-Cl	1720	1635
128c	$-NO_2$	1725	1638
128d	-OMe	1715	1630
129a	-	1705	1635
129b	-	1712	1633

Ross[51] reported Baeyer-Villiger oxidations of the arylidene ketones 128 (a and c) with trifluoroperacetic acid in dichloromethane at 0° and concluded that the product of the oxidation of the ketone 128a was the lactone 134 (X=H) and that the ketone 128c was unreactive under similar conditions. He further reported that the benzylidene ketone 128a was unreactive in peracetic acid. We have confirmed the latter observation and suggest that the lack of reactivity in peracetic acid could arise from the low solubility of the ketones in this medium. Chelghoum[51] later reported similar oxidations on the arylidene ketones 128 (a, c and d) but was unable to reach any satisfactory conclusions due to separatory problems. He

tentatively concluded that the products of the oxidations of the ketones 128 (a and c) were α,β-unsaturated-δ-lactones 135 and that the oxidation of the p-methoxybenzylidene ketone 128d led to inseparable products.

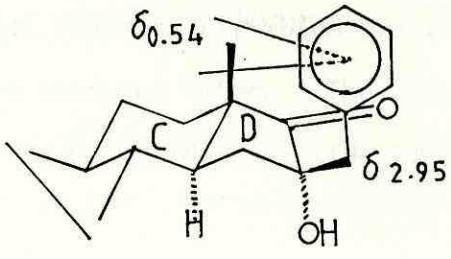
Our investigations on Baeyer-Villiger oxidations of α,β-unsaturated ketones 128 (a, b and c) in the more vigorous conditions with buffered trifluoroperacetic acid in dichloromethane at 0° indicate that the products were the isomeric epoxides 130 (a, b and c) and neither of the lactones 134 nor 135 were obtained (Scheme 11). In the case of the p-methoxybenzylidene ketone 128d, the products of similar Baeyer-Villiger oxidation were not the corresponding epoxides 130d but rather arose from rearrangement of these (vide infra).

Scheme 11

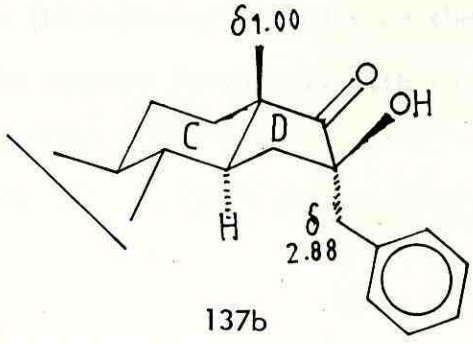


The identification and the stereochemistry of the products was possible only after a careful spectroscopic analysis of the individual epoxides 130a which were separated by preparative t.l.c. The lower t.l.c. product was the major component of the epimeric mixture 130a and had an important singlet at δ 4.15 in the ^{1}H nmr spectrum which was assigned to the epoxide methine proton. The upper t.l.c. product was the minor component and had a corresponding singlet at δ 4.34. The ir spectra of the epoxides 130a showed a band at 1750 cm^{-1} which was assigned to the cyclopentanone C=O. The hydrogenolytic opening of the separated epoxides 130a over palladium catalyst in ethyl acetate gave the α-ketol[64] 137a from the major component and the α-ketol 137b from the minor component (see later, Scheme 12). A careful examination of the ^{1}H nmr and the ^{13}C-nmr spectra of the epoxides 130a and their corresponding α-ketols 137, Table II, suggested that the major epoxide component 130a had α-stereochemistry and that its epimer had β-stereochemistry.

In particular the ^{1}H nmr spectrum of the 16α-ketol 137a showed a singlet at δ 0.54 which was assigned to the C-18 methyl protons. The high field position of the signal was attributed to the shielding of the aromatic ring of the β-benzyl group 137a. Such shielding would not be possible in the epimer 137b which has a corresponding singlet at δ 1.00 and some deshielding by the 16β-OH may occur,



137a



137b

The off-resonance decoupled ^{13}C-nmr spectra of the α-ketols 137 (a and b) had signals at δ 13.7 and δ 15.6 respectively which were assigned to the C-18 atom. The correspondingly high field position of the C-18 atom for the α-ketol 137a in the ^{13}C-nmr spectrum was thought to confirm the 16α-OH stereochemistry. The ^{13}C-nmr spectra also confirmed the presence of the cyclopentanone ketone.

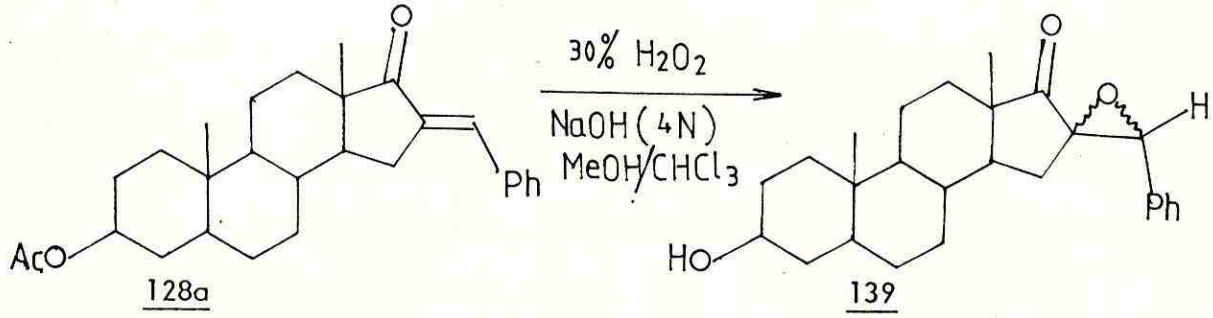
Table II

	$[\alpha]_D^\circ$	^{1}H nmr δ ppm		*^{13}C-nmr δ ppm			
		18	Ph-CH	16	17	18	Ph-C
Major product (130a, epoxide) (α-)	+ 190	0.93	4.15	67.1	215	14.3	63.1
Its α-ketol (137a) (α-)	+ 92	0.54	2.95	79.8	218.5	13.7	44.8
Minor product (130a, epoxide) (β-)	- 121	1.08	4.34	67.2	215	14.4	62.6
Its α-ketol (127b) (β-)	- 20	1.00	2.88	79.8	218.5	15.6	43.7

* see Table VII p. 102

An attempted peroxidation of the benzylidene ketone 128a with hydrogen peroxide and sodium hydroxide (4N) in methanol/chloroform gave a basic fraction 139 which showed two singlets at δ 4.14 and δ 4.33 in the ratio 59:41 respectively which are in line with the expected attack from the less hindered α-face. The chemical shifts compare favourably with those of the benzylidene epoxide 130a (see Table III).

Scheme 17



128a 139

Table III shows the key infra-red and ^1H nmr bands of the mixed epoxides 130 and the assignments are made on the assumption that the above analysis is correct.

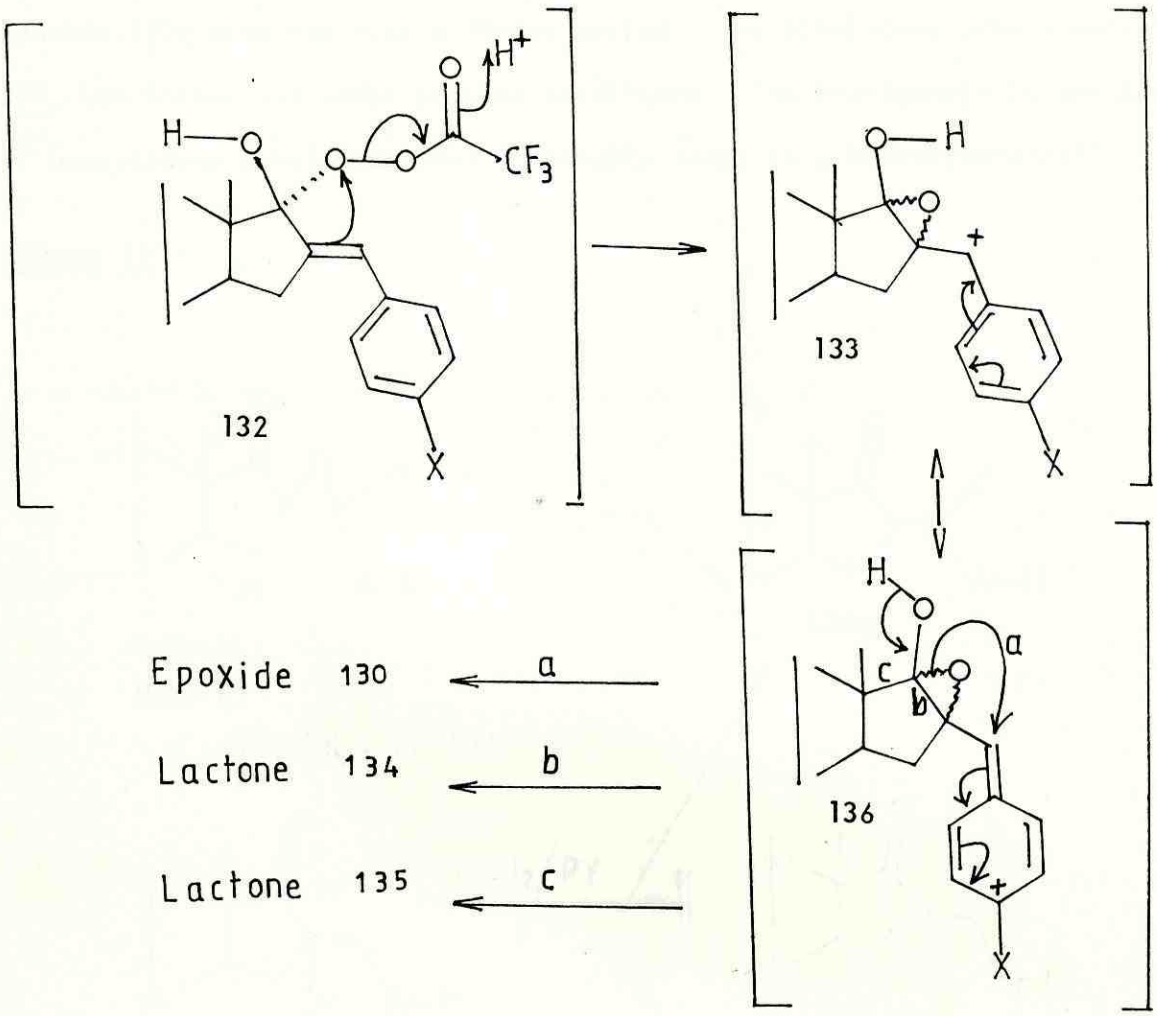
Table III

Epoxide 130	Aryl Substit-uent X	^1H nmr δ ppm Epoxide-H α-epoxide	β-epoxide	ir νC=0 cm^{-1}	α-epoxide %	β-epoxide %
a	H	4.15	4.34	1750	65	35
b	Cl	4.10	4.30	1755	72	28
c	NO_2	4.25	4.45	1750	55	45

The formation of the epoxides 130 could be explained by the peracid attack on the olefin 131[49]. The attack on the 17-ketone could be expected to give the lactones 134 or 135 by a- or b-bond migration. The intermediate 132 also has the peracid group positioned for vinylic participation and could in principle, form the lactones and epoxides through the epoxide-

-intermediate 133 below (Scheme 11a).

Scheme 11a

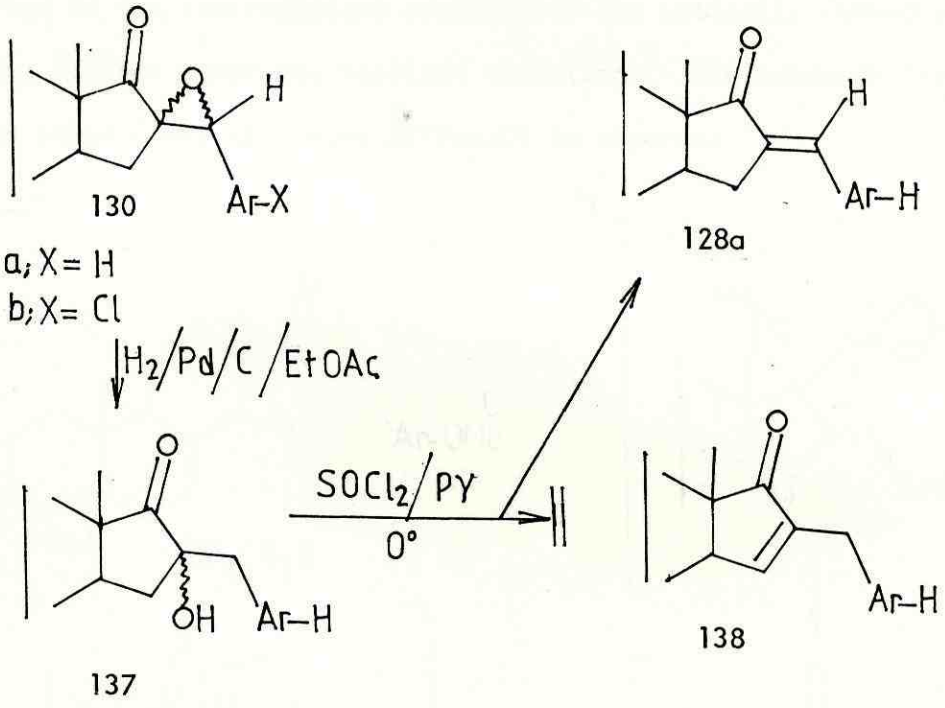


The epoxide benzylic carbocationic intermediate 133 could be stabilised by benzylic conjugation[36]; the extent of this stabilisation will depend on the nature of the substituent X. However, the absence of the lactones 134 and 135 from the oxidation products of 128 (a, b and c) probably rules out 133 as a possible intermediate and that the epoxides are obtained by the direct epoxidation of the olefin, see 131.

The hydrogenolytic opening of the epoxides 130a over palladium catalyst in ethyl acetate to the α-ketols 137a and 137b has already been

discussed. The epoxide epimers 130b under similar conditions reacted rather slowly and with simultaneous hydrogenolysis of C-Cl bond to the epimeric α-ketols 137 (Scheme 12) which had identical ^{1}H nmr spectra with the α-ketols 137a and 137b. No significant hydrogenolysis of the p-nitro-benzylidene epoxide 130c occurred over a 10-day period. The alkylidene α-keto-epoxide 152, was unreactive under similar conditions. The hydrogenolytic opening of benzylidene α-keto-epoxides invariably leads to α-hydroxyketones[64].

Scheme 12



a = 16α-ketol

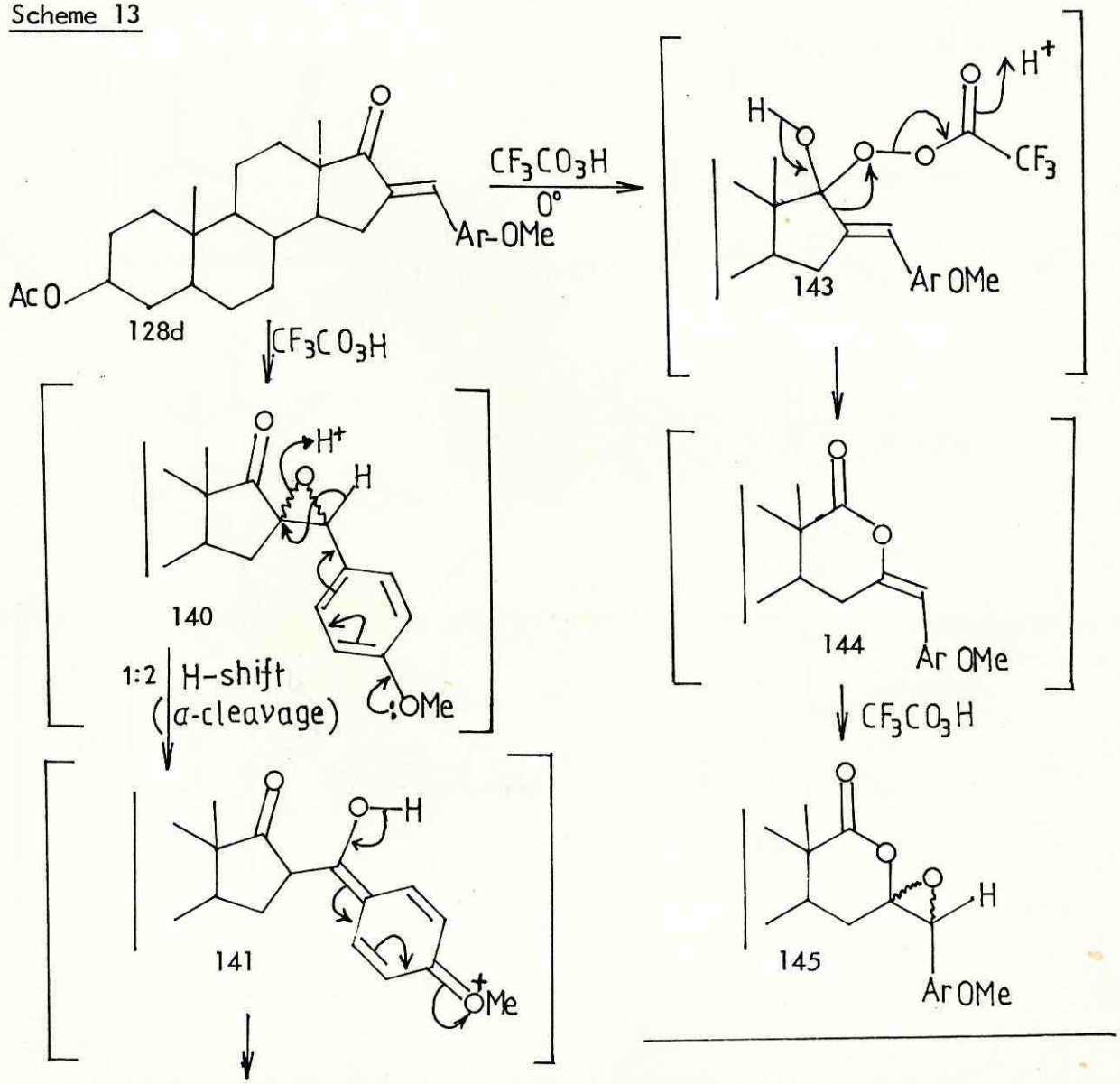
b = 16β-ketol

The dehydration of the individual α-ketols 137 (a or b) or the epimeric mixtures of the α-ketols 137 with thionyl chloride in pyridine at 0° proceeded stereospecifically to the E-benzylidene ketone 128a which was

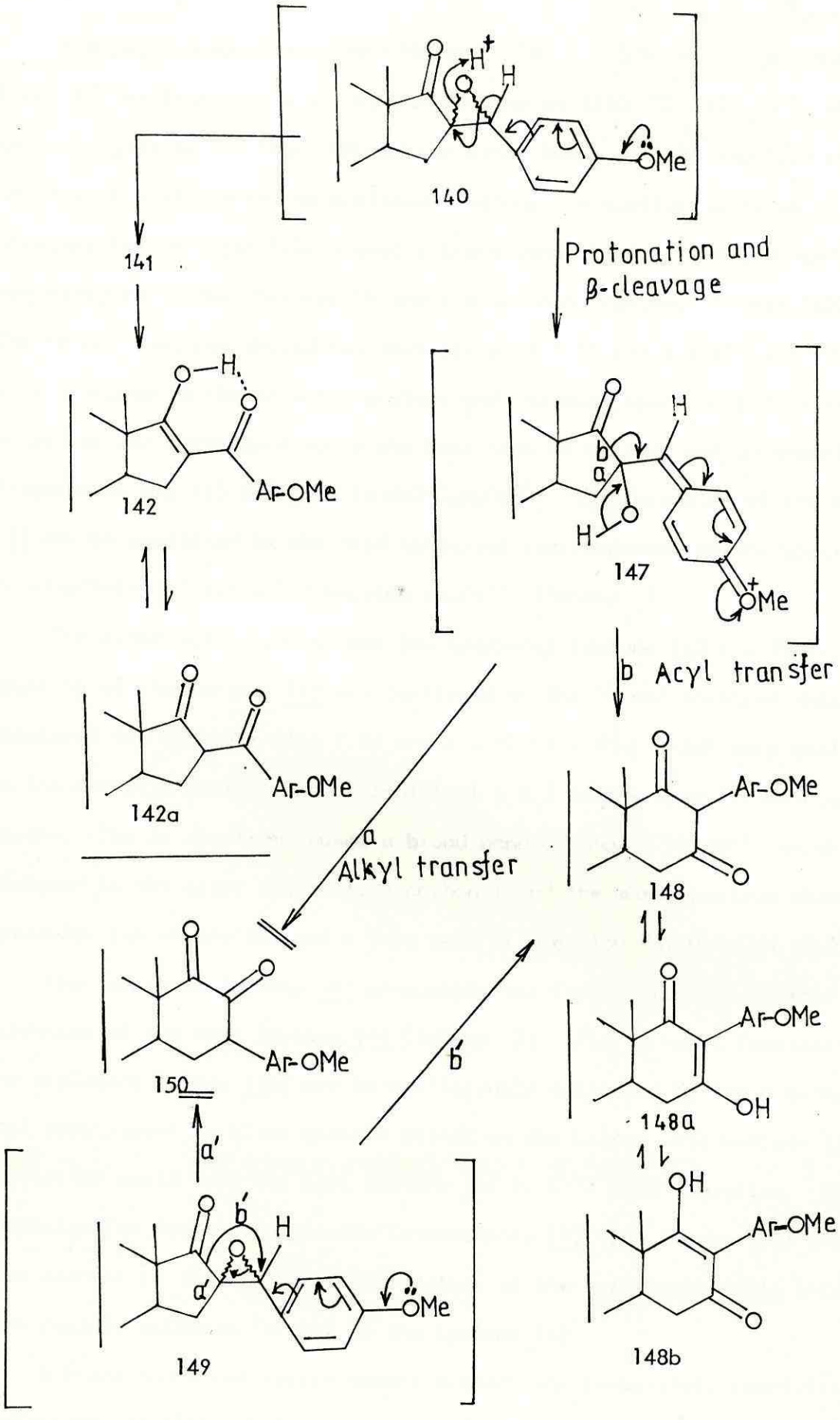
identical in all respects with an authentic sample. No endocyclic olefin 138 was observed from this dehydration.

