25

CHEMISTRY OF 19-NORSTEROIDS : SYNTHETIC APPROACHES TO RING D MODIFIED HORMONE ANALOGUES

by

KIM REDDIE

Submitted in accordance with the requirements
for the degree of

MASTER OF SCIENCE

in the subject

CHEMISTRY

at the
UNIVERSITY OF CAPE TOWN

Supervisor : Professor J. R. Bull

SEPTEMBER 1990

ACKNOWLEDGEMENTS

I would like to express my appreciation to all those whose help and advice contributed to the production of this thesis, and in particular to the following:

Prof. J. R. Bull, my supervisor, for his support and effort he put into my thesis.

My colleagues, Ed Sturrock, Anwar Jardine, Claudia Grundler, Michiel Loedolff, and Dr. L. M. Steer for their support and helpfulness.

SUMMARY

Exploratory studies have been conducted in two research areas, which are expected to converge upon the common theme of selective ring D functionalisation of 19-norsteroids for structure-activity investigation.

The first part of the thesis describes the exploration of new methods for converting steroidal 17-ketones into corresponding 17β-acetoxy-17α-carbaldehydes.

The first method, which entailed the treatment of estrone 3-methyl ether with (methoxymethylene)triphenylphosphorane was disappointingly inefficient, giving rise to a low-yield, separable mixture of (E)- and (Z)-17-(methoxymethylene)-3-methoxyestra-1,3,5(10)-trienes. Owing to the low yield, this approach was abandoned.

In an alternative approach, estrone 3-methyl ether was converted into 17α-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol via the spiro-oxirane. Selective acetylation of the diol gave 17α-acetoxymethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol, which was then dehydrated to give (E)- and (Z)-17-acetoxymethylene-3-methoxyestra-1,3,5(10)-trienes, accompanied by dehydration intermediates, and the product of endocyclic dehydration.

The most successful route to 17-acetoxymethylene-3-methoxyestra-1,3,5(10)-triene entailed hydroboration of the 17-methylene compound to give 17β-hydroxymethyl-3-methoxyestra-1,3,5(10)-triene, which was smoothly oxidised to 3-methoxyestra-1,3,5(10)-triene-17β-carbaldehyde, followed by enol acetylation, to afford an (E)/(Z) mixture of 17-acetoxymethylene compounds. Epoxidation of this mixture, followed by thermal treatment afforded the desired 17β-acetoxy-3-methoxyestra-1,3,5(10)-triene-17α-carbaldehyde.

The second part of the thesis describes the synthesis of estradiol and estriol analogues derived from 14-formyl-19-norsteroids and 14α,17α-etheno-19-norsteroids.

The feasibility of synthesising 19-norsteroids having extended 14α-alkyl chains was examined by the attempted chemoselective 14^1-methylenation of 3-methoxy-17-oxoestra-1,3,5(10)-triene-14-carbaldehyde. Treatment with methylenetriphenylphosphorane afforded 3-methoxy-14α-vinylestra-1,3,5(10)-trien-17-one in low yield (18%). An attempt to improve chemoselectivity through prior protection of the 17-oxo group as the silyl enol ether failed, and attempted acid-catalysed enol acetylation led to apparent rearrangement of ring D. However, treatment of the 14α-formyl-17-ketone with methyl-lithium resulted in highly selective methylation of the formyl group, without the need to protect the 17-oxo group.

Indirect routes to 14α-chain-extended 19-norsteroids were also investigated, for example, through functionalisation of the olefinic bond in 3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol. For this purpose, the regio- and stereoselectivity of hydroboration was examined. Although the reaction gave complex mixtures of all possible isomers, the products were fully characterised and structurally assigned. The influence of bridgehead functionality on hydroboration regioselectivity, and the scope for intramolecular delivery of borane to the bridged olefinic bond, were examined. Although the investigation has not yet yielded conclusive evidence of favourable trends in the regioselective outcome, useful pointers for further study have been demonstrated. Furthermore, the hydroboration method has resulted in the synthesis of novel estriol analogues.

TABLE OF CONTENTS

page

CHAPTER 1 Synthetic Routes to 17β-Acetoxy-3-methoxyestra-1,3,5(10)-triene-17α-carbaldehyde

1.1 Introduction

1.2 Discussion

CHAPTER 1

SYNTHETIC ROUTES TO 17β-ACETOXY-3-METHOXYESTRA-1,3,5(10)-TRIENE-17α-CARBALDEHYDE

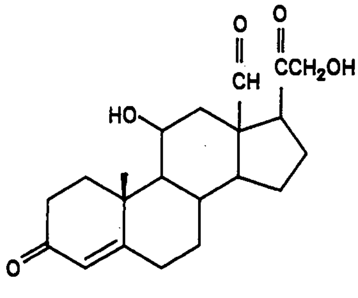
1.1 INTRODUCTION

1.1.1 Background

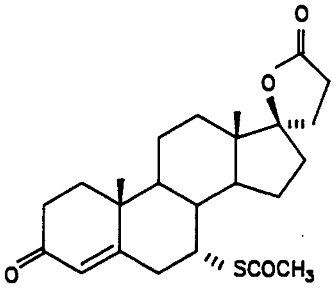
Large numbers of structurally diverse steroids have been studied with respect to their potential as aldosterone antagonists. These steroids share as their most distinctive structural feature, a spirolactone ring attached to C(17) of the steroid nucleus, and it is this structural unit which provides the greatest synthetic challenge and greatest biological interest.

Aldosterone (**1**), a potent mineralcorticoid, is known to play a central role in causing and maintaining edema, by preventing sodium excretion and promoting elimination of potassium, and thus plays an important part in regulating the electrolyte balance of body fluids. An overproduction of aldosterone leads to coronary disorders, liver cirrhosis and hypertension.[1] Thus, considerable attention has been given to the synthesis of steroidal aldosterone antagonists since 1957, when Cella _et_ _al_.,[2] found that spironolactone (7α-acetylthio-3-oxo-17α-pregn-4-ene-21,17-carbolactone)[1] (**2**) possesses an electrolyte regulating activity antagonistic to aldosterone.[3] It decreases edema by competitively inhibiting aldosterone at the receptor level, and functions as a diuretic agent. It is used extensively as an aldosterone antagonist and, in 1981, it constituted a total of 35% of the entire world steroid production.[1]

For therapeutic purposes, spironolactone must be given in rather large doses, thus leading to side effects with prolonged treatment, such as decreased libido, disorders in the menstrual cycle and enlargement of the breasts. This has led to the quest for new analogues of spironolactone displaying higher potency, greater selectivity, and for new, more selective methods of constructing the 17,17-spirolactone moiety.



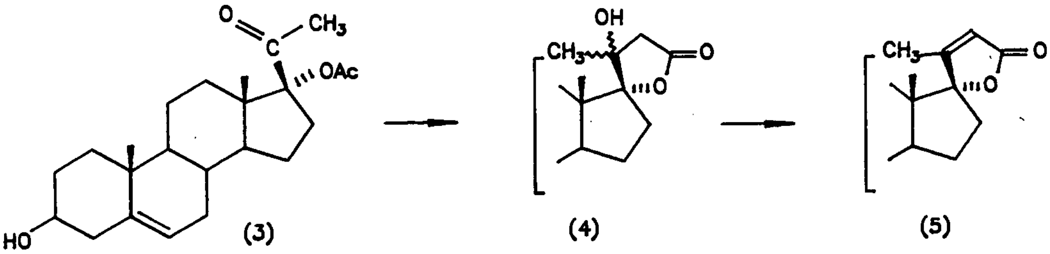
(1)



(2)

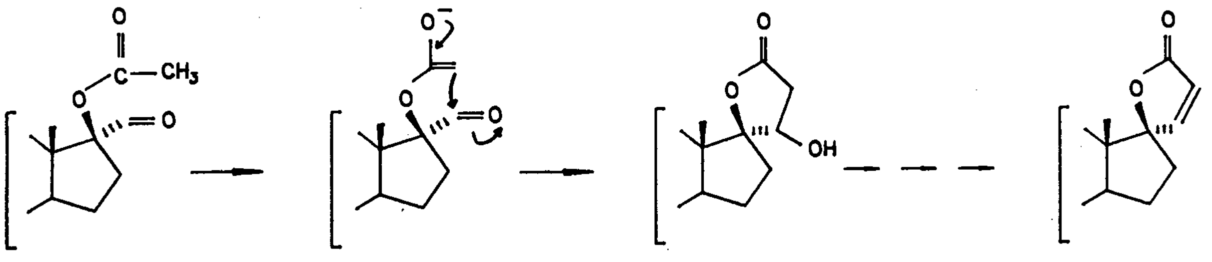
The adventitious intramolecular condensation encountered during treatment of 17α-acetoxypregnan-20-ones[4] (3) with strong bases (Scheme 1.111), suggests a novel approach to the synthesis of potential aldosterone antagonists related to spironolactone.

SCHEME 1·111



In a previous study, Steer[5] investigated the intramolecular condensation of steroidal 17β-acetoxy-17α-carbaldehyde, in order to develop a synthetic route to a new family of 14-functionalised 17,17-spirolactones.[5] Her work demonstrated that efficient intramolecular condensation can be achieved in the presence of hindered bases at -100 °C, and that the condensation product (7) could then be converted uneventfully into the desired spirolactone (8)(Scheme 1.112). The method was applied to a synthesis of 14-hydroxymethyl-3-oxo-19-nor-17α-pregn-4-ene-21,17-carbolactone.[5]

SCHEME 1·112



(7)

(8)

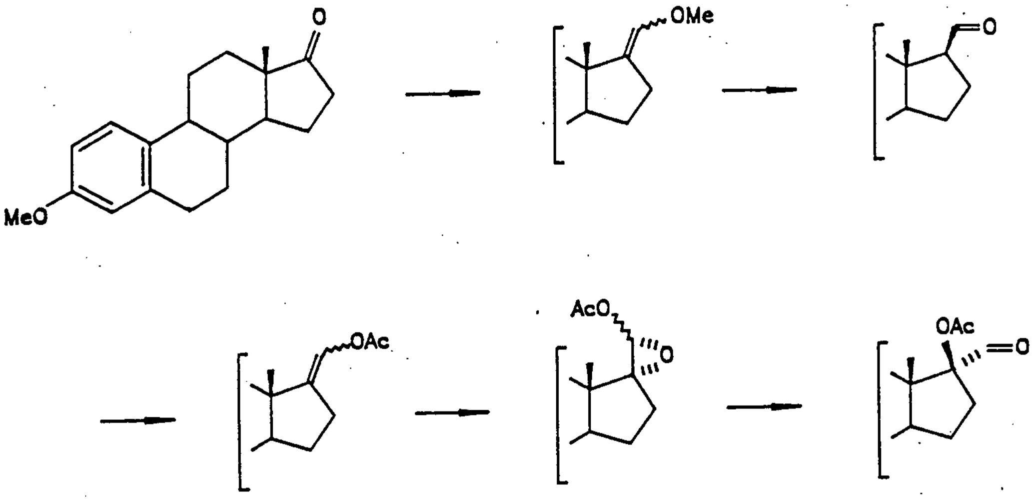
Although a new principle of 17,17-spirolactone synthesis was demonstrated by the work of Steer,[5] it was recognised that the general applicability of the route requires an efficient synthesis of steroidal 17-acetoxy-17-carbaldehydes. However, the methods investigated in the work were beset by the well-known lability of the geminal hydroxy carbaldehydes, and attendant rearrangements.[6]

1.1.2. Objectives and Approach

Numerous methods[7] exist for synthesising the geminal hydroxy aldehydes. Owing to the poor yields, limited application, numerous intermediates, competing rearrangements, and the absence of stereoselectivity, an alternative route to the 17β-acetoxy-17α-carbaldehyde was considered.

We proposed a method based on the methoxymethylenation of estrone 3-methyl ether, followed by oxidation, enol acetylation, and finally, epoxidation and acid catalysed rearrangement (Scheme 1.121).

SCHEME 1·121



Methoxymethylenation of the 17-ketone appeared to offer the most efficient route to the key intermediate, the 17-acetoxymethylene compound. This approach is based upon the reported[8] treatment of androstenolone with (methoxymethylene)triphenylphosphorane[9] in dimethyl sulphoxide, followed by acidic hydrolysis to give the formyl derivative. Enol acetylation of 17-acetyl steroids[10] was used to prepare 17(20)-enol acetates. It has been demonstrated[11,12] that epoxides of enol acetates on exposure to an acidic medium or on thermal treatment, rearrange to the α-acetoxy carbonyl compound.

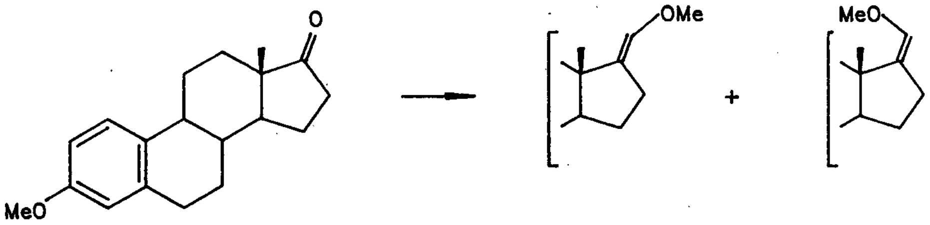
In addition to the above approach, alternative methods of one-carbon functional homologation at C(17) were also considered, and these will be described in sections 1.2.2 and 1.2.3.

1.2 Discussion

1.2.1 Methoxymethylenation of 3-Methoxyestra-1,3,5(10)-trien-17-one

The 17-ketone (**9**) was treated with (methoxymethylene)triphenylphosphorane, generated from a reaction of n-butyl-lithium with the (methoxymethylene)triphenylphosphonium chloride[13] in tetrahydrofuran, to afford a low overall yield (38%) of (E/Z)-17-methoxymethylene-3-methoxyestra-1,3,5(10)-trienes (**10 + 11**), which were separated by chromatography to give the (E)-17-methoxymethylene compound (**10**)(22%), followed by the (Z)-17-methoxymethylene compound (**11**)(16%) (Scheme 1.211).

SCHEME 1·211



(9) (10) (11)

The structures of the respective isomers (**10**) and (**11**) were confirmed by ^{1}H n.m.r. spectra, which revealed in both compounds a triplet at $\delta 5.7$ for the olefinic proton. A tentative assignment of the stereochemistry is proposed, based on the observation that in allylic couplings,[14] J_{cisoid} is always slightly larger than $J_{transoid}$ (Figure 1.211).

FIGURE 1·211

cisoid transoid

Thus, the minor product (**11**) was assigned the (Z)-olefin structure (J 2.4 Hz), and the major product (**10**) was assigned the (E)-olefin structure (J 1.9 Hz). The spectrum of the (Z)-olefin (**11**) exhibited a more shielded C-13 methyl resonance (δ0.8) and a 17^1-methoxy resonance (δ3.5), compared to those of the (E)-olefin (**10**) (δ0.9 and 3.76 respectively).

Despite numerous modifications of the experimental procedure, it was not possible to improve the overall conversion of (**9**) into the desired methoxymethylene compounds (**10 + 11**).

According to the literature,[15-17] Wittig reactions conducted with (methoxymethylene)triphenylphosphorane often fail to provide the corresponding methyl enol ethers in acceptable yields.

Accordingly, we sought alternative approaches to the 17-acetoxymethylene compounds.

