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Approaches to the synthesis of A-ring aromatic steroidal α -methylene lactones as potential anti-tumour agents

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APPROACHES TO THE SYNTHESIS OF
A-RING AROMATIC STEROIDAL α -METHYLENE LACTONES
AS POTENTIAL ANTI-TUMOUR AGENTS

BY

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A DOCTORAL THESIS

Submitted in partial fulfilment of the requirements for
the award of Doctor of Philosophy of the Loughborough University
of Technology.

December 1985.

^c by A.O. AKANNI, 1985.

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DEDICATION

In memory of my father,

SOLOMON AKANNI OLOYEDE

and

TO THE GLORY OF GOD

ACKNOWLEDGEMENTS

I wish to express my gratitude to my supervisor, Dr. B. A. Marples, for his guidance and encouragement throughout the course of this research.

My thanks go to Professor K. W. Bentley, the Head of Department, for providing the necessary facilities to carry out this work.

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I would also like to thank Mr. & Mrs. Bowen for the skilful typing and to the technical staff, M. Harris, G. Hamm, J. Kershaw and H. Madha for their technical assistance.

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May God bless you all.

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GLOSSARY

THF	Tetrahydrofuran
DME	Dimethoxyethane
pTSA	p-Toluene Sulphonic Acid
mCPBA	m-Chloroperbenzoic Acid
HMPT	Hexamethylphosphorus Triamide
DMSO	Dimethyl Sulphoxide
LDA	Lithium Di-isopropylamide
DIBAL	Di-isobutylaluminium Hydride
DMF	N,N-Dimethylformamide
DCC	Dicyclohexylcarbodiimide
NBS	N-Bromosuccinimide
DABCO	Diazobicyclo(2,2,2)octane

SUMMARY

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

An improved synthesis of 3,17 β -diacetoxy-estra-1,3,5(10)-trien-6-one 114, from 17 β -estradiol diacetate 113 is presented using chromium trioxide-3,5-dimethylpyrazole complex. The 3-acetoxy-6-ketone 114 was converted to the 3-benzyloxy-derivative 123 which, on reaction with diethyl cyanomethylphosphonate gave largely (E)-3-benzyloxy-6-cyanomethylene-estra-1,3,5(10)-trien-17 β -ol 136. Reduction and acid hydrolysis of the cyanomethylene compound 136 gave 3-benzyloxy-6-formylmethylene-estra-1,3,5(10)-trien-17 β -ol 138 which was allowed to react with α -(bromomethyl)acrylate and activated zinc to give the α -methylene lactone 200. Additionally, the 3-benzyloxy-6-ketone 123 was converted to (Z)-3-benzyloxy-6-methoxymethylene-estra-1,3,5(10)-trien-17 β -ol 132 by reaction with diphenyl(methoxymethyl)phosphine oxide and LDA. Treatment of 132 with acid gave 3-benzyloxy-6-formyl-estra-1,3,5(10)-trien-17 β -ol 127.

Estrone 72 was first converted to 16-hydroxymethylene estrone 73. Protection of the 16-hydroxymethylene function with butane thiol gave (E)-16-butyl^{thio}methylene estrone 153 which was reduced to the 17 β -hydroxy-derivative 154 and subsequent deprotection of 154 gave 16-formyl-3-hydroxy-estra-1,3,5(10),16-tetraene 155. Reaction of the aldehyde 155 with ethyl- α -(bromomethyl)acrylate and activated zinc gave the α -methylene lactone 198.

(vi)

Conversion of the 16-hydroxymethylene estrone 73 to (E)-16-methoxymethylene estrone 167 was followed by its reduction (NaBH_4) in the presence of CeCl_3 to give 16-methoxymethylene estradiol 168, which was deprotected by treatment with acid to give 16-formyl estradiol 158. Reaction of 158 with methyl α -(bromomethyl)acrylate gave the α -methylene lactone 199.

Acetylation of the 3-benzyloxy-6-ketone 123 afforded the 17 β -acetoxy-derivative 170 which was reduced to 17 β -acetoxy-3-benzyloxy-estra-1,3,5(10)-trien-6 α -ol 171. Reaction of the 6 α -alcohol 171 with allyl bromide gave the allyl ether 172 which was oxidised with OsO_4 - NaIO_4 to give the formylmethoxy-derivative 173. The formylmethoxy-derivative 173 was found to undergo a novel "retro-ene" reaction to give the 3-benzyloxy-6-ketone 170.

Cholesterol 180 was converted to the formylmethoxy-derivative 182 through the glycidyl ether 181. Similarly cholestanol 185 gave the formylmethoxy-derivative 188 through the allyl ether 186 and the glycidyl ether 187 respectively. The formylmethoxy-derivatives 188 and 182 did not undergo the "retro-ene" reaction observed for the estradiol formylmethoxy-derivative 173.

6-Methoxy-1-tetralone 189 was reduced to the alcohol 190 and then allowed to react with allyl bromide to give the allyl ether 191. Cleavage of the allyl ether 191 with OsO_4 - NaIO_4 gave the formylmethoxy-derivative 192 which was found to undergo the "retro-ene" reaction observed for the estradiol formylmethoxy-derivative 173.

I N T R O D U C T I O N

INTRODUCTION

Biological Background

Chemotherapy has long been essential in the management of cancer. However, the completely effective use of chemotherapeutic agents in cancer therapy is yet to be attained. Effectiveness of chemotherapeutic agents is based on their chemotherapeutic indices¹ which are linked to selective toxicity. Thus, to have an effective anti-tumour agent, it must be selectively toxic to the tumour cells leaving the host cells relatively unharmed. Such a concept of drug design and development is usually based on biochemical differences observed between the host and the invading cells.²

With cancer, the main biochemical difference that has been observed is the rapid rate of proliferation of cancer cells. However, this is not true for some cancer cells such as breast cancer which are known not to be rapidly proliferating.³ Moreover, many normal cells of the body such as bone-marrow, intestinal mucosa, skin epithelium and mucosa of the mouth are rapidly proliferating and at an even faster rate than some cancer cells.^{4,5} Hence, this difference alone is not sufficiently distinguishing for the development of very effective anti-tumour agents.

The recent oncogene theory⁶ has proposed the presence of genetic information determining the malignant behaviour of cells (i.e. the oncogene) in normal host DNA. This implies that all cells possess this genetic information for malignant behaviour and such oncogenes must be repressed. Carcinogenesis,

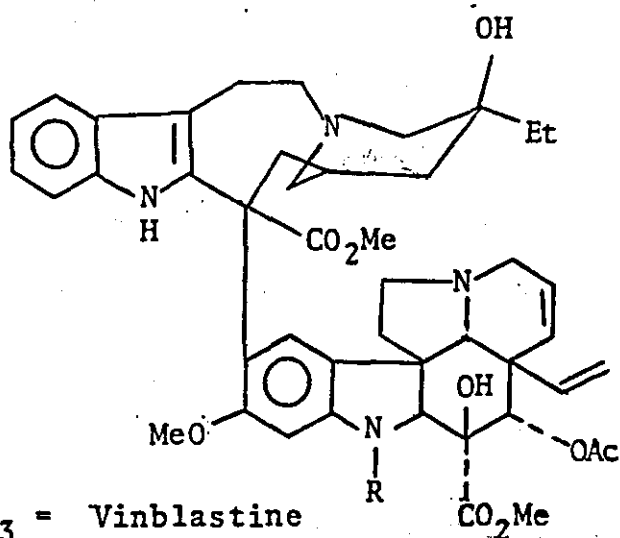
is therefore seen, in this case, as activation of latent oncogenes. This theory predicts the existence of reverse transcriptase (a RNA directed DNA polymerase) in tumour cells, as a biochemical difference from normal cells. However, this enzyme is known to be associated with non-oncogenic viruses and may also be found in normal cells.

Nevertheless, recent progress in molecular biology is providing powerful tools for examining the details of nucleic acid metabolism, and modulation of gene expression. Such techniques will undoubtedly have a major impact on studies of malignant cell metabolism in the near future.

On the current evidence, it would seem that chemotherapeutic agents based on such biochemical differences so far observed, might be effective on cancer cells (i.e. regression of cancer cells) but with attendant and unwanted side effects which could be very detrimental to the host. This notwithstanding, theoretically, it is possible to find among such agents one which could affect particular cancer cells more than the normal cells. This is evident from the fact that chemotherapy has continued to play a major role in cancer therapy. Currently, there are 30-40 anti-cancer drugs in clinical use.

Generally, anti-neoplastic agents can be classified as alkylating agents, anti-tumour antimetabolites (i.e. those that exert their action by enzyme inhibition), anti-tumour antibiotics (which intercalate with DNA) and various miscellaneous compounds⁷ such as the natural products, the Vinca alkaloids vinblastine 1 and vincristine 2, which have subsequently found an important role in cancer chemotherapy.⁸ The alkylating agents include

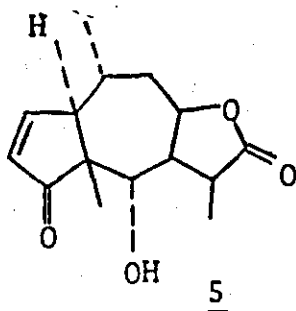
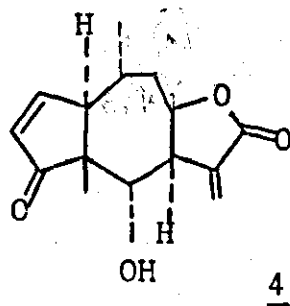
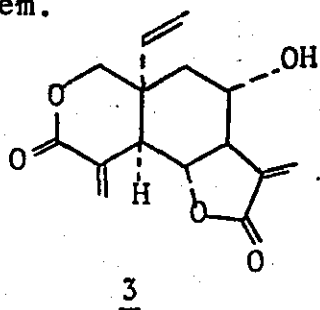
nitrogen mustards, nitrosoureas, triazenoimidazoles, hydrazine derivatives and methanesulphonium esters.



1 $\text{R} = \text{CH}_3$ = Vinblastine

2 $\text{R} = \text{CHO}$ = Vincristine

The discovery that sesquiterpene lactones and/or ketones such as vernolepin 3⁹, helenalin 4¹⁰ and phenolin 5⁴⁰ have cytotoxic effects against animal tumour systems *in vivo* and *in vitro* over a wide range of neoplasias has encouraged interest in them.



Those of particular interest contain the α -methylene lactone moiety, which combine simplicity in structure with requirements for significant cytotoxicity. Their cytotoxic action has been ascribed to a rapid Michael-type addition reaction of biological nucleophiles such as L-cysteine¹¹ or sulphhydryl containing enzymes, e.g. phosphofructokinase¹² and glycogen synthetase.¹³ However, the simple low molecular weight lactones have not been very successful *in vivo* primarily because of low permeability across cell membrane and lack of selectivity.

Danielli¹⁴ has pointed out that selectivity of action of a drug in general can be enhanced by a number of variables on which the drug's activity depends. These variables include:-

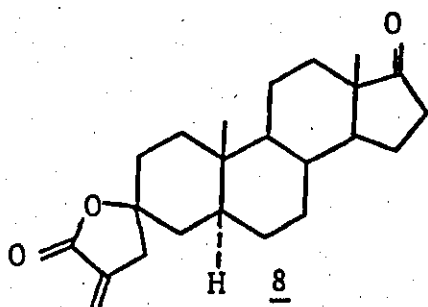
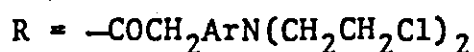
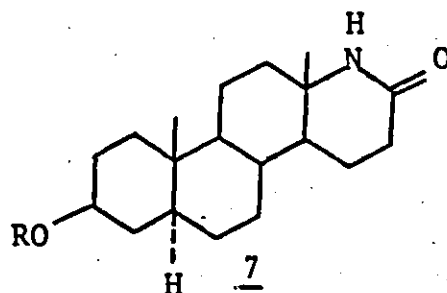
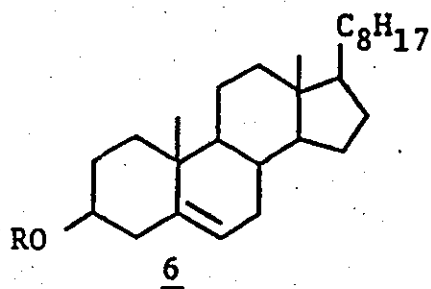
(a) the water-lipid partition coefficient which will affect transport characteristics and pharmacological disposition of the drug,

(b) chemical reactivity which will determine the persistence of the drug after administration, and

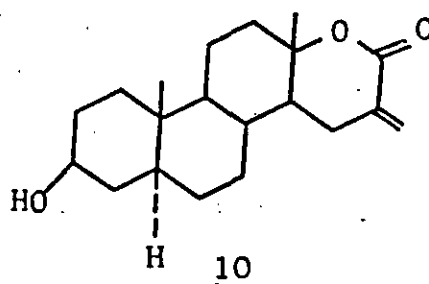
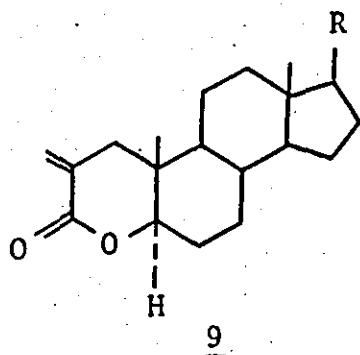
(c) potentiation by enzymic modification that will influence tissue specificity.

A new approach for obtaining selectivity of biologically active alkylating agents has evolved, involving the coupling of alkylating agents to biological carriers. In this form, the biological carrier could be serving a dual role, i.e. carrying the alkylating agents to target specific sites and also overcoming cell-membrane barriers (because of the increase in lipophilicity). In this regard, some steroidal alkylating agents have been synthesised and their activity evaluated

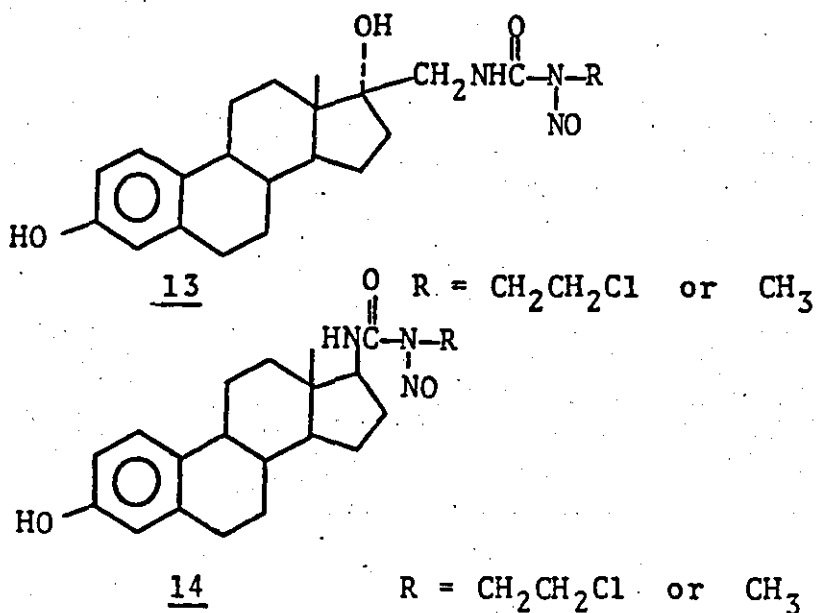
against specific cancer cells. These include steroidal mustard alkylating agents (e.g. 6¹⁵ and 7¹⁶) and the steroidal α -methylene lactone 8¹⁷. These have been found to have considerable cytotoxic effect against experimental tumours.



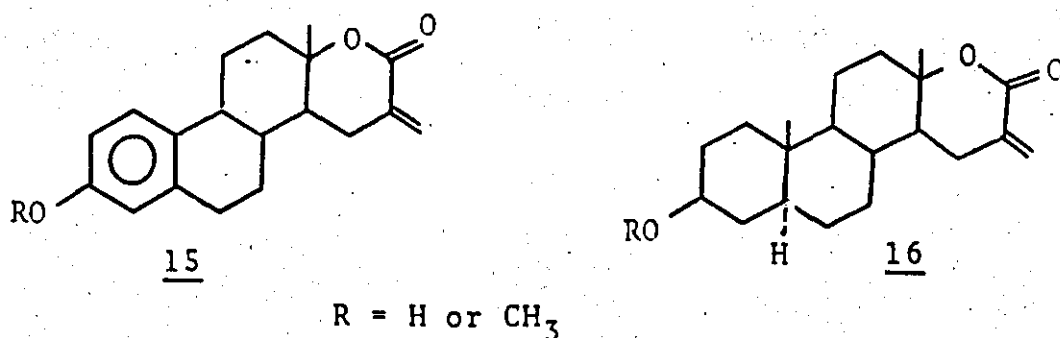
Also Dehal¹⁸ in these laboratories synthesised steroidal lactones 9 and 10 which have been found to be active against nasopharyngeal carcinoma (KB) cells in culture.



Lam²² synthesised steroidal nitrosoureas 13 and 14 with the hope that these would have affinity for the estrogen receptor. Although they were observed to have inhibitory activity against the growth of DMBA-induced rat mammary adenocarcinoma, their affinity for estrogen receptor is yet to be reported.

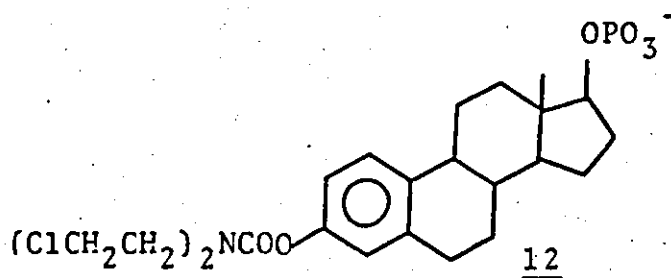
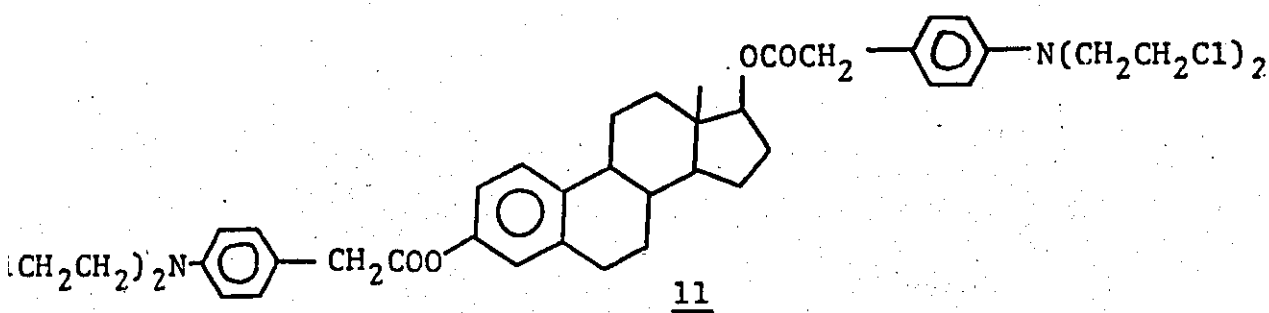


The synthesis of steroidal α -methylene lactones with the objective of having affinity for estrogen receptor and thus being both selective and specific has been studied by Chagonda²³ in these laboratories. The lactones 15 and 16 were synthesised and found to have high cytotoxicity on tissue culture HeLa S₃ cells but to have no affinity for estrogen receptor²⁴.



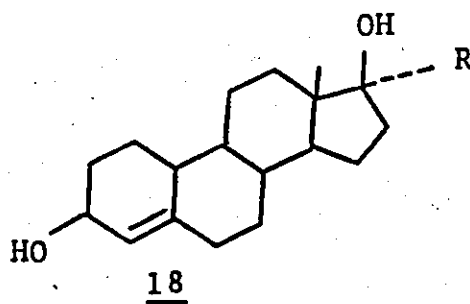
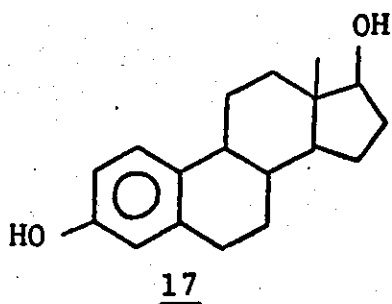
The discovery of estrogen receptors with specific binding affinity in human breast cancer¹⁹ has provided a modified approach in this field. Thus, the use of estrogen as biological carrier could be a step in the right direction. Hamacher²⁰ noted that the use of estrogen hormones as physiological carriers will have a good chance of increasing tumour cell selectivity of cytotoxic groups because of the following reasons: (a) A high proportion of human breast cancers contain estrogen receptors, (b) Estrogen hormone molecules show a high binding affinity to estrogen receptors, (c) The transport mechanism of carrier-receptor complexes could result in the accumulation of cytotoxic derivatives in the nucleus of target cells which is the potential site of action, particularly for alkylating agents.

In this regard, Witliff²¹ synthesised estradiol mustard 11 and estramustine 12. However, these were found to have very low affinity (1/10,000 of that of estradiol) for the estrogen receptor.



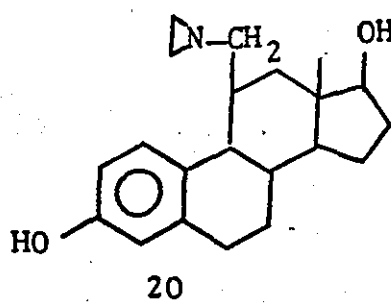
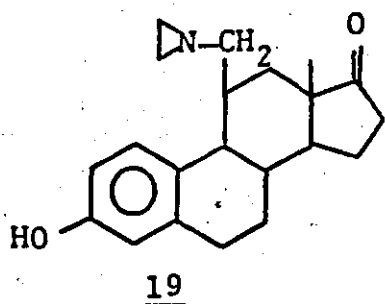
Structure - activity relationship studies on estrogens have highlighted certain important requirements for estrogen receptor binding. Schueler²⁵ noted that two hydrogen bonding groups or simply two hydrogen atoms activated by the inductive effect and held at an optimum distance of 8.55Å from one another were essential. Binding is optimal for 3,17β-dihydroxy derivatives.

Further work has shown this to be an over-simplification. Zeelen and Bergink²⁶ reported two additional factors namely hydrophobic bonding and π-complex formation with the aromatic ring, as essential for binding to ^{an}estrogen receptor. The importance of π-complex formation was demonstrated through the difference in the binding affinity observed between estradiol 17 and 19-norandrost-4-ene-3,17β-diol 18. Based on the binding affinity of estradiol (100%), 18 had a binding affinity of 5%.



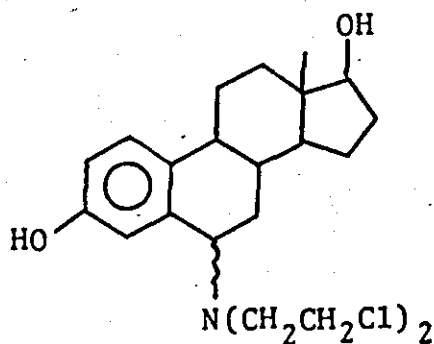
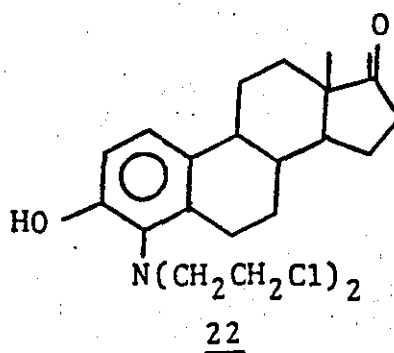
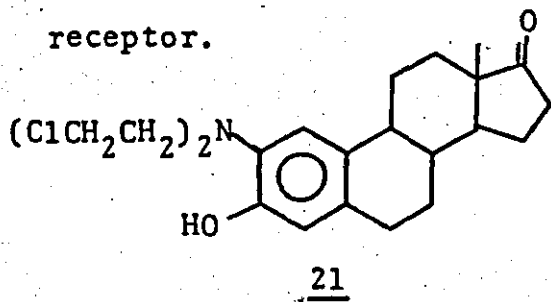
It therefore follows that in the design of anti-tumour agents with estrogen carrier, cognisance must be taken of the importance of the 3- and 17β-hydroxyl groups preferable for receptor binding. Moreover, the cytotoxic moiety to be attached must be at a position remote from both hydroxyl functions in order to

reduce the possibility of steric and electronic effects which might affect binding affinity. With this in mind, Zeelen²⁶ synthesised estradiol and estrone derivatives 19 and 20 which contain the aziridinomethyl residue at C-11.

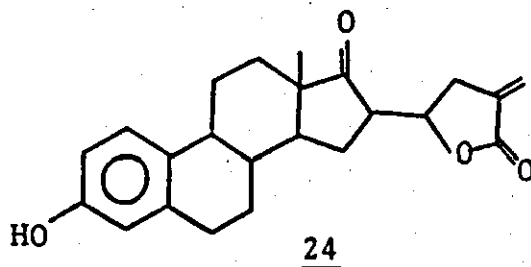


These have been found to have low binding affinity relative to estradiol, but high enough when compared with other estrogen derivatives synthesised as anti-tumour agents.

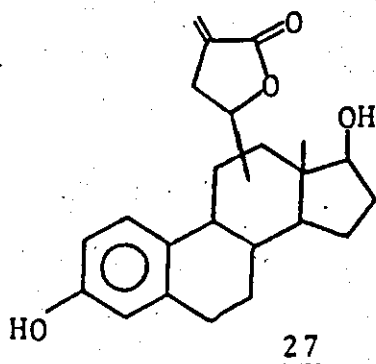
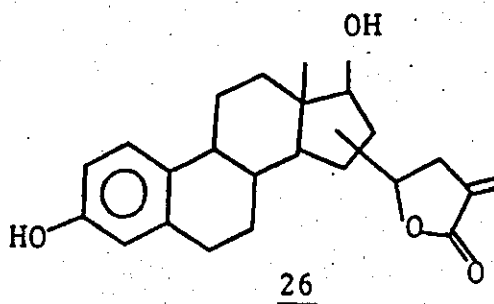
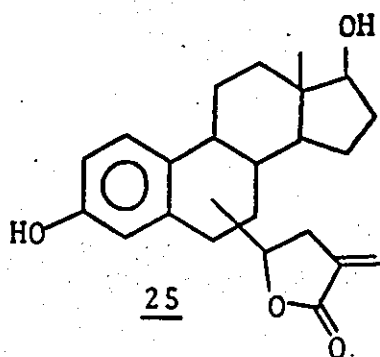
Hamacher²¹ has reported the synthesis of estrogenic N-mustards 21, 22 and 23 which have been found to bind to estrogen receptor.



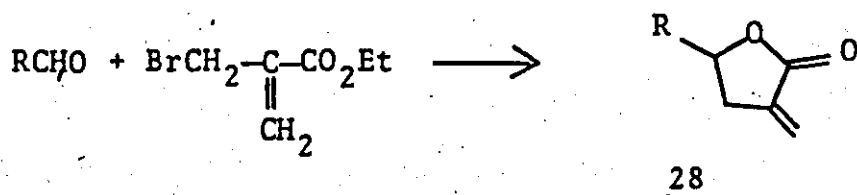
The work of Edge²⁷ in these laboratories led to the synthesis of 24, which it is hoped will have binding affinity for estrogen receptor as well as being cytotoxic.



A direct consequence of these observations is the desire to explore ways of attaching the α-methylene lactone moiety to 17β-estradiol with the ultimate goal of obtaining selective anti-tumour lactones. Since 17β-estradiol is a highly active estrogen, such compounds could have relatively high binding affinity and thereby be useful for treatment of hormone dependent tumours such as prostatic, breast or cervical cancer. Thus the main objective of this work is the synthesis of possible lactones of types 25, 26 and 27, in which the alkylating function would not significantly reduce the estrogen binding affinity.



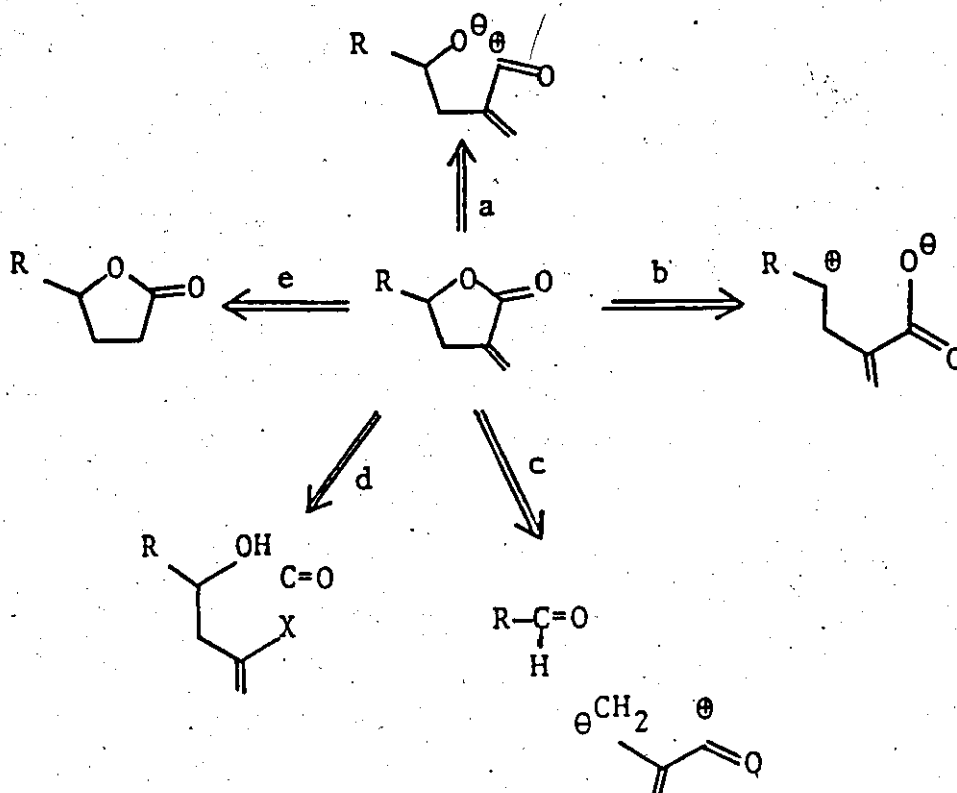
In all cases, it was proposed to synthesise aldehydic derivatives of estradiol and convert them to the α -methylene lactones via a Reformatsky-type reaction leading to α -methylene lactones 28.



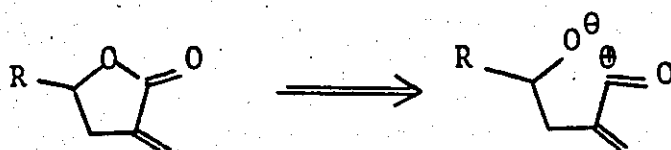
SYNTHETIC APPROACHES TO α -METHYLENE LACTONES

The extensive interests in the synthesis of α -methylene lactones, first initiated by Jones²⁸ has continued to grow due to the cytotoxicity of sesquiterpene lactones. The observation by Kupchan²⁹ on the structure-activity relationship studies of naturally occurring sesquiterpenes that the α -methylene- γ -lactone moiety is essential for significant cytotoxicity has further strengthened such interests. This has led to diversified synthetic approaches which have been extensively reviewed^{30,31}. However, of particular interest is the recent review of Hoffmann³² which contains excellent approaches adaptable to our synthetic objectives. Some of these methods will be highlighted.

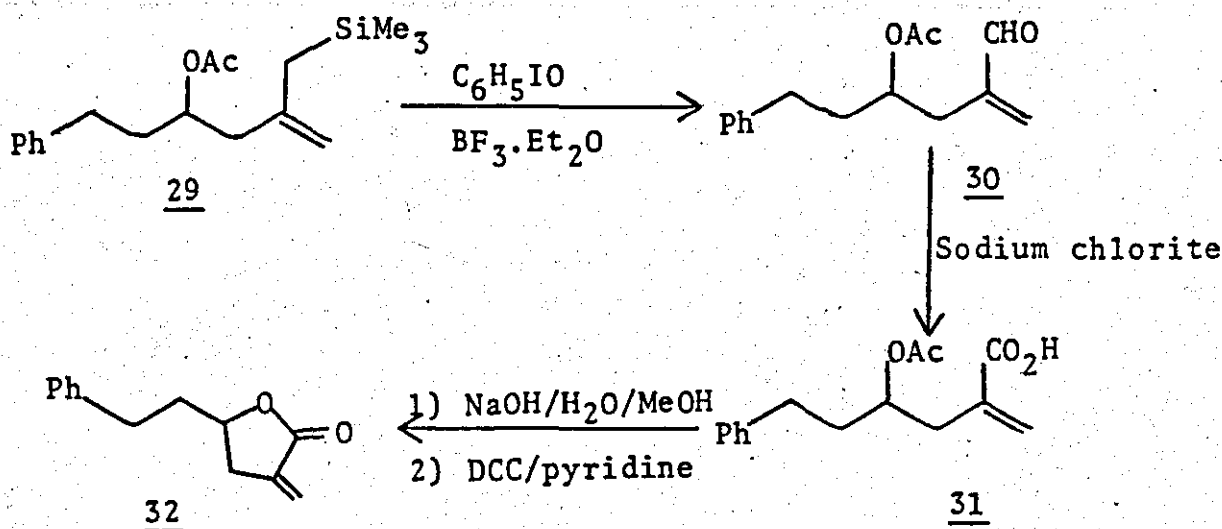
Using the retro-synthetic approach, five routes will be discussed as outlined below:-



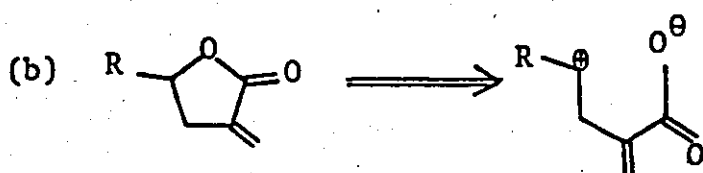
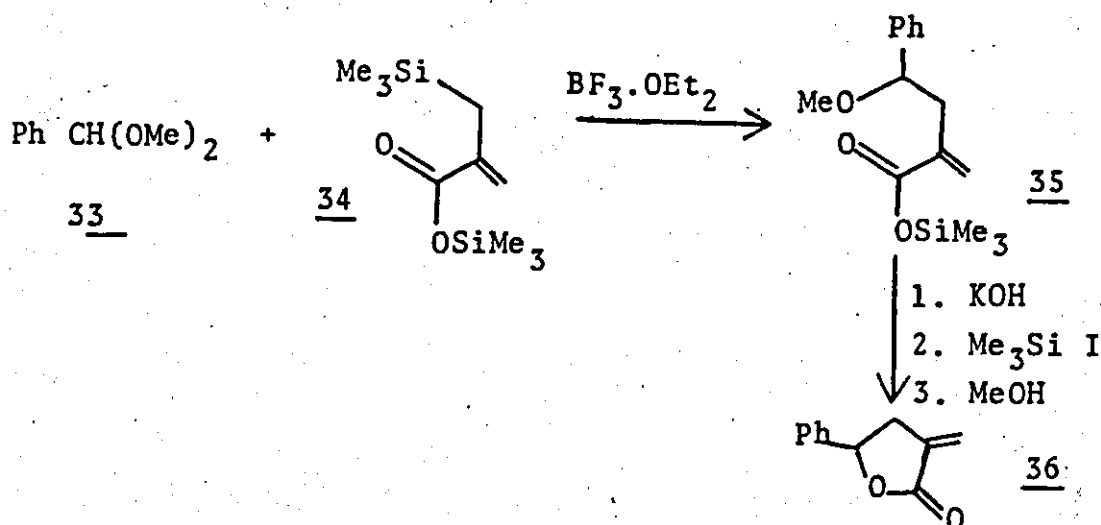
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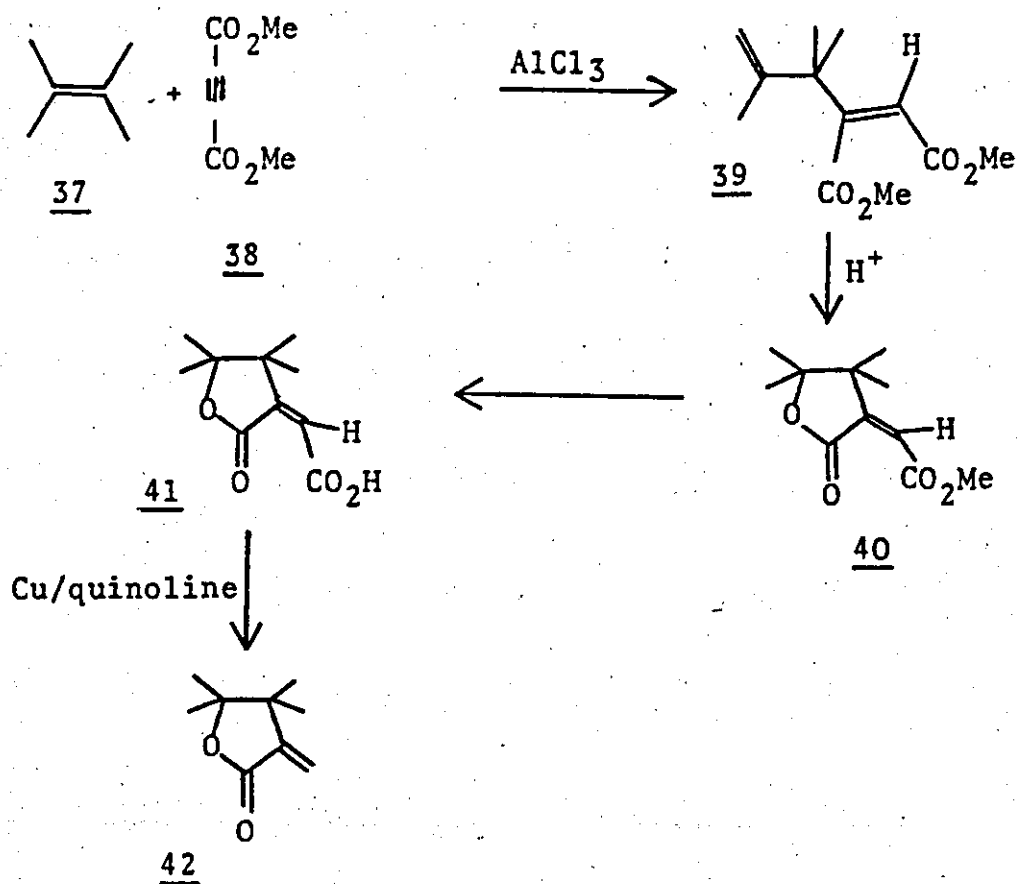
The first approach involves the cyclization of 4-hydroxy-2-methylene butanoic acids. Fujita *et al*³³ reported the use of allylsilane intermediates in the synthesis of α -methylene lactones. The method involved oxidative desilylation by use of iodosylbenzene to give an α,β -unsaturated aldehyde, 30. Oxidation of the aldehyde 30, with sodium chlorite gave the carboxylic acid 31. Alkaline hydrolysis of 31 followed by treatment with dicyclohexylcarbodiimide (DCC) in pyridine afforded the α -methylene lactone 32.