The Baeyer-Villiger oxidation of the arylidene ketone 128d with trifluoroperacetic acid was carried out for ~ 4 hr. and gave an epoxyenol lactone 145 and rearrangement products 142 and 148 (Scheme 13). The rearrangement products 142 and 148 were formed during work-up owing to the removal of buffer. It was observed that up to about 3½hr., the t.l.c. of the reaction medium showed one major spot other than the starting material. However, beyond that time, several other spots began to appear and were attributed to the rearrangement products of the initially formed epoxides oxidising further under the reaction conditions. The products from prolonged reaction times (> 5 hr.) were difficult to separate.

Scheme 13



Scheme 13 (continued)



The major product was the β-diketone 142 (~ 50%) which had important bands in the ir spectrum in dichloromethane at 3550 to 3400 cm^{-1} which was assigned to the free OH and two other bands at 1685 and 1630 cm^{-1} which were assigned to the enolised diketone. A similar spectrum of the diketone 142 in nujol film showed a broad band at νmax 3400-2500 cm^{-1} which was assigned to the chelated OH and a broad band centred at νmax 1600 cm^{-1}. The ^1H nmr spectrum showed two doublets at δ 7.10 and δ 6.90 (J = 9Hz) which were assigned to the aromatic protons and the mass spectrum indicated a molecular ion corresponding to the base peak at m/e 466 and an important fragment at m/e 135 assigned to $MeO\text{-}C_6H_4C{\equiv}O^+$. The formation of the diketone 142 may be explained by the acid catalysed rearrangement of the epoxide intermediate 140 via a 1:2 hydride shift[63] (Scheme 13).

The other major product was the epoxyenol lactone 145 (~ 15%). The identity of the lactone 145 was confirmed by the ^1H nmr spectrum which displayed two doublets at δ 7.05 and δ 6.90 (J = 8Hz) which were assigned to the aromatic protons and a singlet at δ 4.2 to the benzylic methine proton. The ir spectrum showed a broad band at νmax 1730 cm^{-1} which was assigned to the ester and lactone carbonyl and the mass spectrum showed a molecular ion at m/e 482 and a base peak at m/e 150 for $MeO\text{-}C_6H_4\text{-}C{\equiv}O^+$.

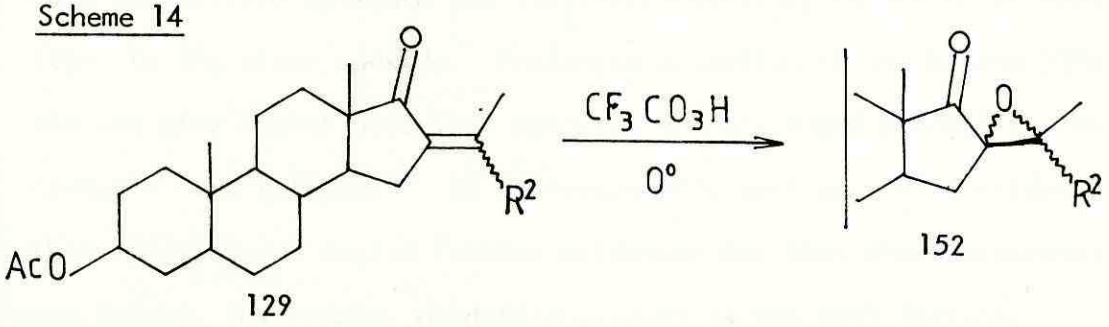
The epoxyenol lactone 145 presumably was formed from the further oxidation of the enol lactone 144 (Scheme 13). The carbonyl function in the arylidene ketone 128d may be sufficiently activated by the p-methoxy aryl substituent to allow peracid attack on the ketone intermediate 143. The latter could form the enol lactone 144 by C-16 bond migration. Vinylic participation leading to epoxide intermediate 133 (see Scheme 11a) could also account in theory, for the formation of the enol lactone 144 which is then rapidly oxidised further to the lactone 145.

A third and minor rearrangement product was tentatively identified as the β-diketone 148 although it was not obtained completely free of the epoxy lactone 145. It showed an infra-red band at 1690 cm^{-1} in dichloromethane which was assigned to the β-diketone 148a or 148b in its enolised form. The ^1H nmr

spectrum showed two doublets at δ 7.98 and at δ 6.93 (J = 9Hz) which were assigned to the aromatic protons. The considerable deshielding of one pair of the aromatic protons may arise from the enolised β-diketone system in 148a and 148b.

The Baeyer-Villiger oxidation of the alkylidene ketones 129 gave predominantly α-epoxides 152.

Scheme 14



a; R^2=Me

b; R^2=Et

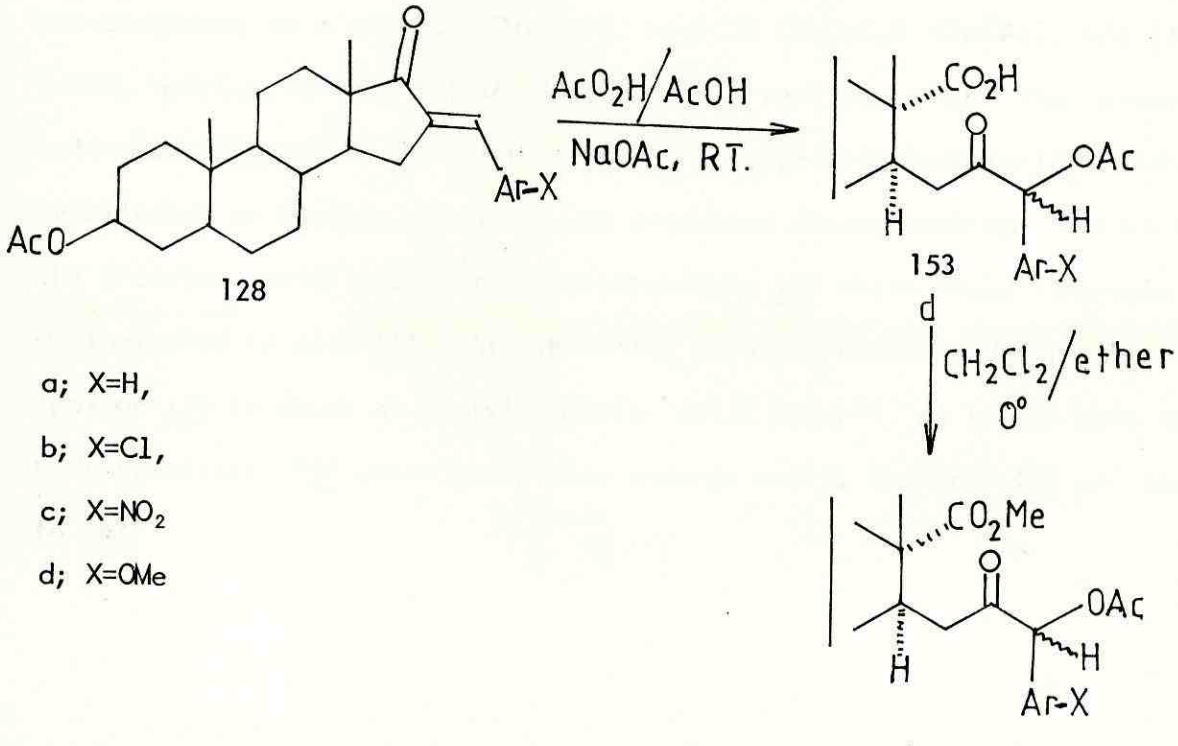
Only one epoxyketone 152a was isolated from the oxidation of the alkylidene ketone 129a and had an important band at 1740 cm^{-1} which was assigned to the cyclopentanone C=O. The ^1H nmr spectrum of the epoxy-ketone 152a showed two singlets at δ 1.38 and δ 1.35 which were assigned to the epoxide methyl protons and two other singlets at δ 0.96 and at δ 0.89 were assigned to the C-18 and C-19 methyl protons respectively. The α-keto-epoxide 152a had $[\alpha]_D$ = + 60° (CCl_4). The 16α-stereochemical assignment for the α-keto-epoxide was made by comparison with benzylidene α-keto epoxides 130 (see Tables II and III) and on the assumption that the peracid attacks from the less hindered α-face.

Two α-keto-epoxides 152b were isolated from the oxidation of the alkylidene ketone 129b through chromatographic separation in the ratio 76:24. The major fraction had an infra red band at νmax 1750 cm^{-1} which was assigned to the cyclopentanone C=O and the ^1H nmr spectrum revealed that this fraction was in fact a mixture of E- and Z-isomers (~ 50:50)

owing to the two singlets at δ 1.35 and at δ 1.32 which were assigned to the E- and Z-epoxide methyl protons. Two other singlets at δ 0.98 and δ 0.88 were assigned to the C-18 and C-19 methyl protons. The minor fraction had corresponding singlets at δ 1.52 and δ 1.38 for the E- and Z-epoxide methyl protons and at δ 0.99 and δ 0.91 for the C-18 and C-19 methyl protons. We have tentatively assigned the 16α-stereochemistry to the major epoxide and 16β- to the minor epoxide. Prolonged oxidation of the ketone 129a (3 days) did not give higher oxidation products or rearranged products. The work of Pinhey[37] and Williams[54] on stereospecific synthesis of epoxides established that epoxyketones resist further oxidation and that where epoxyenol lactones are formed, the primary oxidation product is the enol lactone.

The Baeyer-Villiger oxidation of the arylidene ketones 128 under Walton[53] conditions with 40-45% peracetic acid gave isomeric α-acetoxy keto-acids 153. Previous studies on the oxidation of α-arylidene and α-alkylidene ketones using Walton's conditions[53] were made by Williams[54] and by Handley[55]. Enol lactones[53], epoxyenol esters[54] and ketoacids[55] were obtained.

Scheme 15



128

153

154d

a; X=H,

b; X=Cl,

c; X=NO_2

d; X=OMe

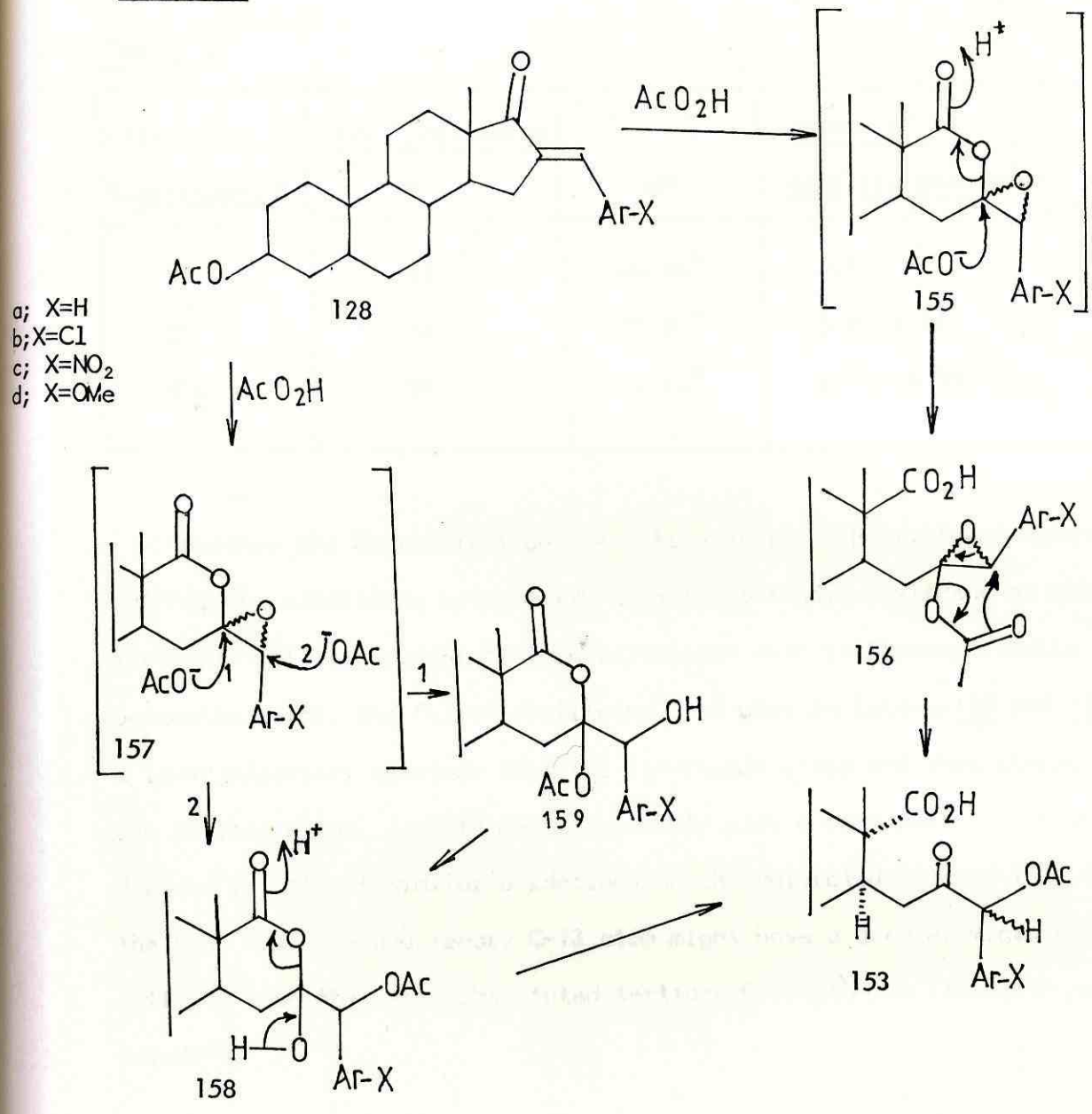
The α-acetoxyketo-acids 153d obtained from the arylidene ketone 128d were separated by preparative t.l.c. The identity of the isomeric acids 153d was established from the spectral studies of the methyl esters 154d. The lower t.l.c. acid was esterified with diazomethane[61] to the lower ester and the upper t.l.c. acid to the upper ester. Both isomeric esters 154d showed a broad band at νmax 1735 cm^{-1} which was assigned to the ester carbonyls and another band at 1720 cm^{-1} in the ir spectra which was assigned to the 16-ketone. The important signals in the ^1H nmr spectra of the methyl esters are given in Table IV.

Table IV

Methyl esters	^1H nmr δ ppm			
154d	benzylic-H	Me-ester	α-ketol acetate	3-acetate
Lower ester	5.83	3.56	2.15	1.90
Upper ester	5.87	3.38	2.15	2.20

The mass spectra did not show the molecular ion but important fragments corresponding to m/e 496 ($M-CH_3CO_2H$), m/e 179 ($MeO_6C_4H-CH=\overset{+}{O}Ac$), m/e 137 (100%, $MeO-C_6H_4-CH=\overset{+}{O}H$) and m/e 60 ($CH_3CO_2H^+$) were recorded. The α-acetoxy-keto-acids 153 may be formed through the epoxide intermediate 155 which may be attacked by acetate at the α- and β-carbons during work-up. Attack at the β-carbon would lead to the hydroxyacetate 158 which could ring-open as indicated to give 153. Attack at the α-carbon could lead through the epoxide 156 in which an acetyl transfer could occur[55] or it may give the hydroxyacetate 159 which could also undergo acetyl transfer 158 and thence to 153.

Scheme 16



Similar oxidations on arylidene ketones 128 (a, b or c) gave α-acetoxyketo-acids 153 which had similar spectral characteristics to 153d with the benzylic methine proton singlets between δ 5.90 and δ 6.10 in the ^{1}H nmr spectra of the chromatographically separated isomeric mixtures (Table V) vide infra

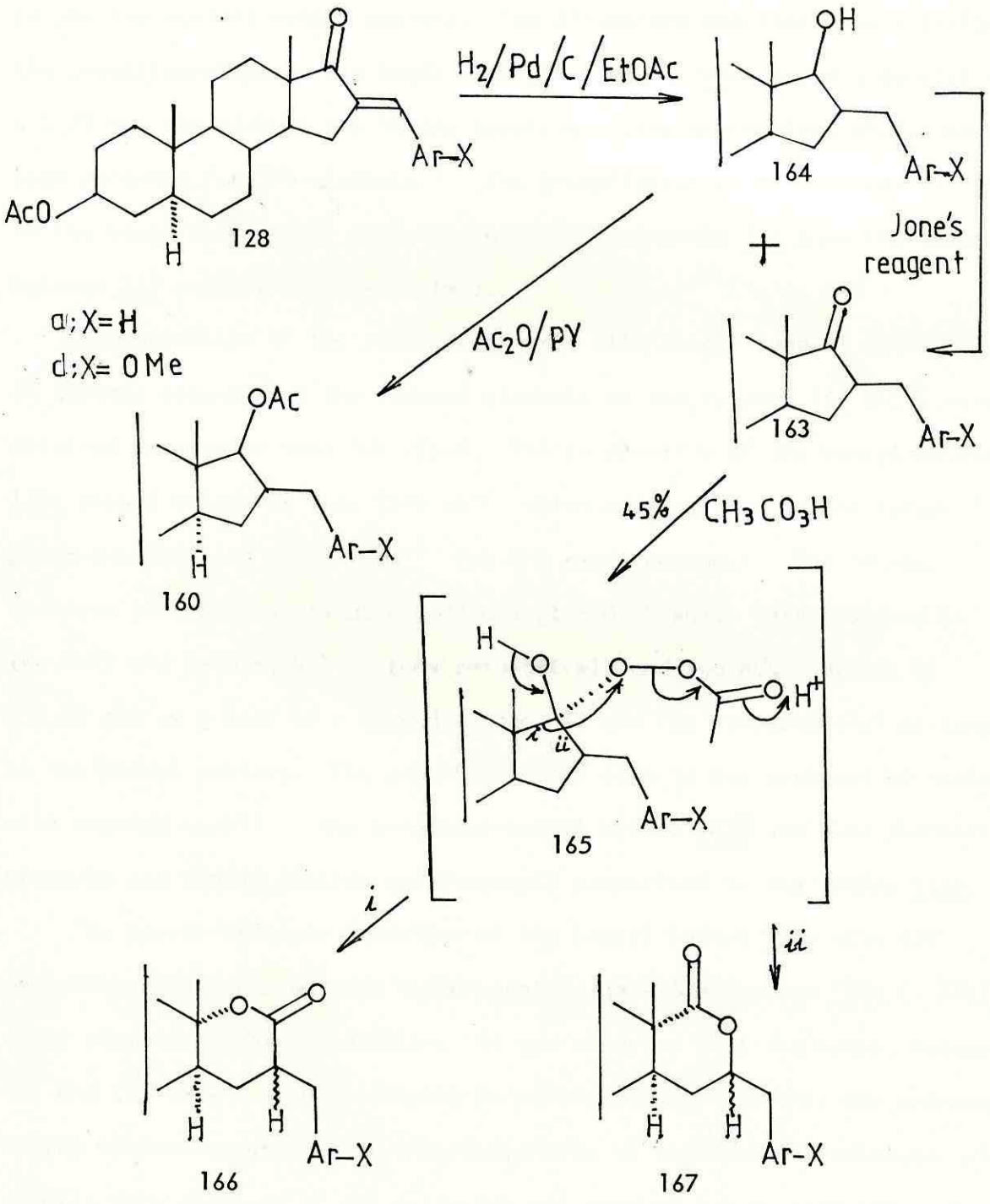
Table V

153 Substituent X	T.L.C. recovered %	MP	^{1}H nmr of Benzylic methine H
H	66	80-86°	5.9
Cl	58	79-83°	5.9; 5.94
NO_2	51	50-60°	6.01; 6.08

Neither the Baeyer-Villiger oxidation of the α,β-arylidene ketones 128 nor the alkylidene ketones 129 gave the intended arylidene or alkylidene lactones. It was evident that in oxidations with trifluoroperacetic and peracetic acids, the fully substituted C-13 atom in ketones 128 and 129 had a lower migratory aptitude than the 16-vinylic group and that steric factors due to the axial C-18 methyl possibly play a part too[83]. It was then decided to attempt similar oxidations on the saturated ketones 163 with the hope that the quartenary C-13 atom might have a greater migratory aptitude than the less substituted tertiary C-16 atom in line with normal trends[84].

The catalytic hydrogenation of α,β-unsaturated ketones 128 (a) and (d) over palladium/charcoal catalyst in ethyl acetate gave a mixture of saturated ketones 163 and 17-alcohols 164, Scheme 18. The alcohol 164a was separated and acetylated to give the 17-acetate 160.

Scheme 18



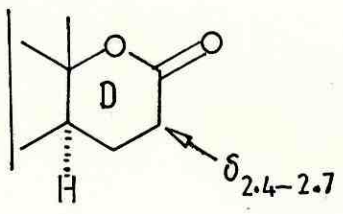
The diacetate 160 revealed two ester carbonyl bands at νmax 1732 cm^{-1} and at 1721 cm^{-1} in the ir spectrum (film). The ^1H nmr spectrum showed a doublet at δ 4.80 (J = 9Hz) which was assigned to the 17-H, a multiplet at δ 4.65 which was assigned to the 3α-H, and two singlets at δ 2.03 and δ 2.01, to the two acetate methyl protons. The 17-acetate was tentatively assigned the β-configuration on the basis that its alcohol 164a showed a doublet at δ 3.75 for the 16-H in the ^1H nmr spectrum. Similar chemical shifts have been recorded for 17β-alcohols[78]. The β-configuration at C-16 was assigned on the basis that Jones' oxidation of the 17-alcohols 164 gave the benzyl ketones 163 exclusively (see later).

