SYNTHESIS AND STRUCTURE ACTIVITY RELATIONSHIPS

OF RING D MODIFIED STEROIDAL HORMONES

by

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"And (consider how) thy Lord has inspired the bee." (Holy Quran, Chapter 16:68.)
The above expression is meant to bring out the wonderful quality of instinct which enables a lowly insect like the bee to construct a geometrical masterpiece such as the honeycomb.
Synthesis and Structure-Activity Relationships of Ring D Modified Steroidal Hormones

The synthesis of steroidal 14α,16-methano, 14α,17-methano-, 14α,17-ethano- and 14α,17-propano estradiol analogues as well as 14α-alkyl and 14α-functionalised-alkyl estradiol analogues was investigated. Furthermore, the synthesis of 17β-hydroxy-17α,14- (epoxymethano)androst-4-en-3-one was undertaken and acid-mediated rearrangement of the 14,17-etheno bridged testosterone analogue gave the 14,16-ethano analogue of androst-4-en-3,17-dione.

Established ring D cycloaddition and oxidative cleavage methodology gave ring D 14α-formyl and 14α,17α-diformyl compounds as key intermediates in the overall synthetic plan. Chemoselective- and stereoselective nucleophilic addition at C-14 of the 14α-formyl-3-methoxyestra-1,3,5(10)-trien-17-one provided access to 14α-alkyl- and 14α-alkyl-functionalised 19-norsteroids for elaboration toward 14α,17-propano- and 14α-alkylamide estradiol analogues. Synthesis of the 14α,17-methano bridged steroid was attainable indirectly through intramolecular pinacol coupling between the 17-oxo- and 14-formyl group of 14α-formyl-3-methoxyestra-1,3,5(10)-trien-17-one. The 14α,16-methano bridged steroid was synthesised via base-mediated intramolecular cyclisation of 14-(toluene-p-sulfonyloxy)methyl-3-methoxyestra-1,3,5(10)-trien-17-one.

Novel compounds were characterised with the aid of high field NMR techniques. A X-ray crystal structure determination of the strained ring D 14α,17-methano bridged estriol analogue corroborated its structure.

The minimum energy conformation of novel estradiol analogues were superimposed on estradiol, and their least square fit values determined and discussed in relation to biological activity. These analogues will contribute toward defining the structural parameters responsible for certain pattern of hormonal activity, and hence, the ultimate goal of predictive drug design.
To my Parents
I declare that 'Synthesis and Structure Activity Relationships of Ring D Modified Steroidal Hormones' is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references.

ANWAR JARDINE
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## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUMMARY</td>
<td></td>
<td>ii</td>
</tr>
<tr>
<td>1.</td>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>2.</td>
<td>OBJECTIVES</td>
<td>46</td>
</tr>
<tr>
<td>3.</td>
<td>DISCUSSION</td>
<td>52</td>
</tr>
<tr>
<td>3.1</td>
<td>Synthesis of 14,17-methano 19-norsteroids</td>
<td>52</td>
</tr>
<tr>
<td>3.2</td>
<td>Synthesis of 14,16-methano 19-norsteroids</td>
<td>70</td>
</tr>
<tr>
<td>3.3</td>
<td>Synthesis of 14α-alkyl estradiol analogues</td>
<td>80</td>
</tr>
<tr>
<td>3.4</td>
<td>Chemoselective homologation of 3-methoxy-17-oxoestra-1,3,5(10)-triene-14-carbaldehyde</td>
<td>92</td>
</tr>
<tr>
<td>3.5</td>
<td>Synthesis of ring D modified androstanes</td>
<td>124</td>
</tr>
<tr>
<td>3.6</td>
<td>Receptor-binding studies</td>
<td>139</td>
</tr>
<tr>
<td>4.</td>
<td>EXPERIMENTAL</td>
<td>143</td>
</tr>
<tr>
<td>4.1</td>
<td>19-Norsteroid Chemistry</td>
<td>143</td>
</tr>
<tr>
<td>4.2</td>
<td>Androstane Chemistry</td>
<td>183</td>
</tr>
<tr>
<td>4.3</td>
<td>Crystal Structure Data</td>
<td>194</td>
</tr>
<tr>
<td>5.</td>
<td>NOMENCLATURE</td>
<td>197</td>
</tr>
<tr>
<td>REFERENCES</td>
<td></td>
<td>206</td>
</tr>
<tr>
<td>APPENDIX</td>
<td>$^{13}$C-NMR tables</td>
<td></td>
</tr>
</tbody>
</table>
SUMMARY

Established ring D cycloaddition-oxidative cleavage methodology gave 3-methoxy-17-oxoestra-1,3,5(10)-triene-14-carbaldehyde as the starting material for further elaboration toward novel ring D modified steroids. Homologation at C-14, followed by intramolecular cyclisation toward strained ring D bicyclo-estradiol analogues, were investigated.

Reductive coupling between the $14^1$- and 17-oxo groups gave $(17^1S)$-3-methoxy-14,17$\alpha$-methanoestra-1,3,5(10)-triene-17$\beta$,17$^1$-diol. This compound was converted into the corresponding estriol analogue for biological evaluation. Selective alcohol protection and deoxygenation at C-17$^1$ gave the 14,17-methano bridged steroid.

Base-mediated intramolecular cyclisation of 14-(tosyloxy)methyl-3-methoxyestra-1,3,5(10)-tri-en-17-one gave 14,16$\alpha$-methano-3-methoxyestra-1,3,5(10)-triene-17-one. The corresponding estradiol analogues have been prepared and submitted for biological evaluation. Ring D expansion of 14-(tosyloxy)methyl-3-methoxyestra-1,3,5(10)-tri-en-17-one gave 3-methoxy-17$\alpha$-homoestra-1,3,5(10),14-tetraen-17$\alpha$-one, which was converted into the 17$\alpha$-homoestradiol analogue for biological evaluation.

Attempts were made to improve the synthesis of 3-methoxy-14-methyl-14$\alpha$-estra-1,3,5(10)-tri-en-17-one for further elaboration toward 14,17-dialkyl analogues of estradiols. Chemoselective and stereoselective synthesis of 14$\alpha$-ethyl- and 14$\alpha$-vinyl estradiol analogues was synthesised and submitted for biological evaluation.

Preliminary investigations opened synthetic routes toward functionalised 14,17-alkano 19-norsteroids. The general approach was based upon homologation at C-14 of the 14$\alpha$-formyl 17-ketone, followed by intramolecular cyclisation. Treatment of the 14$\alpha$-formyl 17-ketone with carbon nucleophiles resulted in highly stereoselective- and chemoselective addition to the 14$\alpha$-formyl group, without prior protection of the 17-oxo group. The resulting 14-alkanols existed primarily as hemiketals. The scope for 14$\alpha$-chain extension was also investigated via the 14$\alpha$-oxiranyl 17-ketone, as well as the 14$\alpha$-carbonitrile 17-ketone.
Chemoselective Horner-Wittig olefination of the 14α-formyl 17-ketone gave (2E and Z)-3-(3-methoxy-17-oxoestra-1,3,5(10)-trien-14-yl)acrylonitrile. Further elaboration of the alkenenitrile products toward the 14α-formylethyl 17-ketone was investigated. Vinylmagnesium bromide addition to the 14α-formyl 17-ketone gave (1'S)-14-allyl-1',17-epoxy-3-methoxyestra-1,3,5(10)-trien-17β-ol. The alcohol was oxidised to give the 3-methoxy-14-(1'-oxoprop-2'-enyl)estra-1,3,5(10)-trien-17-one, in order to investigate the scope for reductive intramolecular cyclisation toward 14,17-propano steroids. Oxidation of the (1'S)-1',17α-epoxy-14-ethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol alcohol gave the 14α-acetyl 17-ketone, which underwent facile base-mediated intramolecular cyclisation to the 17β-hydroxy 17²-ketone. Stereoselective hydride reduction gave (17²S)-3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-17β,17²-diol. Further homologation at C-14 was achieved via Claisen-Carroll methodology, thus opening a synthetic route toward novel 14α-(dialkylamidoalkyl) estradiol analogues. Treatment of the (1'S)-14-allyl-1',17α-epoxy-3-methoxyestra-1,3,5(10)-trien-17β-ol with 5-acetyl Meldrum’s acid gave (5£)-6-(3-methoxyestra-17-oxoestra-1,3,5(10)-trien-14-yl)hex-5-en-2-one.

The cycloaddition route to ring D modification was applied to achieve the synthesis of 14α-functionalised analogues of androst-4-en-3,17-dione. On the basis of established synthetic strategy, the 14,17-etheno bridged analogue of testosterone was synthesised in order to investigate the scope for chemoselective-oxidative cleavage of the ring D double bond, with prior protection of the 3-en-4-one functionality in the form of a Δ5,3-ketal system. Oxidative cleavage of the ring D etheno bridge required chemoselective hydroxylation of the 14,17-etheno bridge, in the presence of the 5,6-double bond of 3,3-ethylenedioxy-14,21-cyclo-14β-pregn-5,15-dien-17α-yl acetate. Moderate selectivity toward ring D etheno hydroxylation provided access toward 17β-hydroxy-17,14-(epoxymethano)androst-4-en-3-one which was synthesised and submitted for biological evaluation. A synthetic route to the 14,16-ethano analogue of testosterone was also investigated. Treatment of 17α-hydroxy-14,21-cyclo-14β-pregn-4-en-3-one with hydrogen bromide in acetic acid, gave Wagner-Meerwein rearrangement products, 17α-hydroxy-15β,17β-ethano-14β-pregn-4,8-dien-3-one and 14,16β-ethano-14β-androst-4-ene-3,17-dione.
1. INTRODUCTION

The modern understanding of hormonal action and the science of endocrinology developed in parallel. Chemical characterisation and subsequent synthesis were followed by elucidation of metabolic pathways. Pioneering work in the development of structure-activity principles was published over the period between 1920 and 1938. In 1923, Allen and Doisy developed an assay for the detection and quantitation of estrogen response.1 With the aid of this assay, chemically related substances were detected and studied. By 1927, it was discovered that the urine of pregnant women is a rich source of estrogens. Two years later, the first steroid hormone, estrone (1), was isolated by Doisy and co-workers.2 The early history of estriol was reviewed by Diczfalusy.3 Herein it was reported that, by 1930, Butenandt and Hildebrandt isolated estriol (2) together with estrone. At this time, the characteristic ring structure of the steroid nucleus was yet to be determined. In the early 1930s, arguments about the absolute structure of steroid hormones were based upon analytical data derived from combustion analysis and chemical degradations. It was reported that the cyclopentanophenanthrene or sterane (3) ring structure, common to all steroids, became generally accepted in 1932, as a result of the work of Rosenheim and King.3 Eight years later, 17\beta-estradiol (4) was isolated by the Doisy group.4 Prior to this, chemically modified hormones were assayed, leading to the discovery of 17α-ethynylestradiol (5) by Inhoffen in 1938.5 The Allen-Doisy assay showed that 17α-ethynylestradiol (5) was 20 times more active than estrone on oral administration. Today, 17α-ethynylestradiol and its 3-methyl ether, mestranol (6) are widely used as estrogens. The discovery that chemical modification of natural hormones can be advantageous, started a new era in structure-activity studies and drug design. Since the isolation of 17β-estradiol, evidence accumulated for the existence of at least 15 other estrogens in human pregnancy urine. The biochemical degradation pathway of estrone was thus established.

It was only around 1949 that a clearer insight into the stereochemistry and conformational properties of steroids started to emerge. In the 1950s, work by Barton and co-workers, illustrated principles of chemical reactivity with respect to the absolute configuration and conformation of steroidal substrates. By this time the therapeutic efficacy of cortisone was established and its chemical synthesis became a primary target. Later, the discovery of a
succession of cortisone analogues with superior anti-inflammatory activity to the natural hormone stimulated widespread interest in steroid chemistry.\textsuperscript{6}

The basic ring structure can be subjected to a wide array of modifications. Introduction of a hydroxyl or carbonyl substituent, unsaturation and angular methyl groups at the junction of the all - trans - transoid array of fused rings, gives rise to several classes of steroid hormones having diverse biological activity. These include the estrogens, androgens, progestins, mineralocorticoids, glucocorticoids and vitamin D.
The minimum requirements for binding to the estrogen and progestin receptors have been reviewed by Duax et al.\textsuperscript{7} Crystal structure analysis and receptor binding affinities were correlated, leading to the conclusion that the steroid A ring is primarily responsible for initiating and maintaining hormone binding to the estrogen and progestin receptors. A comparison between the structure of hormone agonists and antagonists exhibited similarities in ring A and dissimilarities in ring D, thus leading to the conclusion that ring D functionality controls expression of activity. This principle was manifested in the success of tamoxifen (7) (a triphenylethylene derivative), which is routinely used in the endocrine therapy of breast cancer. Tamoxifen and related structures have a strong affinity for the estrogen receptor.

\[ \text{OH} \]
\[ \text{C}_2\text{H}_5 \]
\[ \text{O(CH}_2\text{)}_2\text{N(CH}_3)_2 \]

7

\[ \text{OH} \]

8 testosterone

\[ \text{OH} \]

9 progesterone

\[ \text{OH} \]

10 R=CH\textsubscript{3} cortisone

The 3-oxo-\( \Delta^4 \)-moiety in A ring is common to androgens (8), progestins (9) and corticosteroids (10) and constitutes the area of greatest 'conformational flexibility'. Unsaturation or bulky substituents on rings B, C or D can induce steric strain that is conformationally transmitted to the flexible ring A and hence, strongly influences binding to the receptor.
While numerous research efforts have been spent on partial and total synthesis of steroid hormones and its analogues, the subject of endocrinology entered a new phase in the study of the nature of hormone receptors. Although the existence of specific hormone receptors and their importance in hormone action were postulated in the early 1900s, lack of suitable tests inhibited progress in this area. Due to the progress in steroid synthesis and radiochemistry, radioactively labelled steroid hormones became available in the early 1960s. The hormone-receptor complex could thus be studied by more accurate assay methods. The discovery of the structure of DNA (Watson and Crick, 1953) gave birth to the study of molecular biology. The so-called central dogma of molecular biology was later postulated. It asserts that deoxyribonucleic acid (DNA) self-replicates, that the genetic information contained in DNA is copied onto a ribonucleic acid (RNA) by a process called transcription, and that the information then contained in RNA is translated into protein. During the 1980s the knowledge of amino acid sequencing of proteins and prediction of secondary structure, in addition to graphical computer modelling, led to the identification of putative hormone binding sites. In 1985, Walter et al. published his work on the cloning of the human receptor complementary DNA. In the subsequent years, the cloned glucocorticoid and progesterone receptors have been published. A detailed review of the structure and properties of the steroid hormone receptor was recently published by Raynaud et al. The subject of expression cloning is relatively new and rapidly expanding. Today, enough pure steroid hormone receptor is still being sought to enable structure determination by X-ray crystallography. The wealth of X-ray crystal data of steroids and molecular modelling still constitute the only indirect means of 3-D mapping of the hormone-binding site on the steroid hormone receptor.

Hormone binding to the estrogen receptor is unique, since almost no overlap occurs between binding to the estrogen receptor and the 3-oxo-Δ4 steroid hormone receptors. However, a considerable degree of overlap occurs amongst the binding of the other classes of hormones. This overlap can be reinforced by certain substituents, which manifests itself in increased binding affinity. The latter principle was well illustrated in a structure-activity study of 33 steroid hormones, guided toward the mapping of the progesterone and androgen receptors.
Research on the design of steroid hormone antagonists (opposing hormone overproduction or action) has received considerable attention, while limited success has been achieved in the area of steroid hormone agonists (compensates for hormone inefficiency or failure). The quest for ideal estradiol analogues (agonists) has been neglected, probably due to its association with breast cancer. Estrogens are crucial to the female physiology and probably the best means to prevent post-menopausal osteoporosis. Since the discovery of 17α-ethynylestradiol (5) (Inhoffen, 1938), variations in binding to estrogen receptors in response to substitution of the steroid at C-17 have been reported for both the 8β- and 8α-estradiol series. Compounds of the 8α-series are always less effective than their natural 8β-isomers. However, the reverse is true for the D-homoestradiol (11) series, but the binding affinity of these analogues did not exceed that of 17β-estradiol (4). Introduction of hydroxy groups into ring D of estradiol leads to a decrease in the binding affinity for the estrogen receptor. The ratio of activity between estrone (1), estradiol (4) and estriol (2) is 3:10:1. The introduction of a 11β-OH on estradiol resulted in weaker binding compared to estradiol. Oxidation of the 11β- and 17β-OH analogues of estradiol as well as inversion of configuration at C-9, gives 11-oxo-9β-estrone (12), which displays enhanced binding affinity toward the estrogen receptor, more so than its natural 9α-configuration product. A common feature of the 8α-D-homoestradiol (11) and 11-oxo-9β-estrone (12) is a considerable deviation from overall planarity, which is normal for the natural estradiol series. This phenomenon, illustrate that molecular planarity is not a requirement for activity. Homologation of the 13β-methyl group of estradiol up to the 13β-butyl level lowers binding affinity. The introduction of a methyl group at C-1, C-2 and C-6α resulted in poor binding affinities, whereas methylation at C-7, C-11β, C-12β and C-17 resulted in comparable or better binding than estradiol. Substitution at C-11 and C-7 is of particular interest. Moxestrol (13), the 11β-methoxy derivative of 17β-ethynylestradiol (5), is a highly potent estrogen. However, the 11α-methoxy isomer binds relatively weakly (comparable to estriol) and displays mixed agonist/antagonist properties. A 7α-substituent increases the affinity for the estrogen receptor. Derivatives of estradiol possessing a 7α-alkylamide group displayed pure antagonist properties. The original clinically tested 7α-undecanamide-substituted 17β-estradiol ICI 164384 (14) has been recently compared with its 16-halogenated (15) derivatives. The 15-alkylamide derivatives of 17β-estradiol have also been synthesised; however test results were not available. An interesting feature of 7α- and 11β-substituents is their orthogonal relationship with respect to
the relatively planar steroid skeleton. Simultaneous substitution at 7α and 11β, causes a loss in affinity to the estrogen receptor.

Ponsold et al. synthesised 14,15-methylene derivatives in the androstane and estrane series. The 14,15-methylene-estradiols were later biologically tested and compared to the corresponding 14,15-epoxyestradiols. In a quantitative structure-activity relationships (QSAR) study, it was revealed that hydrophobic interactions around C-14 and C-15 do not impede binding to the estrogen receptor. This conclusion was based on the fact that 14α,15α-methylenestra-1,3,5(10)-tren-3,17β-diol (16) equalled estradiol in affinity to the estrogen receptor, closely followed by 14β,15β-methylenestra-1,3,5(10)-tren-3,17β-diol (17). The 14α,15α- and 14β,15β-epoxyestradiols displayed almost complete loss in activity. Furthermore, it was claimed that 14α-steroids containing a 17β-hydroxyl group exhibit improved receptor binding compared to 14β-configurated steroids, and that a hydrophobic substituent of appropriate size attached to ring D carbon atoms would not necessarily decrease receptor binding.
An alternative to estrogen antagonists as a means of controlling estrogen biosynthesis, is the use of aromatase inhibitors. Aromatase is the cytochrome P-450 dependent enzyme which catalyses the final step in estrogen biosynthesis (Scheme 1.1).

Inhibition of this enzyme as a mechanism for inhibiting estrogen biosynthesis has been widely researched as a possible therapeutic strategy for the treatment of estrogen-dependent breast cancers. The mechanism of action of aromatase and its inhibitors has been reviewed. Most of the inhibitors have been synthesised as a result of interest in the mechanism of action of
the enzyme and hence, time-dependent inactivators of the enzyme was mostly prepared. Drug design was mainly concentrated on 1-, 2- and 19-substituted analogues of androst-4-ene-17-dione (18), and 4-hydroxyandrost-4-ene-3,17-dione (19). The latter compound is clinically used, however its main drawback is adverse metabolic clearance.\(^{17}\) Aminogluthethimide (20) is the only non-steroidal inhibitor of aromatase on the market and CGS 16929A (fadrazole hydrochloride) (21) a heterocyclic azole compound, is currently under clinical trials.\(^{18}\) Low specificity of aminogluthethimide for the cytochrome P-450-dependent enzymes results in broad spectrum inhibition, thus limiting its therapeutic capability.

In recent years, many competitive reversible inhibitors have been produced, but many more are needed in order to study structure-activity relationships more rigorously. Schering produced 1,2-methylenandrost-4-ene-3,17-dione (22) which successfully lowered estrogen levels.\(^{19}\) Later it was shown that \(\Delta^4\)-3-deoxy steroids display competitive reversible inhibition.\(^{20}\) 3-Deoxy analogues of androstenedione, (23) and (24) efficiently blocked aromatase activity, thus demonstrating an important structure-activity principle. Detailed mechanistic studies of aromatase action, supported by a wealth of time-dependent enzyme inactivators and irreversible inhibitors suggests that the haem-iron complex, responsible for 19-hydroxylation, is situated directly above the \(\beta\)-face around the 1,2,19-position of the A ring.
With the intention of designing suicide substrates (binding covalently to the active site), 10-oxiranyl (25) and 10-thiiranyl (26) androstanes were synthesised and biologically evaluated. Both compounds were proved to be potent competitive inhibitors instead. However, only the 19R isomers were active. These results prompted the authors to prepare homologated analogues of these oxiranes and thiiranes as molecular probes of the active site around the haem moiety. Biological evaluation of these compounds displayed weaker binding affinity to aromatase. Recently, a series of 2,19-methylene-bridged androst-4-ene-3,17-diones (27) and (28) have been synthesised. Biological data for (27) were not known at the time; however the series of 2,19-methylene analogues was shown to be time-dependent inactivators of aromatase. Effects of steroid ring D modification on suicide inactivation and competitive inhibition of aromatase by analogues of androsta-1,4-diene have been published.
The results of this study suggested that an oxygen at C-17 does not play a major role in the receptor binding of this series. As long as the five-membered ring is intact, modifications of the ring D, such as C-17 deoxygenation, caused a small decrease in binding affinity.

Hydrophobic groups attached to ring D of the estrone skeleton have a strong effect on the biological properties of these compounds. Numerous methods exist for the introduction of alkyl groups at C-15 and C-16. Groen and Zeelen synthesised (rac)-15α-methylestradiol 3-methyl ether (29) via a biomimetic polyene cyclisation reaction. They compared this product with the partial synthesis product (via 1,4-conjugate addition) in order to establish the stereochemistry at C-15. 16,16-Dimethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (30) has been prepared by treatment of 16-methylene 17-ketones with methylmagnesium iodide. Initial 1,2-addition of the Grignard reagent gives the 17α-methyl derivative, which was subjected to addition of hypobromous acid and subsequent rearrangement to the 16,16-dimethyl 17-ketone, followed by hydride reduction to give (30). The introduction of a single methyl group at C-16 poses the problem of base catalysed isomerism. This problem was circumvented by synthesis via the 16-hydroxymethyl 17-alcohols, to give stereospecifically all the possible isomers for 15-methylated 19-norsteroids.

The introduction of a 14-alkyl group is not so straightforward and poses an interesting problem. The interest in 14-methyl steroids arises from early discoveries about the biochemical pathway of lanosterol (31) to cholesterol (32). Early synthesis of 14-methyl steroids was achieved via degradation of lanosterol (31). 14-Methyl-11-oxo-14α-progesterone (33) has been prepared via this method, which was later further developed toward the synthesis of 14-methylprogesterone (34) and 14-methyltestosterone (35).
Base-mediated 14α-alkylation of cholest-8(14)-en-15-one (36) gave 14α-methyl-cholest-7-en-15-one (37). The biosynthetic relation between cholesterol and lanosterol was thus established. This strategy of 14α-alkylation was refined and used by several groups. The synthesis of the progesterone analogue (33) was improved via base-mediated alkylation of diketone (38). 14-Alkylation of the 15-ketone (39) gave the 14β-methyl compound (40), however the authors incorrectly assigned it as the 14α-methyl compound. This was corrected in a later study, in which the 14-configuration in a derived product was established with the aid of a X-ray crystal structure. Base-mediated methylation of the 15-oxo-17-acetal (41) gave exclusively the 14β-methyl compound (42). Further investigation into 14-methylation of 15-ketones revealed that 14α-alkylation is favoured in the case of 3-methoxy-14-estra-1,3,5(10),8-tetraen-15-one (43), giving rise to an epimeric mixture of compounds (44) and (45) in a ratio 5:1 (14α:14β). However, alkylation of 20,20-ethylenedioxy-3-methoxy-19-norpregna-1,3,5(10)-tri-en-15-one (46) gave exclusively the 14α-methyl product (47).
The stereochemical outcome of 14-alkylation of 15-oxo-steroids is thus influenced by conformational transmission, predisposed by unsaturation at the 8,9 position (43) or 17β-side chain.
The continued interest in 14α-methyl steroids is largely due to the effect the 14α-methyl group has on the conformation of 9β,10α-19-norsteroids (‘retrosteroids’). Formal inversion of configuration at C-9 and C-10 in progesterone (9) leads to retroprogesterone, which is known to enhance gestagenic activity.35 Bull et al.35 studied synthetic routes to 10α-methyl-9β, 10α- (48), 14α-methyl-9β,10α- (49) and 9β-methyl-9β, 10α-systems (50) which were systems devoid of gestagenic activity. A rational for these findings was based upon the argument that only those hormone analogues having a sterically congested α-face in conjunction with 9β,10α-configuration are expected to adopt conformations compatible with affinity for hormone receptors. The energetics of conformational deformation corroborated with their observed biological activities. Retrosteroids provided a unique model for further structure-activity studies in this area.

\[ R = \text{COCH}_3 \text{ or OH} \]

In order to explore this structure-activity hypothesis for retrosteroids, an efficient synthesis of 14α-methyl 19-norsteroids was sought. Bull et al. embarked on a total synthesis of (rac)-14α-methyl estrone 3-methyl ether (51).36 Catalytic hydrogenation of (rac)-3-methoxy-14-methyl-14α-estra-1,3,5(10),9(11)-tetraen-17-one (52) and the corresponding 1,3,5(10),8(9)-tetraen-17-one (53) gave mixtures of 14α-methyl-8β,9β-, 8α,9α, and 8α,9β-estriones.37 After laborious chemical modification and separation, 14α-methyl-8β,9β-estradiol 3-methyl ether (54) was prepared as the major product. A total synthesis of (rac)-14α-methyl estrone 3-
Steroids having a ring D diene system have been known since 1948. The synthetic potential of these systems have been realised by Solo et al. At a time when the Diels-Alder cycloaddition reaction activity principles were studied, Solo applied the cycloaddition method as a means of introducing a 14,17-bridge across the ring D. The reaction between 3β-acetoxyandrosta-5,14,16-triene-17-carbonitrile (56) and maleic anhydride, gave the cycloadduct (57). It was proposed that the stereochemistry of the cycloadduct would closely resemble one of the rotamers of 17α-alkyl or 17α-O-acyl steroids. The enhanced biological activity due to 17α-substitution, led to the assumption that bridged analogues of these hormones might be active. NMR was used to confirm the presence of a cycloadduct, however, the stereochemistry of cycloaddition was not established. They predicted the correct stereochemistry, based on hydrogenation results. Due to steric hindrance, cycloaddition and hydrogenation takes place stereoselectively on the β-face. Cycloaddition of 3β-acetoxy-20-
keto-5,14,16-pregnatriene \((58)\) was performed with methyl acrylate and ethylene to give cycloadducts \((59)\) and \((60)\).\(^{40}\) The former reaction gave a 82\% yield while the latter required a 3 000 atm pressure of ethylene at 160°C for 14h, to give a 53\% yield.

The indirect method toward the 14,17-etheno bridged analogue required decarboxylation of the endo-carbocyclic acid. However, such double bonds were susceptible to intramolecular attack, preventing decarboxylation. The endo-carboxylic acid of \((59)\) was subjected to the conditions of a modified Hunsdiecker reaction, resulting in the formation of an iodolactone \((61)\). In order to circumvent this problem, the authors selectively hydrogenated the 14α,17α-etheno bond of \((59)\), giving the 14α,17α-ethano-16α-(carboxymethyl)pregn-5-en-3β-ol-20-one acetate \((62)\). Hunsdiecker degradation of the carboxylic acid derived from \((62)\) gave 14,17α-ethano-16α-iodopregn-5-en-3β-ol-20-one acetate \((63)\).\(^{41}\) The first absolute evidence of the β-face stereochemistry of cycloaddition was apparent from a X-ray crystal structure of \((63)\). Further support for β-face cycloaddition was derived from NMR shielding effects on the 13β-methyl resonance due to the 14,17-bridge.\(^{42}\)
Both 14α,17α-etheno- (64) and ethano (65) bridged progesterone analogues were thus obtained. The 19-norprogesterone analogues (66) were also synthesised and assayed for Clauberg-activity (gestagenic activity).\textsuperscript{43} Amongst all the compounds tested, the 19-nor-14,17α-ethanopregn-4-ene-3,20-dione (66) gave an activity 17.6 times that of progesterone. The other analogues had activities of the same order as progesterone. An extension of the structure-activity studies into the androstane series prompted Solo et al. to synthesise ring D bridged analogues of testosterone.\textsuperscript{44} Cycloadditions on 3,17-diacetoxyandrosta-3,5,14,16-tetraene (67) was successfully performed using methyl acrylate and hexafluorobut-2-yne, giving low yields (<30%) of cycloadducts (68) and (69) respectively. The cycloadducts had no significant biological activity. Attempts to hydrolyse the 17-acetoxy group resulted in the formation of retro-aldol products.
The synthetic potential of cycloaddition methodology was further exploited by Wiesner et al.,\textsuperscript{45} who synthesised the 17α-methyl cardenolide (71), an analogue of digitoxigenin (72), in order to investigate structure-activity-toxicity relationships in this series of cardioactive steroids. Their synthetic plan involved cycloaddition of ethyl propiolate to the diene (70) to give the cycloadduct with β-face stereoselectivity. Selective hydrogenation of the α-face disubstituted double bond followed by oxidative cleavage of the residual double bond, gave the 14β-formyl product. Oxidation of the 14-formyl group gave the 14-carboxy group, followed by decarboxylation to give the 14,15-double bond. Lactonisation and 14α-hydroxylation was achieved via standard procedures, giving the cardenolide analogue (71).
The use of natural products as chiral auxiliaries or as chiral building blocks gained popularity in recent years. Winterfeld et al. realised the synthetic value of the precedented \( \beta \)-face stereoselectivity of cycloaddition. In a recent review, he describes the use of steroid dienes as chiral templates. Chiral synthesis was achieved via a Diels-Alder cycloaddition, transformation and retro-Diels-Alder sequence. The cycloaddition of 3-methoxy-17-phenylestra-1,3,5(10),14,16-pentaene (73) and appropriately substituted dienophiles gave cycloadducts which were subsequently modified and then released via a retro-Diels-Alder process, to give enantiomerically pure acyclic (74) or cyclic products (75). This principle was further extended to the resolution of enantiomeric mixtures of dienophiles.
Hitherto 14α-methyl synthesis have been achieved via degradation of natural products and total synthesis, employing laborious procedures. Solo et al. demonstrated the stereoselectivity of cycloaddition, however, the unavailability of an effective ethylene equivalent was a major drawback in the synthesis of ethano bridged steroids. The availability of phenyl vinyl sulphone as ethylene equivalent enabled Bull et al. to synthesise etheno bridged steroids with relative ease. The oxidative cleavage method, as performed by Wiesner et al. opened the route to 14α-alkyl and 14α-alkyl-functionalised steroids. Generally, the reaction sequence was based upon cycloaddition of an ethylene equivalent to a steroidal 14,15-diene (A), followed by oxidative cleavage of the olefinic bond in the cycloadduct (B), thus restoring the ring D system (C) with concomitant introduction of a 14α-formyl group. The C-17
substitution in (C) can be predetermined by the appropriate choice of substituents at C-16 and C-17 in the diene (A). An oxygen function at C-17 allowed further oxidative cleavage, leading to the 14α-formyl 17-ketone (D) (Scheme 1.2).

By adaptation of earlier literature methods, Bull et al. synthesised the 14,16-diene (76) from estrone 3-methyl ether (77) in three steps without purification of intermediates. Cycloaddition of diene (76) with phenyl vinyl sulfone gave the single cycloadduct (78). The resultant 16-phenylsulfone group was cleaved with sodium amalgam to give 14,17α-ethano-3-methoxyestra-1,3,5(10)-triene-17β-yl acetate (79), accompanied by a trace of the 16α,17α-cyclo-14,17α-ethano compound (80). Deacetylation of compound (79) gave the 17-alcohol (81). Catalytic hydrogenation of etheno compound (81) gave the ethano bridged steroid (82). Demethylation of (81) and (82) gave the estradiol analogues (83) and (84). The latter diols displayed superior estrogenicity compared to estradiol (4).
Cis-hydroxylation of etheno bridged compound (81) gave a mixture of exo- and endo-diols (85). Periodate cleavage of the ring D triol mixture gave the 14α-formyl 17-ketone (87). Selective deoxygenation of the 14\(^1\)-oxo group was required to obtain the 14α-methyl 17-ketone (51). However, thiketalisation gave a mixture of 14\(^1\),14\(^1\)- and 17,17-thioacetals (73%:16%). Treatment of the 14\(^1\),14\(^1\)-dithioacetal with Raney-Nickel gave, for the first time, 14α-methyl 17-ketone (51), as the enantiomerically pure compound. Selective hydride reduction of the 14α-formyl 17-ketone (87) gave the 14α-hydroxymethyl compound (88). The estradiol analogue of compound (88) displayed moderate estrogenic activity.
Cis-hydroxylation of the 17-acetate (79) followed by periodate cleavage gave the 14,17-dicarbaldehyde (86). The latter compound served as starting material toward the synthesis of novel 14α-functionalised 19-nor analogues of spironolactone (89), an aldosterone antagonist.\textsuperscript{51} Mild base treatment of acetoxy dialdehyde (86) gave a mixture of hemiacetals (90) with the spirolactone ring in place. Selective synthetic transformations gave 14-acetoxyethyl-3-methoxy-19-nor-17α-pregna-1,3,5(10)-tri-en-21,17-carbolactone (91). De-aromatisation using standard Birch conditions led to the spironolactone analogue (92).
Base treatment of the cycloadduct (78) resulted in a clean retroaldol cleavage to give the 14β- (2-phenylsulfonyl)ethyl)-Δ15-17-ketone (93), which was reduced to the 14β-ethyl 17-ketone (94). The cycloaddition method thus provided a facile route to 14β-alkyl 19-norsteroids, hitherto only available via laborious methods. The 14β-ethyl 17-ketone was further elaborated into the 17α- and 17β-estradiol analogues (95) and (96) respectively. Biological evaluation showed that these compounds displayed moderate estrogenic activity.
Cycloaddition with phenyl vinyl sulfone provided an alternative and improved route to 14,17-ethano-19-norprogesterone (66), a super gestagen. The starting material (97) for this synthesis was prepared by Bull et al., following well established methodology. Cycloaddition of phenyl vinyl sulfone with 3-methoxy-19-norpregna-1,3,5(10),14,16-pentaen-20-one (97) gave a single product (98) after 10 days at 145°C. Desulfonylation of the cycloadduct could only be achieved after hydrogenation of the 14,17α-etheno bond and reduction of the 20-ketone, since participation reactions resulted in the formation of the 16α,171-cyclo-14α,17α-ethano compound (99). The transformation of the primary cycloadduct (98) into 3-methoxy-14,17α-ethano-19-norpregna-1,3,5(10)-trien-20-one (100) was achieved in an overall yield of 46% from the dienone (97). Further elaboration of this product toward the 19-norprogesterone analogue (66) was easily accessible via Birch reduction. However, this transformation was deemed unnecessary since this compound has been synthesised and tested before.
Chemoselective differentiation of the 14α- and 17α-formyl groups in (86) was investigated by Bull et al. as part of the continued search for routes to 14α-alkyl- and 14α-alkyl-functionalised 19-norsteroids as aldosterone analogues.\textsuperscript{55} In this work, the diformyl compound (86) was reduced to the triol (101), followed by selective acetonide formation to give compound (102). The latter compound was perfectly suited for 14\textsuperscript{1}-hydroxymethyl protection and subsequent manipulation of the 17,17\textsuperscript{1}-functionality for possible spirolactone formation. The 14\textsuperscript{1}-hydroxymethyl group was effectively protected as the 14\textsuperscript{1}-benzyloxy compound (103). However, attempts to remove the acetonide resulted in low yields of the desired product and decomposition. In order to establish the influence of the benzyl group in the course of the reaction, deprotection of the acetonide (102) was attempted using iodine in methanol. The intended triol (101) was not obtained, but, a facile intramolecular closure took place, resulting in the formation of the epoxymethano compound (104), which was also achieved via acid treatment of the triol (101). This compound was further elaborated toward the 17α,14-epoxymethano-19-norpregn-4-ene-3,20-dione (105).
Reflecting back to the general scheme (scheme 1.2) of cycloaddition-cleavage methodology, Bull et al. envisaged the construction of the 17-acetyl moiety of progesterone via the diene (A) \((X = \text{OAc}, \ Y = \text{Me})\).\(^{56}\) Alkylation at C-16 of estrone 3-methyl ether, followed by standard dienyl acetate synthesis, gave the 3-methoxy-16-methyllestra-1,3,5(10),14,16-pentaen-17-yl acetate (106). Cycloaddition of phenyl vinyl sulfone with diene (106), gave a mixture of regio- and stereoisomers (107 \(\rightarrow\) 109). A reduction in the usual 'ortho'-regioselectivity,
was observed giving rise to cycloadduct (108), and cycloadduct (107) in equal amounts. However, the partial loss in β-face stereoselectivity led to the less important β-face etheno bridge cycloadduct (109).

The synthetically useful compounds (107) and (108) gave a common intermediate (110) upon desulfonylation. Oxidative cleavage of the etheno bridge of (110) gave the 17β-acetoxy-3-methoxy-20-oxo-19-nor-17α-pregna-1,3,5(10)-triene-14-carbaldehyde (111). Conversion of the latter compound into 19-norpregnane analogues was successfully achieved via reductive deacetoxylation associated with inversion of configuration at C-17 with concomitant reduction at C-14. The 14α-hydroxymethyl intermediate was further elaborated into the 14α-hydroxymethyl- and 14α-methyl 19-norprogesterone analogues (112) and (113) respectively.
The 14α-formyl 17α-acetyl compound (111) was perfectly suited for intramolecular cyclisation and was therefore further elaborated into 14,17α-propano bridged steroids. Base-mediated aldol closure, followed by elimination gave compound (114). Reduction of the 171-ketone, followed by hydrogenation of the 172-double bond and 3-demethylation gave the estriol analogue (115). Reductive deoxygenation at C-171 gave access to estradiol analogues (116) and (117). The propeno estradiol analogue (116) displayed superior
estrogenic activity compared to estradiol, whereas the propano derivative (117) was observed to be marginally weaker. The estriol analogue (115) displayed poor estrogenic activity.

The positive effect of the 14,17α-propano- or propeno bridge on estrogen binding, inspired the synthesis of 14,17β-propano- and propeno bridged estradiol analogues for structure-activity studies. Cycloaddition of acrolein with the dienyl acetate (76) gave the cycloadduct (118), which was converted to the 17β-hydroxy-16α-hydroxymethyl tosylate (119). The ring D hydroxyl groups in this compound was perfectly disposed for a Wharton fragmentation to give the 14β-allyl compound (120). Further elaboration via terminal 14β-alkylfunctionalisation followed by intramolecular cyclisation methodology led to 14β,17-propeno-, 14β,17-propano-estradiol and estriol analogues (121), (122) and (123) respectively. Biological evaluation of these compounds displayed poor estrogenicity.
With the intention of extending previous findings of structure-activity relationships of 14α,17α-etheno and 14α,17α-ethano analogues (83) and (84), the synthesis of 14,17α-ethanoestra-1,3,5(10),15-tetraen-3,17β-diol (124) was investigated. The 14,17β-etheno 16α-carboxaldehyde (118) was converted to the estradiol analogue (124) (no biological data available). The transformation was achieved via hydrogenolysis of the 14,17-etheno bond, oxidative elimination of the formyl group and ring A deprotection. Subsequently, Schering reported the synthesis of the estriol (126) via the 14α,17α-ethano-3,17β-dihydroxy-estra-
1,3,5(10)-trien-16-one (125). The estriol (126) displayed superior oral estrogenicity to that of estradiol (4), ethynylestradiol (5) or 14α,17α-ethanoestradiol (84).