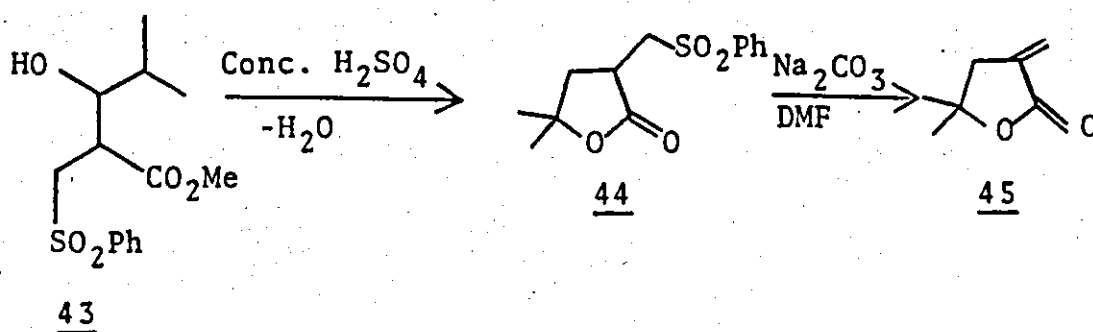
A similar approach was used to convert the dimethyl acetal of benzaldehyde 33 to the α -methylene lactone³⁴ 36, by reaction with the trimethylsilyl ester 34, and dealkylation of the product 35.

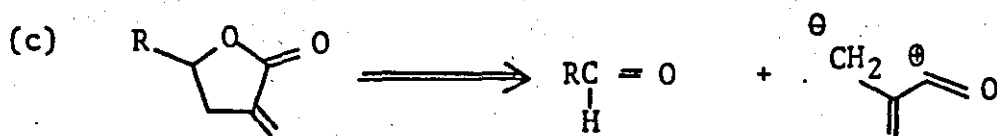


This route involves the cyclisation of 2-methylene-4-pentenoic acids. McCulloch³⁵ synthesised the α -methylene lactone 42 using this approach. The AlCl_3 -catalysed "ene" reaction between dimethyl-1-acetylene dicarboxylate 38 and the alkene 37, followed by acid-catalysed lactonization gave the lactone 40. Hydrolysis of this lactone 40 followed by decarboxylation with copper/quinoline gave the α -methylene lactone 42.



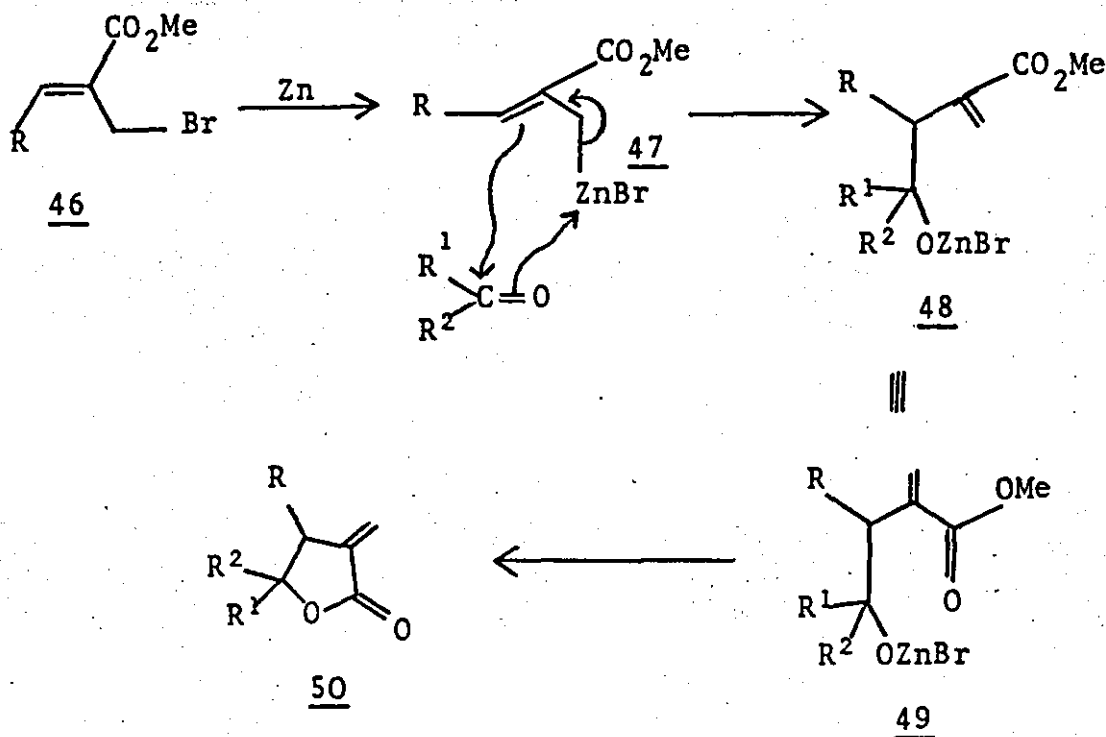
Shono *et al*³⁶ have successfully synthesised α -methylene lactones using this approach. Their method however, involved rather drastic conditions as indicated below in the conversion of the hydroxy ester sulphone **43** via the sulphone lactone **44** to the α -methylene lactone **45**.



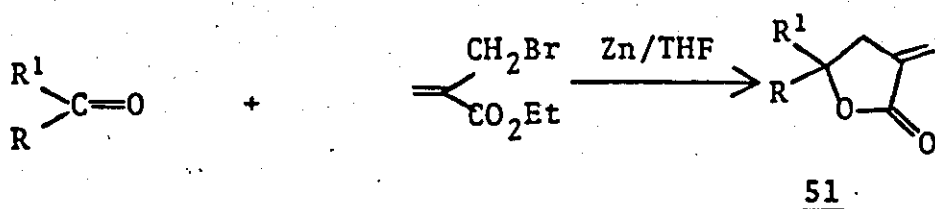


This employs the metal-promoted reaction of aldehydes and ketones with acrylates.

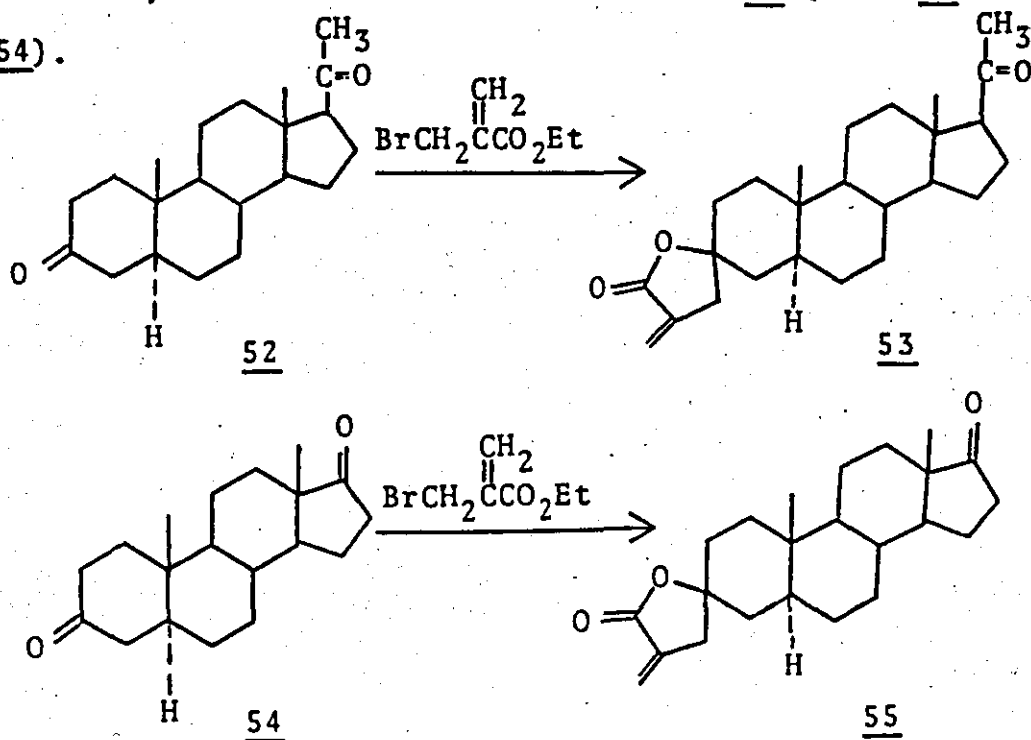
The reaction between α -(bromomethyl)acrylic esters and appropriate aldehydes or ketones in a Reformatsky-type reaction, better known as the Drieding³⁷ - Schmidt³⁸ reaction, has been widely reported in the synthesis of a variety of α -methylene lactones, including monocyclic and spiro- α -methylene lactones. The general scheme of the reaction is outlined below. It involved treatment of 2-bromomethyl-2-alkenoic ester with aldehyde or ketone to give the α -methylene lactone 50 via the organozinc intermediate 48.



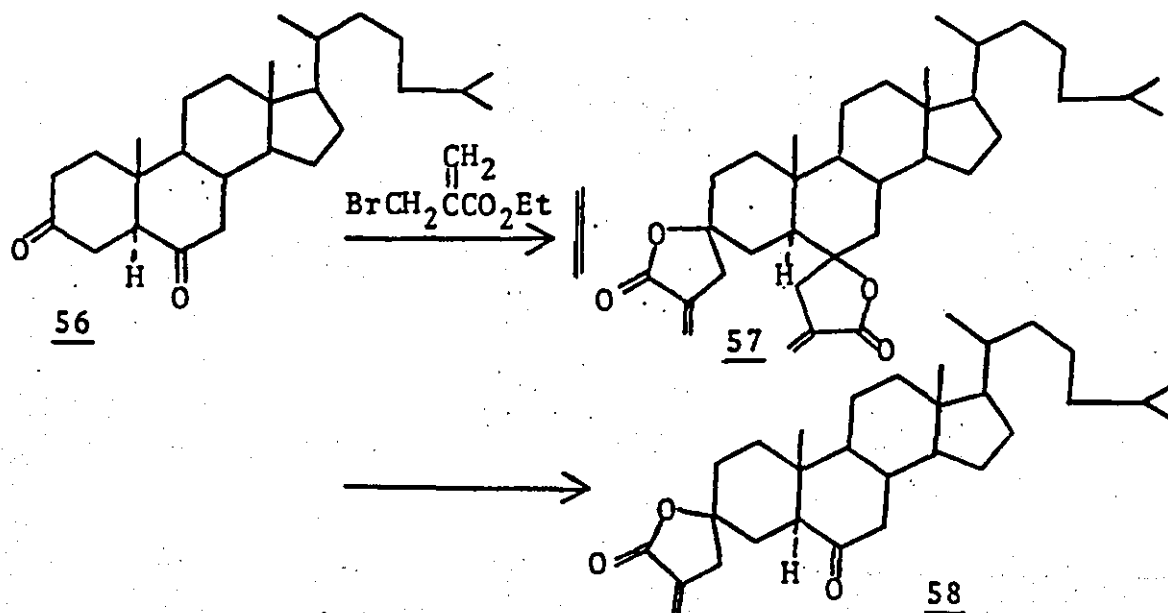
Benezra³⁹ in his studies of allergenic properties of α -methylene lactones synthesised a series of γ -mono-substituted and γ,γ -disubstituted α -methylene lactones using the Drieding - Schmidt reaction, by allowing appropriate aldehydes or ketones to react with ethyl α -(bromomethyl)acrylate as outlined below:-



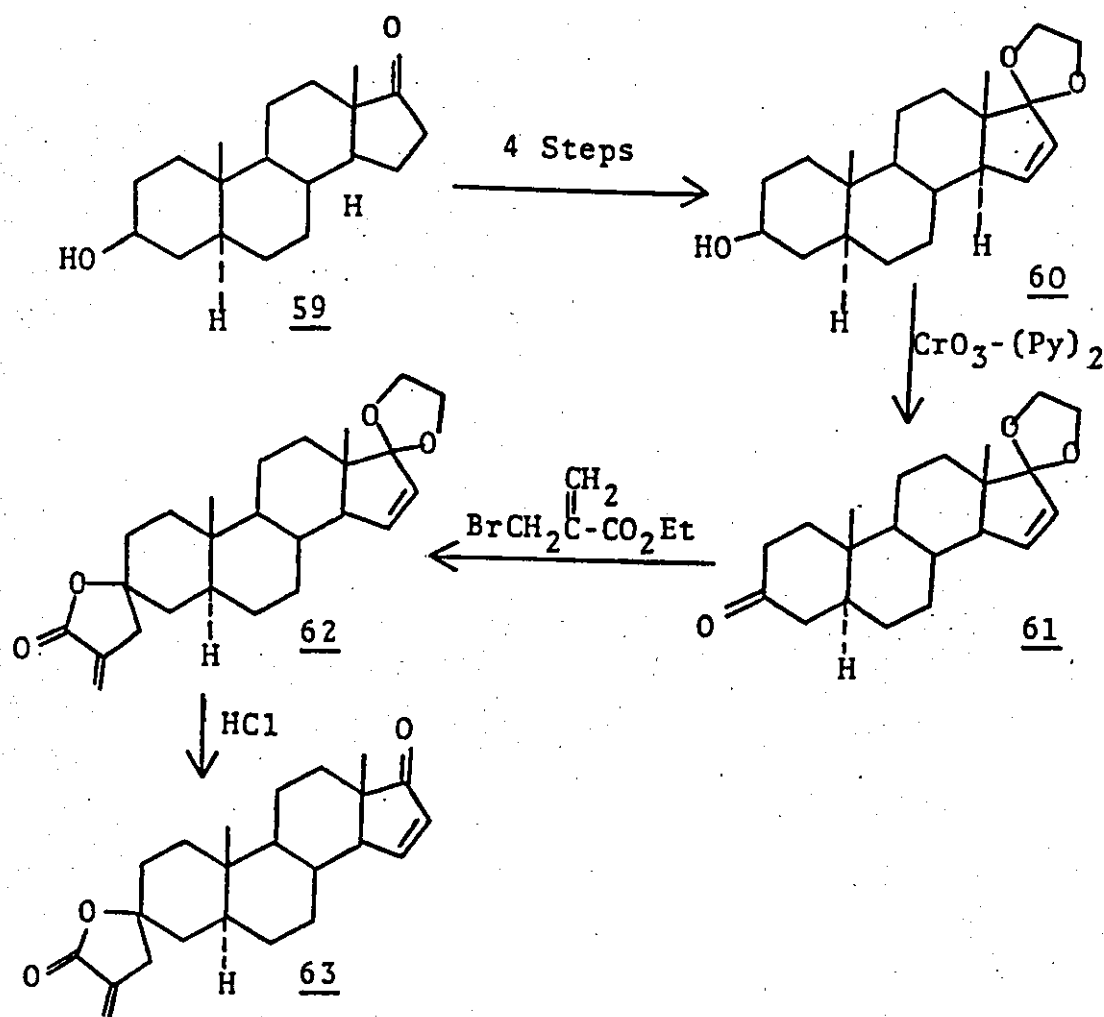
Application of the Drieding - Schmidt reaction in the synthesis of steroidal α -methylene lactones has been reported by Lee and co-workers.⁴⁰ They were able to synthesise novel steroidal α -methylene- γ -spiranolactones using ethyl α -(bromomethyl)acrylate and appropriate steroidal ketones. This has led to the synthesis of steroidal lactones 53 (from 52) and 55 (from 54).



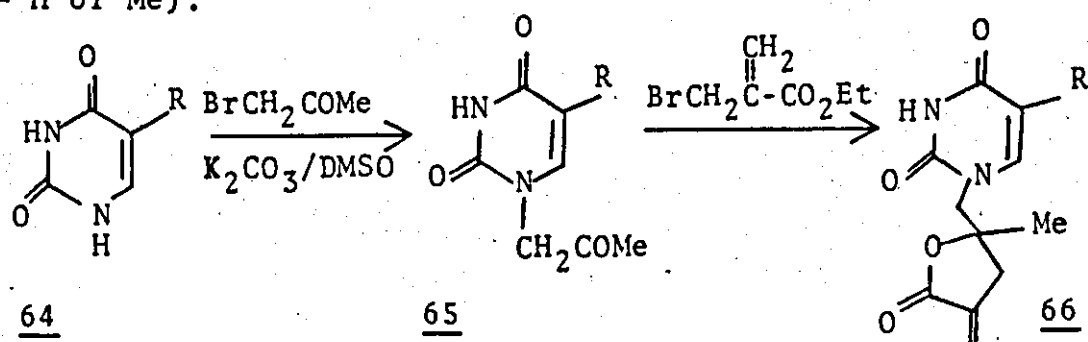
The bis-(α -methylene lactones) of both 52 and 54 could not be synthesised. Also attempts to synthesise the bis-lactone 57 were unsuccessful and only the mono-lactone 58 was obtained from 56.



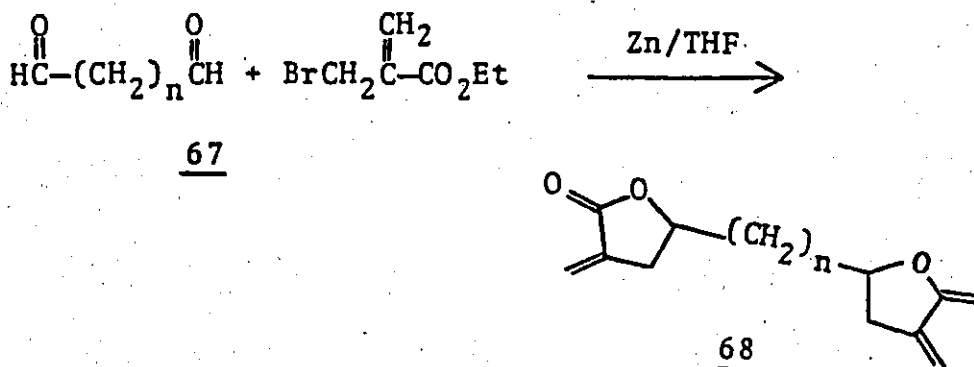
Other bi-functional analogues which contain, in addition to the α -methylene lactone, α,β -unsaturated cyclopentanone ring system were synthesised as shown in the scheme below. Thus 17-ethylenedioxy-5 α -androst-15-en-3 β -ol 60, was synthesised from 5 α -androstan-3 β -ol-17-one 59. Oxidation of 60 with chromium trioxide-pyridine complex gave 61. Subsequent reaction of 61 with ethyl α -(bromomethyl)acrylate gave the ketal lactone 62. Treatment of the latter with concentrated hydrochloric acid provided the bi-functional lactonic cyclopentenone 63.



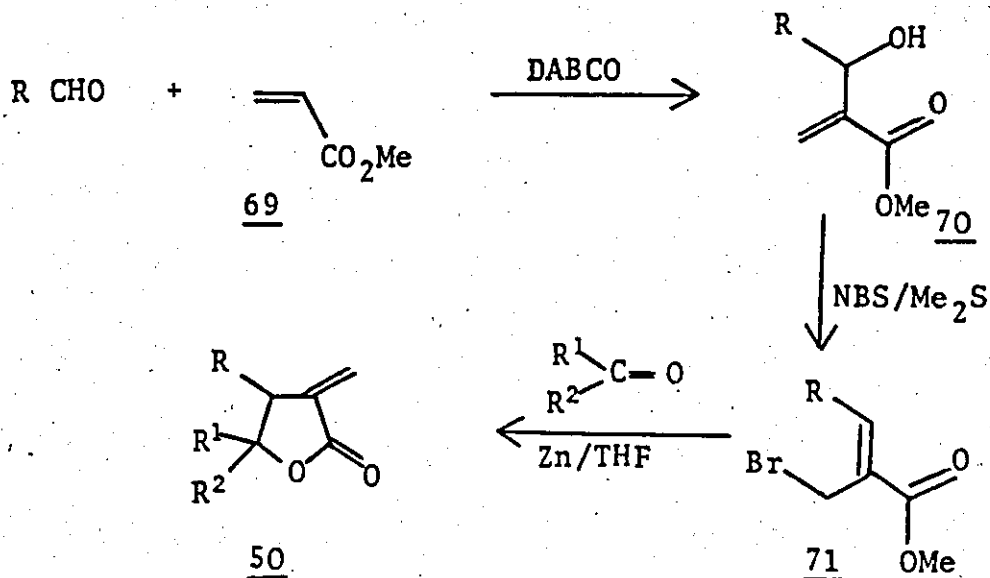
Lee^{40a} later used this approach for the synthesis of α -methylene lactones 66 ($\text{R} = \text{H}$ or Me) derived from uracil 64 ($\text{R} = \text{H}$) and thymine 58 ($\text{R} = \text{Me}$) through the derived ketones 65 ($\text{R} = \text{H}$ or Me).



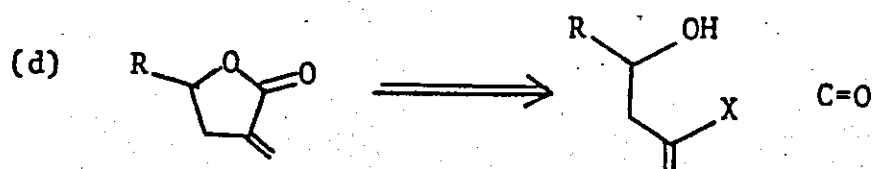
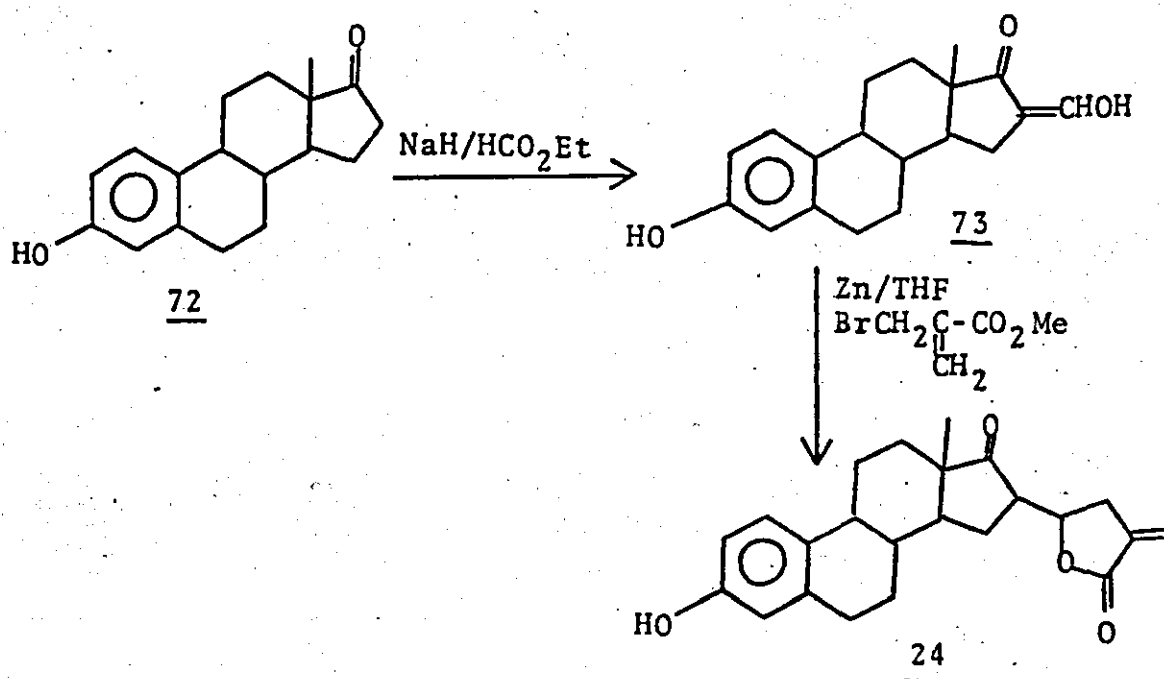
Cassady⁴¹ synthesised a series of open-chain bis(α -methylene- γ -lactones) 68 from dialdehydes 67.



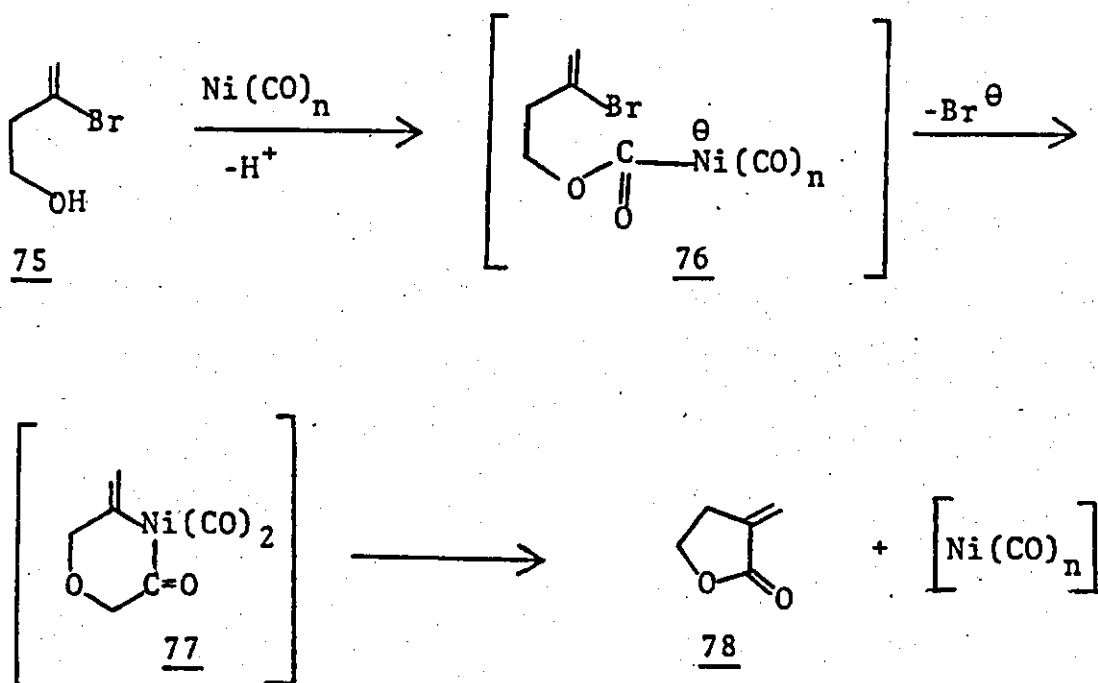
Hoffmann⁴²⁻⁴⁴ employed the coupling of aldehydes with acrylic esters in a DABCO (diazobicyclo{2,2,2}octane)-catalysed reaction. Subsequent reaction of the adduct 70, with NBS is accompanied by allylic rearrangement to give regioselectively and stereoselectively the (Z)-2(bromomethyl)-2-alkenoic esters 71. Zinc-induced coupling of 71 with ketones or aldehydes gave the β -substituted α -methylene lactones 50.



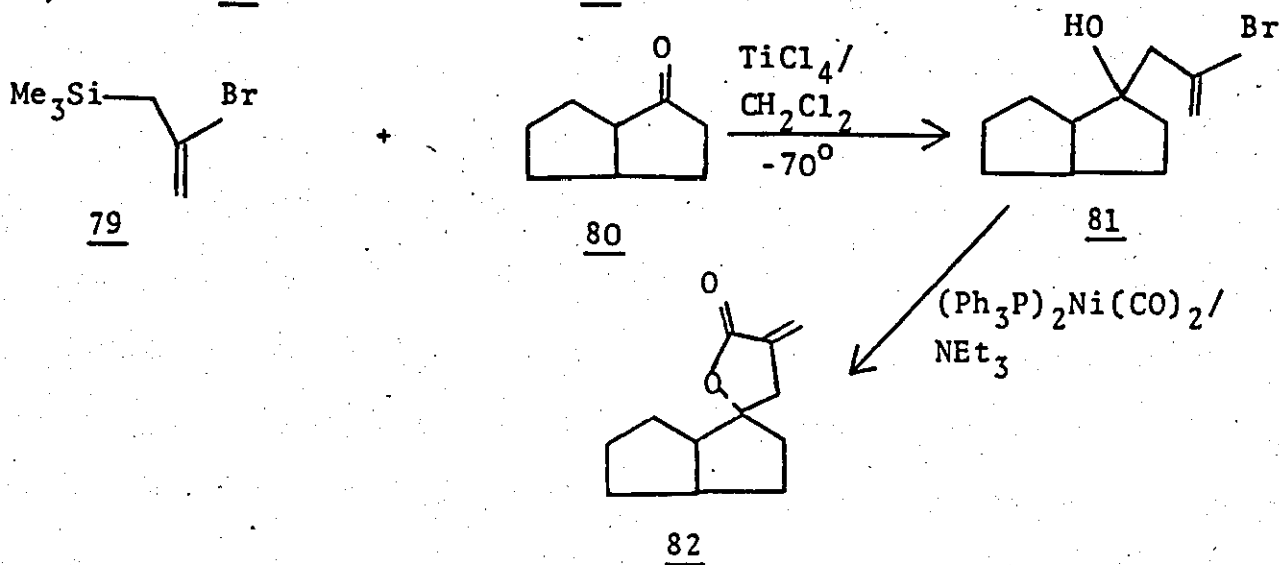
Recently, Edge⁴⁵ in these laboratories synthesised the steroidal lactone 24, using methyl α -(bromomethyl)acrylate and 16-hydroxymethylene estrone 73 in a Drieding - Schmidt reaction.



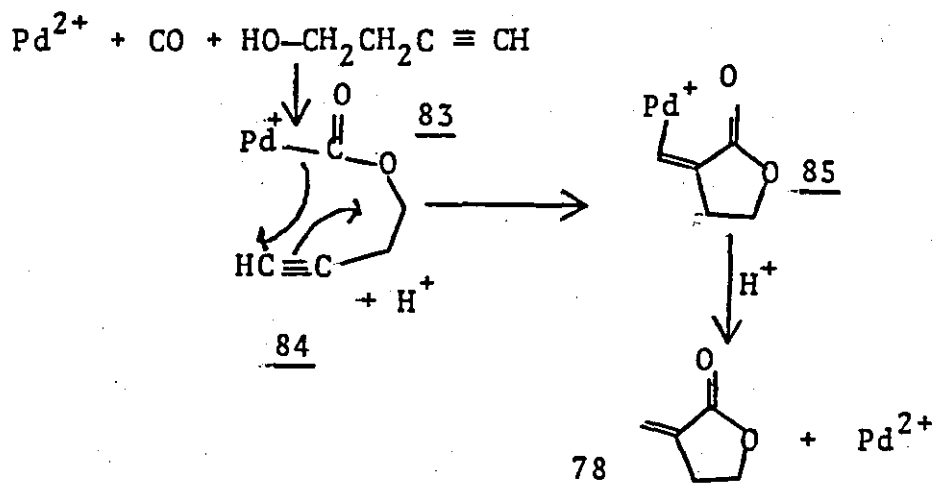
One method of achieving this involves carbonylation of 3-bromo-homoallylic alcohols which is the intramolecular version of the transitional metal-catalysed carbonylation described by Corey and Hegedus⁴⁶. Starting with 3-bromoallyl alcohol 75, Semmelhack and Brickner⁴⁷ synthesised the α -methylene lactone 78 as indicated below employing Ni(CO)₄ as catalyst. The reaction is believed to involve intermediates 76 and 77. The latter (77) extrudes Ni(CO)_n.