The oxidation of the reduced mixtures with Jones' reagent (8N-H_2CrO_4) in acetone reconverted the reduced alcohols to the ketones 163 which were obtained in greater than 80% yield. The ir spectrum of the benzyl ketone 163a showed a band at νmax 1740 cm^{-1} which was assigned to the cyclopentanone C=0, and at 1729 cm^{-1} for the ester carbonyl. The ^1H nmr spectrum showed singlets at δ 0.82 and at δ 0.65 which were assigned to the C-19 and C-18 methyl protons respectively and two ABX-quartets at δ 3.20 and at δ 2.68 (J = 13 and 4, and, 13 and 9Hz respectively) assigned to the benzyl protons. The β-configuration at C-16 was assigned by analogy with related work[77]. The p-methoxy-benzyl ketone 163d was also successfully prepared and showed similar spectroscopic properties to the ketone 163a.

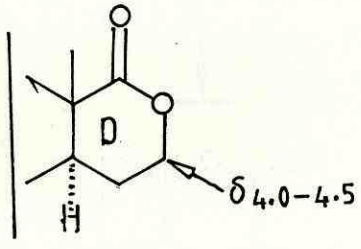
The Baeyer-Villiger oxidation of the benzyl ketone 163a with 45% peracetic acid buffered with sodium acetate gave the lactone 166a (> 71%) after chromatographic separation. It was observed that the benzyl ketones 128 (a) and (d) were sparingly soluble in peracetic acid but this was overcome by adding minimal quantities of tetrahydrofuran to complete the solution. Best results were obtained if the oxidation was carried out at room temperature.

Evidence of the formation of the lactone 166a was indicated by an ir band at νmax 1730 cm^{-1} which was assigned to the lactone and ester C=0.

The ^1H nmr spectrum showed a broad singlet at δ 7.25 which was assigned to the aromatic protons, a multiplet at δ 4.65 was assigned to the $C_3\alpha$-H, two other multiplets at δ 3.05 and at δ 2.75 were assigned to the benzylic and 16-H protons respectively and four singlets at δ 0.98, 0.95, 0.78 and δ 0.74 for the C-18 and C-19 methyl protons which indicated that the oxidation had proceeded with enolisation and subsequent epimerisation at the C-16 atom. The singlets at δ 0.98 and δ 0.95 were assigned to the C-18 methyl protons for the two epimers and are consistent with the formation of 166a and not 166b, Williams[87]. Also, Weidmann's[86] work on the D-ring lactones of estrone concluded that a multiplet at δ 2.40 to δ 2.70 would be expected for the C-16 methylene protons A or at δ 4.00 to δ 4.50 for 16-CH_2 for the other lactone B.



A



B

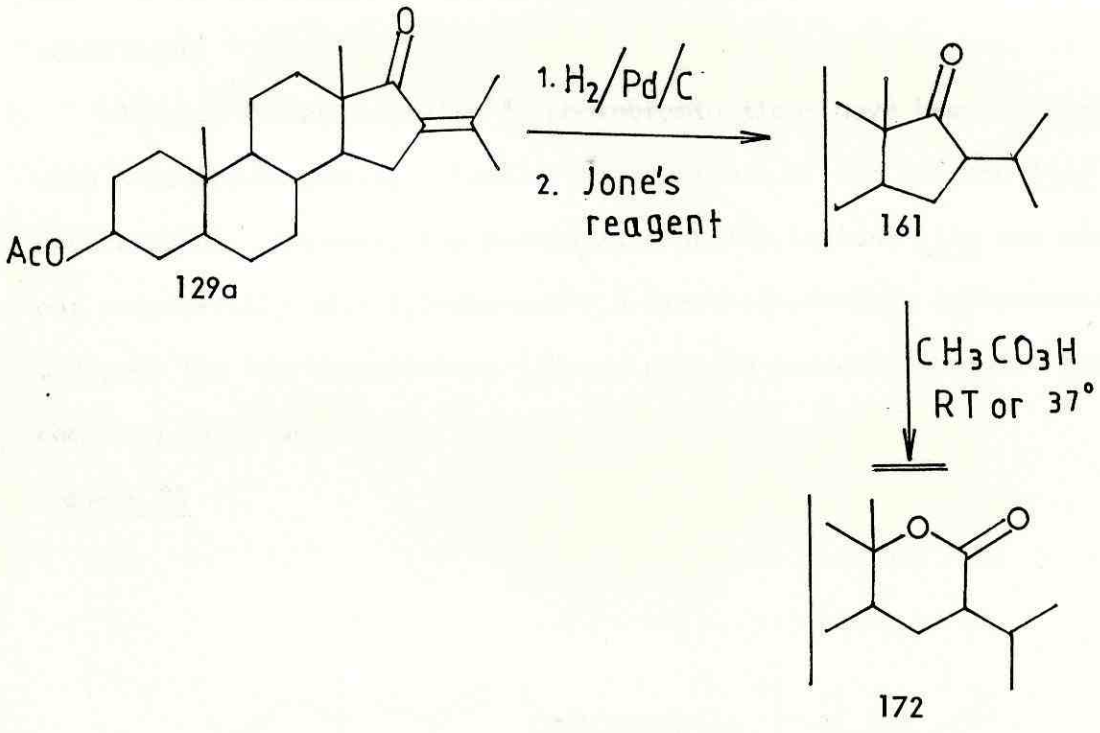
The multiplet at δ 2.75 which was assigned to the 16-H for the lactone 166a seems to confirm this structure.

The mass spectrum for the lactone 166a indicated a molecular ion at m/e,438 (27%) and important fragment ions at m/e, 148 (~ 6%, $C_6H_5C_2H_3\ CO_2^+$), and at m/e, 91 (56%, $C_6H_5CH_2^+$).

The oxidation of the ketone 163d was carried out with 40-45% peracetic acid at 37° for 16 days gave the lactone 166d (< 10%). The low yield was attributed mainly to side reactions such as the oxidation of the aromatic ring possibly owing to the activation of the ring by the methoxy group.

Treatment of the ketone 161 (Scheme 19) with peracetic acid at room or elevated temperatures (37°) did not give the product 172 possibly due to steric hindrance.

Scheme 19



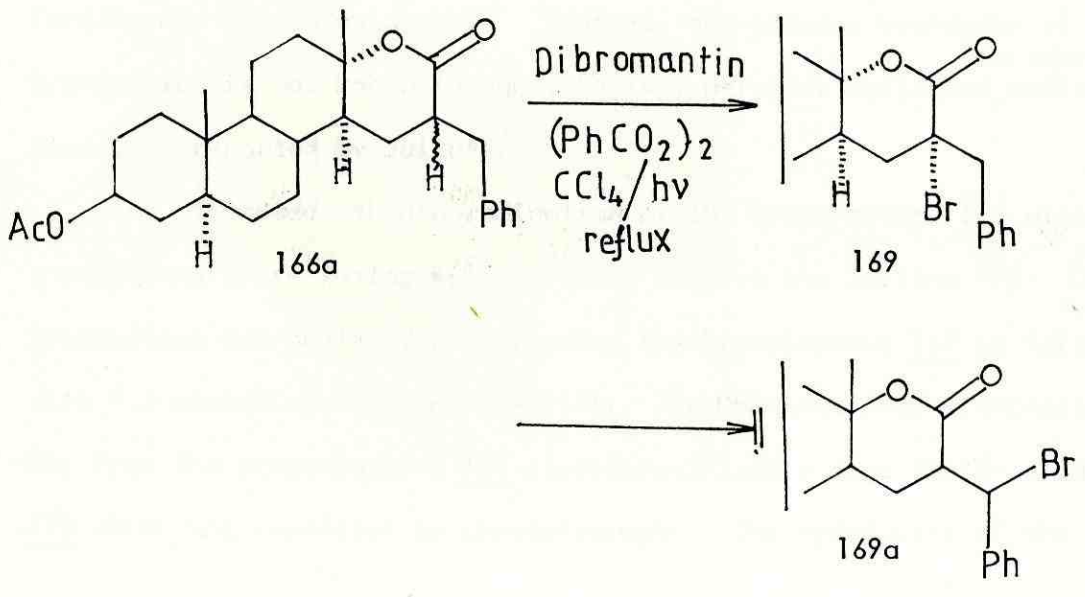
The ketone 161 was obtained by the hydrogenation of the isopropylidene ketone 129a. Its ir spectrum showed a band at 1740 cm^{-1} which was assigned to the cyclopentanone C=0 and another at 1732 cm^{-1}, to the ester C=0. The ^1H nmr spectrum showed two doublets at δ 1.04 and δ 0.87 (J = 7Hz) which were assigned to the diastereotopic methyl protons, and

two singlets at δ 0.88 and at δ 0.81 assigned to the C-19 and C-18 methyl protons respectively. It was not possible to determine absolutely the stereochemistry of the C-16 group though in line with observed trends, the β-configuration could be tentatively assigned to the 16-isopropyl group.

The formation of the lactones 166 (a) and (d) indicated that the quartenary C-13 atom has a greater migratory aptitude than the C-16 atom and is in line with expected trends. Steric factors also play a part for no oxidation of the ketone 161 was detected under similar conditions.

Allylic[58] and benzylic[59] photobrominations have been carried out with N-bromosuccinimide. Similar brominations of the lactone 166a were unsuccessful. However, the bromination of the lactone 166a was carried our successfully with 1,3-dibromo-5,5-dimethylhydantoin (dibromantin)[60] and gave the 16α-bromolactone 169 and not the expected benzylic bromo-compound 169a, Scheme 20.

Scheme 20



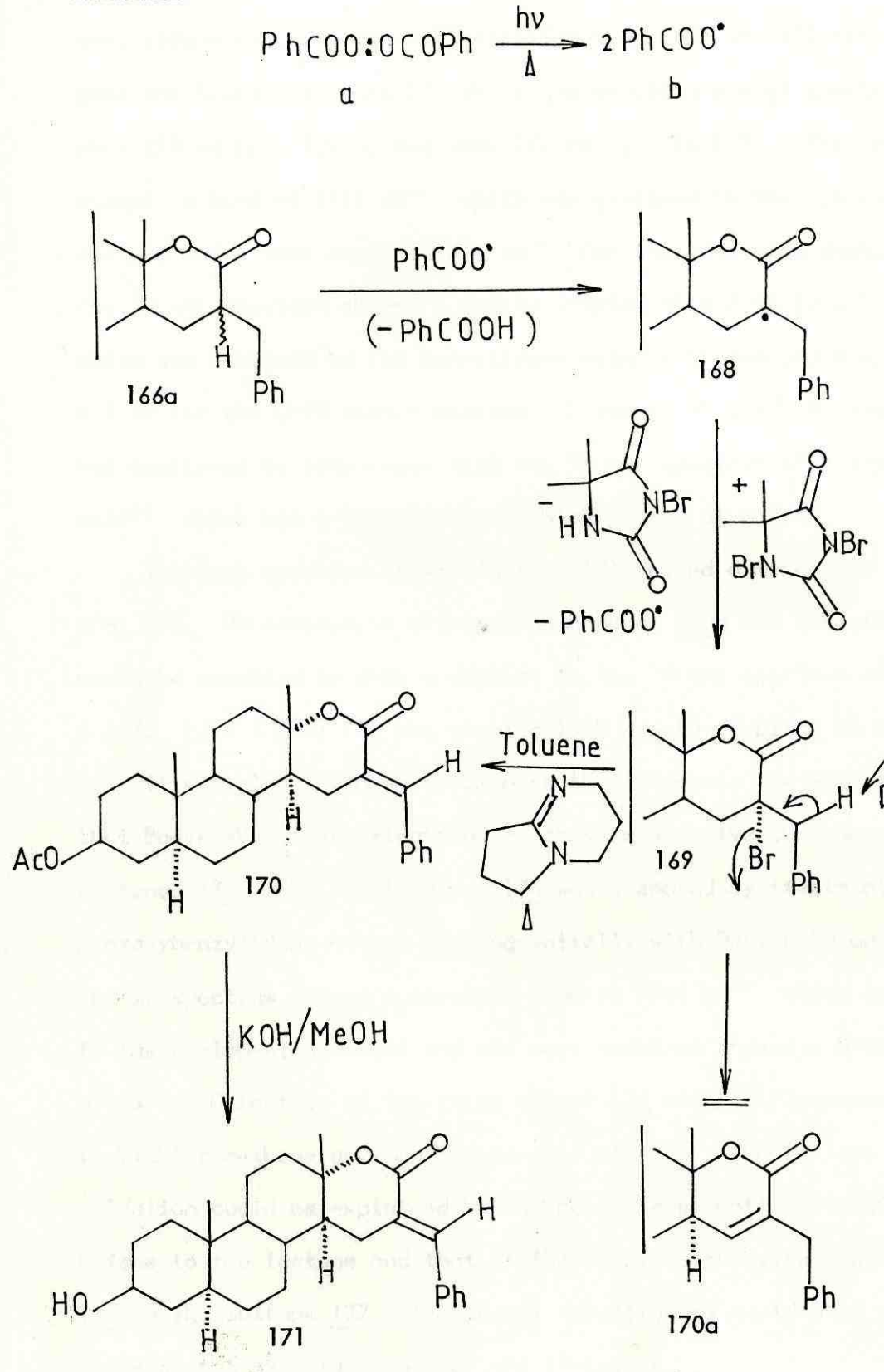
The structure of the lactone 169 was indicated by the ir spectrum which showed a band at νmax 1730 cm^{-1} which was assigned to the lactone and ester C=O and by a band at 710 cm^{-1} which was assigned to the C-Br bond. The ^1H nmr spectrum showed singlets at δ 0.71 and δ 0.62 which were assigned to the C-19 and C-18 methyl protons respectively and in addition, an AB quartet centred at δ 3.70 (J geminal 14Hz) which was assigned to the benzylic methylene protons. The mass spectrum showed a base peak at m/e, 437 (M-Br) and another important peak at m/e, 91 for ($C_6H_5CH_2^+$, 76%). The α-configuration of the bromine at C-16 is tentatively assigned since approach of bromine radicals or brominating agent (dibromantin) on the α-face would be more likely and both epimers of 166a could accordingly give the same bromo-compound assuming an α-lactone radical 168 is involved (see Scheme 21).

There was no indication of the formation of the benzylic bromo-lactone 169a which would be expected to show a low field doublet in the ^1H nmr spectrum for the benzylic methine proton with J ~ 7 to 9Hz due to coupling to the 16-H.

The formation of 16-bromolactone 169 could possibly indicate its thermodynamic stability over the benzylic bromolactone 169a. Steric factors may also play a part. However, the precise mechanism of the bromination is not known though dibenzoyl peroxide initiated α-ester radicals have been reported by Julia[65].

The attempted dehydrobromination of the bromolactone 169 with s-collidine in refluxing xylene failed to give the lactone 170. Dehydrobromination was achieved by refluxing the bromolactone 169 in toluene with 1,5-diazabicyclononene (DBN)[62,14]. The DBN-catalysed elimination of HBr from the bromo-lactone 169 stereospecifically gave the E- product 170 which was separated by chromatography. The hydrolysis of the 3-acetoxy-

Scheme 21


PhCOO:OCOPh
hν
Δ
2 PhCOO•
a
b
166a
Ph
PhCOO•
(-PhCOOH)
168
Ph
NBr
HN
-
+
BrN
NBr
- PhCOO•
Toluene
Δ
AcO
H
H
H
Ph
170
169
Br
H
DBN
Ph
KOH/MeOH
HO
H
H
H
Ph
171
H
Ph
170a

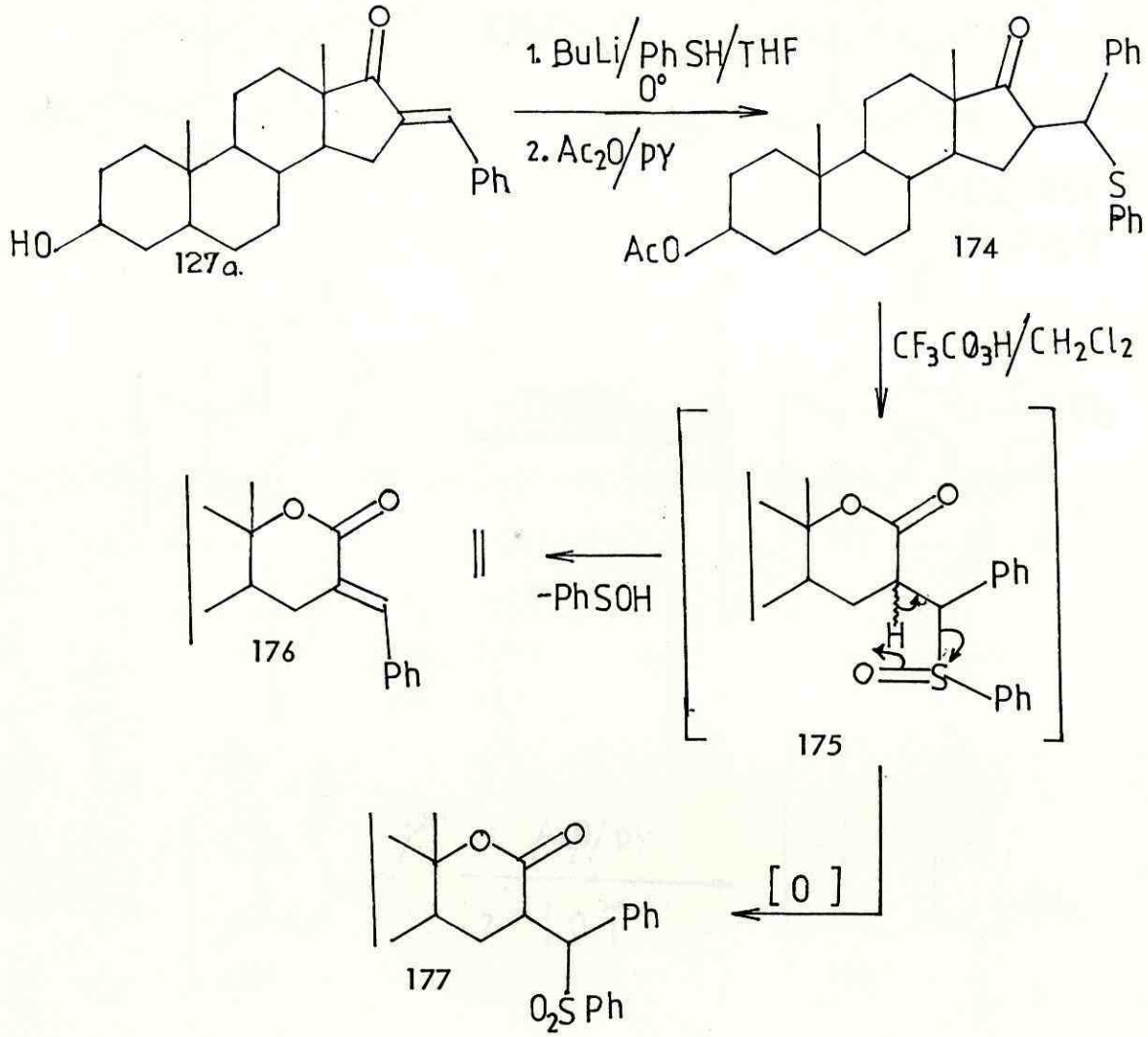
benzylidene lactone 170 with potassium hydroxide in refluxing methanol gave the hydroxy-lactone 171 which had an ultra-violet spectrum with λmax 218 nm (ε = 9,075) and λmax 281 nm (ε = 16,019). The ir spectrum showed a band at 1710 cm^{-1} which was assigned to the α,β-unsaturated lactone and a weak band at 1616 cm^{-1} for the exocyclic double bond. The ^1H nmr spectrum showed a narrow triplet at δ 7.88 (J ~ 1.5 Hz) which was assigned to the benzylidene methine proton and a singlet at δ 1.30 for the C-18 methyl protons. Evidence of the α,β-unsaturation was confirmed by comparison with the ^1H nmr spectrum of trans-cinnamic acid[82] which has a benzylidene methine proton at δ 7.83.

The mass spectrum of the lactone 171 showed a molecular ion at m/e, 394. No endocyclic elimination product 170a was detected which would be expected to show a doublet in the ^1H nmr spectrum at about δ 6.75 (J = 9.5Hz) for the vinylic 15-H due to coupling to the 14α-H[87].

It was also intended to oxidise thiol adducts 174 with the hope that Baeyer-Villiger oxidations on these would give the benzylidene lactones 176. The thiol adduct 174 was prepared by treatment of the hydroxybenzylidene ketone 127a sequentially with BuLi/PhSH and Ac_2O/py. The ir spectrum showed a carbonyl band at 1740 cm^{-1} which was assigned to the cyclopentanone C=O and the mass spectrum showed a M-PhS peak at m/e 379. Oxidation of the thiol adduct 174 with trifluoroperacetic acid in dichloromethane gave an inseparable mixture. The failure of this oxidation could be explained by the possible competing reactions of the ketone to the lactone and that of the benzylic phenylsulfinyl lactone 175 to the sulfone 177. The phenyl substituents could have sterically hindered the peracid attack of the 17-ketone.