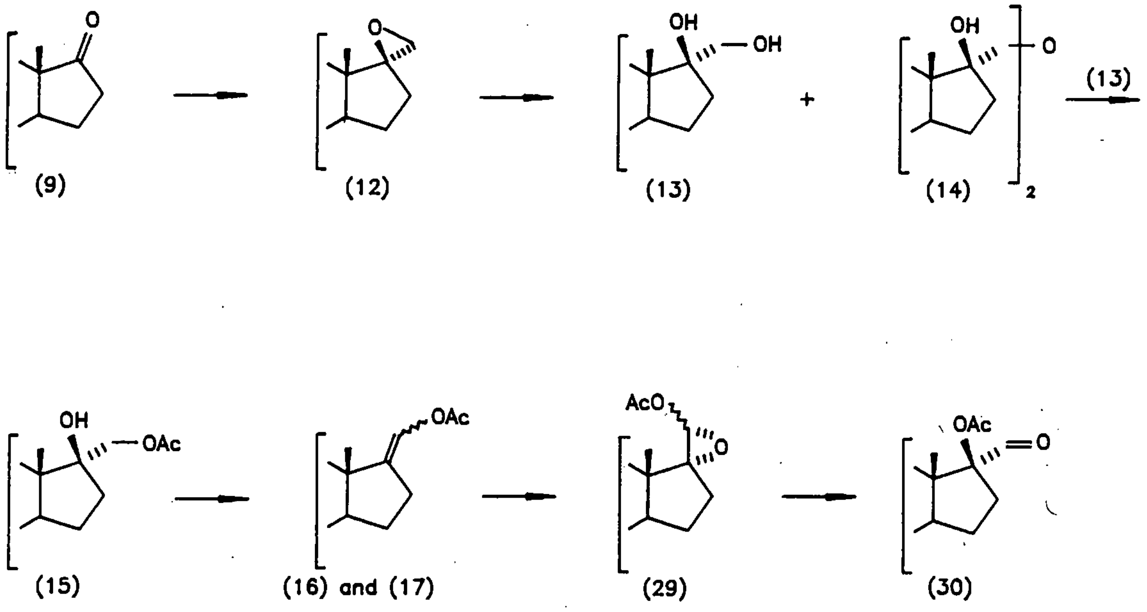
1.2.2 Synthesis and Dehydration of 17α-Acetoxymethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol

In view of the disappointing yield of the desired intermediates (**10 + 11**) in the foregoing experiment, an alternative route to the 17-acetoxymethylene compound was sought. The 17α-acetoxymethyl-17β-alcohol (**15**) is readily available by standard modifications of estrone 3-methyl ether (**9**) (Scheme 1.221), and it was reasoned that controlled dehydration of the compound would lead to the desired product (**16 + 17**) through exocyclic dehydration. It was recognised that competing endocyclic dehydration might detract from the efficiency of the method, but there was no clear indication of the preferred regioselectivity from studies of models or precedents.[18-21]

The conversion of the 17-ketone (**9**) into the 17α-acetoxymethyl-17β-alcohol derivative (**15**) was achieved by the methylenation of the 17-ketone[22] using dimethylsulphonium methylide,[23] to give the

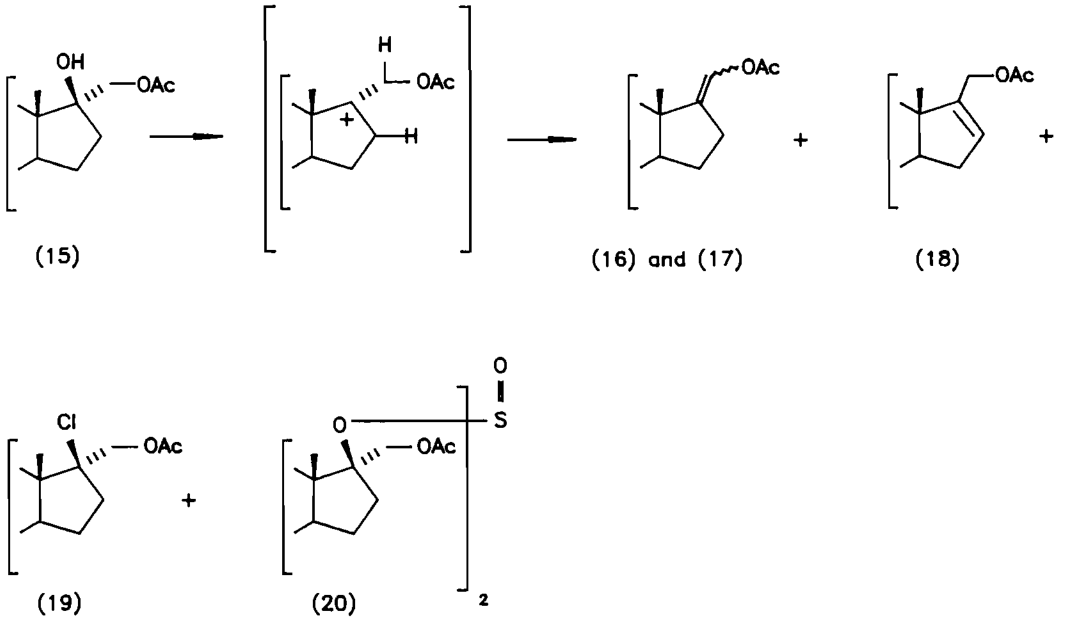
(17S)-spiro-oxirane (**12**)(97%) which, upon base mediated cleavage (0.3 M KOH, 120 °C), yielded the diol (**13**)(79%),^{24} and its dimeric ether (**14**)(12%). Monoacetylation of the diol (**13**) using acetic anhydride and pyridine afforded the 17α-acetoxymethyl-17β-alcohol (**15**),^{5} in good yield (76%). Structural confirmation of the above structures was obtained from spectroscopic data, which were compatible with those reported in the literature.^{22,24}

SCHEME 1·221



Treatment of the monoacetate (**15**) using freshly distilled thionyl chloride in pyridine at 0 °C led to a complex mixture of products, which was chromatographed to give, in order of elution, (E/Z)-17-acetoxymethylene-3-methoxyestra-1,3,5(10)-triene (**16 + 17**)(31%), 17α-acetoxymethyl-3-methoxyestra-1,3,5(10),16-tetraene (**18**)(29%), 17α-acetoxymethyl-17β-chloro-3-methoxyestra-1,3,5(10)-triene (**19**)(15%), and bis-(17α-acetoxymethyl-3-methoxyestra-1,3,5(10)-triene-17β-yl)sulphite (**20**)(9%)(Scheme 1.222). The structures of the products were assigned with the aid of spectroscopic and analytical data.

SCHEME 1·222



The ^1H n.m.r. spectrum for the 17-acetoxymethylene derivative (**16 + 17**) revealed an isomeric mixture in a ratio of ≈1:8 as indicated by the doubling of the 13-methyl and acetoxy methyl signals. Repeated recrystallisation of the mixture (**16 + 17**) afforded the pure (<u>Z</u>)-isomer (**17**).

The structure of the 17-acetoxymethyl-16-ene (**18**) was confirmed by the presence of an AB multiplet at δ4.63 and 4.73 (each 1H, d, <u>J</u> 13.4 Hz) for the 17^1-methylene group, and a broad double doublet at δ5.71 (<u>J</u> 2.9 and 1.4 Hz) for the endocyclic olefinic proton at C-16.

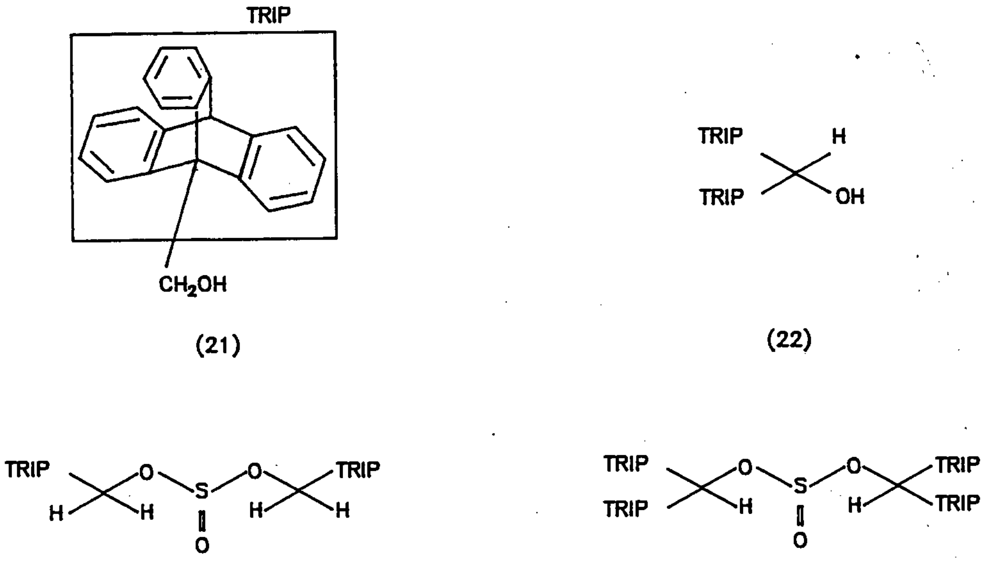
The ^1H n.m.r. spectrum of the chloro derivative (**19**) displayed an AB multiplet at δ4.34 and 4.48 (each 1H, d, <u>J</u> 12.2 Hz) for the 17^1-protons and a singlet at δ2.1 for the acetoxy group. The high resolution mass spectrum showed molecular ions at 376 and 378 (3:1) ratio for the expected molecular formula $C_{22}H_{29}ClO_3$.

The dimeric nature of the sulphite (**20**) was supported by the doubling of ^1H n.m.r. signals, and the bridging sulphite group was evidenced by an i.r. band at v_{max} 1364 (S-O stretch) cm^{-1}. The high resolution mass spectroscopy did not show a molecular ion ($\underline{m}/\underline{z}$ 762), but a peak at ($\underline{m}/\underline{z}$ 358) suggested fragmentation to a monomeric species. Further evidence for the sulphite structure (**20**) was obtained by alkaline hydrolysis, which afforded the diol (**13**).

Furthermore, heating both the chloro compound (**19**) and the sulphite dimer (**20**) afforded mixtures of the dehydration products (**16 + 17**) and (**18**).

A previous study, not involving the dehydration procedure, has shown that alcohols can react with thionyl chloride to give a sulphite ester. Crumrine et al.[25] found that treatment of 1-triptycylcarbinol (**21**) and ditriptycylcarbinol (**22**) using thionyl chloride-dimethylformamide at 58 °C, resulted in the formation of the sulphite esters (**23**) and (**24**), respectively (Scheme 1.223).

SCHEME 1·223



(21)

(22)

(23)

(24)

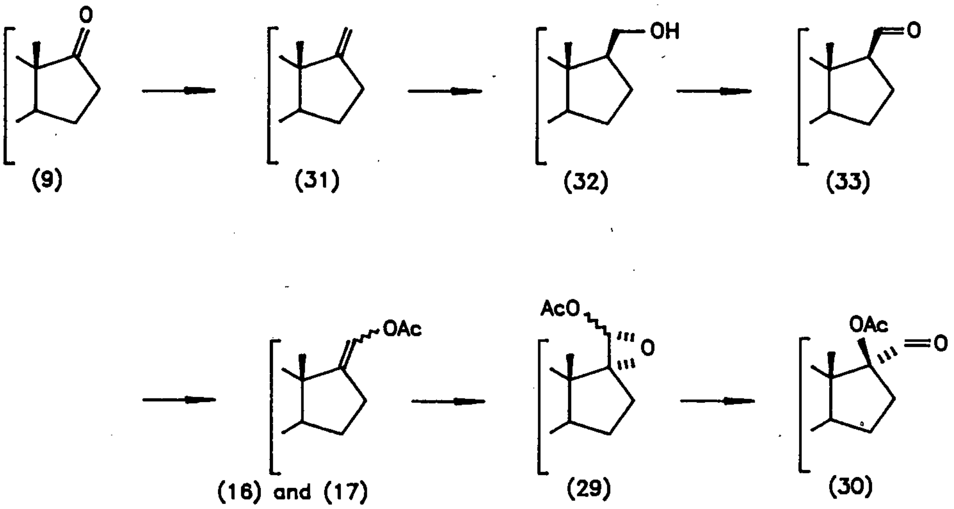
A different dehydrating agent $POCl_3$ was also investigated, but this led to an even more complex array of products.

1.2.3 Hydroboration of 3-Methoxy-17-methylene-estra-1,3,5(10)-triene

As a result of the low yield of the 17-acetoxymethylene compound (**16** + **17**) obtained in the foregoing procedure, an alternative route was investigated. This was based upon sequential methylenation, hydroboration, oxidation and enol acetylation (Scheme 1.231).

Estrone 3-methyl ether (**9**) was methylenated under standard conditions,[26] using methylenetriphenylphosphorane generated by treatment of the corresponding bromide with sodium hydride in dimethyl sulphoxide. The product (**31**)(61%)[27] displayed the expected spectroscopic properties.

SCHEME 1·231



Hydroboration of the 17-methylene compound (**31**) with 9-borabicyclo[3.3.1]nonane (9-BBN) in tetrahydrofuran, followed by alkaline hydrogen peroxide treatment proceeded efficiently to give 17β-hydroxymethyl-3-methoxyestra-1,3,5(10)-triene (**32**)(94%),[28] which was readily isolated and identified.

The ^{1}H n.m.r. spectrum of (**32**) displayed signals at δ3.55 (1H, dd, *J* 10.4 and 7.2 Hz) and 3.71 (1H, dd, *J* 10.4 and 6.7) for the 17^{1}-methylene protons. The non-equivalence of the vicinal couplings between 17^{1}-H_2 and 17α-H suggests a preferred rotameric orientation of the 17β-hydroxymethyl group. Although the 17-configuration of the product could not be deduced from spectroscopic evidence, the assignment is based upon the familiar α-stereoselectivity of reactions at C(17), and is supported by analogous assignments in the hydroboration of 17-ethylidene steroids.[29]

Oxidation of the 17β-hydroxymethyl compound (**32**) with pyridinium chlorochromate[30] in dichloromethane, with sodium acetate as buffer, afforded 3-methoxyestra-1,3,5(10)-triene-17β-carbaldehyde (**33**)(70%).[31] The structure of the product was assigned with the aid of spectroscopic and analytical data.