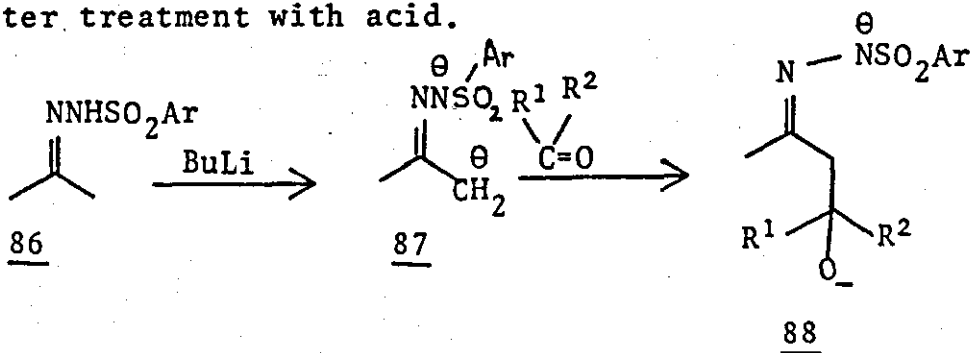
Similarly Trost⁴⁸ synthesised stereoselectively tricyclic spiro- α -methylene lactone **82**, in high yield via the bromohomoallylic alcohol **81** which was obtained by reaction of the bromoallylsilane **79** with the ketone **80**.

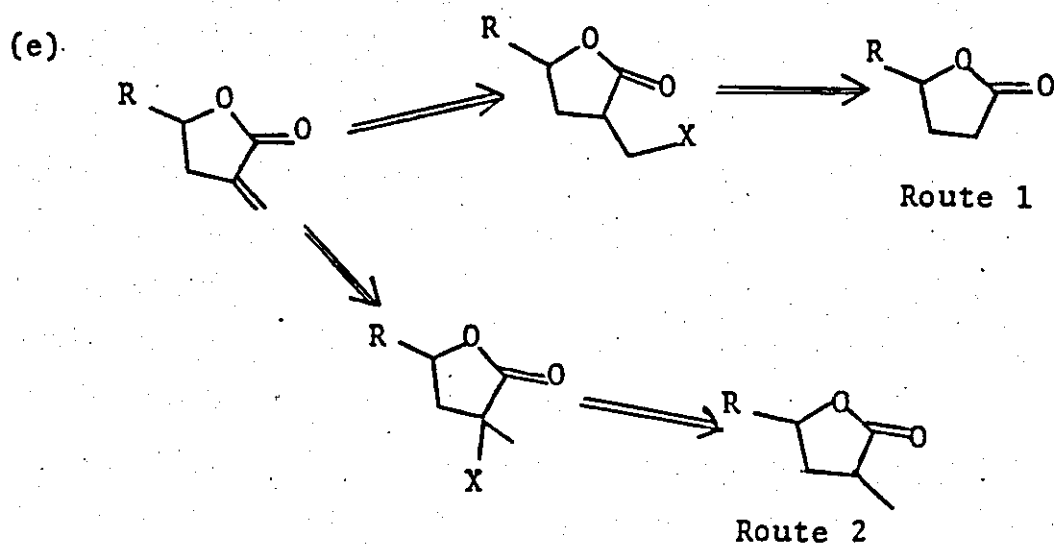
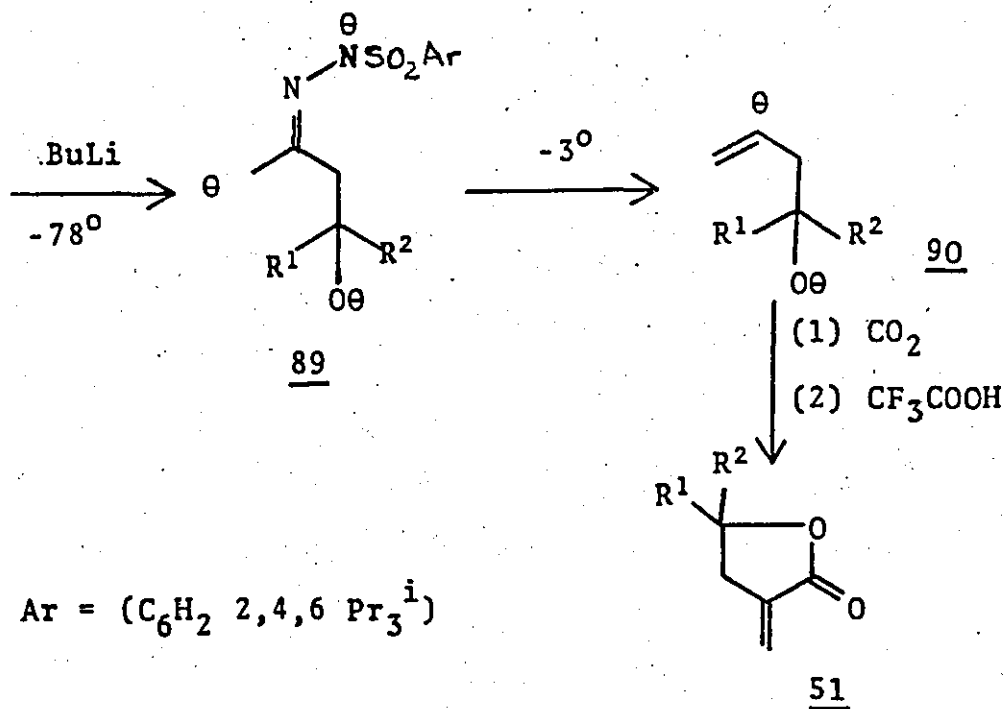


A related carbonylation procedure which employs a palladium-catalysed carbonylation of homopropargyl alcohol 83, has been used by Norton⁴⁹ to synthesise α -methylene lactones. A typical example, leading to the α -methylene lactone 78, is shown below and involves the intermediates 84 and 85.



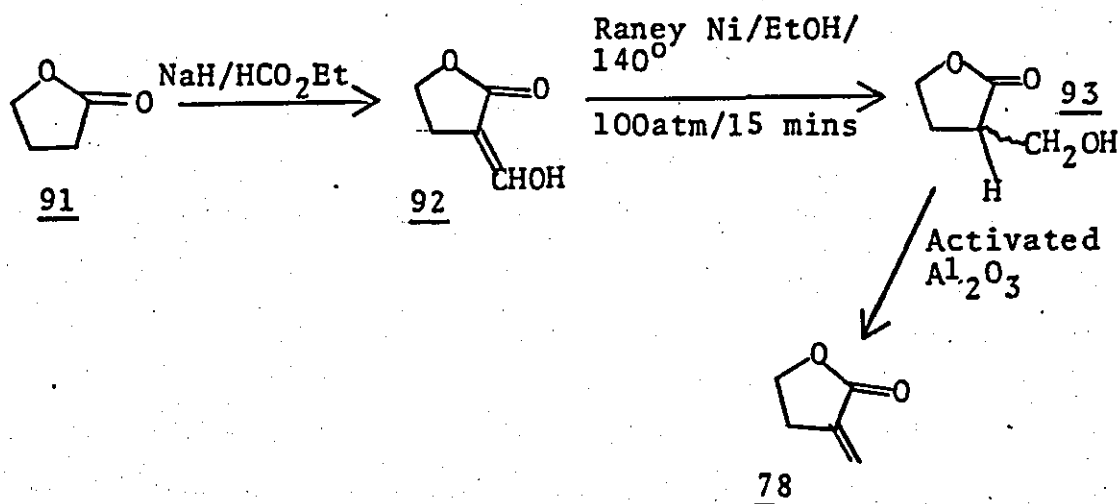
The Shapiro reaction has been employed to synthesise α -methylene lactones.⁵⁰ The bis-anion 87 is allowed to react with a ketone to afford the adduct bis-anion 88 which on reaction with further base, gave the tris-anion 89 which decomposes to the bis-anion 90. Carboxylation of 90 affords the α -methylene lactones 57 after treatment with acid.



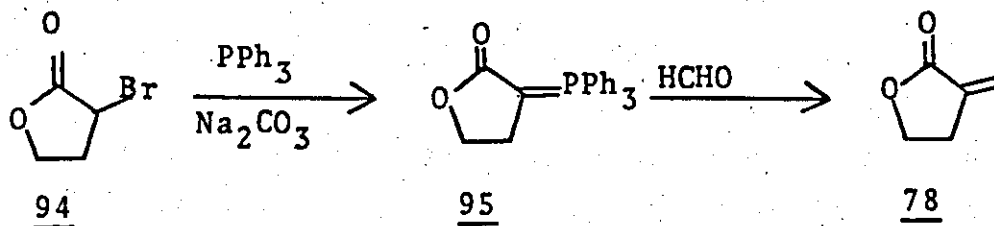


This route, which has been well studied, is basically α -methylenation of 2-oxo-tetrahydrofurans. Using the retro-synthetic approach, there are two possible methods of achieving this. The incorporation of the α -methylene moiety into a preformed lactone has been widely used in the synthesis of α -methylene lactones.

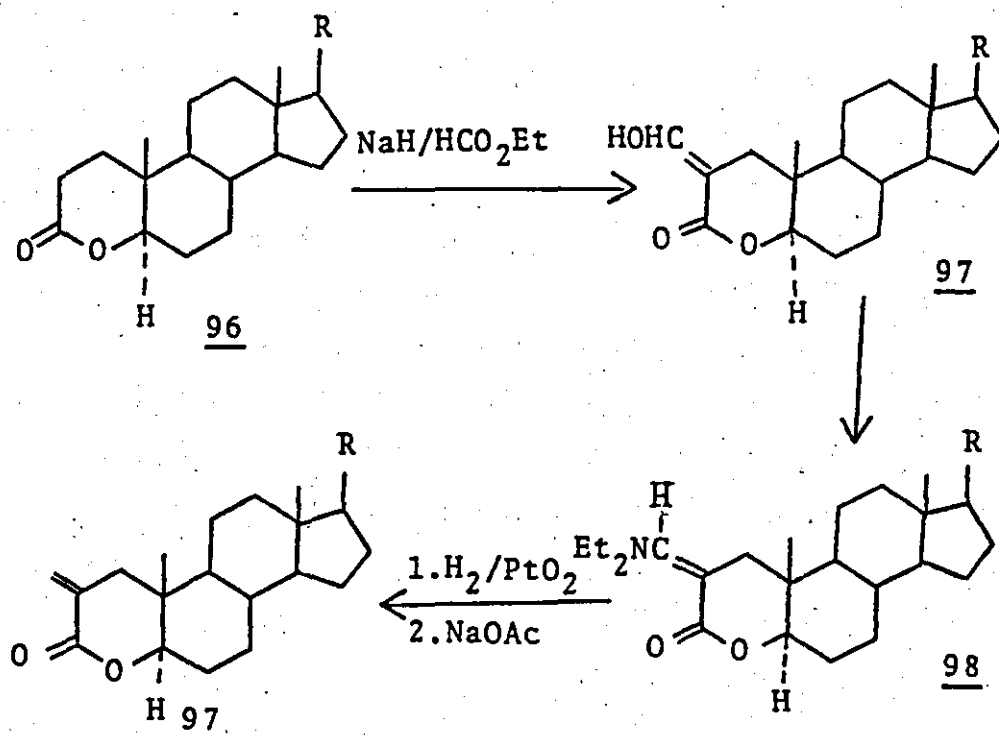
McGraw⁵¹ used a reductive elimination procedure to introduce the α -methylene moiety. A base-catalysed condensation of ethyl formate with the corresponding lactone 91 gave the α -formyl lactone 92 which was catalytically hydrogenated to the α -hydroxymethyl lactone 93. Dehydration led to the desired α -methylene lactone 78.



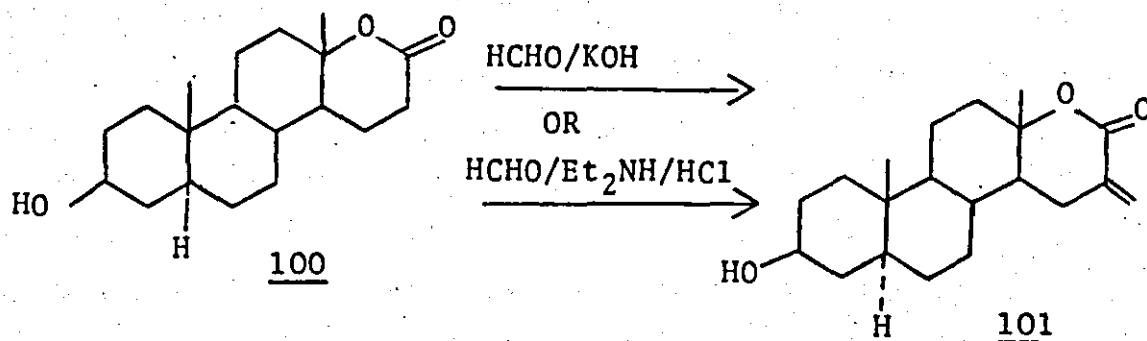
Another approach leading to the α -methylene lactone 78 is exemplified by the Wittig reaction between formaldehyde and a phosphorus ylide 95 formed from the α -bromolactone 94.⁵²



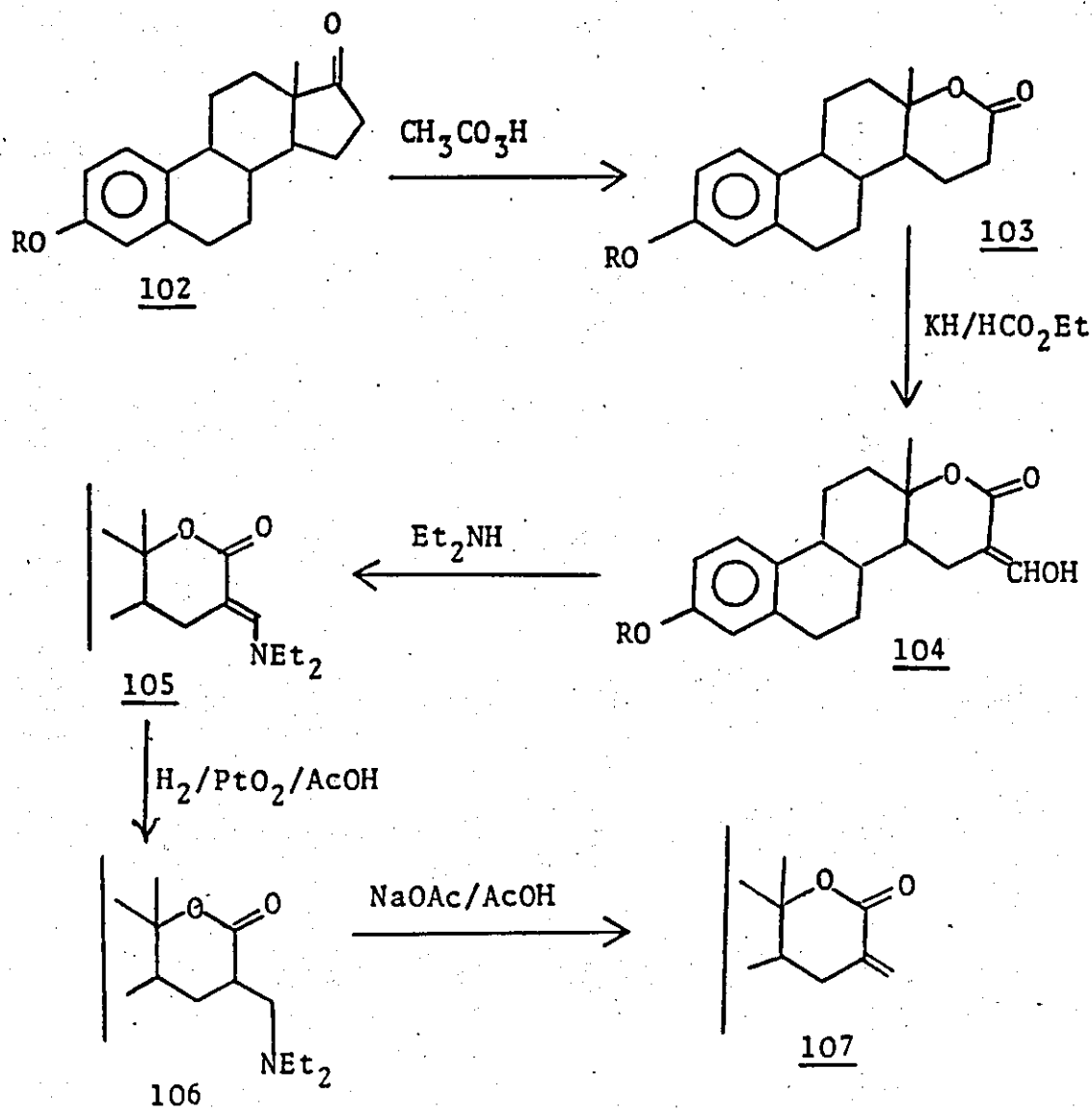
Dehal^{18,53} synthesised novel steroidal α -methylene- δ -lactones using an approach of Yamada *et al.*⁵⁴ Typically, condensation of the lactones 96 with ethyl formate gave the hydroxymethylene lactones 97 which were subsequently converted to the α -methylene lactones 99 through the diethylaminomethylene lactones 98.



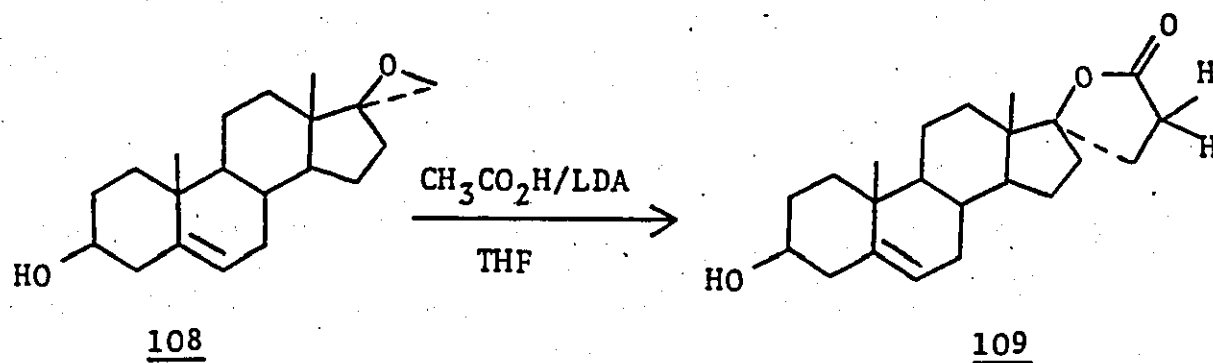
A similar approach to the D-homolactone 100, was not successful. Direct α -methylenation of the D-homolactone was achieved in modest yield through an aldol-type reaction with formaldehyde⁵⁵ and by a Mannich-type reaction with $\text{HCHO}/\text{Et}_2\text{NH}/\text{Et}_2\text{NH}\cdot\text{HCl}$.³⁰



Chagonda^{23,24} has synthesised some estrogen derivatives which contain the α -methylene- δ -lactone group as the D-ring. These were found to be highly toxic towards HeLa S₃ cells and were formed from preformed lactones by extension of the methods developed by Yamada⁵⁴ and Dehal¹⁸. Thus, Baeyer-Villiger oxidation of estrone 102 gave the lactone 103 which was formylated using potassium hydride and ethyl formate to give the hydroxymethylene lactone 104. Amination of 104 with diethylamine led to the enamine 105 and subsequent hydrogenation followed by sodium acetate treatment gave the α -methylene- δ -lactone 107.



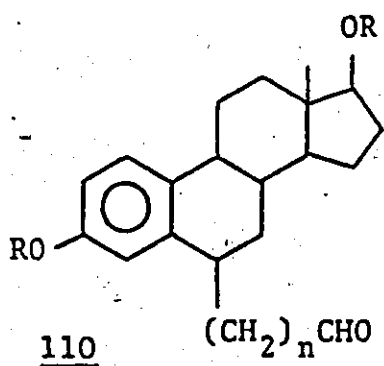
The reactions of bis-anions of carboxylic acids with epoxides to afford butyrolactones, followed by α -methylenation further extends the synthetic methods available.⁹⁹ For example, Cregler⁵⁶ successfully converted (17-S)-spiro(androst-5-ene-17,2'-oxiran)-3 β -ol 108 to 4',5'-dihydro-3 β -hydroxy-(17-R)-spiro{(androst-5-ene-17,2 (3'H)-furan}5'-one 109, with acetic acid and LDA in THF. This could be further elaborated to the α -methylene lactones via the hydroxymethylene derivative.



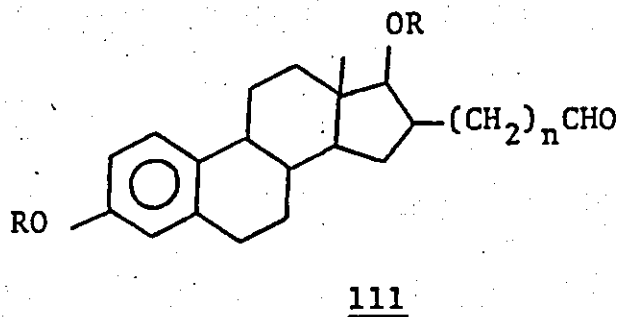
DISCUSSION

DISCUSSION

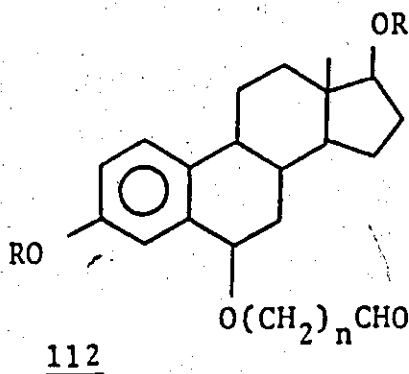
The proposed general approach to the synthesis of the desired steroidal α -methylene lactones involved a convenient Reformatsky-type reaction between methyl or ethyl α -(bromomethyl)acrylate and an appropriate steroidal aldehyde, as reported by Drieding³⁷ and Schimdt³⁸. The first main synthetic targets were aldehydes of types 110 and 111. Additionally, it was thought that the aldehyde function may be attached through an oxygen linkage as in, for example, the alternative target molecules 112. In all of these it was anticipated that direct reaction with methyl or ethyl α -(bromomethyl)acrylate, would be feasible since the aldehyde functions should be relatively sterically unhindered (cf 6-keto-steroids as discussed earlier).



$$n \geq 0$$



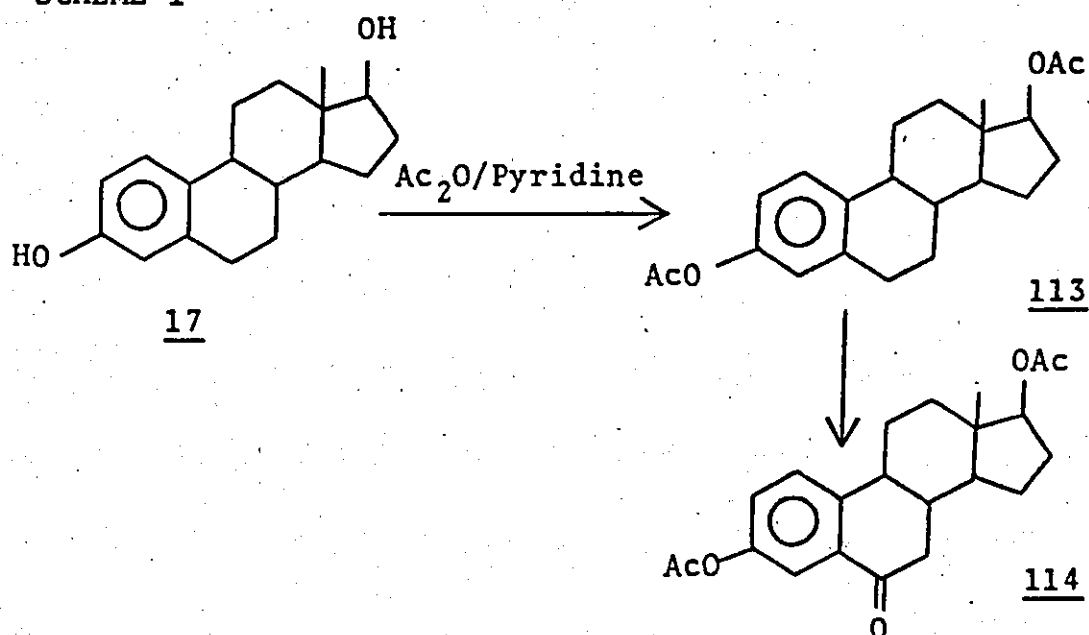
$$n \geq 0$$



$$n > 0$$

It was anticipated that compounds 110 and 112 would be available from the key intermediate 3,17 β -diacetoxy-estra-1,3,5(10)-trien-6-one(6-keto estradiol diacetate) 114 which may be obtained in two steps from 17 β -estradiol 17. Thus, acetylation of 17 β -estradiol 17 with acetic anhydride in pyridine gave the 17 β -estradiol diacetate 113 (94%). The ir spectrum of 113 showed the carbonyl stretching bands at ν_{max} 1770 cm^{-1} (3-OAc) and 1730 cm^{-1} (17-OAc). Also, the ^1H nmr spectrum showed signals for the methyl group of the acetates at δ 2.08 (17-OAc) and δ 2.28 (3-OAc).

SCHEME 1



Benzylic oxidation of 113 gave the 6-ketone 114. Hitherto, this 6-ketone 114 had been synthesised from 17 β -estradiol diacetate 113 using chromic acid oxidation. However, this method gave low and variable yields in the range 10-15%.⁵⁷⁻⁵⁹ An attempt to improve this yield by use of t-butyl chromate was

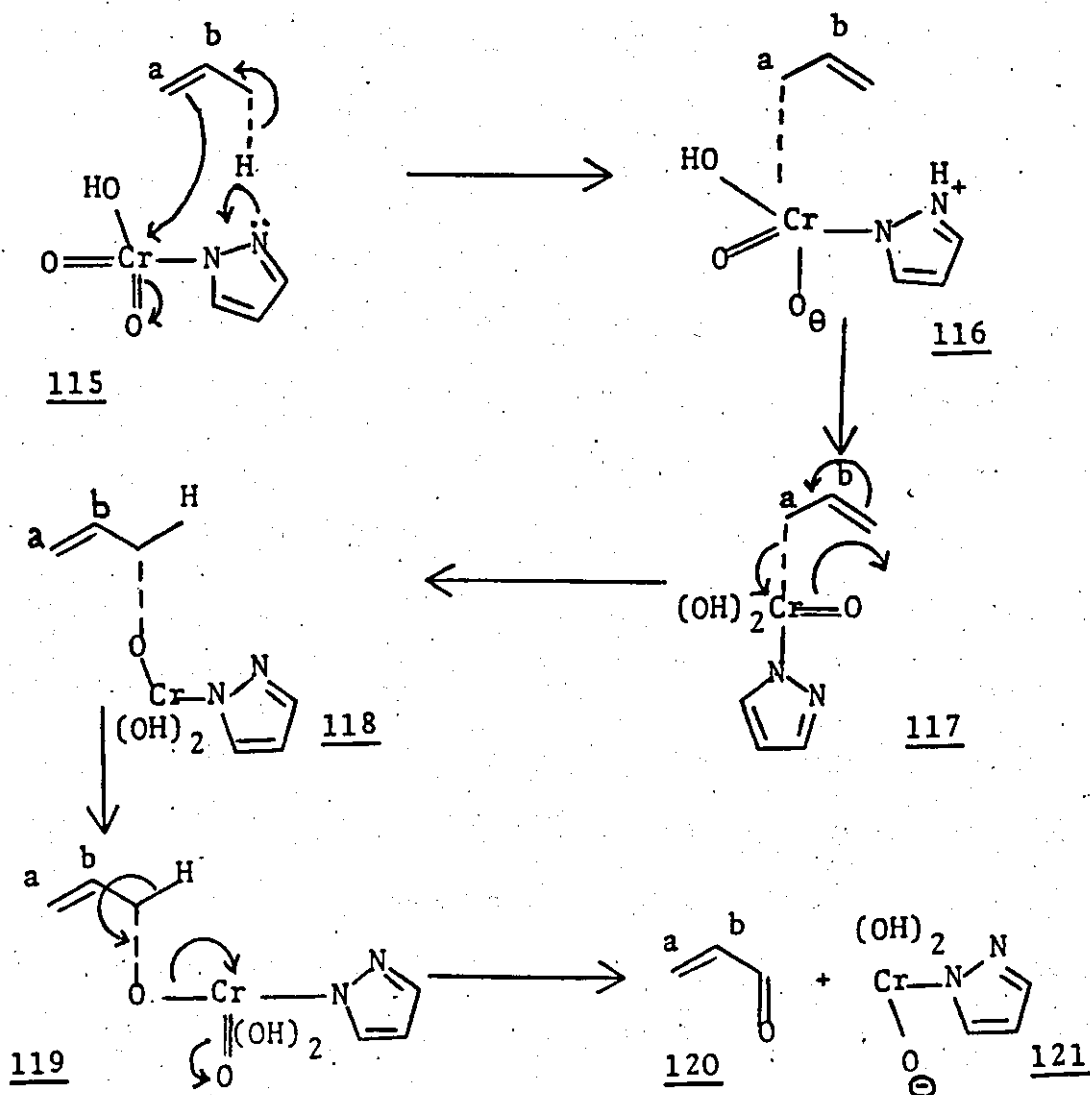
reported to be unsuccessful.⁶⁰ Hence, an alternative more effective route for this oxidation was sought.

The chromium trioxide-3,5-dimethylpyrazole (DMP) complex has recently been reported to be effective for allylic oxidation of steroidal alkenes.⁶¹⁻⁶² This method was adapted for the benzylic oxidation of 113 and gave the desired product 114 in much improved yields (ca 40%). The ir spectrum of 114 showed carbonyl bands at 1675cm^{-1} (ArC=O), 1730cm^{-1} (17-OAc) and 1770cm^{-1} (3-OAc). The ^1H nmr spectrum of 114 showed significant changes from that of 113 as expected, especially in the aromatic region. The 4-H doublet ($J \approx 2.5\text{Hz}$) at $\delta 7.87$ was downfield of that in 113 ($\delta 6.78$) owing to the deshielding effect of the 6-ketone. The 6-methylene multiplet at $\delta 2.85$ in the ^1H nmr spectrum of 113 was absent in 114.

A plausible mechanism for this oxidation has been proposed by Salmond.⁶¹ It assumed, a one to one addition of DMP to CrO_3 gives the complex 115, leaving one free ligand site on the chromium atom, thereby allowing facile attack by the π -electrons of the double bond in an ene reaction in which the removal of hydrogen is facilitated by the basic nitrogen of the pyrazole ligand. In passing from 115 to 116 no reduction of Cr^{VI} has taken place. A proton shift from nitrogen to oxygen will give 117. This is followed by a 2,3 sigmatropic shift of the chromium alkyl 117 to give the intermediate 118 in which oxidation of the steroid takes place and the reduction of Cr^{VI} to Cr^{IV} occurs. Decomposition of the chromate ester 119 to the ketone is aided by an intramolecular

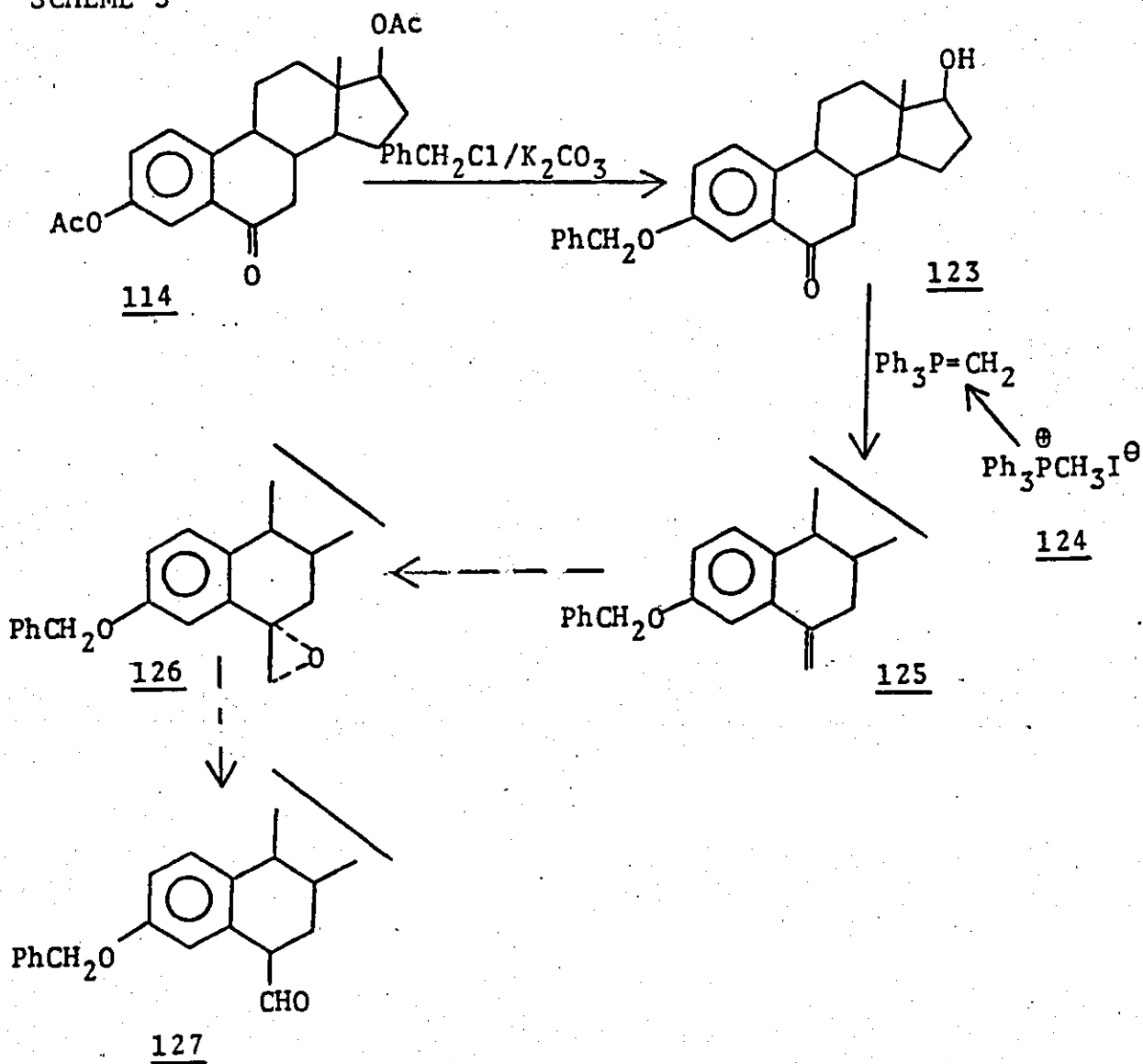
cyclic mechanism. The increased rate observed with this oxidation could be partly due to much increased solubility of the chromium complexes and partly the possibility of intramolecular acceleration by the pyrazole nucleus through hydrogen abstraction. Our successful application of the CrO_3 -DMP oxidation has recently been published^{61a} and similar results have independently been reported by other workers.^{61b} Other improvements in this oxidation include the use of t-butyl hydroperoxide (tBuOOH) and chromium hexacarbonyl $\text{Cr}(\text{CO})_6$ ^{61c}

SCHEME 2



There are various possible methods for converting ketones to homologous aldehydes. Some of these methods have been applied to steroidal ketones⁶³⁻⁶⁶ and we have investigated some applications of the Wittig reaction. Reaction of 6-keto-estradiol diacetate 114 with triphenylphosphonium methyl iodide 124 using either BuLi or dimsyl anion as the base did not proceed satisfactorily, giving low yields. In a survey of Wittig reactions with various keto-steroids⁶⁷⁻⁶⁸, it was observed that hydroxy or acetoxy groups decreased the yield.⁶⁷ In a similar situation, Takadate and Fishman⁶³ successfully used the benzyloxy-derivative, 2,3-dibenzyloxy-17 β -hydroxy-estra-1,3,5(10)-trien-6-one 122, in the preparation of its 6-methylene derivative. Reaction of 114 with benzyl chloride and potassium carbonate in ethanol, according to the procedure of Nambara⁶⁹, gave the 3-benzyloxy-17 β -hydroxy-estra-1,3,5(10)-trien-6-one in over 80% yield. The ir spectrum showed a band at 1675cm⁻¹ (ArCO) but no acetate carbonyl bands. The ¹H nmr spectrum showed an important singlet (2H) at δ 5.08 which was assigned to the methylene group of the benzyloxy group. The benzyloxy-derivative 123 was converted to the 3-benzyloxy-6-methylene-estra-1,3,5(10)-trien-17 β -ol, 125, by reaction with triphenylphosphonium methyl iodide 124 and dimsyl anion as the base in 50% yield. The ir spectrum of 125 did not show any carbonyl band. The ¹H nmr spectrum showed the multiplets of the 6-methylene moiety at δ 5.5 (W₁, \sim 2.5Hz) and δ 4.98 (W₁, \sim 2.5 Hz). In this reaction, dimsyl anion was more effective than BuLi for the generation of the ylide.⁷⁰ Conversion to 126 and 127 was not investigated owing to the relatively low yield of 125.