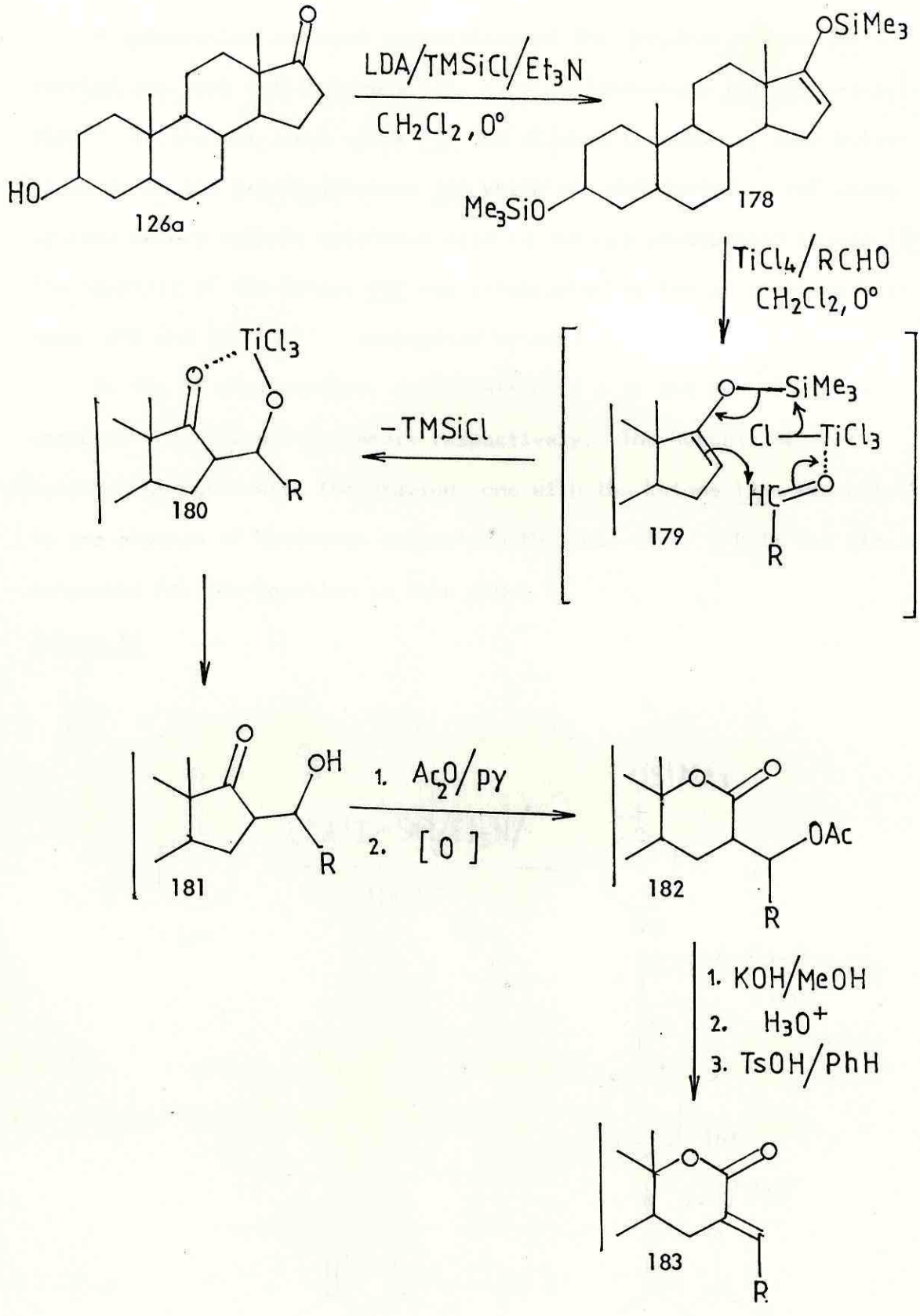
The reaction between the ketone 126a and trimethylchlorosilane gave the trimethylsilyl enol ether 178 which showed λmax 1620 (C=C) in the ir spectrum and δ 4.3 (m, vinyl H) and δ 0.14 (s, $OSiMe_3$) in the

Scheme 22



^{1}H nmr spectrum. An attempt to convert the crude silylenol ether 178 to the β-hydroxy-ketone 181 by reaction with titanium chloride and butyraldehyde[66,67] failed. It was hoped that acetylation of the ketone 181 and subsequent elimination might lead to the lactone 183. The failure of this synthetic route was attributed to the instability of the β-hydroxyketone 181 or the inability of the reagents to align properly in the intermediate 179 so that the reaction might take place. In addition, the silylenol ethers are unstable entities[66,67] and readily hydrolyse to starting ketones.

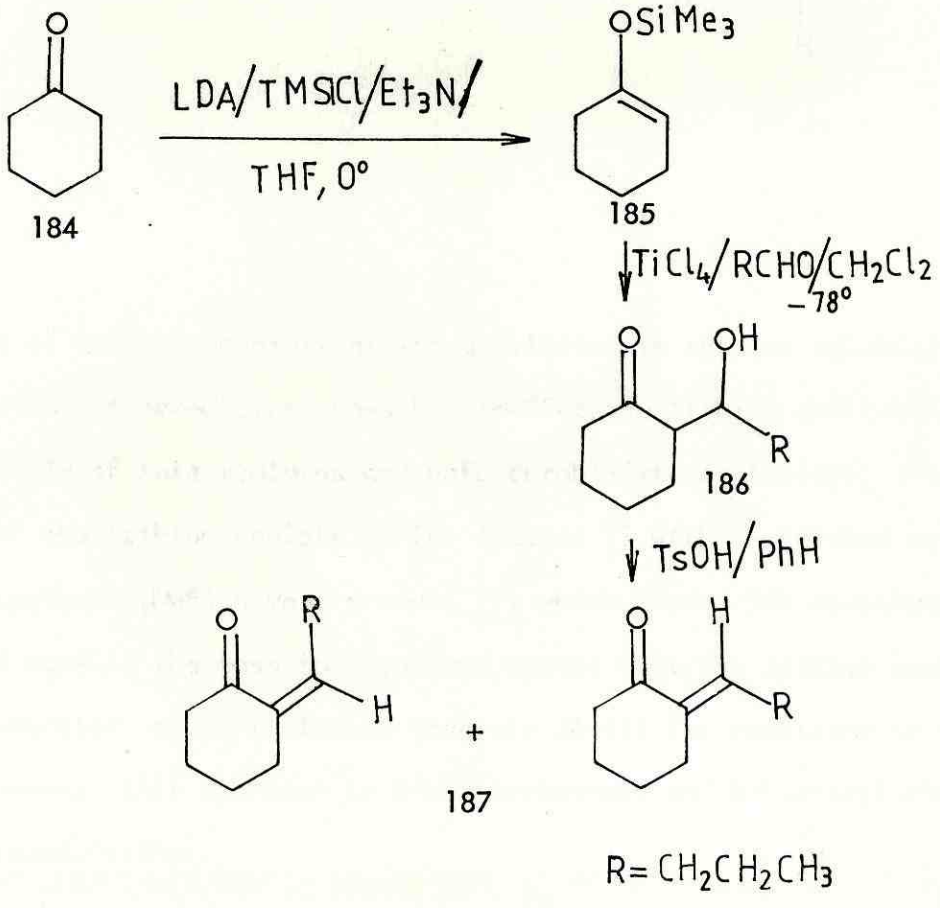
Scheme 23


HO
126a
LDA/TMSiCl/Et3N
CH2Cl2, 0°
OSiMe3
Me3SiO
178
TiCl4/RCHO
CH2Cl2, 0°
SiMe3
Cl
TiCl3
HC
O
R
179
-TMSiCl
TiCl3
O
O
R
180
OH
R
181
1. Ac2O/py
2. [O]
OAc
R
182
1. KOH/MeOH
2. H3O+
3. TsOH/PhH
183
R

A comparative relevant preparation of the β-hydroxyketone 186 was carried out with cyclohexanone 184. The cyclohexanone 184 was o-silylated[68] to the silylenol ether 185 and allowed to condense with butyraldehyde to the β-hydroxyketone 186 which was dehydrated in refluxing benzene with p-toluene sulphonic acid to the α,β-unsaturated ketone 187. The identity of the ketone 187 was established by the ir spectrum with νmax 1690 and 1615 cm^{-1} (conjugated ketone).

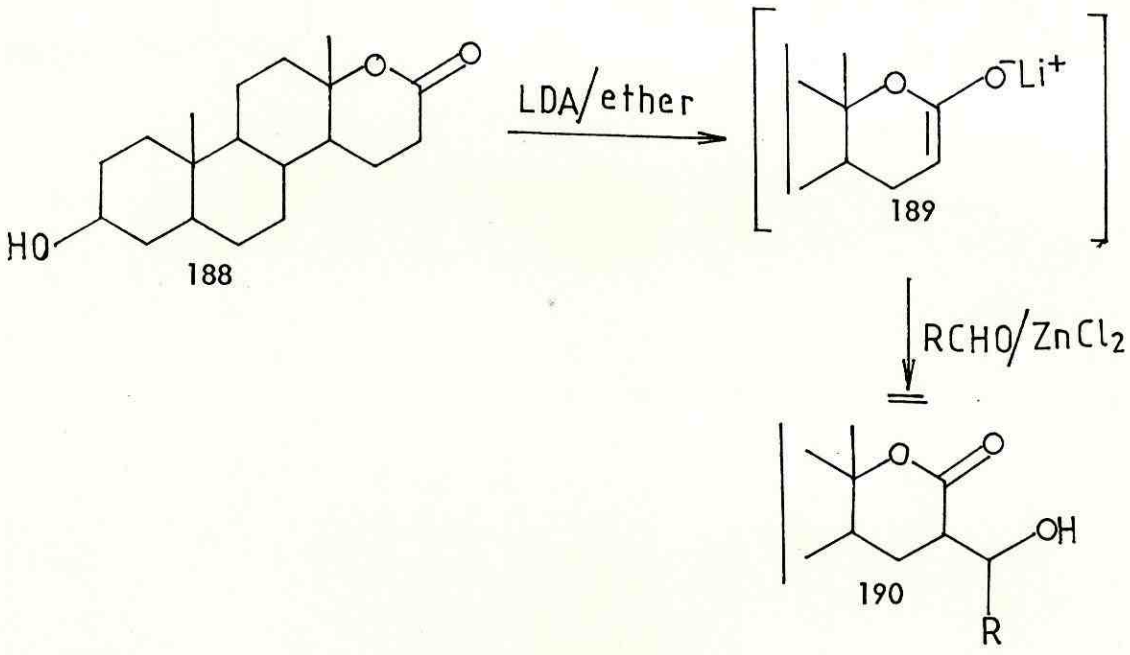
In the ^1H nmr spectrum, multiplets at δ 6.61 and at δ 5.4 were assigned to the E and Z-isomers respectively. The success of this reaction compared with the previous one with the ketone 126a was attributed to the absence of hindrance suggesting the enol-ether 178 is too sterically congested for the reaction to take place.

Scheme 24



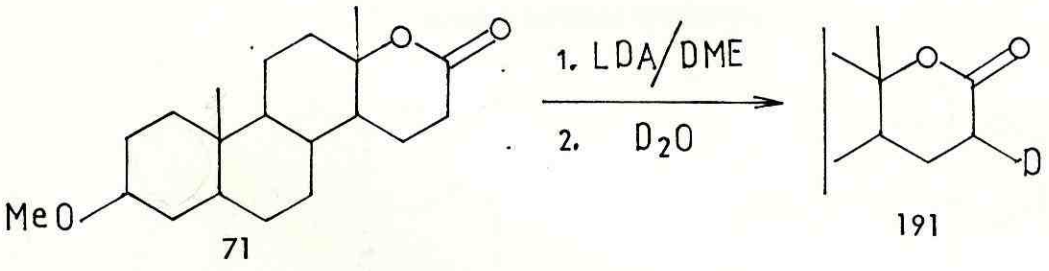
Treatment of the ketone 126a with LDA in ether and subsequent condensation of the enolate with butyraldehyde in the presence of catalytic zinc chloride[88] failed to give the β-hydroxyketone 181. A similar attempt on the hydroxylactone 188 to the β-hydroxylactone 190 also proved unsuccessful.

Scheme 25



The failure of these condensations was attributed to the low solubility of the reacting intermediates, possible ineffective lithium enolisation, the instability of intermediates and unfavourable steric factors. The treatment of the lithium enolate of the lactone 71 with deuterated water in dimethoxyethane (DME) gave a product 191 which showed 50% deuteration at the C-16 atom in the mass spectrum and proved that the lithium enolate could be generated at sufficiently moderate levels for reactions to take place. However, this approach to β-hydroxyketones and β-hydroxylactones was not pursued further.

Scheme 26

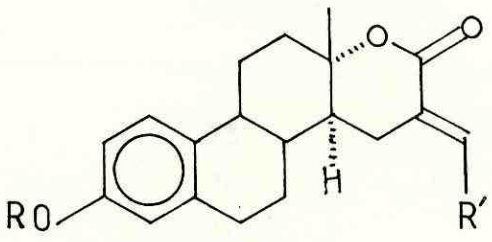


71 191

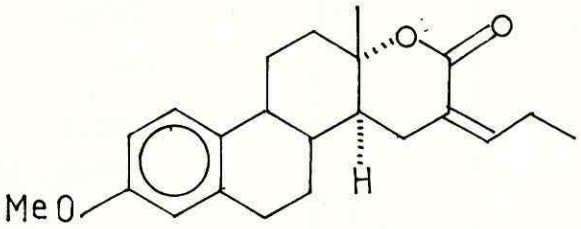
RESULTS AND DISCUSSION

The following lactones were synthesised, and biological tests are currently in progress in our laboratories, by Dr. J. R. Traynor and P. M. Lockey.

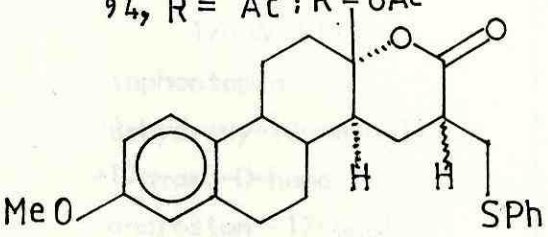
Steroid lactones synthesized



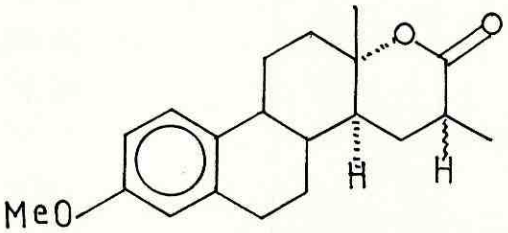
75, R = Me; R′ = H
99, R = Ac; R′ = H
78, R = H; R′ = H
94, R = Ac; R′ = OAc



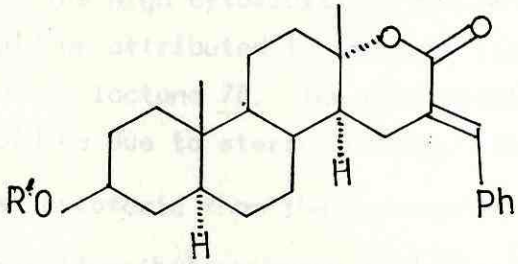
100



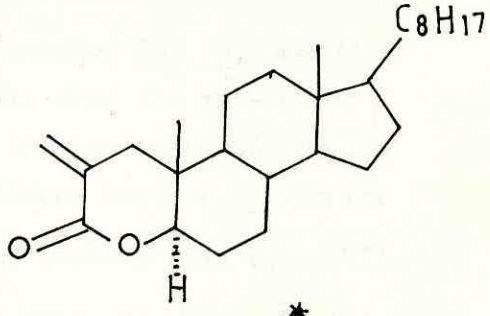
76



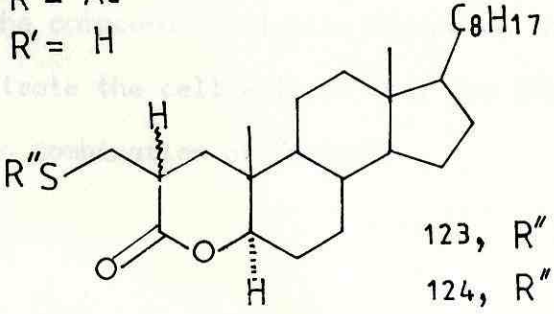
77



170, R′ = Ac
171, R′ = H



122*



123, R″ = Et
124, R″ = Ph

*The lactone 122 was previously synthesised by Dehal[16].

Preliminary LD_{50} results on HeLa S_3 cells indicate considerable cytoxicity for some compounds (LD_{50} < 10 μg/ml) and relative inactivity for others (LD_{50} > 10 μg/ml).

Table VI LD_{50} on HeLa S_3 cells

Compound	LD_{50} μg/ml
75	0.24
76	0.24
77	-
78	0.50
99	0.14
100	>10.00
122[16]	0.82
170 & 171	>10.00
elephantopin[16]	0.30
3β-hydroxy-16-methylene--17a-oxa-D-homo-5α--androstan -17-one[16]	1.00
94	>10.00

The high cytoxicity of the methylene lactones 75, 76, and 99 could be attributed to improved lipophilicity over the more polar hydroxy-lactone 78. The non-reactivity of the lactones 100 and 170 could be due to steric factors. The benzylidene lactone 170 is far less cytotoxic than the hydroxy-16-methylene lactone[16] (see Table VI) whose 16-methylene group is less sterically hindered. The relative cytotoxicity of the compounds will also depend on the ability of the compounds to penetrate the cell wall so that the observed cytotoxicity is the result of a combination of factors.

III

EXPERIMENTAL

EXPERIMENTAL SECTION:

Solvents were distilled using standard methods. Solutions were dried over anhydrous magnesium sulphate and evaporated under vacuo. Preparative TLC plates were prepared from Kieselgel 60PF 254 (Merck). IR spectra were determined with Perkin-Elmer 177 Spectrometer, UV spectra with a Pye-Unicam SP 8-100 Spectrometer, ^{1}H-NMR spectra in $CDCl_3$ with TMS standard at 60 MHz with a Varian EM 360A spectrometer or at 90 MHz with a Perkin-Elmer R_{32} Spectrometer.

Optical rotations were measured at ambient temperature with an AA-10 automatic digital polarimeter. Melting points were measured on a Reichert hot stage apparatus.

^{13}C-NMR spectra were recorded at 20.1 MHz with a Bruker WP-80 spectrospin operating in the Fourier-transform mode. Off resonance and proton noise decoupled spectra were recorded and chemical shifts are relative to internal TMS. The spectra were recorded at ambient temperature for 20 - 30 mg solutions in CD_2Cl_2 unless stated otherwise.

1. 3-Acetoxy-estra-1,3,5-(10)-trien-17-one(69a)[69]

A mixture of estrone (10g) and acetic anhydride (10 ml) in dry pyridine (100 ml) was stirred overnight, poured onto ice (100g), filtered to give estrone acetate (69a, 10.3g, 89%. Crystallisation from ethanol gave 69a, mp 123-125°, (Lit. 123-124°); υmax (film) 1768 (ester C=O) (cyclopentanone C=O), 1610, 1500 (aryl C=C), 1030 and 1010 cm^{-1}; δ 7.3 (dd, J = 7 and 3Hz, 1H, Ar.-H), 6.86 (dd, J = 7 and 3Hz, 1H, Ar.-H), 6.81 (bs, 1H, Ar.-H), 2.9 (m, 2H, benzylic-H), 2.29 (s, 3H, ester-H), 0.91 (s, 3H, 18-H).

2. 3-Acetoxy-17-oxo-17a-oxa-D-homo-estra-1,3,5-(10)-triene (70)[44].

A mixture of estrone acetate (69a, 1.2g) glacial acetic acid (20 ml) and hydrogen peroxide (86%, 10 ml) was left to stand in a water bath (37°) until there were no traces of starting material (T.L.C.), - 5 days. Water was added to precipitate the lactone which was filtered and washed with cold water to give the lactone 70, (0.72g, 57%), mp 156-160° (methanol) (Lit. 149-151°); υmax (film) 1750 (ester C=O), 1715 (lactone C=O), 1610 and 1490 (aryl C=C), 1020 cm^{-1}; δ 7.28 (dd, J = 7 and 3Hz, 1H, Ar.-H), 6.85 (dd, J = 7 and 3Hz, 1H, Ar.-H), 6.8 (bs, 1H, Ar.-H), 2.3 (s, 3H, acetate - H), 1.36 (s, 3H, 18-H).

3. 3-Hydroxy-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)-triene (70a)[44].

Estrone acetate (0.7g) was hydrolysed in methanol (50 ml) under reflux in the presence of potassium hydroxide (0.5g) for 2 hr. The mixture was cooled, acidified with conc. HCl, boiled briefly (15 min.), cooled and filtered to give the hydroxylactone 70a (0.58g, 95%), mp > 265° (Lit. 335-340°); υmax (film) 3205 (phenolic-OH), 1676 (lactone C=O), 1615, 1580 and 1500 (aryl C=C), 1030 cm^{-1}; δ(DMSO and DMF) 9.0 (bs, 1H, -OH), 7.08 (d, J = 9Hz, 1H, Ar.-H), 6.56 (dd, J = 9 and 2Hz, 1H, Ar.-H), 6.51 (bs, 1H, Ar.-H), 1.3 (s, 3H, 18-H); MS (LR) 286 (M, $C_{18}H_{22}O_3$).

4. 3-Methoxy-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)-triene (71)[44,70].

Sodium hydride (0.25g) was cleaned with sodium dried petrol (3x) and covered with dimethylformamide (5 ml) under nitrogen. A solution of the hydroxyestrolactone (70a, 0.55g, 1.92 mmoles) in dimethylformamide (15 ml) and dimethylsulphoxide (15 ml) was added gradually to the suspension of sodium hydride. The mixture was stirred for ½ hr. and freshly distilled dimethylsulphate (1 ml) was added (½ hr.) and stirring was continued for another 2 hr. Concentrated HCl was carefully added to the cooled mixture and then water to precipitate the product. After standing for ½ hr. in ice, filtration gave methoxyestrolactone 71 (0.52g, 89%), mp 167-172° (Lit. 167-172°) (chloroform/methanol), υmax (film) 1725 (lactone C=0), 1610 and 1505 (aryl C=C), 1040 cm^{-1}; δ 7.2 (dd, J = 7 and 3Hz, 1H, Ar.-H), 6.7 (dd, J = 7 and 3Hz, 1H, Ar.-H), 6.62 (bs 1H, Ar.-H), 3.8 (s, 1H, methoxy-H), 1.38 (s, 3H, 18-H); MS 300.1724 (M, $C_{19}H_{24}O_3$), calc. M, 300.1726

5. 3-Methoxy-16-(hydroxymethylene)-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)--triene (72)

Potassium hydride (0.2g) was washed with sodium dried petrol (3x) and covered with 1,4-dioxan (20 ml) under nitrogen. Methoxyestrolactone 71 (0.39, 0.91 mmoles) was added and stirring continued for ½ hr. Ethyl formate (1.0 ml) was added over ½ hr., the mixture was stirred for a further 2 hr. and left to stand overnight at room temperature. A constant stream of dry nitrogen was maintained throughout the experiment.