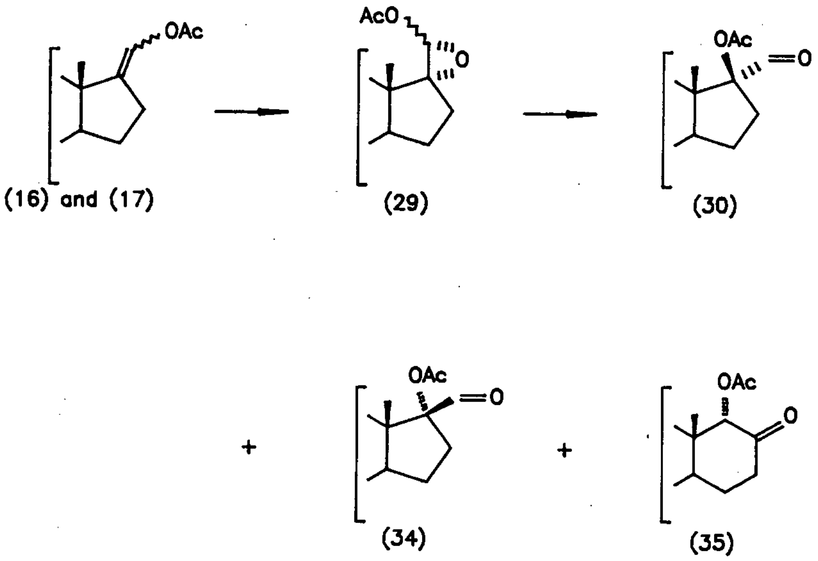
Enol acetylation of the carbaldehyde (**33**) using acetic anhydride and toluene-p-sulphonic acid,[10] afforded (*E*/*Z*)-17-acetoxymethylene-3-methoxyestra-1,3,5(10)-triene (**16 + 17**)(78%) (*ca* 1:3 as determined by ^{1}H n.m.r.).

1.2.4 Epoxidation-Rearrangement of 17-Acetoxymethylene-3-methoxyestra-1,3,5(10)-triene

α-Epoxy acetates[11,12] are known to undergo ready rearrangement, with migration of the acetoxy group to the neighbouring carbon atom, to form α-acetoxy carbonyl compounds. Rearrangements of this nature have been reported to occur in the presence of Lewis acids or silica gel, and upon heating.

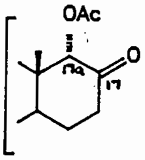
Treatment of (*E*/*Z*)-17-acetoxymethylene compounds (**16 + 17**) with m-chloroperbenzoic acid (MCPBA) in dichloromethane at 0 °C afforded a product (t.l.c.), which was assumed to be the 17α,17^{1}-epoxide (**29**). However, it proved to be exceptionally labile during attempted purification, and it was therefore decided to attempt the desired rearrangement directly upon the total product of epoxidation. In a first experiment, this product was refluxed in toluene for 10 h. The reaction mixture was chromatographed to give 17β-acetoxy-3-methoxyestra-1,3,5(10)-triene-17α-carbaldehyde (**30**)(29%), 17α-acetoxy-3-methoxyestra-1,3,5(10)-triene-17β-carbaldehyde (**34**)(10%), and 17aα-acetoxy-3-methoxy-17a-homoestra-1,3,5(10)-trien-17-one (**35**)(10%)(Scheme 1.241).

SCHEME 1·241

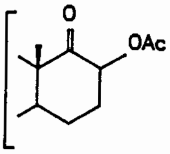


The 17β-acetoxy-17α-carbaldehyde (**30**) was identified by comparison of the physical and spectroscopic properties, with those reported in the literature.[5] However, the epimer appears to be unknown, but was structurally assigned on the basis of distinctive spectroscopic properties. The i.r. revealed the presence of a strong carbonyl absorption at 1725 cm^{-1}, and the ^{1}H n.m.r. spectrum showed the presence of a signal at δ9.53 for the C$\underline{H}$O proton.

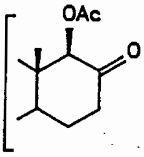
The structure of the further rearrangement product was assigned as the 17aα-acetoxy-17-one (**35**), since its physical and spectroscopic characteristics did not correspond with those of the 17-acetoxy-17a-one (**36**) and the 17aβ-acetoxy-17-one (**37**).[6]



(35)



(36)



(37)

The i.r. and ^{1}H n.m.r. confirmed the α-acetoxyketone grouping by the presence of carbonyl absorptions at 1739 and 1720 cm^{-1}, and a singlet at δ6.04 for the C-17a proton.

Formation of both acetoxy carbaldehydes (**30**) and (**34**) in the reaction sequence suggested that epoxidation of the enol acetate mixture (**16 + 17**) leads to a mixture of 17α,17^1- and 17β,17^1-epoxide intermediates, since the latter can account for the formation of the 17α-acetoxy-17β-carbaldehyde (**34**).

In another experiment, the crude epoxidation product was treated directly with tin tetrachloride at -78 °C to give a complex mixture of products. Chromatography afforded the 17β-acetoxy-17α-aldehyde (**30**)(1%), the 17α-acetoxy-17β-aldehyde (**34**)(5%), the 17aα-acetoxy-17-one (**35**)(3%), accompanied by an unidentified mixture (26%)*, and an unknown compound (**38**)(14%)*.

Small scale experiments carried out with BF$_3$-etherate in benzene, or silica gel, also resulted in complex mixtures containing minute amounts of the desired product (**30**).

* These percentage yields are calculated on starting material.

1.2.5 Conclusion

The attempted development of an efficient synthetic route to 17β-acetoxy-3-methoxyestra-1,3,5(10)-triene-17α-carbaldehyde (**30**) was unsatisfactory. Although it has proved possible to convert estrone 3-methyl ether into the 17-acetoxymethylene compound (**16 + 17**) in a good overall yield (78%), using the reaction sequence of methylenation, hydroboration, oxidation, and enol acetylation, the lability of the epoxidation product precludes satisfactory characterisation and hence controlled rearrangement experiments. It appears that epoxidation of the acetoxymethylene compound (**16 + 17**) is not sufficiently stereoselective for the intended purpose, nor is the desired course of rearrangment strongly favoured. The route.investigated in this work compares unfavourably with the reported method[5] of synthesis of 17β-acetoxy-3-methoxyestra-1,3,5(10)-triene-17α-carbaldehyde (**30**), which is nevertheless not satisfactory for synthetic purposes.

1.3 EXPERIMENTAL

Melting points (m.p.) were determined on a Reichert-Jung Thermovar and are uncorrected. Infrared spectra were recorded in chloroform using a Perkin-Elmer 983 Spectrometer. Ultraviolet spectra were recorded in chloroform using a PU 870 UV/VIS Spectrophotometer. Proton nuclear magnetic resonance (^{1}H n.m.r.) and carbon-13 magnetic resonance (^{13}C n.m.r.) were recorded on a Varian VXR (200 MHz spectrometer) for solutions in deuteriochloroform. Mass spectra were recorded on a VG micromass 16F mass spectrometer at 70 eV, and an ion source temperature of between 180-220 °C. Specific rotations were determined in chloroform, unless otherwise stated, using a Perkin-Elmer 74 polarimeter.

All reactions were monitored by t.l.c. using Merck precoated silica gel plates. Detection was done using an ultraviolet lamp (wavelength 254 nm), as well as spraying with a solution of ammonium ceric sulphate, followed by heating the plate at 150 °C.

Column chromatography was carried out using silica gel (Kieselgel 60, Merck). The amount of silica gel and the eluent are specified in each experiment.

Commonly used solvents were purified as described below.

Tetrahydrofuran : Dried over sodium wire and distilled from sodium using benzophenone as an indicator.

Pyridine : Distilled from potassium hydroxide and stored over potassium hydroxide pellets.

Dimethyl sulphoxide : Distilled from calcium hydride and stored over molecular sieves.

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

The standard work-up refers to the extraction with the solvent specified in parenthesis three times and washing the combined organic layers with water and brine twice. In reactions involving acid treatment, an initial wash was carried out with saturated aqueous sodium hydrogen carbonate. The organic phase was dried over magnesium sulphate and concentrated under reduced pressure.

(Methoxymethylene)triphenylphosphonium chloride

Freshly distilled chloromethyl methyl ether (149 ml, 0.2 mol) was added under nitrogen to a solution of triphenylphosphine (49.78 g, 0.19 mol) in benzene (120 ml). The mixture was allowed to stand for 12 h with occasional shaking to allow the white precipitate to settle out, which was filtered, washed with cold benzene, and crystallised from chloroform-ethyl acetate, to afford (methoxymethylene)triphenylphosphonium chloride (43.91 g, 63%), m.p. 199-202 °C (from chloroform-ethyl acetate) (lit.,^{13} m.p. 201-202 °C); ν_{max} 3053 (C-H), 1584 (C=C), and 1094 (C-O) cm^{-1}; δ(200 MHz) 3.71 (3H, s, Me), 5.75 (2H, d, J 6 Hz, CH_2), and 7.6 (15 H, m, Ar-H) (Found : C, 70.0; H, 5.6%. $C_{20}H_{20}ClOP$ requires C, 70.1; H, 5.8%).

3-Methoxy-17-methoxymethylene-estra-1,3,5(10)-triene (**10** + **11**)

An ethereal solution of n-butyl-lithium (1.6 M; 3.125 ml, 5 mmol) was added dropwise under nitrogen to a stirred suspension of (methoxymethylene)triphenylphosphonium chloride (1.73 g, 5 mmol) in dry tetrahydrofuran (19 ml). Bright red coloration resulted. The mixture was stirred for 1 h, then estrone 3-methyl ether (**9**) (292 mg, 1.03 mmol) in dry tetrahydrofuran (8 ml) was added at 0 °C. After 3 h, the mixture was heated to 40 °C and then refluxed for 16 h. Saturated aqueous ammonium chloride was added and standard work-up (chloroform) afforded the crude product (300 mg). Chromatography [ethyl acetate-hexane (2:98)] on silica gel (29 g) afforded (E)-3-methoxy-17-methoxymethylene-estra-1,3,5(10)-triene (**10**)(71 mg, 22%), m.p. 76-80 °C (from acetone-methanol); $[\alpha]_D$ +22° (c 0.96); ν_{max} 1679 (C=C) and 1111 (C-O) cm^{-1}; δ(200 MHz) 0.9 (3H, s, 13β-Me), 2.79-2.9 (2H, m, 6-H_2), 3.75 (3H, s, 3-OMe), 3.76 (3H, s, 17^1-OMe), 5.7 (1H, t, J 1.9 Hz, 17^1-H), 6.6 (1H, d, J 2.8 Hz, 4-H), 6.7 (1H, dd, J 8.6 and 2.8 Hz, 2-H), and 7.15 (1H, d, J 8.6 Hz, 1-H) (Found : C, 80.8; H, 8.9%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.8; H, 9.1%; M, 312), followed by (Z)-3-methoxy-17-methoxymethylene-estra-1,3,5(10)-triene (**11**)(53 mg, 16%), m.p. 55-57 °C (from acetone-methanol); $[\alpha]_D$ +32° (c 0.6); ν_{max} 1675 (C=C) and 1115 (C-O) cm^{-1}; δ(200 MHz) 0.8 (3H, s, 13β-Me), 2.7-2.9 (2H, m, 6-H_2), 3.5 (3H, s, 17^1-OMe), 3.7 (3H, s, 3-OMe), 5.7 (1H, t, J 2.4 Hz, 17^1-H), 6.6 (1H, d, J 2.8 Hz, 4-H), 6.7 (1H, dd, J 8.6 and 2.8 Hz, 2-H), and 7.2 (1H, d, J 8.6 Hz, 1-H) (Found : C, 80.5; H, 8.9%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.8; H, 9.1%; M, 312), followed by starting material (84 mg, 29%).

Trimethylsulphonium iodide

Dimethyl sulphide (7 ml, 96.5 mmol) and methyl iodide (6.15 ml, 98.6 mmol) were mixed together and allowed to stand at 25 °C for 16 h. Precipitation of the white sulphonium salt resulted. After recrystallisation (ethanol), the product was dried under vacuum at 60 °C to afford trimethylsulphonium iodide (27.31 g, 73%), m.p. 214-218 °C (lit.,[23] m.p. 215-220 °C).

Spiro-17β-oxiranyl-3-methoxyestra-1,3,5(10)-triene (**12**)

Sodium hydride (50%; 1.7 g, 35 mmol) was washed with dry hexane under nitrogen, and dimethyl sulphoxide (52 ml) was added. The mixture was kept at 60-70 °C for 45 min, then cooled to 25 °C, and dry tetrahydrofuran (52 ml) was added. Trimethylsulphonium iodide (14.3 g, 70 mmol) in dimethyl sulphoxide (100 ml) was added dropwise at -5 °C, followed by estrone 3-methyl ether (**9**)(5 g, 17.6 mmol) in dry tetrahydrofuran (140 ml). After 2 h, aqueous ammonium chloride was added. Standard work-up (ethyl acetate) gave a crude product (5.1 g). Chromatography [ethyl acetate-hexane (3:17)] on silica gel (150 g) afforded spiro-17β-oxiranyl-3-methoxyestra-1,3,5(10)-triene (**12**)(5.1 g, 97%), m.p. 102-105 °C (from acetone-methanol); $[\alpha]_D$ +56° (*c* 1.0) [lit.,[22] m.p. 103-105 °C; $[\alpha]_D$ +56° (*c* 1.0)]; δ(200 MHz) 0.92 (3H, s, 13β-Me), 2.64 (1H, d, *J* 5.0 Hz, 17^1-H), 2.7-2.9 (2H, m, 6-H_2), 2.97 (1H, d, *J* 5.0 Hz, 17^1-H), 3.7 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.69 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), and 7.2 (1H, d, *J* 8.5 Hz, 1-H) (Found : C, 80.6; H, 8.5%; M^+, 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.7%; *M*, 298).

17α-*Hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17β-*ol* (**13**)

The 17β-oxirane (**12**)(1.6 g, 5.4 mmol) was added under nitrogen to a stirred solution of potassium hydroxide (1.2 g, 20 mmol) in dry dimethyl sulphoxide (50 ml) and water (9 ml). The mixture was stirred at 120 °C for 3 h, then cooled to 25 °C and water was added. The resultant precipitate was isolated by filtration and dried *in vacuo*. Chromatography [methanol-chloroform (1:19)] of the product (1.8 g) on silica gel (150 g) afforded starting material (**12**)(40 mg, 3%), bis-(3-methoxy-17α-methylestra-1,3,5(10)-trien-17β-ol-17^1-yl)ether (**14**)(360 mg, 12%), m.p. 226-229 °C (from chloroform-methanol); $[\alpha]_D$ +28° (*c* 0.5), [lit.,[5] m.p. 227-229 °C; $[\alpha]_D$ +28° (*c* 0.5)], and 17α-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (**13**) (1.25 g, 79%), m.p. 166-171 °C (from methanol) (lit.,[24] m.p. 168-171 °C); $[\alpha]_D$ +30° (*c* 0.53); ν_{max} 3468 and 3393 (OH) cm^{-1}; δ(200 MHz) 0.92 (3H, s, 13β-Me), 1.94 (1H, dd, *J* 6.9 and 4.4 Hz; exch. by D_2O, 17^1-OH), 2.79-2.90 (2H, m, 6-H_2), 3.48 (1H, dd, *J* 11.0 and 6.9 Hz; exch. by D_2O gives d, *J* 11.0 Hz, 17^1-H), 3.78 (3H, s, 3-OMe), 3.80 (1H, dd, *J* 11.0 and 4.4 Hz; exch. by D_2O gives d, *J* 11.0 Hz, 17^1-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.20 (1H, d, *J* 8.6 Hz, 1-H) (Found : C, 75.7; H, 8.7%; M^+, 316. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%; *M*, 316).