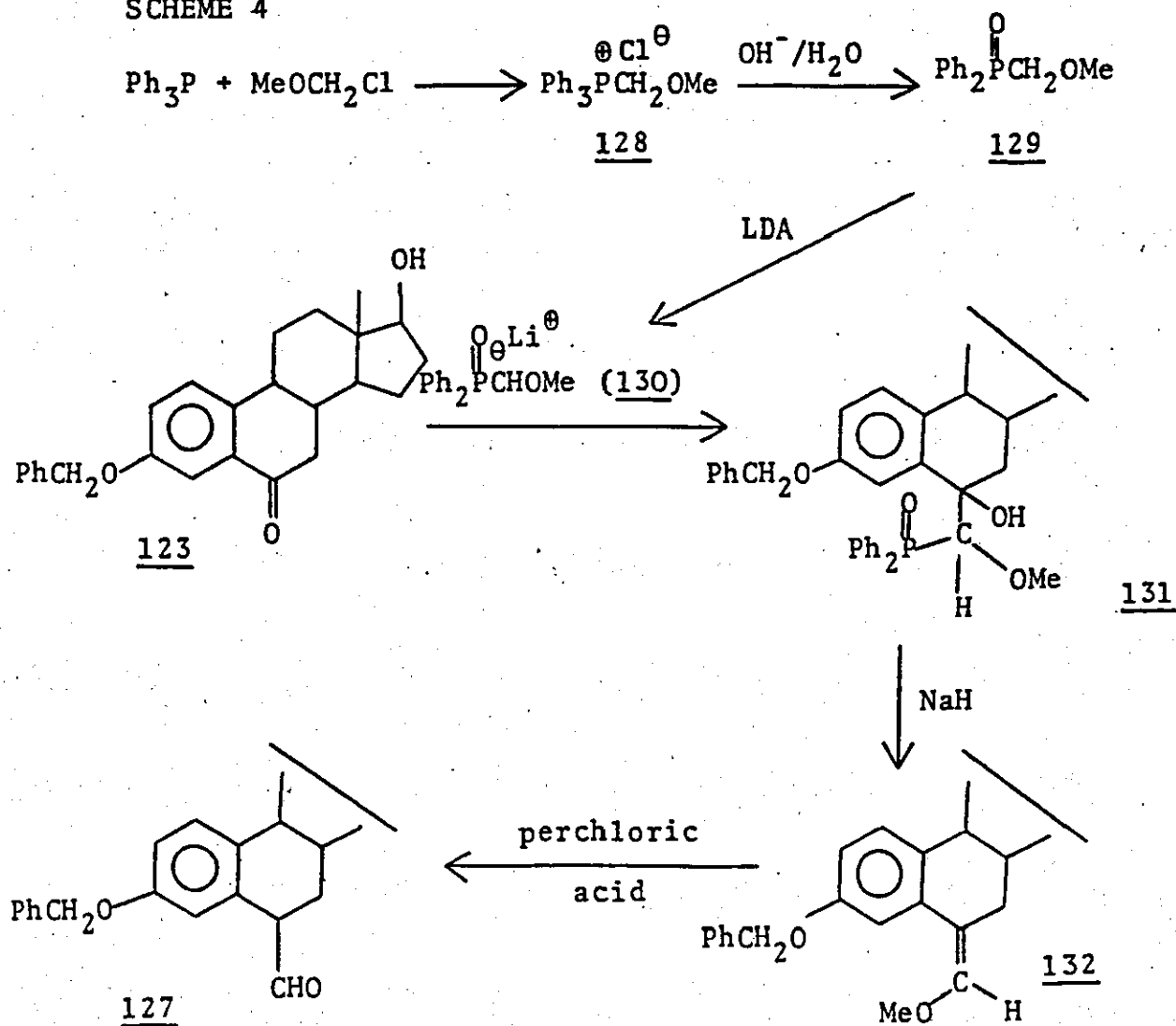
SCHEME 3



The Horner-Wittig (or Emmons-Wadsworth) modification of the Wittig reaction, which employs PO-stabilised carbanions, is known to have some advantages over the Wittig reaction. Firstly, PO-stabilised carbanions are much more nucleophilic than the corresponding phosphonium ylides.⁷¹ Secondly, the phosphinic, phosphonic and phosphorus acid derivatives obtained from these

modifications are all soluble in water. Hence, separation of the by-products from the olefin is easily achieved.⁷² Thirdly, side reactions in these modifications are less frequent than with the corresponding Wittig reactions⁷³. These observations, coupled with the relatively low yield obtained from the Wittig reaction above, prompted the investigation of the reaction of the 6-ketone 123 with the diphenyl(methoxymethyl)phosphine oxide 124, which gave the vinyl ether 132 in 70% yield.

SCHEME 4



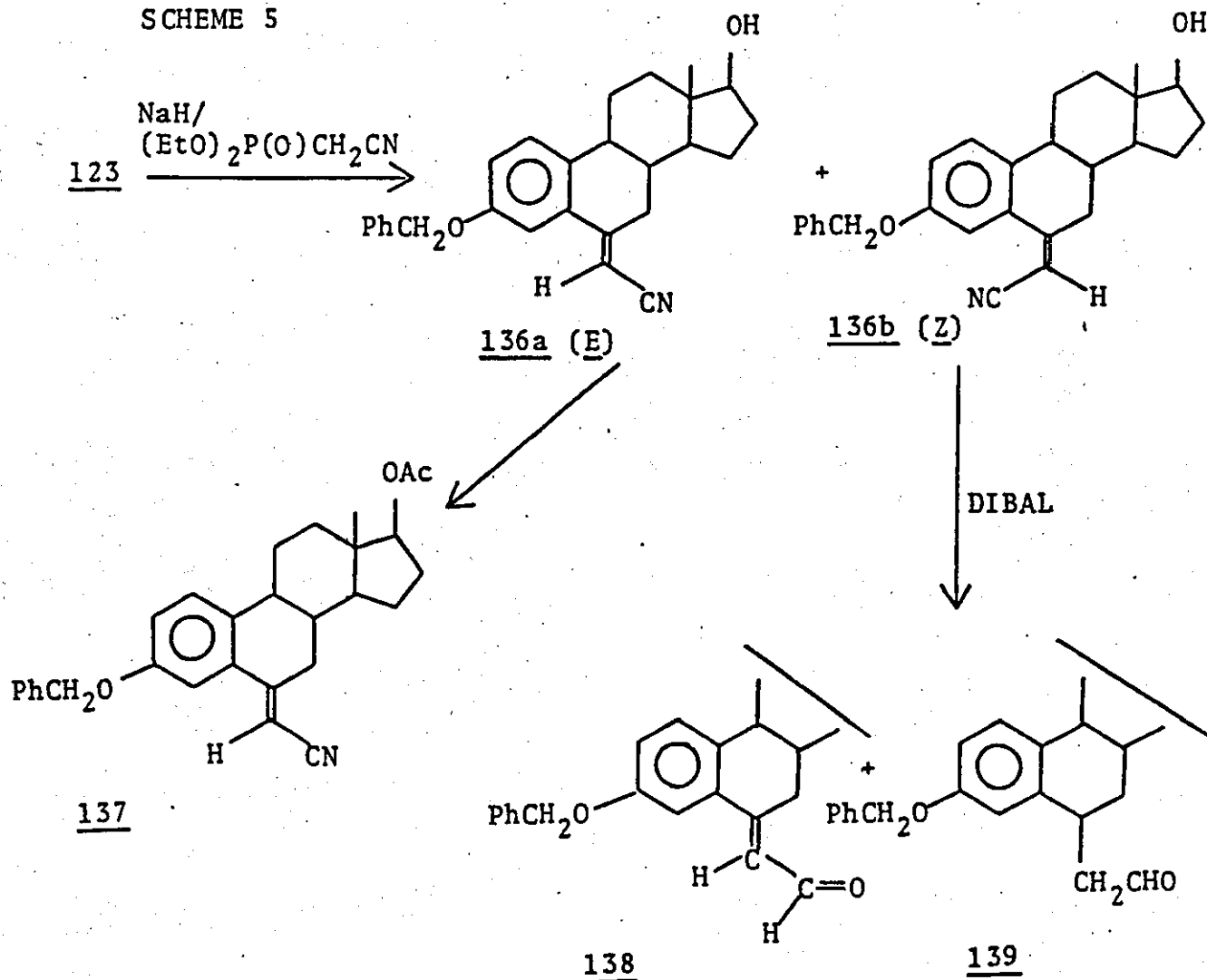
The diphenyl(methoxymethyl)phosphine oxide 129 was obtained from the reaction of triphenylphosphine with chloromethyl ether. Alkaline hydrolysis of the intermediate phosphonium salt 128 gave the diphenyl(methoxymethyl)phosphine oxide 129. The lithium derivative 130 was made by the reaction of the phosphine oxide 129 with lithium di-isopropylamide (LDA) at 0°. Addition of the 6-ketone 123 to the reaction mixture at -78° gave the hydroxy intermediate 131 which was subsequently converted to 3-benzyloxy-17 β -hydroxy-6-methoxymethylene-estra-1,3,5(10)-triene 132 with NaH after chromatographic purification.

Only one geometrical isomer of the vinyl ether 132 was obtained as indicated by the presence of a single olefin proton signal at δ 6.0 (m, W₁, \sim 2.5Hz) in the H¹ nmr spectrum. The Z-configuration was assigned on the basis of the chemical shift of the 4-H doublet (J \sim 3Hz) at δ 7.8 which is downfield of that in 125 (δ 6.8) owing to the deshielding effect of the methoxy group. Moreover, if it were the E-isomer, the methoxy group would be expected to cause the methylene protons at C-7 to move downfield in the ¹H nmr spectrum but this was not observed. Warren⁸⁵ had isolated both E- and Z-geometrical isomers from his studies on the reaction of diphenyl(methoxymethyl)phosphine oxide 124, with various aldehydes such as p-anisaldehyde and crotonaldehyde. It was therefore surprising that we were only able to detect a single product. Furthermore, the product 132 obtained had the opposite configuration to the major isomer obtained from the reaction of the 6-ketone 123 with diethylcyanomethylphosphonate 135 (see later discussion).

Acid hydrolysis of the vinyl ether 132 led to the desired aldehyde 127 which was not crystallised but gave satisfactory spectroscopic data. The ir spectrum of 127 showed the aldehyde carbonyl stretching band at ν_{\max} 1720cm^{-1} . The ^1H nmr spectrum also showed a singlet at $\delta 9.4$ (CHO). The aldehyde 127 was difficult to purify and decomposed on chromatography, so that the yields were relatively low (ca 30%) and it was not possible in the time available to obtain sufficient material to carry forward to the next stage.

Bose⁶⁶ had noted that because of steric constraints at C-6, diethyl cyanomethylphosphonate 135 could be employed satisfactorily owing to the linear nitrile group having low steric demands. Thus, he converted 3 β -hydroxy-cholestan-6-one 133 to the 6-cyanomethylene-derivative 134 by reaction with diethyl cyanomethylphosphonate 135 and dimethyl anion. The reaction of the 6-ketone 123 with diethyl cyanomethylphosphonate 135 using the method of Fishman⁶³ gave 3-benzyloxy-6-cyanomethylene-estra-1,3,5(10)-trien-17 β -ol 136 in 60% yield as a mixture of stereoisomers which could not be separated by preparative tlc. It was proposed to convert the nitrile 136 to the aldehydes 138 and 139 (Scheme 5).

SCHEME 5



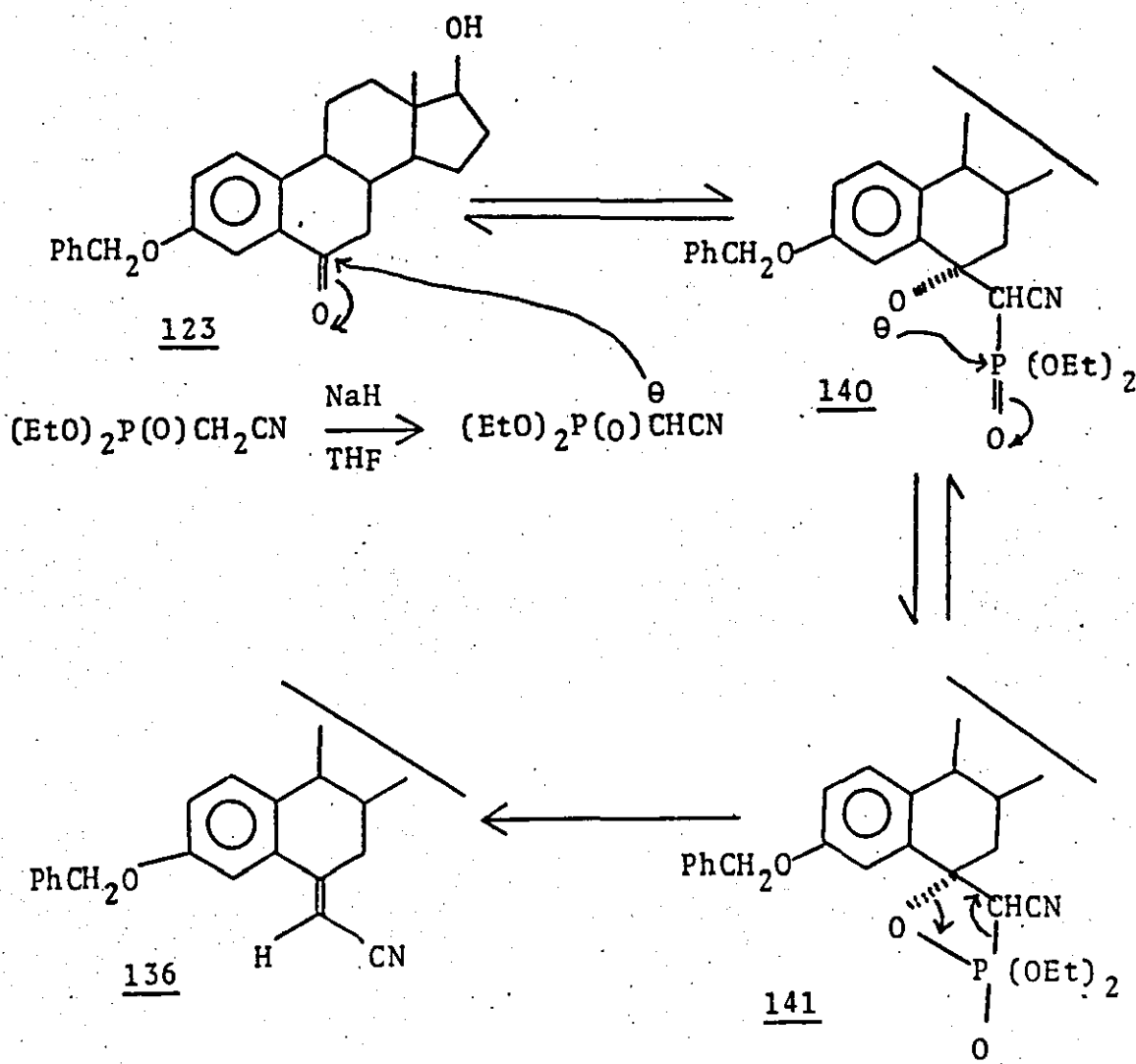
The ir spectrum of the 6-cyanomethylene compound **136** confirmed the presence of the nitrile group ($\nu_{\text{max.}} 2220\text{cm}^{-1}$) and the ^1H nmr spectrum showed signals for the olefinic proton ($=\text{CHCN}$) at $\delta 5.72$ and $\delta 6.2$. These were assigned to the E- and Z- isomers respectively and integration suggested that the E:Z ratio was approximately 4:1. The effect of the nitrile in the E-isomer on the methylene protons at C-7 was very pronounced.

The methylene protons were deshielded and moved downfield to between δ 3.0 and δ 3.43. The nitrile 136 could not be crystallised but acetylation, by reaction with acetic anhydride in pyridine, gave 17 β -acetoxy-3-benzyloxy-6-cyanomethylene-estra-1,3,5(10)-triene 137 which was crystallised. The product thus obtained was the E-isomer containing a small amount (<5%) of the Z-isomer as confirmed by the ^1H nmr spectrum which showed the expected deshielding effect of the nitrile group on the 7-methylene protons and no deshielding effect on the 4-proton (cf ^1H nmr spectrum of the Z-vinyl ether 132).

Although Bose⁶⁶ obtained only one geometrical isomer (E) in the synthesis of 3 β -hydroxy-6-cyanomethylene-cholestane 134, Maisey⁷⁴ obtained a mixture of isomers in his reactions of a series of alkyl phenyl ketones with diethyl cyanomethylphosphonate 135. He noted that the proportion of the cis(Z)-isomer is dependent on the structure of the ketone but, in general, the more thermodynamically stable trans (E)-isomer was the favoured product. Solvent effects are also known to play a part in the control of stereochemistry^{72a, 72b}. While reactions of diethyl cyanomethylphosphonate 135 in benzene, DME or THF, are usually thermodynamically controlled, in HMPT the reaction can be thermodynamically or kinetically controlled depending on the proportions and order of addition of the reagents. From the reaction conditions used in the preparation of the nitrile 136 and the solvent employed (THF), it would be expected that the reaction would be thermodynamically controlled.

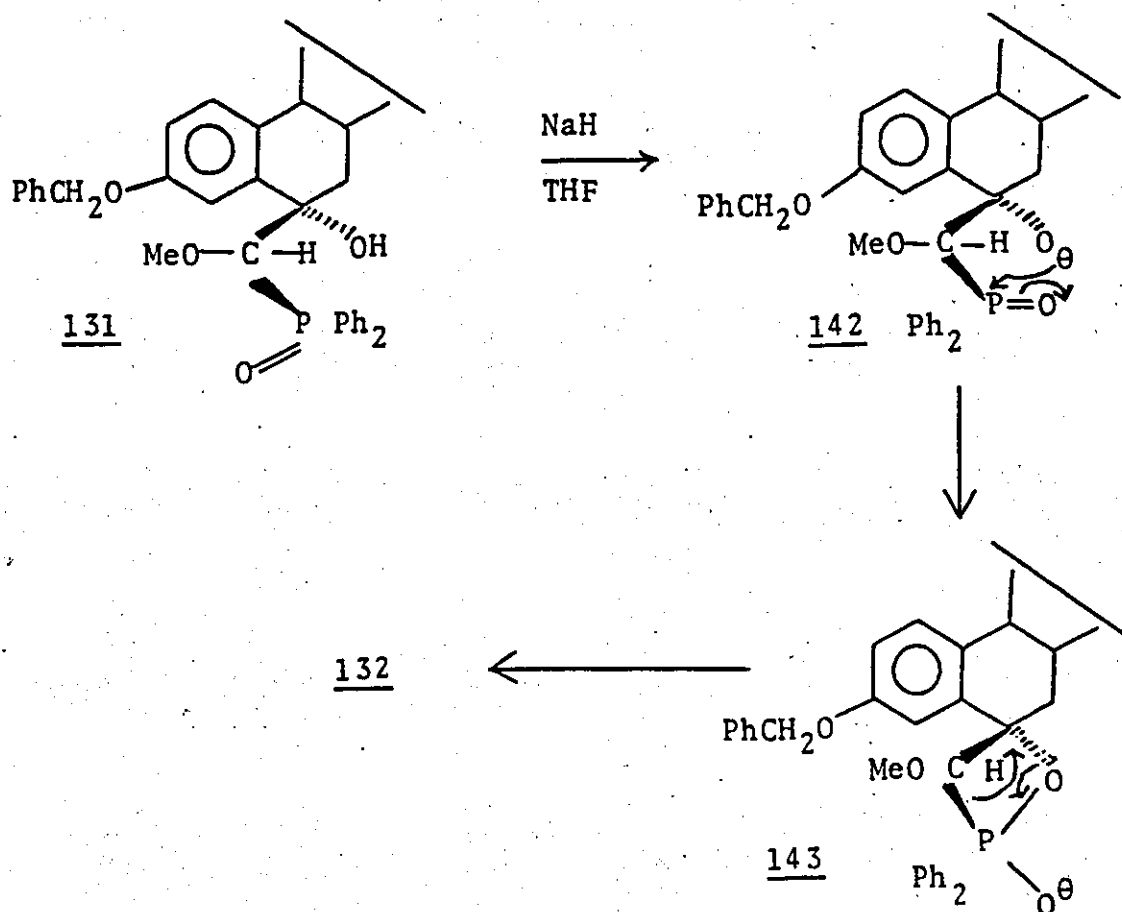
In general, the thermodynamic control arises because of the reversibility of the addition of the phosphorus stabilised carbanions to the carbonyl compound. Thus, in the case of the 6-ketone 123, the formation of the intermediate 140 and possibly the oxophosphatane 141, may be reversible leading then to the (E)-6-cyanomethylene compound 136 (Scheme 6). This would be expected to be more thermodynamically stable than the corresponding Z-isomer in which steric interaction between the 4-H and the cyano group would be significant.

SCHEME 6



It is interesting to note that the 6-cyanomethylene compound 136 has the opposite configuration to that of the vinyl ether 132 (see earlier). It has been reported that the anion of diphenyl(methoxymethyl)phosphine oxide 132 reacts with carbonyl compounds irreversibly⁸⁵ and thus the reactions are kinetically controlled. The reaction of 133 with the 6-ketone 123 is presumed to give the intermediate 131 in which the configuration of the exocyclic chiral carbon is S. Treatment of the intermediate with sodium hydride would cause it to react through the anion 142 and the oxophosphatane 143 to give the Z-vinyl ether 132

SCHEME 7



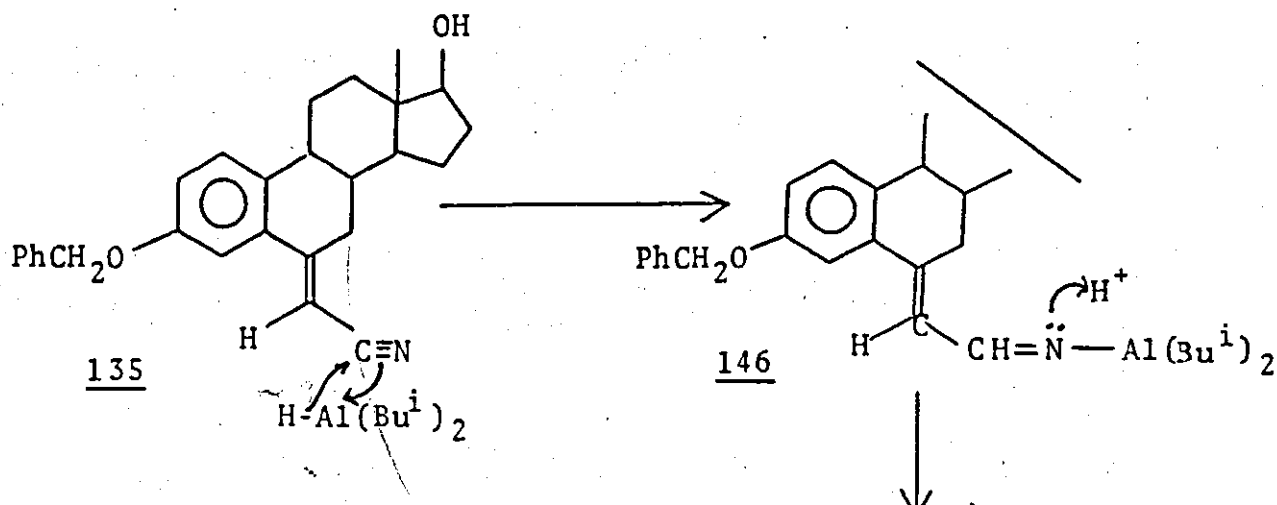
It is not clear why the configuration of the intermediate 131 is S. However, if it is assumed that the anion 133 approaches the 6-carbonyl group from the β -face and that there is some interaction between the phosphorus and the oxygen of the carbonyl group, it is apparent that the methoxy group would be less hindered in the transition state leading to 131 in the S-, rather than the R-configuration. In the latter there could be significant steric interaction with the 7β - and 8β -hydrogen atoms. It is possible that the different stereochemical result in the formation of the 6-cyanomethylene compound 136 and the vinyl ether 132 is also related to the difference in steric demands of the reagents used since the phenyl groups in the diphenyl(methoxymethyl)phosphine oxide 132 are, of course, much larger than the ethoxy groups of the diethyl cyanomethyl phosphonate 135. Attack on the β -face of the 6-ketone 123 has been assumed by analogy with the known course of its reduction with sodium borohydride which leads to the 6α -alcohol 166.⁷⁸

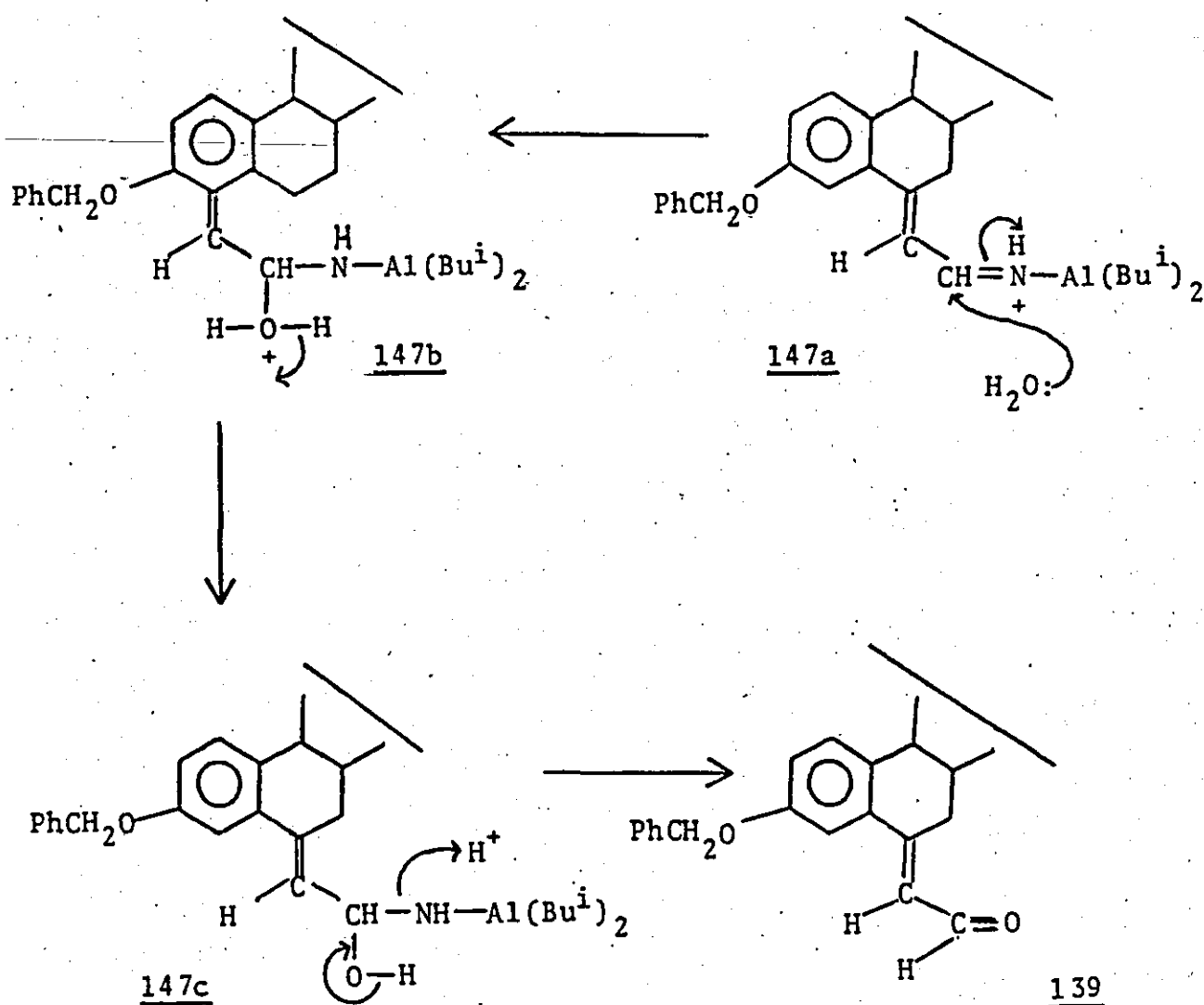
Reduction of the unsaturated nitrile 136 as a mixture of the two isomers was achieved with di-isobutylaluminium hydride (DIBAL) in benzene. The approach used was similar to that of Trofimenko⁷⁷. After chromatography, the α,β -unsaturated aldehyde 138, a single stereoisomer, presumably E (50%), and the saturated aldehyde 139 (5%) were obtained. The presence of 139 showed that DIBAL reduced both the nitrile and the olefinic bond. However, the small amount of 139 (5%) obtained suggested that DIBAL attacked the nitrile before attacking the olefinic bond. Thus, when the reaction time was reduced, no 139 was isolated.

The ir spectrum of 138 showed the expected carbonyl stretching band of the α,β -unsaturated aldehyde at ν_{\max} 1680cm^{-1} . The ^1H nmr spectrum gave important signals at $\delta 10.15$ (d, $J \sim 8\text{Hz}$, CHO) and $\delta 6.5$ (d, $J \sim 8\text{Hz}$, $=\text{CHCHO}$). The large vicinal spin-spin coupling constant of the aldehyde 138 proton to the neighbouring methine proton ($=\text{CHCHO}$) is not totally unexpected as similar couplings have been observed in α,β -unsaturated aldehydes.^{77b} Double irradiation of the methine doublet at $\delta 6.5$ caused the aldehyde doublet at $\delta 10.15$ to collapse to a singlet thus confirming the assignments. The aldehyde 138 was presumed to be the E-isomer because it was obtained from the major product of the Horner-Wittig reaction. The ir spectrum of the saturated aldehyde 139 gave a ν_{\max} at 1720cm^{-1} confirming the presence of the saturated aldehyde function. Also the ^1H nmr spectrum of 139 showed the aldehyde signal at $\delta 9.78$ as triplet ($J \sim 2.5\text{Hz}$) as expected.

The DIBAL reduction involves conversion of the nitrile first to the imine derivative 146, which is subsequently hydrolysed with acid to give the unsaturated aldehyde 138 as outlined below.

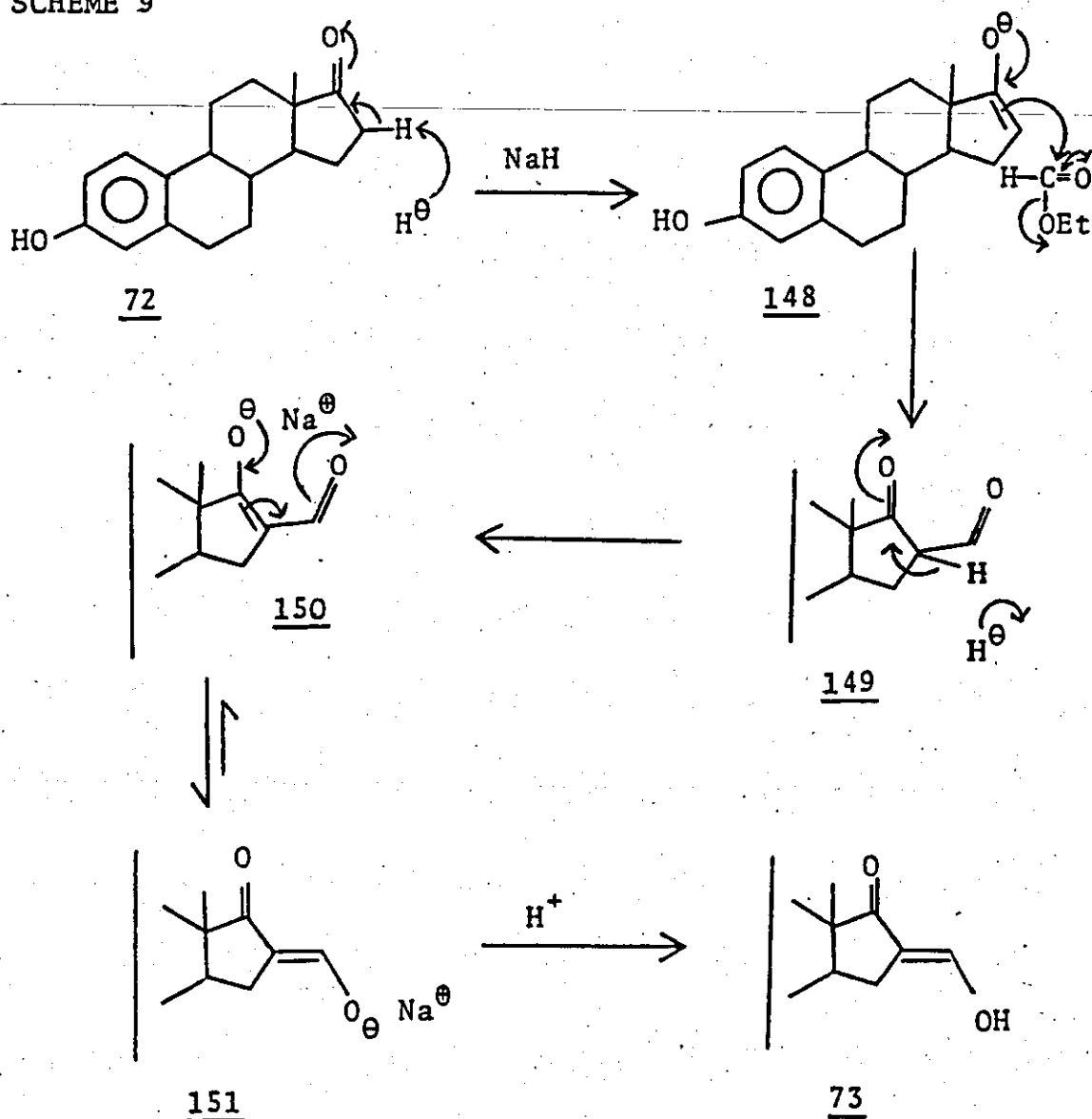
SCHEME 8





Preparation of the aldehydes of type 111 involved the use of estrone 72. Thus the reaction of estrone with sodium hydride and ethyl formate in benzene followed by acidification with dilute HCl gave 16-hydroxymethylene-estrone 73.⁸⁶ The ir spectrum showed bands at ν_{max} 3400cm^{-1} (OH), 1720cm^{-1} (17-CO) and 1635cm^{-1} (C=C). The ^1H nmr spectrum showed signals at $\delta 0.82$ (18-Me) and $\delta 7.43$ (br s, $=\text{CHOH}$). The mechanism for the formation of 73 involves initial proton abstraction with the base, sodium hydride. A Claisen-Schmidt condensation with ethyl formate and subsequent acidification of the alkoxide 150, gives the 16-hydroxymethylene compound 73.