The mixture was quenched with dilute HCl and water and the cooled precipitated solid was filtered and washed with cold water to give the lactone 72 (0.32g, 97%), mp 242-245°; υmax (film) 3500-2500 (H-bonded OH), 2700 (chelated -OH), 1680, 1621, 1035, 1025 cm^{-1}; MS 328.1674 (M, $C_{20}H_{24}O_4$), calc. M, 328.1675

6. 3-Methoxy-16-methylene-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)-triene (75)

A mixture of hydroxymethylene lactone 72, (0.2g, 0.61 mmoles), diethylam (1.0 ml) and benzene was heated overnight (65°). The solvent was evaporated and the crude 3-methoxy-16-(N,N-diethylamino)methylene-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)-triene ——— 73; δ 7.68 (bs, 1H, aminomethylene-H), 3.38 (q, 4H, J = 7Hz, $-N\underline{CH_2}CH_3$), 1.3 (s, 3H, 18-H) and 1.21 (t, J = 7Hz, 6H, $-NCH_2\underline{CH_3}$). The crude product was taken up in glacial acetic acid (40 ml) and reduced with hydrogen in the presence of Adams' catalyst - Platinum oxide (0.05g) at room temperature for 14 hrs. The filtered and partially evaporated hydrogenated lactone 74 was refluxed in glacial acetic acid (40 ml in the presence of sodium acetate (0.1g) for 2 hrs. and extracted into ether.

The ether fraction was washed with water, bicarbonate, water, dried and evaporated to give 0.22g of crude product. Chromatographic separation (toluene-ethyl acetate 8:2) gave two fractions including unsubstituted lactone 71 (27%). The major fraction was made up of 3-methoxy-16-methylene-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)-triene ——75 (32% overall yield), mp 167-169° (ethyl acetate); $[\alpha]_D$ + 6° (c 0.01); λmax (EtOH0 λ^1max = 218 nm (ε^1 = 4,530), λ^2 max = 277 nm (ε^2 = 5,779); υmax (film) 1712 (α,β-unsaturated-δ-lactone), 1622 (conj. C=C), 1610, 1580 and 1500 (aryl, C=C), 1040 cm ; δ (CD_2Cl_2) 7.18 (d, J = 9Hz, 1H, Ar.-H), 6.68 (dd, J = 9 and 3Hz, 1H, Ar.-H), 6.61 (bs, 1H, Ar.-H), 6.45 (d, J ~ 1Hz, 1H, 16-methylene 5.6 (d, J ~ 1Hz, 1H, 16-methylene-H), 3.78 (s, 3H, methoxy-H), 1.33 (s, 3H, 18-H); MS 312.1725(M, $C_{20}H_{24}O_3$), calc. M, 312.1725

Anal. $C_{20}H_{24}O_3$; calc. % :

C, 76.89; H, 7.74

Found : 76.50; 7.90

Reduction of the 16-methylene lactone 75 (20 mg) with H_2 over 5% Pd/C (20 mg) in ethyl acetate gave the reduced 3-methoxy-16-methyl-17-oxo-

17a-oxa-D-homo-estra-1,3,5(10)-triene ——— 77, mp 147-150° (ethyl acetate); υmax (film) 1730 (lactone C=0), 1610, 1585, 1505, 1030, and 1020 cm^{-1}; MS 314.1882 (M, $C_{20}H_{26}O_3$), calc. M, 314.1881 / The ^1H, N.M.R. did not show olefinic protons.

7. 3-Methoxy-16-(phenylthiomethyl)-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)--triene (76).

To ethylene glycol dimethylether (glyme/DME) (5 ml) was added thiophenol (0.03 ml, 0.24 mmoles) and n-butyl-lithium (0.1 ml, 0.24 mmoles) at room temperature under nitrogen. After 15 min., the mixture was cooled to 0°C and the 16-methylene lactone 75 (37 mg, 0.12 mmoles) in DME (10 ml) was added over 10 min. Stirring continued for 1 hr and the reaction was quenched with water. Extraction into ether (2x) and washing with water, saturated sodium chloride, water, drying and evaporating gave a crude oil, 90 mg. Preparatory t.l.c. gave the lactone 76 (0.04g, 80%) oil; υmax 1725 (lactone C=0), 1610, 1582 and 1500 (aryl C=C), 1040 and 1030 cm^{-1}; δ 7.3 (m, 6H, Ar.-H), 6.7 (dd, J ~ 10 and 3Hz, 1H, Ar.-H), 6.65 (bs, 1H, Ar.-H), 3.9 (s, 3H, methoxy-H), 1.38 and 1.33 (2s, 18-H); MS 422.1929 (M, $C_{26}H_{30}SO_3$), calc. M, 422.1916

8. 3-Hydroxy-16-(hydroxymethylene)-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)--triene (93).

A mixture of hydroxyestrolactone 70a (0.3g, 1.05 mmoles), potassium hydride (0.5g), and ethyl formate) (1.0 ml) in dimethylformamide (30 ml) was stirred overnight under nitrogen (18 hr.). The mixture was quenched with dilute HCl and water, with cooling, and the precipitated product was filtered of washed with water and dried to give 3-hydroxy-16-(hydroxymethylene)-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)-triene ——— 93, (0.25g, 76%), mp

262-265°; υmax (film) 3600-2500 (H-bonded OH), 2700 (w, chelated -OH), 1685 and 1610 (formyl lactone), 1585 and 1500 (aryl C=C), 1030 cm^{-1}; δ ($CDCl_3$/DMSO) 8.6 (bs, D_2O exchanged phenolic -OH), 7.82 and 7.2 (2s, hydroxymethylene-H), 7.15 (d, J ~ 8Hz, 1H, Ar.-H), 6.6 (d, J ~ 8Hz, 1H, Ar.-H), 6.55 (bs, 1H, Ar.-H), 2.85 (m, benzylic-H,) 1.3 and 1.28 (2s, 18-H); MS 314.1519 (M, $C_{19}H_{22}O_4$), calc. M, 314.1518

The 3-hydroxymethylene estrolactone 93 was formed as two isomers, E and Z in 6:4 ratio respectively based on the ^1H, N.M.R. of the crude product.

9. 3-Acetoxy-16-(acetoxymethylene)-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)--triene (94).

3-Hydroxy-16-hydroxymethylene estrolactone 93 (0.22g) was acetylated with acetic anhydride (5 ml) in pyridine (20 ml) overnight with stirring. The mixture was poured onto ice (40g) and the precipitated crude product was filtered off to give the diacetate 94 (0.2g, 72%), mp, 215-218°; υmax (film) 1768 (ester C=O), 1706 and 1640 (α-β-unsaturated lactone C=O), 1500 (aryl C=C), 1165 and 1025 cm^{-1}; δ 8.42 (m, enol acetate-H), 7.3, and 6.86 (2d, J ~ 9Hz, Ar.-H), 6.82 (bs, Ar.-H), 2.9 (m, benzylic-H), 2.29 (s, 6H, diacetate-H) and 1.32 (s, 3H, 18-H).

10. 3-Acetoxy-16-methylene-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)-triene (99).

3-Acetoxy-16-acetoxymethylene estrolactone 94 (0.05g, 0.12 mmoles) and diethylamine (2 ml) in benzene (30 ml) was refluxed until there was no further evidence of starting material (t.l.c.), 30 hr. The solvent was evaporated off and N.M.R. on the crude lactone 98 revealed E and Z enamines, δ(60 MHz) 7.6 and 6.55 ppm (enamine-H), 3.28 (m, N-$\underline{CH_2}CH_3$), 2.22 (s, ester-H).

The crude enamine was reduced with H_2/Adams' catalyst (PtO_2, 0.03g) in glacial acetic acid (30 ml) until there was no further uptake of

hydrogen (2 hr.). Filtration and partial evaporation gave the reduced enamine which was refluxed in glacial acetic acid (30 ml) in the presence of sodium acetate (0.01g) for 1 hr. Extraction into ether (200 ml), washing with water, bicarbonate, saturated sodium chloride, water, drying and evaporating gave the crude product, 55 mg. Chromatographic separation (5:5, toluene:ethyl acetate) gave two fractions. The upper t.l.c. fraction gave 3-acetoxy-16-methylene-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)-triene ——— 99 (29% based on the diacetate): mp 167-170° (methanol), $[\alpha]_D$ = 0 (c, 0.02); λmax 217 nm (EtOH), ε = 6,928; υmax (film) 1755 (ester C=O), 1718 and 1625 (λ (α,β-unsaturated lactone) cm^{-1}; δ 60 MHz, 7.18 (d, J ~ 8Hz, 1H, Ar.-H), 6.75 (dd, J = 8 and 2Hz, 1H, Ar.-H), 6.7 (bs, 1H, Ar.-H), 6.41 (nm, cis-1H), 16-methylene-H), 5.52 (nm, trans-1H, 16-methylene-H), 2.78 (m, 3H, benzylic-H), 2.23 (s, 3H, ester-H), 1.32 (s, 3H, 18-H); MS 340.1674 (M, $C_{21}H_{24}O_4$), calc. M, 340.1675; 298.1586 (M $-C_2H_2O$, $C_{19}H_{22}O_3$) calc. 298.1569 (BP).

The lower t.l.c. fraction was 3-hydroxymethylene estrolactone 78 (13% based on the diacetate), mp 226-230° (methanol). Spectral data is given in E.11.

11. 3-Hydroxy-16-methylene-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)-triene (78).

3-Acetoxymethylene estrolactone 99 (0.025g) was refluxed in methanol (20 ml) in the presence of potassium hydroxide (0.05g) for 2 hr. Extraction with chloroform gave 3-hydroxy-16-methylene-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)-triene 78 (0.019g), m.p. 226-230° (methanol); υmax (film) 3600-3100 (H-bonded -OH), 1681 and 1622 (λ (α-β-unsaturated lactone), 1582 and 1500 (aryl C=C), 1102, 1030 and 730 cm ; δ 60MHz (DMSO) 8.64 (s, 1H, Ar.-OH),

7.1 (d, J ~ 8Hz, 1H, C_1-H), 6.62 (dd, J ~ 8 and 2Hz, 1H, C_2-H), 6.53 (bs, 1H, C_4-H), 6.48 (nm, 1H, 16-methylene-H), 5.65 (nm, 1H, 16-methylene-H), 2.9 (m, 3H, benzylic-H), 1.34 (s, 3H, 18-H); MS 298.1567 (M, $C_{19}H_{22}O_3$) calc. M, 298.1569 (BP).

12. 3-Methoxy-16-propylidene-17-oxo-17a-oxa-D-homo-estra-1,3,5(10)-triene (100).

Triphenylphosphonium ethyl bromide ($\Phi_3P^{\oplus}CH_2CH_3Br^{\ominus}$) (0.432g, 1.94 mmoles) was added to benzene (25 ml) followed by n-butyl-lithium (0.6 ml, 2.3 mmoles) and stirred under nitrogen (½hr.). The formyl lactone 72 (0.318 g, 0.97 mmoles) was added to the ylid and the mixture was refluxed after ½ hr. for 16 hr. The mixture was filtered and the filtrate extracted into ether (300 ml) and washed with saturated sodium chloride, water, dried and evaporated to give a gum (0.57g). Chromatographic separation gave five fractions and only one resembled the expected product 100 (18%) mp 176-179° (methanol); $[\alpha]_D$ + 30° (c, 0.01); λmax 218 nm (EtOH); νmax (film) 1725 (α-β-unsaturated lactone), 1610, 1580 and 1500 (aryl C=C), 1040 cm^{-1}; δ 7.22 (dd, J ~ 9 and 3Hz, 1H, C_1-H), 6.72 (dd, J ~ 9 and 3Hz, 1H, C_2-H), 6.65 (bs, 1H, C_3-H), 5.7 (m, E-1H, 16-propylidene-H), 3.8 (s, 3H, methoxy-H), 2.9 (m, 2H, benzylic-H), 1.33 (s, 3H, 18-H); MS 340.2039 (M, $C_{22}H_{28}O_3$), calc. M, 340.2039

13. Cholest-4-en-3-one (113)[71]

A mixture of cholesterol (21g), cyclohexanone (200 ml) and aluminium isopropoxide (5.7g) in toluene (850 ml), was steam-distilled in a 2L three-necked flask until about 400 ml of toluene had distilled over. The orange-coloured reaction mixture was cooled to room temperature and mixed with a saturated solution of potassium-sodium tartarate (120 ml). Steam distillation was continued until a further 500 ml of distillate was collected. Extraction into chloroform gave cholestenone 113 (71%) mp 76-80° (methanol). (Lit. 76-79°); νmax (film) 1680 (conj. C=0) 1615 (conj. C=C) cm^{-1}; δ 60MHz 5.67 (s, 1H, C_4-H), 2.3 (m, C_6-H), 1.2 (bs, C_2-H), 1.9, 0.8 and 0.7 (3s, methyls).

14. 3-Oxo-4-oxa-5α-cholestane (119)[72]

Potassium persulphate (15.0g) and concentrated sulphuric acid (17.0g) were thoroughly ground together and diluted with glacial acetic acid (300 ml). The resultant solution was added to Δ^4-cholestenone (5.0g) and the mixture was vigorously stirred at room temperature for 10 days, protected from light.

The mixture was treated with aqueous potassium hydroxide (50%, 100 ml) and the precipitated salts filtered off. The filtrate was evaporated to dryness and dissolved in ether. The ether layer was washed alternately with water, bicarbonate solution (5%) and water, dried and evaporated to an oil (3.4g). Crystallisation from ethanol gave 3-oxo-4-oxa-5α-cholestane 119 (26%), mp 115-117° (Lit. 116-117°); νmax (film) 1745 (lactone C=0), 1085, 1055 cm^{-1}; δ 60MHz 3.9 (dd, J ~ 10 and 4Hz, 1H, C5α-H), 2.55 (m, 2H, C_2-H), 0.91, 0.82, and 0.68 (3s, methyls).

15. 2-Hydroxymethylene-3-oxo-4-oxa-5α-cholestane (120)[13]

3-Oxo-4-oxa-5α-cholestane 119 (0.6g, 1.5 mmoles) was added to KH

(0.6g, washed with petrol -3x) in 1,4-dioxan (30 ml) under nitrogen. Ethyl formate (1.3 ml) was added over ¼ hr. The mixture was gently stirred (2 hr.) and left to stand overnight. The reaction was quenched with dilute HCl and water, cooled in ice and the precipitated solid was filtered off and washed with cold water to give the hydroxymethylene lactone 120 (96%) mp 237-239° (Lit. 238-240°); νmax (film) 3600-2500 (H-bonded -OH), 1702 and 1610 (formyl lactone), 1040 and 1025 cm^{-1}.

16. 2-Methylene-3-oxo-4-oxa-5α-cholestane (122)[13]:

2-Hydroxymethylene-3-oxo-4-oxa-5α-cholestane 120 (0.25g, 0.6 mmoles) and diethylamine (1.2 ml) in benzene (40 ml) was refluxed under Dean and Stark for 3 days. The solvent was evaporated off and the resultant 2--[(N,N-diethylamino)-methylene]-3-oxo-4-oxa-5α-cholestane 121 was reduced immediately in glacial acetic acid (60 ml) with hydrogen over platinum oxide catalyst (0.05g) overnight. The evaporated reduced lactone was taken up in glacial acetic acid (50 ml) and refluxed (4 hr.) in the presence of potassium hydroxide (0.01g). Extraction into ether (200 ml), washing with water, bicarbonate, water, drying and evaporating gave 0.26g of crude product.

Chromatographic separation (8:2, toluene:ethyl acetate) gave 2--methylene-3-oxo-4-oxa-5α-cholestane 122 (63%) mp 110-112° (Lit. 105-106°); νmax (film) 1725 (α,β-unsaturated lactone), 1625 (conj. C=C), 1043 and 1030 cm^{-1}; δ 60MHz 6.45 (nm, 1H, methylene-H), 5.52 (nm, 1H, methylene-H), 4.00 (dd, J ~ 11 and 5 Hz, 1H, C5α-H), 0.9, 0.82 and 0.65 (3s, methyls); MS 400.3347 (M, $C_{27}H_{44}O_2$), calc. M, 400.3341

Reduction of the impure enamine 121 with hydrogen using 5% Pd/C in glacial acetic acid, ethanol and benzene (4:1:3) over 7 days gave methylene lactone 122 (40%) after chromatographic separation.

17. 2-Phenylthiomethyl-3-oxo-4-oxa-5α-cholestane (124).

Thiophenol (40 μL, 0.4 mmoles) was added to DME (10 ml) followed by n-butyl-lithium (0.16 ml, 0.4 mmoles) at room temperature under nitrogen. After ¼ hr., the mixture was cooled to 0° and 2-methylene-3-oxo-4-oxa-5α-cholestane 122 (0.08g, 0.2 mmoles) in DME (10 ml) was added to it over 10 minutes. The reaction was quenched with water after 1 hr. and extracted into ether (200 ml) and washed successively with water, saturated sodium chloride, water, dried and evaporated to give 110 mg of the crude thiol adduct. Chromatographic separation gave the lactone 124 (49%); νmax (neat) 3400 (w, C=0 overtone), 3050 (Aryl C=C), 1730 (lactone), 1580 (Aryl C=C), 1045, 1025, 740 and 690 cm^{-1}; δ 7.3 (m, Ar.-H), 3.95 (dd, J ~ 11 and 5Hz, C5α-H), 0.93, 0.9, 0.82 and 0.65 (4s, methyls); MS 510.3557 (M, $C_{33}H_{50}SO_2$), calc. M, 510.3531

18. 2-Ethanethiomethyl-3-oxo-4-oxa-5α-cholestane (123)

Thiolation of 122 (0.08g, 0.2 mmoles) with ethane thiol (30 μL, ~ 0.4 mmoles) and n-butyl-lithium (0.16 ml, ~ 0.4 mmoles) in DME (20 ml) under similar conditions as for 124 gave 123 (0.074g, 80%); νmax (paste) 1740 lactone C=0), 1080, 1050 cm^{-1}; δ 4.03 (m, C5α-H), 2.62 (q, J ~ 8Hz, $-S\underline{CH_2}CH_3$), 1.25 (t, J ~ 8Hz, $-SCH_2\underline{CH_3}$), 0.93, 0.89, 0.72 and 0.66 (4s, methyls); MS 462.3535(M, $C_{29}H_{50}SO_2$), calc. M, 462.3531

19. 3β-Acetoxy-5α-androstan-17-one (126)[33]

Acetylation of 3β-hydroxy-5α-androstan-5-ene-17-one 125 (10.0g, 34.67 mmoles) with acetic anhydride (10 ml) in pyridine (100 ml) gave 3β-acetoxy-5α-androstan-5-ene-17-one (9.14g, 80%), mp 170-172° (methanol) (Lit. 168-169°); νmax (film) 1750 (ketone, C=0), 1735 (ester C=0), 1240 1030 cm^{-1}; δ 60MHz 5.35 (bs, 1H, C_6-H), 4.55 (m, 1H, $C_3\alpha$-H), 2.02 (s, 3H, ester-H), 1.05 (s, 3H, 19-H), and 0.9 (s, 3H, 18-H).

Hydrogenation with 10% Pd/C catalyst (0.5g) at room temperature of the acetate in glacial acetic acid/methanol (2:1, 300 ml) for 72 hr. and recrystallisation of the reduced crude acetate gave 3β-acetoxy-5α-androstan-17-one 126 (86%), mp 114-116° (methanol) (Lit. 116-117°); νmax (film) 1750 (ketone C=0), 1740 (ester C=0), 1240, 1030, cm^{-1}; δ 60MHz 4.65 (m, 1H, $C_3\alpha$-H), 2.0 (s, 3H, ester-H), 0.85 (s, 6H, 18 and 19-H).

20. 3β-Hydroxy-5α-androstan-17-one (126a)[73]

3β-Acetoxy-5α-androstan-17-one 126 (0.25g, 0.86 mmoles) was hydrolysed with potassium hydroxide (0.15g) in ethanol (30 ml) under reflux for 2 hr. and extracted into ether (200 ml), washed with water, dried and evaporated to give 3β-hydroxy-5α-androstan-17-one 126a (0.218g, 96%), mp 168-171° (methanol) (Lit. 170-171°); νmax 3500 (OH), 1740 (ketone C=0), 1055 cm^{-1}; δ 60MHz 3.55 (m, 1H, $C_3\alpha$-H) 0.85 and 0.82 (2s, 6H, 18 and 19-H).

21. 3β-Acetoxy-16-benzylidene-5α-androstan-17-one (128a)[74]

To a solution of 3β-acetoxy-5α-androstan-17-one 126 (2.0g, 6.02 mmoles) and benzaldehyde (2.0g) in ethanol (30 ml) was added potassium hydroxide (0.5g). The mixture was refluxed for 15 minutes and stirred overnight at room temperature. The precipitated crude product was filtered off and recrystallised from methanol to give 3β-hydroxy-16-benzylidene-5α-androstan-17-one 127a (62%), mp 181-182° (Lit. 181.5-182.5°);

νmax (film) 3600-3100 (-OH), 1720 (conj. C=O), 1635 (conj. C=C), 1040 cm^{-1}; δ 7.45 (m, 6H, Ph-CH=C), 3.55 (m, 1H, $C_3\alpha$-H), 1.52 (bs, 1H, $C_3\beta$-OH), 0.96 (s, 3H, 18-H) 0.89 (s, 3H, 19-H).