17α-Acetoxymethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (**15**)

Acetic anhydride (8 ml) was added under nitrogen to a solution of the diol (**13**) (3.1 g, 9.8 mmol) in dry pyridine (18 ml). After 30 min, ice was added and the resultant precipitate was isolated by filtration and dried under vacuum to afford a crude product (3.3 g). Chromatography [ethyl acetate-benzene (3:17)] on silica gel (250 g) afforded 17α-acetoxymethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (**15**)(2.73 g, 76%), m.p. 87-89 °C (from benzene-hexane) (lit.,[5] m.p. 89-91 °C); $[\alpha]_D$ +28° (c 0.5); ν_{max} 3476 (OH) and 1716 (C=O) cm^{-1}; δ(200 MHz) 0.94 (3H, s, 13β-Me), 2.15 (3H, s, 17^1-OAc), 2.79-2.9 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 4.09 (1H, d, J 11.3 Hz, 17^1-H), 4.24 (1H, dd, J 11.3 and 0.8 Hz, 17^1-H), 6.61 (1H, d, J 2.8 Hz, 4-H), 6.69 (1H, dd, J 8.7 and 2.8 Hz, 2-H), and 7.20 (1H, d, J 8.7 Hz, 1-H) (Found : C, 73.6; H, 8.4%; M^+, 358. $C_{22}H_{30}O_4$ requires C, 73.7; H, 8.4%; M, 358).

Dehydration of the 17α-Acetoxymethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (**15**)

Freshly distilled thionyl chloride (0.4 ml) was added dropwise under nitrogen to a solution of 17α-acetoxymethyl-17β-alcohol (**15**)(300 mg, 0.84 mmol) in dry pyridine (4 ml) at -15 °C. After 0.5 h at -15 °C, the reaction mixture was poured onto ice. Standard work-up (ethyl acetate), which included washing the organic layer with hydrochloric acid, afforded the crude product (280 mg). Chromatography [ethyl acetate-hexane (1:19) → (1:9) → (1:4) → (1:1)] on silica gel (150 g) afforded a mixture (**16** + **17**)(87 mg, 31%), which was crystallised three times from acetone-methanol, to give (Z)-17-acetoxymethylene-3-methoxyestra-1,3,5(10)-triene (**17**), m.p. 107-109 °C; $[\alpha]_D$ +44° (c 0.5); ν_{max} 1741 (C=O) and 1695 (C=C) cm^{-1}; δ_H(200 MHz) 0.88 (3H, s, 13β-Me), 2.14 (3H, s, 17^1-OAc), 2.79-2.9 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.63 (1H, d, J 2.8 Hz, 4-H), 6.68 (1H, dd, J 8.6 and 2.8 Hz, 2-H), 6.9 (1H, t, J 2.5 Hz, 17^1-H), and 7.18 (1H, d, J 8.6 Hz, 1-H); δ_C(50.1 MHz) 19.2 and 20.8 (COCH_3 and C-18), 23.9 (C-15), 26.5 (C-11), 27.7 (C-7), 2 x 29.8 (C-6 and C-16), 35.8

(C-12), 38.4 (C-8), 42.9 (C-13), 44.0 (C-9), 54.1 (C-14), 55.2 (3-OMe), 111.4 (C-2), 113.8 (C-4), 2 x 126.3 (C-1 and C-17^1), 132.6 (C-10), 2 x 137.4 (C-5 and C-17), 157.4 (C-3), and 168.3 (O*C*OCH$_3$) (Found : C, 77.4; H, 8.3%; *M*$^+$, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.2%; *M*, 340), 17-*acetoxymethyl*-3-*methoxyestra*-1,3,5(10),16-*tetraene* (**18**)(81 mg, 29%), m.p. 61-65 °C (from acetone-methanol); $[\alpha]_D$ +52° (*c* 1.0); ν_{max} 1724 (C=O), 1603 (C=C), and 1233 (C-O) cm^{-1}; δ(200 MHz) 0.86 (3H, s, 13β-Me), 2.09 (3H, s, 17^1-OAc), 2.76-2.9 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 4.63 and 4.73 (each 1H, d, *J* 13.4 Hz, 17^1-H_2), 5.71 (1H, br.dd, *J* 2.9 and 1.4 Hz, 16-H), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.69 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.2 (1H, d, *J* 8.5 Hz, 1-H) (Found : C, 77.5; H, 7.9%; *M*$^+$, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.2%; *M*, 340), 17α-*acetoxymethyl*-17β-*chloro*-3-*methoxyestra*-1,3,5(10)-*triene* (**19**)(47 mg, 15%), m.p. 123-128 °C* (from chloroform-methanol); $[\alpha]_D$ +3° (*c* 0.5); ν_{max} 1734 (C=O), 1604 (C=C), 1234 (C-O), and 707 (C-Cl) cm^{-1}; δ(200 MHz) 0.9 (3H, s, 13β-Me), 2.1 (3H, s, 17^1α-OAc), 2.76-2.8 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 4.34 and 4.48 (each 1H, d, *J* 12.2 Hz, 17^1-H_2), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.69 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found : C, 69.8; H, 7.9%; *M*$^+$, 376/378. $C_{22}H_{29}ClO_3$ requires C, 70.1; H, 7.7%; *M*, 376/378), and *bis*-(17^1-*acetoxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17β-*yl)sulphite* (**20**) (55 mg, 9%), m.p. 150-182 °C ** (from chloroform-methanol); $[\alpha]_D$ +2° (*c* 0.9); ν_{max} 1735 (C=O), 1608 (C=C), 1230 (C-O), and 1364 (S-O) cm^{-1}; δ(200 MHz) 1.0 and 1.1 (each s, 13β-Me), 2.14 (s, 17^1-OAc), 2.7-2.9 (m, 6-H_2), 3.78 (s, 3-OMe), 4.3 and 4.4 (each m, 17^1-H_2), 6.6 (d, *J* 2.6 Hz, 4-H), 6.7 (dd, *J* 8.6 and 2.6 Hz, 2-H), and 7.15 (d, *J* 8.6 Hz, 1-H) (Found : C, 68.9; H, 7.6%; *m/z* 358. $C_{44}H_{58}O_9S$ requires C, 69.3; H, 7.6%; *M*, 762).

* The chloride derivative decomposed on heating to form the 16-tetraene derivative (**18**).

** The sulphite ester decomposed on heating to form the acetoxy olefin (**16 + 17**), the 16-tetraene derivative (**18**), and a very polar compound (t.l.c.).

3-Methoxy-17-methylene-estra-1,3,5(10)-triene (**31**)

Sodium hydride (50%; 1.15 g, 24 mmol) was suspended under nitrogen in dry dimethyl sulphoxide (25 ml). The mixture was warmed to 50 °C for 45 min, then cooled to 25 °C and methyltriphenylphosphonium bromide (10.71 g, 29.9 mmol) in dry dimethyl sulphoxide (75 ml) was slowly added, followed by estrone 3-methyl ether (**9**)(5.72 g, 20 mmol) in tetrahydrofuran (100 ml). The mixture was stirred at 70 °C for 10 h, cooled to 20 °C, and aqueous ammonium chloride was added. Standard work-up (chloroform) afforded the crude product (5.6 g). Chromatography [ethyl acetate-benzene (1:19)] on silica gel (250 g) afforded 3-methoxy-17-methylene-estra-1,3,5(10)-triene (**31**).(3.44 g, 61%), m.p. 77-79 °C (from acetone-methanol)(lit.,[27] m.p. 81-82 °C); $[\alpha]_D$ +53° (*c* 0.5); ν_{max} 1653 (C=C) cm^{-1}; δ(200 MHz) 0.83 (3H, s, 13β-Me), 2.79-2.90 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 4.69 (2H, t, *J* 2.2 Hz, 17^1-CH_2), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.69 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.72 (1H, d, *J* 8.5 Hz, 1-H) (Found : C, 85.1; H, 9.2%; M^+, 282. $C_{20}H_{26}O$ requires C, 85.1; H, 9.2%; *M*, 282).

17β-Hydroxymethyl-3-methoxyestra-1,3,5(10)-triene (**32**)

9-Borabicyclo[3.3.1]nonane (9-BBN) (1.954 g, 16 mmol) was added under nitrogen at 25 °C to 17-methylene-3-methoxyestra-1,3,5(10)-triene (**31**)(860 mg, 3 mmol) dissolved in dry tetrahydrofuran (75 ml). After 2 h, the mixture was cooled to 0 °C, and sodium hydroxide (6 M; 8 ml) was added dropwise followed immediately by hydrogen peroxide (30%, 6 ml). Frothing occurred and a white precipitate resulted. The mixture was warmed to 25 °C and stirred for 16 h, then water was added. Standard work-up (ethyl acetate) afforded a crude product (1 g). Chromatography [ethyl acetate-hexane (2:8)] on silica gel (86 g) afforded 17β-hydroxymethyl-3-methoxyestra-1,3,5(10)-triene (**32**)(844 mg, 94%), m.p. 116-118 °C (from chloroform); $[\alpha]_D$ +68° (*c* 1.0); ν_{max} 3566

(OH) and 1151 (C-O) cm^{-1}; δ_H(200 MHz) 0.66 (3H, s, 13β-Me), 1.6 (1H, s; exch. by D_2O, 17^1-OH), 2.76-2.8 (2H, m, 6-H_2), 3.55 (1H, dd, J 10.4 and 7.2 Hz, 17^1-H), 3.71 (1H, dd, J 10.4 and 6.7 Hz, 17^1-H), 3.75 (3H, s, 3-OMe), 6.61 (1H, d, J 2.7 Hz, 4-H), 6.66 (1H, dd, J 8.6 and 2.7 Hz, 2-H), and 7.18 (1H, d, J 8.6 Hz, 1-H); δ_C(50.1 MHz) 12.5 (C-18), 24.3 (C-16), 25.6 (C-15), 26.4 (C-11), 27.8 (C-7), 29.8 (C-6), 42.1 (C-13), 38.5 (C-12), 38.7 (C-8), 44.0 (C-9), 53.0 (C-14), 54.9 (C-17), 55.2 (3-OMe), 64.5 (C-17^1), 111.4 (C-2), 113.8 (C-4), 126.2 (C-1), 132.9 (C-10), 137.9 (C-5), and 157.3 (C-3) (Found : C, 80.1; H, 9.0%; M$^+$, 300. $C_{20}H_{28}O_2$ requires C, 79.9; H, 9.3%; M, 300).

3-Methoxyestra-1,3,5(10)-triene-17β-carbaldehyde (**33**)

17β-Hydroxymethyl-3-methoxyestra-1,3,5(10)-triene (**32**) (245 mg, 0.82 mmol) in dichloromethane (5 ml), was added to pyridinium chlorochromate (267 mg, 1.24 mmol) and sodium acetate (39 mg, 0.47 mmol) suspended in dichloromethane (6 ml). Standard work-up (dichloromethane) after 1 h afforded the crude product (300 mg). Chromatography [ethyl acetate-hexane (1:9)] on silica gel (13 g) afforded 3-methoxyestra-1,3,5(10)-triene-17β-carbaldehyde (**33**)*(170 mg, 70%), m.p. 128-132 °C (from methanol-water); $[\alpha]_D$ +98° (c 0.9); ν_{max} 1711 (C=O) cm^{-1}; δ(200 MHz) 0.77 (3H, s, 13β-Me), 2.79-2.9 (2H, m, 6-H_2), 3.75 (3H, s, 3-OMe), 6.61 (1H, d, J 2.7 Hz, 4-H), 6.7 (1H, dd, J 8.6 and 2.7 Hz, 2-H), 7.15 (1H, d, J 8.6 Hz, 1-H), and 9.79 (1H, d, J 2.1 Hz, 17^1-H) (Found : C, 80.3; H, 8.5%; M$^+$, 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.7%; M, 298), followed by starting material (10 mg; 16%).

* Compound (**33**) has been reported in the literature,[31] but this source was unavailable to us at the time of writing, and comparative literature data are not given.

(E/Z)-17-Acetoxymethylene-3-methoxyestra-1,3,5(10)-triene (**16** + **17**)

A mixture of acetic anhydride (1 ml), isopropenyl acetate (2 ml), toluene-p-sulphonic acid monohydrate (30 mg, 0.99 mmol) and 3-methoxyestra-1,3,5(10)-triene-17β-carbaldehyde (**33**)(95 mg, 0.32 mmol) in benzene (5 ml) was slowly distilled under nitrogen for 2 h. Isopropenyl acetate was added from time to time to keep the volume above 4 ml. After 2 h, cold water was added. Standard work-up (ether) afforded a crude product (100 mg). Chromatography [ethyl acetate-hexane (1:9)] afforded (E)/(Z)-17-acetoxymethylene-3-methoxyestra-1,3,5(10)-triene [(**16** + **17**), ca 1:3](85 mg, 78%), m.p. 78-108 °C (from acetone-methanol); v_{max} 1741 (C=O) and 1695 (C=C) cm^{-1}; δ(200 MHz) 0.84 and 0.9 (each s, 13β-Me), 2.11 (s, 17^1-OAc), 2.79-2.9 (m, 6-H_2), 3.75 (s, 3-OMe), 6.6 (d, J 2.7 Hz 4-H), 6.66 (dd, J 8.6 and 2.7 Hz, 2-H), 6.8 (t, J 2.0 Hz, 17^1-H of (**16**)), 6.89 (t, J 2.5 Hz, 17^1-H of (**17**)), and 7.17 (d, J 8.6 Hz, 1-H) (Found : C, 77.6; H, 8.2%; M^+, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.2%; M, 340).

Epoxidation and Rearrangement of (E/Z)-17-Acetoxymethylene-3-methoxyestra-1,3,5(10)-triene (**16** + **17**)

(a) m-Chloroperbenzoic acid (50 mg, 0.29 mmol) was added under nitrogen to the uncrystallised enol acetate mixture (**16** + **17** obtained in the foregoing experiment)(50 mg, 0.15 mmol) in dichloromethane (6 ml) at 0 °C. After 7 h at 0 °C, saturated aqueous sodium hydrogen carbonate was added. Standard work-up (dichloromethane) afforded the crude product (50 mg), which was then refluxed in toluene (3 ml) for 10 h and concentrated in vacuo. Chromatography on the crude product (50 mg) [ethyl acetate-hexane (1:19) → (1:9) → (3:7)] on silica gel (9 g) afforded 17β-acetoxy-3-methoxyestra-1,3,5(10)-triene-17α-carbaldehyde (**30**)(16 mg, 29%), m.p. 128-132 °C (from acetone-methanol); $[\alpha]_D$ +20° (c 1.0) [lit.,[5] m.p. 125-128 °C; $[\alpha]_D$ +20° (c 1.0)]; δ(200 MHz) 1.03 (3H, s, 13β-Me), 2.16 (3H, s, 17-OAc), 2.7-2.9 (2H, m, 6-H_2), 3.75 (3H, s, 3-OMe), 6.6 (1H, d, *J* 2.8 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.12 (1H, d, *J* 8.6 Hz, 1-H), and 9.53 (1H, s, 17^1-H) (Found : C, 74.0; H, 7.6%; *M*$^+$, 356. $C_{22}H_{28}O_4$ requires C, 74.2; H, 7.9%; *M*, 356), 17α-*acetoxy*-3-*methoxyestra*-1,3,5(10)-*triene*-17β-*carbaldehyde* (**34**)(8 mg, 15%), m.p. 189-194 °C (from chloroform-methanol); $[\alpha]_D$ +11° (*c* 0.5); ν_{max} 1725 (CHO + AcO) cm^{-1}; δ(200 MHz) 0.77 (3H, s, 13β-Me), 2.16 (3H, s, 17-OAc), 2.7-2.9 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.65 (1H, d, *J* 2.6 Hz, 4-H), 6.7 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H), 7.21 (1H, d, *J* 8.5 Hz, 1-H), and 9.53 (1H, s, 17^1-H) (Found : C, 74.1; H, 7.5%; *M*$^+$, 356. $C_{22}H_{28}O_4$ requires C, 74.2; H, 7.9%; *M*, 356), and 17aα-*acetoxy*-3-*methoxy*-17a-*homoestra*-1,3,5(10)-*trien*-17-*one* (**35**)(8 mg, 15%), m.p. 110-130 °C decomp. (from ethyl acetate-methanol); ν_{max} 1739 and 1720 (C=O) cm^{-1}; δ(200 MHz) 1.23 (3H, s, 13β-Me), 2.12 (3H, s, 17aα-OAc), 2.7-2.9 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.04 (1H, s, 17aβ-H), 6.6 (1H, d, *J* 2.8 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found : C, 74.1; H, 7.6%; *M*$^+$, 356. $C_{22}H_{28}O_4$ requires C, 74.2; H, 7.9%; *M*, 356).