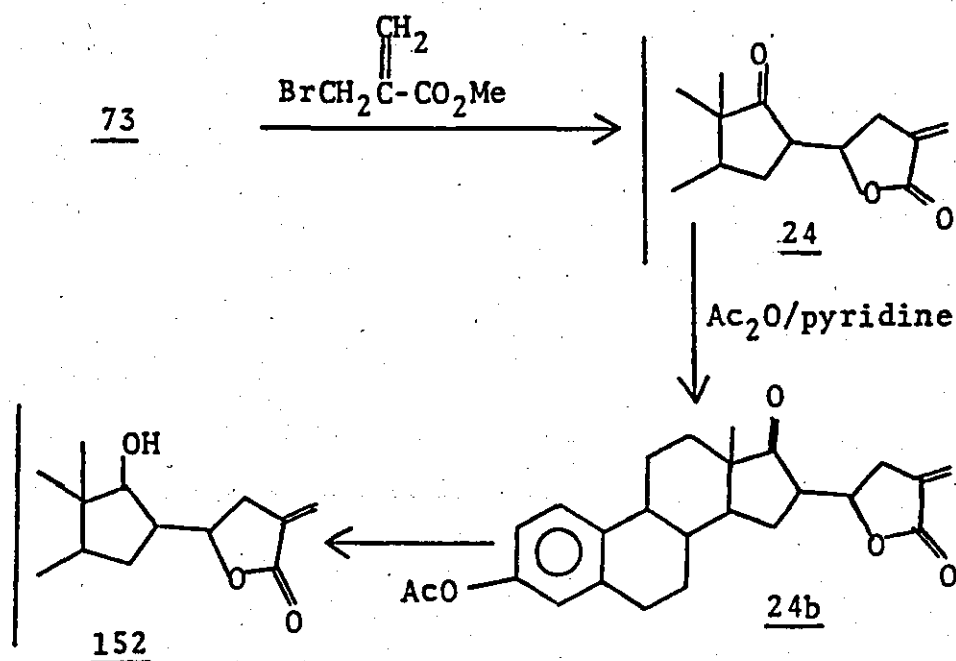
SCHEME 9



16-Hydroxymethylene estrone **73** has been converted to the α -methylene lactone derivative **24** by Edge.²⁷ It was envisaged that it might be possible to convert this lactone **24** to the estradiol derivative **152** by selective reduction (Scheme 10). Hitherto, Edge had found that attempted reduction of the 17-ketone derivative **24** led to no well defined products with NaBH_4 and $\text{Zn}(\text{BH}_4)_2$. The low solubility of the lactone **24** in methanol was thought to affect the reduction as did the temperature employed (room tempera-

ture). It was anticipated that acetylation of the lactone could increase the solubility in methanol and thus allow the reduction to be carried out at low temperature.

SCHEME 10



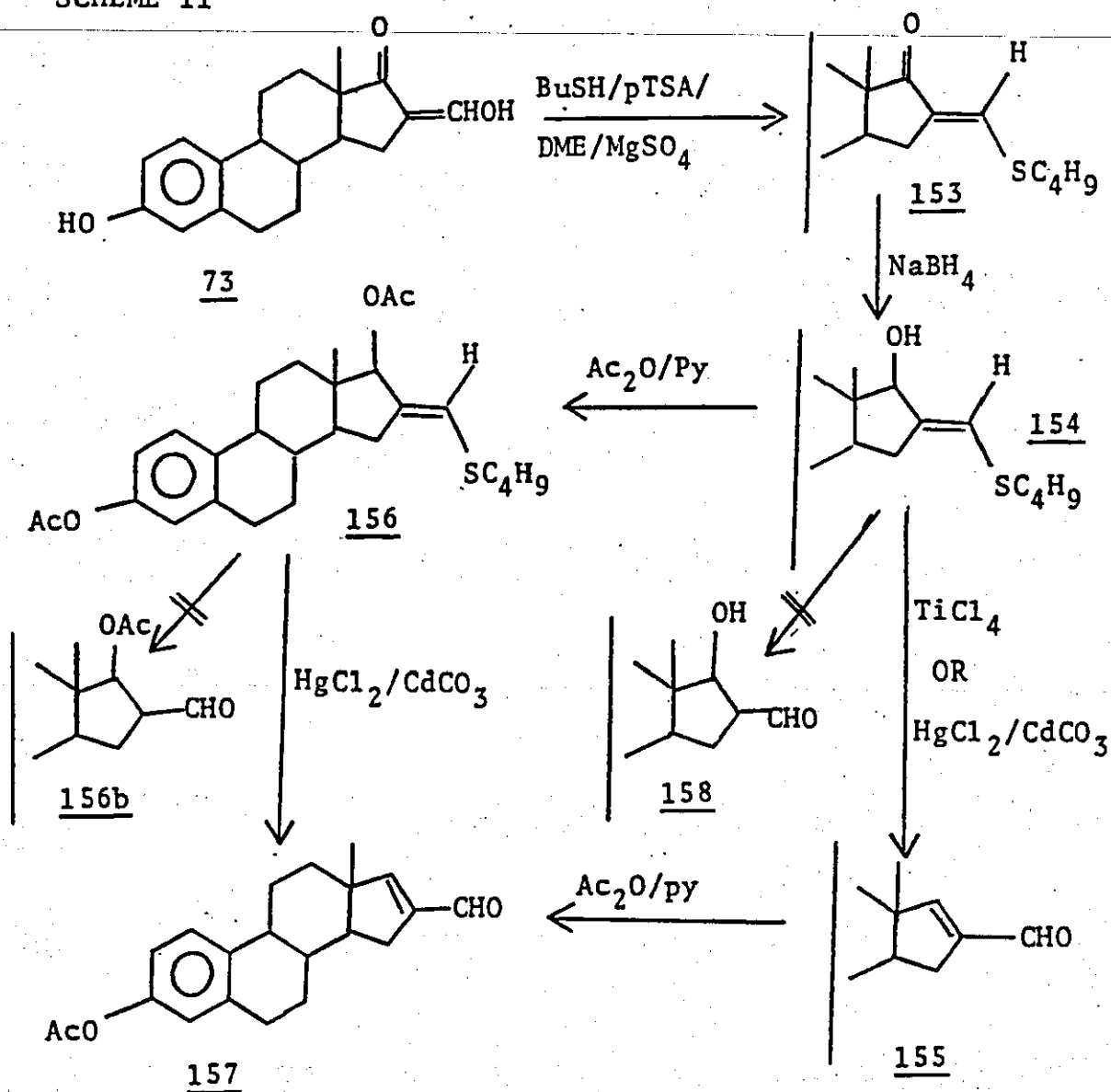
The acetoxy-derivative **24b** was prepared by acetylation of **24** with acetic anhydride in pyridine. The ^1H nmr spectrum of **24b** showed the methylene proton signals ($\text{C}=\text{CH}_2$) at $\delta 5.72$ ($W_{\frac{1}{2}}$ 2.5Hz) and $\delta 6.32$ ($W_{\frac{1}{2}}$ 2.5Hz) and the methyl signal of the acetoxy group at $\delta 2.28$. Attempted reduction of the 3-acetoxy lactone **24b** with sodium borohydride at low temperature (-5°C to 0°C) did not proceed smoothly, giving only about 5% of the hydroxy lactone **152**. An alternative route to the hydroxy lactone **152** was sought. It was anticipated that the protection of the enol function of

the hydroxymethylene compound 73, followed by reduction of the 17-ketone and subsequent deprotection, could give the dihydroxy 16-formyl derivative 158 which could be used for the synthesis of the 17-hydroxy α -methylene lactone 152.

A survey of literature revealed various possible ways of protecting β -keto aldehydes which include acetalization⁸⁸, enol ether⁸⁹ and thioenol ether⁹⁰⁻⁹² formation. When enol ethers are used, reduction of the β -keto function is reported to proceed beyond the desired product, the olefinic bond (C=C) being reduced as well, thus giving over-reduction products.^{88,91}

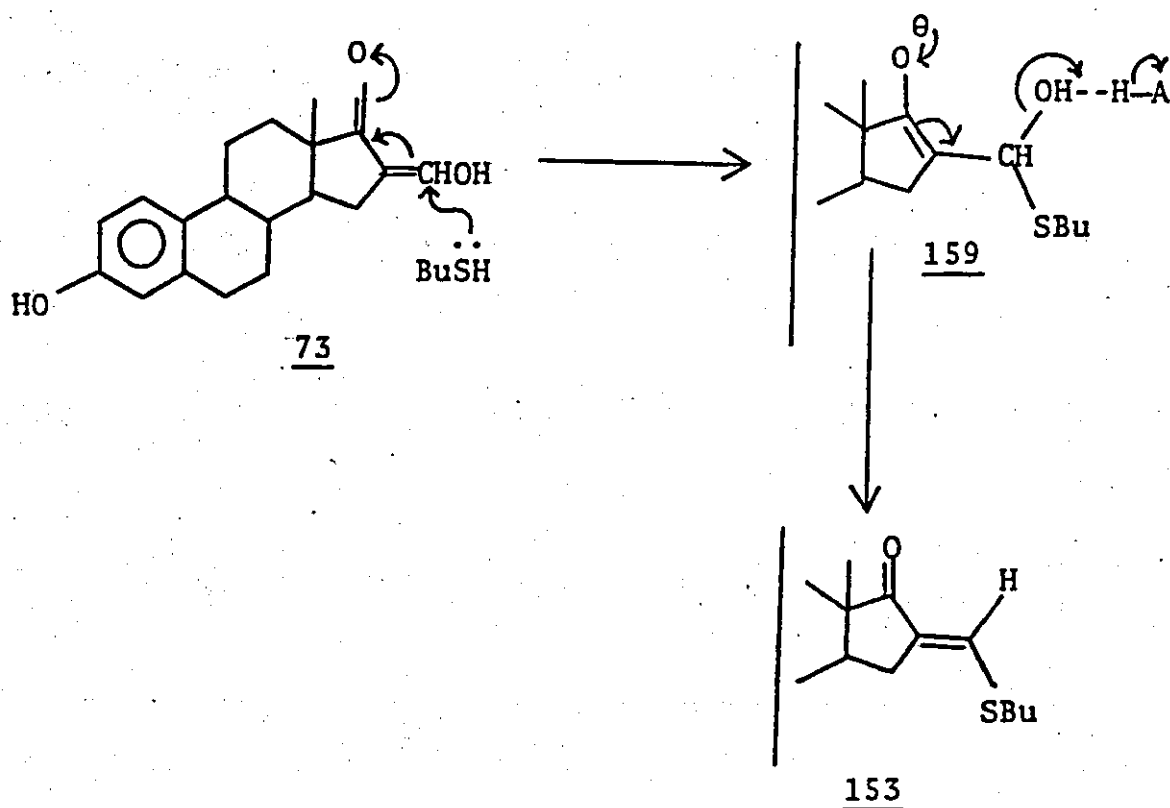
The use of butane thiol to form thioenol ethers has been successfully applied by Ireland^{90,91} to protect hydroxymethylene groups while allowing the reduction of the β -keto functions. Thus, the use of butane thiol for protecting the 16-hydroxymethylene-estrone 73 was studied. Using a modified form of the Bernstein method⁹², 73 was successfully converted to the 16-butylthiomethylene estrone 153 in 90% yield. Because of the low solubility of 73 in benzene, which was the normally recommended solvent, DME was used. The ¹H nmr spectrum of the butylthiomethylene derivative 153 showed only one isomer was formed, since only one olefinic proton signal was observed (δ 7.4, br s, = CHSC₄H₉). The 16-butylthiomethylene compound 153 was assigned the E-configuration because of the relatively low chemical shift observed for this olefinic proton which would result from the deshielding effect of the 17-ketone. The ir spectrum showed the 17-ketone band at 1690cm⁻¹.

SCHEME 11



The probable reaction mechanism of formation of the butylthiomethylene compound **153** involves a Michael-addition of the thiol to the enone system. The E-product would be expected on thermodynamic grounds.

SCHEME 12

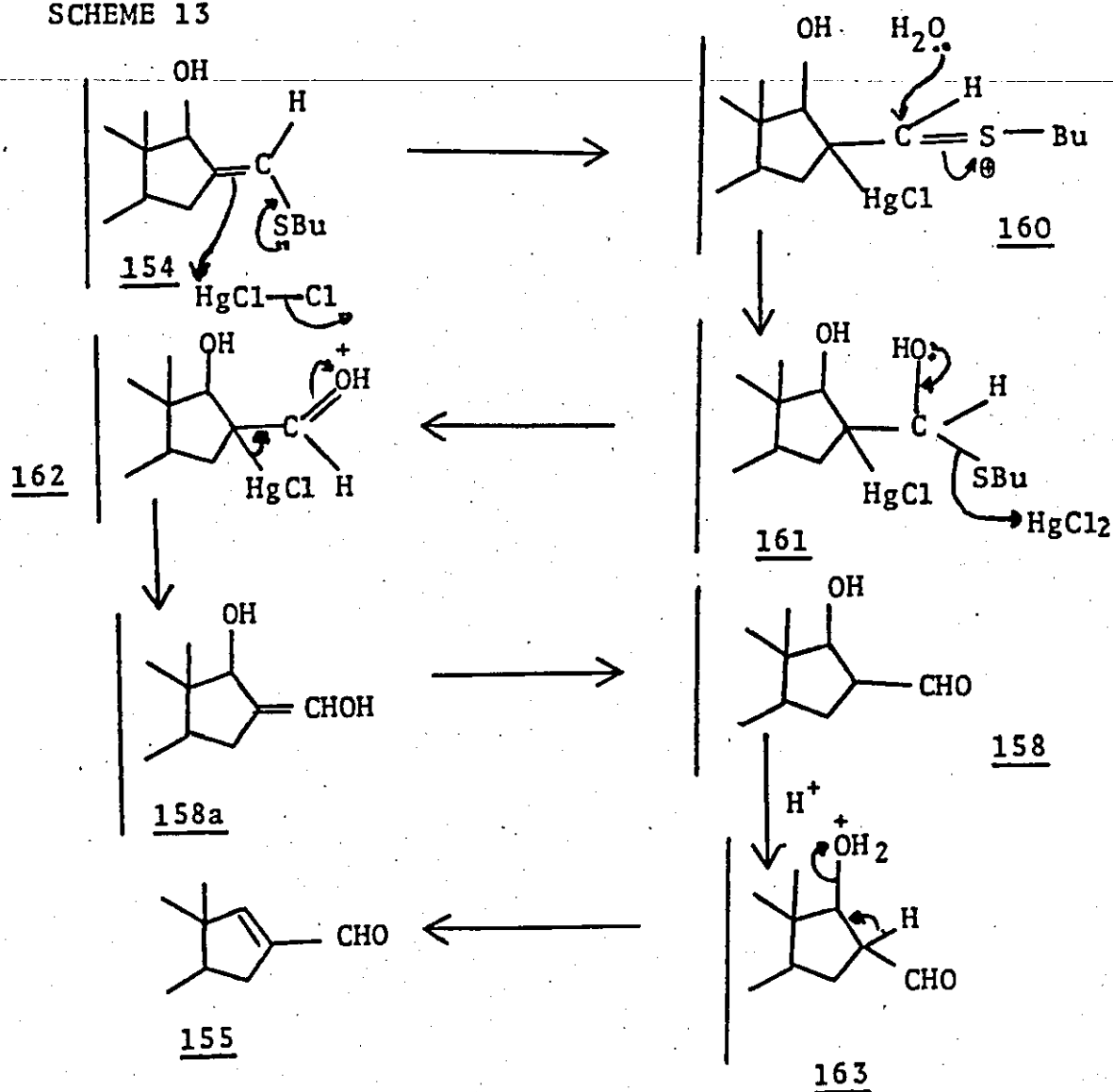


Reduction of the 16-butylthiomethylene-estrone 153 with NaBH_4 gave the 16-butylthiomethylene-estradiol 154 in 80% after chromatographic purification and recrystallisation. The ir spectrum did not show any carbonyl band. The ^1H nmr spectrum of 154 showed some significant differences from that of 153. The 18-CH_3 signal ($\delta 0.7$) was upfield from that in the spectrum of 153 ($\delta 0.9$). Also the signal for the olefinic proton ($\delta 6.1$) was upfield by about 1.3ppm from that in the spectrum of the ketone 153, and the 17-methine proton gave a broad singlet at $\delta 4.06$. This indicated the presence of only one isomer from the

reduction and it seems likely that the product has the 17 β -hydroxy group as the reducing agent would be expected to approach from the α -face.

Deprotection of thioenol ethers has been extensively studied. Wolfron⁹³ and others^{94,95} have used HgCl₂-CdCO₃ to deprotect thioenol ethers and acetals. Attempted deprotection of 154 with HgCl₂-CdCO₃ in acetonitrile/H₂O gave 16-formyl-3-hydroxy-estra-1,3,5,(10),16-tetraene 155 and not the 16-formyl-estradiol 158. The ir spectrum of 155 showed an α,β -unsaturated carbonyl band at 1675cm⁻¹ and the ¹H nmr spectrum showed the aldehyde signal at δ 9.78 as a singlet. No signal for the 17-methine proton was observed at around δ 4.0. Rather, an olefinic proton singlet was observed at δ 7.05 and this was assigned to the 17-methine olefinic proton. The formation of the α,β -unsaturated aldehyde 155 is presumed to involve dehydration of the expected β -hydroxyaldehyde 158 (Scheme 13). It was envisaged that buffering of the reaction mixture with CaCO₃ might prevent the reaction going beyond the expected product 158. This, however, did not prove effective.

SCHEME 13

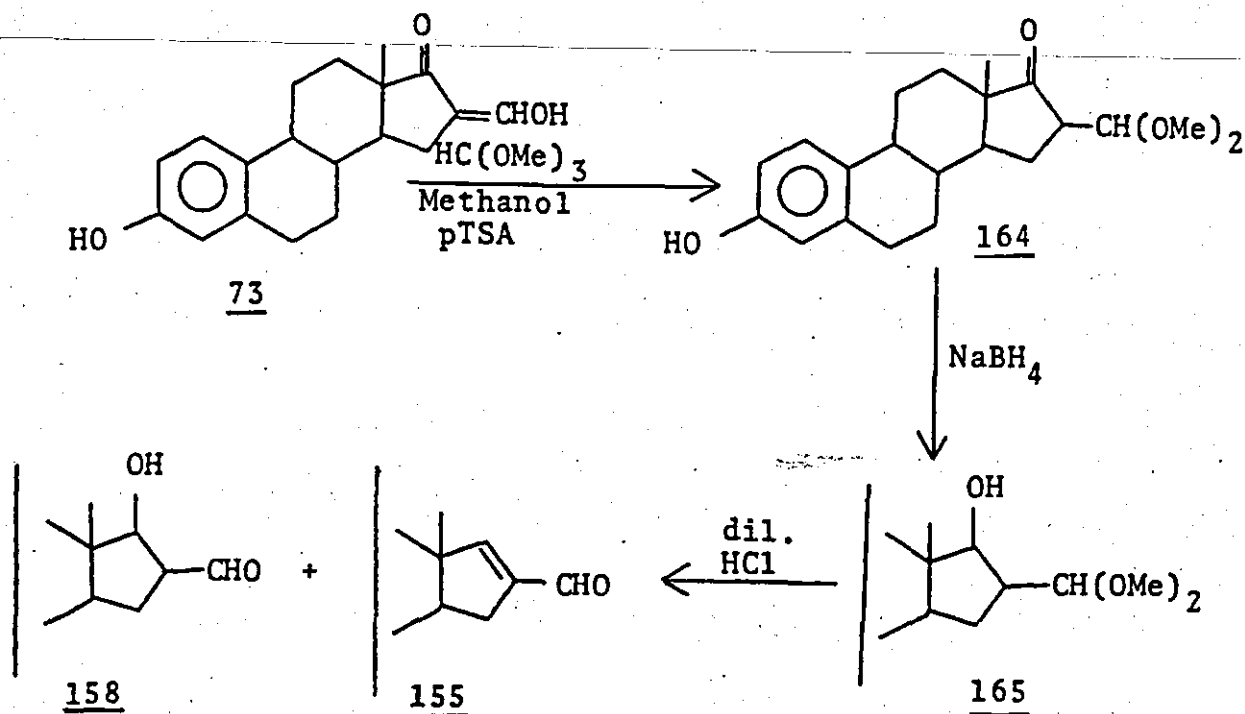


The use of titanium tetrachloride as catalyst in the hydrolysis of thioenol ethers to ketones and aldehydes has been reported.⁹⁶ When the method was applied to the hydrolysis of the 16-butylthio-methylene-estradiol **154** it gave the α,β -unsaturated aldehyde **155** as did the $\text{HgCl}_2\text{-CdCO}_3$ method. Acetylation of the thioenol ether **154** gave the 3,17 β -diacetoxy-derivative **156**. The ^1H nmr spectrum of **156** showed the two methyl signals of the acetoxy groups at $\delta 2.08$ (17-OAc) and $\delta 2.3$ (3-OAc) and the 17-methine proton singlet at $\delta 5.34$ (broad). The ir spectrum of **156** showed the carbonyl

stretching bands of the acetates at 1760cm^{-1} (3-OAc) and 1740cm^{-1} (17-OAc). When the deprotection of 156 was carried out with both $\text{HgCl}_2\text{-CdCO}_3$ and TiCl_4 respectively, the product obtained was 3-acetoxy-16-formyl-estra-1,3,5 (10), 16-tetraene 157. This result was perhaps not surprising since the acetoxy group is a better leaving group than the hydroxyl group. The ir spectrum of 157 showed the carbonyl stretching band of the acetoxy group at 1730cm^{-1} and that of the aldehyde at 1675cm^{-1} . The ^1H nmr spectrum of 157 also showed important signals at $\delta 9.78$ (s, CHO), $\delta 7.0$ (br s, 17-H) and $\delta 2.3$ (s, 3-OAc).

One of the well studied methods of protecting aldehydes is acetalisation. Wenkert⁸⁸ reported the use of trimethyl orthoformate and methanol in the presence of an acid catalyst (pTSA) for the protection of ^{the} aldehyde function of a β -keto-aldehyde. Reaction of 73 with trimethyl orthoformate and methanol in the presence of catalytic amounts of pTSA afforded the 16-dimethoxymethyl estrone 164 in only 10% yield, after chromatographic separation. The ir spectrum confirmed the presence of the 17-ketone ($\nu_{\text{max}} 1720\text{cm}^{-1}$). The ^1H nmr spectrum also showed the methoxy group signals of the acetal at $\delta 3.48$ as a singlet and the neighbouring methine proton ($-\text{CH}(\text{OMe})_2$) at $\delta 4.7$ (d, $J \sim 4\text{Hz}$). The mass spectrum showed the molecular ion at m/z 344.

SCHEME 14



Reduction of **164** with sodium borohydride in methanol gave 16-dimethoxymethyl estradiol **165** in 65% yield. The ir spectrum of **165** did not show any carbonyl absorption band and confirmed the presence of hydroxyl band ($\nu_{\text{max}} 3400\text{cm}^{-1}$). A doublet ^{at} $\delta 3.85$ (J=10Hz and 3Hz) in the ^1H nmr spectrum of **165** was assigned to CH(OMe)_2 ; the ^1H nmr spectrum also showed important signals at $\delta 4.58$ (d, 17-H, 10Hz), 3.37 and 3.42 (two singlets, CH(OMe)_2).

Deprotection of **165** with dilute HCl in acetone gave two products which were identified as 16-formyl-estradiol **158** (50%) and 16-formyl-3-hydroxy-estra-1,3,5(10),16-tetraene **155** (10%) from the spectroscopic data and after chromatographic separation. It was observed that when the reaction time for the

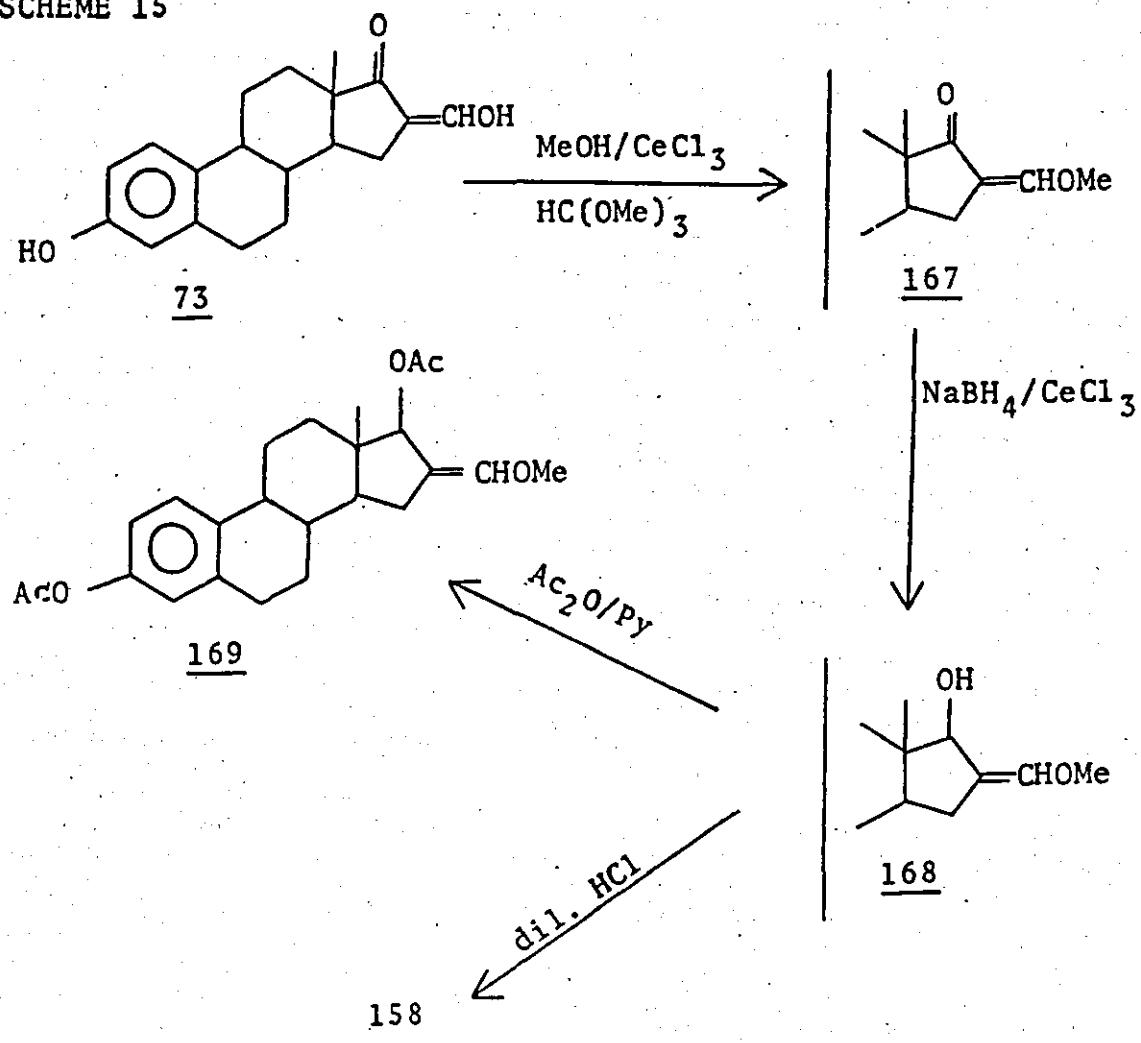
deprotection was reduced to between 20 and 25 minutes, only 158 was obtained. This suggested that the 16-formyl-estradiol 158 was first formed and that this underwent dehydration to give 155. The ir spectrum of 158 confirmed the presence of the hydroxyl group (ν_{\max} 3360cm^{-1}) and the aldehyde group (ν_{\max} 1710cm^{-1}). The ^1H nmr spectrum of the aldehyde at $\delta 9.82$ was a doublet ($J \sim 2\text{Hz}$) and another doublet at $\delta 3.8$ ($J \sim 8\text{Hz}$) was assigned to the 17-H. Using the Karplus equation, the vicinal coupling of 17 α -H to 16 α -H was estimated to be about 7Hz, and 3Hz when the 16 α -H is β . Since the observed coupling constant is 8Hz, it is most likely that the aldehyde has the β -configuration.

Acetylation of 158 gave 156b confirming the presence of the two hydroxyl groups in the former. The ^1H nmr spectrum of 156b showed the two methyl group singlets of the acetoxy groups at $\delta 2.32$ (3-OAc) and $\delta 2.12$ (17-OAc) and the 17-H was at $\delta 4.86$ (d, $J \sim 9\text{Hz}$).

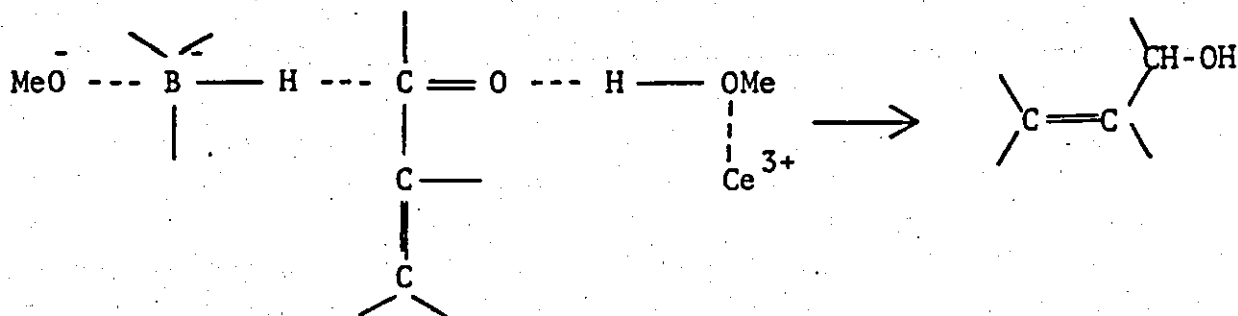
Although the desired 16-formyl estradiol 158 was obtained via acetalization of the 16-hydroxymethylene-estrone 73, the low yield of the acetal, 164, (10%) necessitated a search for alternative routes. Luche^{97 98} reported the use of rare earth chlorides in an efficient synthesis of acetals. In particular, $\text{CeCl}_3 \cdot 6\text{H}_2\text{O}$ has been used to convert ketones and aldehydes to acetals and some selective reactions with the aldehyde function of keto-aldehyde have been observed. Thus, the use of CeCl_3 in the acetalization of 16-hydroxymethylene-estrone 73 was studied. When 73 was allowed to react with methanol in the presence of trimethyl orthoformate and CeCl_3 , the desired acetal 164 was not

obtained. Rather, the product isolated was the enol ether 167 in 90% yield. When the reaction time was increased, no trace of the acetal 164 was observed, only the enol ether 167 was obtained. The ir spectrum of 167 confirmed the presence of the hydroxyl group (ν_{max} 3250cm^{-1}) and the 17-ketone (ν_{max} 1690cm^{-1}). The ^1H nmr of 167 was not the same as that of the acetal 164. A singlet at $\delta 3.9$ confirmed the presence of the methoxy (OMe) group and the 18- CH_3 singlet was at $\delta 0.85$. The methine proton (br s, $W_{1/2}$ 2.5Hz, = CHOMe) signal was at $\delta 7.3$. The ^1H nmr spectrum was similar to that of the thioenol ether 153. The E-configuration was assigned accordingly.

SCHEME 15



The formation of the enol ether 167, rather than the required acetal 164, was not altogether surprising. The reaction was still of some value since the enol ether 167 was reduced to the hydroxy-enol ether 168 (80%) by use of NaBH_4 , in the presence of CeCl_3 .⁹⁷ This method has recently been reported to be successful in similar systems in which hydride reductions, in the absence of CeCl_3 , reduced both the ketone and the double bond.^{88,9} It is believed that the function of Ce^{3+} in these reductions is the complexation of the solvent (i.e. methanol) which then results in a stronger acidic medium. In addition, the Lewis acid nature of CeCl_3 leads to 1,2 reduction selectivity.⁸⁴

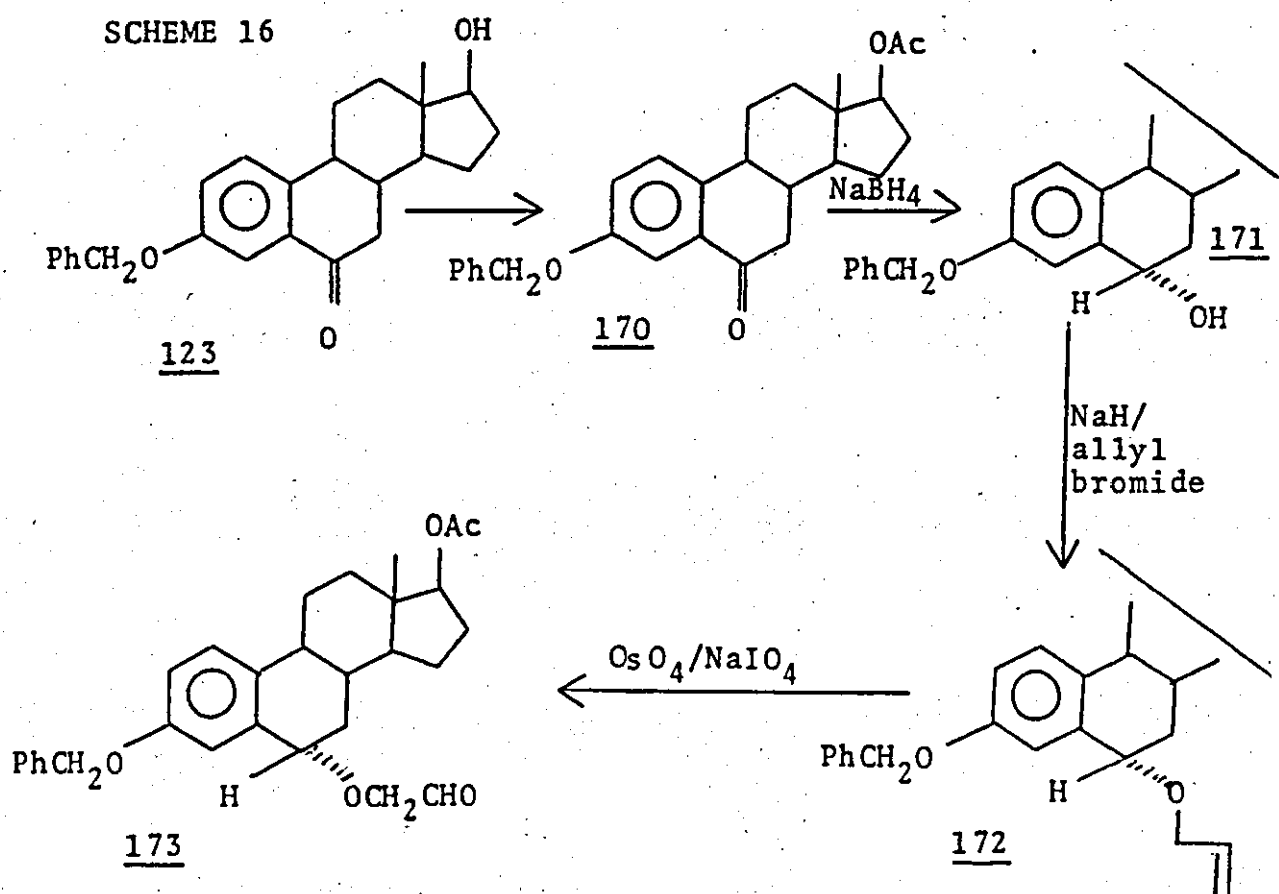


The ir spectrum of 168 did not show any carbonyl absorption band but rather a broad hydroxyl band at 3300cm^{-1} . The ^1H nmr spectrum of 168 showed the 17-H signal at $\delta 4.15$ (br, s) while the olefinic proton ($=\text{CH OMe}$) appeared at $\delta 6.15$ (br s, W 2.5 Hz). As expected, the latter signal is at higher field by about 1.15ppm than its equivalent in the ^1H nmr spectrum of the ketone 167. Acetylation of this estradiol enol ether 168, which is not very crystalline, with acetic anhydride in pyridine, afforded the 3,17β-diacetoxy enol ether 169 which was crystallised to provide an

analytical sample. The ^1H nmr spectrum confirmed the presence of two acetate groups (δ 2.08, 17-OAc and δ 2.28, 3-OAc) and the 17-methine proton signal appeared at δ 5.4 (cf. δ 4.15 for the 17-methine proton in 167). The ir spectrum of 169 had two carbonyl stretching bands at 1770cm^{-1} (3-OAc) and 1730cm^{-1} (17-OAc).