Acetylation with acetic anhydride in pyridine gave 3β-acetoxy-16-benzylidene-5α-androstan-17-one 128a (97%), mp 238-240° (chloroform and ethanol) (Lit. 237-238°); νmax (film) 1730 and 1260 (ester C=O), 1720 (conj. C=O), 1640 (conj.C=C), 1030 cm^{-1}; δ 7.45 (m, 6H, Ph-CH=C), 4.65 (m, 1H, $C_3\alpha$-H), 2.02 (s, 3H, ester-H), 0.96 (s, 3H, 18-H), and 0.89 (s, 3H, 19-H).

22. 3β-Acetoxy-16p-chlorobenzylidene-5α-androstan-17-one (128b)

To a solution of 3β-acetoxy-5α-androstan-17-one 126 (0.6, 1.80 mmoles) and p-chlorobenzaldehyde (0.3g) in ethanol (50 ml) was added a solution of potassium hydroxide (0.2g) in (9:1) ethanol/water (10 ml). The mixture was stirred overnight and the precipitated crude product was filtered and recrystallised from ethanol and water to give 3β-hydroxy-16β-chlorobenzylidene-5α-androstan-17-one 127b (78%), mp 219-221°; νmax (film) 3200 (H-bonded OH 1720 (conj. C=O), 1635 (conj. C=C), 1590, 1495 (aromatic C=C), 1095 (Ar.-Cl) 1050, 1020 and 830 cm^{-1}; δ 7.45 (m, 4H, Ar.-H), 7.31 (s, 1H, benzylidene-H), 3.55 (m, 1H, $C_3\alpha$-H), 0.9 (s, 3H, 18-H), and 0.85 (s, 3H, 19-H).

Acetylation with acetic anhydride in pyridine gave 3β-acetoxy-16p-chlorobenzylidene-5α-androstan-17-one 128b (89%), mp 217-219° (ethanol); $[\alpha]_D$-11° (c, 0.02); νmax (film) 1730 (ester C=O), 1720 (conj. C=O), 1635 (conj. C=C), 1590, 1490 (Ar.-C=C), 1255 (ester C=O), 1095 (Ar.-Cl), 1020 and 835 cm^{-1}; UV λmax 298 nm; δ (CD_2Cl_2) 7.51 and 7.36 (2d, J ~ 7Hz, 4H, Ar-H), 7.31 (s, 1H, benzylidene-H), 4.65 (m, 1H, $C_3\alpha$-H), 1.99 (s, 3H, ester-H), 0.90 (s, 3H, 18-H), and 0.86 (s, 3H, 19-H).

Anal. $C_{28}H_{35}O_3Cl$: calc. % :

C, 73.9; H, 7.75; Cl, 7.79

Found 73.9; 8.0; 7.7

23. 3β-Acetoxy-16p-nitrobenzylidene-5α-androstan-17-one (128c)

To a solution of 3β-acetoxy-5α-androstan-17-one 126 (0.52g , 0.52g, 1.56 mmoles) and p-nitrobenzaldehyde (0.3g, freshly recrystallised from ethanol) in ethanol (30 ml) was added potassium hydroxide (0.4g) solution in ethanol-water (2 ml - 0.25 ml). The mixture was stirred overnight, cooled to 0° and the precipitated crude product (92%) was recrystallised from ethanol to give 3β-hydroxy-16p-nitrobenzylidene-5α-androstan-17-one 127c, mp 268.5-269.5°; νmax (film) 3600-3100 (OH), 1725 (conj. C=0), 1640 (conj. C=C), 1600 and 1500 (Ar.-C=C), 1525, 1355 (Ar.-NO_2), 1050, 930 and 860 cm^{-1}; δ 8.25 and 7.65 (2d, J ~ 9Hz, 4H, Ar.-H), 7.45 (bs, 1H, benzylidene-H), 3.6 (m, 1H, $C_3\alpha$-H), 0.98 (s, 3H, 18-H) and 0.88 (s, 3H, 19-H).

Acetylation with acetic anhydride in pyridine gave 3β-acetoxy-16p-nitrobenzylidene-5α-androstan-17-one 128c (98%), mp 254-256° (ethyl acetate); $[\alpha]_D$ - 13° (c, 0.012); νmax (film) 1732 (ester C=0), 1725 (conj. C=0), 1638 (conj. C=C), 1598 and 1498 (Ar.-C=C), 1520 and 1345 (Ar.-NO_2) cm^{-1}; λmax 320 nm (EtOH); δ (CD_2Cl_2) 8.25 and 7.65 (2d, J ~ 9Hz, 4H, Ar.-H), 7.45 (bs, 1H, benzylidene-H), 4.65 (m, 1H, $C_3\alpha$-H), 2.02 (s, 3H, ester-H), 0.98 (s, 3H, 18-H) and 0.90 (s, 3H, 19-H).

Anal. $C_{28}H_{35}NO_5$: calc. % :

C, 72.23; H, 7.58; N, 3.01

72.1 ; 7.6 ; 3.0

24. 3β-Acetoxy-16p-methoxybenzylidene-5α-androstan-17-one[75] (128d)

To a solution of 3β-acetoxy-5α-androstan-17-one 126 (0.4g, 1.20 mmoles) and anisaldehyde (freshly distilled) (0.2g) in ethanol (15 ml) was added potassium hydroxide (0.25g) solution in ethanol-water (3 ml-0.5 ml). The mixture was refluxed for ½ hr., stirred overnight, cooled to 0° and filtered off to give the crude product (96%). Recrystallisation from dichloromethane and hexane gave 3β-hydroxy-16p-methoxybenzylidene-5α-androstan-17-one 127d, m.p. 220°-222° (Lit. 196-200°); υmax (film) 3540 (OH), 1715 (conj.C=0), 1635 (conj. C=C), 1605 and 1505 (Ar.-C=C), 1250, 1020, and 835 cm^{-1}; δ 7.50 and 6.92 (2d, 4H, Ar.-H), 7.42 (bs, 1H, benzylidene-H), 3.85 (s, 3H, methoxy-H), 3.6 (m, 1H, (3α-H), 0.93 (s, 3H, 18-H), and 0.88 (s, 3H, 19-H).

Acetylation with acetic anhydride in pyridine gave 3β-acetoxy-16p-methoxybenzylidene 128d (92%), mp 191-193° (Lit. 190.5-192°); νmax (film) 1730 (ester C=0), 1715 (conj. C=0), 1630 (conj. C=C), 1605 and 1515 (Ar.-C=C), 1035 and 835 cm^{-1}; λmax 321 nm (EtOH); δ 7.51 and 6.92 (2d, J ~ 9Hz, 4H , Ar.-H), 7.31 (bs, 1H, benzylidene-H), 4.6 (m, 1H, (3α-H), 3.83 (s, 3H, methoxy-H), 2.00 (s, 3H, ester-H), 0.90 and 0.89 (2s, 6H, 18-H and 19-H respectively).

25. 3β-Acetoxy-16-isopropylidene-5α-androstan-17-one (129a)

3β-Hydroxy-5α-androstan-17-one 126a (0.20g, 0.60 mmoles) was refluxed with 10 ml each of acetone and methanol for 24 hr. in the presence of potassium hydroxide (0.30g)[76]. Extraction into ether (250 ml), washing with water, drying and evaporating gave the crude hydroxy product (0.35g).

The crude product was acetylated with acetic anhydride (10 ml) in pyridine (30 ml) overnight with stirring. The reaction mixture was poured onto ice (40g) and the precipitated product was filtered to give

3β-acetoxy-16-isopropylidene-5α-androstan-17-one 129a (0.22g, 86% based on starting material), mp 165-167° (MeOH); $[\alpha]_D$-40° (c, 0.01); λmax (EtOH) 250 nm (ε = 7,000); νmax (film) 1735 (ester C=0), 1705 (conj. C=0), 1635 (conj. C=C), 1250, 1040 and 1030 cm^{-1}; δ 4.65 (m, 1H, $C_3\alpha$-H), 2.22 (s, 3H, isopropylidene-H), 2.03 (s, 3H, ester-H), 1.85 (s, 3H, isopropylidene-H), 0.87 (s, 6H, 18 and 19-H); MS 372 (M, $C_{24}H_{36}O_3$).

Anal. $C_{24}H_{36}O_3$: calc. %:

C, 77.37; H, 9.74

Found 77.2 ; 9.9

26. 3β-Acetoxy-16-isobutylidene-5α-androstan-17-one (129b)

3β-Hydroxy-5α-androstan-17-one 126a (0.50g, 1.50 mmoles) was refluxed w
10 ml each of methanol and methyl-ethyl ketone[76] for 48 hrs. Extraction into ether (300 ml), washing with water (2x), drying and evaporating gave 1.07g of crude product. Chromatographic separation (8:2, toluene:ethyl acetate) gave 3β-hydroxy-16-isobutylidene-5α-androstan-17-one (0.35g, 59%) as a mixture of inseparable isomers.

Acetylation with acetic anhydride (10 ml) in pyridine (40 ml) with stirring overnight and extracted into ether (300 ml). Washing successively with water, dilute HCl, bicarbonate solution, water, drying and evaporating gave 3β-acetoxy-16-isobutylidene-5α-androstan-17-one 129b (0.345g, 88%), mp 123-126° (MeOH and H_2O); λmax ($CHCl_3$) 252 nm (ε = 6,185); νmax (film) 1740 (ester C=0), 1712 (conj. C=0), 1633 (conj. C=C), 1245 and 1030 cm^{-1}; δ 4.7 (m, 1H, $C_3\alpha$-H), 2.2 and 1.83 (2s, olefinic methyls), 2.03 (s, ester-H), 1.01 and 1.03 (2t, J ~ 8Hz, isobutylidene $-CH_2\underline{CH_3}$), 0.86 (s, 18 and 19-H); MS 386.2819

(M, $C_{25}H_{38}O_3$), calc. M, 386.2821

Anal. $C_{25}H_{38}O_3$: calc. %:

C, 77.68 ; H, 9.91

77.8 ; 10.1

BAEYER-VILLIGER OXIDATIONS WITH TRIFLUOROPERACETIC ACID[45,50].

Baeyer-Villiger oxidations were carried out with trifluoroperacetic acid in the presence of disodium hydrogen phosphate buffer. The peroxyacid was generated ——— from trifluoroacetic anhydride and hydrogen peroxide (86.6%). Oxidations were carried out in dichloromethane with 2.5-5.0 molar peracid solutions over the substrate, the 17-ketone. Baeyer-Villiger oxidations were carried out on the following substrates (Expt. 27-32):

27. 3β-Acetoxy-16-benzylidene-5α-androstan-17-one (128a).

Cold trifluoroacetic anhydride (0.85g, 4.1 mmoles) was added to a cold and stirred solution of 86.6% hydrogen peroxide (0.17g, 4.4 mmoles) in dichloromethane (8 ml) over 20 minutes. After ½ hr., the resulting trifluoroperacetic acid solution was added to a vigorously stirred suspension of disodium hydrogen phosphate (0.50g) and 3β-acetoxy-16-benzylidene-5α--androstan-17-one 128a (0.30 g, 0.90 mmoles) in dichloromethane (30 ml) at 0° over ½ hr. The mixture was stirred for 3 hrs. at 0° and at room temperature overnight (18 hr.), filtered, washed with water, dried and evaporated to give a mixture of epoxides (65:35) in 95% yield. Chromatographic separation (95:5 petrol $^{60}/_{80}$:methanol) gave two main products and some starting material.

The lower T.L.C. fraction (0.09g) was recrystallised from ethyl acetate and hexane and gave 3β-acetoxy-16-epoxy-benzyl-5α-androstan-17-one 130a, mp 208-210°; $[\alpha]_D$ + 190° (CH_2Cl_2, C, 0.002); λmax (CCl_4) 261 nm; νmax (CH_2Cl_2) 1752 (cyclopentanone C=O), 1730 (ester C=O), 1255 and 899 cm^{-1}; δ 60MHz 7.35 (m, 5H, Ar.-H), 4.65 (m, 1H, $C_3\alpha$-H), 4.15 (s, 1H, benzyl epoxide -H), 2.02 (s, 3H, ester-H), 0.92 (s, 3H, 18-H), 0.82 (s, 3H, 19-H), MS 436.2610(M^+, $C_{28}H_{36}O_4$), / calc.M, 436.2614 On the basis of spectral data including C-13, this epoxide has α-stereochemistry.

Anal. $C_{28}H_{36}O_4$: calc. %:

C, 77.03; H, 8.31

Found 76.7 ; 8.4

The upper T.C.L. fraction (0.05g), recrystallised from ethyl acetate and ethanol gave an isomer of 130a, mp 194-196°; $[\alpha]_D$-121° (CH_2Cl_2, c, 0.0014); λmax (CCl_4) 262 nm ; νmax (CH_2Cl_2) 1750 (cyclopentanone C=0), 1730 (ester C=0), 1255 and 899 cm^{-1}; δ 60MHz 7.31 (m, 5H, Ar.-H), 4.6 (m, 1H, $C_{3\alpha}$-H), 4.34 (s, 1H, benzylepoxide-H), 2.01 (s, 3H, ester-H), 1.08 (s, 3H, 18-H), 0.86 (s, 3H, 19-H)); MS 436.2609 (M, $C_{28}H_{36}O_4$), / This epoxide has β-stereochemistry. calc. M, 436.2614

28. 3β-Acetoxy-16p-chlorobenzylidene-5α-androstan-17-one (128b)

Under similar conditions as in experiment 27, 3β-acetoxy-16p-chlorobenzylidene-5α-androstan-17-one 128b (0.30g, 0.66 mmoles), disodium hydrogen phosphate (DHP) (0.50g) and trifluoroperacetic acid (3.2 mmoles) in dichloromethane (35 ml), gave a mixture of diastereomeric epoxides, 3β-acetoxy-16--epoxy-p-chlorobenxyl-5α-androstan-17-one 130b (0.27g, 99%), mp 72-82°; λmax (EtOH) 298 nm; νmax (CH_2Cl_2) 1755 (cyclopentanone C=0), 1735 (ester C=0), 1500 (Ar.-C=C), 1099 (Ar.-Cl), 1250 and 1030 cm^{-1}; δ 7.4 and 7.2 (2d, J ~ 8Hz, Ar.-H), 4.65 (m, $C_3\alpha$-H), 4.3 and 4.1 (28:72, 2s, benzylepoxide-H), 2.01 (s, ester-H), 1.06, 0.91, 0.84 and 0.80 (4s, 18 and 19-H); MS 470.2223 (M, $C_{28}H_{35}O_4Cl$), / Attempts to separate the two isomers were unsuccessful. calc. M, 470.2224

29. 3β-Acetoxy-16p-nitrobenzylidene-5α-androstan-17-one (128c)

3β-Acetoxy-16p-nitrobenzylidene-5α-androstan-17-one 128c (0.20g , 0.43 mmoles), DHP buffer (0.30g) and trifluoroperacetic acid (2.2 mmoles) in dichloromethane (30 ml) under similar conditions (expt. 27) gave a mixture of epoxides and some starting material in 85% yield. Chromatographic separation (50:50, 60/80 petrol:ether) gave a major fraction (50%), starting material (20%) and some polar material. The major fraction was identified as a mixture of epoxides, the 3β-acetoxy-16-epoxy-p-nitrobenzyl-5α-androstan-

-17-one 130c, mp 107-114°; λmax (EtOH) 275 nm; νmax (CH_2Cl_2) 1750 (cyclopentanone C=0), 1725 (ester C=0), 1605 (Ar.-C=C), 1526 (Ar.-Cl), 1240, 1025, and 840 cm^{-1}; δ 8.24 and 7.45 (2d, J = 8Hz, Ar.-H), 4.65 (m, $C_3\alpha$-H), 4.45 and 4.25 (2s, benzylepoxide-H), 2.02 (s, ester-H), 1.1, 0.94, 0.86, and 0.82 (4s, 18 and 19-H); MS 481.2462(M, $C_{28}H_{35}NO_6$), calc.M, 481.2464

NMR on the crude product indicated two epoxides in 55:45 abundance. Efforts to separate the two isomers were unsuccessful.

30. 3β-Acetoxy-16p-methoxybenzylidene-5α-androstan-17-one (128d)

Cold trifluoroacetic anhydride (0.94g, 4.45 mmoles) was added to a stirred solution of 86.6% hydrogen peroxide (0.18g, 4.45 mmoles) in dichloromethane (10 ml) and stirred at 0° for 1 hr.

The peracid solution was gradually added to a well stirred suspension of 3β-acetoxy-16p-methoxybenzylidene-5α-androstan-17-one 128d (0.40g, 0.89 mmoles) and DHP buffer (0.40g) in dichloromethane (25 ml). The mixture was stirred at 0° for 4 hours and filtered off. Extraction into dichloromethane (100 ml), washing with water (2x), drying and evaporating gave 0.414g of crude product.

Continuous recrystallisation of the crude product with ethyl acetate gave the epoxyenol lactone 145 (~ 15%), mp 143-145°; $[\alpha]_D$ + 2° (c, 0.02); νmax (CH_2Cl_2) 1730 (ester C=0), 1610 and 1510 (Ar.-C=C), 1700 (w), 1240, 1030 and 840 cm^{-1}; δ 220MHz, (CD_2Cl_2) 7.05 and 6.9 (2d, J = 8Hz, 4H, Ar.-H), 4.65 (m, 1H, $C_3\alpha$-H), 4.2 (s, 1H, benzylic-epoxide-H), 3.8 (s, 3H, methoxy-H), 3.0 (dd, J = 12 and 5Hz, 1H, 15-H, axial), 2.69 (t, J = 12Hz, 1H, 15-H, equat.), 1.98 (s, 3H, ester-H), 0.80 and 0.78 (2s, 6H, 18 and 19-H); MS 482.2661 (M, $C_{29}H_{38}O_6$), calc. M, 482.2668

Anal. $C_{29}H_{38}O_6$; calc. % :

C, 72.17 ; H, 7.94

Found 71.9 ; 7.9

Chromatographic separation (8:2, toluene:ethyl acetate) gave two fractions. The major fraction (~50%) was a β-diketone 142, mp 238-240° (EtOAc/hexane); λmax (EtOH) 239 nm (ε = 9,437) and 272 nm (ε = 7,514), λmax (N-NaOH) 291 nm (ε = 7456); $[\alpha]_D$ - 24° (CH_2Cl_2, c, 0.005); νmax (CH_2Cl_2) 3550-3400 (m, enolic -OH ; 3400-2500 in nujol), 1685, and 1630 (1,3-diketone enolised), 1605 and 1516 (Ar.-C=C), 1240 and 1035 cm^{-1}; δ 7.1 and 6.9 (2d, 4H, J = 9Hz, Ar.-H), 6.1 (bs, 1H, enolised -OH , D_2O exchanged), 4.65 (m, 1H, $C_3\alpha$-H), 3.82 (s, 3H, methoxy-H), 2.02 (s, 3H, ester-H), 1.1 (s, 3H, 18-H), 0.84 (s, 3H, 19-H); MS 466.2706(M, $C_{29}H_{38}O_5$), calc. M, 466.2719

Anal. $C_{29}H_{38}O_5$; calc. % :	C,	H,
	74.64	8.21
Found	74.1	8.2

The minor fraction (~ 25%) was a 1,3-diketone 148, mp 179-182° (EtOH/H_2O); νmax (CH_2Cl_2) 3600-3000 (-OH), 1730 (ester C=0), 1690 (ketone C=0), 1600 and 1505 (Ar.- C=C) 1240 and 1030 cm^{-1}; δ 7.98 and 6.93 (2d, J = 9Hz, 4H, Ar.-H), 4.7 (m, 1H, $C_3\alpha$-H), 3.91 (s, 3H, methoxy-H), 2.02 (s, 3H, ester-H), 1.22 (s, 3H, 18-H), 0.81 (s, 3H, 19-H); MS 466.2743 (M, $C_{29}H_{38}O_5$), calc. M, 466.2719 contaminated with MS 482.2639 (M, $C_{29}H_{38}O_6$), calc. M, 482.2668 possibly the Lactone 145.

31. 3β-Acetoxy-16-isopropylidene-5α-androstan-17-one (129a)

3β-Acetoxy-16-isopropylidene-5α-androstan-17-one 129a (0.11g, 0.30 mmoles), DHP buffer (0.25g) and trifluoroperacetic acid, (0.75 mmoles) in dichloromethane (20 ml) at 0° for 5 hr. gave predominantly the α-epoxide (0.10g, crude product) on extraction with dichloromethane.

Chromatographic inspection indicated one major fraction and some starting material. Recrystallisation from ethyl acetate and petrol $(^{40}/_{60})$ gave 152a, mp 214-216°; $[\alpha]_D$ + 60° (CCl_4, c, 0.005); λmax ($CHCl_3$) 312 nm (ε = 191); νmax (CH_2Cl_2) 1740 (cyclopentanone C=0), 1730 (ester C=0),

1250 and 1030 cm^{-1}; δ 4.65 (m, 1H, $C_3\alpha$-H), 2.03 (s, 3H, ester-H), 1.38 and 1.35 (2s, 6H, isopropyl-H), 0.96 (s, 3H, 18-H), 0.89 (s, 3H, 19-H); MS 388.2612(M, $C_{24}H_{36}O_4$), / This epoxide has α-stereochemistry. calc. M, 388.2613

Anal. $C_{24}H_{36}O_4$: calc. % :

C, 74.19 ; H, 9.34

Found 74.5 ; 9.5

This epoxide resisted reduction with hydrogen in ethyl acetate over 5% Pd/C for 3 days. Prolonged epoxidation did not give a higher oxidation product.