In the light of the excellent biological activity of compound (126), the effect of a hydroxyl group on the α-bridge was investigated. Attempted regioselective hydroboration on the 14,17α-etheno compound (81) was unsuccessful, resulting in an intractable mixture of 17,17\textsuperscript{1}- and 17,17\textsuperscript{2}-diols. Careful chromatographic separation in combination with oxidative cleavage of vicinal diols allowed the isolation and characterisation of the individual diols. The derived estriols displayed poor estrogenicity. Another aspect of this investigation was the accessibility of 14α-functionalised 19-norsteroids via 17,17\textsuperscript{1}-dil cleavage; however unfavourable product distribution and elaborate chromatographic separation made this route unattractive.
The synthetic route toward estradiol analogues (124) and (126) was inefficient due to a low yield (40%) at the decarboxylation step. This route was later improved via the key intermediate (125). Generally, cycloaddition of diene (E) with an 'ethylene equivalent' to give cycloadduct (F), followed by hydrolysis of the concomitant 16-functionality should give the 16-ketone (G).

Two such 'ethylene equivalents' was considered. Firstly, cycloaddition of 2-acetoxyacrylonitrile with dienyl acetate (76) gave the cycloadduct (127). Base hydrolysis of the latter compound gave the 17-hydroxy 16-ketone (128). Hydrogenolysis of the 14,17α-etheno bond, followed by 16-tosylhydrazone formation gave compound (129). Shapiro elimination of tosylhydrazine provided an improved route toward the estradiol analogue (124). Reacetylation of the alcohol (128) gave the 17-acetoxy 16-ketone (125). Hydride reduction of the 14,17-etheno- or ethano 16-ketones favoured 16β-alcohol formation. Mistunobu inversion of the 16β-OH was unsuccessful. In order to circumvent this problem an alternative
route via the 14β-allyl ketone (120) was employed. Ozonolysis of the 14β-allyl group gave the 14β-formylmethyl 17-ketone (130). McMurry coupling of the formyl ketone gave a mixture of the 14α,17α-ethano 16α,17β-diol (131) (71%) and the 14α,17α-ethano 16β,17β-diol (132) (18%).

A further attempt to synthesise the 16-ketone (128) involved cycloaddition of 2-chloroacrylonitrile with dienyl acetate (76) to give the cycloadduct (133). Base hydrolysis of the cycloadduct (133) did not give the expected 16-ketone (128), however a novel rearrangement product (134) was obtained. The latter compound was further elaborated into
estradiol analogues (135), (136) and (137). The synthetic route entailed reductive decyanation of the 16-carbonitrile 17-ketone (134) as well as selective cyclopropyl cleavage. Biological evaluation of these estradiols showed that 17α-hydroxy analogues (135) and (136) displayed moderate estrogenic activity compared to a less active 17β-hydroxy analogue (137).

Ring D functionalised bridged compounds underwent facile rearrangements toward 14,16-ethano or etheno bridged compounds, thus providing routes to a series of estradiol analogues for structure-activity studies. The 16β-hydroxy 17β-acetate (138) was converted into the 16β-mesylate (139). Treatment of the mesylate (139) with basic alumina, did not give the elimination product (3-methyl ether of 124), however, a facile pinacol-type 17\(^1\)\( \rightarrow \)16\( \rightarrow \)abeo rearrangement took place to give the 14α,16α-ethano 17-ketone (140). The derived estradiol analogues (141) and (142) displayed strong estrogenticity.
In a similar fashion, the 14α,17α-etheno 16β,17β-diol (143) rearranged via acidic or mesylation conditions to give the 14α,16α-etheno bridged compound (144).

The facile nature of these rearrangements prompted further investigation into the migratory aptitude of the 16α-methyl 16β,17β-diol (146), which was easily prepared via methylation of the 17β-hydroxy 16-ketone (145). Treatment with boron trifluoride-diethyl ether resulted in the formation of the 16β-methyl 14α,16α-etheno 17-ketone (147). The 14,17-bridged
compounds (149) and (150) were converted into the 14,16-ethano compounds (148) and (151) under these conditions. Compound (148) was also available via hydrogenation of (147).

Treatment of the 14,17α-ethano compound (81) with anhydrous pyridinium hydrochloride gave 14,16-ethano bridged compound (152). Biological evaluation of the corresponding 17β-estradiol (153) displayed strong estrogenic activity.
At this stage available receptor affinity data of ring D modified steroids once again showed the importance of the molecular topology in this region in terms of structure-activity relationships of estradiols and estriols. All the receptor affinity data have been reported as competition factors (CF) (discussed in detail in Chapter 3.6). 17β-Estradiol was taken as the reference substance and therefore has a CF value of unity. Hormone analogues with CFs lower than unity were regarded as superior in activity compared to estradiol, whereas CFs in multiples of unity were regarded as moderate to poor receptor binding activities.

Receptor affinity data (Schering, Berlin) for the 14β-methyl 17β-hydroxyestradiol (CF = 0.9) analogue displays superior estrogenic activity, with a slight decrease for the 17α-hydroxy analogue (CF = 1.3). 14β-Chain extension results in a further reduction in estrogenic activity. The (rac)-14α-methyl 17β-hydroxyestradiol analogue (CF = 3.2) was less active than the corresponding 14β-analogue. The introduction of an 14α,17α-ethano bridge greatly improved receptor binding (CF = 0.6), whereas a 14α,17α-propano bridge caused a slight reduction in receptor affinity (CF = 1.5). The introduction of an 14β,17β-propano bridge caused a large reduction in activity (CF = 69). Unsaturation on 14,17-bridges had a strong influence on receptor binding, thus the 14α,17α-etheno bridged analogue suffered a small reduction in activity (CF = 0.9), relative to the corresponding ethano analogue (84) whereas the 14α,17α-17²-propeno analogue displayed the highest known binding affinity (CF = 0.4) in this series. β-bridged unsaturation, for example, 14β,17β-17ⁿ-propeno (n=1,2) analogues resulted in a further decline in estrogenic activity (CF > 470) in this series.
It is known that estriol (16α-hydroxylation product of 17β-estradiol) experiences a tenfold reduction in affinity for the estradiol receptor. However, the introduction of hydroxyl groups on the bridged analogues revealed interesting properties. The introduction of a 16α-hydroxy group on the β-bridge of 14,17-ethano analogues resulted in superior estrogenic activity, whereas hydroxylation of the α-bridge in the same series resulted in further loss of activity. Hydroxylation of the α-bridge (see estradiol analogue (115)) resulted in a huge reduction in binding affinity (CF = 98 to >500), and was amplified in the 14β,17β-propano series.

Estradiol analogues of 14,16-ethano bridges displayed similar binding affinities in the 14α,16α- and 14β,16β-ethano series, (CF = 1.1), whereas the 14α,16α-ethano 17α-hydroxy analogue (142) displayed increased binding affinity (CF = 0.9). The 17α-hydroxy 15,161-cyclo-14,16-ethano- (135) (CF = 2.5) and 14β,15β-cyclobutano (136) analogues had higher affinities for the estradiol receptor than the corresponding 17β-isomer (137) (CF = 6.5). These results are coherent with that obtained for 14,15-methylene estradiol analogues (16) and (17).

The angular formyl group has hitherto been the focal point for structural modification of the steroid skeleton. Structure-activity studies of aromatase inhibitors involved 10β-methyl functionalisation via the 10β-formyl intermediate (see scheme 1.1 on page 7). The synthetic and possibly biological demethylation of the 10β-methyl group toward 19-norsteroids proceeds via the 10β-formyl intermediate. Similarly, the 13β-methyl group also serves as a cytochrome P-450 hydroxylation site in the transformation of corticosterone (154) into aldosterone (155). Recently the 13β-formyl functionality has been introduced in the androstane and pregnane skeleton for further manipulation toward the synthesis of aldosterone biosynthesis inhibitors.57 In the androstan e series, the 13β-ethynyl derivative (156) gave 85% inhibition, whereas the 13β-vinyl derivative (157) gave 17% inhibition. In the pregnane series, the 13β-allyl derivative (158) gave 100% inhibition, whereas the 13β-vinyl derivative (159) gave 50% inhibition.
The 10β-formyl group has been introduced into the androstane skeleton by Jeger et al. and is now commercially available. The 13β-formyl group in the androstane and pregnane series was synthesised from commercially available pregnenolone. Wiesner et al. reported the synthesis of a 14β-formyl pregnane analogue via cycloaddition-cleavage methodology. This strategy was recently adopted by Bull et al. in the introduction of a 14β-formyl group in the 19-norsteroid skeleton. Cycloaddition of methyl propiolate to dienyl acetate \((\text{76})\) gave the cycloadduct \((\text{160})\). Hydrogenation of the \(\alpha\)-etheno bond, followed by the oxidative cleavage of the residual \(\beta\)-etheno bond gave the 14β-formyl product \((\text{161})\). Hydrolysis of the 17-acetoxyl group and reduction of the 16-carboxyster prior to oxidative cleavage leads to the 14β-formyl 17-ketone \((\text{162})\), whereas complete reduction of the 16-carboxyl to a 16-methyl group led to the progesterone analogue \((\text{163})\).
The chemistry of the 14α-formyl group in the estrane, pregnane and androstane series has not yet been fully exploited, but a number of 14α-analogues of lanosterol and cholesterol have been prepared. 32-Oxygenated steroids are formed during the removal of the 14α-methyl group of lanosterol (31) by the cytochrome P-450 mono-oxygenase, lanosterol 14α-methyl demethylase, which catalyses the first step in the conversion of lanosterol (31) to cholesterol (32). The biosynthetic pathway was proposed to proceed via the 14α-formyl intermediate (164).
Early work was devoted to the synthesis of biosynthetic intermediates, *inter alia* the 14α-formyl compound (164). Chemical modification of the 14α-methyl group could only be realised via remote functionalisation. Barton *et al.* synthesised the key intermediate, 3β-acetoxy-7α-hydroxy-lanostane (165) from lanosterol (31). Heusler *et al.* used the hypoiodite reaction to convert the alcohol (165) into the 14α-oxidised compounds (166), which was further elaborated into the Δ7-14α-formyl compound (164).

Barton *et al.* later used nitrite photolysis to achieve 14α-functionalisation. Photolysis of the nitrite (167), derived from the alcohol (165), gave the oxime (168). Subsequently, the oxime was converted into the 14α-carbonitrile and eventually into the 14α-formyl compound (164).

The introduction of a 14β-carbonitrile group onto the androstane skeleton was achieved by Campbell *et al.*, who converted dehydroepiandrosterone into the 3β,17β-diacetoxy-5α-androstan-16-one (169), followed by α,β-unsaturation to give the enone (170). Treatment of
the latter compound with hydrogen cyanide in the presence of triethylaluminium (Nagata reaction) gave the 14β-carbonitrile 16-ketone (171).

Recently there has been much interest in the lanosterol 14α-methyl demethylase enzyme. Inhibitors of this enzyme may have therapeutic use in the treatment of familial hypercholesterolemia or as antifungal agents. This finding prompted the synthesis of a series of inhibitors, based on the first two steps of C-32 demethylation. Lanosterol analogues were prepared from the 14α-formyl compound (164), which was available via the improvement of earlier synthetic methods. Robinson et al. prepared the C-32 difluoromethyl-, difluoroethyl, propynyl-, vinyl- and ethynyl analogues of lanosterol for biological evaluation. Cooper et al. converted the 14α-carbonitrile (obtained via Barton reaction) into the 14α-aminoethyl and 14-1H-imidazolylmethyl lanost-8-en-3-ol analogues. Robinson later reported the synthesis of 14α-ethyl-, 14α-oxiranyl- and thiiranyl analogues. Sato et al. converted products of hypoiodite oxidation into the 14α-carboxyesters. Anastasia et al. prepared the Δ7-14α-carbonitrile (175) analogue of cholesterol, starting with 3β-acetoxy-cholest-7-ene (172). Chromic acid oxidation gave, inter alia the 8α,14α-epoxy 7-ketone (173), followed by deoxygenation of the epoxide to give the enone (174). The Nagata reaction, followed by reduction and elimination of the 7-oxo functionality gave the carbonitrile (175). Gallagher recently applied this route toward the synthesis of the 14α-formyl compound (164), i.e. via reduction of the 14α-carbonitrile. Many more 14α-functionalised lanosterol and cholesterol analogues have been synthesised as mechanism-based inhibitors of sterol biosynthesis. These analogues can be classified as Δ7 or Δ8-14α-homologated sterols. Biological activity in this series of compounds is dependent on this position of unsaturation. Unsaturation at Δ7 causes
a flattening of the B ring, resulting in an almost orthogonally orientated 14α-functionality, thus allowing maximal chemical reactivity at this position, relative to ring B saturated systems.

At this stage, limitations of ring D modification were largely overcome by the cycloaddition work of Solo et al., followed by Wiesner et al. The cycloaddition route was further developed by Bull et al. via the creative choice of steroidal dienes and dienophiles, thus further increasing the possibilities in ring D modification. Cycloaddition – rearrangement methodology provided easy access to 14,16-ethano bridged steroids. Cycloaddition – fragmentation methodology provided easy access to 14β,17β-propanosteroids. The β-face selectivity of cycloaddition allowed variable 14β-alkyl functionalisation of the primary cleavage product by the appropriate choice of dienophile. However, 14α,17α-functionalisation depends primarily on the choice of diene. A major drawback in the choice of ring D substituted steroidal dienes is the loss in β-face selectivity and reactivity during cycloaddition. Hitherto, synthetic methodology relied on 14α,17α-difunctionalised and 14α-
functionalised 19-norsteroids for further development toward 14α,17α-propano bridged-, 14α,17α-heterobridged- and 14α-alkyl 19-norsteroids. The lability of intermediates in this series of compounds limited rapid progress toward 19-norsteroid analogues. The 14α-series of 19-norsteroids are biologically more active than the corresponding β-analogues. Further development of these compounds can be envisaged via 14α-functionalised 19-norsteroids.
2. OBJECTIVES

The overall objective of this investigation was to exploit cycloaddition-mediated methodology to synthesise ring D modified analogues of estrane- and androstane-derived steroidal hormones. Previous work in the research programme has established that 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol is a powerful oral estrogen, closely resembling estradiol in topological properties, but with apparent resistance to metabolic degradation as a result of the ring D bridged structure. Synthesis of a large number of bridged analogues has hitherto provided an imperfect pattern of structure-activity relationships upon which to develop predictive design principles, and one of the objectives of this investigation was to synthesise analogues characterised by ring D bicyclo[2.1.1]hexanoid structures, in order to study the influence of a contracted bridge structure upon conformational properties and biological activity.

The approach selected for this purpose was to examine intramolecular cyclisation modes for 3-methoxy-17-oxo-estra-1,3,5(10)-triene-14-carbaldehyde (A) and the derived 14α-functionalised-methyl analogues (B). The most direct route to the first target, 14,17α-methanoestra-1,3,5(10)-triene-3,17β-diol (C) was envisaged via a species (B), set up for intramolecular reductive cyclisation. Alternatively, it was expected that intramolecular reductive cyclisation of the 14α-formyl 17-ketone (A) could give a pinacol product (D) amenable to chemoselective differentiation of the hydroxy groups.
Similarly, intramolecular enolate-mediated cyclisation of intermediates (B) was planned as a possible route via the 17-ketone (E) to 14,16α-methanoestra-1,3,5(10)-triene-3,17β-diol (G). It was expected that an analogous intramolecular aldol condensation (A → F) would be attended by difficulties associated with facile reversibility of the aldol reaction leading to product (F).
A complementary aspect of this investigation was to explore the scope for chemoselective differentiation of the carbonyl groups in the 14α-formyl 17-ketone (A), in order to synthesise a range of 14α-alkyl and 14α-functionalised-alkyl analogues of estradiol. In the first place, an improved procedure for chemoselective reductive deoxygenation of the 14α-formyl group was sought, in order to secure an efficient synthesis of 14α-methyl estrone (H) for further study. Although the parent compound has been prepared via total and partial synthesis, the product has not yet been prepared in sufficient quantity for exhaustive study, in particular, stereoselective alkylation at C-17. Products of this nature (I), would constitute ‘17₁,17₂-seco’ analogues of the bridged series.
Similarly, improved chemoselective methylenation of the 14α-formyl 17-ketone (A) would give access to the 14α-vinyl and hence 14α-ethyl analogues of estradiol (J) and (K), whereas chemoselective alkylation could give rise to a range of 14α-chain-extended estrone analogues (L). Such intermediates were expected to be of intrinsic interest as precursors of new estradiol analogues (M) and (N), but could provide new and possibly more efficient synthetic entry to functionalised 14α,17α-ethano and 14α,17α-propano analogues of estradiol, through intramolecular cyclisation. Of particular interest in the overall plan was the possibility of developing a synthetic route to long-chain 14α-dialkylamidoalkyl estradiol analogues (N) \([R = (CH_2)_n CONMeBu, n=6, 8, 10]\) related to 7α-analogues which display 'pure' estrogen antagonism.
As an extension of previous studies carried out on estra-1,3,5(10)-triene systems, cycloaddition strategy was applied to the androstane systems to explore the scope of developing routes to ring D bridged and 14α-alkyl hormone analogues in this series.

For this purpose, it was envisaged that 15α-hydroxyandrost-4-ene-3,17-dione (O) could be converted into a 14,16-dien-17-yl acetate (P), cycloaddition of which with an ethylene equivalent would lead to the 14α,17α-etheno analogue (Q) of testosterone and hence, via rearrangement or oxidative cleavage of (Q) to the derived target systems (R) or (S) respectively. A requisite for the latter operation was the development of methods for chemoselective oxidative cleavage of the bridged olefinic bond of (Q). This objective is unlikely to be readily attained by direct methods, and the introduction of sterically impeding functionality at C-3 will be investigated. Alternatively, an approach based upon conversion of the Δ5-3-oxo moiety into appropriate latent functionality will be explored through i-steroid intermediates.

Selective acid-mediated rearrangement of (Q) analogous to that of the 14,17α-etheno bridged estrane series, are expected to lead to 14,16-ethanoandrostanes (R). Selective oxidative cleavage of the bridged olefinic bond will provide access to 14-functionalised-androstanes (S).

Biological evaluation of the target compounds was expected to provide further insight into the role of ring D modified structures upon structure-activity relationships of steroidal hormone analogues. Of particular interest in this context was the possibility that ring D modified androst-4-ene-3,17-diones could be candidates for evaluation as aromatase inhibitors.
(R=H, OH etc)
3. DISCUSSION

3.1 Synthesis of 14,17-methano 19-norsteroids.

The starting materials for this investigation were prepared via the established cycloaddition-cleavage methodology.\textsuperscript{49} Thus, estrone 3-methyl ether (77) was subjected to bromination-dehydrobromination at C-16, followed by forcing enol acetylation of the resultant mixture of ring D enones, to give the dienyl acetate (76) in 64\% overall yield. Cycloaddition of diene (76) with phenyl vinyl sulfone gave the cycloadduct (78), which underwent desulfonylation in the presence of sodium in liquid ammonia to give the 14α,17α-etheno compound (81). As reported previously,\textsuperscript{49} this product was accompanied by the inseparable by-product (80) of olefinic bond participation during desulfonylation. cis-Hydroxylation followed by oxidative cleavage gave 3-methoxy-17-oxoestra-1,3,5(10)-triene-14-carbaldehyde (87) (60\%). Treatment of the 14α-formyl 17-ketone (87) with lithium tris(s-butyl)borohydride (‘L-Selectride’) in tetrahydrofuran at 0°C gave 14α-hydroxymethyl 17-ketone (88) (97\%). This chemoselective transformation proceeded as efficiently with sodium borohydride-cerium(III) chloride in aqueous propan-2-ol at 0°C.

In the first phase of this investigation, the 14α-hydroxymethyl 17-ketone (88) was converted into the corresponding 14\textsuperscript{1}-tosylate (176) in order to explore the scope for achieving direct intramolecular reductive cyclisation to 3-methoxy-14,17α-methano-estra-1,3,5(10)-tri-en-17α-ol (C) via an intermediate arising from electron transfer to the 17-oxo-group (Scheme 3.1-1).
This approach necessitates transannular bond formation, leading to a 1-hydroxybicyclo[2.1.1]hexanoid system, for which there is little precedent. However, Molander et al.\textsuperscript{82} have demonstrated that treatment of 3-((ω-iodoalkyl))cycloalkanones with samarium(II) diiodide in the presence of a catalytic amount of tris(dibenzoylmethido)iron(III) [Fe(DBM)\textsubscript{3}] at -78°C results in the formation of bicyclo[m.n.1]alkan-1-ols. Of particular interest was the report of a reasonably efficient conversion of 3-iodomethylcyclopentanone into the bicyclo[2.1.1]hexan-1-ol, under these conditions, thus demonstrating that despite the high strain associated with this ring system,\textsuperscript{83} the desired bond formation could be achieved (Scheme 3.1-2, equation 1). It is argued that the mildness of the reaction conditions suggests that the high activation energy is lowered by [Fe(DBM)\textsubscript{3}].\textsuperscript{84} The question of whether the tosylxy group could act as partner in such a process was not addressed, but intramolecular reductive cyclisations of appropriately orientated tosylxy ketones have been reported. In an early study by Stork et al., it was reported that treatment of 10-tosylxymethyl octalones with lithium metal in liquid ammonia gave 9,10-methylene-cis-2-decalones, a vinylogous version of the intended reaction (Scheme 3.1-2, equation 2).\textsuperscript{85} Another example is the use of samarium(II) diiodide to initiate a direct reaction between a presumed radical ion or similar intermediate and a proximate tosylxy group in the reaction leading to a α-cyclopropyl alcohol (Scheme 3.1-2, equation 3).\textsuperscript{86}
In a preliminary study it was reported that treatment of the 14α-tosyloxymethyl 17-ketone (176) with lithium in liquid ammonia at \(-78^\circ C\) failed to give the 14α,17α-methano 17β-alcohol; instead a separable mixture of the 14α-hydroxymethyl 17α-alcohol (177) (71%) and the 14α-hydroxymethyl 17β-alcohol (178) (25%) was obtained (Scheme 3.1-3). Reductive cleavage of primary and secondary tosylates is known to occur in the absence of participating carbonyl groups, and the described reaction course can be ascribed to independent reduction at the two reaction sites.
An attempt was made to achieve intramolecular reductive cyclisation by treating the 14α-tosyloxyethyl 17-ketone (176) with samarium(II) diiodide in tetrahydrofuran. After 2h at -78°C, the reaction mixture was allowed to warm to 20°C and gave a complex mixture of products.
Attempted chromatographic separation was largely unsuccessful, and only a small amount of a product formulated as 3-methoxy-17α-homoestra-1,3,5(10),14-tetraen-17α-one (179) (10%) was isolated (Scheme 3.1-4). The more polar products could not be separated. The reaction leading to the formation of the ring D rearranged product under these conditions is not clear, but it is assumed that the product is an artifact arising from the intervention of a solvolytic process instead of electron transfer. The reaction was also conducted in the presence of a catalytic amount of [Fe(DBM)₃], with or without sodium iodide. In either case, only a trace of 17α-homosteroid (179) was observed after 3 days at 20°C or 24h at reflux. Previously, an attempt to synthesise the 14α-iodomethyl 17-ketone (180) from the 14α-tosyloxymethyl 17-ketone (176) resulted in the formation of the 17α-homosteroid (179). This synthetic route provided access to Δ¹⁴-D-homosteroids, not easily attainable via total synthesis. Accordingly, the foregoing reaction was repeated, and 17α-homosteroid (179) was prepared in good yield (83%) for further elaboration toward estradiol analogues in this series. In order to attain this goal, stereoselective reduction at C-17α was necessary. Thus, treatment of 17α-homosteroid (179) with lithium aluminium hydride at 20°C for 7 min, resulted in the formation of an inseparable mixture of the 17αα-(181) and the 17αβ-alcohol (182) in a ratio of 1:2.3 respectively (Scheme 3.1-5). Furthermore, reduction at C-17α using sodium metal in propan-2-ol gave the same product ratio (ca. 1:2.3), whereas ‘L-Selectride’ gave a 1.5:1 ratio of 17αα- to 17αβ-alcohols. The alcohol mixture derived from lithium aluminium reduction was converted into the corresponding mixture of acetates (183 and 184), which was also chromatographically inseparable. However, NMR examination of the mixture enabled the respective isomeric components to be distinguished by comparison of the signals for the 17α-protons. The 17αα-acetate (183) displayed the 17αβ-proton as a triplet (J 2 x 4.6 Hz) at δ4.88, whereas the 17αβ-acetate (184) displayed the 17αα-proton as a doublet of doublets (J 9.8 and 5.6 Hz) at δ4.80.
Repeated recrystallisation of the pooled acetate mixtures furnished the 17αβ-acetate (184) sufficiently pure for further elaboration. Thus, treatment of the 17αβ-acetate (184) with DIBAL in toluene at reflux for 40h, gave the 17α-homoestra-1,3,5(10),14-tetraen-3,17αβ-diol (185) (75%) (Scheme 3.1-6). The diol (185) was characterised by the appropriate analytical and spectroscopic data, and has been subjected to biological evaluation.

The failure of the 14α-tosyloxymethyl 17-ketone (176) to undergo intramolecular reductive cyclisation under the reaction conditions described here, suggests that the spatial orientation of the centres targeted for interaction is unfavourable, thus allowing competing reduction or solvolytic rearrangement to intervene.
Consideration was thus given to an alternative approach based upon intramolecular cyclisation of the 14α-formyl 17-ketone (87). The principle of reductive coupling of dicarbonyl compounds is well established, and has enjoyed widespread application following the definitive studies by McMurry on low-valent titanium reagents for inter- and intramolecular coupling, leading to pinacols and derived olefins. More recently, samarium(II) diiodide has found increasing use as a reductive coupling reagent, and has been successfully employed for the synthesis of strained structures. These reactions are mechanistically related and are all initiated by electron transfer to the respective carbonyl centres, followed by coupling of the resultant radical anions.

Treatment of the 14α-formyl 17-ketone (87) with samarium(II) diiodide and t-butyl alcohol in refluxing tetrahydrofuran gave a single more polar product (77%), which was formulated as (171S)-3-methoxy-14,17α-methanoestra-1,3,5(10)-triene-17β,171-diol (186) on the basis of supporting analytical and spectroscopic data (Scheme 3.1-7).

The distinctive spectroscopic characteristics which supported the structural assignments included infrared absorption at $\nu_{\text{max}} 3613$ and $3440$ cm$^{-1}$ for the hydroxy groups, and the attendant absence of carbonyl absorption, together with distinctive NMR signals at $\delta_H 4.09$ for the methine 171-proton and $\delta_C 81.8(s)$ and $73.5(d)$ for the hydroxy-attached carbon atoms C-17 and C-171 respectively. In view of the novelty of the structure, a detailed high field NMR study was carried out in order to gain further structural information as well as to establish the configurational assignment at C-171. With the aid of COSY, HETCOR, and
DEPT spectra, it was possible to identify a number of diagnostic signals. The HETCOR spectrum confirmed the connectivity between the $17^1$-H and C-$17^1$. Difference NOE experiments confirmed certain assignments and gave further evidence for the structural assignment and $17^1$S-configuration. Figure 3.1-1 gives the percentage positive NOE resulting from irradiation at $9\alpha$-H, $12\alpha$-H, and $17^1$-H respectively.

![Fig 3.1-1](image)

Unequivocal evidence for the structure of the diol (186) was provided by the X-ray crystal analysis. The atomic numbering and perspective views of the molecule is shown in Figure 3.1-2 and Figure 3.1-3 respectively.

![Fig 3.1-2: Perspective view of the diol (186) with its atomic labelling.](image)
The final fractional atomic coordinates and equivalent isotropic parameters are given in Table 4.3 (Chapter 4). The C-C distances and internal C-C-C angles (excluding the A-B linkages) in rings B and C are 1.48(4) - 1.61(3) Å and 104.0(20) - 115.3(20)° respectively, with the exception of C(13)-C(14)-C(8) (121.6°). This large angle is clearly induced by the adjacent cyclobutyl bridge. The bond lengths associated with the bridged ring D [1.47(3) - 1.67(4) Å] display no abnormalities. The internal bond angles in ring D [80.5(2) - 107.2(2)°] and in the cyclobutyl ring [76.3(2) - 90.7(2)°] conform to expectations for the strained bicyclo[2.1.1] carbon skeleton. The C(17)-C(13)-C(14)-C(15) torsion angle is +65.4(2)°, compared to +45-56° for the normal C(13) ‘envelope’ conformation. This large torsion angle is a consequence of the 14,17-methano bridge.

The reaction leading to the formation of the diol (186) can be rationalised by the mechanism as depicted in Scheme 3.1-8. The most feasible pathway leading to the coupled product can be envisaged via intramolecular ketyl addition to the Sm²⁺ coordinated ketone. Efficient cyclisation can be facilitated by Lewis acid activated ketone (87A). Generally, ketyl addition to carbonyls is a reversible process. However, reversibility can be greatly affected by Lewis acid chelation of the complex, and further reduction to the radical intermediate (87B) by a second equivalent of samarium(II) diiodide would render the process irreversible.86 The
stereochemical outcome of the reaction depends on the orientation of the 14α-formyl group orientation. The orientation of intermediate (87A) is such that nucleophilic ketyl radical addition to the 17-ketone, gives rise to the formation of a product with 17\(^{1}S\)-configuration. Inspection of models revealed that other rotamers are sterically more demanding and incompatible with the proposed mechanism and would lead to the opposite configuration at C-17\(^{1}\).

![Diagram](image)

\[\text{Scheme 3.1-8}\]

The diol (186) was treated with DIBAL in toluene at reflux for 4h, to give (17\(^{1}S\))-14,17α-methanoestra-1,3,5(10)-triene-3,17\(^{\beta}\),17\(^{1}\)-triol (187) (77\%) (Scheme 3.1-9). The triol (187) was characterised by the appropriate spectroscopic data and has been subjected to biological evaluation, the results will be discussed later (see Chapter 3.6).
With the diol (186) in hand, the next step for preparation of the parent estradiol analogue, entailed chemoselective deoxygenation of the 17₁-hydroxy group. Deoxygenation of secondary alcohols has been routinely achieved via hydride reduction of their corresponding tosylates. Hence, selective tosylation of the 17₁-hydroxyl group was attempted. However, treatment of the diol (186) with toluene-\(p\)-sulfonyl chloride in pyridine resulted in a complex mixture of products. An indirect synthesis was considered, based upon selective acetylation of the secondary hydroxyl group (C-17₁), followed by the introduction of a base-stable protecting group at C-17. Subsequent deacetylation would render the 17₁-hydroxyl group free for deoxygenation. Thus, attempted monoacetylation (acetic anhydride-pyridine) at 0°C revealed the presence of two less polar components from an early stage of the reaction (TLC), with eventual accumulation of a single product. It proved impractical to isolate and characterise the obvious intermediate in the reaction. Accordingly, the reaction was allowed to proceed to completion (10h, 24°C) to give a single product (86%) formulated as (17₁-S)-3-methoxy-14,17α-methanoestra-1,3,5(10)-triene-17₁,17₁-diyldiacetate (188) on the basis of supporting analytical and spectroscopic data (Scheme 3.1-10). Infrared absorption at \(\nu_{\text{max.}} 1732(\text{CO})\) together with \(^1\text{H NMR}\) signals at 2.08 and 2.01 (each 3H, s) demonstrated the presence of the 17β- and 17₁-acetoxy groups; in addition, the signal for the 17₁-proton was observed in the appropriate downfield region at \(\delta 5.47 (1\ \text{H, s})\).
Selective deacetylation at C-17\textsuperscript{1} was attempted. Thus, treatment of the diacetate (188) with potassium carbonate in methanol at 0°C resulted in rapid hydrolysis to the diol (186), whereas treatment with 'L-Selectride' in tetrahydrofuran at -78°C gave (17\textsuperscript{1}S)-3-methoxy-14,17α-methanoestra-1,3,5(10)-triene-17β,17\textsuperscript{1}-diol 17-acetate (189) (70%) and the diol (186) (22%) (Scheme 3.1-11). Failure to detect separation of the 17-acetate (189) from the starting diacetate (188) during TLC monitoring of the progress of the reaction complicated further optimisation of the conditions.

Analytical results were consistent with the structures of the 17-acetate (189), which was supported by infrared absorption at $\nu_{\max.}$ 1712(CO) and 3507(OH)cm$^{-1}$, together with NMR signals at $\delta_H$ 2.08 (3H, s) for the 17β-acetoxy group, and 4.28 (1H, s) for the 17\textsuperscript{1}-proton.

With the 17-acetate (189) in hand, it was now possible to synthesise the 17\textsuperscript{1}-tosylate as planned, for attempted reductive deoxygenation at C-17\textsuperscript{1}. Accordingly, treatment of the 17-acetate (189) with toluene-p-sulfonyl chloride in pyridine gave (17\textsuperscript{1}S)-3-methoxy-14,17α-methanoestra-1,3,5(10)-triene-17β,17\textsuperscript{1}-diol 17β-acetate 17\textsuperscript{1}-toluene-p-sulfonate (190) (90%)
The 17-tosyl 17-acetate (190) was characterised by infrared absorption at $v_{\text{max}}$ 1738 (CO) and 1308 (SO) cm$^{-1}$, together with $^1$H NMR signals at 2.39 (3H, s) for the 17β-acetoxy group, and 4.97 (1H, s) for the 17$^1$-proton, as well as the signals associated with the tosylxy group. However, treatment of the 17-tosyloxy 17-acetate (190) with lithium aluminium hydride in tetrahydrofuran at reflux for 10h, resulted only in rapid deacetylation (TLC), followed by progressive decomposition to an intractable mixture of products.

The failure of the 17-tosyloxy 17-acetate (190) to undergo the desired hydride substitution at C-17, may be a consequence of competition from intervening solvolytic reaction pathways. Carbocations generated on bicyclo[2.2.1]heptanes are known to undergo skeletal rearrangements,[66 it is therefore possible that this ring D bicyclo[2.1.1]hexanol system may behave similarly. It has been reported that attempted reduction of a bicyclo[3.1.1]heptene 6-tosylate resulted in the formation of a tricyclic hydrocarbon (40%) (Scheme 3.1-13),[95] and it is claimed that the π-orbitals of the double bond participate during solvolysis of the tosylxy group. This results in intramolecular trapping of the presumed carbocationic intermediates to give the strained bicyclic system. This is corroborated by failure of the reaction to occur in the absence of the olefinic bond.

Consideration was given to an alternative approach to 17-t-deoxyxygenation, based upon radical mediated reactions. The Barton-McCombie deoxygenation of O-alkylthiocarbonyl derivatives of many natural products has been widely used.[96] Recently, a variation of the Barton-McCombie reaction was reported, whereby tributylstannane has been replaced by organosilanes as radical-based reducing agents.[97] Trialkylsilanes are poor reducing agents in
free-radical chain processes. That is, although trialkylsilyl radicals are amongst the most reactive species toward various organic functional groups, the corresponding silanes suffers the drawback of being poor hydrogen atom donors toward alkyl radicals. It was found that silicon-hydrogen bonds can be weakened drastically by successive substitution of silyl groups at the Si-H function. One such reagent, tristrimethylsilylsilane (TTMSS), was first reported by Gilman et al. in 1965, but only found applications in recent years.98,99 The bond dissociation energy of the silicon-hydrogen bond in TTMSS is 331 kJ mol⁻¹ and is 46 kJ mol⁻¹ less than that in Et₃SiH. TTMSS was readily synthesised from SiCl₄ and Me₃SiCl, using the method of Gilman et al. as compiled in a recent publication.100

The 17-acetoxyl 17¹-alcohol (189) was converted to the 17-acetoxyl 17¹-xanthate (191) (in 75% yield) in order to attempt a radical mediated deoxygenation (Scheme 3.1-14). The 17-acetoxyl 17¹-xanthate (191) was characterised by infrared absorption at νₘₐₓ, 1 738(C=O) and 1 066(C=S) cm⁻¹, together with NMR signals at δ_H 2.02 (3H, s) for the 17β-acetoxyl group, 2.39 (3H, s) for the thiomethyl group and 6.36 (1H, s) for the 17¹-proton.

Scheme 3.1-14
A solution of the 17\(^{1}\)-xanthate (191) and TTMSS in xylene was treated with azobisisobutyronitrile at reflux under nitrogen over a period of 24h, to give a mixture of products, which was separated chromatographically. The major product (75\%) was readily identified as the 17\(\beta\)-alcohol (189), whereas the minor product (12\%) displayed analytical and spectroscopic data consistent with the structure of the desired 14\(\alpha\)-methano analogue of estradiol (Scheme 3.1-15).

![Scheme 3.1-15](image)

The 14,17-methano product (192) was characterised by an infrared absorption at \(\nu_{\text{max}}.1727(\text{C}=\text{O})\) and the absence of absorption for the thiocarbonyl group. The 400 MHz \(^1\text{H}\) NMR spectrum of (192) displayed a pattern of high-field signals which could be assigned to specific protons on the bicyclo[2.1.1]hexanoid system in ring D. These assignments were facilitated by a COSY plot which showed diagnostic cross-peaks. The NMR spectrum displayed a doublet (\(J \approx 7.2\) Hz) at \(\delta_{\text{H}} 1.63\) due to the 17\(^{1}\)-H\(\text{S}^{*}\) proton as well as a doublet of triplets (\(J \approx 7.2\) and \(2 \times 3.3\) Hz) at \(\delta 2.22\) due to the 17\(^{1}\)-H\(\text{R}^{*}\) proton (\(\text{R}^{*} = \text{pro-}R, \text{S}^{*} = \text{pro-}S\)). The additional splitting of the 17\(^{1}\)-H\(\text{R}^{*}\) proton is due to a four-bond \textit{exo} coupling to the 15\(\beta\)-
and 16β-protons, which is characteristic of protons in a bicyclo[2.1.1]hexane skeleton.\textsuperscript{101} Figure 3.1-4 shows part (δ3.2 - 0.75) of the NMR spectrum, together with the corresponding COSY plot, of product (192). The signals of the aromatic and methoxy protons, which occurred in the lower field region (below δ3.6) exhibited no coupling with any of the highfield signals and have been excluded from the figure for clarity. Overlapping signals in the highfield region made the full assignment difficult. However, the proposed structure was corroborated by the $^{13}$C-DEPT spectrum.
Figure 3.1-4: 400 MHz NMR Spectrum (83.2 - 0.75) and COSY plot of the 14,17-methano compound (192).
The low yield of the 14,17-methano compound (192) may be due to the instability of the strained cyclobutyl radical (191B) (path a), thus the more favourable intermediate (191C) (path b) predominates. A similar problem was reported during the attempted synthesis of the tricyclic sesquiterpenes of the copaene and ylangene family. Attempted deoxygenation via the thiocarbonyl imidazolide resulted in a 15% yield of a 1:1 mixture of β-copaene and β-ylangene, accompanied by the original alcohol (25%), and the hemithioacetal (40%) (Scheme 3.1-16).
3.2 Synthesis of 14,16-methano 19-norsteroids

Estradiol analogues derived from 14,16-ethano 17-ketones (140 and 152) have been shown to display strong estrogenicity. The synthesis of the first ring contracted analogue in this series, the 14,16-methano 17-ketone (193), served as an inviting target, in order to probe the structure-activity trends in this type of bridged system.

The planned approach was to carry out base-mediated intramolecular cyclisation of the available 14α-tosyloxymethyl 17-ketone (176). This requires the formation of a strained ring D system incorporating a bicyclo[2.1.1]hexanoid framework. The synthesis of simple bicyclo[2.1.1]hexan-2-ones via base-mediated cyclisation is unprecedented, but they have been prepared efficiently via photochemical cyclisation of 1,5-hexadien-3-ones (Scheme 3.2-1, equation 1). However, Heathcock et al. used base-mediated intramolecular cyclisation methodology for the construction of a tricyclo[4.4.0.0²⁷]decane carbon skeleton, a common structural feature of the naturally occurring sequiterpenoids copaene and ylangene (Scheme 3.2-1, equation 2). Subsequently, Mukharji et al. investigated the cyclisation modes of bicyclic tosylxy ketones leading to strained tricyclo[7.1.1.0¹⁶]undecane systems (Scheme 3.2-1, equation 3). These cyclisation modes exemplify the principle of intramolecular enolate-initiated displacement of a tosylate, which would be required for successful synthesis of a 14,16-methano product from the 14α-tosyloxymethyl 17-ketone (176).
Successful base-mediated cyclisation depends on favourable π-orbital alignment of the enolate, which should be approximately co-linear to the line of departure of the tosylate group. An inspection of models revealed the possibility of such a favourable alignment for the 14α-tosyloxymethyl 17-ketone (176).