Deprotection of the hydroxy-enol ether 168 with dilute HCl in acetone afforded the 16-formyl estradiol 158, the structure of which was confirmed by its ^1H nmr spectra.

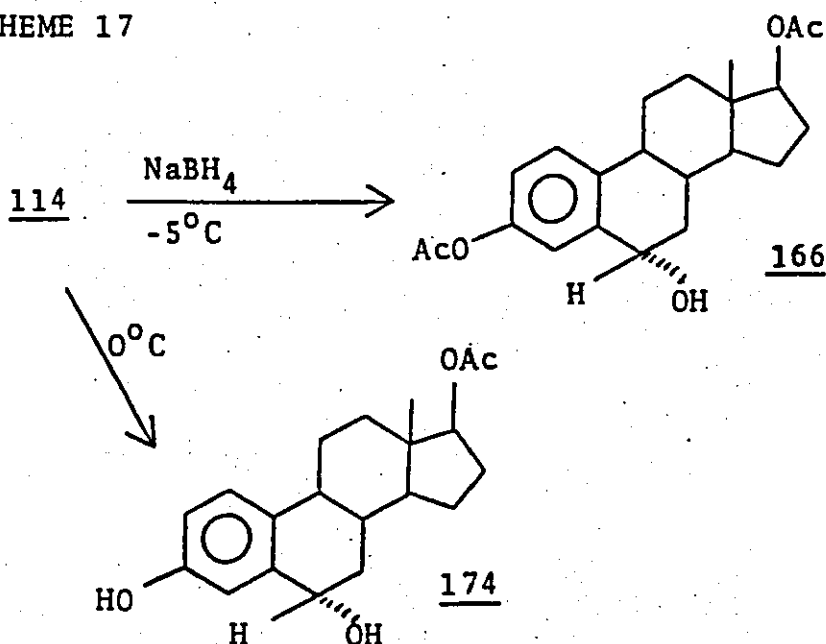
An approach to the third group of target aldehydes 112 (e.g. 173) is shown in Scheme 16.



Acetylation of the 17 β -hydroxy-6-ketone 123 with acetic anhydride in pyridine gave 17 β -acetoxy-3-benzyloxy-estra-1,3,5(10)-trien-6-one 170. The ^1H nmr spectrum of 170 showed the methyl signal of the acetoxy group at δ 2.08 (s). The ir spectrum also showed two carbonyl stretching bands at 1730cm^{-1} (17-OAc) and 1675cm^{-1} (ArC=O). The ketone 170 was reduced to the alcohol, 17 β -acetoxy-3-benzyloxy-6 α -hydroxy-estra-1,3,5(10)-triene 171, by reaction with sodium borohydride at low temperature (0 to 5°C). The ir spectrum of 171 showed the hydroxy group (ν_{max} 3470cm^{-1}) and did not show the carbonyl stretching band of the 6-ketone at ν_{max} 1675cm^{-1} . The chemical shift of the 18-CH₃ signal in the ^1H nmr spectrum in 171 (δ 0.8) was different from that in 170 (δ 0.85). The α -configuration assigned to the alcohol 171 was based on the similar assignment to the alcohol 166 obtained from the reduction of 3,17 β -diacetoxy-estra-1,3,5(10)-triene-6-one 114 with NaBH₄.^{78,79} ORD and chemical evidence was reported to confirm the assignment of the configuration.

It is worth noting that attempts to reproduce the Wintersteiner reduction of the diacetoxy-ketone 114 to the 6 α -hydroxy derivative 166 in most cases led to 17 β -acetoxy-3,6-dihydroxy-estra-1,3,5(10)-triene 174. However, at a lower temperature (-5°C), the desired product 166 was obtained in relatively poor yield (30%). The sensitivity of the 3-acetoxy group led us to investigate the 3-benzyloxy series, starting with the 3-benzyloxy-6-ketone 123.

SCHEME 17



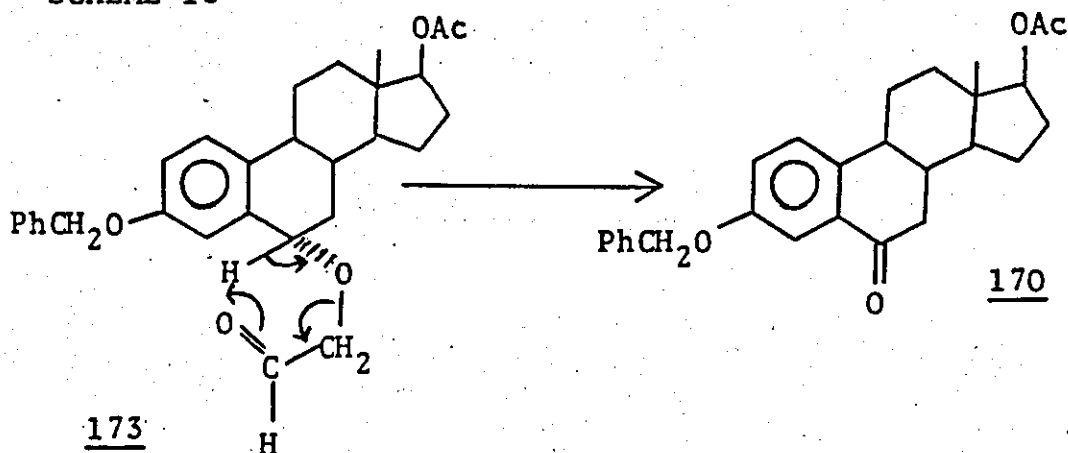
The 3-benzyloxy-alcohol 171 was converted to the allyl ether 172 by reaction with allyl bromide and sodium hydride. The excess NaH used in the reaction was destroyed with dilute acetic acid (10% v/v) to ensure no deacetylation of the 17 β -acetoxy group. Preparative tlc of the crude product followed by crystallisation gave 64% of the allyl ether 172. The ir spectrum of 172 did not show any hydroxyl absorption band and confirmed the presence of the acetate group (ν_{max} 1730cm^{-1}). The ^1H nmr spectrum confirmed the presence of the allyl group by the olefinic proton signals at $\delta 5.25$ (m, $-\text{CH}_2-\text{CH}=\text{CH}_2$), the O-methylene protons at $\delta 4.1$ (br s, $\text{O}-\text{CH}_2-\text{CH}=\text{CH}_2$) and the methylene protons at $\delta 5.2$ (m, $-\text{CH}_2\text{CH}=\text{CH}_2$). The mass spectrum of the allyl ether 172 did not give a molecular ion but rather a fragment at m/z 402 which could be arising from elimination of allyl alcohol ($\text{C}_3\text{H}_6\text{O}$).

Cleavages of olefinic bonds to give aldehydes have been extensively studied^{79b,80}. Lemieux⁷⁹ successfully used osmium tetroxide and sodium periodate in a one-pot reaction. This method has the advantage of not leading to further oxidation of the aldehyde. Moreover, catalytic amounts of OsO_4 are sufficient because the periodate oxidises the osmium in its lower valence forms to the tetroxide, thus regenerating the hydroxylating agent. This method is a combination of two well-known reactions, namely OsO_4 hydroxylation of an olefin and periodate cleavage of 1,2-diols. Thus, oxidation of the allyl ether 172 with OsO_4 - NaIO_4 gave the formylmethoxy-derivative 173, which was found to be unstable during attempts to purify it. The ^1H nmr spectrum of the crude product showed the aldehyde proton signal at $\delta 9.65$ (br s) and the methylene protons ($-\text{OCH}_2\text{CHO}$) at $\delta 4.0$ (br s). The ir spectrum also showed a broad carbonyl stretching band at about 1730cm^{-1} (17-OAc and CHO).

Attempts to purify the aldehyde by preparative tlc of the crude product led to significant reduction in the amount of the aldehyde as was evident from the ^1H nmr spectrum. The ir spectrum of the chromatographed material showed a new low intensity band at 1680cm^{-1} , which is typical of α,β -unsaturated carbonyls. On the basis of these observations, it was assumed that decomposition of the aldehyde 173 was taking place. It was considered that the decomposition could be a thermal novel "retro-ene" reaction (Scheme 18) leading to the 6-ketone 170. This could explain the appearance of the carbonyl stretching band at 1680cm^{-1} .

When the chromatographed material was heated under reflux in dry toluene for 5 hours, under nitrogen, the aldehyde 173 was completely destroyed as indicated by the ^1H nmr spectrum of the product. The ir spectrum showed a more pronounced carbonyl stretching band at 1680cm^{-1} and the 18-Me ($\delta 0.85$) in the ^1H nmr spectrum was identical with that of the 6-ketone 170. The major product isolated by preparative tlc was confirmed as the 6-ketone 170 by its spectroscopic data.

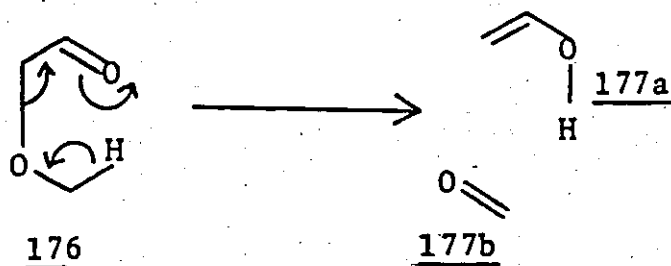
SCHEME 18



A repeat of this fragmentation reaction using the crude oxidation product 173 directly without chromatographic purification gave the same result.

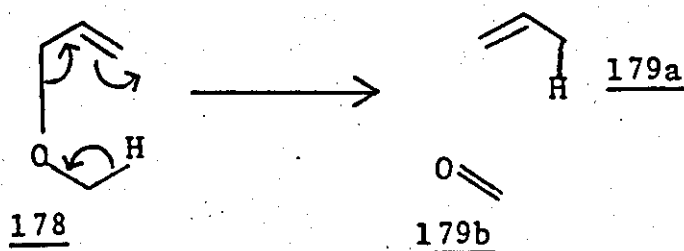
Cookson and Wallis⁸¹ in their studies of the pyrolysis of allyl ethers and related systems drew attention to the possibility of retro-ene reactions of α -methoxycarbonyl compounds (e.g. 176 \rightarrow 177). Only one example of this type of reaction has been reported.

SCHEME 19



Thus, when α -diphenylmethoxy- α -methyl-4-methylpropiophenone was pyrolysed in toluene at 540°C , a product mixture of benzophenone (52%) and α -methyl-4-methylpropiophenone (30%) were obtained. It was also established that allyl ethers fragmented in a similar fashion, when pyrolysed at elevated temperatures as shown in the scheme below.

SCHEME 20

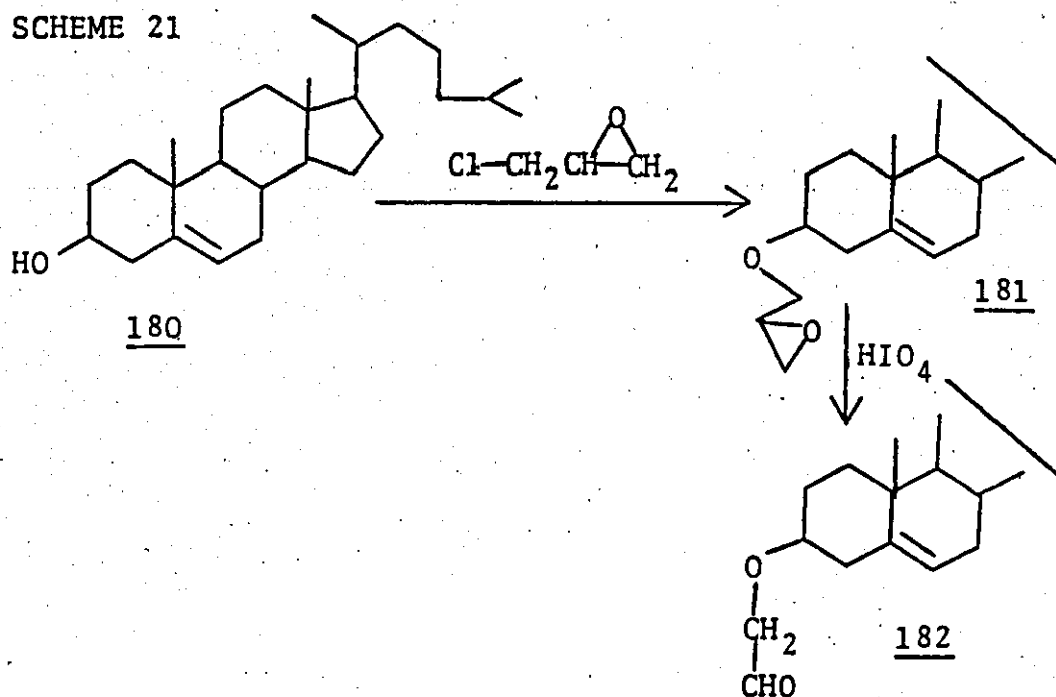


When the allyl ether 172 was heated under reflux in toluene under nitrogen, no fragmentation occurred, probably because of the relatively low temperature employed.


The fragmentation of the aldehyde 173 to the ketone 170 is unusual in that it takes place at a relatively low temperature (ca 110°). It was therefore considered necessary to investigate

further this novel "retro-ene" reaction. One possible important feature of the aldehyde 173 is the benzylic nature of the 6-H. Accordingly, other steroidal formylmethoxy-derivatives were synthesised which did not possess such an activated C-H. Cholesterol and cholestanol were both converted to their formylmethoxy-derivatives, 182 and 188. Scheme 21 outlines the route from cholesterol. The allyl ether route was not applicable because at the oxidation step, the Δ^5 -double bond could also be cleaved.

SCHEME 21

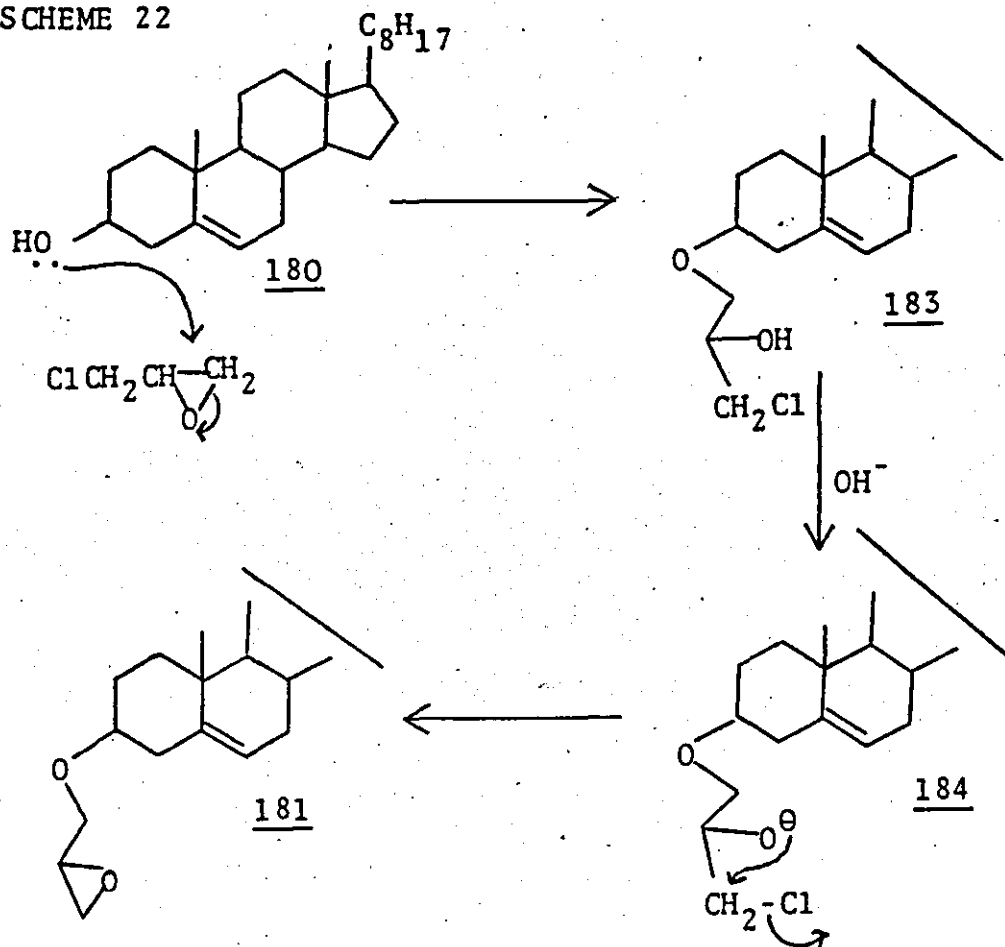


Cholesterol 180 was converted to the glycidyl ether 181 by reaction with epichlorohydrin in aqueous NaOH solution/ CH_2Cl_2 in the presence of benzyltrimethylammonium chloride, a phase transfer catalyst. This method was used by Akio⁸² to convert other aliphatic alcohols to glycidyl ethers. The ^1H nmr spectrum of 181 confirmed the presence of the glycidyl ether function. The methine

proton H^c $\left(\begin{array}{c} (H^a \text{---} O \text{---} CH^d H^e O^-) \\ (H^b \text{---} \text{---} H^c) \end{array} \right)$ was observed as a multiplet which overlapped with the multiplet of the 3-H signal ($\delta 3.0$ - 3.5). An octet ($\delta 3.5$ - 3.9) typical of the AB portion of an ABX system ($J_{AB} \sim 11\text{Hz}$) was assigned to protons H^d and H^e . A triplet ($\delta 2.8$, $J \sim 4.5\text{Hz}$) was assigned to H^b and a quartet ($\delta 2.62$, $J \sim 2.5\text{Hz}$) was assigned to H^a since it is known that cis-vincinal spin-spin coupling constants in epoxides are greater than the trans values. The mass spectrum showed the molecular ion at m/z 442 and a base peak at m/z 368 arising from the loss of $C_3H_6O_2$ (HO ).

The probable reaction mechanism involved in the formation of the glycidyl ether 181 is shown in Scheme 22.

SCHEME 22



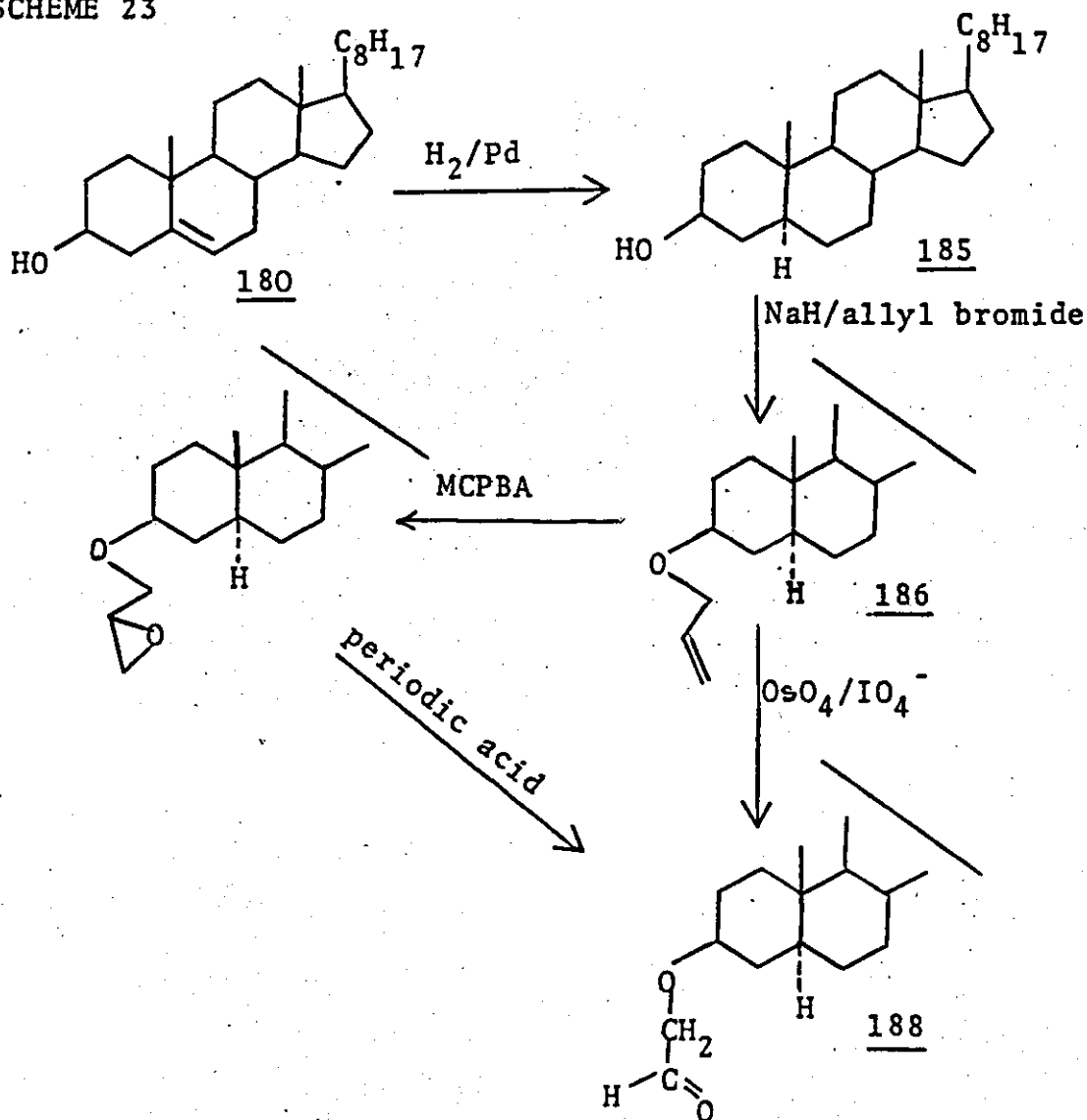
Fieser and Rajagopalan⁸³ had used periodic acid catalysed hydrolysis to cleave steroidal epoxides to diaxial diols. It was thought that the periodic acid might serve to hydrolyse the glycidyl ether and cleave the resultant diols to aldehyde. Reaction of 181 with periodic acid gave the formylmethoxy-derivative 182. The ir spectrum of 182 showed the carbonyl stretching band of the aldehyde at 1730cm^{-1} . The ^1H nmr spectrum also showed the presence of the aldehyde ($\delta 9.65$, br s) and the O-methylene protons at $\delta 4.05$ (br s). The mass spectrum showed the molecular ion at m/z 428 and the base peak at 368 ($M^+ - 60$) owing to the loss of $\text{C}_2\text{H}_4\text{O}_2$ (HOCH_2CHO). When the aldehyde 182 was heated under reflux in toluene under nitrogen for 5 hours, the spectroscopic data (^1H nmr and ir) of the isolated material showed no fragmentation had occurred and that the aldehyde remained unchanged.

Hydrogenation of cholesterol 180 using a palladium catalyst gave 5α -cholestanol 185. Reaction of cholestanol 185 with allyl bromide and sodium hydride in DMF gave the 3β -allyl ether 186. The ir spectrum of 186 did not show any hydroxyl absorption band and the ^1H nmr spectrum confirmed the presence of the allyl group showing important signals at $\delta 3.95$ (d, $J \sim 6\text{Hz}$, $\text{OCH}_2\text{CH}=\text{CH}_2$), $\delta 5.25$ (m, $\text{OCH}_2\text{CH}=\text{CH}_2$) and $\delta 6.0$ (m, $\text{OCH}_2\text{CH}=\text{CH}_2$). The mass spectrum of 186 showed the molecular ion at m/z 444.

Oxidation of 186 with OsO_4 and NaIO_4 gave 3β -formylmethoxy-cholestane 188. The ir spectrum of 188 showed the carbonyl stretching band of the aldehyde at 1725cm^{-1} . The ^1H nmr spectrum also confirmed the presence of the aldehyde ($\delta 9.57$, br s) and the

O-methylene protons (δ 4.05, br s). The mass spectrum of 188 showed the molecular ion at m/z 430.

SCHEME 23

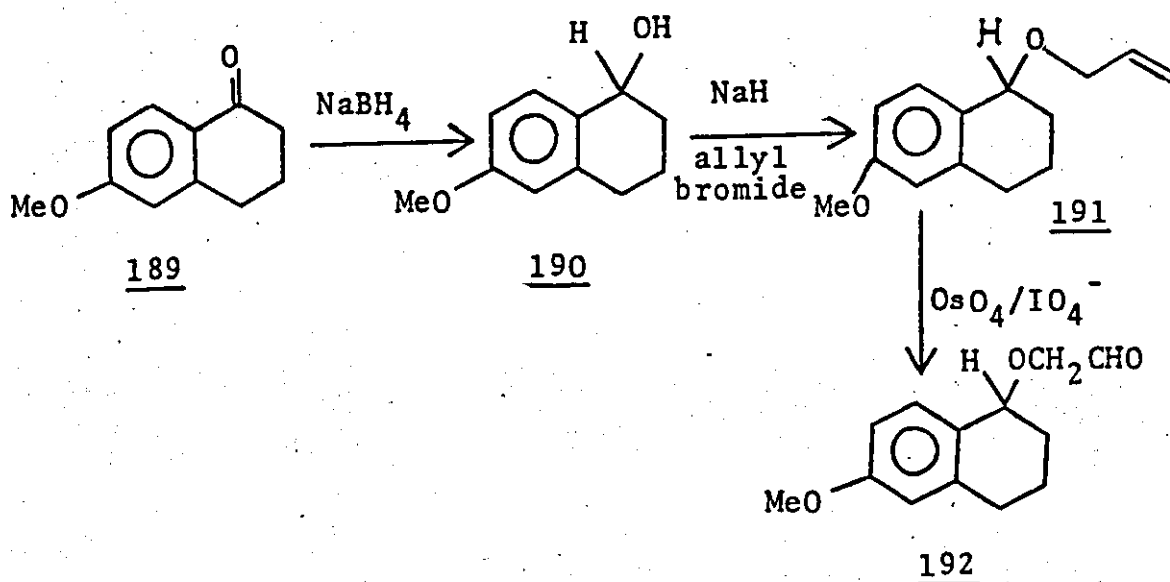


The allyl ether 186 was also converted to the glycidyl ether 187 via oxidation with MCPBA. The ¹H nmr spectrum of 187 was similar to that of the cholesteryl-glycidyl ether 181. Hydrolysis and oxidation of 187 with periodic acid afforded the formylmethoxy-derivative 188. Thus, this aldehyde 188 was obtained

by two different routes. When the aldehyde 188 was heated under reflux in toluene, under nitrogen, no change was observed in the spectroscopic data (^1H nmr and ir), indicating that no fragmentation occurred. Thus, the 3-formylmethoxy-derivatives 182 and 188 of cholesterol and cholestanol, which were not benzylic, did not undergo thermal fragmentation as readily as the 6-formylmethoxy-estradiol derivative 173.

6-Methoxy-1-tetralone 189 was converted to the allyl ether-derivative 191, in two steps as outlined below.

SCHEME 24



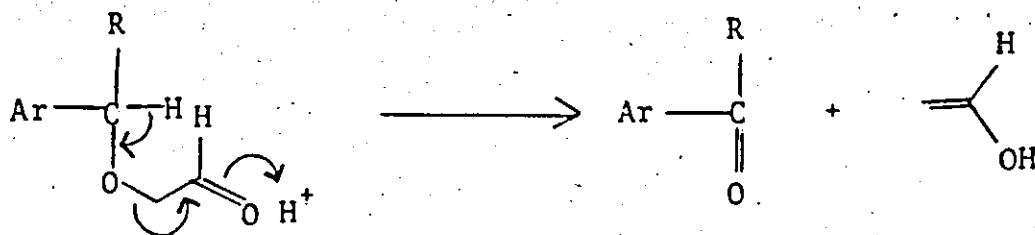
Reduction of 6-methoxy-1-tetralone 189 with NaBH_4 gave 6-methoxy-1-tetralol 190. The ir spectrum of the 1-tetralol, 190, did not show any carbonyl absorption band and confirmed the presence of the hydroxyl group (ν_{max} 3400cm^{-1}). Reaction of 190 with allyl bromide and sodium hydride in benzene gave the allyl ether 191. The ir spectrum of 191 did not show any hydroxyl

absorption band. The ^1H nmr spectrum of 191 confirmed the presence of the allyl group showing important signals at $\delta 5.8$ (m, $\text{OCH}_2\text{CH}=\text{CH}_2$) $\delta 3.9$ (d, $J \sim 7\text{Hz}$, $\text{OCH}_2\text{CH}=\text{CH}_2$), $\delta 5.1$ (m, $-\text{OCH}_2\text{CH}=\text{CH}_2$) and $\delta 3.6$ (s, OMe). The mass spectrum showed the molecular ion at m/z 218.

Oxidation of the allyl ether 191 with $\text{OsO}_4 - \text{NaIO}_4$ gave the formylmethoxy-derivative 192, which was also found to be unstable on chromatography, as was the estradiol-derivative 173. The ^1H nmr spectrum of the crude product 192 showed the aldehyde signal at $\delta 9.55$ (br s) and the O-methylene protons at $\delta 4.0$ (br s). The ir spectrum of crude 192 also showed a carbonyl stretching band at 1720cm^{-1} . However, when the crude product was subjected to preparative tlc, the ir spectrum of the isolated material showed a carbonyl absorption band for the aldehyde ($\nu_{\text{max}} 1720\text{cm}^{-1}$) and the 6-ketone ($\nu_{\text{max}} 1680\text{cm}^{-1}$). When the chromatographed 192 was heated under reflux in toluene under nitrogen, the only isolable product was 6-methoxy-1-tetralone 189, the structure of which was confirmed from its spectroscopic data. The observations confirmed that the thermal fragmentation (a "retro-ene") reaction requires that the C-H bond involved is benzylic.

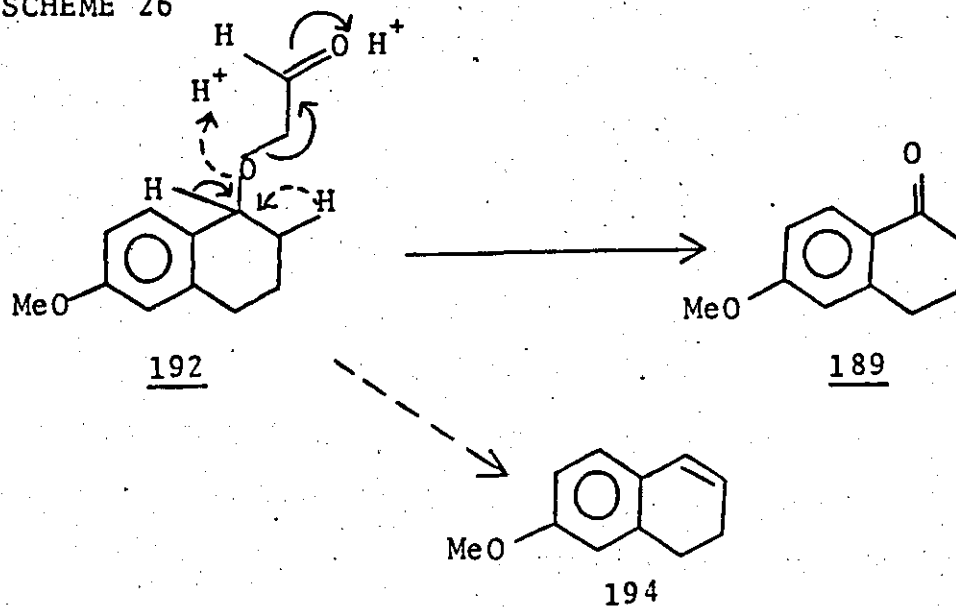
In view of the observation that the fragmentation occurred partially on preparative tlc, the possibility of acid-catalysis being important was considered (Scheme 25).

SCHEME 25



The formylmethoxy-tetralone 192 was stirred in dry benzene with pTSA briefly at room temperature. The product obtained was found to be a mixture of 6-methoxy-1-tetralone 189 and 6-methoxy-3,4-dihydronaphthalene 194. Glc of the mixture showed a ratio of 3:1 of 194:189. The ^1H nmr spectrum of 193 confirmed the presence of the olefinic protons (1-H and 2-H) at $\delta 6.45$ (d) and $\delta 5.9$ (quintet) respectively and the methoxy protons at $\delta 3.75$ (s). The mass spectrum showed the molecular ion at m/z 160. It is apparent that acid-catalysed fragmentation can also lead to the "retro-ene" product. However, the major and competing reaction appears to be the acid-catalysed elimination to give the dihydronaphthalene 194. At this stage it is not clear how general the thermal or acid-catalysed fragmentations are. Further investigation is required.