32. 3β-Acetoxy-16-isobutylidene-5α-androstan-17-one (129b)

3β-Acetoxy-16-isobutylidene-5α-androstan-17-one 129b (0.20g, 0.52 mmoles), DHP buffer (0.30g) and trifluoroperacetic acid (1.3 mmoles) in dichloromethane (25 ml) at 0° for 6½ hrs. (t.l.c.) gave an epoxide crude product 152b 0.185g (89%). Chromatographic separation (8:2, petrol 60/80: ether) on 0.17g gave a lower fraction (0.097g, 57.1%) and an upper fraction (0.03g, 17.6%).

Spectral analysis on the lower and major fraction indicated a 50:50 cis and trans-mixture of α-epoxide, mp 150-155° (ethyl acetate and petrol 40/60); νmax (CCl_4) 1750 (cyclopentanone C=0), 1732 (ester C=0), 1245 and 1030 cm^{-1}; δ 4.7 (m, 1H, $C_3\alpha$-H), 2.04 (s, 3H, ester-H), 1.35 and 1.32 (2s, isobutylepoxide E- and Z-methyls), 0.98 (s, 3H, 18-H), 0.88 (s, 3H, 19-H); MS (LR) 402 (M, $C_{25}H_{38}O_4$).

The upper and minor fraction was a β-epoxide, ~ 50:50 cis- and trans-mixture; νmax (CCl_4) 1750 (cyclopentanone C=0), 1732 (ester C=0), 1245 and 1030 cm^{-1}; δ 4.7 (m, 1H, $C_3\alpha$-H), 2.02 (s, 3H, ester-H), 1.52 and 1.38 (2s, E and Z isobutylepoxide methyls), 0.99 (s, 3H, 18-H), and 0.91 (s, 3H, 19-H).

33. Reduction of 3β-acetoxy-16α-epoxybenzyl-5α-androstan-17-one (130a)

Reduction of the α-epoxide 130a (0.095g, X=H) in ethyl acetate (80 ml) using H_2/10% Pd/C for 26 hrs gave 3β-acetoxy-16α-hydroxy-16β-benzyl-5α-androstan-17-one 137a; mp 180-182° (ethyl acetate-hexane); $[\alpha]_D$ + 92° (CH_2Cl_2, c, 0.01); νmax (film) 3520 (free-OH), 1740 (cyclopentanone C=0), 1730 (ester C=0), 1605 and 1495 (Ar.- C=C), 1245, 1030 and 900 cm^{-1}; δ 60MHz 7.24 (m, 5H, Ar.-H), 4.65 (m, 1H, $C_3\alpha$-H), 2.95 (s, 2H, benzylic-H), 2.21 (bs, 1H, D_2O exchanged, 16α-OH), 2.03 (s, 3H, ester-H), 0.81 (s, 3H, 19-H), 0.54 (s, 3H, 18-H); MS 438.2767 (M, $C_{28}H_{38}O_4$), calc. M, 438.2770

Anal. $C_{28}H_{38}O_4$: calc. % :

C, 76.67 ; H, 8.73

Found 76.5 ; 8.7

34. Reduction of 3β-acetoxy-16β-epoxybenzyl-5α-androstan-17-one (130a)

Reduction of the β-epoxide 130a (0.048g, X=H) in ethyl acetate (60 ml) with hydrogen using 10% Pd/C catalyst (0.06g) at room temperature for 25 hrs gave 3β-acetoxy-16β-hydroxy-16α-benzyl-5α-androstan-17-one 137b; mp 176-178° (ethyl acetate-petrol); $[\alpha]_D$ -20 (CH_2Cl_2, c, 0.008); νmax (film) 3565 (free - OH) 1740 (cyclopentanone C=0), 1730 (ester C=0), 1605 and 1495 (Ar.- C=C), 1245, 1030 and 900 cm^{-1}; δ 60MHz 7.22 (m, 5H, Ar.-H), 4.65 (m, 1H, $C_3\alpha$-H), 2.88 (s, 2H, benzylic-H), 2.45 (bs, 1H, D_2O exchanged, 16β-OH), 2.02 (s, 3H, ester-H), 1.0 (s, 3H, 18-H), 0.81 (s, 3H, 19-H); MS 438.2789 (M, $C_{28}H_{38}O_4$), calc. M, 438.2770 / The resultant 16α- and 16β-hydroxides were dehydrated stereospecifically with thionyl chloride in pyridine to give 3β-acetoxy-16-benzylidene-5α-androstan-17-one 128a: mp and mixed mp 239-241° (Lit.[74] 237-238°); νmax (film) 1730 and 1260 (ester C=0), 1720 conj. C=0), 1630 (conj. C=C), 1030 and 776 cm^{-1}; δ 7.4 (m, 6H, Ar.-CH=C), 4.65 (m, 1H, $C_3\alpha$-H), 2.02 (s, 3H, ester-H)), 0.96 (s, 3H, 18-H), and 0.89 (s, 3H, 19-H).

35. Reduction of 3β-acetoxy-16-epoxy-p-chlorobenzyl-5α-androstan-17-one (130b)

Hydrogenation of 130b (0.50g, X=Cl), with 10% Pd/C catalyst (0.60g) at room temperature in ethyl acetate (250 ml) for 5 days gave 0.30g of crude product on filtration. Chromatographic separation (45:5:50, 60/80 petrol: chloroform:ether) gave one major fraction (0.13g). ^{1}H, N.M.R. revealed two epimeric hydroxides and that reduction had proceeded with hydrogenolysis of C-Cl. Several recrystallisations with ethyl acetate and hexane gave one of the epimers, 3β-acetoxy-16α-hydroxy-16β-benzyl-5α-androstan-17-one 137a, mp 180-182°; $[\alpha]_D$ + 92° (CH_2Cl_2, c, 0.02); νmax film 3460 (free -OH), 1740 (cyclopentanone C=O), 1730 (ester C=O), 1250 and 1030 cm^{-1}; δ 60MHz 7.15 (m, 5H, Ar.-H), 4.55 (m, 1H, $C_3\alpha$-H), 2.91 (s, 2H, benzylic-H), 2.21 (bs, 1H, D_2O exchanged, 16α-OH), 1.99 (s, 3H, ester-H), 0.80 (s, 3H, 19-H), 0.54 (s, 3H, 18-H); MS 438.2767(M, $C_{28}H_{38}O_4$), / calc. M, 438.2770 The β-epoxide was not isolated. However, dehydration with thionyl chloride in pyridine at 0° of the mixture of epoxides gave the E-benzylidene ketone 128a. There was no evidence of the Z-isomer or of the endocylic elimination product, 138.

BAEYER-VILLIGER OXIDATION WITH PERACETIC ACID[53,54]

Reactions with peracetic acid were carried out with 40-45% solution prepared by an equilibration of acetic acid (1.5 moles) and 86% hydrogen peroxide (1.0 moles) with 1% sulphuric acid.

36. Reaction of peracetic acid with 3β-acetoxy-16p-methoxybenzylidene-5α-androstan-17-one (128d)

To a solution of 3β-acetoxy-16p-methoxybenzylidene-5α-androstan-17-one 128d (X=OMe, 0.40g, 0.89 mmoles) in glacial acetic acid (20 ml) saturated with potassium acetate was added 45% peracetic acid and the mixture stirred at room temperature until there was no starting material (T.L.C.) 24 hrs. The mixture was quenched with ether (200 ml) and water (100 ml). The aqueous layer was separated and extracted twice with ether (50 ml). The ethereal solutions were combined, washed consecutively with water (2 x 100 ml), sodium carbonate solution (2 x 100 ml) and again with water (3 x 150 ml). The ether extract was dried and evaporated to give 0.435g of crude product.

Chromatographic inspection revealed two polar products. Preparatory T.L.C. (65:35, toluene : ethyl acetate) gave two fractions : 0.11g lower T.L.C. product and 0.12g upper T.L.C. product as the isomers of 153d (X= -OMe).

Lower T.L.C. product:

MP 83-85°C; νmax (film) 3600-2500 (acid-OH), 1730 (ester C=O), ~ 1715 (ketone C=O), ~ 1700 (acid C=O), 1610 and 1510 (Ar. C=C), 1030 and 835 cm^{-1}; δ 7.32 and 6.9 (2d, J ~ 8Hz, 4H, Ar.-H), 6.3 (bs, 1H, D_2O exchanged, acid -OH), 5.94 (s, 1H, benzylic-H), 4.65 (m, 1H, $C_3\alpha$-H), 3.82 (s, 3H, p-methoxy-H), 2.35 (bs, 1H, 15-H), 2.15 (s, 3H, α-acetoxyl-H), 2.02 (s, 3H, 3β-ester-H), 1.07 (s, 3H, 18-H), 0.72 (s, 3H, 19-H); MS 483.2710 and 482.2657 (M $-CH_3CO_2$, 3.4% and M $-CH_3CO_2H$; 11.8% respect.), (M, $C_{31}H_{42}O_8$), calc. M-$C_2H_3O_2$, 483.2746 and M-$C_2H_4O_2$, 482.2668

A 100mg sample of the acid 153d in ether (10 ml) was methylated with diazomethane at 0°. Diazomethane was generated from N-methyl-N-nitroso-toluene-4-sulphonamide and potassium hydroxide in ethanol[77]. Excess diazomethane was destroyed with glacial acetic acid. The solvent was evaporated off to give 154d(0.092g, 92%) : mp 137-139° (ethanol); $[\alpha]_D$ - 137°($CHCl_3$, C, 0.02); νmax (film) ~ 1735 (ester C=0) ~ 1720 (ketone C=0), 1615 and 1515 (Ar. C=C), 1240, 1030 and 840 cm^{-1}; δ 7.31 and 6.9 (2d, J ~ 8Hz, 4H, Ar.-H), 5.83 (s, 1H, benzylic-H), 4.6 (m, 1H, $C_3\alpha$-H), 3.8 (s, 3H, p-methoxy-H), 3.56 (s, 3H, methyl ester-H), 2.3 (bs, 2H, 15-H), 2.15 (s, 3H, α-acetoxyl-H), 1.99 (s, 3H, 3β-ester-H), 1.05 (s, 3H, 18-H), 0.71 (s, 3H, 19-H); MS 496.2826(M - CH_3CO_2H , 0.6%), (M, $C_{32}H_{44}O_8$), calc. M-$C_2H_4O_2$, 496.2825

Anal. $C_{32}H_{44}O_8$: calc. %

C, 69.04 ; H, 7.97

Found 68.9 ; 8.0

Upper T.L.C. product:

MP 75-80°; λmax (film) 3600-2500 (acid -OH), ~ 1730 (ester C=0), ~ 1710 (ketone C=0), ~ 1700 (acid C=0), 1610 and 1510, (Ar. C=C), 1030, 915 and 840 cm^{-1}; δ 8.5 (bs, 1H, D_2O exchanged acid-OH), 7.3 and 6.9 (2d, J ~ 8Hz, 4H, Ar.-H), 5.95 (s, 1H, benzylic-H), 4.65 (m, 1H, $C_3\alpha$-H), 3.8 (s, 3H, p-methoxy-H), 2.3 (bs, 2H, 15-H), 2.14 (s, 3H, α-acetoxy-H), 2.00 (s, 3H, 3β-ester-H), 1.00 (s, 3H, 18-H), 0.76 (s, 3H, 19-H); MS 482.2660and 483.2698 (M - CH_3CO_2 , 2.4% and M - CH_3CO_2H , 10.3% respect.), (M, $C_{31}H_{42}O_8$), calc. M-$C_2H_3O_2$, 482.2668 and M-$C_2H_4O_2$, 483.2702

Methylation of the acid 153d(0.10g) with diazomethane in ether (10 ml) gave an oil (0.15g). Chromatographic separation (50:50, 60/80 petrol : ether) gave 0.0949 of the methyl ester 154d an isomer of the methylation product from the lower T.L.C. fraction. Attempts to crystallise this methylated fraction were unsuccessful: mp 55-60°; $[\alpha]_D$ + 52° (C, 0.02);

νmax (film) 1735 (ester C=0), ~ 1720 (ketone C=0), 1610 and 1510 (Ar. C=C), 1240, 1030 and 830 cm^{-1}; δ 7.3 and 6.89 (2d, J = 8Hz, 4H, Ar.-H), 5.87 (s, 1H, benzylic-H), 4.65 (m, 1H, $C_3\alpha$-H), 3.81 (s, 3H, p-methoxy-H), 3.38 (s, 3H, methylester-H), 2.3 (bs, 2H, 15-H), 2.15 (s, 3H, α-acetoxy-H), 2.01 (s, 3H, 3β-ester-H), 1.00 (s, 3H, 18-H), and 0.76 (s, 3H, 19-H),

MS 377.2336 ($M-C_{10}H_{11}O_3$, 23%) calc. 377.2327; 179.0708 ($M-C_{22}H_{33}O_5$, 12%) calc, 179.0708

37. REACTION OF 3β-ACETOXY-16-BENZYLIDENE-5α-ANDROSTAN-17-ONE (128a) WITH HYDROGEN PEROXIDE.

To a solution of 3β-acetoxy-16-benzylidene-5α-androstan-17-one 128a (0.20 g, 0.48 mmoles) in methanol (30 ml) and chloroform (20 ml) was added 30% H_2O_2 and 4N-NaOH (9 ml) and the mixture was left overnight at 0° and at room temperature for 12 hr. Extraction into ether, washing with water, drying and evaporating gave a crude product (0.101 g); νmax 3600-3200 (OH), 1740 (cyclopentanone C=0), 1720 (α,β-unsaturated ketone), 1632 (conj. C=0) cm^{-1}; δ 7.35 (m, aromatic H), 4.34 and 4.14 (2s, epoxide H), 3.55 ($C_3\alpha$-H), 1.08, 0.95, 0.93, 0.88, 0.84 and 0.79 (6s, C-18 and C-19).

The integration of the epoxide methine proton singlets at δ 4.34 and δ 4.14 indicated the presence of two α-epoxy-ketones 139 in the ratio 41:59 respectively. The two singlets at δ 0.95 and δ 0.88 were assigned to the C-19 and C-18 methyl protons of the hydrolysed benzylidene ketone (cf 127a).

The aqueous fraction was acidified with dilute HCl and extracted into ether and gave a crude (0.095 g) of hydrolysed mixtures which were not separated.

REDUCTION OF α,β-UNSATURATED STEROIDAL 17-KETONES

Hydrogenations were carried out in ethyl acetate with 5% Pd/C catalyst at room temperature. Reduced ketones were reoxidised back to the ketone with 8N-chromic acid in acetone (Jones' reagent).

38. Reduction of 3β-acetoxy-16-benzylidene-5α-androstan-17-one (128a)[77].

Hydrogenation of 3β-acetoxy-16-benzylidene-5α-androstan-17-one 128a (X=H, 0.60g, 1.43 mmoles) with 5% Pd/C catalyst (0.15g) in ethyl acetate (100 ml) for 8 hrs. gave a crude product which was chromatographed (8:2, toluene : ethyl acetate) to give two fractions. The lower T.L.C. fraction (0.287g) was crystallised from ethyl acetate and gave 3β-acetoxy-16-benzyl-17-hydroxy-5α--androstane 164 : mp 189-191°; $[\alpha]_D$ + 36° (C, 0.02) ; νmax (film) 3540 (free -OH), 1715 (ester C=O), 1600 and 1499 (Ar. C=C), 1250, 1065 and 1030 cm^{-1}; δ 7.23 (m, 5H, Ar.-H), 4.65 (m, 1H, $C_3\alpha$-H), 3.75 (dd, J = 9 and 6Hz, D_2O exchanged to J = 9Hz, 17-H), 3.09 (dd, J = 18 and 9Hz, benzylic-H), 2.4 (m, 2H, benzylic-H and 16-H), 2.36 (bs, D_2O exchanged, 17-OH), 2.03 (s, 3H, ester-H), 0.83 (s, 6H, 18 and 19-H);

MS 424.2964(M, $C_{28}H_{40}O_3$), calc. M, 424.2977.

Anal. $C_{28}H_{40}{}_3$: calc. %

C, 79.2 ; H, 9.5

Found 78.9 ; 9.6

The upper T.L.C. fraction (0.336g) was crystallised from ethyl acetate and methanol and gave 3β-acetoxy-16 -benzyl-5β-androstan-17-one 163a : mp 139-141°; $[\alpha]_D$ + 82 (C, 0.02); λmax (EtOH) 258 nm (ε = 1454) and 297 nm (ε = 710); νmax (film) 1740 (cyclopentanone C=O), 1729 (ester C=O) 1600 and 1499 (Ar.-H), 1240 and 1030 cm^{-1}; δ 7.2 (m, 5H, Ar.-H), 4.65 (m, 1H, $C_3\alpha$-H), 3.2 and 2.68 (2dd, J = 13 and 4Hz, and J = 13 and 9Hz, benzylic-H), 2.38 (m, 16α-H), 2.02 (s, 3H, $C_3\alpha$-H), 0.82 (s, 3H, 19-H), 0.65 (s, 3H, 18-H);

MS 422.2822(M, $C_{28}H_{38}O_3$), calc. M, 422.2821

Anal. $C_{28}H_{38}O_3$: calc. % :

C, 79.6 ; H, 9.1

Found 79.6 ; 9.3

Alternately the hydrogenated crude mixture was oxidised with Jones' reagent in acetone and extraction into ether gave 163a in good yield (90%).

39. Acetylation of 3β-acetoxy-16-benzyl-5α-androstan-17-ol (164)

3β-Acetoxy-16-benzyl-5α-androstan-17-ol 164 (0.10g, 0.24 mmoles) in pyridine (30 ml) and acetic anhydride (5 ml) was stirred overnight and poured onto ice (40 g) and recovered quantitatively as the diacetate. Recrystallisation from ethyl acetate and methanol gave 3β,17-diacetoxy-16-benzyl--5α-androstane 160, mp 183-184°; $[\alpha]_D$ + 22° (C, ~ 0.02); νmax (film) 1732 (ester C=0), 1721 (ester C=0), 1602, 1583 and 1500 (Ar. C=C), 1242, 1060 and 1032 cm^{-1}; δ 7.2 (m, 5H, Ar.-H), 4.8 (d, J = 9Hz, 17-H), 4.65 (m, 1H, $C_3\alpha$-H), 2.03 and 2.01 (2s, 6H, ester-H), 0.88 (s, 3H, 18-H), 0.82 (s, 3H, 19-H); MS 406.28% due to loss of CH_3CO_2H, (M, $C_{30}H_{42}O_4$), calc.M-$C_2H_4O_2$, 406.2872

Anal. $C_{30}H_{42}O_4$: calc. % :

C, 77.2 ; H, 9.1

Found 77.2 ; 9.3

40. Reduction of 3β-acetoxy-16p-methoxy-benzylidene-5α-androstan-17-one (128d)

3β-Acetoxy-16p-methoxybenzylidene-5α-androstan-17-one 128d (X=OMe, 0.71g, 1.09 mmoles) in ethyl acetate (150 ml) was reduced with hydrogen using 5% Pd/C catalyst (0.25g) for 3 hrs. The reduced mixture was oxidised with Jones' reagent in acetone and extracted in ether (300 ml), washed with water, dried and evaporated to give 3β-acetoxy-16p-methoxybenzyl-5α--androstan-17-one 163d (X=OMe, 0.662g, 71%): mp 183-185° (acetone); $[\alpha]_D$ + 76° (C, 0.03); νmax (film) 1740 (ketone C=0), 1730 (ester C=0), 1612, 1585 and 1515 (Ar. C=C), 1238 and 1029 cm^{-1}; δ 7.1 and 6.91 (2d, J = 9Hz, 4H, Ar.-H), 4.65 (m, 1H, $C_3\alpha$-H), 3.8 (s, 3H, methoxy-H), 3.12 (dd, J ~ 13 and 4Hz, 1H, benzylic-H), 2.63 (dd, J ~ 13 and 9Hz, 1H, benzylic-H) 2.03 (s, 3H, ester-H), 0.82 (s, 3H, 19-H), 0.63 (s, 3H, 18-H); MS 452.2930 (M, $C_{29}H_{40}O_4$), calc. M, 452.2927

Anal. $C_{29}H_{40}O_4$: calc. % :

C, 76.96 ; H, 8.91

Found 76.7 ; 9.3

41. Reduction of 3β-acetoxy-16-isopropylidene-5α-androstan-17-one (129a)

3β-Acetoxy-16-isopropylidene-5α-androstan-17-one 129a (0. 24g, 0.65 mmoles) in ethyl acetate (60 ml) was reduced with hydrogen using 5% Pd/C catalyst (0.10g) until there was no obvious uptake of hydrogen. Oxidation of the reduced mixture with Jones' reagent and extraction into ether (250 ml) gave an oil (0.245g). Crystallisation from methanol and water gave 3β-acetoxy-16-isopropyl-5α-androstan-17-one 161 (0.103g) : mp 145-147°; $[\alpha]_D$ + 69° (C, 0.03); νmax (film) 1740 (cyclopentanone C=0), 1732 (ester C=0), 1250 and 1030 cm^{-1}; δ 4.7 (m, 1H, $C_3\alpha$-H), 2.05 (s, 3H, ester-H), 1.04 and 0.87 (2d, J = 7Hz, isopropyl-CH_3), 0.88 and 0.81 (2s, 19-H and 18-H respect.); MS 374.2821(M, $C_{24}H_{38}O_3$), calc. M, 374.2821

Anal. $C_{24}H_{38}O_3$: calc. % :

C, 76.96 ; H, 10.23

Found 76.9 ; 10.4

42. Baeyer-Villiger oxidation of 3β-acetoxy-16β-benzyl-5α-androstan-17--one (163a) with peracetic acid.

To 3β-acetoxy-16β-benzyl-5α-androstan-17-one 163a (0.32 g, 0.76 mmoles) in glacial acetic acid (20 ml) and enough tetrahydrofuran to dissolve the ketone completely (~ 5 ml) was added 86.6% hydrogen peroxide (10 ml), 10% sulphuric acid (1 ml) and sodium acetate (0.5g). The mixture was briefly stirred and left to stand at room temperature for 9 days. Excess peracid and peroxide was destroyed with aqueous ferrous sulphate. Extraction into ether, washing with water, bicarbonate, water again, drying and evaporating gave a crude product which was chromatographed (8:2, toluene : ethyl acetate) to give one major fraction 166a (X=H, 0.295g, 89%) as a mixture of 16α- and β-epimers. Crystallisation from ethanol gave 3β-acetoxy-16-benzyl-17-oxo-17a-oxa-D-homo-5α-androstane 166a: mp 132-138°; νmax (film) 1730 (ester and lactone C=0), 1605 and 1599 (Ar. C=C), 1240 and 1030 cm^{-1}; δ 7.25 (bs, 5H, Ar.H), 4.65 (m, 1H, $C_3\alpha$-H), 3.05 (m, 2H, benzylic-H), 2.75 (m, 16-H) /2.0 (s, 3H, ester-H), 0.98, 0.95, 0.78, 0.74 (4s, 18-H and 19-H); MS 438.2771 (M, $C_{28}H_{38}O_4$), calc. M, 438.2770

43. Baeyer-Villiger oxidation of 3β-acetoxy-16β-p-methoxybenzyl-5α-androstan-17-one (163d) with peracetic acid.

A mixture of the ketone 163b (0.5g, 1.1 mmoles), sodium acetate (0.3g), tetrahydrofuran (10 ml) and 45% peracetic acid (25 ml) was left to stand in a water bath at 37°C. The progress of the reaction was followed by T.L.C. which was stopped after 16 days. Small amounts (0.5 ml) of 86% peroxide were added at intervals of 4 days to compensate for any peroxide decomposition.