Treatment of the 14α-tosyloxymethyl 17-ketone (176) with sodium hydride in tetrahydrofuran at reflux for 2h, gave a single product in 91% yield (Scheme 3.2-2).
The infrared absorption spectrum of the product (193) displayed carbonyl absorption, $v_{\text{max}}$ $1744 \text{cm}^{-1}$, which falls in the range for strained bicyclo[2.1.1]hexanones ($1735 - 1762 \text{ cm}^{-1}$).\(^{103}\) The product was formulated as 14,16α-methano-3-methoxyestra-1,3,5(10)-trien-17-one (193) on the basis of its 400 MHz NMR spectrum. Figure 3.2-1(a) shows part (δ1.8 - 2.2) of the 400 MHz spectrum of compound (193) in a deuteriochloroform solution. The 16β-proton signal appeared as a triplet ($J$ 2x2.7 Hz) at δ 2.81 (omitted for clarity) and the 15α-proton as a doublet of doublets ($J$ 6.2 and 2.7 Hz) at δ 2.08. Other diagnostic signals present, but partially obscured, were those of the pro-R 161-proton at δ1.92 ($J$ 6.2 and 2.7 Hz), the 15β-proton at δ1.86 ($J$ 10.0 and 6.2 Hz) and the pro-S 161-proton at δ1.82 ($J$ 10.0 and 6.2 Hz). These signals all appeared as doublet of doublets as expected. The $^{13}$C NMR displayed distinctive signals at δ37.3(t), 37.0(t) and 52.0(d) due to C-15, C-161 and C-16 respectively. Figure 3.2-1(b) shows part (δ1.27 - 1.47) of the 400 MHz spectrum of (193) in deuteriobenzene solution. This spectrum allowed the unambiguous assignment of the 15α-proton at δ1.45 ($J$ 7.0 Hz and 2.7 Hz), the pro-S 161-proton at δ1.40 ($J$10.0 and 7.0 Hz) and the 15β-proton at δ1.31 ($J$ 10.0 and 7.0 Hz) each as doublet of doublets. The pro-R 161-proton signal was totally obscured by the 15α- and pro-S 161-proton signals. The 400 MHz COSY spectra corroborated the correlation between the ring D protons and HECTOR, DEPT and NOE analysis were consistent with this structure. Irradiation of 13β-Me ($δ$ 1.13) led to enhancement of the 15β-H and irradiation of 15α-H ($δ$ 2.08) led to enhancement of 16β-H, thus confirming the order of assignments in the spectrum (Figure 3.2-2).
Figure 3.2.1: 400 MHz NMR Spectrum of 14,16-Methano Compound (193) in a) CDCl₃ and b) C₆D₆.
Overlapping of signals made a full assignment of all protons impossible. However, the diagnostic signals were clear enough and were comparable with literature values for bicyclo[2.1.1]hexanoid systems (Figure 3.2-3).\textsuperscript{106, 107}

Assignments reported for a range of bicyclo[2.1.1]hexanones correlated well with the assignments and coupling constants of the ring D protons of (193). The major diagnostic
feature is the abnormally large four-bond coupling between 15β-H and pro-S 16¹-H \((J \approx 10.0\ Hz)\) together with the vicinal coupling of 16β-H with pro-R 16¹-H and 15α-H \((J \approx 2.7\ Hz)\). The correlation between coupling constants and dihedral angles is well established. The coupling constant reaches a maximum at 0° (~ 8 Hz) and 180° (~ 10 Hz) and minimum at 90° (~ 0 Hz). Looking down the C₁₆-C₁₅ bond, the arrangement of 15α-H, 16β-H and 15β-H is as depicted in Figure 3.2-4. Most notably, the ring constraints necessitate non-equivalence of the torsion angle relationships between 16β-H and the neighbouring protons on C-15.

![Figure 3.2-4: Arrangement of 15α-H, 16β-H and 15β-H, viewed along C₁₆-C₁₅ bond of compound (193).](image_url)

The coupling constant between Hₐ and Hₐ (see Figure 3.2-3) will then be negligible, and that between Hₐ and Hₐ will be in the order of 3 - 4 Hz. Similarly, the coupling constant between 16β-H and 15β-H is negligible, and that between 16β-H and 15α-H is 2.7 Hz.

Reduction of the 14,16-methano 17-ketone (193) to 17β- and/or 17α-alcohols would lead to precursors of estradiol analogues in this series. Reduction of the 14,16-methano 17-ketone (193) with lithium aluminium hydride, DIBAL, ‘L-Selectride’ and sodium in propan-2-ol respectively, resulted in 1:1 mixtures of 17α- and 17β-alcohols (194 and 195) (Scheme 3.2-3). Not only was there no evidence of stereoselective reduction under any of these reaction conditions, but the isomeric mixture was inseparable. Attempts to achieve separation of these isomeric mixtures via 17-functionalisation (as esters or ethers) also failed.
Doubling of signals in the NMR spectra of the mixture (194 and 195) made assignments difficult; however a triplet was observed at δ 3.96 (J 2 x 1.6 Hz) and a doublet at δ3.86 (J 1.0 Hz) (integrating jointly for one proton) due to the 17β-H and 17α- of the respective alcohols. The observed coupling constants corresponded with literature values (J 0.5 - 1.5 Hz) for comparable protons in bicyclo[2.1.1]hexanols.101,107 The poor stereoselectivity of hydride addition to the C-17 carbonyl of the 14,16-methano 17-ketone (193) was not surprising considering the high degree of symmetry around the carbonyl group (Figure 3.2-5).

In view of the failure to separate the alcohols (194 and 195), it was decided to synthesise the estrone analogue for biological evaluation, in the hope that it might act as a precursor for biological reduction to give the natural 17β-OH isomer. Early studies demonstrated the interconvertability of estrone and estradiol in the body.108 Other than DIBAL, several methods exist for the cleavage of aryl alkyl ethers.109 Deprotection of the 3-methyl ether
without reduction at C-17 could be achieved by the use of a mixture of chlorotrimethylsilane and sodium iodide, a convenient in situ method for the generation of iodotrimethylsilane reagent. Thus, treatment of the 14,16-methano 17-ketone (193) with chlorotrimethylsilane and sodium iodide in acetonitrile at reflux for 16h, gave 3-hydroxy-14,16α-methanoestra-1,3,5(10)-trien-17-one (196) (82%) (Scheme 3.2-4).

Figure 3.2-6 shows parts of the 400 MHz NMR spectrum of compound (196) in deuteriochloroform. The chemical shifts and coupling constants of the signals of ring D protons of (196) were consistent with the previously observed values. Of particular interest was the signal for the pro-R 16\(^1\)-proton, which was much sharper than the underlying 7β-proton signal and could be unambiguously assigned. Thus, all the characteristic proton-proton couplings of the ring D bicyclo[2.1.1]hexane system have been reconciled for this series of compounds.

As a further objective, the synthesis of a 17-ethynylestradiol analogue bearing the 14,16-methano bridge was attempted. It was planned to conduct this experiment by treating the 14,16-methano 17-ketone (193) with acetylide anion. However, in an unrelated experiment in which the 14α-tosyloxymethyl 17-ketone (176) was treated with equimolar acetylide anion, the intended displacement of the tosylate group with the acetylide anion did not occur, but resulted only in the formation of the 14,17-methano 18-ketone (193) in 84% yield. Consequently, treatment of the 14α-tosyloxymethyl 17-ketone (176) with excess lithium acetylide ethylene diamine complex, gave an inseparable mixture of 17α- and 17β-ethynyl alcohols (197) and (198) in a 1:1 ratio and 81% yield (Scheme 3.2-5).
Figure 3.2-6: Part of the 400MHz spectrum of compound (196)

\( J \) 10.0 and 6.2 Hz

16\( \beta \)-H

\( J \) 2x 2.7 Hz

15\( \beta \)-H 16\( ^1 \)-H\(^5\)*

\( J \) 6.2 and 2.7 Hz

16\( ^1 \)-H\(^R\)*

15\( \alpha \)-H
The infrared spectrum of the 17-ethynyl mixture (197 and 198) exhibited hydroxy absorption bands at $v_{max}$ 3341 and 3625 cm$^{-1}$ and an ethynyl absorption band at 2460 cm$^{-1}$. The 400 MHz NMR displayed singlets at δ2.59 and 2.60 integrating jointly for one proton (17α- and 17β-ethynyl protons) and a triplet at δ2.52 ($J = 2 \times 2.8$ Hz, 16β-H), as well as two singlets at δ1.06 and 1.21 integrating jointly for three protons (13β-Me). In view of the failure to separate the isomeric mixture (197 and 198), further work in this series was discontinued. However, the essential finding in this part of the investigation is the ready formation of the 14α,16α-methano analogue of estrone through intramolecular displacement. This will open the way for further investigation into selective reactions in this series and the possible development of new hormone analogues based upon more stereoselective functional group modification.
3.3 Synthesis of 14α-alkyl estradiol analogues

Synthesis of 14α-methyl steroids has received considerable attention for two main reasons, firstly, as an estradiol analogue and secondly, as an intermediate toward the synthesis of a series of retrosteroids. Hitherto, an efficient synthetic route to these compounds has not been established, the best so far being via cycloaddition-cleavage methodology. In this approach, selective deoxygenation of the 141-oxo group of the 14α-formyl 17-ketone (87) was attempted. However, thioketalisation gave a mixture of 141,141- and 17,17-thioketals (73:16). Treatment of the 141,141-dithioacetal with Raney-Nickel gave the 14α-methyl 17-ketone (51) (63%). Although the chemoselective reactivity of the formyl ketone thus favoured the observed reaction course during thioketalisation, this route suffered from the necessity for tedious chromatographic separation of the thioketals as well as a moderate yield for the Raney-Nickel reduction.

Previous studies have demonstrated the potential for the development of a synthetic route toward 14α-methyl steroids via the 14α,17α-diformyl compound (88). Accordingly, hydride reduction of the 14α,17α-diformyl compound (88) gave the triol (199), followed by selective protection of either the 171-hydroxy group as the 171-ethers or esters (200) or simultaneously the 17- and 171-hydroxyl groups as the acetonide (201). Subsequently, oxidation of the acetonide (201) gave the 14α-formyl compound (202). Attempted Wolff-Kishner deoxygenation at C-141 of compound (202) gave the desired 14α-methyl compound (203) in 21% yield.
Although overall efficiency of the reaction sequence was poor, all of the reaction steps prior to the last one were high yielding. Accordingly, an attempt was made to improve the last step and the Wolff-Kishner deoxygenation was repeated with minor modifications, such as slightly lower temperatures and a shorter refluxing period. A yield of 54% was obtained, but was considered unsatisfactory to validate this synthetic route toward 14α-methyl steroids. Further investigations using this approach were therefore suspended.

It has been reported that attempted deoxygenation of the 14α-tosyloxymethyl 17-ketone (176) via lithium triethylborohydride ('super-hydride') reduction of the tosylate, resulted in the formation of the 14,17-oxetane (204) (Scheme 3.3-2, equation 1). Similarly, attempted tributylstannane reduction of the 141-methyl xanthate (205) was also unsuccessful, resulting in a low yield of impure product (51) together with inseparable impurities. We therefore consider the application of tris(trimethylsilyl)silane (TTMSS) for this step, since it has been reported that free radical deoxygenation as xanthate esters proceeds smoothly, and without
some of the complications arising from the presence of tin residues in the reaction mixture as in the case of the stannane-mediated deoxygenations. The xanthate (205) was prepared according to literature procedures and treated with TTMSS in the presence of azobis(isobutyronitrile) in toluene at reflux for 9h, to give 3-methoxy-14-methyl-14α-estra-1,3,5(10)-trien-17-one (51) (86%) (Scheme 3.3-2, equation 2). All spectroscopic data were consistent with those recorded in the literature for the known product. This methodological adaptation thus provided an acceptable yield of the 14α-methyl 17-ketone (51) for the first time.

Attempted alkylation of the 14α-methyl 17-ketone (51) with excess methylmagnesium iodide or methyllithium was unsuccessful, resulting in no reaction. Organocerium reagents were considered, since they are far more reactive than the carbanion species alone, having the ability to facilitate 1,2-addition across potentially enolizable ketones. A combination of methylmagnesium iodide or methyllithium with cerium trichloride also gave no reaction. It is therefore evident that steric hindrance associated with the 14α-methyl group prevents nucleophilic alkylation of the 17-oxo group.

Scheme 3.3-2
Accordingly, attention reverted to exploiting the chemoselective reactivity of the 14α-formyl 17-ketone (87) in order to synthesise estradiol analogues in which different 14α-alkyl groups are present. Previous studies have shown that 14β-ethyl estradiol analogues (95) and (96) (see introduction) displayed moderate estrogenic activity comparable to that of 14β-methyl estradiols, thus inviting an investigation of 14α-alkyl chain extension for structure-activity studies. Reddie attempted the 14α-methylenation via treatment of the 14α-formyl 17-ketone (87) with methylenetriphenylphosphorane in tetrahydrofuran at reflux for 48h, resulting in a low yield (18%) of 3-methoxy-14-vinylestra-1,3,5(10)-tri-en-17-one (207). The reaction appeared to be chemoselective toward the 141-oxo group, since no 17-methylene derivatives were detected. However, the low yield suggested that both carbonyl groups in (87) are hindered toward the sterically demanding Wittig reagent.

In a report of a similar study, Robinson et al. described the preparation of ring D modified analogues of lanosterol for use as inhibitors of 14α-methyl demethylase.76 In particular, they reported that treatment of 4,4-dimethyl-14-formylcholest-7-en-3β-ol with Oshima's methylenation reagent (Zn/CH2Br2/TiCl4), gave the 14α-vinyl analogue in 57% yield. Furthermore, treatment of 4,-dimethyl-14-formylcholest-7 -en-3 β-ol with (methoxymethyl)triphenylphosphonium chloride and n-butyllithium in tetrahydrofuran at reflux for 2h, gave a mixture of isomeric methyl enol ethers (70%). Acid treatment of the latter mixture, gave the 32-formyl lanosterol derivative.

The aforementioned results demonstrate increased reactivity of the 14α-formyl group in this series as compared to that of the related estrone analogue. This enhanced reactivity is due to the presence of a Δ7-bond, which may cause a flattening of ring C of the 14-formyl cholesterol derivative, thus exposing the formyl group to the sterically demanding Wittig reagent.

The Peterson reaction, a silicon-equivalent of the Wittig reaction, is a complementary method for the preparation of a wide variety of substituted and functionalised alkenes.112 Very often, Peterson olefination succeeds where Wittig reagents failed,113 since the transition state generated by nucleophilic attack of an α-silylcarbanion is sterically much less demanding and
elimination of the resultant β-hydroxysilane can be achieved under a variety of reaction conditions.

Treatment of the 14α-formyl 17-ketone (87) with an excess of trimethylsilylmethylmagnesium chloride at 25°C for 4h gave (1'S)-1',17α-epoxy-14-trimethylsilyethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (206) (80%) (see Appendix for nomenclature rules) (Scheme 3.3-3).

The infrared spectrum of the product (206) displayed no carbonyl absorption neither did the 13C NMR spectrum exhibit a carbonyl signal, thus leading to the assumption of hemiketal formation. The NMR displayed a doublet of triplets (J 11.6 and 2 x 1.8 Hz) at δ4.60 due to the 1'-protons, together with distinctive signals at 0.05 (9H, s) due to the trimethylsilyl protons, a doublet of doublets (J 14.3 and 1.8 Hz) at 0.58, and a doublet of doublets (J 14.3 and 11.5 Hz) at 0.95, due to the 2'-protons respectively. The additional splitting of the 1'-proton (J 1.8 Hz) arose from 4J in a W-configuration with 15β-H, thus implying the 1'S configuration. A detailed study of this observation will be discussed in Section 3.4. All analytical and spectroscopic data were consistent with this structure.

Elimination of the trimethylsilyl group in β-hydroxysilanes can be carried out under basic or acid conditions.112 Treatment of the β-hydroxysilane (206) with potassium hydride112 at 20°C gave an intractable mixture of products, whereas treatment with acetic acid and a catalytic amount of tetrabutylammonium fluoride112 or Nafion-H®114 in dichloromethane gave no reaction. However, treatment of the β-hydroxysilane (206) with boron trifluoride diethyl
ether complex at 0°C for 1 h then at 25°C for 8 h gave 3-methoxy-14-vinylestra-1,3,5(10)-trien-17-one (207) (74%) (Scheme 3.3-4).

All spectroscopic and analytical data corresponded well with those recorded earlier for the product of Wittig reaction. The improved yield of compound (207), made further elaboration toward new 14α-alkyl 19-norsteroids possible.

Treatment of the 14α-vinyl 17-ketone (207) with lithium aluminium hydride in tetrahydrofuran at 20°C for 30 min, afforded a separable mixture of the 17β-alcohol (208) (28%) and the 17α-alcohol (209) (34%) in a ratio of 1:1.2 (Scheme 3.3-5). The isomers were readily distinguished by a comparison of the 1H NMR signals for the 17-protons. Thus, the 17β-alcohol (208) displayed 17α-H as doublet of doublets (J 9.0 and 6.0 Hz) at δ3.82, whereas the 17α-alcohol (209) displayed 17β-H as a doublet of doublets (J 7.3 and 1.1 Hz) at δ3.70.
The poor stereoselectivity of hydride addition to the C-17 carbonyl group of the 14α-vinyl 17-ketone (207) was unsurprising, since the presence of a 14α-alkyl group was expected to diminish the α-face stereoselectivity found in unsubstituted steroidal 17-ketones. Although this result served our purpose in providing access to both isomeric estradiol analogues for further development, it was of interest to establish whether variations in the reduction conditions could be found to give the ‘natural’ 17β-isomer stereoselectively.

Dissolving metal reduction was immediately considered, since it was expected to favour formation of the product of thermodynamic control. Treatment of the 14α-vinyl 17-ketone (207) with sodium in isopropanol at reflux for 1h, gave exclusively the 17β-alcohol (208) (94%).

Despite clear evidence of steric hindrance at C-17, 17-ethynylation was nevertheless attempted. Treatment of the 14α-vinyl 17-ketone (207) with lithium acetylide ethylenediamine complex in tetrahydrofuran or dimethoxyethane at 15°C for 3 days, failed to give any product of 17-ethynylation. Similarly, the 14α-vinyl 17-ketone (207) failed to react with alkyl Grignards. Hence, further studies in this direction were abandoned.

In order to synthesise the 14α-ethyl product, hydrogenation of the 14α-vinyl group was necessary. Thus, treatment of the 14α-vinyl 17β-alcohol (208) with a catalytic amount of palladium on charcoal (10%) in ethyl acetate under an atmosphere of hydrogen for 34h at 20°C gave 14-ethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (210) (85%) (Scheme 3.3-6).
The product and starting material were inseparable on TLC, and the progress of catalytic hydrogenation was therefore followed by $^1$H NMR inspection of the reaction mixture at various intervals to follow the extent of reduction through disappearance of signals for the 14α-vinyl protons. The 14α-ethyl 17β-alcohol (210) was characterised by the presence of a three-proton triplet, superimposed on the singlet for the 13β-methyl group at δ 0.91. The signal for the 17α-proton appeared as a doublet of doublets ($J$ 9.0 and 6.0 Hz) at δ 4.16. All other spectroscopic and analytical data were consistent with this structure. The 14α-ethyl 17β-alcohol (210) was also accessible via the 14α-vinyl 17-ketone (207). Catalytic hydrogenation of 14α-vinyl 17-ketone (207) with palladium on charcoal (10%) for 48h at 20°C gave 14-ethyl-3-methoxyestra-1,3,5(10)-trien-17-one (211) (88%) (Scheme 3.3-7). Once again, the product and starting material were inseparable on TLC and therefore NMR monitoring of the course of reaction was necessary.
The 14α-ethyl 17-ketone (211) displayed infrared absorption at $v_{\text{max}}$, 1727 cm$^{-1}$ for the carbonyl group. It was possible to assign most of the signals in the $^1$H NMR spectrum, with the aid of a COSY and HETCOR plot. The chemical shifts and coupling constants are summarised in Table 3.3-1.

Table 3.3-1: Assignments and Couplings for the Protons of Product (211)

<table>
<thead>
<tr>
<th>Assignment</th>
<th>$\delta$(ppm)</th>
<th>Mult.</th>
<th>$\text{J}$/Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-H</td>
<td>7.19</td>
<td>d</td>
<td>8.6</td>
</tr>
<tr>
<td>2-H</td>
<td>6.69</td>
<td>dd</td>
<td>8.6 2.9</td>
</tr>
<tr>
<td>4-H</td>
<td>6.60</td>
<td>d</td>
<td>2.9</td>
</tr>
<tr>
<td>6-H$_2$</td>
<td>2.85</td>
<td>m</td>
<td>-</td>
</tr>
<tr>
<td>7α-H</td>
<td>1.44-1.68</td>
<td>m</td>
<td>-</td>
</tr>
<tr>
<td>7β-H</td>
<td>1.84-1.96</td>
<td>m</td>
<td>-</td>
</tr>
<tr>
<td>8β-H</td>
<td>1.78</td>
<td>br t</td>
<td>12.6 12.6 $W_j/3.8$</td>
</tr>
<tr>
<td>9α-H</td>
<td>2.79</td>
<td>td</td>
<td>12.6 12.6 5.2</td>
</tr>
<tr>
<td>11α-H</td>
<td>2.31</td>
<td>ddd</td>
<td>13.6 5.2 5.2 2.4</td>
</tr>
<tr>
<td>11β-H</td>
<td>1.44-1.68</td>
<td>m</td>
<td>-</td>
</tr>
<tr>
<td>12α-H</td>
<td>1.72</td>
<td>tdd</td>
<td>13.6 13.6 5.2 0.3</td>
</tr>
<tr>
<td>12β-H</td>
<td>1.44-1.68</td>
<td>m</td>
<td>-</td>
</tr>
<tr>
<td>13β-Me</td>
<td>1.02</td>
<td>br s</td>
<td>$W_j/0.8$ Hz</td>
</tr>
<tr>
<td>15α-H</td>
<td>1.44-1.68</td>
<td>m</td>
<td>-</td>
</tr>
<tr>
<td>15β-H</td>
<td>2.11</td>
<td>m</td>
<td>$W_j/23.7$</td>
</tr>
<tr>
<td>16α-H</td>
<td>2.20</td>
<td>dt</td>
<td>18.7 8.8 8.8</td>
</tr>
<tr>
<td>16β-H</td>
<td>2.40</td>
<td>ddd</td>
<td>18.7 9.2 0.6</td>
</tr>
<tr>
<td>3-OMe</td>
<td>3.77</td>
<td>s</td>
<td>-</td>
</tr>
<tr>
<td>14$^1$H$_R$*†</td>
<td>1.88</td>
<td>m</td>
<td>$W_j/24.1$</td>
</tr>
<tr>
<td>14$^2$H$_S$*†</td>
<td>0.82-0.95</td>
<td>m</td>
<td>-</td>
</tr>
<tr>
<td>14$^3$CH$_3$</td>
<td>0.82-0.95</td>
<td>m</td>
<td>-</td>
</tr>
</tbody>
</table>

† Interchangeable pro-$R$ ($R^*$) pro-$S$ ($S^*$)

Figure 3.3-1 shows part (δ0.6–3.2) of the NMR spectrum, together with the corresponding COSY plot of the 14α-ethyl 17-ketone (211) recorded in deuteriochloroform.
Figure 3.3.1-1: COSY Spectrum of (211)
Treatment of the 14α-ethyl 17-ketone (211) with lithium acetylide-ethylenediamine complex in dimethoxyethane at 15°C for 2 days also failed to give any product of 17-ethynylation.

With the 17β-alcohols (208) and (210) in hand, the preparation of the corresponding estradiols entailed demethylation at C-3. The individual alcohols (208) and (210) dissolved in toluene were treated at reflux with excess DibalH for 12h, to give 14-vinylestra-1,3,5(10)-triene-3,17β-diol (212) (73%) and 14-ethylestra-1,3,5(10)-triene-3,17β-diol (213) (55%) respectively (Scheme 3.3-8).

![Scheme 3.3-8](image)

The respective products (212) and (213) were characterised by appropriate analytical and spectroscopic data, and have been subjected to biological evaluation (see Section 3.6).

The foregoing studies served to demonstrate that simple 14α-alkyl analogues of estradiol are readily accessible via chemoselective modification of the 14α-formyl 17-ketone (87), but that the poor reactivity of the 17-oxo group toward nucleophiles precluded synthetic access to
14α,17α-dialkyl analogues by this route. Aspects of the chemoselective reactivity of the 14α-formyl group were developed further in pursuit of 14α-chain extended systems which are described in the next section.
3.4 Chemoselective homologation of 3-methoxy-17-oxoestra-1,3,5(10)-triene-14-carbaldehyde

This phase of the work was devoted to an investigation into the scope of synthesising estrone derivatives bearing functionalised alkyl chains at the 14α-position. Two particular objectives were considered. In this part, the introduction of functionalised two- and three-carbon chains at this position would enable new intramolecular cyclisation methods between the chain terminus and C-17 to be investigated, in order to provide an entry to 14α,17α-ethano and 14α,17α-propano estradiols bearing regiodefined functionality on the bridges. Previously developed synthetic routes to 14α,17α-alkano estradiols suffer from some limitations for the introduction of such functionality.61 A second objective was to develop methods for the introduction of extended 14α-chains which could be used to synthesise 14α-(ω-dialkylamidoalkyl)estradiols for evaluation as estrogen antagonists.12,13,14

Although the chemoselective reactivity of the 14α-formyl 17-ketone (87), which is evident in the reactions which have already been described in this and earlier work, was expected to be useful for the intended purposes, it was also of interest to protect the 17-oxo group of the 14α-formyl 17-ketone (87) in order to apply forcing reaction conditions for homologation of the 14α-formyl group. Previous studies gave some indication of all the problems which could be expected in this approach. Thus, an attempt to achieve chemoselective enol acetylation of the 17-oxo group by treating the 14α-formyl 17-ketone (87) with acetic anhydride and isopropenyl acetate in the presence of a catalytic amount of toluene-p-sulfonic acid, resulted in rearrangement in ring D, to give a hitherto unidentified product.61 However, it was subsequently shown that the 14α-formyl 17-ketone (87) undergoes rearrangement in the presence of acid to give 17α-homoequilenin derivatives.87 It was therefore concluded that a preferred approach to chemoselective differentiation of the carbonyl groups in the 14α-formyl 17-ketone (87) should entail a base-mediated reaction.
Reddie has reported that an attempt to prepare a silyl enol ether via chemoselective formation of the Δ¹⁶-enolate of the 14α-formyl 17-ketone (87) with lithium diisopropylamide followed by trapping with t-butyldimethylsilyl chloride (TBDMSCl) failed, as only starting material was recovered. However, it has been reported that treatment of estrone 3-methyl ether with trimethylsilyl triflate (TMSOTf) and triethylamine resulted in the formation of a labile silyl enol ether. The 14α-formyl 17-ketone (87) was subjected to similar reaction conditions, resulting in the formation of a much less polar product (TLC observation). However, upon neutral work-up only starting material was obtained. This approach was thus abandoned.

An alternative approach to exploring the reactivity of the 14α-formyl group under forcing conditions would be to reverse the chemoselectivity of reduction of the 14α-formyl 17-ketone (87) to give the 17β-hydroxy 14α-carbaldehyde. It has been reported that selective reduction of ketones in the presence of aldehydes has been achieved using cerium trichloride hexahydrate dissolved in an ethanol-water mixture. The success of this reaction depends on the selective hydration and consequent protection of the aldehyde during the course of the reaction of the ketone. However, treatment of the 14α-formyl 17-ketone (87) under the prescribed conditions, resulted in the formation of the 14α-hydroxymethyl 17-ketone (88) in quantitative yield.

It has been shown that, in solution, the 14α-hydroxymethyl 17-ketone (88) exists in a state of equilibrium with the corresponding hemiketal (214) (Scheme 3.4-2). An X-ray crystallographic determination showed that the hemiketal structure is preferred in the solid state. A diagnostic feature of the hemiketal (214) is the unusually large four-bond
coupling in a \( W \)-configuration ("W-coupling") of 4.1 Hz between the \( 1' \)-proton and \( 15\beta \)-proton.

The reactivity of the primary hydroxyl group and the \( 17\)-oxo group are influenced by this equilibration. Thus, acetylation of the equilibrium mixture, using acetic anhydride and pyridine gave the \( 14\alpha \)-acetoxyethyl \( 17 \)-ketone (215) (R=Ac) (Scheme 3.4-3).\(^{49}\) However, benzylation of the mixture by treatment with sodium hydride, followed by benzyl bromide gave exclusively the epoxy ether (216) (R=Bn),\(^{55}\) whereas silylation with imidazole and TBDMSCl gave a mixture of the \( 17\)-oxo-\( 14\)-TBDMS ether (217) (R=SiMe\(_2\)Bu\(_3\)) and the \( 1',17\alpha \)-epoxy ether (218) (R=SiMe\(_2\)Bu\(_3\)) in a 1:2 ratio.

A further option for synthesis of \( 17\xi \)-hydroxy \( 14 \)-carbaldehydes was envisaged via complete hydride reduction of the \( 14\alpha \)-formyl \( 17 \)-ketone (87), followed by selective oxidation of the \( 14\)-hydroxyl group in the resultant \( 14,17\xi \)-diol(s).\(^{49}\) Reduction with lithium aluminium hydride, gave \( 14,17\alpha \)- and \( 14,17\beta \)-diols (177) and (178) respectively. Oxidation of the alcohol mixture gave the \( 14\alpha \)-formyl \( 17\beta \)-alcohol (219) in an unsatisfactory yield (41%), accompanied by \( 14\alpha \)-formyl \( 17 \)-ketone (87) (32%), and the \( 14\alpha \)-hydroxymethyl \( 17 \)-ketone (88/214) (16%) (Scheme 3.4-4). The low yield of compound (219) made this route impractical for further exploitation.
The foregoing reactions demonstrated that an approach to generating substrates for forcing reaction of the 14α-formyl group, without interference from the 17-oxo group, was unsuccessful. It was therefore necessary to rely upon the demonstrated 141'-chemoselectivity.
of the 14α-formyl 17-ketone (87) in order to pursue the objective of this work. In view of
the limited success of conventional Wittig homologation methodology in this substrate,
attention was turned to exploiting simpler carbanionic nucleophiles. A preliminary study has
demonstrated that the 14α-formyl 17-ketone (87) undergoes preferential 141-methylation.61
This reaction was repeated; treatment of the 14α-formyl 17-ketone (87), with methyllithium
gave the 141-methylated compound, which existed predominantly as the hemiketal (220)
(85%) (Scheme 3.4-5).

The structure of the hemiketal (220) was supported by the absence of carbonyl absorption in
the infrared spectrum. In addition, the 1H NMR spectrum showed the presence of a three-
proton doublet (J 6.3 Hz) at δ1.25 for the 1'-methyl protons and a quartet of doublets
(J 3 x 6.2 and 2.3 Hz) at 4.57 due to the 1'-proton. Further evidence supporting the structure
of the hemiketal (220) was distinctive 13C NMR signals at δ18.8(q), 73.2(d), and 109.5(s) due
to C-2', C-1', and C-17 respectively. The additional coupling (2.3 Hz) of the 1'-proton
arose from four-bond W-coupling with the 15β-proton. This phenomenon is uniquely
associated with a large four-bond coupling between the exo protons of the oxabicyclo[2.2.1]heptanoid structure of ring D.49,119 The observed orientation of the 1'-proton implies a 1'S configuration at C-1'. The formation of a single diastereoisomer,
provides clear evidence of highly preferred face selectivity during methylation. The major
product formed in the nucleophilic addition to a carbonyl group in possession of an
asymmetric α-carbon can be predicted by Cram's rule, according to which it is formed by
approach of the reagent to the less hindered side of the carbonyl group when the rotational
conformation of the molecule is such that the carbonyl is flanked by the two least bulky
groups on the adjacent chiral centres. Models were used to investigate possible orientations of the 14α-formyl group that could explain the observed face selectivity. On the basis of Cram's rule, two possible orientations of the 14α-formyl group were considered; firstly, such that the approach of the nucleophile has to be from the direction of ring D as depicted in Figure 3.4-1a (re face obscured by 7α-H), and secondly, from the direction between C(8) and C(15) depicted in Figure 3.4-1b (re face obscured by 12α-H).

![Figure 3.4-1](image)

**Figure 3.4-1** Newman projection about C(14)⁻⁻C(14).

It has been reported that the addition of methylmagnesium bromide to 32-formyl lanost-7-en-3β-ol gives a mixture of diastereoisomers, of which the absolute stereochemistry is yet to be determined.\(^\text{120}\) Unsaturation at Δ⁷ induces a flattening of ring B, thus minimising steric hindrance due to the 7α-proton and hence, nucleophilic addition on either face of the formyl group is observed. This result indirectly illustrates the influence of ring B on the approach of nucleophiles on the 14α-formyl group if the orientation in Figure 3.4-1a is considered.

The practical scope of the diastereoselective reaction was further investigated. Grignard methodology was considered in order to extend the diversity in alkylation for the purpose of 14α-chain extension and 14,17-cyclisation. The synthesis of functionalised 14α,17α-propano 19-norsteroids was envisaged via the introduction of a three-carbon fragment at C-14. This could be achieved via chemoselective ethylmagnesium bromide addition to the 14-formyl group, followed by elimination of the resultant hydroxyl group as an ester to give the 14α-prop-2'-enyl derivative (Scheme 3.4-6). Regioselective hydroboration of the alkene at C-2'.
followed by oxidation of the resultant alcohol, would provide access to a 14α-acetonyl 17-ketone, which is ideally disposed for intramolecular base-mediated cyclisation.

Thus, treatment of the 14α-formyl 17-ketone (87) with an excess of ethylmagnesium bromide at 20°C for 45 min, gave the expected hemiketal (221) (29%) accompanied by 14-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17-one (88/214) (55%) as the major product. The structure of the latter compound was confirmed by direct comparison with authentic material, and conversion into the 14-acetoxymethyl compound (215) for further characterisation. It is known that under certain conditions, reduction may intervene during the Grignard reaction. This process is prevalent with hindered carbonyl compounds and requires that the Grignard reagent possess a β-hydrogen. Ethylated product (221) displayed spectroscopic characteristics similar to that of the methylated product (220). The absence of carbonyl absorption in the infrared spectrum and the presence of a broad doublet ($J_{10.2}$ and $W_{15.0}$ Hz) at $\delta_H 4.17$ due to $1^\prime$-$H_{exo}$ confirmed that the product exists as the hemiketal. Dimethylaminopyridine (DMAP) catalysed acetylation of the hemiketal (221) gave a single less polar product (72%) (Scheme 3.4-7). This product was characterised as the $1^\prime,17\alpha$-epoxy 17β-acetate (222) by the presence of carbonyl absorption in the infrared spectrum, together with distinctive $^1$H NMR signals at $\delta_{14.30}$ (doublet, $J 10.3$ and $W_{15.0}$ Hz) due to the $1^\prime$-proton, and 1.04 (triplet, $J 2 \times 7.2$ Hz) due to the $3^\prime$-methyl protons. It is evident that acetylation of the stable hemiketal structure gave the $1^\prime,17\alpha$-epoxy 17β-acetate (222), instead of the acetate of the secondary alcohol.
Although the poor yield of desired product (221) detracted from the intended purpose, it was of interest to ascertain whether elimination of the masked 1'-hydroxy group could be carried out to give a 14α-prop-2-enyl derivative. However, attempted mesylation of product (221) with methanesulfonyl chloride in pyridine at 0°C for 1h, gave a single less polar product (223) (74%), which displayed spectroscopic features consistent with the mesylate ester of the hemiketal structure (Scheme 3.4-7). The product was characterised as the 1',17α-epoxy 17β-mesylate (223) by the absence of carbonyl absorption in the infrared spectrum together with distinctive 1H NMR signals at δ4.41 (doublet of triplets, J 10.8 and 2 x 3.6 Hz) due to the 1'-proton and 13C NMR signals at δ11.4(s) and 82.7(d) due to C-17 and C-1' respectively.

The desired elimination of the mesylate group in compound (223) requires deprotonation at the 2'-position, which is difficult. The low yield and the failure of compound (221) to form secondary esters susceptible to elimination, precluded further exploitation of the hemiketal (221). An alternative approach to synthesis of functionalised three-carbon 14α-chains was considered via chemoselective 141-vinylation of the 14α-formyl 17-ketone (87). It was hoped
that the resultant side-chain allylic alcohol might display different reactivity toward esterifying agents, in which event a pathway to vinylogous intramolecular cyclisation could be investigated (Scheme 3.4-8).

Treatment of the 14α-formyl 17-ketone (87) with an excess of vinylmagnesium bromide in tetrahydrofuran at 0°C for 6h, gave the expected hemiketal (224) (85%) (Scheme 3.4-9).
The product (224) was characterised by the absence of carbonyl absorption in the infrared spectrum, together with diagnostic signals in the $^1$H NMR spectrum. A doublet of quartets ($J 5.2$ and $3 \times 1.9$ Hz) appeared at $\delta 4.89$ due to the $1^\prime$-proton. The additional coupling (1.9 Hz) of the $1^\prime$-proton arose from four-bond "W-coupling" with the $15\beta$-H, which was confirmed by a corresponding correlation in the COSY spectrum (Figure 3.4-2). All other data were consistent with this structure. Further evidence for this structure was the appearance of a doublet of triplets ($J 10.5$ and $2 \times 1.9$ Hz) at $\delta 5.21$ due to $3^\prime$-$H_{cis}$, a doublet of triplets ($J 17.0$ and $2 \times 1.9$ Hz) at $5.47$ due to $3^\prime$-$H_{trans}$, and a doublet of doublet of doublets ($J 17.0, 10.5$ and $5.2$ Hz) at $5.94$ due to the $2^\prime$-proton. Long-range allylic coupling ($^4J 1.9$ Hz) was observed for both of the $3^\prime$-protons.

Acetylation of the hemiketal (224) (acetic anhydride-triethylamine, $0^\circ$C, 16 h) gave the $1^\prime,17\alpha$-epoxy $17\beta$-acetate (225) (60%) (Scheme 3.4-10). The infrared spectrum of the acetate displayed carbonyl absorption at $v_{max} 1750$ cm$^{-1}$. The $^1$H NMR spectrum displayed a doublet of quartets ($J 5.2$ and $3 \times 1.8$ Hz) at $\delta 4.98$ due to the $1^\prime$-proton, a doublet of triplets at $5.22$ ($J 10.5$ and $2 \times 1.8$ Hz) due to $3^\prime$-$H_{cis}$, a doublet of triplets at $5.56$ ($J 16.9$ and $2 \times 1.8$ Hz) due to $3^\prime$-$H_{trans}$, and a doublet of doublet of doublets at $5.94$ ($J 16.9, 10.5$ and $4.9$ Hz) due to the $2^\prime$-proton. Further evidence in support of the structure of (225) was the presence of distinctive $^{13}$C NMR signals at $\delta 80.2$(d) and 110.7(s), due to C-1$^\prime$ and C-17 respectively.

It was hoped that mesylation of product (224) would give the $1^\prime,17\alpha$-mesylate, which is required for effective elimination (see Scheme 3.4-8). However, treatment of the hemiketal (224) with methanesulfonyl chloride in triethylamine at $0^\circ$C for 1h, gave the $1^\prime,17\alpha$-epoxy $17\beta$-mesylate (226) (78%) (Scheme 3.4-10). The $17\beta$-mesylate (226) was characterised by the absence of carbonyl absorption in the infrared spectrum, together with the diagnostic signals in the $^1$H NMR at $\delta 3.20$ (singlet) and $5.02$ ($W_{v/2} 10.5$ Hz) due to the sulfonylmethyl- and $1^\prime$-protons respectively.
Figure 3.4-2: COSY NMR Spectrum of Compound (224)
The formation of 17β-esters (225) and (226) further demonstrated the generality of hemiketal esterification as the preferred reaction course, and clearly precluded any prospect of developing the intended intramolecular cyclisation route to 14α,17α-propano steroids.

A parallel investigation into Grignard allylation of the 14α-formyl 17-ketone (87) proceeded with expected chemoselectivity and subsequent closure to give the hemiketal (227) (82%) (Scheme 3.4-11).
Again, the structure was evident from distinctive spectroscopic data. Although further work on the product was precluded by time constraints and the availability of material, it provides possible scope for overcoming the problems encountered in the foregoing investigations. Thus, oxidative cleavage of the product (227), followed by β-elimination would give a 14α-3'-oxopropan-1-yl 17-ketone and could be used to study intramolecular cyclisation (Scheme 2.4-12).