SCHEME 26

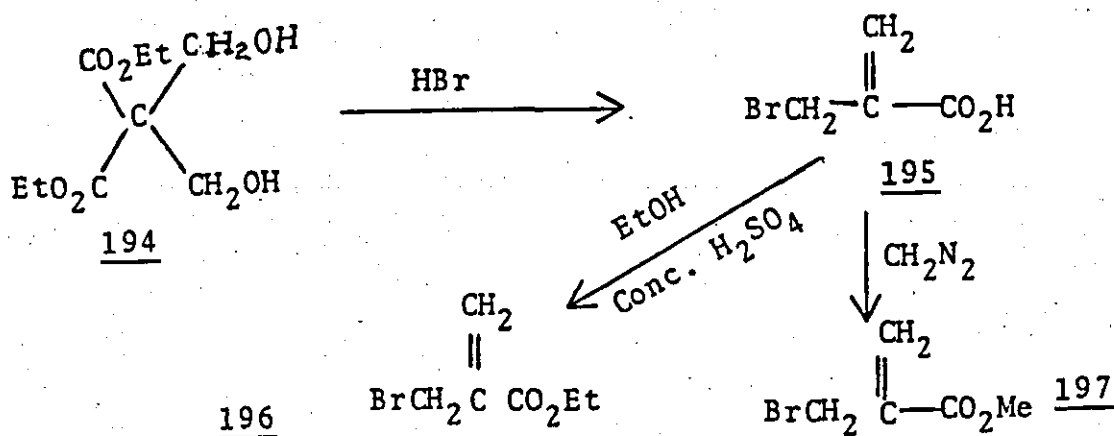


The target aldehydes 138, 155 and 158 were converted to the desired α -methylene lactones 198, 199 and 200 respectively by use of the Drieding-Schmidt reaction. The acrylate used was either methyl or ethyl α -(bromomethyl)acrylate obtained from the α -

(bromomethyl)acrylic acid 195. Reaction of diethyl bis(hydroxymethyl)malonate 194 with hydrobromic acid (48%) gave the α -(bromomethyl)acrylic acid 195 in 36% yield.¹⁰⁰

Ethyl α -(bromomethyl)acrylate 196 was obtained from the concentrated sulphuric acid-catalysed reaction of the acrylic acid 195 with ethanol. The ^1H nmr confirmed the presence of the ester moiety with signals at δ 4.28 (quartet, $\text{CO}_2\text{CH}_2\text{CH}_3$) and δ 1.3 (t, $\text{CO}_2\text{CH}_2\text{CH}_3$).

SCHEME 27

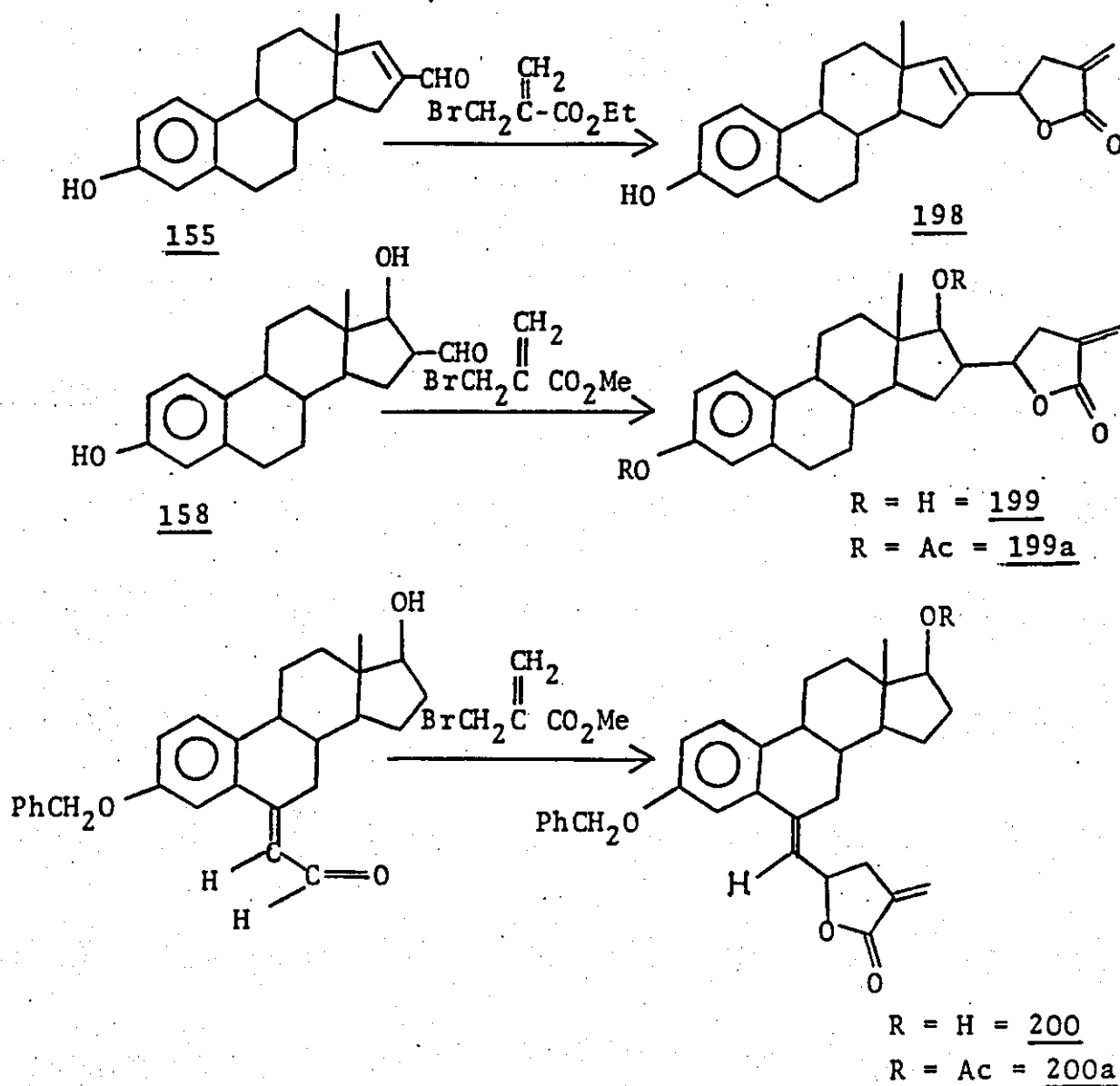


Methyl α -(bromomethyl)acrylate 197 was obtained by the reaction of the acrylic acid 195 with calculated amounts of ethereal diazomethane. Unreacted acrylic acid 195 was washed out with Na_2CO_3 solution and this aqueous extract could be acidified to afford the acrylic acid 195.

Reaction of the 16-formyl-3-hydroxy-estra-1,3,5(10),16-tetraene 155 with ethyl α -(bromomethyl)acrylate 196 and activated zinc in THF gave the expected α -methylene lactone 198 which contained polymeric by-products. After preparative tlc and

crystallisation, the α -methylene lactone 198 was obtained in 40% yield. The ^1H nmr spectrum of 198 confirmed the presence of the α -methylene lactone moiety and showed important signals at $\delta 5.7$ (m, $W_{1/2}$ 3Hz, $\text{C}=\underline{\text{CH}}_2$), $\delta 6.3$ (m, $W_{1/2}$ 3Hz, $\text{C}=\underline{\text{CH}}_2$), $\delta 5.15$ (t, $J \sim 9\text{Hz}$, $\underline{\text{CH}}-\text{OCO}$)

SCHEME 28



and $\delta 5.98$ (br s, 17-H). The ir spectrum showed important bands at 3400cm^{-1} (OH), 1755cm^{-1} ($\text{C}=\text{O}$ of lactone) and 1670cm^{-1} ($\text{C}=\text{C}$).

Similarly, the aldehyde 158 was converted to the desired α -methylene lactone 199 by reaction with activated zinc and methyl α -(bromomethyl)acrylate 197 in THF. Preparative tlc followed by crystallisation gave a pure sample of 199 which was highly insoluble in most solvents. The ^1H nmr spectrum (in DMSO-acetone) of 199 showed the α -methylene lactone moiety and showed important signals at $\delta 6.1$ (br s, $W_{\frac{1}{2}}$ 4Hz, $\text{C}=\underline{\text{CH}_2}$), $\delta 5.7$ (br s, $W_{\frac{1}{2}}$ 4Hz, $\text{C}=\underline{\text{CH}_2}$), $\delta 4.6$ (m, CHOCO) and $\delta 3.6$ (m, 17-H). The ir spectrum showed the lactone carbonyl at $\nu_{\text{max}} 1745\text{cm}^{-1}$. Acetylation of the α -methylene lactone 199 with acetic anhydride in pyridine gave the diacetoxo-derivative 199a. The ^1H nmr spectrum confirmed its structure and showed important signals at $\delta 2.12$ (s, 17-OAc), $\delta 2.32$ (s, 3-OAc), $\delta 6.1$ (br s, $W_{\frac{1}{2}}$ 4Hz, $\text{C}=\underline{\text{CH}_2}$), $\delta 5.7$ (br s, $W_{\frac{1}{2}}$ 4Hz, $\text{C}=\underline{\text{CH}_2}$) and $\delta 4.6$ (m, 17-H and CHOCO).

The aldehyde 138 was also converted to the α -methylene lactone 200 by reaction with activated zinc and methyl α -(bromomethyl)acrylate 197. Preparative tlc of the crude product was carried out several times to free the product 200 of polymerized by-products. The α -methylene lactone thus isolated could not be crystallised. The ^1H nmr spectrum confirmed the presence of the α -methylene lactone moiety and showed important signals at $\delta 6.38$ (br s, $W_{\frac{1}{2}}$ 3Hz, $\text{C}=\underline{\text{CH}_2}$), $\delta 5.78$ (br s, $W_{\frac{1}{2}}$ 3Hz, $\text{C}=\underline{\text{CH}_2}$), $\delta 5.48$ (q, $J \sim 8\text{Hz}$, CHOCO) and $\delta 6.05$ (d, $J \sim 8\text{Hz}$, $=\underline{\text{CH}}-\text{CHOCO}$). Double irradiation of the quartet at $\delta 5.45$ caused the doublet at $\delta 6.05$ to collapse to a broad singlet, thus confirming the assignment. Acetylation

of 200 by reaction with acetic anhydride in pyridine gave the 17-acetoxy-derivative 200a. Preparative tlc afforded pure 200a which also, unfortunately, did not crystallise. The ^1H nmr spectrum of 200a confirmed its structure and showed important signals at $\delta 6.38$ (m, $W_{1/2}$, 3Hz, $\text{C}=\underline{\text{CH}}_2$), $\delta 5.78$ (m, $W_{1/2}$, 3Hz, $\text{C}=\underline{\text{CH}}_2$), $\delta 5.47$ (q, $J \sim 8\text{Hz}$, $\underline{\text{CHOCO}}$), $\delta 6.02$ (d, $J \sim 8\text{Hz}$, $=\underline{\text{CH}} \text{ CHOCO}$), $\delta 4.8$ (t, $J \sim 9\text{Hz}$, 17-H) and $\delta 2.1$ (s, 3-OAc).

The stereochemistry of the α -methylene lactones 199 and 200 are not known. However, it is most probable that the α -methylene lactone 199 is an isomeric mixture as evident from the broad signal of the 18-Me of the chromatographed material.

Biological tests for anti-tumour activity and estrogen receptor binding affinity are to be carried out on the synthesised α -methylene lactones 198, 199 and 200 by Dr J.R. Traynor in these laboratories. The results from the biological tests will further determine any other work that would be carried out.

EXPERIMENTAL

Solvents were distilled using standard methods. Solutions were dried over anhydrous magnesium sulphate and evaporated *in vacuo*. Preparative T.L.C. plates were prepared from Kieselgel 60PF 254 (Merck). Ir spectra were determined with a Perkin-Elmer 177 spectrometer. ^1H nmr spectra were determined in CDCl_3 or otherwise specified solvents containing TMS at 60 MHz with a Varian EM 360A spectrometer or at 90 MHz with a Perkin-Elmer R32 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 and are uncorrected. ^{13}C nmr spectra were recorded at 20.1 MHz with a Bruker WP-80 spectrometer operating at the Fourier-transform mode. Mass spectra were recorded on a Kratos MS 80 mass spectrometer using a DS-55 data system. Ether refers to diethyl ether.

1. 3,17 β -Diacetoxy-estra-1,3,5(10)-triene (113)

A mixture of 17 β -estradiol (5g) and acetic anhydride (18 ml) in dry pyridine (70 ml) was heated under reflux for 1 h ; cooled and poured onto ice/water (100g). The resulting precipitate was filtered and crystallised from methanol/water to give 17 β -estradiol diacetate (6.12g, 94%), m.p. 127-128°C (lit.⁵⁷ 126-128°C); ν max (mull) 1770 (C=O, 3-OAc) and 1730cm⁻¹ (C=O, 17-OAc); δ 0.82 (s, 3H, 18-Me), δ 2.08 (s, 3H, 17-OAc), δ 2.28 (s, 3H, 3-OAc), δ 4.7 (t, $J \sim 8$ Hz, 1H, 17-H), δ 6.88 (br s, 1H, 2-H), δ 7.3 (d, $J \sim 8$ Hz, 1H, 1-H), δ 6.79 (s, 1H, 4-H).

2. 3,17 β -Diacetoxy-estra-1,3,5(10)-trien-6-one (114)

3,5-Dimethylpyrazole (12.5g) was added in one portion to a stirred mixture of dry CrO₃ (13.2g) in methylene chloride (80 ml) at -25°. After 15 min., a solution of the estradiol diacetate (2.0g) in methylene chloride (10 ml) was added to the stirred complex. The stirred reaction mixture was maintained at -15 to -20°C for 4 h , after which NaOH solution (5M, 50 ml) was added and the resultant mixture was stirred for a further 30 min. at -5° to 0°. The methylene chloride layer was separated and the aqueous layer was extracted with methylene chloride (2 x 50 ml). The combined methylene chloride layer was washed with dilute HCl (2M, 2 x 100 ml) and brine (2 x 100 ml) and dried. Basification of the HCl extracts afforded 3,5-dimethylpyrazole which was recrystallised from petroleum-ether (b.p. 60-80°, 60% recovery). Filtration and evaporation of the methylene chloride layer gave a crude product which was chromatographed on silica, eluting with petroleum-

ether (b.p. 40-60) and petroleum ether/ethyl acetate (4:1) to afford the 6-ketone 114, (968mg, 48%). Recrystallisation from ethanol gave a pure sample of the 6-ketone 114 (0.8g ; 40%), m.p. 173-174°C (lit.⁵⁷ 173-175°C), $[\alpha]_D^{20}$ (c, 2%, CHCl₃); ν_{\max} (mull) 1675 (C=O, 6-ketone), 1730 (C=O, 17-OAc) and 1770cm⁻¹ (C=O, 3-OAc); δ 0.83 (s, 3H, 18-CH₃), 2.08 (s, 3H, 17-OAc), 2.30 (s, 3H, 3-OAc), 4.75 (t, $J \sim 8$ Hz, 1H, 17-H), 7.38 (m, 2H, 1-H and 2-H), 7.8 (d, $J \sim 2.5$ Hz, 1H, 4-H).

3. 3,17 β -Dihydroxy-estra-1,3,5(10)-trien-6-one

6-Keto-estradiol-diacetate 114 (0.5g) was suspended in methanolic KOH solution (5%, w/v, 15 ml) and stirred at room temperature for about 4 h. The progress of the reaction was monitored on t.l.c. It was diluted with water and extracted with CHCl₃ (x3). The CHCl₃ extracts were washed with brine, dried and evaporated. Recrystallisation from ethanol gave pure sample (0.25g ; 62%), m.p. 278-280°C (lit.⁵⁹ 280-282°C), ν_{\max} (mull) 3500, 3200 (OH), 1670 (C=O), 1620 and 1570cm⁻¹ (C=C); δ (DMSO d₆) 0.78 (s, 3H, 18-Me), 3.7 (t, $J \sim 8$ Hz, 1H, 17-H), 4.12 (d, $J \sim 5$ Hz, 1H, 17-OH, D₂O exchangeable), 7.1 (m, 2H, 1-H and 2-H), 7.4 (d, $J \sim 5$ Hz, 1H, 4-H).

4. 3-Benzoyloxy-17 β -hydroxy-estra-1,3,5(10)-trien-6-one (123)

6-Keto-estradiol-diacetate 114 (1g) was suspended in absolute ethanol (80 ml). Anhydrous K₂CO₃ (1g) and benzyl chloride (1 ml) were added to the suspension. The resulting reaction mixture was heated under reflux for 5-6 h. The product was concentrated, extracted with ethyl acetate, washed with water, dried and evap-

orated to give a crude product (1g, 86%). Recrystallisation from methanol gave a pure sample (0.92g; 80%), m.p. 174-176°C (lit.⁶⁹ 175-177°C), ν_{\max} (mull) 3540 (OH), 1675 (C=O) and 1615 cm⁻¹ (C=C); δ 0.78 (s, 3H, 18-Me), 3.7 (t, $J \sim 8$ Hz, 1H, 17-H), 5.08 (s, 2H, PhCH₂O), 7.37 (s, 5H, C₆H₅CH₂O).

5. 3-Benzoyloxy-6-methylene-estra-1,3,5(10)-trien-17 β -ol (125)

Sodium hydride (0.5g, 50% in oil dispersion) was washed with dry light petroleum ether (x3). The flask was flushed with nitrogen to remove all traces of the petroleum ether. DMSO (4 ml) was introduced into the flask with a syringe and the resulting suspension warmed to about 75° for 45 min. in an oil-bath under nitrogen. To the dark green solution, methyltriphenylphosphonium iodide (7.6g) in THF (20 ml) was added. After stirring for 15 min. at 0°, the ketone 123 (0.5g) in THF (10ml) was added and the resulting reaction mixture stirred at 60-65° for 24 h, at which time it was diluted with ice-water (50 ml) and extracted with CH₂Cl₂ (x4). The combined CH₂Cl₂ extracts were washed with water and brine, dried and evaporated. The crude product was chromatographed (toluene - ethyl acetate, 2:1) to give an oily product 125 (0.3g; 60%), $[\alpha]_D^{25} -56^\circ$ (c, 5%), ν_{\max} 3360 (OH, broad) and 1600 cm⁻¹ (C=C); δ 0.78 (s, 3H, 18-Me), 3.75 (t, $J \sim 8$ Hz, 1H, 17-H), 4.98 (br s, $W_{1/2}$ 2.5 Hz, 1H, C=CH₂), 5.1 (s, 2H, PhCH₂O), 5.5 (br s, $W_{1/2}$ 2.5 Hz, 1H, C=CH₂), 6.88 (m, 1H, 2-H), 7.25 (d, $J \sim 3$ Hz, 1H, 4-H), 7.42 (br s, 5H, C₆H₅CH₂O) (Found: M⁺, 374.2241. C₂₆H₃₀O₂ requires M, 374.2246).

6. 3-Benzoyloxy-6-formyl-estra-1,3,5(10)-trien-17 β -ol (127)

The enol ether 132 (0.3g) was taken up in THF (30 ml) and perchloric acid (30%, 5 ml) added. The mixture was stirred at room temperature and the progress of the reaction monitored on tlc. After 1½ h, the reaction mixture was diluted with water and extracted with CH₂Cl₂ (x3). The combined organic extracts were washed with water, dried and evaporated. Preparative tlc of the crude product gave a fairly pure sample of the aldehyde 127 (0.1g; 30%) as an oily product. ν_{\max} (film) 1720 (C=O, aldehyde) and 1610 cm⁻¹ (C=C); δ 9.4 (s, 1H, CHO), 5.05 (s, 2H, PhCH₂O), 3.75 (t, J 8Hz, 1H, 17-H), 0.8 (s, 3H, 18-Me) (Found: M^+ , 390.2223. C₂₆H₃₀O₃ requires M, 390.2195).

7. 3-Benzoyloxy-6-methoxymethylene-estra-1,3,5(10)-trien-17 β -ol (132).

Diphenyl(methoxymethyl) phosphine oxide was first prepared from triphenylphosphine (24g) and chloromethyl ether (8g) in dry benzene (60 ml) at 50° for 96 h. A white precipitate of methoxymethyltriphenyl phosphonium chloride (30g) was filtered off and washed with ether. This was heated under reflux with aqueous NaOH solution (50 ml, 30% w/v). Benzene formed was allowed to distill out of the reaction mixture. When evolution of benzene ceased, the mixture was allowed to cool, extracted with CHCl₃ (x3) and the combined CHCl₃ extracts dried and evaporated. The crude product was recrystallised from ethyl acetate to give diphenyl (methoxymethyl)phosphine oxide (20g; 90%) m.p. 113-116°C (Lit,⁸⁵ 116-117°C).

Lithium di-isopropylamide (LDA) was prepared from di-isopropylamine (1.6 ml) and BuLi (4.4 ml, 2.4M solution) at 0° under nitrogen. To this was added dry diphenyl(methoxymethyl) phosphine oxide (2.2g) in dry THF (60 ml) at 0° for 10 min. The mixture was cooled to -78° and the 6-ketone 123 (0.5g) in THF (10 ml) added. The resulting reaction mixture was allowed to warm up to room temperature and stirred overnight. It was poured into saturated ammonium chloride solution (100 ml) and extracted with ether (x4). The combined ether extracts were washed with water, dried and evaporated. Chromatographic separation of the crude product (toluene - ethyl acetate, 2:1) gave an oily gum (0.45g). This was stirred with NaH (0.1g) in THF (20 ml) overnight to give the desired product 132 (0.38g; 70%), ν_{\max} (film) 3400 (OH, broad) and 1610cm^{-1} (C=C); δ 7.85 (d, J_v 3Hz, 1H, 4-H), 6.0 (br s, 1H, =CHOMe), 5.0 (s, 2H, PhCH₂O), 3.65 (s, 3H, OMe), 3.65 (br t, 1H, 17-H), 0.75 (s, 3H, 18-Me) (Found: M^+ ; 404.2361. $C_{27}H_{32}O_3$ requires M , 404.2351).

8. 3-Benzoyloxy-6-cyanomethylene-estra-1,3,5(10)-trien-17 β -ol
(136).

Sodium hydride (0.4g, 50% in oil dispersion) was washed three times with dry petroleum-ether (b.p. 40-60) in a three-neck flask. This was flushed with nitrogen until the last traces of the petroleum ether had been removed. THF (10 ml) was added to the flask and cooled to 0°C. To this suspension was added diethyl cyanomethylphosphonate (1g) in THF (10 ml) with stirring at 0°. After stirring for 30 min., 123 (0.4g) in THF (10 ml) was added and the resulting

reaction mixture stirred at room temperature for 24-36 h. After this period, the reaction mixture was concentrated to a small volume, poured onto ice-water and extracted with ethyl acetate (x4). The combined organic extracts were washed with water, dried and evaporated. The crude product was subjected to preparative tlc (toluene-ethyl acetate, 2:1) to give an oily product ¹³⁶ (0.25g; 60%), ν_{\max} (film) 3475 (OH, broad), 2220 (C=N), 1610 and 1590 cm^{-1} (C=C); δ 0.75 (s, 3H, 18-Me), 3.75 (t, $J \sim 8\text{Hz}$, 1H, 17-H), 5.12 (s, 2H, PhCH_2O), 5.72 (s, 1H, CHCN), 6.2 (s, CHCN), 7.05 (m, 1H, 2-H), 7.2 (d, $J \sim 3\text{Hz}$, 1H, 4-H), 7.45 (s, 5H, $\text{C}_6\text{H}_5\text{CH}_2\text{O}$); (Found: M^+ ; 399.2188, $\text{C}_{27}\text{H}_{29}\text{O}_2\text{N}$ requires M , 399.2198).

The oily product (0.15g) was acetylated by stirring in pyridine (5 ml) and acetic anhydride (1 ml) overnight to give 17 β -acetoxy-3-benzyloxy-6-cyanomethylene-estra-1,3,5(10)-triene 137 after the usual work up. Recrystallisation from ethanol gave analytically pure sample (0.15g; 90%), m.p. 134-135° and 148-150°, ν_{\max} (film) 2220 (C=N), 1730 (C=O, 17-OAc), 1625 (C=C) 1600 and 1580 cm^{-1} (C=C); δ 0.85 (s, 3H, 18-Me), 2.1 (s, 3H, 17-OAc), 4.8 (t, $J \sim 8\text{Hz}$, 1H, 17-H), 5.15 (s, 2H, PhCH_2O), 5.75 (br s, 1H, CHCN), 7.45 (s, 5H, $\text{C}_6\text{H}_5\text{CH}_2\text{O}$). (Found: C, 78.5; H, 7.1; N, 3.1%; M^+ , 441.2303. $\text{C}_{29}\text{H}_{31}\text{O}_3\text{N}$ requires C, 78.88; H, 7.08; N, 3.17% M , 441.2304).

9. 3-Benzyloxy-6-formylmethylene-estra-1,3,5(10)-trien-17 β -ol (138).

The unsaturated nitrile 136 (0.45g) was taken up in dry benzene (20 ml) and DIBAL (1.5 ml, 25% w/v in toluene) added under nitrogen with a syringe. The reaction mixture was stirred at room temperature under nitrogen for 4 h before destroying any unreacted

DIBAL with methanol and the reaction mixture poured onto ice/dilute H_2SO_4 . More dilute H_2SO_4 and methanol were added to dissolve solid crumbs that were formed. This mixture was extracted with ether (x4) and the combined organic extracts were washed with water, dried and evaporated. Preparative tlc of the crude product (toluene-ethyl acetate, 2:1) afforded the aldehyde 138 as an oily gum (0.24g, 53%), ν_{max} (film) 3450 (OH, broad), 1670 (C=O, aldehyde), 1620 and 1600cm^{-1} (C=C); δ 10.15 (d, $J \sim 8\text{Hz}$, 1H, CHO), 7.42 (s, 5H, $\text{C}_6\text{H}_5\text{CH}_2\text{O}$), 7.08 (d, $J \sim 2.5\text{Hz}$, 1H, 4-H), 6.5 (d, $J \sim 8\text{Hz}$, 1H, $=\text{CHCHO}$), 5.1 (s, 2H, PhCH_2O), 3.78 (t, $J \sim 8\text{Hz}$, 1H, 17-H), 6.75 (s, 3H, 18-Me) (Found: M^+ ; 402.2192 $\text{C}_{27}\text{H}_{30}\text{O}_3$ requires M, 402.2195).

10. 3,17 β -Diacetoxy-estra-1,3,5(10)-trien-6 α -ol (166)

6-Keto-estradiol diacetate 114 (0.25g) was suspended in dry methanol (50 ml) and cooled to about -5° . Sodium borohydride (0.25g) in methanol (25 ml) was added dropwise, such that there was no appreciable rise in temperature of the resulting mixture. This was stirred at -5° for 30-45 min., before acidifying with dilute acetic acid (10% v/w) to adjust the pH between 5 and 7. It was diluted with water, extracted with CH_2Cl_2 (x2). The combined CH_2Cl_2 extracts were washed with water, brine, dried and evaporated. The crude product was subjected to preparative tlc (toluene-ethyl acetate, 2:1) and crystallised from ethyl acetate-hexane to give pure 155 (95mg, 38%). Some of the starting ketone 114 (100mg, 40%) was also isolated, m.p. $127-129^\circ$

(lit., ⁷⁸128-129°C), ν_{\max} (film) 3380 (OH, broad), 1760 (C=O, 3-OAc), 1730 (C=O, 17-OAc), 1600 and 1580 cm^{-1} (C=C); δ 0.82 (s, 3H, 18-Me), 2.08 (s, 3H, 17-OAc), 2.3 (s, 3H, 3-OAc), 4.75 (q, $J \sim 9\text{Hz}$, 2H, 6H and 17-H), 6.95 (m, 1H aromatic proton), 7.3 (m, 2H, aromatic protons).

11. 16-Hydroxymethylene-3-hydroxy-estra-1,3,5(10)-trien-17-one
(73).

Sodium hydride (8g, 60% in oil dispersion) was washed three times with petroleum-ether (b.p. 40-60). The flask was flushed with nitrogen to remove the last traces of the petroleum ether. Dry benzene (100 ml) was introduced and estrone (5g) added. The mixture was stirred for 1 h, before adding ethyl formate (20 ml, freshly distilled over P_2O_5). The reaction mixture was stirred at room temperature until there was no estrone left (ca 24-36 h). The reaction mixture was poured onto ice/dilute HCl and the white precipitate formed was filtered off. The precipitate was washed thoroughly with water and dried under vacuum at 80° to give the desired product (5g, 91%), m.p. 227-229° (lit.⁸⁷ 229-231°), ν_{\max} (mull) 3400 (OH, broad), 1720 (C=O), 1635 (C=C) and 1590 cm^{-1} (C=C); δ (DMSO- d_6), 0.82 (s, 3H, 18-Me), 2.73 (br t), 7.43 (br s, 1H).

12. 4(3-Acetoxy-17-keto-estra-1,3,5(10)-trien-16-yl)-2-methylene-4
butanolide (24b)

Activated zinc (0.5g), ethyl α -(bromomethyl)acrylate (0.7g) and 16-hydroxymethylene estrone (1g) were suspended in dry THF (75 ml) under nitrogen. The reaction mixture was heated to reflux under nitrogen overnight, ca 16-24 h. It was cooled and

poured onto ice/dil. HCl, extracted with chloroform (X4), washed with water and brine. It was dried and evaporated. The crude product was subjected to flash chromatography (petroleum-ether (b.p. 40-60)-acetone 2:1) and then recrystallised from acetone/petroleum ether to give the lactone 24 (mixed isomers) m.p. 234-237° (0.25g, 20%) ν_{\max} (mull) 1760 (C=O, lactone), 1665 (C=C, lactone) and 1600 cm^{-1} (C=C)

The lactone 24 (0.15g) and acetic anhydride (0.5 ml) were stirred together in pyridine (5 ml) at room temperature for 24 h. The reaction mixture was poured onto ice and extracted with CH_2Cl_2 (x3). The combined CH_2Cl_2 extracts were washed with dilute HCl (x3), water and brine. This was dried and evaporated. The crude product was subjected to preparative tlc (petroleum-ether (40-60)-acetone, 2:1) and recrystallised (x2) from acetone-hexane to afford the acetoxylactone 24b (mixed isomers) (0.1g, 60%) m.p. 153-155°C, ν_{\max} (film) 1760 (C=O, broad, 3-OAc and C=O lactone) and 1605 cm^{-1} (C=C); δ 0.98 (br s, 3H, 18-Me), 2.3 (s, 3H, 3-OAc), 4.9 (m, 1H, -CH lactone), 5.72 (br s, 1H, C=CH₂, lactone), 6.32 (br s, 1H, C=CH₂, lactone) (Found: M^+ , 408.1945 $\text{C}_{25}\text{H}_{28}\text{O}_5$ requires M, 408.1937).

13. 16-Butylthiomethylene-3-hydroxy-estra-1,3,5(10)-trien-17-one (153).

16-Hydroxymethylene estrone (1g) was dissolved in dry DME (50 ml), MgSO_4 (2g), pTSA (50mg) and n-butane thiol (5 ml) were added. The resulting reaction mixture was stirred and warmed up to 60° in an oil-bath overnight. It was diluted with water and extracted with CHCl_3 (x3). The combined CHCl_3 extracts were washed with brine, dried and evaporated. Some dry toluene was added and removed *in vacuo* to ensure total removal of the thiol.

The crude product was subjected to preparative tlc (petroleum-ether (40-60) - acetone, 2:1) to give the product 153 (1.1g, 89%). Recrystallisation from methanol gave pure 153 (1.0g, 81%), m.p. 177-178°C, $[\alpha]_D^{25} + 128^\circ$ (c, 0.5%); ν_{\max} (mull) 3308 (broad, OH), 1690 (C=O), 1610 and 1590 cm^{-1} (C=C); δ 0.9 (s, 3H, 18-CH₃), 6.58 (s, 1H, 4-H), 7.12 (d, $J \sim 10\text{Hz}$, 1H, 1-H), 7.1 (br s, 1H, CHSC₄H₉); (Found: C, 74.6; H, 8.4; S, 8.7; M^+ ; 370.1966. C₂₃H₃₀O₂S requires C, 74.56; H, 8.16; S, 8.64; M, 370.1966).

14. 16-Butylthiomethylene-3,17 β -dihydroxy-estra-1,3,5(10)-triene (154).

The butylthiomethylene estrone 153, (1g) was suspended in methanol (100 ml). This was cooled to 0° in ice-bath before adding sodium borohydride (0.5g). The reaction mixture was stirred for about 2 h, while monitoring the progress of the reaction on tlc. It was diluted with water and extracted with CHCl₃ (x4). The CHCl₃ extracts were washed with water and brine, dried and evaporated to give the crude product. Recrystallisation from ethanol gave pure sample of 154 (0.8g, 80%), m.p. 85-88°C, $[\alpha]_D^{25} - 39.4^\circ$ (c, 1%); ν_{\max} (mull) 3340 (broad OH), 1610 and 1590 cm^{-1} (C=C); δ 0.7 (s, 3H, 18-Me), 4.06 (br s, 1H, 17-H), 6.1 (br s, 1H, CHSC₄H₉), 6.6 (s, 1H, 4-H), 6.69 (d, $J \sim 2\text{Hz}$, 1H, 2-H), 7.15 (d, $J \sim 9\text{Hz}$, 1H, 1-H) (Found: M^+ , 372.2114. C₂₃H₃₂O₂S requires M, 372.2123).

The dihydroxy product 154 (0.2g) was acetylated by stirring in pyridine (5ml) with acetic anhydride (1ml) to give 16-butyl^{thio}methylene-3,17 β -diacetoxystestra-1,3,5(10)-triene 156, which was recrystallised

from ethanol after the usual work up (0.18g, 73%) m.p. 142-144°C, $[\alpha]_D + 3.7^\circ$ (c, 1.1%); ν_{\max} (mull) 1760 (C=O, 3-OAc), 1740 (C=O, 17-OAc), 1640 (C=C), 1610cm^{-1} (C=C); δ 0.76 (s, 3H, 18-Me), 2.08 (s, 3H, 17-OAc), 2.3 (s, 3H, 3-OAc), 5.34 (br s, 1H, 17-H), 5.86 (br s, 1H, CHSC_4H_5), 6.83 (s, 1H, 4-H), 7.3 (d, $J \sim 10\text{Hz}$, 1H, 1-H), 6.9 (d, 1H, 2-H) (Found: C, 71.1; H, 8.3; S, 7.1; M^+ , 456.2333. $\text{C}_{27}\text{H}_{36}\text{SO}_4$ requires C, 71.02; H, 7.95; S, 7.0; M, 456.2334).

15. 16-Formyl-3-hydroxy-estra-1,3,5(10),16-tetraene (155)

To the 16-butylthiomethylene estradiol, 154, (0.5g) in a mixture of acetonitrile (50 ml) and water (25 ml) were added mercuric chloride (0.25g) and CaCO_3 (0.1g). The resulting reaction mixture was heated under reflux and the progress of the reaction monitored on tlc. After 24 h, it was diluted with water (50 ml) and extracted with CHCl_3 (x3). The CHCl_3 extracts were washed with water and brine, dried and evaporated. Chromatographic purification of the crude product (diethyl ether - petroleum-ether (40-60), 2:1) gave the product 155 (0.2g, 45%).