(b) m-Chloroperbenzoic acid (255 mg, 1.48 mmol) was added under nitrogen to the uncrystallised enol acetate mixture (**16** + **17** obtained in the foregoing experiment)(250 mg, 0.74 mmol) in dichloromethane (15 ml) at 0 °C. After stirring for 7 h, the mixture was cooled to -78 °C and tin tetrachloride (1 M; 0.5 ml, 0.5 mmol) was added dropwise over 1 min. The mixture was brought up to 0 °C and aqueous sodium hydrogen carbonate was added. Standard work-up (dichloromethane), which included neutralising the organic layer with pyridine, afforded the crude product (250 mg). Chromatography [ethyl acetate-hexane (1:39) → (1:19) → (1:9)] on silica gel (25 g) afforded an inseparable mixture (65 mg), followed by 17β-acetoxy-3-methoxyestra-1,3,5(10)-triene-17α-carbaldehyde (**30**)(3 mg, 1%), 17α-acetoxy-3-methoxyestra-1,3,5(10)-triene-17β-carbaldehyde (**34**)(14 mg, 5%), 17aα-acetoxy-3-methoxy-17a-homoestra-1,3,5(10)-trien-17-one (**35**)(8 mg, 3%), and the unknown compound (**38**)(34 mg, 14%), m.p. 115-118 °C (from ethyl acetate-methanol); $[\alpha]_D$ +41° (*c* 0.6); ν_{max} 1706 (C=O) cm^{-1};

δ_H(200 MHz) 2.14 (3H, s, 17^1-OAc), 3.78 (3H, s, 3-OMe), 6.65 (1H, d, *J* 2.7 Hz, 4-H), 6.75 (1H, dd, *J* 8.7 and 2.7 Hz, 2-H), and 7.2 (1H, d, *J* 8.7 Hz, 1-H); δ_C (50.1 MHz) 19.6 (?), 29.9 (CO*C*H_3), 27.7 (C-7), 30.3 (C-6), 31.6 (?), 41.1 (?), 41.7 (?), 42.0 (C-9), 45.8 (C-8), 53.8 (C-14), 55.2 (3-OMe), 112.0 (C-2), 113.5 (C-4), 126.8 (C-1), 130.6 (C-10), 137.8 (C-5), 157.8 (C-3), 208.9 and 211.8 (*C*O and *C*OCH_3) (Found : C, 75.7; H, 8.4%; *M*$^+$, 300).

CHAPTER 2

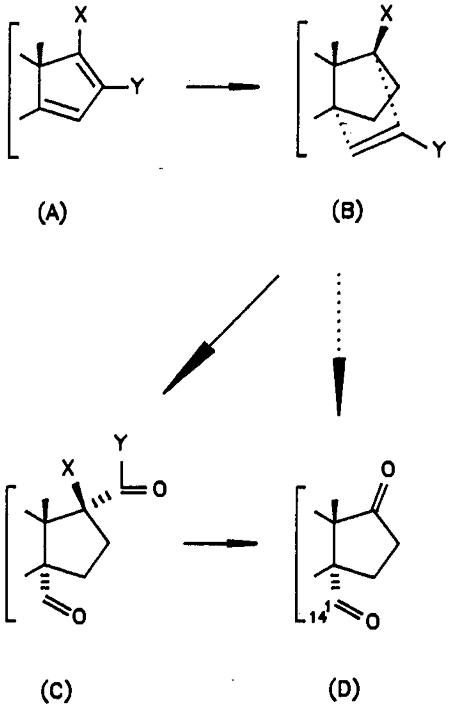
THE SYNTHESIS OF ESTRADIOL AND ESTRIOL ANALOGUES DERIVED FROM 3-METHOXY-17-OXOESTRA-1,3,5(10)-TRIENE-14-CARBALDEHYDE AND 3-METHOXY-14,17α-ETHENOESTRA-1,3,5(10)-TRIEN-17β-OL DERIVATIVES

2.1 INTRODUCTION

2.1.1 Background

The feasibility of synthesising 19-norsteroids having extended 14α-alkyl chains is suggested by the reaction sequence based upon Diels-Alder cycloaddition of an ethylene equivalent to a steroidal 14,16-diene (**A**), followed by oxidative cleavage of the residual olefinic bond in the cycloadduct (**B**). In this way the ring D system (**C**) could be restored with the introduction of a 14α-formyl group, and with the concomitant 17-substituent patterns determined by choice of 16- and 17-substituents in the starting diene. Implicit in the approach was that an oxygen function at C(17) would also allow extended oxidative cleavage, leading to the 14α-formyl-17-ketone (**D**)(Scheme 2.111).[32] This prompted an investigation into the extension of the 14α-alkyl chain, based upon chemoselective reactions of the 14α-formyl group in (**D**), or upon regioselective functionalisation of the olefinic bond in (**B**), followed by ring-cleavage.

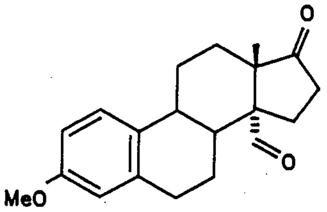
SCHEME 2·111



2.12 Objectives and Approach

The availability of products having 14α-functionality and their 14α,17α-etheno bridged precursors, invited an investigation of estradiol and estriol analogues having extended 14α-alkyl chains for structure activity studies.

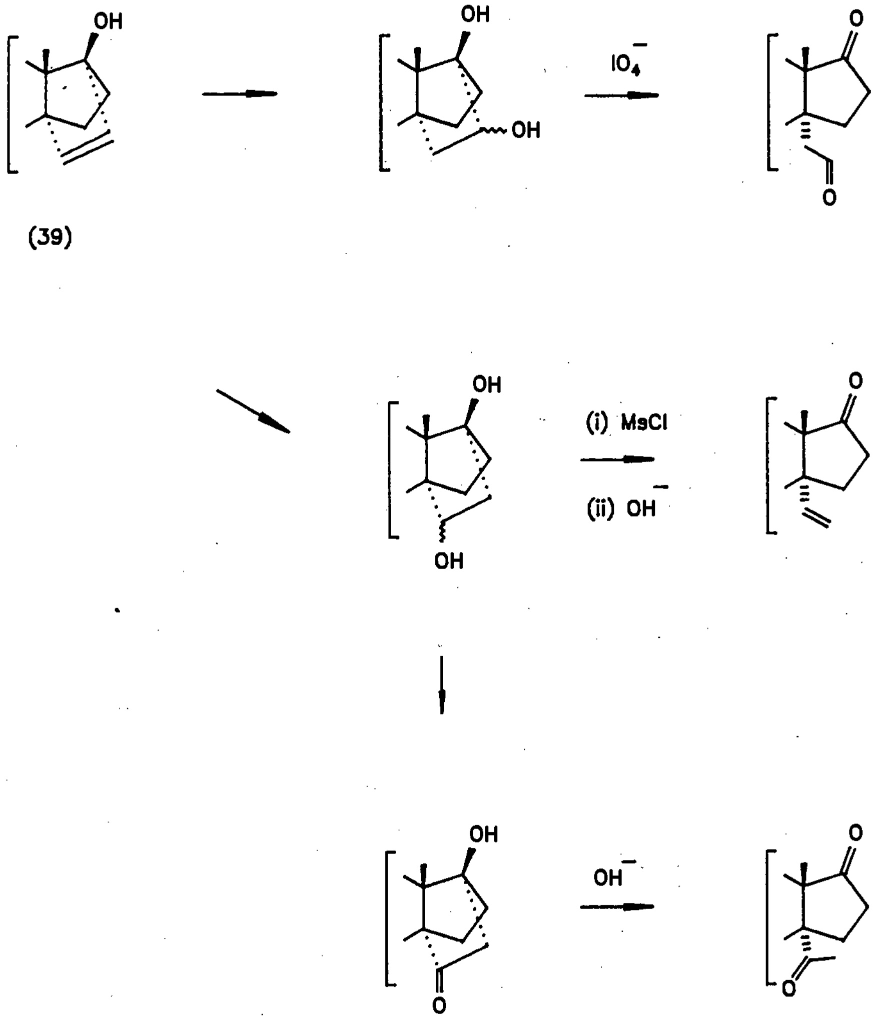
A direct approach to the objective could be envisaged through chemoselective 14^1-alkylation of the 14α-formyl-17-ketone (**40**).



(40)

Alternatively, regioselective hydration of a 14α,17α-etheno compound could be used to obtain intermediates of direct or indirect cleavage of the bridge, followed by further elaboration of the 14α-functionalised alkyl products (Scheme 2.121).

SCHEME 2·121



2.2 Discussion

2.2.1 Selective Chain Extension of 3-Methoxy-17-oxoestra-1,3,5(10)-triene-14-carbaldehyde at C(14^{1})

Treatment of the 14α-formyl-17-ketone (**40**) with a suspension of the methylenetriphenylphosphorane^{26} at 0°C, followed by refluxing for 48 h, afforded 3-methoxy-14α-vinylestra-1,3,5(10)-trien-17-one (**41**), in low yield (18%), accompanied by an uncharacterisable mixture and starting material (Scheme 2.211).

SCHEME 2·211

(40) (41)

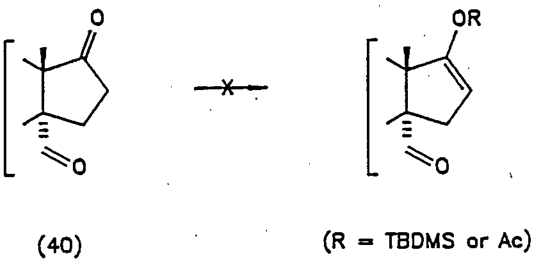
The ^{1}H n.m.r. spectrum of the compound (**41**) displayed a diagnostic ABC multiplet for the vinyl group at δ5.14 (dd, $\underline{J}$ 17.7 and 0.9 Hz, 14^{2}-H), 5.22 (dd, $\underline{J}$ 11.5 and 0.9 Hz, 14^{2}-H), and 6.1 (ddd, $\underline{J}$ 17.7, 11.5, and 0.9 Hz, 14^{1}-H), assigned as follows: $\underline{J}$(trans)14^{1},14^{2} 17.7 Hz, $\underline{J}$(cis)14^{1},14^{2} 11.5 Hz, and $\underline{J}$(gem)14^{2},14^{2} 0.9 Hz. The additional splitting observed with 14^{1}-H signal was ascribed to four-bond coupling with the 15β-proton; molecular models suggest that rotation about the C(14)-C(14^{1}) bond should be restricted, and that the vinyl group will favour a conformation in which a $\underline{W}$-configuration is adopted in the bonds connecting 14^{1}-H and 15β-H.

The reaction appeared to be chemoselective since no 17-methylene derivative was detected. However, the low yield suggested that both carbonyl groups in (**40**) are rather unreactive towards the sterically demanding Wittig reagent.

In an attempt to apply more forcing reaction conditions, an experiment was conducted in which the 14α-formyl-17-ketone (**40**) was treated with lithium diisopropylamide, followed by trapping with t-butyldimethylchlorosilane (TBDMSCl), in the hope of protecting the 17-carbonyl group as the corresponding silyl enol ether. Only starting material was recovered.

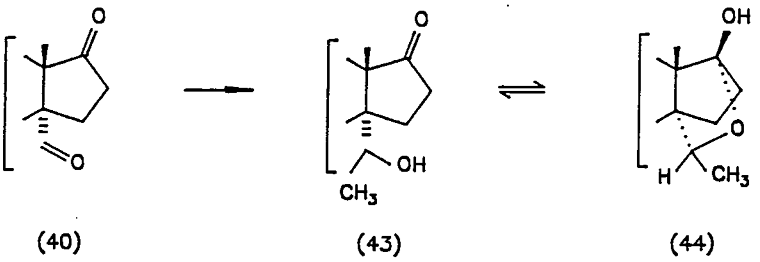
In an alternative approach, the 14α-formyl-17-ketone (**40**) was treated under enol acetylation conditions (Scheme 2.212). However, this led to partial conversion into an unidentified product (**42**) arising from probable skeletal rearrangement. Time did not permit a structural investigation of this product.

SCHEME 2·212



However, the scope for possible chemoselective functionalisation of the 14α-formyl-17-ketone (**40**) was demonstrated by treatment with methyl-lithium at 0 °C, which afforded 14-(1-hydroxy)ethyl-3-methoxyestra-1,3,5(10)-trien-17-one (**43**) in a good yield (85%), which exists in solution mainly as the hemiketal (**44**)(Scheme 2.213).

SCHEME 2·213



The structure of the hemiketal (**44**) was confirmed by the strong hydroxyl absorption peak at 3374 cm^{-1} in the infrared spectrum, and ^{1}H n.m.r. displayed a doublet (J 0.7 Hz) at δ0.96 for the 14^{1}-methyl group, and a diagnostic signal at δ4.55 (dq, J 3 x 6.2 and 2.2 Hz) for 14^{1}-H. The additional splitting of the 14^{1}-H (J 2.2 Hz), and of the 13-methyl signal (J 0.7 Hz) arose from ^{4}J coupling in a W-configuration with 15β-H and the 12α-H respectively.

This result thus demonstrates scope for exploring chemoselective differentiation of the carbonyl groups in the formyl ketone, for example, through dehydration to the vinyl compound (**41**), or more directly, by carrying out a Peterson-type olefination on the formyl ketone. Lack of time precluded further investigation of this approach.