![Scheme 3.4-12](image)

A summary of the spectroscopic results for the products obtained in the foregoing Grignard alkylations revealed a consistent pattern of diastereoselectivity in product formation. Thus, all products showed multiplicity for the $^1$H NMR signal of the 1'-proton, which accommodates the familiar four-bond coupling with the 15β-proton, and consequently, 1'S configuration (see Figure 3.4-3 and Table 3.4).
Other approaches to chemoslective $^{14^1}$-homologation and functional group modification of the $^{14\alpha}$-formyl 17-ketone (87) were also considered. Of particular interest was chemoselective reaction with a methylide species in order to generate a $^{14\alpha}$-oxiranyl 17-ketone for possible regioselective alkylation at C-2 or rearrangement to give useful intermediates for further study on intramolecular cyclisation methods. Dimethyl sulfonium methylide has found wide application as an efficient reagent for converting carbonyl compounds into the corresponding oxiranes. The established trend in chemoselectivity and stereoselectivity in $^{14^1}$-reactions of the $^{14\alpha}$-formyl 17-ketone (87) was expected to give a single product.

Treatment of the $^{14\alpha}$-formyl 17-ketone (87) with excess dimethylsulfonium methylide anion at 0°C for 20h, gave exclusively (14$^{15}$)-3-methoxy-14-oxiranylestra-1,3,5(10)-trien-17-one (228) (82%) (Scheme 3.4-13). The configuration at C-14$^1$ was assumed at this stage (proven later in this chapter), since nucleophilic addition is now known to occur on the pro-$S$ face of the 14-formyl group. The $^{14\alpha}$-oxiranyl 17-ketone (228) was characterised by carbonyl
absorption at \( \nu_{\text{max}} \) 1733 cm\(^{-1}\) in the infrared spectrum and distinctive signals in the \(^1\text{H}\) NMR spectrum, amongst others, a triplet \( (J 2 \times 4.3 \text{ Hz}) \) at 82.74 and an apparent triplet \( (J 2 \times 3.5 \text{ Hz}) \) at 3.33, and a doublet of doublets \( (J 4.3 \text{ and } 2.8 \text{ Hz}) \) at 2.83, due to the \( 14^2-\text{H}_{S*} \), \( 14^1-\text{H} \) and \( 14^2-\text{H}_{R*} \) respectively. The coupling relationships between the three signals were confirmed by the corresponding correlations in the COSY spectrum.

![Diagram](image)

**Scheme 3.4-10**

The reactivity of the 14\(\alpha\)-oxiranyl 17-ketone (228) towards various nucleophiles was investigated in order to ascertain whether this could provide a useful and perhaps more general approach toward 14\(\alpha\)-chain extension. In the first instance, treatment with dimethylcuprate, which is known to attack the least substituted position of the oxirane,\(^{123}\) resulted in recovery of starting material.

The alternative approach toward nucleophilic attack on the oxirane through treatment with a Grignard reagent, was also attempted. In this case, it was recognised that the scope for rearrangement under the influence of the Lewis acidity of a Grignard reagent could give rise to the respective products of 1,2-hydride shift, namely a 14\(\alpha\)-acetyl (229) intermediate leading to a 14\(^1\)-branched alkyl chain (Scheme 3.4-14, equation 1), or a 14\(\alpha\)-formylmethyl (230) intermediate leading to a 14\(^2\)-alkyl 14\(^2\)-alcohol (Scheme 3.4-14, equation 2). The successful use of this \textit{in situ} rearrangement-alkylation methodology is exemplified in the construction of the C-17 side chain of lanosterol analogues.\(^{124}\)
However, treatment of the 14α-oxiranyl 17-ketone (228) with methylmagnesium iodide in diethyl ether at 20°C for 15 min, gave a single more polar product (76%). The infrared spectrum of this product exhibited hydroxyl absorption at $\nu_{\text{max}}.3571 \text{ cm}^{-1}$, but no carbonyl absorption, and was subsequently characterised as the hemiketal of the halohydrin (231) (Scheme 3.4-15) on the basis of its NMR spectra.
Distinctive $^1$H NMR signals appeared at δ 3.06 (multiplet, $W_0/2 25.6$ Hz) due to the 2'-protons, and 4.52 (doublet of triplets, $J 8.4$ and $2 \times 2.4$ Hz) due to the 1'-proton. The diagnostic "W-coupling" (additional 2.4 Hz) between the 1'- and 15β-proton was consistent with hemiketal structure and confirms the earlier assumption of $14^1\delta$-configuration of the 14α-oxiranyl 17-ketone (228). Further evidence for the hemiketal structure was the presence of signals at δc 109.6(s), 79.6(d), and 9.2(t) due to C-17, C-1' and C-2'. The high shielding of C-2' was consistent with the expectation for an iodomethyl group. Further corroboration of this structure was obtained by treatment of the iodohydrin (231) with lithium aluminium hydride at 20°C for 10 min, to give the hemiketal (220). The reaction mechanism leading to the formation of the iodohydrin is not entirely clear. However, iodohydrins have been prepared via regioselective opening of epoxides with magnesium iodide, and it is assumed that this species was able to compete for reaction upon the 14α-oxirane since the alternative modes of attack were slow.

The failure of the Grignard reagent to induce prior rearrangement was therefore unsurprising, but it was then considered that deliberate treatment of the 14α-oxirane with a Lewis acid might give rise to either the 14α-acetyl- (229) or 14α-formylmethyl 17-ketone (230).

Treatment of the 14α-oxiranyl 17-ketone (228) with boron trifluoride diethyl ether complex in a mixture of tetrahydrofuran and benzene (1:1) at 0°C for 24h, gave a single product in 63% yield. The infrared spectrum of the compound displayed carbonyl absorption at
$v_{\text{max}}$ 1704 cm$^{-1}$, which was indicative of a cyclohexanone structure. On the basis of spectroscopic ($^1$H- and $^{13}$C NMR) and analytical data analysis, the compound was characterised as the 17a-homosteroid (179) (Scheme 3.4-16).

The likely course of events leading to the formation of the 17a-homosteroid is not completely understood. However, it is known that a 14$^1$-carbocationic intermediate may promote ring D expansion.$^{89}$ Accordingly, the scheme represents a plausible proposal for the ring expansion step of the reaction. The subsequent deformylation does not appear to have precise literature analogy. However, the well known ring contraction of 4,5-epoxy 3-ketones, mediated by boron trifluoride diethyl ether complex, is accompanied by spontaneous deformylation of the intermediate ring contracted $\alpha$-formyl ketone, and it could have argued that a similar bond cleavage could be induced in this ring D expansion by the resultant stabilisation of the product (Scheme 3.4-17).$^{127}$
One of the possible products which could have been conceived through a favourable Lewis acid mediated rearrangement of the 14α-oxirane is the corresponding 14α-formylmethyl compound (230) (Scheme 3.4-14). This intermediate would be particularly useful for 14α-chain extension methodology since the 141-formyl group was expected to be much more reactive than the 14α-formyl group in compound (87). Alternative methodology to this end was considered. There are numerous methods available for converting carbonyl compounds into homologated aldehydes. In fact, this approach has been applied to a 14α-formyl steroid.\textsuperscript{76}

An attempt was made to synthesise the 14-formylmethyl 17-ketone (228), directly from the 14α-formyl 17-ketone (87), using toluene-\textit{p}-sulfonylmethyl isocyanide (TosMIC)\textsuperscript{128} under the prescribed conditions. However, the reaction resulted in the formation of an intractable mixture of polar products. Further attempts toward the synthesis of the 14α-formylmethyl compound (230) was envisaged via one-carbon homologation of the 141-formyl group by
treatment with \( \alpha \)-silyl- and \( \alpha \)-phosphonate carbanions derived from methoxymethyltrimethylsilane\(^{129}\) and diethylmethoxymethyl phosphonate\(^{130}\) respectively. Thus, treatment of the \( 14\alpha \)-formyl 17-ketone (87) with methoxymethyltrimethylsilane and sec-butyllithium at \(-25^\circ\text{C}\) for 30 min, followed by \( 25^\circ\text{C}\) for 16h gave no reaction. However, treatment of the \( 14\alpha \)-formyl 17-ketone (87) with diethyl methoxymethylphosphonate and sodium hydride at \( 20^\circ\text{C}\) for 2h, gave an inseparable mixture of products. This approach to \( 14\alpha \)-chain extension was not further investigated.

The results of the foregoing studies on \( 14^1 \)-homologation of the \( 14\alpha \)-formyl 17-ketone (87) led to two major conclusions. In the first place, conventional Wittig methodology appears to offer limited scope for efficient conversion to \( 14\alpha \)-alkenyl chains under the conditions which have hitherto been described. Secondly, the complications arising from the interfering formation of hemiketals from primary Grignard alkylation products detracted from methods designed to exploit derivatives of the masked \( 14^1 \)-hydroxy group. The latter problem was reconsidered in terms of prior oxidation, which would lead to \( 14\alpha - 1' \)-oxoalkyl 17-ketones, which could serve as a possible intermediate for intramolecular reactions involving the 17-oxo group.

In the simplest application of this approach, it was reasoned that oxidation of the product (220) of Grignard methylation would give a \( 14\alpha \)-acetyl 17-ketone (229), which might be induced to undergo intramolecular aldol condensation leading to a regiodefined system of a \( 17^2 \)-oxo-\( 14\alpha \)-,\( 17\alpha \)-ethano 17\( \beta \)-alcohol. This product has previously been synthesised\(^{61}\) in poor yield via hydroboration-oxidation of a \( 14\alpha \)-,\( 17\alpha \)-etheno 17\( \beta \)-alcohol (81), and a practical synthesis would open the route for \( 17^2 \)-chain extension in the bridged estradiol series.

Accordingly, the hemiketal (220) was treated with Jones' reagent in acetone at \( 0^\circ\text{C}\), to give the \( 14\alpha \)-acetyl 17-ketone (229) (94\%) (Scheme 3.4-18). The product was characterised by the presence of carbonyl absorptions at \( \nu_{\text{max}} \) 1736 and 1686 cm\(^{-1}\) in the infrared spectrum, together with a singlet at \( \delta_{2.26} \) (\( 14^1 \)-CH\(_3\)) in the \( \text{H} \) NMR spectrum.
The 14α-acetyl 17-ketone (229) was treated with an excess sodium hydride in tetrahydrofuran at 20°C for 16h, to give 17β-hydroxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-one (232) (80%) (Scheme 3.4-19). The 17β-hydroxy 17β-ketone (232) was characterised by the presence of carbonyl and hydroxyl absorptions in the infrared spectrum at $\nu_{\text{max.}} 1738$ and 3597 cm$^{-1}$ respectively, supported by the appearance of a doublet ($J$ 17.8 Hz) at $\delta_\text{H} 2.22$ due to $17^1$-H$_\text{endo}$ and a doublet of doublets ($J$ 17.8 and 4.2 Hz) at 2.64 due to $17^1$-H$_\text{exo}$ in the $^1$H NMR spectrum. The additional four-bond "W-coupling" (4.2 Hz) is typical for a bicyclo[2.2.1]heptanoid system.$^{119}$ Analytical data for the 17β-hydroxy 17β-ketone (232) correlated well with the authentic report.$^{61}$
Treatment of the $17\beta$-hydroxy $17^2$-ketone (232) with lithium aluminium hydride in tetrahydrofuran at 18°C for 10 min, gave the $(17^2S)$-$17\beta,17^2$-diol (233) (85%) (Scheme 3.4-20).

The $^1$H NMR spectrum of product (233) exhibited a doublet of doublets ($J$ 8.2 and 4.6 Hz) at $\delta$4.11 due to the $17^2$-proton, which was indicative of the stereochemistry of hydride addition. Indirect evidence for the structure of this compound is the absence of four-bond "W-coupling" between the $17^2$- and $15\beta$-H (0.8 – 1.5 Hz) which was observed for opposite stereochemistry of the alcohol group at C-$17^2$. Analytical data for the $(17^2S)$-$17\beta,17^2$-diol (233) correlated well with the authentic report. The stereoselectivity of reduction of the $17^2$-ketone was consistent with the pattern observed in simple bicyclo[2.2.1]heptanones. The steric environment of the carbonyl group in the $17\beta$-hydroxy $17^2$-ketone (232) is comparable to that of camphor, since it has a 1,3-syn relationship with C-12 (Scheme 3.4-21). Accordingly, endo-approach by hydride is preferred, leading to the exclusive formation of the $(17^2S)$-$17\beta,17^2$-diol (233).
It was also of interest to synthesise the 14α-nitrile compound, since stoichiometric Grignard addition may lead directly to the required 14α-alkanones. The conversion of aldehydes into nitriles can be achieved via numerous methods, in particular, treatment with hydroxylamine hydrochloride in the presence of an acid.\textsuperscript{132} In a report of a variation of the latter reaction, aldehydes have been converted into nitriles via their $N,N$-dimethylhydrazones.\textsuperscript{133} Thus, treatment of the 14α-formyl 17-ketone (87) with an excess $N,N$-dimethylhydrazine in the presence of molecular sieve (3Å) at 20°C for 24h, gave a single less polar product. Without rigorous purification, the compound was characterised as the 14α-$N,N$-dimethylhydrazone 17-ketone (234), following the presence of characteristic absorptions in the infrared spectrum at $\nu_{\text{max.}}$ 1729(CO) and 1700(CN) cm$^{-1}$, together with diagnostic signals in the $^1$H NMR spectrum at 52.69 and 6.62, assigned to $-N(CH_3)_2$ and 14-CH=N respectively. Subsequently, the crude product (234) was treated with selenium dioxide and hydrogen peroxide at 10°C for 48h, to give the 14α-carbonitrile 17-ketone (235) in 61% overall yield (Scheme 3.4-22). The infrared spectrum exhibited carbonyl and nitrile absorption at 1743(CO) and 2227(CN) cm$^{-1}$ respectively. Spectroscopic and analytical results were consistent with the molecular formula C$_{20}$H$_{23}$O$_2$N. The moderate yield of this reaction detracted this approach toward 14α-chain extension and was therefore not pursued.
The success of the intramolecular closure of a two-carbon 14α-chain encouraged the expectation that the approach could be extended to intramolecular closure of a three-carbon 14α-chain to provide a new synthetic approach to 14α,17α-propano analogues of estradiol. Although the foregoing methodology has not provided direct access to suitably functionalised 14α-alkyl precursors for this purpose, the possible scope for an adapted alkylidenation process on the 14α-formyl 17-ketone (87) was reconsidered. It was reasoned that a sterically less hindered phosphonate species could enable Horner-Wittig methodology to be applied. It is well known that the ester stabilised carbanions of triethylmethylphosphonates with aldehydes and ketones leads to the formation of alkenyl esters. However, treatment of a solution of the 14α-formyl 17-ketone (87) in tetrahydrofuran with the triethylmethylphosphonate carbanion at reflux for 16h give no reaction.

The reaction of diethyl cyanomethylphosphonate anion with aldehydes and ketones leads to the formation of alkenenitriles. This reagent has been successfully used in the conversion of the C-10 angular formyl group of k-strophanthidin into the 10-cyanoethylene group. Treatment of the 14α-formyl 17-ketone (87) with excess diethyl cyanomethylphosphonate carbanion in tetrahydrofuran at 0°C for 5h, gave (2Z)-3-(3-methoxy-17-oxoestra-1,3,5(10)-trien-14-yl)acrylonitrile (236) (9%) and (2E)-3-(3-methoxy-17-oxoestra-1,3,5(10)-trien-14-yl)acrylonitrile (237) (76%) (Scheme 3.4-23).
The infrared spectrum of the (2Z)-acrylonitrile (236) displayed diagnostic carbonyl and nitrile absorptions at $\nu_{\text{max}}$ 1734 and 2219 cm$^{-1}$ respectively. Distinctive $^1$H NMR signals appeared at $\delta$5.52 and 6.62 (doublets, $J$ 13.0 Hz), due to the 2- and 3-protons respectively. The observed coupling constants for the 2- and 3-protons was typical for the (Z)-stereochemistry. The infrared spectrum of the (2E)-acrylonitrile (237) displayed diagnostic carbonyl and nitrile absorptions at $\nu_{\text{max}}$ 1735 and 2225 cm$^{-1}$ respectively. Distinctive $^1$H NMR signals appeared at $\delta$5.42 and 6.68 (doublets $J$ 17.0 Hz), due to the 2- and 3-protons respectively. The observed coupling constants for the 2- and 3-protons was typical for the (E)-stereochemistry. The $^{13}$C NMR spectra displayed characteristic signals for the nitrile carbons at $\delta$116.6 and 116.9 for the E- and Z-isomers respectively. An inspection of models revealed that the betaine intermediate leading to the formation of the Z-isomer (236) is sterically more demanding than the betaine leading to the E-isomer. Thus, the reaction of the diethyl cyanophosphonate anion in tetrahydrofuran is thermodynamically controlled.

This successful alkylidenation opened the way to exploring routes to the synthesis of a terminally functionalised 14$\alpha$-propyl chain which could serve as an intermediate for intramolecular cyclisation to 14$\alpha$,17$\alpha$-propano estradiols. According to the synthetic plan, hydrogenation of the $\Delta^2$-bond of the alkenenitriles was necessary to give the 14$\alpha$-cyanoethyl 17-ketone (238) for further elaboration toward the intended goal. Catalytic hydrogenation of the E-isomer (237) over palladium on charcoal (5%) in tetrahydrofuran, under a hydrogen atmosphere at 20$^\circ$C for 48h, gave the 14$\alpha$-cyanoethyl 17-ketone (238) (70%) (Scheme 3.4-...
Hydrogenation of the Z-isomer (236) proceeded similarly, but more slowly. The 14α-cyanoethyl 17-ketone (238) was characterised by the presence of infrared absorption at \( \nu_{\text{max}} \) 732(CO) and 2 248(CN) cm\(^{-1}\) and the appearance of a methylene carbon signal in the \(^{13}\)C NMR spectrum at \( \delta \) 15.4 (t) due to C-2. The low field position for this signal is common for methylenes attached to a cyano group. 136

The following step required conversion of the 14α-cyanoethyl group into the corresponding 14α-formylethyl group in order to conduct an intramolecular reductive cyclisation between the chain terminus and the 17-oxo group. The favoured reagent for this purpose is diisobutylaluminium hydride (DIBAH). 137 In the first instance, it was of interest to establish whether the relative rates of reduction of the cyano group and the 17-oxo group would differ sufficiently to enable a selective reduction to be performed on the 14α-cyanoethyl group without concomitant reduction at C-17. An attempt to perform the reaction at -80°C for 1h in the presence of a slight excess of DIBAH was unsuccessful, since the reaction of the 14α-cyanoethyl 17-ketone (238) with ca. 1.5 molar equivalents of DIBAH in toluene at -80°C for 1h (after which the reaction ceased), resulted in the formation of a complex mixture of products. Attempted chromatographic separation gave starting material (238) (29%), 14α-cyanoethyl 17α-alcohol (239) (22%) and a further mixture of inseparable products (Scheme 3.4-25). The 14α-cyanoethyl 17α-alcohol (239) was characterised by nitrile absorption at \( \nu_{\text{max}} \) 2 246 cm\(^{-1}\) in the infrared spectrum. The NMR spectra displayed doublet of doublets (\( J \) 7.7 and 2.1 Hz) at \( \delta \) H 3.96 due to the \( \beta' \)-H as well as distinctive signals at \( \delta \) C 79.9(d) and 120.8(s) due to C-17' and the nitrile carbon respectively. The observed coupling constants
for $17\beta$-H together with the appearance of the $13\beta$-Me at $\delta_H0.82$ was characteristic of $17\beta$-H stereochemistry.$^{38}$

This result is not surprising and it was decided to conduct an exhaustive reduction with DIBAH with the intention of re-oxidizing the expected mixture of $14\alpha$-formylethyl 17-alcohols (240) to the desired intermediate, the corresponding $14\alpha$-formylethyl 17-ketone (241). Accordingly, treatment of $14\alpha$-cyanoethyl 17-ketone (238) with an excess of DIBAH in toluene at $-78^\circ C$ for 1 h, resulted in the formation of an inseparable mixture of polar products, the infrared spectrum of which displayed absorption at $\nu_{\max}3507(\text{OH})$ and 1718(CO) cm$^{-1}$, but no nitrile or ketone absorptions. However, attempted Swern,$^{138}$ pyridinium dichromate,$^{139}$ pyridinium chlorochromate$^{140}$ and Dess-Martin$^{141}$ oxidations of the mixture was unsuccessful and resulted in the formation of mixtures of uncharacterisable products. Scarcity of material at this stage of the project precluded further investigation, but
the foregoing results have demonstrated the feasibility of synthesising a three-carbon 14α-chain with functionality which may be used for this purpose. It is clear that further experimentation will be necessary and that possible prior protection of the 17-oxo group may be advantageous. In order to circumvent the difficulty associated with oxidation, it may be necessary to protect the 17-oxo group as the ketal at an earlier stage of the synthesis. However, Wittig-Horner mediated homologation provided a route to the 14α-formylethyl 17-ketone, and hence scope for intramolecular pinacol coupling toward functionalised 14α,17-propano bridged steroids. This investigation served its purpose in demonstrating the scope for further elaboration of the 14α-cyanoethyl 17-ketone (238) toward 14α,17α-propano estradiol analogues.

The earlier result in which successful vinylation of the 14α-formyl 17-ketone (87) also gave a masked form of a functionalised three-carbon 14α-substituted 17-ketone (224) was reconsidered. It was reasoned that oxidation of the product would lead to a 141-oxopropenyl chain at C-14, in which the scope for a novel form of an intramolecular reductive cyclisation could be explored (Scheme 3.4-26).

Scheme 3.4-26

A first attempt to conduct the oxidation of (224) under Swern conditions resulted in the formation of a single less polar product. This product was characterised as the 1',17α-epoxy 17-O-thiomethyl ether following the presence of a singlet at δH2.17 (S-CH3) in the 1H NMR spectrum. Attempted oxidation with various other oxidants was unsuccessful, resulting in either no reaction or poor yields. However, efficient oxidation was achieved by treatment of
the hemiketal (224) with the Dess-Martin reagent in dichloromethane at 25°C for 6h, to give 3-methoxy-14-(1-oxoprop-2-enyl)estra-1,3,5(10)-triene-17-one (242) (83%) (Scheme 3.4-27).

![Diagram](image)

**Scheme 3.4-27**

The 14α-acroyl 17-ketone (242) was characterised by the presence of two carbonyl absorption bands in the infrared spectrum at $v_{\text{max}}$ 1736 and 1677 cm$^{-1}$ respectively. The $^1$H NMR spectrum of product (242) exhibited a doublet of doublets for the signals at $\delta$ 5.60 ($J$ 10.4 and 1.8 Hz), due to $3^\prime$H$_{\text{cis}}$, 6.20 ($J$ 6.7 and 1.8 Hz), due to $3^\prime$H$_{\text{trans}}$, and 6.84 ($J$ 16.7 and 10.4 Hz) due to $2^\prime$-H.

Reductive intramolecular cyclisation between the terminus of an enone and a carbonyl carbon mediated by lithium in ammonia provided a method of annulation in the construction of a perhydroindanedione. Treatment of the 14α-acroyl 17-ketone (242) with lithium in liquid ammonia resulted in the formation of an inseparable mixture of products, whereas treatment with an excess samarium diiodide in the presence of t-BuOH in tetrahydrofuran at 25°C for 1h, resulted in the formation of a single more polar product (243) (75%). The infrared spectrum of this compound displayed absorption at $v_{\text{max}}$ 3440(Oh) and 1727(CO) cm$^{-1}$ and the mass spectrum displayed a molecular ion, $M^+$ 340 indicating a formal reduction of the starting material. Insufficient amounts of the 14α-acroyl 17-ketone (242) detracted further investigation of this reaction. Gross overlapping of signals in the high field region of the $^1$H NMR of (243) complicated its analysis and $^{13}$C NMR data could not be reconciled with that of a 14α,17α-propanone bridged structure.
One of the objectives in this phase of the work, was the exploitation of synthetic routes to 14α-(ω-dialkylamidoalkyl)estradiol analogues. Estradiol analogues bearing a 7α-(dialkylamidoalkyl) chain display pure antagonist properties,12,13 and subsequently, the 15α- and 15β-(dialkylamidoalkyl)-14 as well as the 14α,17α-ethano 7α-(dialkylamidodecyl)143 estradiol analogues have been synthesised for biological evaluation. The latter estradiol analogue displayed strong antagonistic properties.

With the hemiketal (224) in hand, Claisen methodology was considered for the introduction of dialkylamidoalkyl chains of variable lengths. It has been reported that Claisen condensation via the β-keto ester served as an ideal method of stereocontrolled side chain extension of sterols.144 A variation of the Claisen reaction, the Carroll reaction, was successfully employed in the synthesis of vitamin E side chains.145 The Carroll reaction is dependent on the efficient formation of a β-ketoester, which is easily attainable via alkanolysis of acyl Meldrum's acids.146 During the Carroll reaction, treatment of a vinyl alcohol with appropriately functionalised acyl Meldrum's acids, results in the in situ formation of the β-ketoester, followed by the Claisen rearrangement to give the corresponding alkenone (Scheme 3.4-28).
5-Acetyl Meldrum's acid was prepared according to literature methods\textsuperscript{147} in order to investigate the scope for Carroll mediated chain extension at C-14\textsuperscript{1}. Thus, treatment of the hemiketal (224) with 5-acetyl Meldrum's acid at reflux in benzene for 5h, then for 2h in xylene, gave the (5E)-6-(3-methoxy-17-oxoestra-1,3,5(10)-trien-14-yl)hex-5-en-2-one (244) (84\%) (Scheme 3.4-29).

\begin{center}
\textbf{Scheme 3.4-29}
\end{center}

The infrared spectrum of product (244) exhibited two carbonyl absorptions at $\nu_{\text{max}}$ 1729 and 1713 cm$^{-1}$ respectively. The $^1$H NMR exhibited a singlet at 82.10 due to the 1-methyl protons, a doublet of triplets ($J$ 16.0 and 2 x 6.7 Hz) at 5.54 due to the 5-proton, and a doublet of doublets ($J$ 16.0 and 1.0 Hz) at 5.68 due to the 6-proton. The large vicinal coupling of 16.0 Hz between the 5-proton and 6-proton together with the 1.0 Hz allylic coupling between the 6-proton and 4-proton was indicative of (E)-stereochemistry. Further evidence supporting the structure of product (244) was the presence of distinctive signals in the $^{13}$C NMR spectrum at 8208.5(s), 132.2(d), 130.8(d), and 30.6(q) due to the 2-, 5-, 6- and 1-carbons respectively. The rationalisation of this stereocontrolled rearrangement can be envisaged via the proposed 6-membered transition state of the intermediate $\beta$-ketoester (Scheme 3.4-30).
This approach has opened the route toward 14α-(dialkylamidoalkyl) analogues of estradiol. Modified acyl Meldrum’s acid derivatives prepared via the condensation of acyl-ω-functionalised carbon chains could be envisaged for this investigation.

Scheme 3.4-30
3.5 Synthesis of ring D modified androstanes

The purpose of this investigation was to develop synthetic routes to new ring D modified androstanes and pregnanes. Petit et al. reported the synthesis of a 14α-methyl analogue of testosterone via the degradation of lanosterol.29 Solo et al. reported the attempted synthesis of 14α,17α-bridged analogues of testosterone via Diels-Alder cycloaddition methodology. However, their efforts were frustrated by low yields (<30%), due to the unavailability of a suitable ethylene equivalent.44 A preliminary study demonstrated the successful application of the cycloaddition approach to achieve the synthesis of a 14,17-etheno analogue of testosterone (253), starting with 15α-hydroxyandrost-4-ene-3,17-dione (245) (Scheme 3.5-1).148 As an extension of this work, the scope for chemoselective oxidative cleavage of the ring D etheno bridge in the presence of unsaturation at Δ5 was investigated.

Accordingly, the 14,17-etheno compound (253) was synthesised using adaptations of prescribed procedures.148 The starting material, 15α-hydroxy 17-ketone (245), is readily available via microbiological hydroxylation of androst-4-ene-3,17-dione.149 Enol acetylation of the 15α-hydroxy 17-ketone (245) under forcing conditions gave the bis-dienyl acetate (246), which was treated with phenyl vinyl sulfone in xylene at 145°C for 96h, to give the cycloadduct (247) (Scheme 3.5-1). Careful base-mediated hydrolysis of the 3,5-dien-3-yl acetate gave the 17-acetoxy enone (248). The infrared spectrum of compound (248) displayed carbonyl absorption at νₓ-max. 1745 and 1665 cm⁻¹, indicating the preservation of the 17α-acetoxy group and the regeneration of the 4-en-3-one system. Further evidence for the structure of compound (248) is the presence of distinctive ¹H NMR signals at δ 4.15 (doublet of doublets, J 8.5 and 4.9 Hz) due to the 20-proton, a singlet at 5.76 due to the 4-proton, and doublets (J 6.2 Hz) at 6.10 and 6.36 due to the 15- and 16-protons respectively. Desulfonylation required prior protection of the Δ4-3-oxo functionality via ketalisation, which resulted in the migration of the Δ4-bond to the 5,6-position, to give the 3,3-ethylenedioxy sulfone (249). Reductive desulfonylation has previously been achieved using sodium-amalgam,148 or samarium diiodide in the presence of hexamethylphosphoric triamide.150 In our hands, desulfonylation was more conveniently achieved using sodium metal in liquid ammonia, to give the 17α-hydroxy olefin (250) (88%). The 17α-hydroxy olefin (250) was characterised by distinctive signals in the ¹H NMR spectrum at δ 5.39 (multiplet, W½ 9.6 Hz),...
Scheme 3.5-1
5.86 and 5.96 (doublets, $J\ 6.1\ Hz$), due to the 6-, 15- and 16-protons respectively, together with $^{13}\text{C} \text{NMR}$ signals at $\delta\ 135.9$ (d), 134.0 (d), 121.7 (d), 90.5 (s), due to C-15, C-16, C-6 and C-17 respectively. Acetylation of the 17α-hydroxy olefin (250) gave the 17α-acetoxy olefin (251). Acid-mediated hydrolysis of the 3-ketal gave the 17α-enone (252), followed by base-mediated deacetoxylation, to give the testosterone analogue (253).

The efficient synthesis of the 14α,17α-etheno analogue of testosterone (253) thus set the scene for exploration of methods for chemoselective oxidative cleavage of the 14,17-etheno bond. In this way it was expected that access could be given to the 14α-formyl analogue of androst-4-ene-3,17-dione and hence, a variety of 14α-functionalised analogues of testosterone. In the first instance, consideration was given to methods for protecting ring A functionality or at least, ensuring that a substrate could be elaborated to give the best prospect of chemoselective reaction of the etheno bridge. In order to perform selective reactions at ring D, the ring A enone side chain was generally protected as the 3α,5-cyclosteroid ($i$-steroid) (Scheme 3.5-2). The synthesis of the $i$-steroid starting with the $\Delta^4$-3-one is a multistep, cumbersome procedure. Subsequent to ring D hydroxylation, enone regeneration requires further steps. However, Nes et al. used this approach for the hydroxylation of the $\Delta^{17,20}$-$i$-steroid (254) (scheme 3.5-2). It was reported that treatment of various 5,17(20)-pregnene-20-carbonitriles (255) with a molar equivalent amount of osmium tetroxide in pyridine followed by treatment with sodium disulfite provided α-hydroxy ketones and aldehydes but with no regioselectivity toward the $\Delta^{17,20}$-double bond. However, when an electron withdrawing group (carboxyethyl) was introduced at C-20, regioselective hydroxylation of the 17(21)-bond was achieved in moderate yield (60%). All hydroxylations were performed over 3 days at 25°C in pyridine (Scheme 3.5-2).
Following the foregoing literature reports, it was considered that ring A protection in the form of a 3,3-ethylenedioxy group seemed to be a more practical approach for exploring chemoselective hydroxylation. It was expected that the ring D etheno bond may display a similar pattern of reactivity toward osmylation as in the case of the 14α,17α-etheno bond of the estradiol analogue. Treatment of the 17α-acetoxy olefin (251) with a molar equivalent of osmium tetroxide in pyridine at 4°C for 24h, followed by treatment of the reaction mixture with sodium disulfide for 1h, gave a mixture of products. Chromatographic separation afforded starting material (251) (32%), followed by 3,3-ethylenedioxy-14,21-cyclo-14β-pregn-5-ene-15β,16β,17α-triol 17-acetate (256) (24%) and 3,3-ethylenedioxy-14,21-cyclo-14β-pregn-5-ene-15α,16α,17α-triol 17-acetate (257) (22%) (Scheme 3.5-3). The isomers were readily distinguished by NMR spectroscopy. The signals for the 15- and 16-H protons of diol (256) appeared as doublets of doublets (J 9.4 and 1.5 Hz, after D$_2$O exchange) at δ4.22 and 4.33
respectively, whereas these same protons of (257) appeared as doublets ($J$ 7.6 Hz, after D$_2$O exchange) at $\delta$3.99 and 4.49 respectively. (Figure 3.5-1). This demonstrates the $\text{exo,exo}$-orientation in the former case, through the larger magnitude of the vicinal coupling and the four bond W-coupling to the 20$\beta$- and 21$\beta$ protons.$^{49}$

\begin{align*}
\text{Scheme 3.5-3} \\
\end{align*}
In another experiment the 17α-acetoxy olefin (251) was treated with a molar equivalent osmium tetroxide over a period of 48h under similar conditions as before, to give a mixture of products. Chromatographic separation afforded the diols (256) (21%) and (257) (18%) as well as 3,3-ethylenedioxy-14,21-cyclo-5β,14β-pregnane-5,6β,15β,16β,17α-pentaol 17-acetate (258) (10%), followed by 3,3-ethylenedioxy-14,21-cyclo-5β,14β-pregnane-5,6β,15α,16α,17β-pentaol 17-acetate (259) (7%) (Scheme 3.5-4).

The tetraol isomers (258 and 259) were readily distinguished by 1H NMR. The signals for the 15- and 16-protons of tetraol (258) appeared as doublet of doublets (J 9.4 and 2.0 Hz, after D₂O exchange) at δ4.19 and 4.37 respectively, whereas those of tetraol (259) appeared as doublets (J 7.6 Hz, after D₂O exchange) at δ4.19 and 4.52 respectively. Tetraol (258) displayed a triplet (J 2 x 2.9 Hz) at δ3.52 and tetraol (259) displayed a triplet (J 2 x 3.0 Hz) at δ3.59 due to the 6α-proton. Inspection of a model revealed that the torsion angles between the 6α-, 7α- and 7β-H in (258) or (259) is ca. 60° giving rise to the typical vicinal coupling (J 3.0 Hz), indicating stereoselective β-face cis-hydroxylation of the Δ⁵-double bond. This result is not surprising, considering the most likely conformation of the A-B ring system (Figure 3.5-2). It is clear that α-face approach of the hydroxylating agent is hindered by the 3,3-ethylenedioxy group.
It has been reported that cis-hydroxylation of the 14α,17α-etheno analogue of estradiol gives a 1:2 mixture of the 17αS,17αS- and 17βR,17βR-diols. 49 This was in concordance with the observations of Kishi et al. for the osmylation of allylic alcohols and their derivatives. 154 However, no significant difference in the amount of endo in relation to exo hydroxylated products was observed.

A striking observation of the stoichiometric hydroxylations is the product distribution after 24h and after 48h. After 24h, starting material and ring D hydroxylated products (256 and 257) were observed, and tetraols (258) and (259) were not observed. After 48h, no starting material remained, and as expected, no single cis-hydroxylation at the Δ5-double bond was observed. The fact that no starting material was observed implies that one osmium tetroxide molecule can hydroxylate two double bonds simultaneously, assuming that all the starting material is converted to hydroxylated products. This is not a novel phenomenon and can be confirmed by various literature observations as reviewed by Schröder. 155 More recently, the isolation and X-ray crystal structure determination of the bisglycolate (260) supported intermolecular double dihydroxylation (Scheme 3.5-6). 156 Catalytic olefin dihydroxylation has been shown to afford diols with enantiomeric excesses that could only be rationalised by virtue of an osmium (VIII) trioxoglycolate complex such as (260). 157
maximum yield of diols, (256) and (257), an optimum reaction time between 24h and 48h must be investigated.

Hazardous toxicity and high costs are major drawbacks in the use of osmium tetroxide. Although stoichiometric oxidations of alkenes by osmium tetroxide usually give better yields of diol products and are particularly applicable for the small-scale oxidation of precious materials, it is common, for reasons of cost and convenience, to use osmium tetroxide in conjunction with a secondary oxidant, continuously regenerating the tetroxide. Commonly used oxidants are trimethylamine N-oxide and N-methylmorpholine N-oxide. These oxidants minimise over-oxidation that leads to the formation of keto or acid products. Osmium tetroxide, linked to insoluble cross-linked polymers and copolymers bearing tertiary
amino functions, has been used in the presence of secondary oxidants, to accomplish the
catalytic hydroxylation of olefins.\textsuperscript{158}

Osmium tetroxide bound to a poly(vinylpyridine) polymer (Reillex\textsuperscript{TM}) was used to achieve
catalytic osmylation. Thus, the 17\textalpha-acetoxy olefin (251) was treated with
poly(vinylpyridine)-osmium tetroxide polymer and a stoichiometric amount of trimethylamine
N-oxide in aqueous tetrahydrofuran at reflux for 4h. The reaction was monitored by TLC and
stopped as soon as tetraols (258) and (259) was detected. Chromatographic separation of the
mixture afforded starting material (251) (53\%), diols (256) (17\%), (257) (14\%) and a mixture
of tetraols (258 + 259) (3\%). The polymer was filtered and used in at least two more cycles,
before all hydroxylating activity was lost. The loss in activity is due to osmium tetroxide
leaching out of the polymer matrix whilst in solution. However a method that claims to fully
immobilise the osmium tetroxide has been devised and used as a cis-dihydroxylation agent.\textsuperscript{159}
At this stage, sufficient diols were accumulated for further elaboration and no further
optimisation was investigated. With ring D diols (256) and (257) in hand, further elaboration
toward 14\alpha,17-difunctionalised and 14\alpha-functionalised pregnanes and androstanes was
possible.

Treatment of the 17\textalpha-acetoxy-15,16-diols (256) and (257) with methanolic potassium
hydroxide gave the 17\alpha,15,16-triols (261) which were not isolated due to poor solubility in
organic solvents. The triols were not characterised, but immediately treated with aqueous
sodium metaperiodate in a mixture of ethanol and benzene (1:2) at 20\textdegree C for 1h, to give 3,3-
ethylenedioxy-17-oxoandrost-5-ene-14-carbaldehyde (262) (65\%) (Scheme 3.5-6). The 14\alpha-
formyl 17-ketone (262) was characterised by the presence of strong carbonyl absorption at
1 740 cm\textsuperscript{-1} in the infrared spectrum and a singlet at 810.07 (14\alpha-CHO) in the \textsuperscript{1}H NMR
spectrum.
The 14α-formyl 17-ketone (262) could provide access to functionalised 14α-alkyl androstanes. However, a parallel study with the estradiol analogues has not yet been investigated. Chemoselective hydride reduction was expected to give the 14-hydroxymethyl compound, but the moderate yield of the 14α-formyl 17-ketone (262), detracted this approach. An alternative route to the 14-hydroxymethyl compound was envisaged, via the 14α,17α-dicarbaldehyde which was available via direct sodium metaperiodate cleavage of the 17α-acetoxy 15,16-diols (256) and (257). Thus, treatment of the 17α-acetoxy 15,16-diols (256) and (257) with aqueous sodium metaperiodate in ethanol at 20°C for 1h gave 17α-acetoxy-3,3-ethylenedioxyandrost-5-ene-14,17α-dicarbaldehyde (263) (94%) (Scheme 3.5-7). The 14,17-dicarbaldehyde (263) was characterised by the presence of carbonyl absorption at 1728 cm\(^{-1}\) in the infrared spectrum. The \(^1\)H NMR spectrum exhibited a singlet at 69.23 and a doublet (\(J\) 1.4 Hz) at 610.00, due to 17α-CHO and 14α-CHO respectively. The observed coupling (1.4 Hz) was assigned to long range W-coupling between 14α-CHO and the 15β-proton.