The mixture was extracted into ether and washed successively with ferrous sulphate solution, water, bicarbonate, water and evaporated to give an oil, 0.54g. Chromatographic separation (8:2, toluene : ethyl acetate) gave one major non-polar fraction, the lactone 166d, (0.05g, 10%); νmax 1730 (ester and lactone C=O), 1615, 1590 and 1515 (aryl C=C); δ 7.15 and 6.82 (2d, J = 9Hz, 4H, Ar.-H), 4.65 (bs, 1H, $C_3\alpha$-H), 3.81 (s, 3H, methoxy-H), 3.02 (ABX-q, J = 13 and 6Hz, 1H, benzylic-H), 2.76 (m, 16-H), 2.36 (m, benzylic-H), 2.02 (s, 3H, ester-H), 0.98, 0.95, 0.78 and 0.75 (4s, 18-H and 19-H).

The yield was low and no further treatment was made on this product.

44. 3β-Acetoxy-16-benzylidene-17-oxo-17a-oxa-D-homo-5α-androstane (170).

A mixture of the androstan-lactone 166a (0.295g, 0.67 mmoles), 1,3-dibromo-5,5-dimethylhydantoin[60] (0.572g) and dibenzoyl peroxide (0.05g, added at intervals) in carbon tetrachloride (50 ml) was refluxed under light (2 x 160 watt lamps) until there was no evidence of starting material (T.L.C.), 5 hrs. Filtration and extraction into carbon tetrachloride and washing with dilute HCl, 10% bicarbonate solution, water, drying and evaporating gave a brown paste. A small amount was chromatographed and recrystallised from acetone and methanol and gave the bromolactone 169 : mp 211-213°; $[\alpha]_D$ - 96° (C, 0.005); νmax (film) 1730 (ester and lactone C=O), 1600 and 1590 (Ar. C=C), 1240, 1030 and 710 cm^{-1}; δ 7.28 (bs, 5H, Ar.-H), 4.65 (m, 1H, $C_3\alpha$-H), 4.1 and 3.25 (2d, J = 14Hz, 2H, benzylic-H), 2.02 (s, 3H, ester-H), 0.71 (s, 3H, 19-H), 0.62 (s, 3H, 18-H); MS 437.2695 (M -Br, B.P.), (M, $C_{28}H_{37}Br\ O_4$), calc. M-Br, 437.2691

The crude product was dehydrobrominated with 1,5-diazabicyclononene[62] (4 ml) in refluxing toluene (30 ml) under nitrogen until there was no bromo-compound (3 hr.). Extraction into ether (250 ml), washing with cold 10% HCl, saturated brine, water, drying and evaporating gave 0.23g of crude product. Chromatographic separation (8:2 toluene : ethyl acetate) gave one major fraction (0.10g, 44%) identified as 3β-acetoxy-16-benzylidene-17-oxo-

-17a-oxa-5α-androstane 170 : mp 200-202° (methanol); $[\alpha]_D$ - 88°(C, 0.01); λmax (EtOH) 219 and 282 nm; νmax (film) 1738 (ester C=0), 1710 and 1610 (α,β-unsaturated lactone), 1585 and 1590 (Ar. C=C), 1240 and 1020 cm^{-1}; δ 7.88 (nt, J ~ 1.5 Hz 1H, benzylidene-H), 7.46 (m, 5H, Ar.-H), 4.65 (m, 1H, $C_3\alpha$-H), 2.03 (s, 3H, ester-H), 1.32 (s, 3H, 18-H), 0.81 (s, 3H, 19-H): MS 436.2622(M, $C_{28}H_{36}O_4$), calc. M, 436.2617

Anal. $C_{28}H_{36}O_4$: calc. % :

C, 77.03 ; H, 8.31

Found 76.7 ; 8.65

45. 3β-Hydroxy-16-benzylidene-17-oxo-17a-oxa-D-homo-5α-androstane (171).

Hydrolysis of the benzylidene lactone 170 (0.07g, 0.16 mmoles) with potassium hydroxide (0.2g) in methanol (40 ml) under reflux for 1 hr. gave 171 (0.04g, 63%) on chromatographic separation (6 : 4, toluene : ethyl acetate) : mp 120-122° (methanol and water); $[\alpha]_D$ - 128° (C, 0.01); λmax (EtOH) 218 nm (ε = 9, 075) and 281 nm (ε = 16,019); νmax (film) 3600-2500 (acid-OH), 1710 and 1616 (conj. lactone), 1580 and 1498 (Ar.- C=C), 1045, 1020, and 770 cm^{-1}; δ 7.88 (nt J ~ 1.5 Hz, 1H, benzylidene-H), 7.43 (m, 5H, Ar.-H), 3.62 (m, 1H, $C_3\alpha$-H), 1.3 (s, 3H, 18-H), 0.78 (s, 3H, 19-H); MS 394.2504(M, $C_{26}H_{34}O_3$), calc. M, 394.2508.

46. Baeyer-Villiger oxidation of 3β-acetoxy-16-benzyl-16-phenylthiomethyl-5α-androstan-17-one (174) with trifluoroperacetic acid.

3β-Hydroxy-16-benzylidene-5α-androstan-17-one 127a (0.30 g, 0.88 mmoles) was added to a mixture of thiophenol (0.5 ml) and n-butyl-lithium (2.5 ml) in tetrahydrofuran (25 ml) at 0°. The reaction was stirred overnight under nitrogen (22 hr.) and quenched with water. Extraction into ether and chromatographic separation (6:4, ether : 60/80 petrol) gave one major fraction (0.197g, 51%), a mixture of isomers; νmax 3600-3200 (OH), 1740 (ketone

C=0); MS (LR) 379 (M -SPh), (M, $C_{32}H_{40})_2S_1$).

Acetylation of the hydroxythiol adduct with acetic anhydride (10 ml) in pyridine (50 ml) gave 3β-acetoxy-16-benzyl-16-phenylthiomethyl-5α-androstan-17-one 174 (0.196g, paste) on extraction with ether: νmax 1740 (ketone C=0), 1730 (ester C=0), 1600 (Ar. C=C), 1245, and 1030 cm^{-1}; δ 60MHz 7.2 (m, Ar.-H), 6.35 (nm, benzylic methine), 4.65 (m, $C_3\alpha$-H) and 2.0 (s, ester-H).

Oxidation of the ketone 174 under Emmons conditions with trifluoroperacetic acid led to an intractable mass.

47. Reaction of Androstan-trimethylsilyl enol ether (178) with butyraldehyde.

Diisopropylamine (0.23g, 2.27 mmoles) and n-butyl-lithium (1.2 ml, 2.27 mmoles) were added to tetrahydrofuran (20 ml) at 0° and stirred under nitrogen for ¼ hr. 3β-Hydroxy-5α-androstan-17-one 126a (0.30g, 1.03 mmoles) was added to the LDA solution followed by chlorotrimethylsilane[68] (1 ml) and triethylamine (5 ml). The mixture was stirred overnight (0° - 10°C, 22 hr.) and partitioned between pentane (250 ml) and cold aqueous sodium bicarbonate with which it was washed (3x), dried and evaporated to give disilyl ether 178 in quantitative yield as a paste: νmax 1620 (enol C=C); δ 4.3 (nm, vinyl-H) 3.45 (m, $C_3\alpha$-H), 0.81 (s, 18-H) and 19-H), 0.1 and 0.19 (2s - $OSiMe_3$).

A cross aldol[66,67] attempt between the trimethylsilyl enol ether 178 (0.45g, 1.03 mmoles), butyraldehyde (0.11 ml, 1.24 mmoles) and titanium tetrachloride (0.14 ml), 1.24 mmoles) in dichloromethane (20 ml) at -78° for 1 hr. did not show the expected product 181 on extraction with ether. Hydrolysis of the crude product in refluxing methanol followed by acetylation gave the ketone 126, which was the acetylated product of the starting material 126a.

Table VII

^{13}C Chemical shifts data for steroids

Compd	*C 1	2	3	4	5	6	7	8	9	10	11	12
127a	37.0	31.2	71.3	38.2	45.1	28.5	31.8	34.9	54.7	35.9	20.7	31.6
128a	37.1	27.9	73.9	34.4	45.2	28.8	32.2	35.2	55.0	36.2	21.0	31.5
130a	37.0	27.8	73.8	34.4	45.1	28.6	31.5	35.3	54.6	36.1	20.6	31.1
130a	37.1	27.8	73.8	34.4	45.1	28.6	31.8	34.9	54.8	36.2	20.7	31.3
137a	37.1	27.8	73.9	34.4	45.1	28.7	31.3	34.7	54.8	36.1	20.7	32.7
137b	37.1	27.9	73.9	34.4	45.2	28.7	31.3	34.7	55.1	36.1	20.6	32.1
						B						
1	38.8	22.2	26.9	29.1	47.2	29.1	32.5	35.5	55.1	36.4	20.5	39.0
2	38.8	22.3	26.9	29.1	47.2	29.1	32.5	35.5	55.0	36.5	20.6	39.3
3	37.1	31.6	71.2	38.2	44.9	28.8	32.5	35.9	54.7	35.6	21.3	38.9
4	36.9	27.6	73.5	34.1	44.7	28.7	32.4	35.9	54.6	35.6	21.3	38.9
5	36.9	31.4	70.9	38.0	44.8	28.4	30.9	35.0	54.4	35.6	20.5	31.6
6	36.9	27.7	73.6	38.1	139.9	121.8	31.5	31.5	50.1	36.7	20.4	30.8
7	154.3	127.7	185.6	124.8	165.3	32.1	31.9	36.0	60.9	42.2	206.9	50.4

Chemical shifts in parts per million, relative to Me_4Si. Solvent [a] $CHCl_3$, [b] $CDCl_3$, [c] CD_2Cl_2

B - Values taken from J.W.Blunt and J.B.Stothers, Organic Magnetic Resonance 9 (8), 439 (1977).[85]

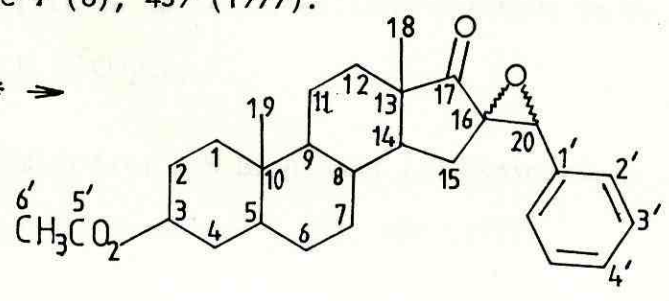


Table VII (continued)

	^{13}C Chemical shift data for steroids													
	13	14	15	16	17	18	19	20	1'	2'	3'	4'	5'	6'
127a	47.7	49.7	29.4	135.9	209.9	14.5	12.4	133.1	136.4	129.1	130.5	129.3		
128a	48.0	50.0	29.7	135.3	209.7	14.7	12.4	132.8	136.8	129.1	130.8	129.6	170.7	21.5
130a	48.1	48.7	26.1	67.1	215	14.3	12.4	63.1	134.7	126.7	130.0	128.8	169.8	21.5
130a	48.3	47.1	24.7	67.2	215.0	14.4	12.4	62.6	135.4	127.1	128.9	128.9	170.8	21.5
137a	48.5	47.7	28.2	79.8	218.5	13.7	12.4	44.8	136.8	128.6	131.0	127.2	170.8	21.5
137b	47.8	46.3	28.2	79.8	218.5	15.6	12.4	43.7	136.4	128.8	130.9	127.4	170.8	21.5
	B													
1	41.9	52.3	37.3	71.8	52.2	18.8	12.3							
2	40.3	54.3	37.3	71.9	51.5	19.1	12.3							
3	40.8	54.5	25.5	20.5	40.4	17.6	12.4							
4	40.8	54.5	25.5	20.5	40.5	17.6	12.3						169.9	21.3
5	47.7	51.4	21.8	35.8	220.8	13.8	12.3						170.2	21.4
6	47.4	51.6	21.9	35.8	220.6	13.5	19.4							
7	50.1	49.8	21.7	35.9	215.7	14.8	19.0							

Chemical shifts in parts per million relative to Me_4Si. Solvent [a] $CHCl_3$, [b] $CDCl_3$, [c] CD_2Cl_2.

B - Values taken from J.W.Blunt and J.B.Stothers, Organic Magnetic Resonance 9 (8), 439 (1977).[85]

Table VII (continued)

Key to Compounds

127a	3β-Hydroxy-16-benzylidene-5α-androstan-17-one[b]
128a	3β-Acetoxy-16-benzylidene-5α-androstan-17-one[b]
130a	3β-Acetoxy-16α-20-epoxy-20-phenyl-5α-androstan-17-one[c]
130a	3β-Acetoxy-16β-20-epoxy-20-phenyl-5α-androstan-17-one[c]
137a	3β-Acetoxy-16β-benzyl-16α-hydroxy-5α-androstan-17-one[c]
137b	3β-Acetoxy-16α-benzyl-16β-hydroxy-5α-androstan-17-one[c]

B

1	5α-Androstan-16α-ol[a]
2	5α-Androstan-16β-ol[a]
3.	5α-Androstan-3β-ol[a]
4	5α-Androstan-3β-yl-acetate[a]
5.	3β-Hydroxy-5α-androstan-17-one[a]
6	3β-(Acetyloxy)androst-5-ene-17-one[a]
7	Androsta-1,4-diene-3,11,17-trione[a]

TABLE VIII MASS SPECTRA

Comp'd	Important Fragment ions (% of Base Peak)	Composition	Obs.mass	Calc.mass
71	M (100%, BP)	$C_{19}H_{24}O_3$	300.1724	300.1726
72	M (70%)	$C_{20}H_{24}O_4$	328.1674	328.1675
	M-$C_4H_5O_3$ (BP)	$C_{16}H_{19}O$	227.1442	227.1436
75	M (BP)	$C_{20}H_{24}O_3$	312.1725	312.1725
77	M (BP)	$C_{20}H_{26}O_3$	314.1882	314.1881
76	M (97%)	$C_{26}H_{30}O_3S$	422.1929	422.1916
	M-$C_{10}H_{11}O_2S$ (BP)	$C_{16}H_{19}O$	227.1429	227.1435
	M-$C_{19}H_{23}O_3$ (14%)	C_7H_7S	123.0266	123.0268
100	M (BP)	$C_{22}H_{28}O_3$	340.2039	340.2039
	M-$C_6H_8O_2$ (50%)	$C_{16}H_{20}O$	228.1512	228.1514
122	M (86%)	$C_{27}H_{44}O_2$	400.3347	400.3341
	M-$C_{11}H_{23}$ (BP)	$C_{16}H_{21}O_2$	245.1533	245.1541
123	M (53%)	$C_{29}H_{50}O_2S$	462.3535	462.3531
	M-CH_3 (4%)	$C_{28}H_{47}O_2S$	447.3261	447.3297
	M-C_2H_5S (24%)	$C_{27}H_{45}O_2$	401.3425	401.3419
	M-C_2H_6S (23%)	$C_{27}H_{44}O_2$	400.3337	400.3341
	M-$C_8H_{15}O_2S$ (BP)	$C_{21}H_{35}$	287.2738	287.2738
124	M (33%)	$C_{33}H_{50}O_2S$	510.3557	510.3531
	M-$C_{17}H_{27}S$ (12%)	$C_{16}H_{23}O_2$	247.1714	247.1698
	M-$C_{24}H_{42}$ (BP)	$C_9H_8O_2S$	180.0245	180.0245

MASS SPECTRA

Comp'd	Important Fragment ions % of Base Peak	Composition	Obs.mass	Calc.mass
129b	M (BP)	$C_{25}H_{38}O_3$	386.2819	386.2821
	M-$C_9H_{15}O_3$ (27%)	$C_{16}H_{23}$	215.1803	215.1800
130a	M (52%)	$C_{28}H_{36}O_4$	436.2610	436.2614
	M-$C_{12}H_{13}O_4$ (56%)	$C_{16}H_{23}$	215.1797	215.1800
(α-epoxide)	M-$C_{18}H_{28}O_2$ (51%)	$C_{10}H_8O_2$	160.0530	160.0524
	M-$C_{20}H_{30}O_3$ (BP)	C_8H_6O	118.0426	118.0419
130a	M (41%)	$C_{28}H_{36}O_4$	436.2609	436.2614
	M-$C_{12}H_{13}O_4$ (55%)	$C_{16}H_{23}$	215.1799	215.1799
(β-epoxide)	M-$C_{18}H_{28}O_2$ (14%)	$C_{10}H_8O_2$	160.0516	160.0524
	M-$C_{20}H_{30}O_3$ (BP)	C_8H_6O	118.0428	118.0427
137a	M (5%)	$C_{28}H_{38}O_4$	438.2767	438.2770
	M-C_7H_7 (4%)	$C_{21}H_{31}O_4$	347.2198	347.2222
	M-C_8H_7O (19%)	$C_{20}H_{31}O_3$	319.2266	319.2273
(α-hydroxy)	M-$C_{12}H_{14}O_4$ (BP)	$C_{16}H_{24}$	216.1880	216.1878
137b	M (7%)	$C_{28}H_{38}O_4$	438.2789	438.2770
(β-epoxide)	M-$C_{12}H_{14}O_4$ (BP)	$C_{16}H_{24}$	216.1882	216.1878
142	M (BP)	$C_{29}H_{38}O_5$	466.2706	466.2719
	M-$C_{18}H_{28}O_2$ (87%)	$C_{11}H_{10}O_3$	190.0634	190.0630
	M-$C_{20}H_{30}O_3$ (25%)	$C_9H_8O_2$	148.0531	148.0524
	M-$C_{21}H_{31}O_3$ (1%)	$C_8H_7O_2$	135.0454	135.0446
145	M (~ 1%)	$C_{29}H_{38}O_6$	482.2661	482.2668
	M-$C_{21}H_{31}O_4$ (BP)	$C_8H_7O_2$	135.0447	135.0446

MASS SPECTRA

Comp'd	Important Fragment ions (% Base Peak)	Composition	Obs.mass	Calc.mass
154d	M (NOT SHOWN)	$C_{32}H_{44}O_8$	-	
	M - $C_2H_4O_2$ (~ 1%)	$C_{30}H_{40}O_6$	496.2826	496.2825
	M - $C_{10}H_{11}O_3$ (~ 41%)	$C_{22}H_{33}O_5$	377.2323	377.2328
	M - $C_{22}H_{33}O_5$ (~ 12%)	$C_{10}H_{11}O_3$	179.0707	179.0708
	M - $C_{30}H_{40}O_6$ (~ 3%)	$C_2H_4O_2$	60.0204	60.0211
	M - $C_{24}H_{35}O_7$ (BP)	C_8H_9O	137.0607	137.0603
166a	M (27%)	$C_{28}H_{38}O_4$	438.2771	438.2770
	M - C_8H_7O (24%)	$C_{20}H_{31}O_3$	319.2294	319.2273
	M - $C_{21}H_{31}O_4$ (55%)	C_7H_7	91.0555	91.05547
	M - $C_{12}H_{15}O_4$ (BP)	$C_{16}H_{23}$	215.1807	215.1800
169	M (NOT SHOWN)	$C_{28}H_{37}BrO_4$	-	
	M - Br (BP)	$C_{28}H_{37}O_4$	437.2695	437.2691
	M - $C_{12}H_{13}BrO_4$ (68%)	$C_{16}H_{24}$	216.1880	216.1878
	M - $C_{18}H_{28}BrO_2$ (13%)	$C_{10}H_9O_2$	161.0590	161.0502
	M - $C_{21}H_{30}BrO_4$ (76%)	C_7H_7	91.0562	91.0528
171	M (73%)	$C_{26}H_{34}O_3$	394.2504	394.2508
	M - $C_{10}H_{11}O_3$ (BP)	$C_{16}H_{23}$	215.1805	215.1799
	M - $C_{16}H_{26}O$ (9%)	$C_{10}H_8O_2$	160.0537	160.0524
	M - $C_{17}H_{27}O_2$ (3%)	C_9H_7O	131.0497	131.0497

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