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

3-Methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol (**39**) was synthesised according to the cycloaddition method by Bull and Thompson.[32] The desulphonylation product of the cycloadduct (**39**) contains an inseparable by-product (**45**), as reported.[32]

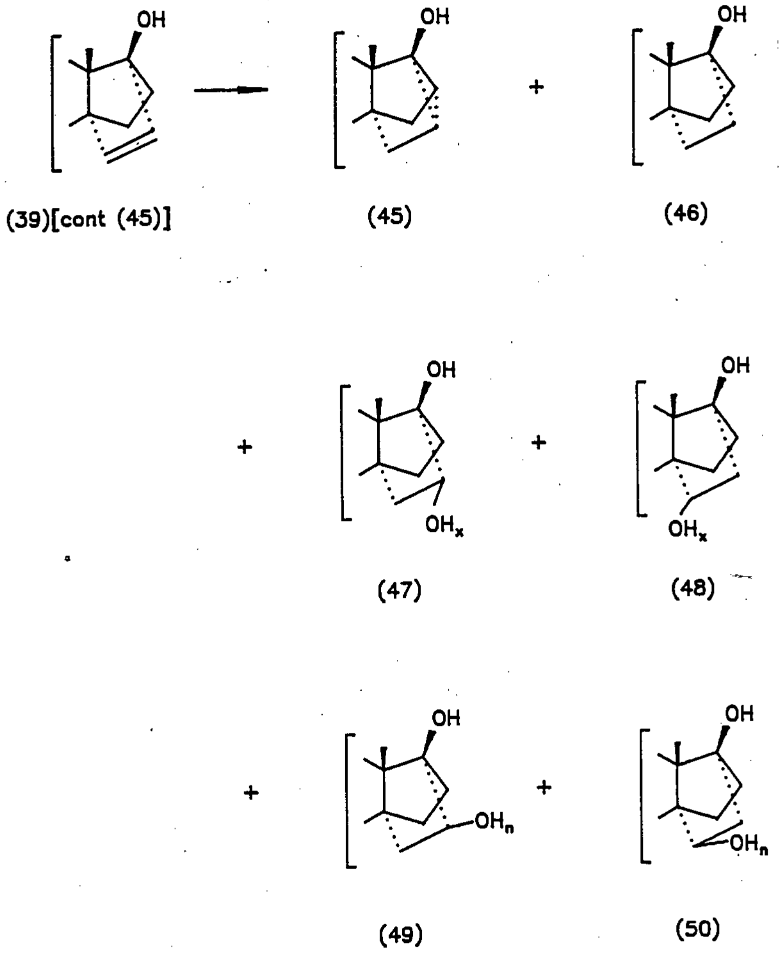
The 14α,17α-etheno-17β-alcohol (**39**)[containing ca 10% of (**45**)] in tetrahydrofuran was treated with borane-tetrahydrofuran at <10 °C. After 48 h at 25 °C, the solution was cooled to 0 °C, and treated with alkaline peroxide to give a mixture of products (Scheme 2.221). Chromatography gave, in order of elution, the 16α,17^{1}-cyclo-17β-alcohol (**45**)(10%) and the 14α,17α-ethano-17β-alcohol (**46**)(2%), followed by the hydration products in order of elution:

(i) $(17^1\underline{R})$-3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-17β,17^1-diol **(47)** (7%),

(ii) $(17^2\underline{S})$-3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-17β,17^2-diol **(48)** (10%),

(iii) an inseparable mixture (55%)(<u>ca</u> 1:1 by ^{1}H n.m.r.) of $(17^1\underline{S})$-3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-17β,17^2-diol **(49)** and $(17^2\underline{R})$-3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-17β,17^2-diol **(50)**.

SCHEME 2·221

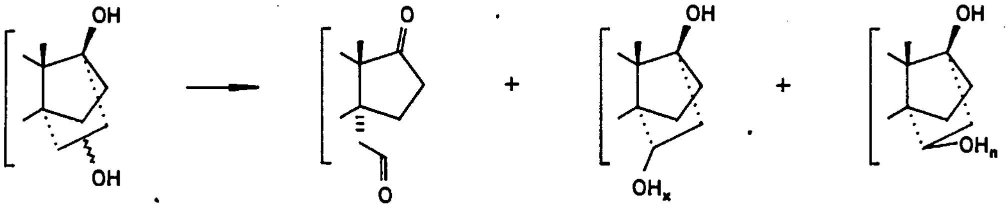


x = exo, n = endo

The cyclopropyl (**45**) and the dihydro (**46**) derivatives were identified by comparative physical and spectroscopic data.^{32}

The structures of the diols (**47**)-(**50**) were assigned on the basis of spectroscopic properties and selective chemical transformations. Thus, the total diol mixture (**47-50**) was subjected to periodate oxidation, resulting in selective conversion of (**47**) and (**49**) into 14α-formylmethyl-3-methoxyestra-1,3,5(10)-trien-17-one (**51**), whilst leaving the $17\beta,17^2$-diols (**48**) and (**50**) unchanged. This mixture was separated chromatographically, thereby also providing access to pure (**50**)(Scheme 2.222).

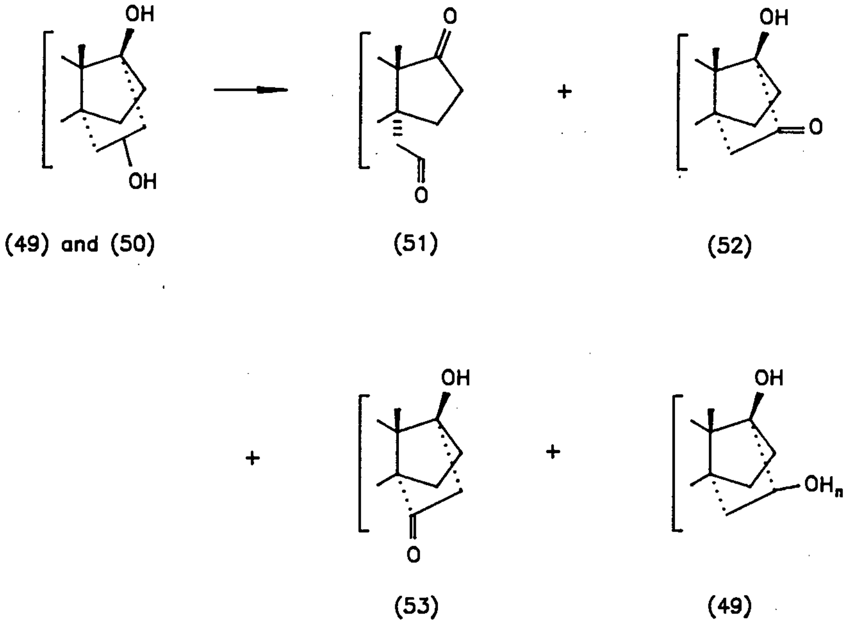
SCHEME 2·222



(47–50) (51) (48) (50)

In a separate experiment, the inseparable mixture of (**49**) and (**50**) was oxidised with Jones' reagent at 0 °C; after 1 h, the reaction was incomplete, and chromatography of the mixture gave the 14α-formylmethyl compound (**51**), two hydroxy ketones (**52**) and (**53**), and unchanged (**49**)(Scheme 2.223).

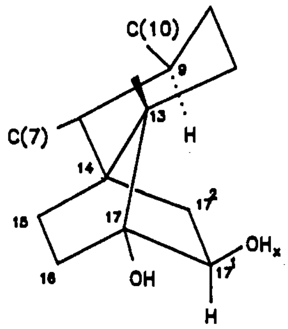
SCHEME 2·223



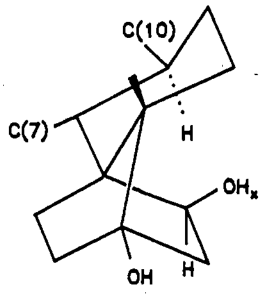
These experiments, not only established the regiochemistry of the four diols, but provided access to pure samples of each for spectroscopic examination.

The stereochemistry of each of the products (**47**)-(**50**) was determined with the aid of characteristic coupling patterns and chemical shifts (Figure 2.221)(Table 1).

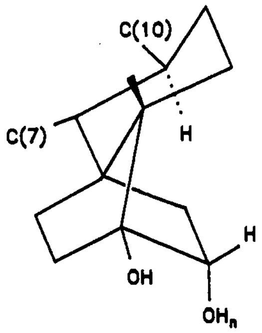
FIGURE 2·221



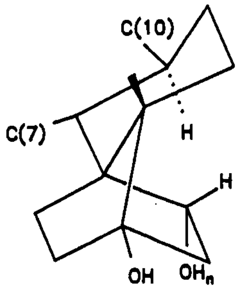
(47)



(48)



(49)



(50)

x = exo, n = endo

Table 1: ^{1}H N.m.r. data for diols

diol	%	CHOH	9α-H
(**47**)	7	δ3.79 obsc. (dd, J 8.4 and 3.1 Hz)	δ2.64
(**48**)	10	δ4.15 (dd, J 8.2 and 4.6 Hz)	δ3.4
(**49**)	27	δ4.3 br. (ddd, J 10.7, 4.0 and ca 1.5 Hz)	obsc.
(**50**)	27	δ4.6 (br. ddd, J 10.2, ca 2, and ca 0.8 Hz)	obsc.

The exo isomers (**47**) and (**48**) both displayed sharp multiplets for the C$\underline{H}$OH proton, although that of (**47**) was partly obscured by the 3-OMe signal. Their J values (ca 8.3 Hz) were smaller than those (ca 10.4 Hz) of the endo isomers (**49**) and (**50**), for coupling with the neighbouring syn-periplanar proton. This is consistent with the observation that $^3J_{endo,endo}$ is generally smaller that $^3J_{exo,exo}$ in bicyclo[3.3.1]heptanes.[33] Furthermore, the proximity of the 17^2-hydroxy group in (**48**) exerted a distinctive deshielding effect upon the 9α-H signal, as noted in related systems,[32,34] and the C$\underline{H}$OH multiplets in (**49**) and (**50**) showed additional splitting (0.8-1.5 Hz) arising from ^4J coupling in a W-configuration with 16β-H and 15β-H respectively.

With these assignments in hand, it was possible to interpret the regio- and stereoselectivity of the reaction. In the first place, there is negligible regio differentiation between C(17^1) and C(17^2) (ca 1.1 : 1), suggesting that the bridgehead hydroxy group does not influence the orientation of reagent approach. However, a distinct preference (ca 3:1) for endo-attachment is evident. It is known that bicyclo[2.2.1]hept-2-enes[35] display extremely high exo-stereoselectivity in hydroboration, whereas norbornenes (having 7,7-dimethyl substituents[35]), favour endo-addition (ca 3.5 : 1). The 14α,17α-etheno compound is similarly disubstituted on the bridge (i.e. at C(13)), and further hindered on the exo-face by the elements of ring B and C. Accordingly, it would be expected that endo-stereoselectivity should be even more strongly favoured. In fact, the trend is contrary, and it may be possible that the bridgehead hydroxy-group at C(17) is responsible, although there is no obvious mechanistic explanation based upon the interaction between the reagent and this hydroxy group.

Periodate cleavage and Jones' oxidation not only provided access to pure samples of the endo diols, but also provided an approach to analogues for 14α-functionalisation e.g. 14α-formylmethyl compound (**51**), and the ketones (**52**) and (**53**).

The total diol mixture (**47-50**) was treated with 6% aqueous sodium metaperiodate in ethanol to give a mixture, which was chromatographed to afford 14α-formylmethyl-3-methoxyestra-1,3,5(10)-trien-17-one (**51**)(53%), the (17^{2}S)-diol (**48**)(11%), and the (17^{2}R)-diol (**50**)(15%) (see Scheme 2.222).

The structure of the 14α-formylmethyl compound (**51**) was assigned on the basis of formyl proton signal at δ9.87 (dd, *J* 3.5 and 2.8 Hz), and the two carbonyl absorption bands in the infrared spectrum at 1734 and 1713 cm^{-1}, due respectively to the 17-carbonyl and 14-formyl groups.

In the alternative approach for separating the endo isomers, the mixture of diols (**49 + 50**) was treated with Jones' reagent to afford a mixture which, on column chromatography, afforded the 14α-formylmethyl compound (**51**)(4%), 17β-hydroxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17^1-one (**52**)(17%), 17β-hydroxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17^2-one (**53**)(31%), and the (17^{1}S)-diol (**49**)(30%) (see Scheme 2.223).

Structural elucidation of the 17^1-ketone (**52**) and the 17^2-ketone (**53**) was made with the help of comparative t.l.c. scale experiments on the individual (17^{1}R)- and (17^{2}S)-diols (**47**) and (**48**), respectively.

One of the diols (**47**), arising from this study, was converted into the corresponding estriol analogue (**54**)(61%) by treatment with diisobutylaluminium hydride (DIBAH) in refluxing toluene for 72 h (Scheme 2.224). The product has been submitted for evaluation as an estrogen.

SCHEME 2·224

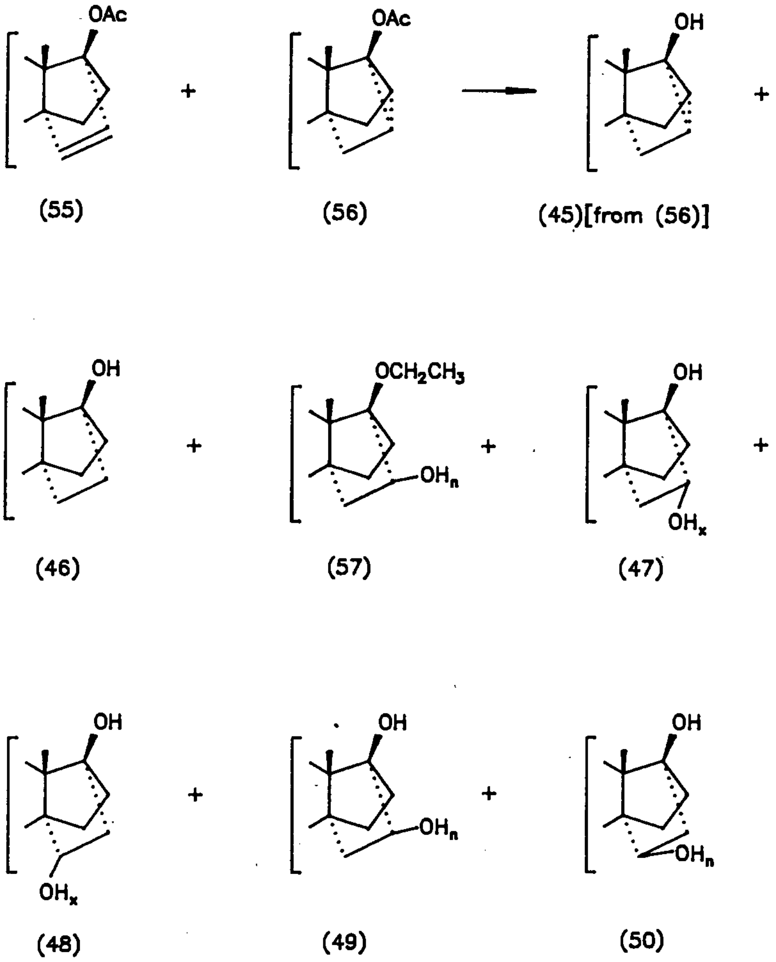
(47) (54)

2.2.3. Hydroboration of Bridgehead functionalised Derivatives of 3-Methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol

In the light of the foregoing hydroboration results, it was decided to examine the scope for modifying the regio- and stereoselectivity through protection or potentiation of the bridgehead hydroxy group. A start was made with the acetoxy olefin (**55**), since it is known that reaction conditions can be adjusted to minimise any hydrolytic cleavage of ester bonds.

Treatment of the acetoxy olefin (**55**)[containing _ca_ 8% of (**56**)] for a prolonged period with borane-dimethyl sulphide led to a mixture which was chromatographed to give, in order of elution, starting material (**55**)(3%), the 16α,14^1-cyclo-17β-alcohol (**45**)(8%), the 14α,17α-ethano-17β-alcohol (**46**)(11%), (17^1_S_)-17β-ethoxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17^1-ol (**57**)(12%), followed by the diols (**47**)-(**50**)(32%)(Scheme 2.231).