Treatment of the 14,17-dicarbaldehyde (263) with lithium aluminium hydride in tetrahydrofuran at 20°C for 45 min gave the 14\(^1\),17\(^i\),17β-triol (Scheme 3.5-8). Water was added in order to destroy excess lithium aluminium hydride, followed by immediate treatment with aqueous sodium metaperiodate at 20°C for 35 min. The in situ 17,17\(^1\)-dil cleavage gave 3,3-ethylenedioxy-14-(hydroxymethyl)androst-5-en-17-one (265) (89%), which exists in equilibrium with the preponderant hemiketal (264) (Scheme 3.5-8).
The infrared spectrum of the product mixture displayed absorptions at $v_{\text{max}}$ 3 459 cm$^{-1}$ (OH) and 1 728 (weak, OH) cm$^{-1}$ and the $^1$H NMR spectrum displayed doubling of several signals (ca 2:1). The unusually large $W$-coupling ($J$ 3.9 Hz) between $^{14}$1-H$_{exo}$ and $^{15}\beta$-H was typical for hemiketal formation. The 14-hydroxymethyl 3-ketal (265) was readily converted into the corresponding 14$\alpha$-acetoxymethyl compound (266) (79%) (Scheme 3.5-9).
NMR spectrum displayed doublets with a typical AB coupling pattern \( (J = 11.5 \text{ Hz}) \) at \( \delta = 4.08 \) and 4.11 due to the \( 14^1 \)-protons respectively (Scheme 3.5-9).

![Scheme 3.5-9](image)

Finally, treatment of the alcohol mixture (264) with dilute acid, gave 17\(\beta\)-hydroxy-17\(\alpha\),14-(epoxymethano)androst-4-en-3-one (267) (62\%) (Scheme 3.5-10). The enone (267) exists exclusively in the hemiketal form, unlike the 14-hydroxymethyl 3-ketal (265). The compound was characterised by the presence of hydroxyl (\( v_{\text{max}} \) 3400 cm\(^{-1}\)) and \( \alpha,\beta \)-unsaturated carbonyl absorption (\( v_{\text{max}} \) 1657 cm\(^{-1}\)) in the infrared spectrum, thus indicating the restoration of the enone functionality. The \( ^1H \) NMR spectrum exhibited a diagnostic W-coupling \( (J = 2.9 \text{ Hz}) \) between \( 14^1\text{-H}_{\text{exo}} \) and \( 15\beta\text{-H} \), as well as a singlet at \( \delta = 5.72 \) due to 4-H. Compound (267) has been subjected to biological evaluation.

![Scheme 3.5-10](image)
In conclusion, this investigation demonstrated that it is possible to synthesise 14α-functionalised analogues of androst-4-ene-3,17-dione via the cycloaddition method. However, further experimentation is necessary in order to improve the cis-hydroxylation step. Although cis-hydroxylation at the Δ5-double bond in compound (251) was seen as a drawback in our efforts to synthesise ring D modified androstanes, it can be deliberately prepared for exploring routes to 6-functionalised analogues of androst-4-ene-3,17-dione. For this purpose, the synthetic potential of tetraol (258) was investigated. Treatment of tetraol (258) with dilute hydrochloric acid at 20°C for 6h gave a mixture of products. Only one compound was clearly isolable and was identified as 14,21-cyclo-14β-pregn-4-en-3-one-6β,15β,16β,17α-tetraol 17-acetate (268) (23%). The infrared spectrum exhibited hydroxyl absorption (ν_{max} 3 438 cm⁻¹) and carbonyl absorptions (ν_{max} 1 709 and 1 671 cm⁻¹). The 1H NMR spectrum exhibited a doublet of doublets (J 9.4 and 1.9 Hz) at δ4.22 and 4.35 for the 15- and 16-protons respectively, as well as a triplet (J 2 x 3.0 Hz) at δ4.37 due to the 6α-proton. This coupling constant was consistent with that observed for 6β-hydroxycholest-4-en-3-one (doublet of doublets, J 4.1 and 2.3 Hz).

With selective ring D diol protection and controlled deketalisation methods, the yield of (268) may be optimised. Further elaboration of compound (268) could provide entry into new 6-functionalised pregnanes or androstanes for biological evaluation.

It has been shown that under acidic conditions 14,17-etheno bridged estradiol analogues undergo ring D rearrangements leading to the formation of 14,16-ethano 17-ketones.66
This work was extended into the androstane series in order to investigate whether similar rearrangement patterns would provide a synthetic route to 14,16-ethano analogues of androst-4-ene-3,17-dione. The substrate for this investigation was synthesised via deketalisation of the 17α-acetoxy olefin (251) (81%), followed by deacetoxylation with ethanolic sodium ethoxide to give the 17α-hydroxy enone (253) (78%) (Scheme 3.5-1).

Treatment of a solution of 17α-hydroxy-14,21-cyclo-14β-pregna-4,15-dien-3-one (253) in benzene with hydrogen bromide in acetic acid (48%) at 20°C for 5h, gave 14,16β-ethano-14β-androst-4-ene-3,17-dione (269) (39%) and 17α-hydroxy-15β,17β-ethano-14β-pregna-4,8-dien-3-one (270) (41%) (Scheme 3.5-12). The infrared spectrum of compound (269) displayed carbonyl absorptions at $\nu_{\text{max}}$ 1 730 and 1 657 cm$^{-1}$ respectively. The $^{13}$C-NMR spectrum displayed a methine signal at δ 57.3 and a carbonyl signal at δ 219.0 due to C-16 and C-17 respectively. Apart from the 4-proton at δ 5.76, all other signals appeared in the highfield region (below δ 3.0) and displayed gross overlapping. Although direct evidence for the 14β-configuration was not forthcoming from the spectroscopic data, the assignment followed from mechanistic and steric considerations. The infrared spectrum of (270) displayed absorptions at $\nu_{\text{max}}$. 3 400 (OH) and 1 657 (CO) cm$^{-1}$. However, the absence of the C-8 and C-9 methine signals and the appearance of a tetrasubstituted olefinic bond (δ136.7 and 129.6) in the $^{13}$C-NMR spectrum supported this structure.66

A rationale for these rearrangements has been proposed in the literature.66 Protonation of the etheno bridge, followed by neighbouring bond migration leads to the formation of the various products. In the presence of hydrogen bromide, the formation of product (269) could be envisaged via a 20(17→16)$\text{abeo}$-rearrangement (path a), whereas, the formation of product (270) could be envisaged via a 21(14→15)$\text{abeo}$-rearrangement to give intermediate (253C) (path b), and subsequent hydride migration from C-8 to C-14 and accompanying elimination of 9α-H (path c). The spiroketal (271) was not observed in this experiment (Scheme 3.5-12). Dichloromethane was used as solvent for the rearrangement study on the estradiol analogue leading to the spiroketal (271) as major product (46%). However, for the pregnane analogue, benzene was used as solvent, thus contributing toward suppressing delocalisation of the carbocation in the reaction leading to the formation of the spiroketal (271).
Further optimisation of the yield of the 14,16-ethano compound (269) was not carried out. However, variation in solvent and acid catalysts may lead to different ratios of the various rearrangement products. Nevertheless, these compounds are novel ring D modified androstane analogues that could be elaborated into new ring D bridged analogues of testosterone, which could be of biological interest.

Scheme 3.5-12
3.6 Receptor-binding studies

In order to establish structure-activity patterns, it is desirable to compare calculated ('molecular mechanics', MM) and actual crystal structure conformations. The results presented here constitute a preliminary contribution toward developing a model for structure-activity relationships and predictive drug design.

The affinity of the hormone analogue for the receptor can be measured in terms of a 'competition factor' (CF), which is defined as the ratio of the concentration of the test sample (C_{test}) and that of the reference substance (C_{ref}) required for 50% competition.\(^{160}\) Estradiol is taken as the reference substance and therefore has a CF value of unity. Hormone analogues with competition factors of less than unity are potentially more active than estradiol.

\[
C_f = \frac{C_{test \ at \ 50\% \ competition}}{C_{ref \ at \ 50\% \ competition}}
\]

The competition factors and relative minimum energy (MM2) of biologically tested estrogen analogues are given in Table 3.6. All analogues were superimposed on estradiol in its minimum energy conformation and the root mean squares fit value determined after atom pairing.\(^{161}\) The analogues (212) and (185) (Scheme 3.6-1) exhibit a high affinity for the hormone receptor. The root mean squares fit value of (212) (0.089Å) correlates well with its estrogenic activity. Conversion of the 14α-vinyl group of (212), into the 14α-ethyl group of (213), resulted in 50% loss in estrogenic activity. Furthermore, when comparing 14α-ethyl compound (213) with 14β-ethyl compound (95), there is an improvement in the root mean squares fit and another 60% loss in estrogenic activity.\(^{52, 161}\) It is now known that the 14β-alkyl and 14β,17β-propano estradiol analogues exhibit poor affinities for the estrogen receptor. The 17α-homoestradiol analogue (185) has a relatively high affinity for the estrogen receptor; however its root mean squares fit value is comparable to that of the 14β-ethyl compound (95)\(^{52}\). Estriol analogue (186) displayed a poor affinity for the estrogen receptor, which is consistent with a high root mean squares fit. The 14,16-methano 17β-diols (194 and 195) were separated with the aid of HPLC, and converted into estradiol analogues (194A and 195A). Molecular modelling results suggest that the 17β-OH compound (194A) gives a better
Table 3.6:

<table>
<thead>
<tr>
<th>Energy minimized structure superimposed on ED&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CF&lt;sup&gt;b&lt;/sup&gt;</th>
<th>E (kJmol&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>RMS&lt;sup&gt;c&lt;/sup&gt; (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>187</td>
<td>210</td>
<td>297.4</td>
<td>0.434</td>
</tr>
<tr>
<td>194A</td>
<td>d</td>
<td>278.9</td>
<td>0.203</td>
</tr>
<tr>
<td>212</td>
<td>1.5</td>
<td>171.0</td>
<td>0.089</td>
</tr>
</tbody>
</table>

(a) ED = Estradiol  (b) CF = competition factor  (c) RMS = root mean squares fit.
(d) Not available yet
<table>
<thead>
<tr>
<th>Energy minimized structure superimposed on ED\textsuperscript{a}</th>
<th>( C_F )</th>
<th>( E(\text{kJmol}^{-1}) )</th>
<th>RMS (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>213</td>
<td>3.0</td>
<td>205.5</td>
<td>0.264</td>
</tr>
<tr>
<td>95</td>
<td>7.2</td>
<td>189.4</td>
<td>0.239</td>
</tr>
<tr>
<td>185</td>
<td>1.8</td>
<td>103.4</td>
<td>0.229</td>
</tr>
</tbody>
</table>
estradiol fit (RMS 0.203Å) than the corresponding 17α-OH (195A) (RMS 0.398Å, E_min 279.5 kJmol⁻¹). Both estradiol analogues displayed strong estrogenic activity (pers. comm. Schering, Berlin).

![Chemical Structures](image)

**Scheme 3.6-1**

The receptor affinity data available suggests that low root mean squares (RMS) values does not always correspond to low competitions factors (CFs). Thus, further investigation using a larger population of ring D modified steroid receptor affinity data is necessary in order to establish any trend(s) in structure-activity relationships in this series of compounds. However, it is clear that the 14α-alkyl- and 14α,17α-alkyl bridged analogues of estradiol display higher receptor affinities than the corresponding β-series and, therefore, provides an interesting basis on which structure-activity principles can be built.
4. EXPERIMENTAL

All melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Specific rotations ([α]D) were determined in chloroform, unless otherwise specified, using a Perkin-Elmer 141 polarimeter and are recorded in units of 10⁻¹ deg cm² g⁻¹. Infrared spectra were recorded in chloroform using a Perkin-Elmer 983 spectrophotometer. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a Varian VXR-200 (4.7T) or a Varian Unity (9.4T) spectrometer, for solutions in deuteriochloroform, unless otherwise specified. Tetramethylsilane (TMS) was used as internal standard. The chemical shifts (δ) are given in ppm relative to TMS (δ 0.00). Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded on a Varian VXR-200, 50 MHz and Varian Unity, 100 MHz, for solutions in deuteriochloroform, unless otherwise specified. The chemical shifts (δ) are given in ppm relative to the TMS signal which was centred at δ 0.00. The following abbreviations have been used in the ¹H and ¹³C NMR spectra: s, singlet; d, doublet; dd, doublet of doublet of doublets; t, triplet; q, quartet; m, multiplet; qd, quartet of doublets; dt, doublet of triplets; td, triplet of doublets; tt, triplet of triplets; ddt, doublet of doublet of triplets; br, broad; obs., obscured; exch., exchange, Wv, peak width(Hz) at half height and J, coupling constant(Hz). Elemental analyses were performed using a Heraus CHN-rapid combustion analyser. Mass spectra were recorded on a VG micromass 16F mass spectrometer (operating at 70 eV with an accelerating voltage of 4kV). All reactions were monitored by thin-layer chromatography (TLC) using Merck F₂₅₄ precoated silica gel plates. Detection was done using an ultraviolet lamp (wavelength 254 nm) and by heating the plate at 200°C after spraying with a 1% solution of ceric ammonium sulfate in 3 M sulfuric acid. Column chromatography
was carried out on silica gel and the eluent mixture used are specified in each experiment.

Commonly used solvents were purified and dried as follows:

**Tetrahydrofuran:** Dried over sodium wire and then distilled from sodium and benzophenone under argon immediately before use.

**Methanol:** Distilled from magnesium powder under nitrogen and stored over 3Å molecular sieves.

**Benzene, toluene and xylene:** Distilled from sodium wire under nitrogen and stored over sodium wire.

**Triethylamine and pyridine:** Distilled from potassium hydroxide under nitrogen and stored over potassium hydroxide pellets.

**Dichloromethane:** Distilled from phosphorus pentoxide and stored over 4Å molecular sieves.

**Ether:** Distilled from sodium wire under nitrogen immediately before use.

**Ethyl acetate:** Washed with saturated aqueous sodium carbonate and brine, dried over sodium sulfate, and distilled.

**Dimethyl sulfoxide and N,N-dimethylformamide:** Distilled from calcium hydride under reduced pressure, and stored over 4Å molecular sieves.
'Standard work-up' refers to procedures in which the reaction mixture was extracted with the solvent in parenthesis, washed successively with brine and water, dried over anhydrous magnesium sulfate and evaporated on a Buchi Rotary Evaporator.
3-Methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (76).

The dienyl acetate (76) was prepared according to literature procedures. Rigorous drying of all solvents and inorganic salts was very important to ensure reproducible yields. Crystallisation of the product from acetone-hexane gave the dienyl acetate (76), followed by filtration of the mother liquor through silica gel (200 g), to give a combined yield of (14.6 g, 64%), m.p. 123-125°C (lit., m.p. 123-125°C).

3-Methoxy-16α-phenylsulfonyl-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate (78)

A mixture of dienyl acetate (76) (10 g, 28.4 mmol) and phenyl vinyl sulfone (6.3 g, 37.5 mmol) in xylene (18 ml) was heated in a sealed tube at 145°C for 72 h. Direct chromatography of the product mixture on silica gel (800 g) [toluene-ethyl acetate (19:1)] gave the sulfone (78) (12.2 g, 87%), m.p. 180-183°C (from benzene-hexane) (lit., 180-181.5°C).

3-Methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol (81)

The sulfone (78) (4.2 g, 8.56 mmol) in dry tetrahydrofuran (100 ml) was added to a solution of sodium metal (4.0 g, 0.174 mol) in dry liquid ammonia (1000 ml) and dry tetrahydrofuran (345 ml). The mixture was stirred for 2 h, then solid ammonium chloride was added. The ammonia was evaporated at atmospheric pressure and the residual tetrahydrofuran was evaporated under reduced pressure. Standard work-up (chloroform) gave a crystalline residue (2.3 g). Filtration of the residue through silica gel (46 g) [toluene-ethyl acetate (20:1)] gave the 14,17α-etheno bridged alcohol (81) (2.1 g, 79%), m.p. 149-154°C (from benzene-hexane) (lit., m.p. 151-152°C). The product was contaminated with an inseparable amount of (171R)-3-methoxy-14,17α-ethano-16α,171-cycloestra-1,3,5(10)-trien-17β-ol (80) as an inseparable impurity, which was quantified in a subsequent experiment.
Hydroxylation of the 14,17α-Etheno compound (81)

Osmium tetroxide (1.2 g, 4.73 mmol) was added to a solution of the compound (81) [containing unseparated cyclopropyl alcohol (80)] (1.2 g, 3.87 mmol) in pyridine (72 ml), and the mixture was stirred at 25°C for 18 h. Aqueous sodium hydrogen sulfite (10%, 170 ml) was added slowly (20 min) to the cooled reaction mixture, and stirring was continued for 2 h. Extraction with ethyl acetate gave a crystalline residue (1.5 g). Chromatography of the residue on silica gel (120 g) [toluene-ethyl acetate (1:1)-(8:1)] gave the cyclopropyl alcohol (80) (71 mg, 6%), followed by a separable mixture of triols (85) (83%), M+ 344. It was not necessary to separate the triols for our purpose.

3-Methoxy-17-oxoestra-1,3,5(10)-triene-14-carbaldehyde (87).

Aqueous sodium periodate (6%, 38 ml) was added to a stirred solution of the triols (85) (762 mg, 2.22 mmol) in absolute ethanol (60 ml) and the mixture was stirred at 25°C for 1 h. Extraction with ethyl acetate gave, after evaporation of the solvent, a crystalline residue which was recrystallised from methanol to give the 14α-formyl 17-ketone (87) (284 mg, 41%), m.p. 171-172°C (from ethyl acetate) (lit., 49 m.p. 171-173°C). The mother-liquor residue was chromatographed on silica gel (8 g) [toluene-ethyl acetate (100:1)] and gave further 14α-formyl 17-ketone (87) (131 mg, 19%). Further elution gave more polar organic residues which was once again treated with aqueous sodium periodate, resulting in variable amounts (<5%) of the 14α-formyl 17-ketone (87) after purification.

14-Hydroxymethyl-3-methoxyestra-1,3,5(10)-tri-en-17-one (88/214).

a) Lithium tri(s-butyl)borohydride (1 M in tetrahydrofuran; 0.77 ml) was added to stirred solution of the 14α-formyl 17-ketone (87) (200 mg, 0.64 mmol) in dry tetrahydrofuran (10 ml) at 0°C under nitrogen. After 1 h at 0°C, water was added
(3 ml), followed by cold hydrogen peroxide (30%, 7 ml) and 6 M sodium hydroxide (4.5 ml), and the mixture was stirred for a further 2 h. Standard work-up (ethyl acetate) gave a crystalline residue (230 mg), which was recrystallised from acetone-hexane to give 14-hydroxymethyl 17-ketone (88/214) (195 mg, 97%), m.p. 164-167°C (from acetone-hexane), [lit.,49 m.p. 164-166°C (from acetone-hexane)].

b) A solution of the 14α-formyl 17-ketone (87) (650 mg, 2.1 mmol) in a mixture of 2-propanol (60 ml) and water (10 ml), was treated with cerium trichloride heptahydrate (780 mg). The mixture was stirred at 0°C for 10 min, followed by the addition of sodium borohydride (119 mg, 3.5 mmol). The mixture was stirred for a further 15 min, after which excess sodium borohydride was destroyed with acetone (5 ml). Standard work-up (ethyl acetate) gave crystalline residue (655 mg). Chromatography of the residue on silica gel (66 g) [ethyl acetate-toluene (3:7)] gave the 14-hydroxymethyl 17-ketone (88/214) (630 mg, 97%), m.p. 160-164°C (from benzene-hexane), [lit.,49 m.p. 164-166°C (from acetone-hexane)]; (Found: C, 76.8; H, 8.5%; M+, 314. C20H36O3 requires C, 76.4; H, 8.3%; M, 314).

14- (Toluene-p-sulfonyloxy) methyl-3-methoxyestra-1,3,5(10)-trien-17-one (176).
A solution of the 14-hydroxymethyl 17-ketone (214) (705 mg, 2.26 mmol) and toluene-p-sulfonyl chloride (2.14 g, 11.2 mmol) in pyridine (10 ml) was stirred at 20°C under nitrogen for 13 h. Water (40 ml) was added, followed by extraction with ethyl acetate. The extract was washed with hydrochloric acid (10%; 3 x 25 ml), saturated aqueous sodium hydrogen carbonate and brine (1 x 25 ml), dried (MgSO4) and concentrated under reduced pressure to give an oily residue (1.06 g). Filtration of the residue through silica gel (10 g) [ethyl acetate toluene (1:4)] gave 14-(toluene-p-sulfonyloxy)methyl 17-ketone (176) as a colourless foam (952 mg, 90%); \(\nu_{\max} \) 1730(C=O) and 1305(S=O) cm\(^{-1}\); \(\delta_H \) 1.01 (3H, s, 13β-Me), 2.42 (3H, s, SO3C6H4CH3), 3.55 and 4.35 (each 1H, d, J 11.5 Hz, 14α-H2), 3.76 (3H, s, 3-OMe),
6.58-7.16 (3H, m, 1-, 2- and 4-H), and 7.28-7.76 (4H, m, -SO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}CH\textsubscript{3}) (Found: C, 69.2; H, 6.6%; \textit{M}+ 468. C\textsubscript{27}H\textsubscript{32}O\textsubscript{5}S requires C, 69.2; H, 6.8%; \textit{M}, 468).

\textbf{Samarium(II) diiodide reduction of the 14-(toluene-p-sulfonyloxy)methyl 17-ketone (176).}

Samarium metal (54 mg, 0.36 mmol) was flame dried under a flow of nitrogen for 5 min, then cooled. Dry tetrahydrofuran (1 ml) was added, followed by diiodoethane (91 mg, 0.32 mmol) and the mixture was stirred at 20°C for 1 h. A solution of the 14-(toluene-p-sulfonyloxy)methyl 17-ketone (176) (92 mg, 0.2 mmol) in dry tetrahydrofuran (1 ml) was added to the deep blue solution of samarium(II) iodide at -78°C. The reaction mixture was stirred at -78°C under nitrogen for 2 h, then equilibrated to 20°C. Addition of saturated aqueous sodium hydrogen carbonate prior to extraction, prevents emulsification. Standard work-up (diethyl ether) gave an oily residue (71 mg). Chromatography of the residue on silica gel (2 g) [ethyl acetate-toluene (1:4)] gave 3-methoxy-17a-homoestra-1,3,5(10),14-tetraen-17a-one (179) (6 mg, 10%), m.p. 137-140°C (from methanol), [lit.,89 m.p. 137-139°C (from methanol)], \textit{M}+ 296, followed by at least six more polar products, which was not isolated.

\textbf{3-Methoxy-17a-homoestra-1,3,5(10),14-tetraen-17a-one (179).}

A solution of the 14-(toluene-p-sulfonyloxy)methyl 17-ketone (176) (256 mg, 0.55 mmol) and sodium iodide (246 mg, 5.6 mmol) in diglyme (6 ml) was heated at 100°C under nitrogen. The mixture was stirred for 28 h, cooled, followed by extraction with ethyl acetate. The extract and washed with aqueous sodium thiosulfate (1x20 ml, 10%), saturated aqueous sodium hydrogen carbonate, brine, dried (MgSO\textsubscript{4}) and concentrated under reduced pressure to give a crystalline residue (171 mg). Filtration of the residue through silica gel (3.5 g) [toluene] gave the 17a-homosteroid (179) (136 mg, 83%), m.p. 132-135°C (from chloroform-
methanol), [lit., 89 m.p. 137-139°C (from methanol)]; \([\alpha]_D + 115^\circ \text{ (c 1.0)}\), [lit., \(89^\circ\) \(\text{c} 0.52\)]; \(\nu_{\text{max}} 1704(\text{C} = \text{O})\) and 1607(\(\text{C} = \text{C}\)) \(\text{cm}^{-1}\); \(\delta_{11}(\text{C}_6\text{D}_6)\) 1.18 (3H, s, 13\(\beta\)-Me), 2.70 (2H, m, 6-H\(_2\)), 3.43 (3H, s, 3-OMe), 5.26 (1H, dd, \(J 4.1\) and 2.8 Hz, 15-H), 6.69 (1H, d, \(J 2.7\) Hz, 4-H), 6.81 (1H, dd, \(J 8.7\) and 2.7 Hz, 2-H), 7.08 (1H, d, \(J 8.7\) Hz, 1-H); \(\delta_{13c} 215.8\) (C-17a), 157.6 (C3), 146.1 (C-14), 137.6 (C-5), 131.9 (C-10), 127.1 (C-1), 116.2 (C-15), 113.6 (C-4), 112.0 (C-2), 55.2 (3-OMe), 48.1 (C-13), 44.6 (C-8), 40.4 (C-9), 35.7 (C-17), 35.1 (C-16), 30.4 (C-6), 27.5 (C-12), 25.9 (C-7), 25.3 (C-11), and 22.4 (C-18) (Found: C, 80.9; H, 8.2%; \(M^+\), 296. \(\text{C}_{20}\text{H}_{24}\text{O}_2\) requires C, 81.0; H, 8.2%; \(M^+\), 296).

3-Methoxy-17a-homoestra-1,3,5(10),14-tetraen-17a\(\xi\)-ol (181) and (182).

(a) A solution of the 17a-homosteroi (179) (50 mg, 0.17 mmol) in dry tetrahydrofuran (2.5 ml) was treated with lithium aluminium hydride (32 mg, 0.85 mmol) at 20°C under nitrogen. The mixture was stirred for 7 min, followed the addition of saturated aqueous ammonium chloride. Standard work-up (ethyl acetate) gave an oily residue (49 mg). Filtration of the residue through silica gel (1 g) [ethyl acetate-toluene (1:4)] gave an inseparable mixture of 3-methoxy-17a-homoestra-1,3,5(10),14-tetraen-17a\(\xi\)-ol (181) and 3-methoxy-17a-homoestra-1,3,5(10),14-tetraen-17a\(\beta\)-ol (182) (48 mg, 96%); \(\nu_{\text{max}} 3250(\text{OH})\) \(\text{cm}^{-1}\); \(\delta_{11} 1.09\) \(\text{[}2.1\text{H}, \text{s}, 13\beta\)-Me of (182)\], 1.14 \(\text{[}0.9\text{H}, \text{s}, 13\beta\)-Me of (181)\], 2.88 (2H, m, 6-H\(_2\)), 3.52-3.62 (1H, m, 17a\(\alpha\)-H of (182) and 17a\(\beta\)-H of (181)), 3.78 (3H, s, 3-OMe), 5.35 \(\text{[}0.7\text{H}, \text{dd,} J 3.4\) and 2.6 Hz, 15-H of (182)\], 5.40 \(\text{[}0.3\text{H}, \text{dd,} J 3.5\) and 2.8 Hz, 15-H of (181)\], 6.63 (1H, d, \(J 2.8\) Hz, 4-H), 6.73 (1H, dd, \(J 8.6\) and 2.8 Hz, 2-H), and 7.24 (1H, d, \(J 8.6\) Hz, 1-H) (Found: \(M^+\), 298. \(\text{C}_{20}\text{H}_{26}\text{O}_2\) requires \(M\), 298).

(b) A solution of the 17a-homosteroi (179) (54 mg, 0.18 mmol) in dry tetrahydrofuran (3 ml) was treated with lithium tri(s-butyl)borohydride (L-selectride) (1 M in tetrahydrofuran, 0.55 mmol) at 0°C under nitrogen. After stirring for 15 min, water (1 ml) was added, followed by cold hydrogen peroxide (30%, 3 ml)
and sodium hydroxide (6 M, 2.3 ml) and the mixture was stirred for a further 2 h. Standard work-up (ethyl acetate) gave an oily residue (49 mg). Filtration of the residue through silica gel (1 g) [ethyl acetate-toluene (1:9)] gave an inseparable mixture of alcohols (181) and (182) (1.5:1) (43 mg, 80%)

3-Methoxy-17α-homoestra-1,3,5(10),14-tetraen-17α-yl acetate (183) and (184).
Alcohols (181) and (182) (46 mg, 0.16 mmol), derived from L-selectride reduction, was treated with acetic anhydride (1 ml, 10.6 mmol) and pyridine (1.1 ml) at 20°C under nitrogen. After stirring for 7 h, ice and solid sodium hydrogen carbonate was added, followed by extraction with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate, dried (MgSO₄) and concentrated under reduced pressure to give an oily residue (42 mg). Chromatography of the residue on silica gel (2 g) [toluene] gave an inseparable mixture of 17α-acetates, 3-methoxy-17α-homoestra-1,3,5(10),14-tetraen-17α-yl acetate (184), and 3-methoxy-17α-homoestra-1,3,5(10),14-tetraen-17β-yl acetate (183), (34 mg, 65%) m.p. 138-142°C (ethyl acetate-hexane); [α]D +31° (c 0.46); νmax 1721 (C=O) cm⁻¹; δH 1.14 ['1.8H', s, 13β-Me of (183)], 1.25 ['1.2H', s, 13β-Me of (184)], 2.08 and 2.09 [3H, s, 17α-OAc of (183) and 17β-OAc of (184)], 2.89 (2H, m, 6-Hz), 3.77 (3H, s, 3-OMe), 4.80 [0.4H', dd, J 9.8 and 5.6 Hz, 17αα-H of (184)], 4.88 [0.6H', t, J 2 x 4.6 Hz, 17αβ-H of (183)], 5.36 [0.4H', m, W 4.4 Hz, 15-H of (184)], 5.43 [0.6H', dd, J 3.5 and 2.6 Hz, 15-H of (183)], 6.63 (1H, d, J 2.8 Hz, 4-H), 6.72 (1H, dd, J 8.6 and 2.3 H, and 2-H), and 7.22 (1H, d, J 8.6 Hz, 1-H) (Found: C, 77.9; H, 8.1%; M⁺, 340. C22H26O3 requires C, 77.6; H, 8.3%; M, 340).

17α-Homoestra-1,3,5(10),14-tetraene-3,17αβ-diol (185).
A solution of the 3-methyl ether (184) [with a trace of (183)] (61 mg, 0.18 mmol) in toluene (4 ml) was treated with diisobutylaluminium hydride (1.5 M in toluene, 1.2 ml, 1.79 mmol) under nitrogen. The mixture was refluxed for 40 h, cooled,
followed by the addition of hydrochloric acid (10%, 5 ml). Standard work-up (ethyl acetate) gave a crystalline residue. Recrystallisation from ethyl acetate-hexane gave 17α-homoestra-1,3,5(10),14-tetraene-3,17α-diol (185) (38 mg, 75%), m.p. 102-104°C; ν<sub>max</sub> 3292(OH) cm<sup>-1</sup>, (Found: C, 80.5; H, 8.2%; M<sup>+</sup>, 284. C<sub>19</sub>H<sub>24</sub>O<sub>2</sub> requires C, 80.2; H, 8.5%; M, 284).

(17<SUP>1</SUP>S)-3-Methoxy-14,17α-methanoestra-1,3,5(10)-triene-17β,17α-diol (186).

Samarium metal (386 mg, 2.57 mmol) was dried by heating it under a flow of nitrogen for 5 min, then cooled. Dry tetrahydrofuran (4 ml) was added, followed by diiodoethane (542 mg, 2.02 mmol) and the mixture was stirred at 25°C for 1 h. A solution of the 14α-formyl 17-ketone (87) (200 mg, 0.64 mmol) in dry tetrahydrofuran (1.5 ml) was added to the deep blue samarium(II) diiodide solution, followed by t-butyl alcohol (0.3 ml). The mixture was refluxed for 3 h under nitrogen, then cooled, and saturated aqueous sodium hydrogen carbonate (15 ml) was added. The mixture was extracted with ethyl acetate and extract was successively washed with aqueous sodium thiosulfate (10%), and brine, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure, to give a crystalline residue (199 mg).

Filtration of the residue through silica gel (4 g) [ethyl acetate-toluene (1:1)] gave the diol (186) (154 mg, 77%), m.p. 147-150°C (from ethyl acetate-hexane); [α]<sub>D</sub> +35<sup>°</sup> (c 1.1); ν<sub>max</sub> 3613(OH) and 3440(OH) cm<sup>-1</sup>; δ<sub>δ</sub> (400 MHz) 0.83 (3H, s, 13β-Me), 1.14-1.20 (3H, m, 15α-H, 12β-H and 8β-H), 1.34-1.46 (2H, m, 7α-H and 11β-H), 1.56 (1H, ddd, J 10.7, 9.0, and 3.3 Hz, 15β-H), 1.70 (1H, ddd, J 10.7, 9.0 and 3.3 Hz, 16α-H), 1.79-1.90 (3H, m, 16β-, 12α- and 7β-H), 2.23 (1H, ddd, J 13.0, 6.7 and 3.0 Hz, 11α-H), 2.40 (1H, t, J 2 x 11.1 Hz, 9α-H), 2.60 and 3.00 (each 1H, br s exch. by D<sub>2</sub>O, 17β- and 17<sup>1</sup>-OH), 2.76 (2H, m, 6-H<sub>2</sub>), 3.70 (3H, s, 3-OMe), 4.09 (1H, s, 17<sup>1</sup>-H), 6.54 (1H, d, J 2.6 Hz, 4-H), 6.63 (1H, dd, J 8.6 and 2.6 Hz, 2-H) and 7.13 (1H, d, J 8.6 Hz, 1-H); δ<sub>C</sub> (100.6 MHz) 157.5 (C-3), 138.0 (C-5), 132.5 (C-10), 126.4 (C-1), 113.9 (C-4), 111.4 (C-2), 81.8 (C-17), 73.5 (C-17<sup>1</sup>), 55.2 (3-OMe), 49.6 (C-14), 40.8 (C-13), 40.3...
(17S)-14,17α-Methanoestra-1,3,5(10)-triene-3,17β,17α-triol (187).

A solution of the 3-methyl ether (186) (65 mg, 0.21 mmol) in toluene (1 ml) was treated with diisobutylaluminium hydride (1.5 M in toluene; 1.4 ml, 2.1 mmol) at reflux under nitrogen for 4 h. Hydrochloric acid (10%; 20 ml) was added to the cooled mixture. Standard work-up (ethyl acetate) gave a crystalline residue (51 mg). Chromatography of the residue on silica gel (3 g) [ethyl acetate-toluene (4:1)] gave the estriol (187) (49 mg, 79%), m.p. 272-274°C (from chloroform-methanol);

\[ \delta_{\text{D}} +14^\circ (c 0.5) \]

(Found: \( M^+ \), 300.170 C19H24O3 requires \( M \), 300.173).

(17S)-3-Methoxy-14,17α-methanoestra-1,3,5(10)-triene-17β,17α-diyldiacetate (188).

The 17β,17α-diol (186) (327 mg, 1.04 mmol) was treated with acetic anhydride (1.6 ml) and pyridine (1.8 ml) at 24°C under nitrogen for 10 h. Ice and solid sodium hydrogen carbonate was added, followed by standard work-up, to give a oily residue (450 mg). Filtration of the residue through silica gel (5 g) [ethyl acetate-toluene (1:10)] gave the diacetate (188) (356 mg, 86%), as an oil; \( \delta_{\text{D}} +74^\circ (c 1.4) \);

\( \nu_{\text{max}} \) 1732(C=O) cm\(^{-1}\); \( \delta_{\text{H}} \) 1.04 (3H, s, 13β-Me), 2.01 and 2.03 (each 3H, s, 17β-and 17α-OAc), 2.34 (1H, ddd, \( J \) 13.2, 7.0 and 3.4 Hz, 11α-H), 2.63 (1H, t, \( J \) 2 x 11.7 Hz, 9α-H), 2.80 (2H, m, 6-H\(_2\)), 3.77 (3H, s, 3-OMe), 5.47 (1H, s, 17α-H), 6.61 (1H, d, \( J \) 2.8, 4-H), 6.70 (1H, dd, \( J \) 8.6 and 2.8 Hz, 2-H) and 7.22 (1H, d, \( J \) 8.6 Hz, 1-H);

\( \delta_{\text{C}} \) 170.4, 169.9 (17- and 17α-OAc), 157.5 (C-3), 137.8 (C-5), 132.2 (C-10), 126.5 (C-1), 113.8 (C-4), 111.6 (C-2), 84.5 (C-17), 72.0 (C-17α), 55.2 (3-OMe), 49.5 (C-14), 41.3 (C-13), 39.8 (C-9), 38.1 (C-8), 29.9 (C-6), 28.2 (C-16), 26.1 (C-7), 24.6 (C-11), 23.3 (C-12 and C-15), 21.1, (17- and 17α-OAc) and 13.8 (C-18) (Found: \( M^+ \), 398.210. C\(_{24}\)H\(_{30}\)O\(_5\) requires \( M \), 398.209).
(17'S)-3-Methoxy-14,17α-methyl-oestra-1,3,5(10)-trien-17β,17α-diol 17-acetate (189).

Lithium tri(s-butyl)borohydride (L-selectride) (1 M in tetrahydrofuran, 1.22 ml, 1.22 mmol) was added to a solution of the diacetate (188) (323 mg, 0.81 mmol) in dry tetrahydrofuran (10 ml) at -78°C over 10 min. The mixture was stirred at -78°C for 3 h under nitrogen, then aqueous 50% acetic acid (5 ml) was added, followed by standard work-up (ethyl acetate) to give a crystalline residue (330 mg). Filtration of the residue through silica gel (2 g) [ethyl acetate-toluene (3:100 to 1:1)] gave 17β-acetoxy 17α-alcohol (189) (201 mg, 70%), m.p. 137-140°C (from ethyl acetate-hexane); [α]D + 12° (c 1.4); νmax 3507 (OH) and 1712 (C=O) cm⁻¹; δH (400 Hz) 0.97 (3H, d, J 0.6 Hz, 13β-CH₃), 1.22-1.34 (3H, m, 8β-, 11β- and 15α-H), 1.48-1.62 (3H, m, 7α-, 12β- and 15β-H), 1.87-1.96 (2H, m, 7β- and 12α-H), 2.06-2.14 (2H, m, 16α- and 16β-H), 2.08 (3H, s, 17β-CH₃), 2.31 (1H, ddd, J 13.5, 7.0 and 3.4 Hz, 11α-H), 2.52 (1H, td, J 2 x 11.7 and 3.4 Hz, 9α-H), 2.83 (2H, m, 6-H₂), 3.50 (1H, br s exh. by D₂O, 17α-OH), 3.77 (3H, s, 3-CH₃), 4.28 (1H, s, 17α-H), 6.63 (1H, d, J 2.8 Hz, 4-H), 6.71 (1H, dd, J 8.6 and 2.8 Hz, 2-H) and 7.21 (1H, d, J 8.6 Hz, 1-H); δc(100.6 MHz) 172.7 (17-CH₃), 157.5 (C-3), 138.2 (C-5), 132.5 (C-10), 126.2 (C-1), 113.8 (C-4), 111.4 (C-2), 86.2 (C-17), 71.5 (C-17α), 55.2 (3-CH₃), 49.1 (C-14), 40.2 (C-13), 40.0 (C-9), 38.4 (C-8), 29.8 (C-6), 28.0 (C-16), 25.9 (C-7), 23.9 (C-11), 23.8 (C-15), 23.4 (C-12), 13.5 (C-18), 21.2 (17-CH₃) (Found: C, 74.1; H, 7.9%; M⁺, 356. C₂₂H₂₄O₄ requires C, 74.1; H, 7.9%; M, 356) followed by the 17β,17α-diol (186) (55 mg, 22%).

(17'S)-3-Methoxy-14,17α-methanoestra-1,3,5(10)-trien-17β,17α-diol 17β-acetate 17α-toluene-p-sulfonate (190).

A solution of the 17β-acetoxy 17α-alcohol (189) (122 mg, 0.34 mmol) and toluene-p-sulfonyl chloride (133 mg, 0.69 mmol) in pyridine (5.5 ml) was stirred at 20°C under nitrogen for 48 h. Water (10 ml) was added, followed by extraction with ethyl
acetate. The extract was successively washed with hydrochloric acid (10%, 3 x 20 ml), saturated aqueous sodium hydrogen carbonate and brine (1 x 20 ml), dried (MgSO₄) and concentrated under reduced pressure to give a crystalline residue (191 mg). Filtration of the residue through silica gel (2 g) [ethyl acetate-toluene (1:9)] gave the 17β-acetoxy 17α-toluene-p-sulfonate (190) (158 mg, 90%), m.p. 94-98°C (from diethyl ether); νmax 1738(CO) and 1308(SO) cm⁻¹; δH(400MHz) 1.04 (3H, s, 13β-Me), 1.20 (3H, m, 11β-H, 15α-H, 8β-H and 7α-H), 1.52 (1H, dt, J 14.2 and 2 x 3.3 Hz, 12β-H), 1.70 (1H, ddd, J 12.4, 9.2 and 3.4 Hz, 16α-H), 1.79 (3H, s, 17β-OAc), 1.80 obsc. (1H, m, δν 24.5 Hz, 7β-H), 1.91 (1H, td, J 2 x 14.2 and 3.9 Hz, 12α-H), 2.01 (1H, ddd, J 12.4, 9.2 and 3.4 Hz, 15βH), 2.18 (1H, dddd, J 12.4, 9.2, 3.4 and 1.6 Hz, 16α-H), 2.30 (1H, ddd, J 11.5, 6.9 and 3.4 Hz, 11α-H), 2.39 (3H, s, SO₃-C₆H₄CH₃), 2.47 (1H, td, J 2 x 11.7 and 3.4 Hz, 9α-H), 2.77 (2H, m, 6-H₂), 3.76 (3H, s, 3-OMe), 4.97 (1H, s, 17β-H), 6.60 (1H, d, J 2.9 Hz, 4-H), 6.70 (1H, dd, J 8.7 and 2.9 Hz, 2-H), 7.17 (1H, d, J 8.7 Hz, 1-H) and 7.29-7.81 (4H, m, SO₃-C₆H₄CH₃) (Found: M⁺ 510.207. C₂₉H₃₄O₆S requires; M, 510.208).