Alternatively, the deprotection was carried out with TiCl_4 in acetonitrile. Thus, the 16-butylthiomethylene-estradiol (0.25g) was dissolved in acetonitrile (25ml) and TiCl_4 (0.5 ml) added. The mixture was stirred for 20 min., during which time it turned deep red. Water (10 ml) was added and the reaction mixture stirred for a further 4 h. It was diluted with water and extracted with CHCl_3 (x3). The CHCl_3 extracts were washed with brine, dried and evaporated. Chromatographic separation of the crude product, followed by recrystallisation from methanol

or acetone/petrol, gave pure sample (0.1g, 52%) m.p. 253-255°C, $[\alpha]_D + 88^\circ$ (c, 5%, THF), ν_{\max} (KBr) 3310 (broad, OH), 1675 (C=O, aldehyde), 1610 and 1585cm^{-1} , (C=C), δ 0.92 (s, 3H, 18-Me), 6.65 (s, 1H, 4-H), 6.75 (br s, 1H, 2-H) 7.05 (br s, 1H, 17-H), 7.18 (d, $J \sim 10\text{Hz}$, 1H, 1-H), 9.78 (s, 1H, CHO) (Found: M^+ 282.1625. $\text{C}_{19}\text{H}_{22}\text{O}_2$ requires M, 282.1620)

16. 3-Acetoxy-16-formyl-estra-1,3,5(10),16-tetraene (157)

A mixture of 16-formyl-3-hydroxy-estra-1,3,5(10),16-tetraene (0.1g) and acetic anhydride (0.5 ml) in pyridine (5 ml) were stirred together overnight. It was poured onto ice-water and extracted with CH_2Cl_2 (x3). The combined CH_2Cl_2 extracts were washed with brine, dried and evaporated. Recrystallisation from ethanol gave pure sample (90mg, 78%), m.p. 148-150°C, $[\alpha]_D + 48^\circ$ (c, 0.5%); ν_{\max} (film) 1730 (C=O, 3-OAc), 1675 (C=O, aldehyde) and 1600cm^{-1} (C=C); δ 0.92 (s, 3H, 18-Me), 2.3 (s, 3H, 3-OAc), 6.85 (s, 1H, 4-H), 6.95 (br s, 1H, 2-H), 7.0 (br s, 1H, 17-H), 7.3 (d, $J \sim 10\text{Hz}$, 1H, 1-H), 9.78 (s, 1H, CHO): (Found: C, 77.9; H, 7.6%; M^+ , 324.1724. $\text{C}_{21}\text{H}_{24}\text{O}_3$ requires C, 77.75; H, 7.40%; M, 324.1724).

17. 16-Dimethoxymethyl-3-hydroxy-estra-1,3,5(10)-trien-17-one (164).

16-Hydroxymethylene estrone 73 (0.8g) dry methanol (50 ml) and trimethyl orthoformate (5 ml) were heated to reflux under nitrogen in an oil-bath, pTSA (50mg) was added as catalyst. After about 4 h the reaction mixture was diluted with CHCl_3 (100 ml), washed with brine (x2), dried and evaporated. Preparative tlc of

the crude product (petroleum-ether (40-60) - acetone, 2:1) gave the acetal (0.16g, 16%) which was recrystallised from CHCl_3 /petroleum ether(40-60) to give crystalline sample(0.1g,10%),m.p. $213-215^\circ\text{C}$, $[\alpha]_D + 16$ (c, 1%, THF); ν_{max} (mull) 3380 (OH, broad), 1720 (C=O) and 1600cm^{-1} (C=C); δ 0.92 (s, 3H, 18-Me), 3.48 (s, 6H, $\text{CH}(\text{OMe})_2$), 4.7 (d, $J \sim 4\text{Hz}$, 1H, $\text{CH}(\text{OMe})_2$), 6.64 (s, 1H, 4-H), 7.2 (d, $J \sim 10\text{Hz}$, 1H, 1-H) (Found: M^+ ; 344.1998. $\text{C}_{21}\text{H}_{28}\text{O}_4$. requires M, 344.1987).

18. 16-Dimethoxymethyl-3,17 β -dihydroxy-estra-1,3,5(10)-triene
(165)

To a suspension of 16-dimethoxymethyl estrone (0.15g) in methanol (25 ml) was added sodium borohydride (45mg) in methanol (10 ml). This was stirred at room temperature and the progress of the reaction monitored on tlc until all the starting material had disappeared (ca 1½ h). The reaction mixture was diluted with water and extracted with CHCl_3 (x3). The combined CHCl_3 extracts were washed with brine, dried and evaporated. Crystallisation of the oily product from ethanol gave fairly pure sample (0.12g, 80%), m.p. $232-234^\circ\text{C}$, $[\alpha]_D + 67.5^\circ$ (c, 0.77%, THF); ν_{max} (mull) 3300 (OH, broad), 1600 (C=C) and 1510cm^{-1} (C=C); δ 0.82 (s, 3H, 18-Me), 3.37 (s, 3H, $\text{CH}(\text{OMe})_2$), 3.42 (s, 3H, $\text{CH}(\text{OMe})_2$), 3.85 (dd, $J \sim 10\text{Hz}$ and 3Hz , 1H, $\text{CH}(\text{OMe})_2$), 4.58 (d, $J \sim 10\text{Hz}$, 1H, 17-H), 6.56 (s, 1H, 4-H), 6.65 (br s, 1H, 2-H), 7.1 (d, $J \sim 9\text{Hz}$, 1H, 1-H) (Found: M^+ , 346.2143. $\text{C}_{21}\text{H}_{30}\text{O}_4$ requires M, 346.2144).

19. 16-Methoxymethylene-estra-1,3,5(10)-trien-17-one (167)

A mixture of 16-hydroxymethylene estrone (1g), trimethyl orthoformate (2.5g) and methanolic CeCl_3 solution (0.4M, 20 ml) were stirred together at room temperature overnight. It was diluted with water and extracted with CHCl_3 (x3). The combined CHCl_3 extracts were washed with water and brine. It was dried and evaporated. Chromatographic purification of the crude product (petroleum-ether (40-60) - acetone, 2:1), followed by crystallisation from acetone/petroleum ether afforded pure sample (0.9g, 86%), m.p.: 255-257°C, $[\alpha]_D^{25} + 104^\circ$ (c, 1%, CHCl_3); ν_{max} (KBr), 3250 (OH), 1690 (C=O), and 1615cm^{-1} (C=C); δ 0.9 (s, 3H, 18-Me), 3.9 (s, 3H, OMe), 6.12 (s, 1H, 4-H), 6.22 (d, 1H, 2-H), 7.15 (d, $J \sim 9\text{Hz}$, 1H, 1-H), 7.25 (br s, 1H, CHOMe) (Found: C, 77.0; H, 8.0%. M^+ : 312.1726. $\text{C}_{20}\text{H}_{24}\text{O}_3$ requires C, 76.89; H, 7.74%, M, 312.1725).

20. 16-Methoxymethylene-3,17 β -dihydroxy-estra-1,3,5(10)-triene (168)

The 16-methoxymethylene estrone 167 (0.8g) was suspended in methanol (50 ml) and cooled in ice-bath. CeCl_3 (0.4g) was added to the suspension and stirred for about 2-3 min. before adding sodium borohydride (0.2g). The resulting mixture was stirred for about 45 min. It was diluted with CHCl_3 (100 ml) and washed with brine, dried and evaporated. The crude product was subjected to preparative tlc (petroleum-ether (40-60) - acetone, 2:1) to give an oily solid that could not be crystallised. ν_{max} (film) 3300 (OH, broad) and 1610cm^{-1} (C=C), δ 0.7 (s, 3H, 18-Me), 3.13 (s, 3H,

OMe), 4.15 (br s, 1H, 17-H), 6.15 (br s, CHOMe), 6.62 (s, 1H, 4-H), 7.15 (d, $J \sim 10\text{Hz}$, 1H, 1-H) (Found: M^+ ; 314.1887. $\text{C}_{20}\text{H}_{26}\text{O}_3$ requires M, 314.1882).

The above product 168, was acetylated by stirring 100mg of it in pyridine (5 ml) and acetic anhydride (0.5 ml) at room temperature overnight. After the usual work up, it was crystallised from methanol to give the 3,17 β -diacetoxy-16-methoxy-methylene-estra-1,3,5(10)-triene 169 (90mg, 82%), m.p. 159-161°C, ν_{max} (mull) 1770 (C=O, 3-OAc), 1730 (C=O, 17-OAc), and 1610 cm^{-1} (C=C); δ 0.82 (s, 3H, 18-Me), 2.16 (s, 3H, 3-OAc); 2.30 (s, 3H, 17-OAc), 3.6 (s, 3H, OMe), 5.38 (br s, 1H, 17-H), 6.0 (s, 1H, CHOMe), 6.85 (s, 1H, 4-H), 6.95 (br s, 1H, 2-H), 7.35 (d, $J \sim 10\text{Hz}$, 1H, 1-H): (Found: C, 72.39; H, 7.8; $\text{C}_{24}\text{H}_{30}\text{O}_5$ requires C, 72.33; H, 7.59).

21. 16-Formyl-3,17 β -dihydroxy-estra-1,3,5(10)-triene (158)

The 16-dimethoxymethyl-3,17 β -dihydroxy-estra-1,3,5(10)-triene 165 (0.15g) was dissolved in acetone (25 ml). To this was added 2N HCl (5 ml) and the resulting reaction mixture stirred at room temperature for 20-30 min, while monitoring the progress of the reaction by tlc. The reaction mixture was diluted with water and extracted with CHCl_3 (x3). The combined CHCl_3 extracts were washed with brine, dried and evaporated. Chromatographic purification of the crude product gave the aldehyde 158 which was crystallised from methanol- H_2O .

Similarly the enol ether 168 (0.3g) was deprotected with dilute HCl in acetone as above to give the same aldehyde 158 (0.2g, 70%), m.p. 203-206°C, $[\alpha]_D + 75^\circ$ (c, 0.5%, THF); ν_{\max} (KBr) 3360 (OH, broad), 1710 (C=O, aldehyde), and 1610cm^{-1} (C=C); δ (DMSO d_6), 0.8 (s, 3H, 18-Me), 3.8 (d, 1H, $J \sim 9\text{Hz}$, 17-H), 9.82 (d, 1H, $J \sim 2\text{Hz}$, CHO) (Found: M^+ 300.1738 $\text{C}_{19}\text{H}_{24}\text{O}_3$ requires M, 300.1725).

The 16-formyl-estradiol 158 (0.1g) was acetylated by stirring with acetic anhydride (0.5ml) in pyridine (2ml) to give the 3,17 β -diacetoxy-16-formyl-estra-1,3,5(10)-triene^{156b}. Crystallisation from ethanol gave pure sample (0.1g, 94%) m.p. 128-130°C, ν_{\max} (film) 1740, (C=O, broad, 17-OAc, 3-OAc and CHO) and 1610cm^{-1} (C=C), δ 9.84 (d, $J \sim 2\text{Hz}$, 1H, CHO), 4.86 (d, $J \sim 9\text{Hz}$, 1H, 17-H), 2.12 (s, 3H, 17-OAc), 2.32 (s, 3H, 3-OAc), 0.9 (s, 3H, 18-CH₃); (Found: C, 71.7; H, 7.7%; M^+ ; 384.1937. $\text{C}_{23}\text{H}_{28}\text{O}_5$ requires C, 71.9; H, 7.3%; M, 384.1937).

22. 17 β -Acetoxy-3-benzyloxy-estra-1,3,5(10)-trien-6-one (170)

A mixture of 123 (1g) and acetic anhydride (5 ml) in dry pyridine (10 ml) was stirred overnight at room temperature, poured onto ice-water and the precipitate filtered off to give the crude product (1.1g, 100%). Recrystallisation from ethanol gave pure 170 (1g, 95%), m.p. 151.5-152.5°C, $[\alpha]_D -18.3^\circ$ (c, 5%, CHCl_3), ν_{\max} (mull) 1730 (C=O, 17-OAc), 1675 (C=O, 6-ketone) and 1610cm^{-1} (C=C); δ 0.85 (s, 3H, 18-Me), 2.08 (s, 3H, 17-OAc), 4.75 (t, $J \sim 8\text{Hz}$, 1H, 17-H), 5.15 (s, 2H, PhCH_2O), 7.25 (m, 2H, 1-H and 2-H), 7.45 (s, 5H, $\text{C}_6\text{H}_5\text{CH}_2\text{O}$), 7.7 (d, $J \sim 2.5\text{Hz}$, 1H, 4-H) (Found: C, 77.6; H, 7.3%; M^+ , 418.2149. $\text{C}_{27}\text{H}_{30}\text{O}_4$ requires C, 77.48; H, 7.23%; M, 418.2144).

23. 17 β -Acetoxy-3-benzyloxy-estra-1,3,5(10)-trien-6 α -ol (171)

17 β -Acetoxy-3-benzyloxy-estra-1,3,5(10)-trien-6-one, 170, (0.5g) was suspended in dry methanol (100 ml) and cooled to between 0 and 5°. Sodium borohydride (0.25g) in methanol (25 ml) was added dropwise to the ketone 170, and stirred at that temperature. The progress of the reduction was monitored on tlc. After about 1 h, it was acidified with dilute acetic acid (10%, v/v) to adjust the pH of the reaction mixture to between 5 and 7. It was diluted with water and extracted with methylene chloride (x3). The combined CH₂Cl₂ extracts were washed with NaHCO₃ solution (5%, w/v), water and brine. It was dried, evaporated and crystallised from ethanol to give the alcohol 171 (0.35g, 70%), m.p. 143-144°C, $[\alpha]_D^{25} + 54.2^\circ$ (c, 2%), ν_{\max} (mull) 3470 (OH), 1725 (C=O, 17-OAc) and 1600 cm⁻¹ (C=C); δ 0.8 (s, 3H, 18-Me) 2.08 (s, 3H, 17-OAc), 4.75 (m, 2H, 17-H and 6-H), 5.1 (s, 2H, PhCH₂O), 6.86 (m, 1H, 2-H), 7.3 (s, 1H, 4-H), 7.45 (s, 5H, C₆H₅CH₂O) (Found: C, 77.25; H, 7.5%; M⁺, 420.2304. C₂₇H₃₂O₄ requires C, 77.1; H, 7.67%; M, 420.2300).

24. 17 β -Acetoxy-6 α -allyloxy-3-benzyloxy-estra-1,3,5(10)-triene (172).

Sodium hydride (0.2g, 50% in oil dispersion) was washed with dry, light petroleum-ether (x3) in a flask. The flask was flushed with nitrogen to remove all traces of the petroleum-ether (b.p. 40-60). DMF (50 ml), the alcohol 171 (0.5g) and allyl bromide (5 ml) were added to the NaH. The resulting reaction mixture was warmed to between 60 and 70° overnight. Excess NaH was destroyed

with dilute acetic acid (10% v/v), diluted with water and extracted with ether (x4). The combined ether extracts were washed several times with water, dried and evaporated. The crude product was subjected to preparative tlc (toluene-ethyl acetate, 4:1). Crystallisation of the oily product from ethanol gave the allyl ether 172 (0.35g, 64%), m.p. 118-120°C, $[\alpha]_D^{25} -26^\circ$ (c, 5%), ν_{\max} (mull) 1730 (C=O, 17-OAc), and 1600cm^{-1} (C=C); δ 0.82 (s, 3H, 18-Me), 2.08 (s, 3H, 17-OAc), 4.1 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$), 7.45 (br s, 5H, $\text{C}_6\text{H}_5\text{CH}_2\text{O}$) (Found: C, 77.8; H, 7.4%; $\text{C}_{30}\text{H}_{36}\text{O}_4$ requires C, 78.2; H 7.83%).

25. 17 β -Acetoxy-3-benzyloxy-6 α -formylmethoxy-estra-1,3,5(10)-triene (173)

The allyl ether 172 (0.2g) was dissolved in a mixture of dioxane (15 ml) and water (5 ml). To this was added OsO_4 (20mg) and stirred for 5 min. at 24-26°C. Sodium periodate (3g) was added over a period of 30 min. to the stirred reaction mixture. The resulting reaction mixture was stirred for additional 2-3 h, during which time the colour of the mixture turned from dark brown to pale yellow. The mixture was diluted with water and extracted with ether (x3). The combined ether extracts were washed with water, dried and evaporated to give a crude product. Chromatographic purification of the crude product led to some fragmentation of the aldehyde to the ketone 170. When the crude product was heated under reflux in toluene under nitrogen it gave the ketone 170.

The aldehyde was found to be highly unstable. ν_{\max} (film) 1725 (broad, C=O, aldehyde and 17-OAc) and 1600cm^{-1} (C=C); δ 0.8 (s, 3H, 18-Me), 4.0 (s, 2H, OCH_2CHO), 4.7

(m, 2H, 6 α -H and 17-H), 5.1 (s, 2H, PhCH₂O), 7.45 (s, 5H, C₆H₅CH₂O), 9.65 (s, 1H, CHO).

26. 6 α ,17 β -Diacetoxy,3-benzyloxy-estra-1,3,5(10)-triene

The alcohol-derivative 171 (0.1g) and acetic anhydride (0.5 ml) in pyridine (5 ml) were stirred together overnight. The reaction mixture was poured onto ice/water and extracted with CH₂Cl₂ (x2). The combined CH₂Cl₂ extracts were washed with dilute HCl and brine, dried and evaporated. Recrystallisation from CHCl₃/petroleum-ether (b.p. 40-60) gave pure sample (95mg, 86%), m.p. 214-215°C, ν_{\max} 1750 (broad, C=O, 17-OAc and 6-OAc) and 1600cm⁻¹ (C=C); δ 0.8 (s, 3H, 18-Me), 2.08 (s, 3H, 17-OAc), 2.12 (s, 3H, 6-OAc), 4.75 (t, J \sim 8Hz, 1H, 17-H), 5.08 (s, 2H, PhCH₂O), 6.1 (t, J \sim 8Hz, 1H, 6-H), 6.85 (s, 1H, 4-H), 7.43 (s, 5H, C₆H₅CH₂O) (Found: M⁺, 462.2403. C₂₉H₃₄O₅ requires M, 462.2406).

27. 3 β -(2,3-epoxypropan-1-oxy)cholesten-5-ene (181)

To cholesterol (2g) in CH₂Cl₂ (50 ml) was added a solution of NaOH (50% w/v, 50g), epichlorohydrin (10 ml) and trimethylbenzylammonium chloride. The stirred reaction mixture was maintained at about 50°C for 24-36 h. After this period, it was diluted with water and extracted with CH₂Cl₂ (x3). Chromatographic separation of the crude product on alumina column using petroleum-ether (b.p. 40-60) - ethyl acetate (4:1) as eluent gave the starting material, cholesterol (1g) and the glycidyl ether (0.65g, 28%). Recrystallisation from ethanol gave pure sample of 181 (0.6g, 26%), m.p. 75-77°C, $[\alpha]_D$ -36.1° (c, 1%);

60.68 (s, 3H, 18-Me), 0.82 (s, 3H, 19-Me), 0.89 (s, 6H, 25- and 26-CH₃), 1.0 (s, 3H, 21-CH₃), 2.62 (q, J_v 2.5Hz, 1H, CH₂-O-CH-), 2.8 (t, J_v 5Hz, 1H, CH₂-O-CH-), 3.20 (m, 2H, CH₂-O-CH- and 3-H), 3.7 (m, 2H, CH₂-CH-O-CH₂), 5.4 (br s, 1H, 6-H) (Found: C, 81.6; H, 11.4%; M⁺, 442.3800. C₃₀H₅₀O₂ requires C, 81.39; H, 11.38%; M, 442.3811).

28. 3β-formylmethoxy-cholesten-5-ene (182)

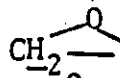
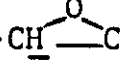
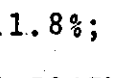
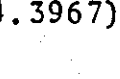
Cholesteryl glycidyl ether 181 (0.3g) and periodic acid (0.3g) were dissolved in DME (30 ml) and water (10 ml). The reaction mixture was stirred at 50-60° for 12-15 h. The progress of the reaction was monitored on tlc. The mixture was diluted with water (50 ml) and extracted with ether (x3). The combined ether extracts were washed with water, dried and evaporated. Preparative tlc of the crude product (toluene-ethyl acetate, 4:1) gave the aldehyde, 182 (0.2g, 65%), m.p. 75-77°C, [α]_D -34° (C, 0.94%). ν_{max} 1730cm⁻¹ (C=O aldehyde); δ0.62 (s, 3H, 18-Me), 0.84 (s, 3H, 19-Me), 0.92 (s, 6H, 25- and 26-CH₃) 1.0 (s, 3H, 21-Me); 4.05 (br s, 2H, OCH₂CHO), 5.3 (br s, 1H, 6-H), 9.65 (br s, 1H, CH₂CHO) (Found: M⁺, 428.3657, C₂₉H₄₈O₂ requires M, 428.3654).

29. 3β-allyloxy-5α-cholestane (186)

Sodium hydride (1g, 50% oil dispersion) was washed three times with dry petroleum-ether (b.p. 40-60) in a three-neck flask. The flask was flushed with nitrogen to remove the traces of petroleum ether left. Dry DMF (60 ml), cholestanol (1g) and allyl bromide (10 ml) were added to the flask. The resulting reaction mixture was warmed to 50-60°C overnight. Excess NaH was destroyed

with methanol, diluted with water and extracted with ether (x3). The combined ether extracts were washed several times with water, dried and evaporated. The crude product was subjected to preparative tlc (toluene-ethyl acetate, 4:1). Recrystallisation from methanol gave pure sample of the allyl ether 186 (0.78g, 68%), m.p. 70-71°C, $\{\alpha\}_D + 12.3^\circ$ (c, 0.65%); δ 0.66 (s, 3H, 18-Me), 0.8 (s, 3H, 19-CH₃), 0.9 (s, 6H, 25- and 26-Me), 4.05 (d, $J \sim 6$ Hz, -OCH₂CH=CH₂), 5.25 (m, 2H, OCH₂C=CH₂), 6.0 (m, 1H, OCH₂CHCH₂) (Found: C, 83.9; H, 12.5%; M^+ , 428.4043. C₃₀H₅₂O requires C, 84.04; H, 12.5%; M, 428.4018).

30. 3 β -(2,3-epoxypropan-1-oxy)-5 α -cholestane (187)

To the 3 β -allyloxy-cholestane (0.3g) in methylene chloride (50ml) was added m-chloroperbenzoic acid (MCPBA) (0.15g) in CH₂Cl₂ (25ml). The reaction mixture was stirred at room temperature and the progress of the reaction monitored on tlc. After 5 days, it was diluted with CH₂Cl₂ (100 ml), washed successively with saturated sodium sulphite solution, sodium hydrogen carbonate (1M) and water. The CH₂Cl₂ extract was dried and evaporated. Chromatographic purification of the crude product (toluene-ethyl acetate, 4:1) and crystallisation from ethanol gave the glycidyl ether, 187 (0.15g, 48%), m.p. 83-85°C, $\{\alpha\}_D + 14.8^\circ$ (c, 1.1%), ν_{\max} (film) 1250cm⁻¹; δ 0.66 (s, 3H, 18-Me); 0.82 (s, 3H, 19-CH₃), 0.9 (s, 6H, 25- and 26-CH₃) 2.65 (q, $J \sim 2.5$ Hz, , 2.8 (t, $J \sim 4.5$ Hz, , 3.25 (m, 2H, 3 α H and -CH₂-, 3.70 (m, 2H, ) (Found: C, 81.1; H, 11.8%; M^+ , 444.3968, C₃₀H₅₂O₂ requires C, 81.02; H, 12.1%; M, 444.3967).

31. 3 β -formylmethoxy-cholestane (188)

The 3 β -allyloxy cholestane (0.3g) was dissolved in a mixture of dioxane (15 ml) and water (5 ml). Osmium tetroxide (25 mg) was added to the solution and the resulting reaction mixture stirred at 24-26° for 5 min. Sodium periodate (3g) was added over a 30 min. period. The progress of the reaction was monitored on tlc. After about 3 h, the reaction mixture was diluted with water and extracted with ether (x3). The organic extracts were combined and washed with water, dried and evaporated. Preparative tlc of the crude product (0.22g, 71%), ν_{\max} 1725 (C=O, aldehyde); δ 0.65 (s, 3H, 18-Me), 0.82 (s, 6H, 19- and 21-CH₃), 0.9 (s, 6H, 25- and 26-Me), 4.12 (br s, 2H, OCH₂CHO), 9.87 (br s, 1H, CHO). (Found: M⁺, 430.3817. C₂₉H₅₀O₂ requires M, 430.3811).

32. 6-Methoxy-1-allyloxy-1,2,3,4-tetrahydronaphthalene (191)

6-Methoxy-1-tetralone (2g) was suspended in methanol (100 ml) and sodium borohydride (0.5g) in methanol (25 ml) added. The resulting reaction mixture was stirred at room temperature for about 2 h. It was diluted with water and extracted with CH₂Cl₂ (x2). The combined CH₂Cl₂ extracts were washed with water and brine, dried and evaporated to give an oil, 6-methoxy-1-tetralol, 190 (1.8g, 90%).

The α -tetralol 190 was taken up in dry benzene (50 ml) and added to sodium hydride (0.5g 50% in oil dispersion) which had been washed with dry petroleum ether (b.p. 40-60). Allyl bromide (5 ml) was added and the stirred reaction mixture heated to about 60° overnight under nitrogen. It was diluted with water and

extracted with ether (x3). The combined ether extracts were washed with water, dried and evaporated. Chromatographic purification of the crude product gave the allyl ether 191 (1.5g, 6½%), ν_{\max} (film) 1600cm^{-1} (C=C); δ 1.8 (m, 4H, 3- and 4-CH₂), 2.6 (m, 2H, 2-CH₂), 3.62 (s, 3H, OMe), 3.9 (d, $J \sim 7\text{Hz}$, 2H, CH₂=CHCH₂O), 4.3 (br s, 1H, 1-H), 5.1 (m, 2H, CH₂=CH-), 5.8 (m, 1H, CH₂=CH-), 6.45 (s, 1H, 5-H), 6.6 (d, $J \sim 3\text{Hz}$, 1H, 7-H), 7.15 (d, $J \sim 15\text{Hz}$, 1H, 8-H) (Found: M^+ ; 218.1312. C₁₄H₁₈O₂ requires M, 218.1307).

33. 6-Methoxy-1-formylmethoxy-1,2,3,4-tetrahydronaphthalene (192)

The allyl ether 191 (1g) was taken up in a mixture of dioxane (45 ml) and water (15 ml). To this was added OsO₄ (50mg) and the mixture stirred for 5 min. at 24-26°C. Sodium periodate (3g) was added over a period of 30 min. The progress of the reaction was monitored on tlc. After about 1½ h, the reaction mixture was diluted with water and extracted with ether (x3). The combined ethereal extracts were washed with water, dried and evaporated. ν_{\max} (film) 1720 (C=O, aldehyde) and 1600cm^{-1} (C=C); δ 1.85 (m, 4H, 3- and 4-CH₂), 2.66 (br m, 2H, 2-CH₂), 3.65 (s, 3H, -OMe), 4.0 (br s, 2H, CH₂CHO), 4.35 (br s, 1H, 1-H), 6.5 (br s, 2H, 5-H and 7-H), 7.2 (d, $J \sim 13\text{Hz}$, 1H, 8-H), 9.55 (br s, 1H, CHO).

34. α -(Bromomethyl)acrylic acid (195)

Diethyl bis(hydroxymethyl)malonate 27.5g) and hydrobromic acid (48%, 71ml) were stirred together in a three-neck flask. The mixture was heated to 85°-90°. At this temperature, a mixture

of ethyl bromide and water was allowed to distill off for 2 h. The reaction mixture was left at this temperature for 10-15 h. At the end of this period, the mixture was concentrated on a rotary evaporator at 65-70°. About 50 ml of water was removed. The residue was cooled in a freezer overnight. Crystals of the -(bromomethyl)acrylic acid were filtered off in the cold to give, after drying, 7.5g (36%), m.p. 70-72°C, (lit.,¹⁰⁰ 71-73°). ν_{max} (KBr) 1690 (C=O) and 1625cm⁻¹ (C=C), δ 4.18 (s, 2H, CH₂Br), 6.09 (s, 1H, C=CH₂), 6.50 (s, 1H, C=CH₂).

35. Ethyl α -(bromomethyl)acrylate (196)

In a nitrogen flushed 100 ml, three-neck flask equipped with magnetic stirrer, Dean-Stark trap and condenser, was placed (bromomethyl)acrylic acid (5g) and dry benzene (36 ml). The solution was heated to reflux and 6 ml of a binary azeotrope of benzene and water is distilled off. The Dean-Stark trap is removed and absolute ethanol (12 ml) and concentrated H₂SO₄ (0.2 ml) added slowly. The contents of the flask were heated under reflux for 36 h, under nitrogen, the condensate during this time is passed through molecular sieves before it is returned to the flask. The flask was cooled and benzene-ethanol azeotrope (15 ml) distilled off. About 18 ml of benzene was added and another azeotrope (20 ml) distilled off. After which the mixture was poured into cold water and neutralised with solid Na₂CO₃ (1.5g). This was extracted with ether (x4) and the ether extracts dried (Na₂SO₄) for 4 h and evaporated to give the ester 196, oil (3.8g, 67%), ν_{max} (film) 1730cm⁻¹ (C=O); δ 1.3 (t, 3H,

$\text{CO}_2\text{CH}_2\text{CH}_3$), 4.28 (quarter, 2H, CO_2CH_2), 4.2 (s, 2H, CH_2Br), 5.98 (s, 1H, $\text{C}=\text{CH}_2$), 6.32 (s, 1H, $\text{C}=\text{CH}_2$).

36. Methyl α -(bromomethyl)acrylate (197)

α -(Bromomethyl)acrylic acid (1g) was dissolved in ether (20 ml) and diazomethane in ether (generated from Diazald, ethanol and KOH) added until there was no more effervescence. The ethereal mixture was washed with Na_2CO_3 solution and water, dried and evaporated to give the methyl α -(bromomethyl)acrylate (0.8g), ν_{max} 1725cm^{-1} ($\text{C}=\text{O}$) and 1635cm^{-1} ($\text{C}=\text{C}$); δ 3.86 (s, 3H, CO_2Me), 4.22 (s, 2H, CH_2Br), 6.02 (s, 1H, $\text{C}=\text{CH}_2$), 6.4 (s, 1H, $\text{C}=\text{CH}_2$).

37. 4-(3-Hydroxy-estra-1,3,5(10)-tetraen-16-yl)-2-methylene-4-butanolide (198)

Activated zinc (0.15g), dry THF (75 ml), ethyl- or methyl-(bromomethyl)acrylate (0.2g) and the aldehyde 155 (0.6g) were heated under reflux with stirring under nitrogen. A pinch of p-dihydroquinone was added to the reaction mixture to reduce the extensive polymerisation of the acrylate. After about 5 h, more acrylate (0.1g) was added to the reaction mixture. It was then left under reflux overnight. It was cooled, poured onto ice/dilute HCl and extracted with CHCl_3 (x4). The crude product was subjected to preparative tlc and crystallised from acetone/petroleum ether (40-60) to give pure sample of the lactone¹⁹⁸ (0.3g, 40%), m.p. $226-228^\circ\text{C}$, $[\alpha]_{\text{D}} + 71^\circ$ (c, 0.5%,

THF), ν_{\max} (KBr) 3400 (OH), 1755 (C=O, lactone), 1670 (C=C, lactone) 5.7 (m, $W_{\frac{1}{2}}$, 2.5 Hz, 1H, C=CH₂), 5.98 (br s, 1H, 17-H), 6.3 (m, $W_{\frac{1}{2}}$ 2.5 Hz, 1H, C=CH₂) (Found C, 78.63; H, 7.8; M^+ , 350.1891. $C_{23}H_{26}O_3$ requires C, 78.82; H, 7.48; M , 350.1882).

38. 4-(3,17B-Dihydroxy-estra-1,3,5(10)-trien-16-yl)-2-methylene-4-butanolide (199)

Activated zinc (0.15g), dry THF (100 ml), methyl- α -(bromo-methyl)acrylate (0.2g) and the aldehyde 158 (0.5g) were heated under reflux while stirring under nitrogen with magnetic stirrer. After about 8 h, more acrylate (0.15g) was added to the mixture which was left to reflux overnight. It was cooled, poured onto ice/dilute HCl and extracted with $CHCl_3$ (x4). The combined $CHCl_3$ extracts were washed with brine, dried and evaporated. Chromatographic purification, followed by crystallisation from acetone/petrol (40-60) gave the lactone 199 (0.18g, 30%), m.p. 252-255°, $[\alpha]_D^{25} + 24^\circ$ (c, 0.25%, THF), ν_{\max} (KBr) 3350 (OH, broad) 1750 (C=O lactone), 1665 (C=C, lactone), 1610 (C=C) cm^{-1} ; δ 6.1 (br s, 1H, C=CH₂), 5.7 (br s, 1H, C=CH₂), 4.6 (br s, 1H, CHO CO lactone), 3.6 (br, 1H, 17-H), 0.8 (s, 3H, 18-Me) (Found C, 74.4; H, 7.6; M^+ , 368.1991. $C_{23}H_{28}O_4$ requires C, 74.97; H, 7.66; M , 368.1987).

Acetylation of the lactone 199 (0.1g) with acetic anhydride (1 ml) in pyridine (2 ml) gave the acetylated lactone 199a (80mg, 74%).

ν max (film) 1740 (broad, 17-OAc, 3-OAc, C=O, lactone);
6.38 (br s, 1H, C=CH₂), 5.75 (br s, 1H, C=CH₂), 4.65 (m, 2H,
CHOCO lactone and 17-H), 0.9 (s, 3H, 18-Me).

39. (E)-5-(17 β -Acetoxy-3-benzyloxy-estra-1,3,5(10)-trien-6-ylidene)-2-methylene-4-pentanolide (200a)

Activated zinc (0.15g), methyl α -(bromomethyl)acrylate (0.2g) and the aldehyde 138 (0.45g) were heated under reflux in THF (100 ml) under nitrogen. After about 5 h, more acrylate (0.1g) was added and the reaction mixture left under reflux overnight. It was cooled, poured onto ice/dilute HCl and extracted with CHCl₃ (x3). The combined CHCl₃ extracts were washed with water and brine, dried and evaporated. The crude product was subjected to preparative tlc (petroleum-ether (40-60)/acetone 2:1) to give an oily product. Acetylation of this lactone (0.2g) in pyridine (5 ml) with acetic anhydride (0.5 ml) followed by further chromatographic purification, gave the pure lactone 200a as an oil (0.2g, 35%), $[\alpha]_D^{25} -37.5^\circ$ (c, 1.5%), ν max (film) 1760 (C=O lactone), 1735 (C=O, 17-OAc), 1600cm^{-1} (C=C), 7.3-6.5 (m, 8H aromatic protons), 6.5 (m, W_{1/2}, 2.5 Hz, 1H, C=CH₂, lactone), 5.8 (d, J \sim 9 Hz, -C=CH₂), 5.5 (m, W_{1/2}, 2.5 Hz, C=CH₂, lactone), 5.2 (q, J \sim 8Hz, 1H, CHOCO, lactone) 5.0 (s, 2H, PhCH₂O), 4.75 (t, J \sim 8.5 Hz, 17-H). (Found: M⁺, 512.2571. C₃₃H₃₆O₅ requires M, 512.2563).

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