SCHEME 2·231

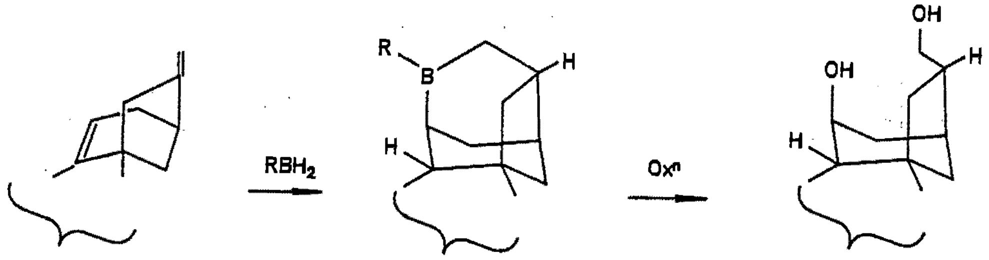


The cyclopropyl (**45**) and the dihydro (**46**) derivatives were identified by comparative physical and spectroscopic data.[32]

The structure of the 17β-ethoxy-17^1-alcohol (**57**) was confirmed by ^{1}H n.m.r., which revealed a diagnostic triplet at δ1.17 for the methyl protons, and an overlapping pair of quartets (each 3 x *J* 7 Hz) centred at δ3.62 for the methylene protons of the ethyl ether group, and a characteristic multiplet at δ4.6 (ddd, *J* 10.5, 3.6, and 1.2 Hz) for the 17^1-H_{exo}. Clearly, the presence of the acetoxy group at the bridgehead position had no beneficial effect upon selectivity or reactivity, and thus this experiment was not repeated. Furthermore, the overall conversion to the diols is inefficient.

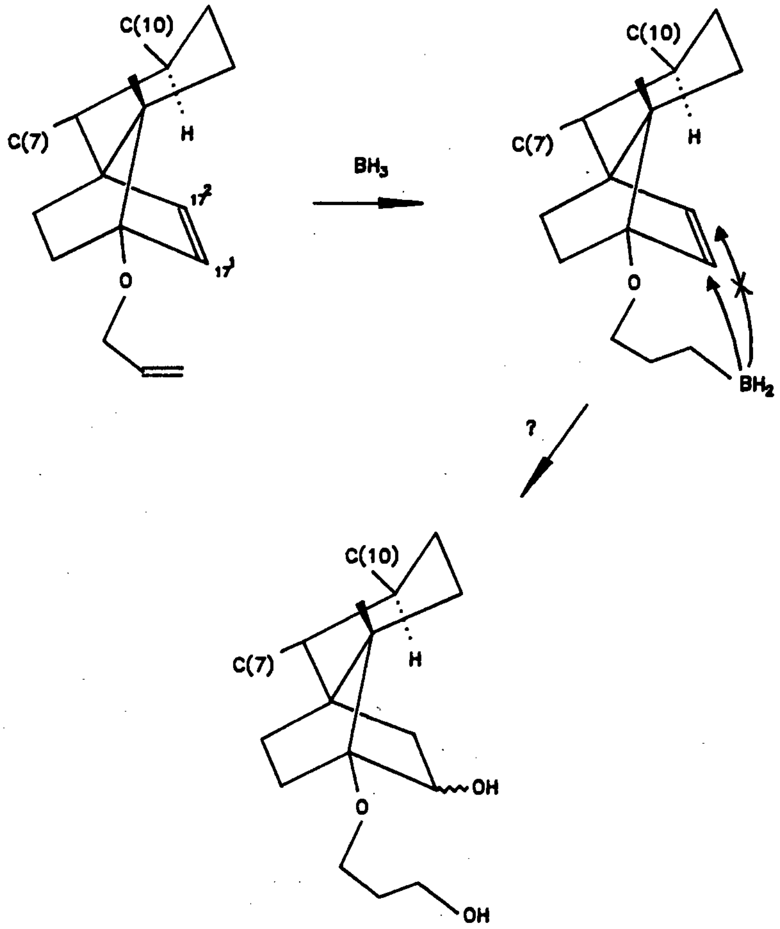
Attention was turned to the consideration of bridgehead functional groups which might influence regio- or stereoselectivity through intramolecular participation. The principle of intramolecular hydroboration is well known.[36] Recent literature examples include the work of Harada et al.,[37] who showed that intramolecular hydroboration of allylic alcohol derivatives proceed with syn selectivity opposite to that of the intermolecular counterpart. In another recent publication, Mander et al.[38] showed that hydroboration of suitable 9(11),16-diene gibberellins involved the initial addition of the borane to the exo-face of the more accessible Δ^{16} -ene function, followed by intramolecular addition to the upper face of the $\Delta^{9(11)}$-double bond, upon which oxidation then afforded an 11β,17-diol (Scheme 2.232).

SCHEME 2·232



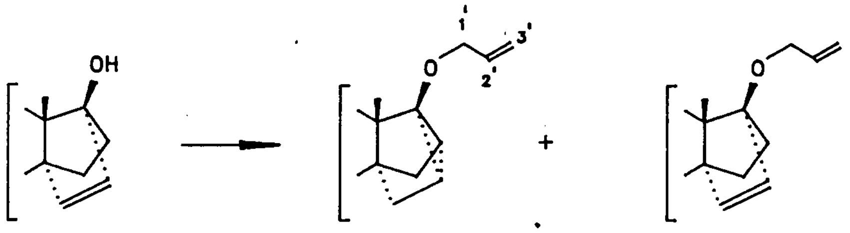
We initially chose to explore the scope for an intramolecular reaction by carrying out hydroboration on the 17β-allyloxy olefin (**59**). It was hoped that initial attack by borane on the terminal position of the allyl group might facilitate regioselective, intramolecular delivery of borane at $C(17^1)$, rather than the more remote $C(17^2)$ position (Figure 2.231).

FIGURE 2·231



Treatment of the hydroxy olefin (**39**)[containing (**45**)] with sodium hydride in 1,2-dimethoxyethane, followed by allyl bromide, gave after work-up and chromatography, the cyclopropyl derivative (**58**)(27%)[obtained from the impurity (**45**) in the hydroxy olefin (**39**)], and the 17β-allyloxy olefin (**59**)(66%)(Scheme 2.233).

SCHEME 2·233



(39)[cont (45)] (58)[from (45)] (59)

The cyclopropyl derivative (**58**) and the 17β-allyloxy olefin (**59**) were identified by ^{1}H n.m.r., which displayed a distinctive A_2XYZ system for the allyl ether group (see Table 2):

Table 2: ^{1}H N.m.r. for the allyl ether group

proton	(**58**)	(**59**)
1'-H_2	δ4.05 (br.d, *J* 5.2 Hz, and $W_{\frac{1}{2}}$ *ca* 4.8 Hz*)	δ4.15 (br.d, *J* 5.3 Hz, and $W_{\frac{1}{2}}$ *ca* 4.8 Hz*)
2'-H	δ5.9 (m**, *J* 17.3, 10.3, and 2 x 5.2 Hz)	δ6.0 obsc.(m**, *J* *ca* 17.3, *ca* 10.3, and 2 x *ca* 5.3 Hz)
3'-H_{cis}	δ5.11 (ddd, *J* 10.3, 2.8, and 1.6 Hz)	δ5.15 (ddd, *J* 10.3, 2.7 and 1.5 Hz)
3'-H_{trans}	δ5.25 (ddd, *J* 17.3, 3.5, and 1.6 Hz)	δ5.3 (ddd, *J* 17.3, 3.3, and 1.5 Hz)

* This signal shows an unresolved triplet structure, and $W_{\frac{1}{2}}$ *ca* 4.8 Hz for each component part of the broad doublet.

** A theoretical twelve line multiplet degenerated into 10 lines through signal overlap.

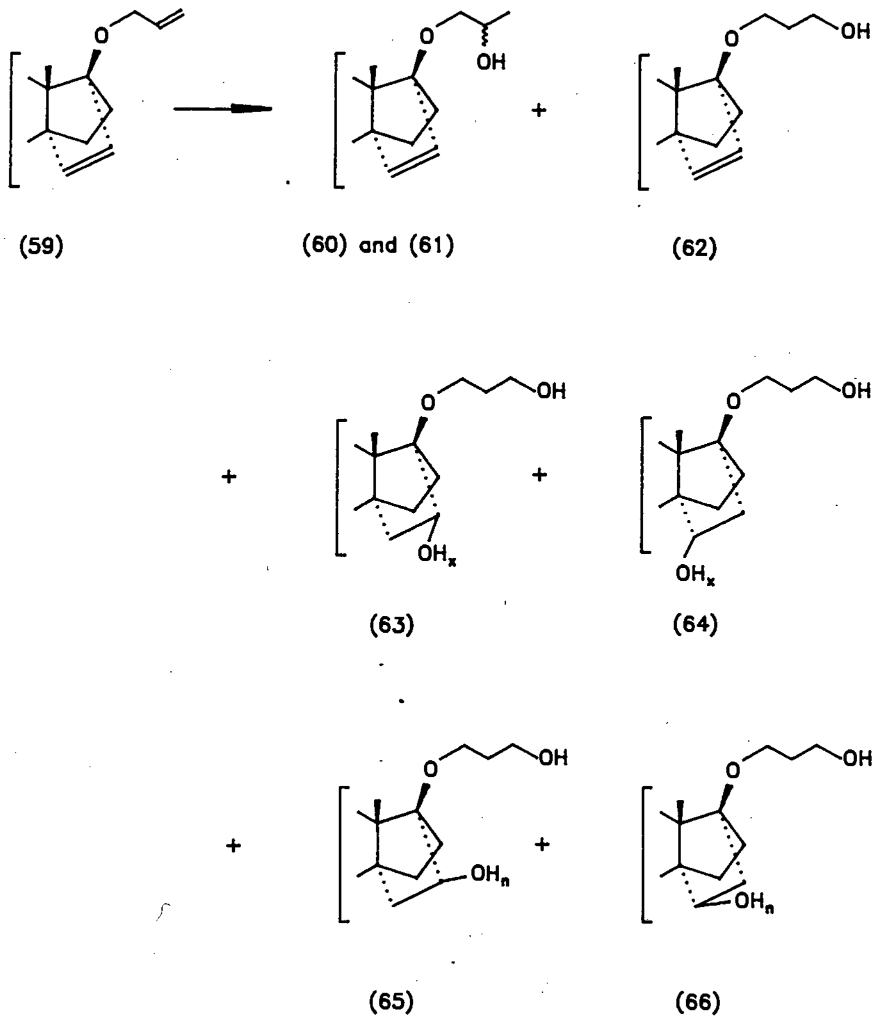
Hydroboration of the allyl ether (**59**) proceeded very slowly at 25 °C, although there was evidence that initial addition of borane on the allyl group occurred quite readily. Accordingly, after a period at 25 °C, the reaction was allowed to proceed under reflux in tetrahydrofuran for 48 h. After oxidative work-up, the complex mixture was chromatographed. The products of exclusive attack on the allyl group comprised ca 53% of the total, viz. (2'-R/S)-17β-(2-hydroxypropoxy)(**60 + 61**), and 17β-(3-hydroxypropoxy)(**62**) compounds, whereas products of attack at both olefinic bonds comprised only ca 17% of the total, viz., (in order of elution):

(i) $(17^1\underline{R})$-17β-(3-hydroxypropoxy)-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17^1-ol (**63**)(3%),

(ii) $(17^2\underline{S})$-17β-(3-hydroxypropoxy)-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17^2-ol (**64**)(5%),

(iii) an inseparable mixture (9%)(ca 2:1 by ^{1}H n.m.r.) of $(17^1\underline{S})$-17β-(3-hydroxypropoxy)-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17^1-ol (**65**), and $(17^2\underline{R})$-17β-(3-hydroxypropoxy)-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17^2-ol (**66**)(Scheme 2.234).

SCHEME 2·234



The structures of the products were assigned mainly on the basis of ^{1}H n.m.r. spectroscopic data summarised in Tables 3 and 4.

Table 3: ^{1}H N.m.r for 17β-hydroxypropoxy group

(**60**) and (**61**)	δ1.17 (d, J 6.4 Hz, 2'-CH_3) δ3.4 (m, 2'-H) δ3.6 (ddd, J 9.2, 3, and 2.1 Hz,1'-H)
(**62**)	δ1.85 (m, 2'-CH_2) δ3.82 (m, 1'- and 3'-CH_2)

Table 4: ^{1}H N.m.r for the diols

diol	%	C<u>H</u>OH	9α-H
(63)	3	δ4.1 (dd, *J* 8.4 and 2.7 Hz)	δ2.64
(64)	5	δ4.12 (dd, *J* 8.5 and 4.6 Hz)	δ3.4
(65)	6	δ4.6 br. (ddd, *J* 10.5, 3.6, and *ca* 1.5 Hz)	obsc.
(66)	3	δ4.73 (br. ddd, *J* 10.5, *ca* 2.1, and *ca* 0.7 Hz)	obsc.

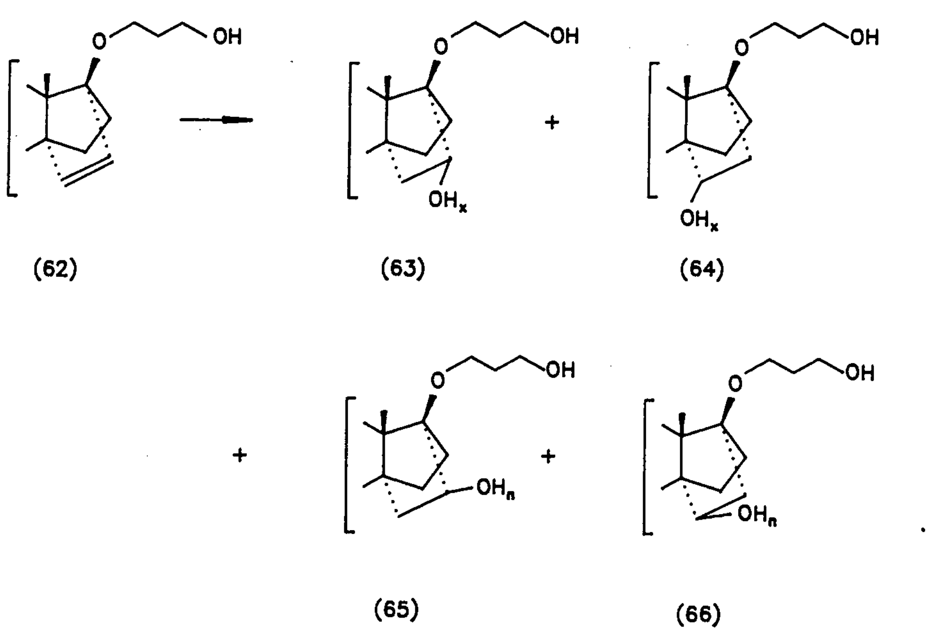
The 17β-hydroxypropoxy group signals for the diols were characteristic for that of the 17β-(3-hydroxypropoxy) group.

It is evident from this result that the presence of the allyl group, not only did not promote hydroboration, but failed to give any discernible regioselectivity in hydroboration on the bridge. Indeed, it is most probable that no intramolecular participation occurred.

The major product **(62)** from the previous reaction was then examined to demonstrate whether the terminal hydroxy group might achieve the desired objective through intramolecular delivery of borane via an alkoxy borane intermediate.