(17S)-3-Methoxy-14,17α-methanoestra-1,3,5(10)-triene-17β,17α-diol 17β-acetoxy 17α-methyl xanthate (191).

Sodium hydride (40 mg, 50% suspension in oil, 0.83 mmol) was added to a solution of the 17β-acetoxy 17α-alcohol (189) (107 mg, 0.30 mmol) in N,N-dimethylformamide (1 ml), followed by carbon disulfide (1 ml). The mixture was stirred at 25°C under nitrogen for 30 min. Methyl iodide (2 ml) was added and the mixture was stirred for a further 30 min, then water (10 ml) was added and the resultant mixture was extracted with ethyl acetate. The extract was successively washed with aqueous sodium thiosulfate (10%) and water, dried (MgSO₄) and concentrated under reduced pressure, to give a yellow crystalline residue (131 mg). Chromatography of the residue on silica gel (8 g) [ethyl acetate toluene (1:9)] gave the 17β-acetoxy 17α-methyl xanthate (191) (100 mg, 75%), m.p. 158-161°C (from
Diethyl ether; $[\alpha]_D + 172^\circ$ (c 2.6); $\nu_{\text{max.}}$ 1738 (C=O) and 1066 (C=S) cm$^{-1}$;

$\delta$H(200 MHz) 1.08 (3H, s, 13β-Me), 1.62 (1H, dt, J 14.1 and 2 x 3.5 Hz, 12β-H), 2.36 (1H, ddd, J 13.1, 6.9 and 3.5 Hz, 11α-H), 2.02 (3H, s, 17β-OAc), 2.59 (3H, s, OCSMe), 2.66-2.84 (2H, m, 9α-H and 6-H2), 6.36 (1H, s, 171-H), 6.60 (1H, d, J 2.8 Hz, 4-H), 6.71 (1H, dd, J 8.7 and 2.8 Hz, 2-H) and 7.22 (1H, d, J 8.7 Hz, 1-H);

$\delta$C(50 MHz) 214.8 (C=S), 169.8 (17-OAc), 157.5 (C-3), 137.9 (C-5), 132.2 (C-10), 126.5 (C-1), 113.8 (C-4), 111.5 (C-2), 84.8 (C-17), 80.6 (C-171), 55.2 (3-OMe), 51.2 (C-14), 41.2 (C-13), 39.8 (C-9), 38.0 (C-8), 29.9 (C-6), 28.4 (C-16), 26.1 (C-7 and C-15), 24.9 (C-12), 23.7 (C-11), 21.1 (17-OAc), 18.6 (S-Me) and 13.8 (C-18), (Found: C, 64.6; H, 6.9%; $M^+$, 446. C$_{24}$H$_{30}$O$_4$S$_2$ requires C, 64.5; H, 6.8%; $M$, 446).

Tris(trimethylsilyl)silane.

Lithium metal (3.76 g) was added to chlorotrimethylsilane (27.6 ml; 23.6 g, 0.217 mol) in dry tetrahydrofuran (50 ml). Silicon tetrachloride (7.5 g, 0.044 mol) in dry tetrahydrofuran (40 ml) was added slowly over 6 h. The mixture was stirred at 20°C under nitrogen for 28 h. Unreacted lithium and insoluble salts were removed by filtration (under nitrogen atmosphere) and immediately deactivated with 95% ethanol. The homogeneous dark brown filtrate was treated with crushed ice and acidified with hydrochloric acid (10%). The organic layer was separated and dried (MgSO$_4$) and concentrated under reduced pressure to give a product (15.9 g) (colourless, waxy-solid). Filtration of the residue through alumina (160 g) using petroleum ether (b.p. 60-70°C) as eluent, gave tetrakis(trimethylsilyl)silane (13.44 g, 95%).

Methyllithium (29 ml, 1.5 M in diethyl ether) was added dropwise to tetrakis(trimethylsilyl)silane (12.4 g) dissolved in a mixture of dry tetrahydrofuran (50 ml) and diethyl ether (10 ml), while stirring at 20°C under nitrogen. The mixture was stirred for 24 h, followed by the addition of ice cold hydrochloric acid (10%, 20 ml) (with care!). The mixture was extracted with diethyl ether and the
extract was washed with saturated aqueous sodium hydrogen carbonate, dried (MgSO₄) and concentrated under reduced pressure, to give a product (8.62 g). Distillation gave tris(trimethylsilyl)silane (5.4 g, 55%), b.p. 60°C/1.25 mmHg (lit., b.p. 38°C/1 mmHg).

3-Methoxy-14,17α-methanoestra-1,3,5(10)-trien-17β-yl acetate (192)

A solution of the xanthate (191) (95 mg, 0.21 mmol) in xylene (5 ml) was treated with tris(trimethylsilyl)silane (533 mg, 2.13 mmol). Azobisisobutyronitrile (140 mg, 0.85 mmol) was added in small portions over a period of 24 h at reflux under nitrogen. The reaction mixture was allowed to cool and was then directly chromatographed on silica gel (10 g) [ethyl acetate-hexane (1:9)], to give 14,17α-methano 17β-acetate (192) (9 mg, 12%), m.p. 84-86°C (from diethyl ether-hexane); [α]D -25° (c 1.38); νmax. 1727 (C = O) cm⁻¹; δH(400 MHz) 0.95 (3H, d, J 0.8 Hz, 13β-Me), 1.22-1.42 (4H, m, 7α-, 8β- and 11β-H and 15β-H), 1.54 (1H, dt, J 14.2 and 2 x 3.3 Hz, 12β-H), 1.63 (1H, d, J 7.2 Hz, 171-Hs*), 1.75 (1H, td, J 2 x 10.2 and 3.6, 16α-H), 1.82-1.91 (2H, m, 7β-H and 16β-H), 2.01 (3H, s, 17β-OAc), 2.02-2.12 (1H, m, 12α-H and 15α-H), 2.22 (1H, dt, J 7.2 and 2 x 3.3 Hz, 171-Hr*), 2.30 (1H, ddd, J 13.3, 6.9 and 3.3 Hz, 11α-H), 2.40 (1H, t, 2 x 11.8 Hz, 9α-H), 2.83 (2H, m, 6-H₂), 3.76 (3H, s, 3-OMe), 6.62 (1H, d, J 2.8 Hz, 4-H), 6.70 (1H, dd, J 8.7 and 2.8 Hz, 2-H), and 7.22 (1H, d, J 8.7 Hz, 1-H); δC(100.6 Hz) 170.5 (17-OAc), 157.5 (C-3), 138.1 (C-5), 132.7 (C-10), 126.3 (C-1), 113.8 (C-4), 111.4 (C-2), 82.4 (C-17), 55.2 (3-OMe), 47.0 (C-14), 46.6 (C-13), 40.1 (C-9 and C-171), 38.7 (C-8), 29.6 (C-6), 28.6 (C-15), 28.5 (C-16), 27.0 (C-12), 26.0 (C-7), 23.6 (C-11), 21.5 (17-OAc), and 14.7 (C-18) (Found: M⁺, 340.203. C₂₂H₂₈O₃ requires M, 340.204), followed by 17β-acetoxyl 17α-alcohol (189) (57 mg, 75%) S* = pro-S; R* = pro-R
3-Methoxy-14,16α-methanoestra-1,3,5(10)-trien-17-one (193).

a) Sodium hydride (298 mg, 60% suspension in oil, 7.5 mmol) was added to a solution of the 14-(toluene-p-sulfonyloxy)methyl 17-ketone (176) (349 mg, 0.75 mmol) in dry tetrahydrofuran (4 ml). After refluxing for 2 h under nitrogen, aqueous saturated ammonium chloride was added. Standard work-up (chloroform) gave a crystalline residue (245 mg). Filtration of the residue through silica gel (5 g) [ethyl acetate-toluene (1:19)] gave 14,16α-methano 17-ketone (193) (200 mg, 91%), m.p. 133-137°C (from diethyl ether); [α]D +102° (c 1.0); νmax 1744(C=O) cm⁻¹; δH(400 Hz) 1.13 (3H, s, 13β-Me), 1.46-1.60 (2H, m, 7α-and 11β-H), 1.60 (1H, td, J 2 x 10.8 and 2.3 Hz, 8β-H), 1.73 (1H, dt, J 13.9 and 2 x 4.0 Hz, 12β-H), 1.80-1.87 (2H, m, 7β- and 12α-H), 1.82 obsc. (1H, dd, J 10.0 and 6.2 Hz, 161-Hr), 1.86 obsc. (1H, dd, J 10.0 and 6.2 Hz, 15β-H), 1.92 (1H, dd, J 6.2 and 2.7 Hz, 161-Hr), 2.08 (1H, dd, J 6.2 and 2.7 Hz, 15α-H), 2.31-2.40 (2H, m, 9α- and 11α-H), 2.81 (1H, t, J 2 x 2.7 Hz, 16β-H), 2.90 (2H, m, 6-H₂), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, J 2.7 Hz, 4-H), 6.73 (1H, dd, J 8.6 and 2.7 Hz, 2-H), and 7.21 (1H, d, J 8.6 Hz, 1-H), δC(100.6 MHz) 219.0 (C-17), 157.6 (C-3), 137.7 (C-5), 131.7 (C-10), 126.8 (C-1), 113.8 (C-4), 111.8 (C-2), 55.8 (C-14), 55.2 (3-OMe), 52.0 (C-16), 46.3 (C-13), 39.1 (C-9), 37.7 (C-15), 37.5 (C-8), 37.0 (C-16'), 30.0 (C-6), 29.4 (C-12), 26.7 (C-7), 24.9 (C-11), and 16.0 (C-18) (Found: C, 81.2; H, 8.4%; M*, 296. C20H24O2 requires C, 81.0; H, 8.2%; M, 296).

b) Lithium acetylide ethylenediamine (23 mg, 0.25 mmol) was added to a solution of the 14-(toluene-p-sulfonyloxy)methyl 17-ketone (176) (96 mg, 0.21 mmol) in dimethyl sulfoxide at 25°C under nitrogen. After stirring for 1.5 h, aqueous saturated ammonium chloride was added. Standard work-up (chloroform) gave crystalline residue (66 mg). Chromatography of the residue on silica gel (2 g) [ethyl acetate-toluene (1:9)] gave 14,16α-methano 17-ketone (193) (55 mg, 84%).
3-Methoxy-14,16α-methanoestra-1,3,5(10)-trien-17β-ol (194) and (195).

A solution of the 14,16α-methano 17-ketone (193) (58 mg, 0.2 mmol) in 2-propanol (1 ml) was treated with sodium (70 mg) in small portions over 20 min at reflux. After refluxing for 40 min, the mixture was cooled to 0°C, followed by the addition of methanol (3 ml) and saturated aqueous ammonium chloride. Standard work-up (chloroform) gave a crystalline residue (53 mg). Chromatography of the residue on silica gel (5 g) [ethyl acetate-toluene (1:9)] gave an inseparable mixture of 3-methoxy-14,16α-methanoestra-1,3,5(10)-trien-17β-ol (194) and (195) (43 mg, 74%), m.p. 130-134°C (from diethyl ether); [α]D +86° (c 0.9); νmax. 3301(OH) cm⁻¹; δH 0.90 [1.5H’, s, 13β-Me of (195)], 1.00 [1.5H’, d, J 0.6 Hz, 13β-Me of (194)], 1.48 (1H, br s exch. with D2O, 17β-OH), 2.74 (2H, m, 6-H2), 3.70 (3H, s, 3-MeO), 3.86 (0.5H’, d, J 1.0 Hz, 17β-H), 3.96 (0.5H’, t, J 2 x 1.6 Hz, 17β-H), 6.55 (1H, d, J 2.8 Hz, 4-H), 6.64 (1H, dd, J 8.6 and 2.8 Hz, 2-H), 7.14 (0.5H’, d, J 8.6 Hz, 1-H) and 7.16 (0.5H’, d, J 8.6 Hz, 1-H) (Found: C, 80.2; H, 8.6%; M⁺, 298. C20H26O2 requires C, 80.5; H, 8.8%; M, 298).

3-Hydroxy-14,16α-methanoestra-1,3,5(10)-trien-17-one (196)

Sodium iodide (154 mg, 1.03 mmol) was added to a solution of the 3-methyl ether (193) (76 mg, 0.25 mmol) and chlorotrimethylsilane (0.143 ml, 1.03 mmol) in acetonitrile (5 ml). After refluxing under nitrogen for 16 h, the reaction mixture was cooled. Standard work-up (ethyl acetate), including a sodium thiosulfate wash gave a crystalline residue (65 mg). Chromatography of the residue on silica gel (1 g) [ethyl acetate-toluene (1:9)] gave 3-hydroxy-14,16α-methanoestra-1,3,5(10)-trien-17-one (196) (59 mg, 82%), m.p. 268-272°C (from chloroform); νmax. 3593(OH) and 1744(C=O) cm⁻¹; δH(400 MHz) 1.13 (3H, d, J 0.73 Hz, 13β-Me), 1.45-1.57 (2H, m, 7α- and 11β-H), 1.64 (1H, td, J 2 x 12.0 and 2.3 Hz, 8β-H), 1.76 (1H, dt, J 13.0 and 2 x 3.3 Hz, 12β-H), 1.82 (1H, dd, J 10.0 and 6.2 Hz, 16α-Hα, 18.6 Hz, 16β-Hβ, 18.6 Hz, 16β-Hβ), 1.91 (1H, dd, J 6.2 and 2.7 Hz, 16β-Hβ, 2.08 (1H, dd, J 6.2 and
2.7 Hz, 15α-H), 2.30-2.38 (2H, m, 9α- and 11α-H), 2.81 (1H, t, $J = 2 \times 2.7$ Hz, 16β-H), 2.85 (2H, m, 6-H2), 4.81 (1H, br s, 3-0H), 6.58 (1H, d, $J = 2.8$ Hz, 4-H), 6.64 (1H, dd, $J = 8.4$ and 2.8 Hz, 2-H) and 7.16 (1H, d, $J = 8.4$ Hz, 1-H) (Found: $M^+$, 282.163. $C_{19}H_{22}O_2$ requires; $M$, 282.162).

$S^* = \text{pro-S; } R^* = \text{pro-R}$

3-Methoxy-14,16α-methano-19-nor-17β-pregna-1,3,5(10)-trien-20-yne-17-ol (197) and (198).

Lithium acetylide ethylenediamine (46 mg, 0.5 mmol) was added to a solution of the 14-(toluene-p-sulfonyloxy)methyl 17-ketone (176) (116 mg, 0.25 mmol) in dimethyl sulfoxide at 25°C. The mixture was stirred under nitrogen for 1.5 h, followed by the addition of aqueous saturated ammonium chloride. Standard work-up (chloroform) gave a crystalline residue (80 mg). Chromatography of the residue on silica gel (2 g) [ethyl acetate-toluene (1:9)] gave an inseparable mixture (1:1) of 3-methoxy-14,16α-methano-19-nor-17α-pregna-1,3,5(10)-trien-20-yne-17-ol (197) and 3-methoxy-14,16α-methano-19-nor-17β-pregna-1,3,5(10)-trien-20-yne-17-ol (198) (67 mg, 81%); $\nu_{\text{max}}$ 3625(OH), 3431(OH) and 2460(C=O) cm$^{-1}$; $\delta_H$ 1.06 ['1.5H', d, $J = 0.7$ Hz, 13β-Me of (198)], 1.21 ['1.5H', d, $J = 0.6$ Hz, 13β-Me of (197)], 1.84 obs. (1H, dd, $J = 10.3$ and 7.3 Hz, 15β-H), 1.98 ['0.5H', br s exch. by D$_2$O, 17β-OH of (197)], 2.20 ['0.5H', s, 17α-OH of (198)], 2.59 ['0.5H', s, 17α-C=CH of (198)], 2.60 ['0.5H', s, 17β-C=CH of (197)], 2.52 (1H, t, $J = 2 \times 2.8$ Hz, 16β-H), 2.82 (2H, m, 6-H2), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, $J = 2.8$ Hz, 4-H), 6.71 (1H, dd, $J = 8.6$ and 2.8 Hz, 2-H) and 7.21 (1H, d, $J = 8.6$ Hz, 1-H) (Found: $M^+$ 322.192. $C_{22}H_{26}O_2$ requires; $M$, 322.193).

\((17S)-2',2'-\text{Dimethylspiro}[14-hydroxymethyl-3-methoxyestra-1,3,5(10)-triene-17,4'}[1,3]\text{dioxolane}] (201).\)

Triol (199) was obtained via lithium aluminium hydride reduction of the 14α,17α-dicarbaldehyde (88). Subsequently, the triol (199) was converted to the 17β,171-
acetonide (201), m.p. 180-183°C (from chloroform-methanol); (lit.,55 m.p. 179-181°C) (Found: C, 74.3; H, 8.8%; $M^+$, 386. $C_{24}H_{34}O_4$ requires C, 74.6; H, 8.9%; $M$, 386).

(17S)-2',2'-Dimethylspiro[14-carbaldehyde-3-methoxyestra-1,3,5(10)-triene-17,4'[1,3]dioxolane] (202).

Pyridinium chlorochromate (PCC) on basic alumina (1.2 mmol PCC / gram alumina; 340 mg) was added to a solution of the 14-hydroxymethyl acetonide (201) in dichloromethane (10 ml). The mixture was stirred at 25°C under nitrogen for 5 h. Diethyl ether was added and the mixture was filtered. The filtrate was concentrated under reduced pressure to give a crystalline residue (108 mg). Filtration of the residue through silica gel (1 g) [ethyl acetate-toluene (19:1)] gave the 14α-formyl acetonide (202) (68 mg, 53%), m.p. 156-159°C (from chloroform-methanol); (lit.,87 m.p. 154-156°C); $\nu_{max}$ 1705 (C=O) cm$^{-1}$; (Found: C, 75.2; H, 8.2%; $M^+$, 384. $C_{24}H_{32}O_4$ requires C, 75.0; H, 8.4%; $M$, 384).

(17S)-2',2'-Dimethylspiro[14-methyl-3-methoxyestra-1,3,5(10)-triene-17,4'[1,3]dioxolane] (203).

A mixture of the 14-formyl acetonide (202) (70 mg, 0.18 mmol), anhydrous hydrazine (0.4 ml) and ethylene glycol (5 ml) was heated to 100°C until complete reaction of starting material (2.5 h). The mixture was cooled and potassium hydroxide pellets (180 mg) were added. Excess hydrazine was removed by distillation and the reaction mixture was then heated to 200-210°C for 4 h. The mixture was cooled to 20°C and neutralised with hydrochloric acid (5%). Standard work-up (chloroform) gave an oily residue (53 mg). Chromatography of the residue through silica gel (8 g) [ethyl acetate-toluene (1:4)] gave the 14α-methyl acetonide (203) (38 mg, 54%), m.p. 159-164°C (from chloroform-methanol), [lit.,87 m.p. 166-170°C (from chloroform-methanol)]; $[\alpha]_D +52^\circ$ (c 1.0), $\delta_H$ 0.80 (3H, s, 14α-Me), 1.04
(3H, s, 13β-Me), 1.34 and 1.37 (6H, 2 x s, acetonide-Me), 2.79-2.90 (2H, m, 6-H2 and 9α-H), 3.76 (3H, s, 3-OMe), 3.74 and 4.28 (each 1H, d, J 8.7 Hz, 17α-H2), 6.60 (1H, d, J 2.7 Hz, 4-H), 6.70 (1H, dd, J 8.6 and 2.7 Hz, 2-H) and 7.20 (1H, d, J 8.6 Hz, 1-H) (Found: C, 78.2; H, 8.9%; M+, 370. C24H34O3 requires C, 77.8; H, 9.3%; M, 370).

14-Hydroxymethyl-3-methoxy-14-estra-1,3,5(10)-trien-17-one 141-methyl xanthate (205).

The 141-methyl xanthate (205) was prepared from the 14-hydroxymethyl 17-ketone (214) according to the literature method49, m.p 150-153°C (from diethyl ether), [lit.,49 m.p. 148-150°C (from methanol-diethyl ether)] (Found: C, 64.9; H, 7.2%; M+, 404. C22H23O3S2 requires C, 65.3; H, 7.0%; M, 404).

3-Methoxy-14-methyl-14-estra-1,3,5(10)-trien-17-one (51).

A solution of the 141-methyl xanthate (205) (146 mg, 0.36 mmol) in toluene (4 ml) was treated with tris(trimethylsilyl)silane (180 mg, 0.72 mmol). Azobis(isobutyronitrile) (54 mg, 0.33 mmol) in toluene (3 ml) was added over 9 h at reflux under nitrogen. The mixture was cooled and concentrated under reduced pressure to give an oily residue (400 mg). Filtration of the residue through silica gel (4 g) [ethyl acetate-hexane (1:9)] gave 3-methoxy-14-methyl-14-estra-1,3,5(10)-trien-17-one (51) (86 mg, 86%), m.p. 137-141°C (benzene-hexane); [α]D +126° (c 1.0); [lit.,49 m.p. 139-141°C (from benzene-hexane), [α]D +113° (c 0.9)]; νmax 1733(C=O) cm⁻¹; δH 0.90 and 1.03 (each 3H, s, 13β- and 14α-Me), 2.48 (1H, ddd, J 19.1, 9.0 and 2.7 Hz, 16β-H), 2.90 (2H, m, 6-H2), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, J 2.7 Hz, 4-H), 6.73 (1H, dd, J 8.6 and 2.7 Hz, 2-H), 7.20 (1H, d, J 8.6 Hz, 1-H) (Found: C, 80.2; H, 8.5%; M+, 298. C20H26O2 requires C, 80.5; H, 8.8%; M, 298).
(1'S)-1',17α-Epoxy-14-(2-trimethylsilylethyl)-3-methoxyestra-1,3,5(10)-trien-17β-ol (206).

A solution of the 14α-formyl 17-ketone (87) (50 mg, 0.16 mmol) in dry tetrahydrofuran (0.5 ml) was added to trimethylsilylmethylmagnesium chloride [prepared from chloromethyltrimethylsilane (1.23 g; 1.4 ml, 10 mmol) and magnesium (0.24 g, 10 mmol) in diethyl ether (2 ml)] at 0°C. The mixture was stirred at 25°C under nitrogen for 4 h. Standard work-up (chloroform) gave a crystalline residue which was recrystallised from ethyl acetate to give the hemiketal (206) (51 mg, 80%), m.p. 181-184°C (from ethyl acetate); [α]D +68° (c 1.0); νmax. 3405 (OH) cm⁻¹; δH (400 MHz) 0.05 (9H, s, -Si(CH₃)₃), 0.58 (1H, dd, J 14.3 and 1.8 Hz, 2'-H), 0.95 (1H, dd, J 14.3 and 11.6 Hz, 2'-'H), 0.97 (3H, s, 13β-Me), 1.32-1.52 (4H, m, 7α-, 11β-, 12β- and 15β-H), 1.54 (1H, td, J 2 x 12.0 and 1.7 Hz, 8β-H), 1.69 (1H, ddd, J 12.4, 9.2 and 5.4 Hz, 16β-H), 1.80 (1H, m, W ν 22.7 Hz, 7β-H), 1.94 (1H, td, J 2 x 12.4 and 3.3 Hz, 15α-H), 2.08-2.20 (2H, m, 12α- and 16α-H), 2.46 (1H, m, W ν 23.9 Hz, 11α-H), 2.60 (1H, s, exch. by D₂O, 17β-OH), 2.74 (1H, td, J 2 x 12.0 and 4.4 Hz, 9α-H), 2.82 (2H, m, 6-H₂), 3.78 (3H, s, 3-OMe), 4.60 (1H, dt, J 11.6 and 2 x 1.8 Hz, 1'-H), 6.61 (1H, d, J 2.8 Hz, 4-H), 6.72 (1H, dd, J 8.6 and 2.8 Hz, 2-H), and 7.25 (1H, d, J 8.5 Hz, 1-H) (Found: C, 70.0; H, 8.9%; M⁺, 400).

C₃₅H₃₆O₃Si·½H₂O requires C, 70.4; H, 9.1%; M⁺, 409).

3-Methoxy-14-vinylestra-1,3,5(10)-trien-17-one (207).

A solution of the hemiketal (206) (50 mg, 0.16 mmol) in dichloromethane (2 ml) was treated with boron trifluoride diethyl ether complex (0.060 ml, 0.48 mmol) at 0°C for 1 h under nitrogen. The mixture was stirred at 25°C for a further 8 h. Filtration through alumina (1 g) (eluted with dichloromethane) gave the 14α-vinyl 17-ketone (207) (37 mg, 74%), m.p. 123-126°C (from ethyl acetate-hexane), [lit.⁶ m.p. 127-132°C (from acetone-methanol)]; [α]D +112° (c 0.92); νmax. 1731(C=O), 1572(C=C) cm⁻¹; δH 1.12 (3H, s, 13β-Me), 1.88 obsc. (1H, td, J 2 x 11.7 and 2.5 Hz,
8β-H), 2.66 (1H, td, J 2 x 11.7 and 4.7 Hz, 9α-H), 2.85 (2H, m, 6-H₂), 3.77 (3H, s, 3-O-Me), 5.16 (1H, dd, J 17.6 and 0.9 Hz, 14²-Hcis), 5.24 (1H, dd, J 11.5 and 0.9 Hz, 14²-Htrans), 6.04 (1H, ddd, J 17.6, 11.5 and 0.9 Hz, 14¹H), 6.62 (1H, d, J 2.8 Hz, 4-H), 6.71 (1H, dd, J 8.6 and 2.8 Hz, 2-H) and 7.20 (1H, d, J 8.6 Hz, 1-H) (Found: C, 81.1; H, 8.0%; M⁺, 310. C₂₁H₂₆O₂ requires C, 81.3; H, 8.4%; M, 310).

Hydride reduction of the 14α-vinyl 17-ketone (207).

A solution of the 14α-vinyl 17-ketone (207) (50 mg, 0.16 mmol) in dry tetrahydrofuran (3 ml) was treated with lithium aluminium hydride (20 mg, 0.52 mmol) at 20°C under nitrogen. The mixture was stirred for 30 min, followed by the addition of saturated aqueous ammonium chloride. Standard work-up (ethyl acetate) gave an oily residue (34 mg). Chromatography of the residue on silica gel (1 g) [ethyl acetate-toluene (1:4)] gave 3-methoxy-14-vinylestra-1,3,5(10)-trien-17α-ol (209) (19 mg, 38%), m.p. 85-90°C (from ethyl acetate-hexane); [α]D +2° (c 0.2); νmax. 3613(OH) cm⁻¹; δH 0.89 (3H, s, 13β-Me), 2.72 (1H, td, J 2 x 12.0 and 5.4, 9α-H), 2.80 (2H, m, 6-H₂), 3.70 (1H, dd, J 7.3 and 1.1 Hz, 17β-H), 3.76 (3H, s, 3-O-Me), 5.31 (1H, dd, J 10.8 and 1.5 Hz, 14²-Hcis), 5.33 (1H, dd, J 17.7 and 1.5 Hz, 14²-Htrans), 6.52 (1H, d, J 2.8 Hz, 4-H), 6.60 (1H, dd, J 17.7 and 10.8 Hz, 14¹-H), 6.70 (1H, dd, J 8.7 and 2.8 Hz, 2-H), and 7.21 (1H, d, J 8.7 Hz, 1-H) (Found: C, 80.3; H, 9.4%; M⁺, 312. C₂₁H₂₅O₂ requires C, 80.7; H, 9.0%, M, 312), followed by 3-methoxy-14-vinylestra-1,3,5(10)-trien-17β-ol (208) (15 mg, 30%), m.p. 143-149°C (from ethyl acetate-hexane); [α]D +49° (c 1.0); νmax. 3610(OH) cm⁻¹; δH 0.92 (1H, s, 13β-Me), 1.42 (1H, s, exch. by D₂O, 17β-OH), 1.74 (1H, td, J 2 x 11.7 and 2.8 Hz, 8β-H), 2.32 (1H, m, Wv 24.9 Hz, 11α-H), 2.60 (1H, td, J 2 x 11.7 and 5.1 Hz, 9α-H), 2.74 (2H, m, 6-H₂), 3.72 (3H, s, 3-O-Me), 3.82 (1H, dd, J 9.0 and 6.0 Hz, 17α-H), 5.08 (1H, dd, J 17.3 and 1.5 Hz, 14²-Htrans), 5.12 (1H, dd, J 11.3 and 1.5 Hz, 14²-Hcis), 6.30 (1H, dd, J 17.3 and 11.3 Hz, 14¹-H), 6.54 (1H, d, J 2.8 Hz, 4-H), 6.66 (1H, dd, J 8.6 and 2.8 Hz,
2-H), and 7.15 (1H, d, J 8.6 Hz, 1-H) (Found: C, 80.5; H, 9.1%; M+, 312. C_{21}H_{28}O_2 requires C, 80.7; H, 9.0%; M, 312).

3-Methoxy-14-vinylestra-1,3,5(10)-trien-17β-ol (208).

A solution of the 14α-vinyl 17-ketone (207) (104 mg, 0.34 mmol) in 2-propanol (5 ml) was treated with sodium (200 mg) in small portions over 20 min at reflux. After refluxing for 40 min, the mixture was cooled to 0°C, followed by the addition of methanol (5 ml) and saturated aqueous ammonium chloride. Standard work-up (chloroform) gave a crystalline residue (110 mg). Filtration of the residue through silica gel (2 g) [ethyl acetate-toluene (1:4)] gave the 14α-vinyl 17β-alcohol (208) (98 mg, 94%), as characterised above.

14-Ethyl-3-methoxyestra-1,3,5(10)-trien-17-one (211).

A solution of 14α-vinyl 17-ketone (207) (95 mg, 0.31 mmol) in ethyl acetate (2 ml) containing 10% Pd/C (30 mg) was stirred at 20°C under hydrogen for 48 h (NMR monitoring). The catalyst was removed by filtration, and the filtrate was concentrated to give a crystalline residue (103 mg). Filtration of the residue through silica gel (2 g) [ethyl acetate-hexane (1:9)] gave 14α-ethyl 17-ketone (211), (84 mg, 88%), m.p. 112-118°C (ethyl acetate-hexane); [α]_D +115° (c 1.0); \nu_{\text{max}}. 1727 (C=O) cm^{-1}; \delta_\nu (400 MHz) 0.82-0.95 (4H, m, 14α-H and 14β-H), 1.02 (3H, s, W_{\nu} 0.8 Hz, 13β-Me), 1.44-1.68 (4H, m, 7α-, 11β-, 12β- and 15α-H), 1.72 (1H, tdd, J 2 x 13.6, 5.2 and 0.8 Hz, 12α-H), 1.78 (1H, br t, J 2 x 12.6 and W_{\nu} 3.8 Hz, 8β-H), 1.88 (1H, m, W_{\nu} 24.1 Hz, 14α-H), 2.11 (1H, m, W_{\nu} 23.7 Hz, 15β-H), 2.20 (1H, dt, J 18.7 and 2 x 8.8 Hz, 16α-H), 2.31 (1H, ddt, J 13.6, 2 x 5.2 and 2.4 Hz, 11α-H), 2.40 (1H, ddd, J 18.7, 9.2 and 0.6 Hz, 16β-H), 2.79 (1H, td, J 2 x 12.6 and 5.2 Hz, 9α-H), 2.85 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.60 (1H, d, J 2.9 Hz, 4-H), 6.69 (1H, dd, J 8.6 and 2.9 Hz, 2-H), and 7.19 (1H, d, J 8.6 Hz, 1-H); \delta_c 219.8 (C-17), 157.5 (C-3), 137.5 (C-5), 133.3 (C-10), 127.0 (C-1), 113.8 (C-4), 111.7 (C-2), 55.2 (OMe), 54.6 (C-...
14-Ethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (210).

A solution of 14α-vinyl 17β-alcohol (208) (80 mg, 0.26 mmol) in ethyl acetate (2 ml) containing 10% Pd/C (20 mg) was stirred at 20°C under hydrogen for 34 h (NMR monitoring). The catalyst was removed by filtration, and filtrate was concentrated to give a crystalline residue (84 mg). Filtration of the residue through silica gel (2 g) [ethyl acetate-toluene (1:4)] gave the 14α-ethyl 17β-alcohol (210) (69 mg, 85%), m.p. 143-148°C (from ethyl acetate-hexane); [α]D +76° (c 1.0); δH 0.80-1.00 (6H, m, 14a-CH3 and 13β-Me), 2.70-2.86 (3H, m, 6-H2 and 9α-H), 3.76 (3H, s, 3-0Me), 4.16 (1H, dd, J 9.0 and 6.0 Hz, 17α-H), 6.60 (1H, d, J 2.8 Hz, 4-H), 6.70 (1H, dd, J 8.6 and 2.8 Hz, 2-H), and 7.18 (1H, d, J 8.6 Hz, 1-H) (Found: C, 80.4; H, 9.8%; M+, 314. C21H32O2 requires C, 80.2; H, 9.6%; M, 314).

Deprotection of 3-Methyl ethers (208) and (210).

(a) Diisobutylaluminium hydride (1.5 M in toluene; 1 ml, 1.5 mmol) was added to a stirred solution of the 3-methyl ether (208) (39 mg, 0.13 mmol) in toluene (1 ml) under nitrogen and the mixture was refluxed for 12 h. Hydrochloric acid (10%; 10 ml) was added to the cooled mixture. Standard work-up (ethyl acetate) gave a crystalline residue (40 mg). Chromatography of the residue on silica gel (3 g) [ethyl acetate-toluene (3:7)] gave 14-vinylestra-1,3,5(10)-triene-3,17β-diol (212) (27 mg, 73%), m.p. 157-159°C (from chloroform-hexane); [α]D +43° (c 1.0, tetrahydrofuran); νmax. 3295br(OH) cm⁻¹; (Found: C, 80.3; H, 9.4%; M+ 298. C20H26O2 requires C, 80.5; H, 8.8%; M, 298).

(b) Similar treatment of the 3-methyl ether (210) (40 mg, 0.13 mmol), followed by chromatography gave 14-ethyl estra-1,3,5(10)-triene-3,17β-diol (213) (20 mg, 55%),
m.p. 95-98°C (from chloroform-hexane); $[\alpha]_D +82^\circ$ (c 1.1, tetrahydrofuran);

$\nu_{\text{max.}}$ 3305br(OH) cm$^{-1}$; (Found: C, 80.3; H, 9.2%; $M^+$ 300. $C_{20}H_{28}O_2$ requires C, 79.9; H, 9.4%; $M$, 300).

(1'S)-1',17a-Epoxy-14-ethyl-3-methoxyestra-1,3,5(10)-tri-en-17β-ol (220).

Methyllithium (1.6 M in hexane; 1.4 ml, 2.24 mmol) was added dropwise to a solution of the 14α-formyl 17-ketone (87) (122 mg, 0.39 mmol) in dry tetrahydrofuran (8 ml) at 0°C under nitrogen. The mixture was stirred for 4 h, followed by the addition of saturated aqueous ammonium chloride. Standard work-up (chloroform) gave a crystalline residue (138 mg). Filtration of the residue through silica gel (2.8 g) [ethyl acetate-toluene (3:7)] gave the 14-ethyl alcohol (220) (104 mg, 81%), m.p. 148-153°C (ethyl acetate-hexane) [lit.,61 m.p. 150-155°C (from ethyl acetate-methanol)]; $\nu_{\text{max.}}$ 3374(OH) cm$^{-1}$; $\delta$H 0.98 (3H, s, 13β-Me), 1.25 (3H, d, J 6.2 Hz, 2'-CH$_3$), 1.31-1.62 (5H, m, 7α-, 8β-, 11β-, 12β-, and 16β-H), 1.68-1.90 (2H, m, 7β- and 15β-H), 1.94-2.18 (12α-, 15α-, and 16α-H), 2.4 (1H, m, $\nu$H 21.1 Hz, 11α-H), 2.69 (1H, br s exch. with D$_2$O, 17β-OH), 2.70-2.86 (3H, m, 6-H$_2$ and 9α-H), 3.77 (3H, s, 3-OMe), 4.57 (1H, qd, J 3 x 6.2 and 2.3 Hz, 1'-H), 6.60 (1H, d, J 2.8 Hz, 4-H), 6.72 (1H, dd, J 8.6 and 2.8 Hz, 2-H), and 7.23 (1H, d, J 8.6 Hz, 1-H); $\delta$c 157.4 (C-3), 137.4 (C-5), 132.6 (C-10), 127.0 (C-1), 113.7 (C-4), 111.7 (C-2), 109.5 (C-17), 73.2 (C-1'), 55.1 (OMe), 50.7 (C-13), 48.5 (C-14), 40.6 (C-8), 37.6 (C-9), 33.6 (C-6), 31.1 (C-16), 25.7 (C-11), 25.6 (C-12), 25.1 (C-15), 21.3 (C-7), 18.8 (C-2'), and 15.5 (C-18) (Found: C, 76.6; H, 8.3%; $M^+$, 328. $C_{21}H_{38}O_3$ requires C, 76.8; H, 8.5%; $M$, 328).

**Ethyl magnesium bromide addition to the 14α-formyl 17-ketone (87).**

A solution of the 14α-formyl 17-ketone (87) (80 mg, 0.26 mmol) in dry tetrahydrofuran (0.5 ml) was added to ethylmagnesium bromide [prepared from bromoethane (0.1 ml, 1.3 mmol) and magnesium (28 mg, 1.17 mmol) in diethyl
ether (0.5 ml) at 20°C. The mixture was stirred at 20°C under nitrogen for 45 min. Standard work-up (chloroform) gave an oily residue (87 mg). Chromatography of the residue on silica gel (9 g) [ethyl acetate-hexane (1:4)] gave (1'S)-1',17α-epoxy-14-propyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (221) (20 mg, 23%), m.p. 173-177°C (from diethyl ether); [α]D +59° (c 0.76); νmax 3576(OH) cm⁻¹; δH(CDCl₃) 0.88 (3H, s, 13β-Me), 2.60 (2H, m, 6-H₂), 3.50 (3H, s, 3-OMe), 4.17 br (1H, d, J 10.2 Hz and W½ 5.0 Hz, 1'-H), 6.70 (1H, d, J 2.7 Hz, 4-H), 6.80 (1H, dd, J 8.4 and 2.7 Hz, 2-H), and 7.20 (1H, obsc. by C₆H₆, 1-H) (Found: C, 76.9; H, 8.6%; M+, 342. C₂₂H₃₀O₃ requires C, 77.2; H, 8.8%; M, 342), followed by 14-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17-one (88/214) (45 mg, 56%), m.p. 159-162°C (from benzene-hexane), [α]D +56° (c 1.0); νmax 3439(OH), 1730(C=O) cm⁻¹; The NMR displayed an equilibrium mixture of the 14-hydroxymethyl alcohol and the hemiketal (2:3) in C₆D₆. (Found: C, 76.1; H, 8.6%; M*, 314. C₂₀H₂₆O₃ requires C, 76.4; H, 8.3%; M, 314).

14-Acetoxymethyl-3-methoxyestra-1,3,5(10)-trien-17-one (215).

A solution of the 14-hydroxymethyl 17-ketone (88/214) (45 mg, 0.14 mmol) and acetic anhydride (0.5 ml, 5.3 mmol) in pyridine (0.5 ml) was stirred at 25°C under nitrogen for 2 h. Ice and solid sodium hydrogen carbonate were added. Standard work-up (chloroform) gave an oily residue (49 mg). Filtration of the residue through silica gel (1 g) [ethyl acetate-toluene (1:10)] gave the 14α-acetoxymethyl 17-ketone (215) (36 mg, 71%), m.p. 143-145°C (from ethyl acetate-hexane), [lit.,⁴⁹ m.p. 149-150°C (from methanol)]; [α]D +55° (c 1.0), [lit.,⁴⁹ [α]D +91° (c 0.94)]; νmax 1734(C=O) cm⁻¹; δH 1.06 (3H, s, 13β-Me), 2.03 (3H, s, 14α-OAc), 2.76-2.94 (2H, m, 9α-H and 6-H₂), 3.77 (3H, s, 3-OMe), 4.12 and 4.32 (each 1H, d, J 12.1 Hz, 14α-H₂), 6.62 (1H, d, J 2.8 Hz, 4-H), 6.72 (1H, dd, J 8.6 and 2.8 Hz, 2-H), and 7.18 (1H, d, J 8.6 Hz, 1-H) (Found: C, 74.1; H, 7.7%; M*, 356. C₂₂H₂₈O₄ requires C, 74.1; H, 7.9%; M, 356).
A solution of the hemiketal (221) (16 mg, 0.05 mmol), acetic anhydride (0.5 ml, 5.3 mmol) and dimethylaminopyridine (ca. 3 mg) in pyridine (0.5 ml) was stirred at 20°C under nitrogen for 3 h. Ice and saturated hydrogen carbonate was added. Standard work-up (chloroform) gave an oily residue (17 mg). Chromatography of the residue on silica gel (0.5 g) [ethyl acetate-toluene (1:10)] gave the 17β-acetate (220) (13 mg, 72%), m.p. 162-165°C (from ethyl acetate-hexane); [α]D +61° (c 1.3); νmax. 1750(C=O) cm⁻¹; δH 0.98 (3H, s, 13β-Me), 1.04 (3H, t, J 2 x 7.2 Hz, 3'-CH₃), 2.07 (3H, s, 17-0Ac), 2.70-2.88 (3H, m, 6-H₂ and 9α-H), 3.77 (3H, s, 3-0Me), 4.30 br (1H, d, J 10.3 and W₂ 5.0 Hz, 1'-H), 6.60 (1H, d, J 2.8 Hz, 4-H), 6.72 (1H, dd, J 8.6 and 2.8 Hz, 2-H), and 7.24 (1H, d, J 8.6 Hz, 1-H) (Found: C, 75.0; H, 8.0%; M⁺, 384. C₂₅H₃₂O₄ requires C, 75.0; H, 8.4%; M, 384).

A solution of the hemiketal (221) (32 mg, 0.09 mmol) and methanesulfonyl chloride (0.21 ml, 2.7 mmol) in pyridine (2 ml) was stirred at 0°C for 1 h and allowed to equilibrate to 20°C. The mixture was stirred under nitrogen for 12 h, followed by the addition of saturated aqueous sodium hydrogen carbonate and ice. Standard work-up (chloroform) gave a crystalline residue (46 mg). Filtration of the residue through silica gel (1 g) [ethyl acetate-toluene (1:4)] gave the 17β-methanesulfonate (223) (29 mg, 74%), m.p. 136°C (dec.) (from chloroform-methanol); [α]D +46° (c 1.0); νmax. 1359(S=O) and 1194(S-O) cm⁻¹; δH(400 MHz) 1.02 (3H, t, J 2 x 7.3 Hz, 3'-CH₃), 1.04 (3H, s, 13β-Me), 1.81 (1H, m, W₂ 23.4 Hz, 7β-H), 2.18 (1H, td, J 2 x 12.3 and 3.8 Hz, 12α-H), 2.46 (1H, m, W₂ 26.7 Hz, 11α-H), 2.77 (1H, td, J 2 x 11.8 and 4.2 Hz, 9α-H), 2.82 (2H, m, 6-H₂), 3.18 (3H, s, 17β-OMs), 3.77 (3H, s, 3-0Me), 4.41 (1H, dt, J 10.8 and 2 x 3.6 Hz, 1'-
H), 6.60 (1H, d, J 2.8 Hz, 4-H), 6.73 (1H, dd, J 8.8 and 2.8 Hz, 2-H), and 7.23 (1H, d, J 8.8 Hz, 1-H); \( \delta_c \) 157.6 (C-3), 137.3 (C-5), 132.1 (C-10), 127.1 (C-1), 114.3 (C-17), 113.8 (C-4), 111.9 (C-2), 82.7 (C-1'), 55.2 (3-OMe), 51.1 (C-14), 49.0 (C-13), 41.0 (17-OMs), 40.3 (C-8), 37.6 (C-9), 32.7 (C-16), 30.9 (C-6), 26.7 (C-15), 26.6 (C-7), 25.9 (C-11), 25.4 (C-12), 25.3 (C-2'), 15.0 (C-18), and 12.1 (C-3') (Found: C, 65.7; H, 7.6%; \( M^+ \), 420. \( \text{C}_{23}\text{H}_{32}\text{O}_{5}\text{S} \) requires C, 65.7; H, 7.7%; \( M^+ \), 420).

\[(1'S)-14\text{-Allyl}-1',17\text{-epoxy-3-metlzoxyestra-1,3,5(10)-trien-17}\text{-ol} \quad \text{(224)}\]

A solution of the 14\text{-formyl} 17 ketone (87) (300 mg, 0.96 mmol) in dry tetrahydrofuran (8 ml) was added to vinylmagnesium bromide [prepared from vinylbromide (0.5 ml, 7.1 mmol) and magnesium (183 mg, 7.6 mmol) in dry tetrahydrofuran (10 ml)] at 0°C. The reaction mixture was stirred at 20°C under nitrogen for 6 h. Standard work-up (chloroform) gave a crystalline residue (385 mg). Filtration of the residue through silica gel (4 g) [ethyl acetate-toluene (1:4)] gave the hemiketal (224) (285 mg, 87%), m.p. 118-124°C (from methanol); [\( \alpha \)]D +52° (c 0.46); \( \nu_{max} \text{3574(OH) cm}^{-1} \); \( \delta_{1h}(400 \text{MHz}) \) 1.00 (3H, d, J 0.8 Hz, 13\text{-Me}), 1.34-1.56 (4H, m, 7\text{-}, 11\text{-}, 12\text{-}, and 15\text{-H}), 1.60 (1H, td, J 2 x 12.0 and 2.0 Hz, 8\text{-H}), 1.74-1.86 (2H, m, 7\text{-H} and 16\text{-H}), 1.94-2.02 (2H, m, 15\text{-H} and 16\text{-H}), 2.14 (1H, td, J 2 x 13.0 and 4.0 Hz, 12\text{-H}), 2.48 (1H, m, \( \nu_{w} \text{26.7 Hz, 11-H} \)), 2.74 (1H, brs exch. by D\text{2}O, 17\text{-OH}), 2.80-2.90 (3H, m, 6-H\text{2} and 9\text{-H}), 3.78 (3H, s, 3-OMe), 4.89 (1H, dq, J 5.2 and 3 x 1.9 Hz, 1'\text{-H}), 5.21 (1H, dt, J 10.5 and 2 x 1.9 Hz, 3'\text{-Hpraak}), 5.47 (1H, dt, J 17.0 and 2 x 1.9 Hz, 3'\text{-Htrans}), 5.94 (1H, ddd, J 17.0, 10.5 and 5.2 Hz, 2'\text{-H}), 6.61 (1H, d, J 2.8 Hz, 4-H), 6.73 (1H, dd, J 8.6 and 2.8 Hz, 2-H), and 7.25 (1H, d, J 8.6 Hz, 1-H); \( \delta_c \) 157.6 (C-3), 137.9 (C-2'), 137.6 (C-5), 132.5 (C-10), 127.0 (C-1), 116.2 (C-3'), 113.8 (C-4), 111.8 (C-2), 109.9 (C-17), 78.5 (C-1'), 55.2 (3-OMe), 51.9 (C-14), 48.2 (C-13), 40.7 (C-8), 37.7 (C-9), 33.2 (C-6), 31.0 (C-16), 26.6 (C-7), 25.4 (C-12 and C-15), 25.0 (C-11), and 15.5 (C-18) (Found: C, 78.0; H, 8.4%; \( M^+ \), 340. \( \text{C}_{22}\text{H}_{28}\text{O}_{5} \) requires C, 77.6; H, 8.3%; \( M^+ \), 340).
(1'S)-14-Allyl-1',17α-epoxy-3-methoxyestra-1,3,5(10)-trien-17β-yl acetate (225).

A solution of the hemiketal (224) (85 mg, 0.25 mmol) and acetic anhydride (1 ml, 10.6 mmol) in triethylamine (1 ml) was stirred at 40°C under nitrogen for 16 h. Ice and saturated aqueous sodium hydrogen carbonate was added. Standard work-up (chloroform) gave an oily residue (105 mg). Filtration of the residue through silica gel (2.1 g) [ethyl acetate-toluene (1:10)] gave the 17β-acetate (225) (58 mg, 60%), m.p. 173-176°C (from ethyl acetate-hexane); [α]D +96° (c 1.0); νmax. 1750 (C=O) cm⁻¹; δH (400 MHz) 1.00 (3H, d, J 0.6 Hz, 13βMe), 1.36-1.56 (4H, m, 7α-, 11β-, 12β- and 15β-H), 1.60 (1H, td, J 2 x 12.0 and 2.0 Hz, 8β-H), 1.78 (1H, m, Wν 22.1 Hz, 7β-H), 1.94-2.05 (2H, m, 15α-H and 16β-H), 2.09 (3H, s, 17β-OAc), 2.20 (1H, tdd, J 2 x 13.0, 4.0 and 0.6 Hz, 12α-H), 2.46 (1H, m, Wν 26.6 Hz, 11α-H), 2.66 (1H, m, Wν 28.5 Hz, 16α-H), 2.80-2.88 (3H, m, 6-H2 and 9α-H), 3.78 (3H, s, 3-OMe), 4.98 (1H, dq, J 5.2 and 3 x 1.8 Hz, 1'-H), 5.22 (1H, dt, J 10.5 and 2 x 1.8 Hz, 3'-Hcis), 5.56 (1H, dt, J 16.9 and 2 x 1.8 Hz, 3'-Htrans), 5.94 (1H, ddd, J 16.9, 10.5 and 4.9 Hz, 2'-H), 6.61 (1H, d, J 2.8 Hz, 4-H), 6.73 (1H, dd, J 8.6 and 2.8 Hz, 2-H), and 7.22 (1H, d, J 8.6 Hz, 1-H); δc 169.4 (17-OAc), 157.6 (C-3), 137.5 (C-2'), 137.1 (C-5), 132.4 (C-10), 126.9 (C-1), 116.6 (C-3'), 113.8 (C-4), 111.8 (C-2), 110.7 (C-17), 80.2 (C-1'), 55.2 (3-OMe), 50.2 (C-14), 49.8 (C-13), 40.4 (C-8), 37.7 (C-9), 31.1 (C-16), 30.9 (C-6), 26.6 (C-7), 25.7 (C-12 and C-15), 25.5 (C-11), 21.6 (17-OAc), and 15.4 (C-18) (Found: C, 75.4; H, 8.0%; M⁺, 382. C23H30O4 requires C, 75.4; H, 7.9%; M, 382).

(1'S)-14-Allyl-1',17α-epoxy-3-methoxyestra-1,3,5(10)-trien-17β-yl methanesulfonate (226).

A solution of the hemiketal (224) (50 mg, 0.15 mmol) and methanesulfonyl chloride (0.013 ml, 0.17 mmol) in dry triethylamine (1 ml) was stirred at 0°C under nitrogen for 1 h. Ice and saturated aqueous sodium hydrogen carbonate was added. Standard work-up (chloroform) gave an oily residue (56 mg). Filtration of the
residue through silica gel (1 g) [toluene] gave the 17β-methanesulfonate (226) (48 mg, 78%), m.p. 142-145°C (from ethyl acetate-hexane); [α]D +25° (c 0.6); νmax. 1361 (S=O) and 1183 (S-O) cm⁻¹; δH 1.07 (3H, s, 13βMe), 2.76-2.90 (3H, m, 6-H2 and 9α-H), 3.20 (3H, s, S(O)CH3) 3.78 (3H, s, 3-OMe), 5.02 br (1H, m, WH 10.5 Hz, 1'-H), 5.26 (1H, dt, J 10.5 and 2 x 1.8 Hz, 3'-Hcis), 5.51 (1H, dt, J 16.9 and 2 x 1.8 Hz, 3'-Htrans), 5.92 (1H, ddd, J 16.9, 10.5 and 4.9 Hz, 2'-H), 6.62 (1H, d, J 2.8 Hz, 4-H), 6.74 (1H, dd, J 8.6 and 2.8 Hz, 2-H), and 7.24 (1H, d, J 8.6 Hz, 1-H); δC 157.6 (C-3), 137.4 (C-2'), 136.7 (C-5), 131.9 (C-10), 126.9 (C-1), 116.7 (C-3'), 114.6 (C-17), 113.8 (C-4), 111.9 (C-2), 80.9 (C-1'), 55.2 (3-OMe), 50.7 (C-14), 50.1 (C-13), 41.1 (OMs), 40.2 (C-8), 37.7 (C-9), 32.2 (C-16), 30.8 (C-6), 26.5 (C-7), 25.9 (C-11), 25.4 (C-12 and C-15), and 15.1 (C-18) (Found: C, 66.2; H, 7.2%; M+, 418. C23H30O5S requires C, 66.0; H, 7.2%; M, 418).

(1'S)-14-(But-3-en-1-yl)-1',17α-epoxy-3-methoxyestra-1,3,5(10)-trien-17β-ol (227). A solution of the 14α-formyl 17-ketone (87) (90 mg, 0.29 mmol) in dry tetrahydrofuran (0.5 ml) was added to allylmagnesium bromide [prepared from allyl bromide (177 mg; 0.126 ml, 1.44 mmol) and magnesium (45 mg, 1.88 mmol) in diethyl ether (1.0 ml)] at 20°C under nitrogen. The mixture was stirred for 10 min, followed by the addition of solid ammonium chloride. Standard work-up (chloroform) gave a crystalline residue (102 mg), which was recrystallised from diethyl ether-hexane to give the hemiketal (227) (70 mg, 68%), m.p. 145-147°C (from diethyl ether-hexane); [α]D +55° (c 1.0); νmax 3575 (OH) and 1572 (C=C) cm⁻¹; δH (400 MHz) 0.98 (3H, d, J 0.8 Hz, 13β-Me), 1.54 (1H, t, J 2 x 10.8 Hz, 8β-H), 2.08 (1H, td, J 2 x 13.1 and 4.3 Hz, 12α-H), 2.42 (1H, m, WH 24.0 Hz, 11α-H), 2.52 (1H, br s exch. by D2O, 17β-OH), 2.80 obsc. (1H, td, J 2 x 10.8 and 4.3 Hz, 9α-H), 2.84 (2H, m, 6-H2), 3.78 (3H, s, 3-OMe), 4.40 (1H, dt, J 10.0 Hz and 2 x 2.1 Hz, 1'-H), 5.05 (1H, dd, J 10.1 and 1.8 Hz, 4'-Hcis), 5.09 (1H, dd, J 17.1 and 1.8 Hz, 4'-Htrans), 5.93 (1H, qt, J 17.1, 10.1 and 2 x 6.8 Hz, 3'-H), 6.60 (1H, d, J 2.8 Hz, 4-H), 6.73 (1H,
dd, J 8.6 and 2.8 Hz, 2-H), and 7.24 (1H, d, J 8.6 Hz, 1-H) (Found: C, 76.0; H, 8.2%; M+, 354. C_{23}H_{30}O_{3.5}H_{2}O requires C, 76.0%; H, 8.6%; M, 363).

(14^1S)-3-Methoxy-14-oxiranylestra-1,3,5(10)-trien-17-one (228).

Sodium hydride (50% dispersion in oil; 20 mg, 0.42 mmol) was washed twice with dry tetrahydrofuran (2 ml), removing the solvent each time, under nitrogen. Dimethyl sulfoxide (0.5 ml) was added and the mixture was stirred at 70-75°C for 45 min. The mixture was cooled to -5°C, followed by the addition of dry tetrahydrofuran (0.5 ml). A solution of trimethylsulfonium iodide (86 mg, 0.42 mmol) in dimethyl sulfoxide (1 ml) was added dropwise whilst stirring. After 10 min, a solution of the 14a-formyl 17-ketone (87) (50 mg, 0.16 mmol) in dry tetrahydrofuran (1.5 ml) was added dropwise at -5°C. The resulting mixture was stirred at -5°C for 1 h, then at 0°C under nitrogen for 20 h. Water (2 ml) was added, and the product was extracted with chloroform. The extract was dried (MgSO4) and concentrated under reduced pressure, to gave an oily residue (66 mg). Filtration of the residue through alumina (2 g) [chloroform] gave 14α-oxiranyl 17-ketone (228) (43 mg, 82%), m.p. 141-144°C (from ethyl acetate-hexane); [α]D +88° (c 0.5);

$\nu_{\text{max}}. 1733 \text{ cm}^{-1}$; $\delta_H(400 \text{ MHz})$ 1.16 (3H, s, 13β-Me), 1.59-1.74 (4H, m, 7α-, 11α-, 15α- and 15β-H), 1.78-1.90 (2H, m, 7β- and 12β-H), 2.00 (1H, td, J 2 x 12.1 and 2.2 Hz, 8β-H), 2.16 obsc. (1H, td, J 2 x 13.8 and 4.8 Hz, 12α-H), 2.27 (1H, dt, J 18.6 and 2 x 8.4 Hz, 16α-H), 2.38 (1H, ddd, J 18.6, 7.7 and 4.6 Hz, 16β-H), 2.51 (1H, m, W_{ef} 24.2 Hz, 11β-H), 2.74 (1H, t, J 2 x 4.3 Hz, 14^2-H_{R^-}), 2.83 (1H, dd, J 4.3 and 2.8 Hz, 14^2-H_{R^+}), 2.94 (2H, m, 6-H_{2}), 2.97 (1H, td, J 2 x 12.1 and 5.6 Hz, 9α-H), 3.33 (1H, t, J 2 x 3.5 Hz, 14^1-H), 3.80 (3H, s, 3-OMe), 6.65 (1H, d, J 2.8 Hz, 4-H), 6.75 (1H, dd, J 8.6 and 2.8 Hz, 2-H), and 7.22 (1H, d, J 8.6 Hz, 1-H) (Found: C, 76.8; H, 7.6%; M+, 326. C_{21}H_{26}O_{3} requires C, 77.3; H, 8.0%; M, 326).
(1'S)-1',17α-Epoxy-14-iodoethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (231).

The 14α-oxiranyl 17-ketone (228) (35 mg, 0.11 mmol) was added to methylmagnesium iodide [prepared from iodomethane (77 mg; 34 μl, 0.54 mmol) and magnesium (21 mg, 0.86 mmol) in diethyl ether (0.5 ml)] at 20°C. The mixture was stirred for 15 min, followed by the addition of solid ammonium chloride.

Standard work-up (chloroform) gave a crystalline residue (50 mg). Chromatography of the residue on silica gel (2.5 g) [ethyl acetate-toluene (3:7)] gave the hemiketal (231) (38 mg; 78%), double m.p. 103-108°C-154-158°C (from methanol); [α]D +53° (c 0.9); νmax 3571(OH) cm⁻¹; δH 0.78 (3H, s, 13β-Me), 1.38 obsc. (1H, td, J 2 x 13.0 and 3.5 Hz, 8β-H), 1.98 (1H, m, W=24.0 Hz, 11α-H), 2.32 (1H, td, J 2 x 12.0 and 4.1 Hz, 9α-H), 2.54 (2H, m, 6-H2), 3.06 (2H, m, W=25.6 Hz, 2'-H2), 3.29 (1H, br s exch. by D2O, 17β-OH), 3.46 (3H, s, 3-0Me), 4.52 (1H, dt, J 8.4 and 2 x 2.4 Hz, 1'-H) 6.67 (1H, d, J 2.8 Hz, 4-H), 6.80 (1H, dd, J 8.6 and 2.8 Hz, 2-H), and 7.08 (1H, d, J 8.6 Hz, 1-H), δC 157.5 (C-3), 136.9 (C-5), 131.9 (C-10), 127.0 (C-1), 113.7 (C-4), 111.9 (C-2), 109.6 (C-17), 79.6 (C-1'), 55.1 (3-0Me), 52.9 (C-14), 49.5 (C-13), 40.4 (C-8), 37.7 (C-9), 33.3 (C-16), 30.9 (C-6), 26.4 (C-7), 26.1 (C-15), 24.9 (C-12), 23.9 (C-11), 15.5 (C-18) and 9.2 (C-2') (Found: C, 55.1; H, 5.9%; M+, 453.

C21H26IO3 requires C, 55.6; H, 5.8%; M, 453).

**Boron trifluoride induced rearrangement of the 14α-oxiranyl 17-ketone (228).**

A solution of the 14α-oxiranyl 17-ketone (228) (40 mg, 0.12 mmol) in dry tetrahydrofuran (1 ml) and benzene (1 ml) was treated with boron trifluoride diethyl ether complex (20 μl) at 0°C under nitrogen for 24 h. Standard work-up (ethyl acetate) gave a crystalline residue (35 mg). Chromatography of the residue on silica gel (2.6 g) [ethyl acetate-toluene (1:9)] gave the 3-methoxy-17α-homoestra-1,3,5(10),14-tetraen-17α-one (179) (25 mg, 63%), mixed m.p. 132-135°C (from chloroform-methanol), [lit.,89 m.p. 137-139°C (from methanol)]; νmax 1704(C=O)
and 1607(C = C) cm⁻¹; NMR data identical to previously characterised product. (Found: C, 80.9; H, 8.2%; \( M^+ \), 296. \( \text{C}_{20}\text{H}_{24}\text{O}_2 \) requires C, 81.0; H, 8.2%; \( M \), 296).

14-Acetyl-3-methoxyestra-1,3,5(10)-trien-17-one (229).

Chromic acid (8N; 0.060 ml, 0.48 mmol) was added dropwise to a solution of the hemiketal (220) (92 mg, 0.28 mmol) in acetone (2 ml) at 0°C. The mixture was stirred for 4 h followed by the addition of saturated aqueous sodium disulfite. Standard work-up (ethyl acetate) gave a crystalline residue (86 mg). Filtration of the residue through silica gel (2 g) [ethyl acetate-toluene (1:4)] gave 14α-acetyl 17-ketone (229) (81 mg, 94%), m.p. 154-156°C (ethyl acetate-hexane); \([\alpha]_D + 194^\circ\) (c 1.7); \( \nu_{\text{max}} \) 1736(C = O), 1686(C = O) cm⁻¹; \( \delta_H \) 1.03 (3H, s, 13β-Me), 1.46 (1H, m, \( W_m \) 43.4 Hz, 16α-H), 1.72 (1H, ddd, \( J \) 13.7, 5.0 and 1.8 Hz, 15α-H), 1.92-2.20 (2H, m, 7α- and 7β-H), 2.26 (3H, s, 141-CH₃), 2.90 (2H, m, 6-H₂), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, \( J \) 2.7 Hz, 4-H), 6.75 (1H, dd, \( J \) 8.6 and 2.7 Hz, 2-H), and 7.18 (1H, d, \( J \) 8.6 Hz, 1-H) (Found: C, 76.8; H, 7.8%; \( M^+ \), 326. \( \text{C}_{21}\text{H}_{26}\text{O}_3 \) requires C, 77.2; H, 8.0%; \( M \), 326).

17β-Hydroxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-one (232).

Sodium hydride (50% dispersion in oil; 65 mg, 1.35 mmol) was added to a solution of the 14α-acetyl 17-ketone (229) (50 mg, 0.15 mmol) in dry tetrahydrofuran (1 ml) at 0°C under nitrogen. The mixture was stirred at 20°C for 16 h followed by the addition of saturated aqueous ammonium chloride. Standard work-up (chloroform) gave a product (38 mg). Recrystallisation of the product, gave 17-hydroxy 17β-ketone (232) (32 mg, 64%), m.p. 182-186°C (from acetone-methanol) [lit.\( ^{61} \) m.p. 186-189°C (from acetone-methanol)]; \([\alpha]_D + 95^\circ\) (c 1.0), [lit.,\( ^{61} \) \([\alpha]_D + 101^\circ\) (c 1.0)]; \( \nu_{\text{max}} \) 3597(OH) and 1738(C = O) cm⁻¹; \( \delta_H \) 1.01 (3H, s, 13β-Me), 2.22 (1H, d, \( J \) 17.8 Hz, 171-H\text{endo} ), 2.64 (1H, dd, \( J \) 17.8 and 4.2 Hz, 171-H\text{exo} ), 2.82 (2H, m, 6-H₂), 3.77 (3H, s, 3-OMe), 6.63 (1H, d, \( J \) 2.8 Hz, 4-H), 6.70 (1H, dd, \( J \) 8.6 and 2.8 Hz, 2-H).
and 7.16 (1H, d, J 8.6 Hz, 1-H) (Found: C, 77.0; H, 7.9%; M+, 326. C_{21}H_{26}O_{3} requires C, 77.2; H, 8.0%; M, 326).

(17^2S)-3-Methoxy-14,17α-ethanoestra-1,3,5(10)-triene-17β,17^2-diol (233).

Lithium aluminium hydride (9 mg, 0.24 mmol) was added to a solution of the 17-hydroxy 17^2-ketone (232) (14 mg, 0.04 mmol) in dry tetrahydrofuran (0.5 ml) at 18°C under nitrogen. The mixture was stirred for 10 min followed by the addition of ethyl acetate (0.3 ml) and saturated aqueous ammonium chloride. Standard work-up (ethyl acetate) gave a crystalline residue (15 mg). Chromatography of the residue on silica gel (0.5 g) [ethyl acetate-toluene (3:7)] gave the 17β,17^2-diol (233) (12 mg, 85%), m.p. 88-92°C (from ethyl acetate-hexane), [lit., 61 m.p. 91-96°C (from ethyl acetate-hexane)]; [α]D +42° (c 1.0), [lit., 61 [α]D +33° (c 0.7)]; ν_{max} 3601(OH) cm\(^{-1}\); δH 0.91 (3H, s, 13β-Me), 2.86 (2H, m, 6-H₂), 3.40 (1H, dt, J 2 x 11.8 and 3.2 Hz, 9α-H), 3.77 (3H, s, 3-OMe), 4.11 (1H, dd, J 8.2 and 4.6 Hz, 17^2-H), 6.62 (1H, d, J 2.7 Hz, 4-H), 6.70 (1H, dd, J 8.6 and 2.7 Hz, 2-H), and 7.18 (1H, d, J 8.6 Hz, 1-H) (Found: C, 77.0; H, 9.0%; M+, 328. C_{21}H_{28}O_{3} requires C, 76.8; H, 8.6%; M, 328).

3-Methoxy-17-oxoestra-1,3,5(10)-triene-14-carbonitrile (235).

A solution of the 14α-formyl 17-ketone (87) (50 mg, 0.16 mmol) in a mixture of dry tetrahydrofuran (0.5 ml) and methanol (1 ml) was treated with N,N-dimethylhydrazine (48 mg, 0.8 mmol). Molecular sieve 3Å (0.5 g) was added and the mixture was stirred at 20°C for 24 h. The solvent was evaporated under reduced pressure and the residual crude 14α-N,N-dimethylhydrazone 17-ketone (234) (63 mg) exhibited the following characteristics; ν_{max} 1729(C=O) and 1700(C=N) cm\(^{-1}\); δH 1.08 (3H, s, 13β-Me), 2.69 (6H, s, N(CH₃)₂), 2.88 (2H, m, 6-H₂), 3.77 (3H, s, 3-OMe), 6.62 obsc. (1H, s, CH=N), 6.62 (1H, d, J 2.8 Hz, 4-H), 6.72 (1H, dd, J 8.5 and 2.8 Hz, 2-H), and 7.20 (1H, d, J 8.5 Hz, 1-H). The crude 14α-N,N-dimethylhydrazone 17-ketone (234) was dissolved in methanol (1 ml), treated with
hydrogen peroxide (30%; 0.5 ml, 4.41 mmol) and selenium dioxide (50 mg, 0.46 mmol). The mixture was stirred at 20°C for 48 h, followed by standard work-up (chloroform) to give a crystalline residue (47 mg). Chromatography of the residue on silica gel (2 g) [ethyl acetate-benzene (1:20)] gave the 14α-carbonitrile 17-ketone (235) (30 mg, 61%), m.p. 157-159°C; [α]D +90° (c 0.9); νmax 1743 (C=O), 2227 (C≡N) cm⁻¹; δH 1.04 (3H, s, 13β-Me), 2.80-3.00 (3H, m, 6-H2 and 9α-H), 3.79 (3H, s, 3-OMe), 6.65 (1H, d, J 2.8 Hz, 4-H), 6.75 (1H, dd, J 8.6 and 2.8 Hz, 2-H), and 7.22 (1H, d, J 8.6 Hz, 1-H) (Found: C, 77.2; H, 7.7; N, 4.5%; M+, 309. C20H23O2N requires C, 77.6%; H, 7.5; N, 4.5%; M, 309).

Wittig-Horner olefination of the 14α-formyl 17-ketone (87).

Diethyl cyanomethylphosphonate (0.22 ml, 240 mg, 1.36 mmol) in dry tetrahydrofuran (5 ml) was added to a suspension of sodium hydride (50% dispersion in oil, 72 mg, 1.5 mmol) in dry tetrahydrofuran (5 ml) at 0°C while stirring. A solution of 14α-formyl 17-ketone (87) (385 mg, 1.23 mmol) in dry tetrahydrofuran (5 ml) was added. The mixture was stirred at 0°C under nitrogen for 5 h. Standard work-up (ethyl acetate) gave an oily residue (438 mg). Chromatography of the residue on silica gel (40 g) [ethyl acetate-hexane (1:9)-(1:4)] gave (2Z)-3-(3-methoxy-17-oxoestra-1,3,5(10)-trien-14-yl)acrylonitrile (236) (43 mg, 9%), as an oil; [α]D + 93° (c 1.0); νmax 2035 (C≡N) and 1719 (C=O) cm⁻¹; δH 1.18 (3H, s, 13′,8-Me), 2.86 (2H, m, 6′-H2), 3.78 (3H, s, 3-OMe), 5.52 (1H, d, J 13.0 Hz, 2-H), 6.62 (1H, d, J 13.0 Hz, 3-H), 6.63 (1H, d, J 2.5 Hz, 4′-H), 6.73 (1H, dd, J 8.5 and 2.5 Hz, 2′-H), and 7.18 (1H, d, J 8.5 Hz, 1′-H); δC 216.9 (C-17′), 157.7 (C-3′), 153.9 (C-3), 137.5 (C-5′), 131.4 (C-10′), 127.0 (C-1′), 166.6 (CN), 113.7 (C-4′), 112.1 (C-2′), 101.9 (C-2), 55.2 (3-OMe), 52.3 (C-13′), 53.4 (C-14′), 44.2 (C-8′), 37.9 (C-9′), 34.2 (C-16′), 29.9 (C-6′), 26.3 (C-7′), 25.8 (C-12′), 25.6 (C-15′), 24.6 (C-11′) and 17.8 (C-18′) (Found: C, 78.6; H, 7.4; N, 4.5%, M+, 335.190. C25H26NO2 requires C, 78.8; H, 7.5; N, 4.2%; M, 335.189) followed by (2E)-3-(3-methoxy-17-oxoestra-
1,3,5(10)-tri-en-14-yl)acrylonitrile (237) (315 mg, 76%), as an oil; $[\alpha]_D + 130^\circ$ (c 1.0);
$\nu_{\text{max}}$ 2225 (C=N) and 1735 (C=O) cm$^{-1}$; $\delta_H$ 1.17 (3H, s, 13'β-Me), 2.90 (2H, m, 6'-H$_2$), 3.79 (3H, s, 3-OMe), 5.42 (1H, d, J 17.0 Hz, 2-H), 6.63 (1H, d, J 8.6 Hz, 4'-H), 6.74 (1H, dd, J 8.6 and 2.5 Hz, 2'-H), 6.98 (1H, d, J 17.0 Hz, 3-H), and 7.20 (1H, J 8.6 Hz, 1'-H); $\delta_C$ 216.3 (C-17'), 157.8 (C-3'), 155.9 (C-3), 137.1 (C-5'), 131.6 (C-10'), 126.9 (C-1'), 116.9 (CN), 113.8 (C-4'), 112.1 (C-2'), 102.6 (C-2), 55.2 (3-OMe), 53.0 (C-14'), 51.7 (C-13'), 42.4 (C-8'), 38.2 (C-9'), 33.5 (C-16'), 29.9 (C-6'), 26.1 (C-7'), 25.6 (C-12' and C-15'), 23.7 (C-11') and 18.1 (C-18') (Found: C, 80.2; H, 7.7; N, 4.3%, $M^+$, 335.190. $C_{22}H_{25}NO_2$ requires C, 78.8; H, 7.5; N, 4.2%; $M$, 335.189).

3-(3-methoxy-17-oxoestra-1,3,5(10)-tri-en-14-yl)propionitrile (238).

A solution of the (2E)-acrylonitrile (237) (358 mg, 1.07 mmol) in dry tetrahydrofuran (18 ml) containing 5% palladium on carbon (370 mg) was stirred at 20°C under hydrogen for 48 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give a crystalline residue (378 mg). Filtration of the residue through silica gel (3.8 g) [ethyl acetate-toluene (1:19)] gave the propionitrile (238) (252 mg, 70%), m.p. 183-186°C (from ethyl acetate); $[\alpha]_D + 192^\circ$ (c 1.0); $\nu_{\text{max}}$ 2248 (C=N) and 1732 (C=O) cm$^{-1}$; $\delta_H$ 1.06 (3H, s, 13'β-Me), 2.74 obsc. (1H, td, J 2 x 12.3 and 6.1 Hz, 9'α-H), 2.90 (2H, m, 6'-H$_2$), 3.78 (3H, s, 3-OMe), 6.62 (1H, d, J 2.7 Hz, 4'-H), 6.74 (1H, dd, J 8.6 and 2.7 Hz, 2'-H) and 7.20 (1H, d, J 8.6 Hz, 1'-H); $\delta_C$ 217.5 (C-17'), 157.7 (C-3'), 136.8 (C-5'), 132.3 (C-10'), 127.1 (C-1'), 119.4 (CN), 113.8 (C-4'), 112.0 (C-2'), 55.2 (3-OMe), 54.6 (C-14'), 45.4 (C-13'), 42.7 (C-8'), 37.3 (C-9'), 33.4 (C-16'), 31.2 (C-6'), 27.0 (C-12'), 25.9 (C-7'), 25.6 (C-3), 25.0 (C-15'), 24.9 (C-11'), 17.9 (C-18') and 14.5 (C-2) (Found: C, 78.3; H, 8.4; N, 4.2%; $M^+$, 337. $C_{22}H_{21}NO_2$ requires C, 78.3; H, 8.1; N, 4.2%; $M$, 337).
DIBAH reduction of propionitrile (238).

Diisobutylalumininium hydride (1.5 M in toluene; 0.415 ml, 0.62 mmol) was added slowly (over 15 min) to a solution of the nitrile (238) (140 mg, 0.42 mmol) in toluene (15 ml) at -80°C. After 1 h at -80°C, dilute acetic acid (0.5M, 10 ml) was added, followed by standard work-up (ethyl acetate) to give an oily residue (125 mg). Chromatography of the residue on silica gel (13 g) [ethyl acetate-toluene (1:4)] gave starting material (238) (40 mg, 29%), followed by 3-(17α-hydroxy-3-methoxyestra-1,3,5(10)-trien-14-yl)propionitrile (239) (31 mg, 22%), m.p. 122-125°C (from ethyl acetate-hexane); [α]D +97° (c 1.0); νmax 3507(OH) and 2246(C=N) cm⁻¹; δH 0.82 (3H, s, 13'-β-Me), 1.80 (1H, s, exch. by D₂O, 17'-OH), 2.70-2.90 (3H, m, 6'-H₂ and 9'-α-H), 3.77 (3H, s, 3-OMe), 3.96 (1H, dd, J 7.7 and 2.1 Hz, 17'-β-H), 6.60 (1H, d, J 2.7 Hz, 4'-H), 6.72 (1H, dd, J 8.6 and 2.7 Hz, 2'-H) and 7.21 (1H, d, J 8.6 Hz, 1'-H); δC 157.4 (C-3'), 136.8 (C-5'), 132.3 (C-10'), 126.9 (C-1'), 120.8 (CN), 113.8 (C-4'), 111.8 (C-2'), 79.9 (C-17'), 55.2 (3-OMe), 50.0 (C-14'), 47.6 (C-13'), 44.4 (C-8'), 36.8 (C-9'), 32.7 (C-16'), 31.2 (C-6'), 29.2 (C-3), 27.2 (C-12'), 26.2 (C-7'), 26.0 (C-15'), 24.3 (C-11'), 22.4 (C-18'), and 14.5 (C-2) (Found: C, 77.6; H, 8.8; N, 4.1%; M⁺, 339. C₂₂H₂₉N0₂ requires C, 77.8; H, 8.6; N, 4.1%; M, 339) followed by an inseparable mixture of more polar products (43 mg).

3-Methoxy-14-(1-oxoprop-2-enyl)estra-1,3,5(10)-trien-17-one (242).

A solution of the hemiketal (224) (140 mg, 0.41 mmol) in dry methylene chloride (10 ml) was added to a suspension of the periodinane (Dess-Martin reagent) (700 mg, 1.65 mmol) in dry methylene chloride (20 ml). The mixture was stirred at 25°C under nitrogen for 6 h, followed by the addition of sodium thiosulfate (10% in water, 20 ml) and saturated sodium hydrogen carbonate (20 ml). The mixture was stirred for 10 min, followed by extraction with diethyl ether (3x10 ml). The combined organic layers was washed with saturated aqueous sodium hydrogen carbonate (2x20 ml) then dried (MgSO₄) and concentrated under reduced pressure.
to give an oily residue (145 mg). Filtration of the residue through silica gel (1.5 g) [ethyl acetate-toluene (1:4)] gave the 14α-acroyl 17-ketone (242) (115 mg, 83%), m.p. 122-125°C (from diethyl ether); [α]D +173° (c 1.0); νmax. 1736(C=O) and 1677(C=O) cm⁻¹; δH(400 MHz) 1.06 (3H, d, J 0.8 Hz, 13β-Me), 1.46 (1H, m, 7α-, 8β-, 11β- and 12β-H), 2.12-2.20 (2H, m, 7β- and 11α-H), 2.28-2.42 (4H, m, 9α-, 12α-, 15β- and 16β-H), 2.88 (2H, m, 6-H₂), 3.77 (3H, s, 3-O Me), 5.60 (1H, dd, J 10.4 and 1.8 Hz, 3'-Hcis), 6.20 (1H, dd, J 16.7 and 1.8 Hz, 3’-Htrans), 6.62 (1H, d, J 2.7 Hz, 4-H), 6.72 (1-H, dd, J 8.7 and 2.7 Hz, 2-H), 6.84 (1H, dd, J 16.7 and 10.4 Hz, 2’-H), and 7.16 (1H, d, J 8.7 Hz, 1-H); δC 215.6 (C-17), 202.0 (C-1’), 157.6 (C-3), 137.5 (C-5), 134.0 (C-2’), 131.7 (C-10), 128.6 (C-3’), 128.2 (C-1), 113.7 (C-4), 112.3 (C-2), 62.1 (C-14), 55.2 (3-O Me), 52.2 (C-13), 41.8 (C-8), 40.5 (C-9), 32.6 (C-12), 32.0 (C-6), 28.4 (C-16), 26.9 (C-15), 26.1 (C-7), 24.6 (C-11), and 19.1 (C-18) (Found: C, 78.2; H, 7.5%; M⁺, 338. C₂₂H₂₆O₃ requires C, 78.1; H, 7.7%; M, 338).

Samarium diiodide treatment of the 14α-enone 17-ketone (242)

Samarium metal (105 mg, 0.70 mmol) was flame dried under a flow of nitrogen for 5 min, then cooled. Dry tetrahydrofuran (5 ml) was added, followed by diiodoethane (191 mg, 0.68 mmol) and the mixture was stirred at 25°C for 1 h. A solution of the 14α-acroyl 17-ketone (242) (57 mg, 0.17 mmol) in dry tetrahydrofuran (1 ml), followed by t-butanol (0.1 ml) was added to the deep blue solution of samarium(II) iodide at -78°C. The reaction mixture was stirred at -78°C under nitrogen for 2 h. Standard work-up (ethyl acetate) gave a crystalline product (48 mg). Chromatography of the residue on silica gel (5 g) [chloroform-methanol (99:1)] gave product (243) (43 mg, 75%), m.p. 192-195°C (dec.) from (chloroform-methanol); [α]D +61°; νmax. 3439(OH) and 1728(CO) cm⁻¹, δH(C₃D₈N) 1.16 (3H, s, 13β-Me), 2.80 (3H, m, 9α- and 6-H₂), 3.01 (1H, t, J 2 x 5.1 Hz), 3.72 (3H, s, OMe),
6.79 (1H, d, J 2.8 Hz, 4-H), 6.91 (1H, dd, J 8.6 and 2.8 Hz, 2-H), 7.28 (1H, d, J 8.6 Hz, 1-H), M+340

5-Acetyl 2,2-dimethyl-1,3-dioxane-4,6-dione.

A solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (1.0 g, 6.94 mmol) in dichloromethane (10 ml) and pyridine (1.3 ml) at 0°C, was treated with a solution of acetyl chloride (1.2 ml; 1.3 g, 7.4 ml) in dichloromethane (5 ml). The mixture was stirred at 0°C for 1 h, then at 20°C for 1 h. The mixture was concentrated under reduced pressure, followed by the addition of benzene to promote the precipitation. The mixture was filtered, and the filtrate was concentrated to give a crystalline product, which was dissolved in toluene and filtered through celite. Excess pyridine was azeotropically removed with toluene. Crystallisation from benzene-hexane gave 5-acetyl 2,2-dimethyl-1,3-dioxane-4,6-dione, m.p. 78-82°C, (lit.,145 m.p. 83.5-84.5°C).

(5E)-6-(3-Methyl-17-oxoestra-1,3,5(10)-trien-14-yl)hex-5-en-2-one (244).

A solution of the hemiketal (224) (143 mg, 0.42 mmol) and 5-acetyl 2,2-dimethyl-1,3-dioxane-4,6-dione (5-acyl Meldrum's acid) (100 mg, 0.54 mmol) was refluxed in benzene (2 ml) for 5 h. The benzene was gradually replaced with xylene (3 ml) by distillation. After refluxing for 2 h, the reaction mixture was cooled. Direct chromatography on silica gel (16 g) [ethyl acetate-toluene (1:4)] gave (5E)-6-(3-methoxy-17-oxoestra-1,3,5(10)-trien-14-yl)hex-5-en-2-one (244) (121 mg, 75%), m.p. 97-100°C (from diethyl ether); [α]D +105° (c 1.0); νmax. 1729(C=O) and 1713(C=O) cm⁻¹; δH(400 MHz) 1.09 (3H, s, 13’β-Me), 1.42 (1H,ddd, J 23.9, 12.2 and 6.7 Hz, 7’α-H), 1.55 (1H, ddd, J 26.0, 12.8, and 5.0 Hz, 11’α-H), 1.62-1.70 (3H, m, 15’α- and 15’β-H), 1.75 (1H, m, W2/2 23.9 Hz, 7’β-H), 1.83 (1H, td, J 2 x 11.7 and 2.4 Hz, 8’β-H), 1.98-2.18 (3H, m, 12’α-, 12’β- and 16’β-H), 2.10 obsc. (3H, s, 1-CH3), 2.34-2.46 (6H, m, 11’β-, 16’α-H, 3-H2 and 4-H2), 2.60 (1H, td, J 2 x 12.1 and 5.0 Hz, 9’α-H),
2.84 (2H, m, 6'-H₂), 3.76 (3H, s, 3-OMe), 5.54 (1H, dt, J 16.0 and 2 × 6.7 Hz, 5-H),
5.68 (1H, dd, J 16.0 and 1.0 Hz, 6-H), 6.60 (1H, d, J 2.8 Hz, 4'-H), 6.70 (1H, dd, J 8.6
and 2.8 Hz, 2'-H), and 7.18 (1H, d, J 8.6 Hz, 1'-H); δ C 219.1 (C-17'), 208.5 (C-2),
158.1 (C-3'), 138.3 (C-5'), 133.5 (C-10'), 132.2 (C-5), 130.8 (C-6), 127.5 (C-1'),
114.4 (C-4'), 112.4 (C-2'), 55.8 (3-OMe), 53.9 (C-14'), 49.6 (C-13'), 44.1 (C-4), 42.9
(C-8'), 38.2 (C-9'), 34.8 (C-3), 30.8 (C-6'), 30.6 (C-1), 28.3 (C-16'), 27.5 (C-15'),
26.8 (C-12'), 26.3 (C-7'), 24.4 (C-11'), and 18.4 (C-18') (Found: C, 78.9; H, 8.8%;
M⁺, 380. C₂₅H₃₂O₃ requires C, 78.9; H, 8.5%; M, 380).
4.2. Androstane chemistry

*Androsta-3,5,14,16-tetraene-3,17-diyi diacetate (246)*

The 15α-hydroxy 17-ketone (245) (6 g, 19.9 mmol) was dissolved in a solution of acetic anhydride (60 ml) and isopropenyl acetate (60 ml). Toluene-p-sulfonic acid (3.714 g, 21 mmol) was added and the resulting solution was refluxed under nitrogen for 8 h. The reaction mixture was cooled and then neutralised with aqueous sodium hydrogen carbonate. Standard work-up (toluene) afforded a brown crystalline residue (7.5 g). Flash chromatography of the residue on silica gel (150 g) [ethyl acetate-toluene (3:97)] gave androsta-3,5,14,16-tetraene-3,17-diyi diacetate (246) (6.1 g, 84%), m.p. 106-108°C (from chloroform-methanol); [α]D +62° (c 1.0) [lit.,148 m.p. 106-110°C; [α]D +67° (c 0.9)]; νmax. 1745 (C=O) cm⁻¹; δH 1.04 (each 3H, s, 10β-Me and 13β-Me), 2.07 and 2.14 (each 3H, s, 3-and 17-OAc), 5.43 (1H, t, J 2 x 4.0 Hz, 6-H), 5.66 (1H, d, J 2.1 Hz, 4-H), 5.74 (1H, t, J 2 x 2.3 Hz, 15-H), and 6.05 (1H, d, J 2.3 Hz, 16-H) (Found: C, 75.0; H, 7.7%; M+, 368. C23H28O4 requires C, 75.0; H, 7.7%; M, 368).

*(20R)-3-Oxo-20-phenylsulfonyl-14,21-cyclo-14β-pregna-4,15-dien-17α-yl acetate (248)*

The bis(dienyl acetate) (246) (7.28 g, 21.3 mmol) and phenyl vinyl sulfone (3.93 g, 23.4 mmol) were dissolved in xylene (1.3 ml) in an ampoule. The ampoule was heated to 145°C under nitrogen, then sealed. After 4 days at 145°C, the ampoule was cooled and the xylene was evaporated under reduced pressure. The residue (12.0 g) was treated with sodium ethoxide (0.1 M, 160 ml) in ethanol (806 ml). After stirring at 20°C for 1 h dry ice was added and the mixture concentrated under reduced pressure. Standard work-up (chloroform) afforded a brown crystalline residue (11.2 g). Filtration of the residue through silica gel (140 g) [ethyl acetate-toluene (3:7)] gave (20R)-3-oxo-20-phenylsulfonyl-14,21-cyclo-14β-pregna-4,15-dien-17α-yl acetate (248) (7.7 g, 73%), m.p. 244-247°C (from chloroform-methanol); [α]D +132° (c 1.0) [lit.,148 m.p. 244-247°C, [α]D +136° (c 1.0)]; νmax. 1745 (C=O), 1665 (C=O), and 1620 (C=C) cm⁻¹; δH 0.91 and 1.14 (each 3H, s, 10β- and 13β-Me),
1.60 (1H, s, 17α-OAc), 4.15 (1H, dd, J 8.5 and 4.9 Hz, 20-H) 5.76 br (1H, s, 4-H), 6.10 and 6.36 (each 1H, d, J 6.2 Hz, 15- and 16-H) and 7.51-7.91 (5H, m, CαH5); δc 199.1 (C-3), 169.9 (C-5), 168.9 (17-OAc), 140.7 (C-4'), 133.5 (C-15), 131.1 (C-16), 129.9 (C-20), 129.1 (C-2' and C-6'), 128.3 (C-3' and C-5'), 124.1 (C-4), 94.5 (C-17), 66.9 (C-21), 62.3 (C-1'), 55.2 (C-14), 49.5 (C-9), 38.4 (C-13 and C-10), 35.6 (C-8), 35.5 (C-1), 33.8 (C-2), 32.3 (C-6), 31.3 (C-7) 28.2 and 27.3 (C-12 and C-11), 20.9 (17-OAc), 17.5 (C-19), and 14.5 (C-18) (Found: C, 70.1; H, 6.9%; M+, 494. C29H34O5S requires C, 70.4; H, 6.9%; M, 494).

(20R)-3,3-Ethyleneoxy-20-phenylsulfonyl-14,21-cyclo-14β-pregna-5,15-dien-17α-yl acetate. (249)
The sulfone (248) (1.0 g, 2.0 mmol) and toluene-p-sulfonic acid (86 mg) were dissolved in a solution of benzene (345 ml) and ethylene glycol (8.6 ml), and the resulting solution was refluxed, with percolation of condensate through molecular sieves (4Å, 17 g). After 1 h, the molecular sieves were renewed, and the reaction mixture was refluxed for a further 3 h, then cooled. The reaction mixture was neutralised with saturated aqueous sodium hydrogen carbonate, followed by standard work-up (toluene) to give a crystalline residue (1.1 g). Filtration of the residue through silica gel (30 g) [ethyl acetate-toluene (3:7)] gave the 3-ketal (249) (1.0 g, 94%), m.p. 239-242°C (from chloroform-methanol); [α]D +61° (c 1.0) [lit.,148 m.p. 234-237°C, [α]D +51° (c 1.1)]; νmax. 1745(C=O) cm⁻¹; δH 0.85 and 0.92 (each 3H, s, 10β- and 13β-Me), 1.57 (3H, s, 17α-OAc), 1.90 obsc. (1H, dd, J 12.8 and 5.0 Hz, 15α-H), 2.10 obsc. (1H, dd, J 14.5 and 2.3 Hz, 4β-H), 2.54 (1H, ddd, J 14.5, 5.9 and 3.8 Hz, 4α-H), 3.90 (4H, m, OCH₂CH₂O), 4.16 (1H, dd, J 8.5 and 5.2 Hz, 20-H), 5.36 (1H, m, Wv 8 Hz, 6-H), 6.15 and 6.32 (each 1H, d, J 6.4 Hz, 15- and 16-H), and 7.53-7.89 (5H, m, CαH5) (Found: C, 69.3; H, 7.3%; M+,538. C31H38O₅S requires C, 69.2; H, 7.1%; M, 538).
Reduction of the Sulfone (249)

The sulfone (249) (2.55 g, 4.74 mmol) in dry tetrahydrofuran (75 ml) was added to a solution of sodium (2.18 g, 95 mmol atom) in dry liquid ammonia (700 ml) and tetrahydrofuran (75 ml). The mixture was stirred for 1 h, then solid ammonium chloride was added. The ammonia was evaporated, and the residual tetrahydrofuran was evaporated under reduced pressure. Standard work-up (chloroform) gave a crystalline residue (1.51 g). Chromatography of the residue on silica gel (30 g) [ethyl acetate-toluene (3:7)] gave 3,3-ethylenedioxy-14,21-cyclo-14β-pregna-5,15-dien-17α-yl acetate (250) (1.34 g, 80%), m.p. 163-166°C (ethyl acetate-hexane); [α]D +35° (c 1.0); νmax. 3457 br (OH) cm⁻¹; δH (400 MHz) 0.88 (3H, d, J 0.8 Hz, 13β-Me) and 0.99 (3H, s, 10β-Me), 1.04 (1H, dt, J 13.0, and 2 x 3.5 Hz, 12β-H), 1.12 (1H, dd, J 12.2, 8.7 and 3.3 Hz, 21β-H), 1.23 (1H, td, J 2 x 12.4 and 3.7 Hz, 9α-H), 1.46-1.60 (2H, m, 8β- and 20β-H), 1.70 (1H, s, exch. by D₂O, 17-OH), 2.13 (1H, dd, J 14.4 and 3.0 Hz, 4β-H), 2.59 (1H, ddd, J 14.4, 5.9 and 3.5 Hz, 4α-H), 3.94 (4H, m, OCH₂CH₂O), 5.39 (1H, m, W 9.6 Hz, 6-H), and 5.86 and 5.96 (each 1H, d, J 6.1 Hz, 15- and 16-H); δc (100.6 MHz) 139.9 (C-5), 135.9 (C-15), 134.0 (C-16), 121.7 (C-6), 109.4 (C-3), 90.5 (C-17), 64.5 and 64.2 (ketal), 57.6 (C-13), 56.5 (C-14), 46.1 (C-9), 41.9 (C-4), 36.5 (C-10), 36.2 (C-20), 32.3 (C-8), 31.8 (C-2) and 31.0 (C-11), 28.7 (C-21), 26.9 (C-12), 26.3 (C-7), 21.3 (C-1), 18.8 (C-19) and 13.8 (C-18) (Found: C, 77.2; H, 9.1%; M⁺,356. C₂₃H₃₂O₃ requires C, 77.5; H, 9.1%; M,356).

3,3-Ethylenedioxy-14,21-cyclo-14β-pregna-5,15-dien-17α-yl acetate (251)

The 17-hydroxy olefin (250) (1 g; 2.8 mmol) was dissolved in a solution of dimethylaminopyridine (8.35 mg), triethylamine (19 ml) and acetic anhydride (2.3 ml). The reaction mixture was stirred at 20°C for 4 h, then methanol (5 ml) was added and stirring was continued for a further 30 min. Ice and solid sodium hydrogen carbonate were added, followed by standard work-up (chloroform) to give a crystalline residue (1.45 g). Filtration of the residue through silica gel (15 g) [ethyl
acetate-toluene (3:7)] gave the 17α-acetate (251) (1.02 g; 91%), m.p. 152-154°C (from ethyl acetate-hexane); [α]D -19° (c 1.0); νmax 1731(C=O) cm⁻¹; δH 0.89 and 0.98 (each 3H, s, 10β- and 13β-Me), 2.01 (3H, s, 17α-OAc), 2.10 (1H, dd, J 14.3 and 2.3 Hz, 4β-H), 2.55 (1H, ddd, J 14.3, 5.6 and 3.3 Hz, 4α-H), 3.92 (4H, m, OCH₂CH₂O), 5.39 (1H, m, W adulteration 9.4 Hz, 6-H), 5.98 and 6.22 (each 1H, d, J 6.1 Hz, 15- and 16-H) (Found: C, 75.0; H, 8.2%; M⁺, 398. C₂₅H₄₅O₄ requires C, 75.3; H, 8.6%; M, 398).

3-Oxo-14,21-cyclo-14β-pregna-4,15-dien-17α-yl acetate (252)
The 3-ketal (251) (200 mg, 0.50 mmol) was dissolved in methanol (2 ml) and conc. hydrochloric acid (0.035 ml). After stirring at 20°C for 3 h, the reaction mixture was neutralised with sodium hydrogen carbonate and the methanol was evaporated under reduced pressure. Standard work-up (chloroform) afforded a crystalline residue (180 mg). Chromatography of the residue on silica gel (18 g) [ethyl acetate-toluene (3:7)] gave the enone (252) (144 mg, 81%), m.p. 202-206°C (from methanol-chloroform); [α]D +142° (c 1.0) [lit.,148 m.p. 204-205°C; [α]D +128° (c 0.9) νmax 1730(C=O) and 1664(C=O) cm⁻¹; δH 0.89 and 1.11 (each 3H, s, 10β- and 13β-Me) 2.02 (3H, s, 17α-OAc), 5.70 (1H, br s, 4-H), 5.87 (1H, d, J 6.2 Hz, 15-H) and 6.20 (1H, d, J 6.2 Hz, 16-H) (Found: C, 78.3; H, 8.6%; M⁺, 354. C₂₃H₃₀O₃ requires C, 78.0; H, 8.5%; M, 354).

17α-Hydroxy-14,21-cyclo-14β-pregna-4,15-dien-3-one (253)
The 17α-acetoxy olefin (252) (186 mg) was treated with ethanolic sodium ethoxide (0.01 M, 23 ml) at 25°C for 6 h. Dry ice was added, followed by evaporation of the ethanol under reduced pressure. Standard work-up (chloroform) gave a crystalline residue (160 mg). Chromatography of the residue on silica gel (16 g) [ethyl acetate-toluene (1:4)] gave 17α-hydroxy olefin (253) (128 mg, 78%), m.p. 193-196°C (from ethyl acetate-hexane); [α]D +122° (c 1.0) [lit.,148 m.p. 196-198°C; [α]D +178.5° (c 1.0)]; νmax 3426(OH) and 1657(C=O) cm⁻¹; δH 0.90 and 1.16 (each 3H, s, 10β- and
13β-Me), 2.04 (1H, ddd, J 13.4, 4.8 and 3.7 Hz, 1β-H), 5.75 (1H, s, 4-H), 5.88 (each 1H, s, 15-H and 16-H) (Found: C, 80.4; H, 9.2%; M+, 312. C_{21}H_{28}O_{2} requires C, 80.7; H, 9.0%; M, 312).

**Hydroxylation of the 17-acetoxy olefin (251)**

Method a): Osmium tetroxide (100 mg, 0.39 mmol) was added to the 17-acetoxy olefin (251) (156.6 mg, 0.39 mmol) in pyridine (5 ml), and the reaction mixture was maintained at 4°C in the dark for 24 h, then treated with aqueous sodium hydrogen sulfite (3.74 ml, 10%) for 1 h. Standard work-up (chloroform) gave a crystalline residue (166 mg). Chromatography of the residue on silica gel (16 g) [ethyl acetate-benzene (3:7)] gave starting material (251) (45 mg, 32%), followed by 3,3-ethylenedioxy-14,21-cyclo-14β-pregn-5-ene-15β,16β,17α-triol 17-acetate (256) (41 mg, 24%), m.p. 210-213°C (from chloroform-hexane); [α]_D -31° (c 1.0); ν_{max} 3427(OH) and 1707(C=O) cm\(^{-1}\); δ H 1.03 and 1.04 (each 3H, s, 10β- and 13β-Me), 2.10 (3H, s, 17α-OAc), 3.36 (1H, d, J 4.2 Hz, exch. by D_2O, 16-OH), 3.97 (4H, m, OCH_2CH_2O), 4.22 (1H, dd, J 9.4 and 1.5 Hz, 15-H), 4.33 (1H, ddd, J 9.4, 4.2 and 1.5 Hz → dd J 9.4 and 1.5 Hz on D_2O exch., 16-H), 5.13 (1H, s, exch. by D_2O, 15-OH), and 5.36 (1H, m, Wv 9.0 Hz, 6-H) (Found: C, 68.9; H, 7.8%; M+, 432. C_{25}H_{36}O_{6} requires C, 69.4; H, 8.4%; M, 432), followed by 3,3-ethylenedioxy-14,21-cyclo-14β-pregn-5-ene-15α,16α,17α-triol 17-acetate (257) (37 mg, 22%), m.p. 225-230°C (from chloroform-hexane); [α]_D -30° (c 1.0); ν_{max} 3494(OH) and 1724(C=O) cm\(^{-1}\); δ H 0.95 and 1.00 (each 3H, s, 10β- and 13β-Me), 2.10 (3H, s, 17α-OAc), 2.56 (1H, ddd, J 14.4, 5.4 and 2.7 Hz, 4α-H), 2.90 (1H, d, J 5.7 Hz, exch. by D_2O, 16-OH), 2.96 (1H, d, J 5.3 Hz, exch. by D_2O, 15-OH), 3.87 (4H, m, OCH_2CH_2O), 3.99 (1H, dd, J 7.6 and 5.3 Hz → d, J 7.6 Hz on D_2O exch., 15-H), 4.49 (1H, dd, J 7.6 and 5.3 Hz → d, J 7.6 Hz on D_2O exch., 16-H), and 5.39 (1H, m, Wv 9.0 Hz, 6-H) (Found: C, 69.2; H, 7.9%; M+, 432. C_{25}H_{36}O_{6} requires C, 69.4; H, 8.4%; M, 432)
Method b): Osmium tetroxide (1 g, 3.93 mmol) was added to a solution of the 17-acetoxy olefin (251) (1.56 g, 3.92 mmol) in pyridine (50 ml). The mixture was maintained at 4°C in the dark for 3 days, then treated with aqueous sodium hydrogen sulfite (37 ml, 10%) for 1 h. Standard work-up (chloroform) gave a crystalline residue (1.72 g). Chromatography of the residue on silica gel (52 g) [ethyl acetate-toluene (1:1) then (7:3)] gave the diol (256) (359 mg, 21%) and the diol (257) (300 mg, 18%), followed by 3,3-ethylenedioxy-14,21-cyclo-5β,14β-pregnane-5,6β,15β,16β,17α-pentaol 17-acetate (258) (168 mg, 10%), m.p. 194-196°C (from ethyl acetate-chloroform); [α]D -4° (c 1.0); νmax. 3449(OH) and 1708(C=O) cm⁻¹; δH 0.98 and 1.07 (each 3H, s, 10β- and 13β-Me), 2.06 (3H, s, 17α-OAc), 2.14 (1H, d, J 14.2 Hz, 4β-H), 2.45 (1H, ddd, J 12.2, 10.0 and 4.0 Hz, 8β-H), 2.75 br (1H, s exch. by D2O, 6α-OH), 3.35 (1H, d, J 4.6 Hz, exch. by D2O, 16-OH), 3.52 (1H, t, J 2 x 2.9 Hz, 6α-H), 3.90 (4H, m, OCH2CH2O), 4.05 (1H, s, exch. by D2O, 5β-OH), 4.19 (1H, dd, J 9.4 and 2.0 Hz, 15-H), 4.37 (1H, ddd, J 9.4, 4.6, and 2.0 Hz → dd, J 9.4 and 2.0 Hz on D2O exch., 16-H) and 5.10 (1H, s, exch. by D2O, 15-OH) (Found: C, 64.0; H, 8.5%; M⁺, 466. C25H33O8 requires C, 64.4; H, 8.2%; M, 466) followed by 3,3-ethylenedioxy-14,21-cyclo-5β,14β-pregnane-5,6β,15α,16α,17α-pentaol 17-acetate (259) (116 mg, 7%), m.p. 205-210°C (from ethyl acetate-chloroform); [α]D +7.6° (c 1.0); νmax. 3502(OH) and 1723(C=O) cm⁻¹; δH 0.91 and 1.02 (each 3H, s, 10β- and 13β-Me), 2.07 (3H, s, 17α-OAc), 2.28 (1H, J 13.9 Hz, 4β-H), 2.60 (1H, m, Wv 28.0 Hz, 8β-H), 2.84 br (1H, s exch. by D2O, 6β-OH), 3.05 (1H, d, J 6.0 Hz, exch. by D2O, 16-OH), 3.12 (1H, d, J 5.1 Hz, exch. by D2O, 15-OH), 3.59 (1H, t, J 2 x 3.0 Hz, 6α-H), 3.90 (4H, m, OCH2CH2O), 4.02 (1H, dd obsc., J 7.6 and 5.4 → d, J 7.6 Hz on D2O exch., 15-H), 4.04 (1H, s, exch. by D2O, 5β-OH), and 4.52 (1H, dd, J 7.6 and 5.8 Hz → d, J 7.6 Hz on D2O exch., 16-H) (Found: C, 64.0; H, 8.5%; M⁺, 466. C25H38O8 requires C, 64.4; H, 8.2%; M, 466).
Method c): Poly(vinylpyridine) (2g) was stirred in cyclohexane (15 ml) with osmium tetroxide (100 mg, 0.39 mmol) at 25°C under a nitrogen atmosphere for 24 h. The polymer was filtered off, washed with cyclohexane and dried under vacuum. The mass of the dried polymer was 2.1 g, indicating that the whole amount of osmium tetroxide was complexed. The polymer contained ca. 9.2 mmol of osmium tetroxide per gram.

The acetoxy olefin (251) (500 mg, 1.26 mmol) in tetrahydrofuran (2.5 ml) and water (1 ml), was treated with trimethylamine-N-oxide (200 mg, 1.82 mmol) and the poly(vinylpyridine)-osmium tetroxide polymer (600 mg, ca. 0.12 mmol OsO₄). The mixture was refluxed at 70°C for 4 h. After cooling, the resin was filtered and washed with tetrahydrofuran (10 ml). The water was removed by filtration through anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give an oily residue (491 mg). Chromatography of the residue on silica gel (25 g) [ethyl acetate-toluene (3:7), (1:1), then (7:3)] gave starting material (251) (263 mg, 53%), the diol (256) (92 mg, 17%), followed by diol (257) (76 mg, 14%) and then a mixture of tetraols (258) and (259) (16 mg, 3%).

3,3-Ethylendioxy-17-oxoandrost-5-ene-14-carbaldehyde (262)
A mixture of the acetoxy diols, (256) and (257) (36 mg, 0.08 mmol) in tetrahydrofuran, was treated with methanolic potassium hydroxide (3%, 10 ml) for 5 min. The mixture was neutralised with an excess of ammonium chloride and the solvent was evaporated under reduced pressure. Standard work-up (chloroform), gave a mixture of 15,16,17-triols, which was treated with aqueous sodium metaperiodate (6%, 1.34 ml) in ethanol (2 ml) and benzene (4 ml). The reaction mixture was stirred at 20°C for 1 h. Standard work-up (chloroform) gave a crystalline residue which was recrystallised from ethyl acetate to give the 14α-formyl 17-ketone (262) (19 mg, 65%), m.p. 149-151°C; [α]D +21° (c 1.0);
\(\nu_{\text{max.}} 1740 (\text{C}=\text{O}) \text{ cm}^{-1}; \delta_H 1.03 \text{ and } 1.07 \text{ (each } 3\text{H, s, } 10\beta- \text{ and } 13\beta-\text{Me}), 2.58 \text{ (1H, ddd, } J 14.2, 5.9 \text{ and } 3.5 \text{ Hz, } 4\alpha-\text{H}), 3.95 \text{ (4H, m, OCH}_2\text{CH}_2\text{O}, 5.39 \text{ (1H, m, } \nu\nu 9.0 \text{ Hz, } 6-\text{H}), \text{ and } 10.07 \text{ (1H, s, } 14\alpha-\text{CHO}) \text{ (Found: C, 73.7; H, 8.1%; } M^+, 358. \text{ C}_{22}\text{H}_{30}\text{O}_4 \text{ requires C, 73.7; H, 8.4%; } M, 358).\)

17\(\beta\)-Acetoxy-3,3-ethylenedioxyandrost-5-ene-14,17\(\alpha\)-dicarbaldehyde (263)

Aqueous sodium metaperiodate (6\%, 2.5 ml) was added to a stirred solution of the 17\(\alpha\)-acetoxy-15,16-diol (257) (64 mg, 0.15 mmol) in absolute ethanol (6 ml). After stirring for 1 h at 20°C, standard work-up (chloroform) gave a crystalline residue, which was recrystallised from ethyl acetate-hexane to give the 14,17\(\alpha\)-dicarbaldehyde (263) (60 mg, 94\%), m.p. 152-156°C; [\(\alpha\)]\(D\) -38° (c 1.0);
\(\nu_{\text{max.}} 1728 (\text{C}=\text{O}) \text{ cm}^{-1}; \delta_H 1.08 \text{ and } 1.21 \text{ (each } 3\text{H, s, } 10\beta- \text{ and } 13\beta-\text{Me}), 2.04 \text{ (3H, s, } 17\beta-\text{OAc}), 2.31 \text{ (1H, ddd, } J 12.0, 9.0 \text{ and } 1.4 \text{ Hz, } 15\beta-\text{H}), 2.50 \text{ (1H, ddd, } J 14.0, 5.4 \text{ and } 3.1 \text{ Hz, } 4\alpha-\text{H}), 2.70 \text{ (1H, dt, } J 15.0, 2 \times 9.0 \text{ Hz, } 16\alpha-\text{H}), 3.90 \text{ (4H, s, OCH}_2\text{CH}_2\text{O), 5.22 \text{ (1H, m, } \nu\nu 9.0 \text{ Hz, } 6-\text{H}), 9.23 \text{ (1H, s, } 17\alpha-\text{CHO}), \text{ and } 10.00 \text{ (1H, d, } J 1.4 \text{ Hz, } 14\alpha-\text{CHO}) \text{ (Found: C, 69.4; H, 7.7%; } M^+, 430. \text{ C}_{25}\text{H}_{34}\text{O}_6 \text{ requires C, 69.7; H,7.9%; } M, 430).\)

Hydride reduction of the 14,17-dicarbaldehyde (263).

A solution of the 14,17-dicarbaldehyde (263) (60 mg, 0.14 mmol) in anhydrous tetrahydrofuran (15 ml) was added over 5 min to a stirred suspension of lithium aluminium hydride (24 mg, 0.62 mmol) in anhydrous tetrahydrofuran (2 ml) at 20°C under nitrogen. After stirring the mixture for 45 min, water (0.5 ml) was added, followed by sodium metaperiodate (6\%, 3 ml) and stirring was continued at 20°C for 35 min. Standard work-up (chloroform) gave a crystalline residue which was recrystallised from ethyl acetate-hexane to give 3,3-ethylenedioxy-14-(hydroxymethyl)androst-5-en-17-one (264) in equilibrium with 3,3-ethylenedioxy-14,17\(\alpha\)-(epoxymethano)androst-5-en-17\(\beta\)-ol (265) (40 mg, 89\%), m.p. 215-220°C;
14-Acetoxymethyl-3,3-(ethylene dioxy)androst-5-ene-17-one (266)

A solution of the 14-hydroxymethyl 17-ketone (265) (50 mg, 0.14 mmol) and acetic anhydride (1.5 ml, 16 mmol) in dry pyridine (1.6 ml) was stirred at 25°C for 1.5 h. Ice and solid sodium hydrogen carbonate were added. Standard work-up (ethyl acetate) gave a crystalline product, which was purified by recrystallisation to give 14-acetoxymethyl 17-ketone (266) (44 mg, 79%), m.p. 185-190°C; [α]D 3° (c 1.0); νmax 1737 (C=O) cm⁻¹; δH 0.96 and 1.05 (each '2.1H', s, 10β- and 13β-Me of (264)), 2.12 (1H, dd, J 14.3 and 2.8 Hz, 4β-H), 2.43 (1H, ddd, J 14.3, 5.3 and 2.9 Hz, 4α-H), 3.42 (1H, dd, J 7.3 Hz, 141-H of (264)), 3.50 and 3.80 (each '1.0H', s, 10β- and 13β-Me), 3.92 (4H, m, OCH2CH2O), 3.98 (1H, dd, J 7.3 and 3.9 Hz, 141-H of (264)), and 5.20 (1H, m, WH 9.0 Hz, 6-H) (Found: C, 73.0; H, 9.2%; M⁺, 402. C22H32O4 requires C, 73.3; H, 9.0%; M, 402).

17β-Hydroxy-17α,14-(epoxymethano)androst-4-en-3-one (267)

Trifluoroacetic acid (0.75 ml) and water (0.65 ml) was added to a solution of 14α-hydroxymethyl 3-ketal (265) (43 mg, 136 mmol) in tetrahydrofuran (4.3 ml). The reaction mixture was stirred at 20°C for 24 h, then neutralised with saturated sodium hydrogen carbonate. Standard work-up (chloroform) gave an oily residue (34 mg). Chromatography of the residue on silica gel (3.4 g) [ethyl acetate-toluene (3:7)] gave the enone (267) (23 mg, 62%), m.p. 123-125°C (from ethyl acetate-hexane); [α]D +35° (c 0.46); νmax 3400br(OH) and 1657 (C=O) cm⁻¹; δH 1.00 and 1.21 (each 3H, s, 10β- and 13β-Me), 3.55 (1H, d, J 8.7 Hz, 141-Hα), 3.84 (1H, dd, J 8.7 and 2.9 Hz, 141-
H_a), 5.72 (1H, s, 4-H) (Found: C, 76.3; H, 8.9%; M*, 316. C_{20}H_{28}O_{3} requires C, 75.9; H, 8.9%; M, 316).

14,21-Cyclo-14β-pregn-4-en-3-one-6β,15β,16β,17α-tetraol 17-acetate (268)

Tetraol (258) (94 mg, 0.20 mmol) was dissolved in tetrahydrofuran (0.5 ml). Dilute hydrochloric acid (5 M, 0.28 ml) was added and the reaction mixture was stirred at 20°C for 6 h. The reaction mixture was neutralised with saturated sodium hydrogen carbonate, followed by standard work-up (chloroform) to give an oily residue (68 mg). Chromatography of the residue on silica gel (7 g) [ethyl acetate-toluene (1:1)] gave the enone (268) (18 mg, 23%), m.p. 210-216°C (from ethyl acetate-hexane); [α]_D -12° (c 1.0); \nu_{max} 3438 br(OH), 1709(C=O), and 1671(C=O) cm⁻¹; δ_H 1.08 and 1.38 (each 3H, s, 10β- and 13β-Me), 2.11 (3H, s, 17α-OAc) 4.22 (1H, dd, J 9.4 and 1.9 Hz, 15-H), 4.35 obs. (1H, dd, J 9.4 and 1.9 Hz, 16-H), 4.37 obs. (1H, t, J 2 x 3.0 Hz, 6α-H) and 5.81 (1H, s, 4-H) (Found: C, 67.8; H, 7.6%; M*, 404. C_{23}H_{32}O_{6} requires C, 68.3; H, 7.9%; M, 404).

Acid induced rearrangement of (259)

Hydrogen bromide in acetic acid (48%, 1.6 ml) was added to a solution of the 17α-hydroxy compound (259) (94 mg, 0.30 mmol) in dry benzene (20 ml). After stirring at 20°C for 5 h, the reaction mixture was neutralised with saturated sodium hydrogen carbonate. Standard work-up (ethyl acetate) gave an oily residue (80 mg). Chromatography of the residue on silica gel (8 g) [ethyl acetate-toluene (1:9)] gave 14,16β-ethano-14β-androst-4-ene-3,17-dione (269) (37 mg, 39%), m.p. 142-146°C (from ethyl acetate-hexane); [α]_D +108° (c 1.0); \nu_{max} 1730(C=O) and 1657(C=O) cm⁻¹; δ_H 1.02 and 1.18 (each 3H, s, 10β- and 13β-Me), and 5.76 (1H, br s, 4-H); δ_C 219.0 (C-17), 199.3 (C-3), 169.5 (C-5), 124.2 (C-4), 59.4 (C-13), 58.1 (C-14), 57.3 (C-16), 46.0 (C-15), 42.2 (C-9), 40.6 (C-8), 38.6 (C-10), 36.5 (C-1), 33.8 (C-2), 32.4 (C-6), 31.6 (C-7), 30.4 (C-12), 29.0 (C-16'), 27.8 (C-16''), 24.7 (C-11), 16.2
(C-19) and 10.4 (C-18) (Found: C, 80.5; H, 9.3%; M+, 312. C_{21}H_{28}O_{2} requires C, 80.7; H, 9.0%; M, 312), followed by 17α-hydroxy-15β,17β-ethano-14β-pregna-4,8-
dien-3-one (270) (38 mg, 41%), m.p. 89-95°C (from ethyl acetate-hexane); [α]D
+187° (c 1.0); ν_{max.} 3600, 3400(OH), 1657(C=O) and 1620(C=C) cm⁻¹; δ_{H} 1.06 and
1.29 (each 3H, s, 10β- and 13β-Me) and 5.8 (1H, s, 4-H); δ_{C} 199.2 (C-3), 171.7 (C-5),
136.7 (C-9), 129.6 (C-8), 123.3 (C-4), 85.6 (C-17), 57.1 (C-14), 40.6 (C-10), 39.9 (C-
13), 36.3 (C15 and C-1), 34.3 (C-11), 33.4 (C-2), 31.7 (C-6), 31.3 (C-7), 31.0 (C-20),
30.7 (C-21), 29.9 (C-12), 22.4 (C-19), 21.8 (C-18) and 20.2 (C-16) (Found: C, 80.2; H,
9.4%; M+, 312. C_{21}H_{28}O_{2} requires C, 80.7; H, 9.0%; M, 312).
4.3 Crystal Structure Data

The structure was solved by direct methods (SHELXS-86\textsuperscript{162}) and refined using SHELXL93\textsuperscript{163}. The crystal was of very poor quality and weakly diffracting. Consequently, the structure could not be well refined. The non-hydrogen atoms were treated isotropically and hydrogens were fixed in calculated positions and refined with a common isotropic temperature factor. Some of the data obtained from the crystal structure determinations are listed in tables below.

Table 4.3a: Crystallographic data acquisition and refinement details for compound (186)

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Table 4.3b  Fractional atomic coordinates ($x10^{-4}$) and thermal parameters ($A^{-2}$ x $10^{-3}$) with e.s.d.s in parentheses for 186

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5. NOMENCLATURE

The compounds synthesised in this investigation were named according to the IUPAC steroid rules. A compound with a skeleton that differs from the fundamental parent systems by changes in the side chain(s) can often be named by several different methods involving either side chain lengthening or shortening and/or alkylation and/or addition of carbon atoms associated with a functional group. The preferred name is selected by the following recommendations applied in order (3S-6.3):

(a) A name should be derived by the fewest number of modifications of the fundamental parent system. Both detachable (e.g. alkyl) and non-detachable (e.g. homo or nor) prefixes are considered as modifications.

(b) Non-detachable prefixes are preferred to detachable prefixes.

A parent steroid skeleton name will be derived, considering natural stereochemistry at bridgehead positions, namely 8β, 9α, 10β, 13β and 14α and a side chain at position 17 assumed to be β-orientated (3S-1.5). The parent skeletons frequently considered in this investigation are estra-1,3,5(10)-triene (A), androst-4-en-3-one (B) and pregn-4-en-3-one (C).

![Image of chemical structures](image-url)
The configuration of hydrogen (or a substituent) at the bridgehead position is always to be designated by adding $\alpha$, $\beta$, $\xi$ (uncertain stereochemistry) after the numeral, this numeral and letter being placed immediately before the stem name. The stereochemistry of double bonds in the side chain should be indicated by using the $E$, $Z$ convention (3S-2.6). Locants on side chain fragments were primed for the purpose of $^{13}$C NMR identification and the numbering followed the basic rules. The above rules are illustrated in the figure of 3-methoxy-14-vinylestra-1,3,5(10)-trien-17-one (206). However, it is unambiguous and simpler to name the chain extended 14$\alpha$-alkyl compound (244) as; (5$E$)-6-(3-methoxy-17-oxoestra-1,3,5(10)-triene-14-yl)hex-5-en-2-one, whereby the attached alkyl chain is treated as the parent skeleton (see also compounds 236 and 237 in Chapter 3.4). Note that no 'a' followed by the number 14, implies natural stereoselectivity.

When additional rings are formed within, or on a steroid nucleus, it is often desirable to retain the steroid stem name, since it implies the stereochemistry of most of the chiral centres (3S-10.0). Steroids with non-adjacent ring positions linked by a bridge, e.g. -O-O- or -(CH$_2$)$_n$- are named by the appropriate name and locants to indicate its attachment and $\alpha$ or $\beta$ to indicate stereochemistry where necessary. With linear bridges the atoms may be labelled for identification by the superscripts number starting from the higher numbered attachment position. Chiral centres not defined by the parent name will be designated by their absolute stereochemistry at these positions, defined by $\alpha$, $\beta$, $R$ or $S$, prefixed by the appropriate locant (3S-1.3). This is illustrated in the figures of (17$S$)-3-methoxy-14,17$\alpha$-methanoestra-3-methoxyestra-1,3,5(10)-triene-17$\beta$17$^1$-diol (186), 14,16$\alpha$-methano-3-methoxyestra-1,3,5(10)-tri-en-17-one (193), and 3-methoxy-14,17$\alpha$-ethenoestra-1,3,5(10)-tri-en-17$\beta$-ol (81). Alcohols derived from alkylation of the 14$^1$-formyl group of compound (87) (section 3.6) exist almost exclusively in the hemiketal form. In contrast to rule 3S-10.1, they were named, (1$'S$)-1$'$,17$\alpha$-epoxy-3-methoxy-14-alkylestra-1,3,5(10)-tri-en-17$\beta$-ol. In their open form, the
attached alkyl chains are treated as the parent skeleton, thus named as (1S)-1-(3-methoxy-17-oxoestra-1,3,5(10)-tri-en-14-yl)alkanol (e.g. (221) alkyl = propyl and alkanol = propanol). However, the open form alcohols never existed in significant proportions and were therefore not characterised accordingly.

When an additional ring is formed by means of a direct link between any two carbon atoms of the steroid ring system or the attached side chain, the name of the steroid is prefixed by cyclo; this prefix is preceded by the numbers of the positions joined by the new bond and α, β or ζ denoting the configuration associated with the new bond, unless that designation is already implicit in the name (3S-2.10). A good illustration of the application of this rule follows in the figure of 17α-hydroxy-14,21-cyclo-14β-pregn-4,15-dien-3-one (253).
REFERENCES


149. K. Petzoldt, DE 3,403,862 (*Chem. Abs.*, 1986, **104**, 166905q). The 15α-hydroxy 17-ketone (245) was kindly donated by Schering AG.


161. P. de Koning and J.R. Bull, unpublished results, calculations performed using SYBYL V3.4b, Tripos Inc., St Louis, MO.


### $^{13}$C NMR Data of the Estrone Derivatives

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* interchangeable
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