The 17β-(3-hydroxypropoxy) compound **(62)** in tetrahydrofuran was treated with borane-tetrahydrofuran at 0 °C. After 48 h at 25 °C, afforded a mixture which was chromatographed to give the $(17^1\underline{R})$-isomer **(63)**(19%), the $(17^2\underline{S})$-isomer **(64)**(15%), and an inseparable mixture (42%)(*ca* 2:1 by ^{1}H n.m.r.) of the $(17^1\underline{S})$- and $(17^2\underline{R})$-isomers **(65)** and **(66)**(42%) (Scheme 2.235).

SCHEME 2·235



The spectroscopic and physical data for the isomers (**63-66**) were identified with those obtained in the previous experiment.

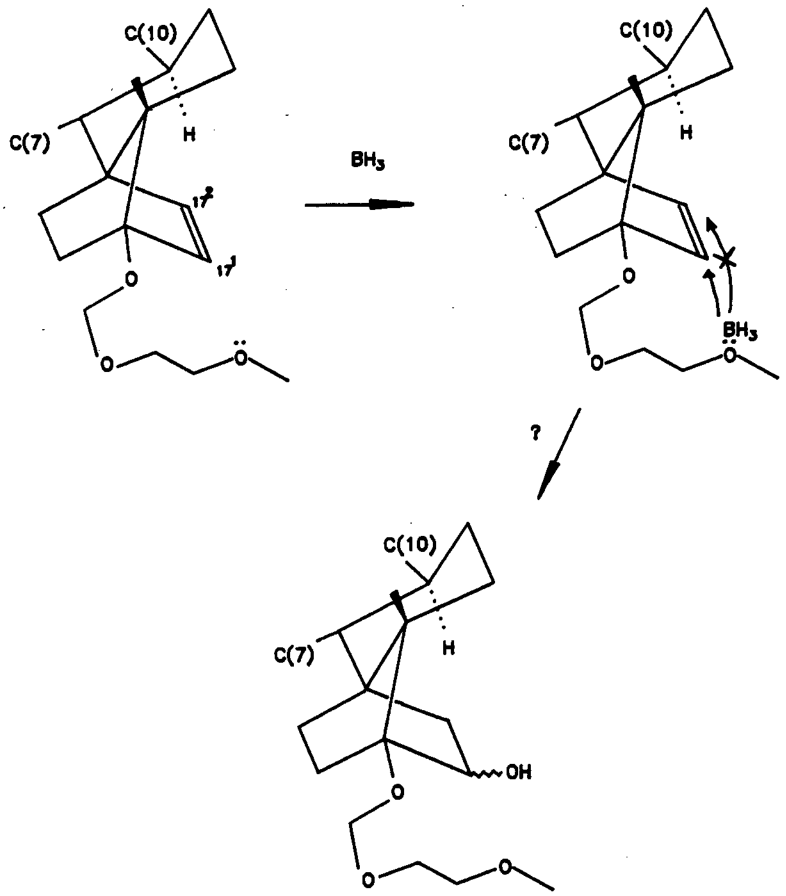
These results suggest first of all, that the reaction appeared to proceed more readily than the allyloxy derivative, and further, that no favourable change in product distribution was obtained (see Table 5).

Table 5: Regio- and stereo chemical outcome for the reactions via the allyl ether and the hydroxypropyl ether compounds

Substituent	$C(17^1)$: $C(17^2)$	exo : endo
allyl ether	1.1 : 1	1 : 1.1
hydroxypropyl ether	1.2 : 1	1 : 1.2

We then chose to explore the scope for an intramolecular reaction by carrying out hydroboration on the 17β-methoxyethoxymethoxy (MEMO) compound (**67**). It was hoped that the directive effect exhibited by the terminal oxygen of the MEMO group on the attack by borane might facilitate regioselective, intramolecular delivery of borane at C(17^1), rather than the more remote C(17^2) position (Figure 2.232).

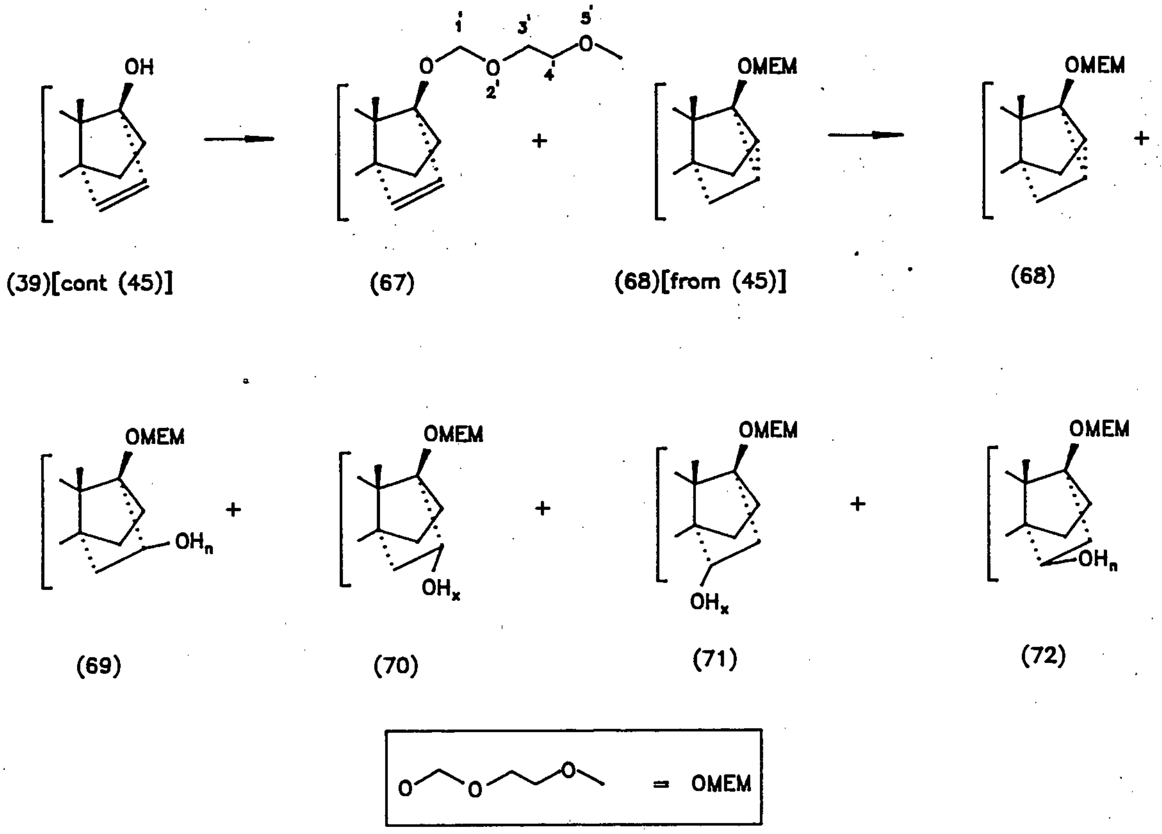
FIGURE 2·232



Treatment of the hydroxy olefin (**39**)[containing (**45**)] with sodium hydride in 1,2-dimethoxyethane, followed by methoxyethoxymethyl chloride (MEMCl), gave after work-up and chromatography, an inseparable mixture (50%) of the 17β-methoxyethoxymethoxy compound (**67**), and the 17β-methoxyethoxymethoxy cyclopropyl compound (**68**)[obtained from the impurity (**45**) in (**39**)], followed by starting material (**39**)[containing (**45**)](22%)(Scheme 2.236). Hydroboration of the MEMO mixture (**67**) and (**68**) with borane-tetrahydrofuran for 72 h at 25 °C, afforded a mixture, which was chromatographed to give the 17β-MEMO-cyclopropyl compound (**68**)(30%), followed by the hydration products, in order of elution:

(i) an inseparable mixture (26%)(*ca* 2:3 by ^{1}H n.m.r.) of (17^1*S*/*R*)-17β-MEMO-17^1-alcohols (**69**) and (**70**),
(ii) (17^2*S*)-17β-MEMO-17^2-alcohol (**71**)(18%),
(iii) (17^2*R*)-17β-MEMO-17^2-alcohol (**72**)(8%)(Scheme 2.236).

SCHEME 2·236



The MEMO compounds (**68-72**) were identified by ^{1}H n.m.r., which displayed the characteristic signals for the MEMO group, and the signals for the 17^1- and 17^2-protons are summarised in Table 6.

Table 6: ^{1}H N.m.r. for the MEM ethers

alcohol	%	CH̲OH	9α-H
(**69**)	16	δ3.6-4 (obsc.)	δ2.3
(**70**)	10	δ4.35 (ddd, *J* 10.4, 3.8, and *ca* 1.2 Hz)	δ2.3
(**71**)	18	δ4.12 (dd, *J* 8.6 and 4.7 Hz)	δ2.4
(**72**)	8	δ4.71 (obsc. ddd, *J* 10.9, *ca* 2, and *ca* 0.8)	obsc.

Owing to the susceptibility of the MEM ethers (**69-72**) to hydrolyse on handling, the compounds were not fully characterised, but were then individually hydrolysed with toluene-p-sulphonic acid on a t.l.c. scale to give the corresponding diols (**47-50**), which were identified by comparison with those obtained previously.

There is no regio differentiation between C(17^1) and C(17^2)(*ca* 1:1), suggesting that the bridgehead group does not influence the orientation of reagent approach. However, a distinct preference (*ca* 2:1) for the *exo*-attachment is evident. This contrasts with the *endo*-selectivity obtained in the previous experiments, and suggests that coordination between the reagent and the terminal oxygen atom of the MEMO group may indeed have occurred. It is possible that an oxygen atom ε-removed from the 17-O may provide the minimum chain length for such an intramolecular interaction, and that the *exo*-face of the olefinic bond is more accessible in this case.

We also examined the scope for modifying the regio- and stereoselectivity by carrying out a hydroboration on the precursor[32] (**73**) of the acetoxy olefin (**55**), in which the presence of the sterically demanding 16α-phenylsulphonyl group might be expected to inhibit *endo*-attack, particulary at C(17^1). However, hydroboration of the 17β-acetoxy-16α-phenylsulphonyl compound (**73**) with borane-tetrahydrofuran proved unsuccessful, giving rise to only 17β-hydroxy-16α-phenylsulphonyl compound (**74**)(32%)(Scheme 2.237), and intractable mixtures (110 mg).

SCHEME 2·237

(73) (74)

2.2.4 Conclusion

The experiments described in this section reveal that direct olefination of the 14α-formyl-17-ketone (**40**) is unlikely to succeed, but efficient chemoselective methylation of the 14^1-oxo group suggests that indirect olefination methods may provide a way of circumventing the problem and hence, potentiating the 14α-group for characterisation. In the parallel study on hydroboration, the results are summarised in Table 7.

Table 7: Regio- and stereo chemical outcome of the hydroboration reactions

17β-substituent	$C(17^1)$: $C(17^2)$	exo : endo
hydroxy	1.1 : 1	1 : <u>ca</u> 3
acetoxy	<u>ca</u> 1.1 : 1	1 : <u>ca</u> 3
allyl ether	1.1 : 1	1 : 1.1
hydroxy propyl ether	1.2 : 1	1 : 1.2
MEM ether	1 : 1	<u>ca</u> 2 : 1

With these results in hand, it was possible to interpret the regio- and stereoselectivity of the different hydroboration reactions. In the first place, there is negligible regio differentiation between C(17^1) and C(17^2)(_ca_ 1:1) in all experiments, suggesting that the bridgehead substituent does not influence the directional orientation of reagent approach.

However, a distinct preference for the _endo_-attachment is evident, except in the case of the 17β-MEM group. This result provides the only evidence hitherto obtained, of an intramolecular participation effect by a bridgehead substituent. It is clear that more work will be necessary to verify this unexpected result. Ideally, the work should be carried out upon model 1-substituted bicyclo[2.2.1]hept-2-enes in order to obtain a clear picture of the trends, without the complicating features of the residual steroidal skeleton. It is unlikely that directional effects modifying _exo/endo_-selectivity could be used to advantage in the work outlined here. The purpose would rather be to improve the regioselectivity of attack at C(17^1) and C(17^2), so that one of two possible bridge-cleavage routes (Scheme 2.121) could be applied to an efficient synthesis of a functionalised two-carbon chain at C(14). Our findings suggest that the models chosen for this investigation are inappropriate, and that further work should be directed toward examination of shorter chains at C(17), for example methoxymethyl or methylthiomethyl ethers, or longer chains using substituted borane reagents.

One of the compounds prepared in the investigation represents a new bridged estriol analogue (**54**), and has been submitted for biological evaluation.

2.3 EXPERIMENTAL

For general directions, see page 15.

3-Methoxy-14α-vinylestra-1,3,5(10)-trien-17-one (**41**)

An ethereal solution of n-butyl-lithium (1.6 M; 1 ml, 1.6 mmol) was added dropwise under nitrogen to a suspension of methyltriphenylphosphonium chloride (573 mg, 1.6 mmol) in dry tetrahydrofuran (7 ml). After 30 min, the 14α-formyl-17-ketone (**40**)(100 mg, 0.32 mmol) in dry tetrahydrofuran (3 ml) was slowly added at 0 °C. The temperature was gradually increased to 40 °C, refluxed for 48 h, then saturated aqueous ammonium chloride was added. Standard work-up (chloroform) afforded a crude product (100 mg). Chromatography [ethyl acetate-hexane (2:8)] on silica gel (10 g) afforded 3-methoxy-14α-vinylestra-1,3,5(10)-trien-17-one (**41**)(18 mg, 18%), m.p. 127-132 °C (from acetone-methanol); v_{max} 1652 (C=C) cm^{-1}; δ(200 MHz) 1.1 (3H, s, 13β-Me), 2.6-2.9 (2H, m, 6-H_2), 3.75 (3H, s, 3-OMe), 5.14 (1H, dd, *J* 17.7 and 0.9 Hz, 14^2-H), 5.22 (1H, dd, *J* 11.5 and 0.9 Hz, 14^2-H), 6.1 (1H, ddd, *J* 17.7, 11.5 and 0.9 Hz, 14^1-H), 6.6 (1H, d, *J* 2.8 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found : C, 81.2; H, 8.3%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; *M*, 310), followed by an uncharacterisable mixture (16 mg), and by starting material (23 mg).

Enol acetylation of 3-Methoxy-17-oxoestra-1,3,5(10)-triene-14-carbaldehyde (**40**)

Toluene p-sulphonic acid (20 mg) was added under nitrogen to the 14α-formyl-17-ketone (**40**)(94 mg, 0.3 mmol) in acetic anhydride (5 ml) and isopropenyl acetate (5 ml). Distillation after 12 h resulted in product formation. Chromatography [ethyl acetate-hexane (2:8)] on silica gel (9 g) afforded an unknown product (**42**)(30 mg), m.p. 143-154 °C decomp. (from acetone-methanol); v_{max} 1749 (C=O) cm^{-1}; δ_H(200 MHz) 1.02 (3H, s, 13β-Me), 2.08 (3H, s, OAc), 2.12 (3H, s, OAc), 2.6-2.9 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.6 (1H, d, *J* 2.8 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 6.71 (1H, d, *J* 1.5 Hz), and 7.2 (1H, d, *J* 8.6 Hz, 1-H); δ_C(50.1 MHz) 15.2 (C-18), 2 x 21.5 (2 x $COCH_3$), 24.3 (C-17), 24.4 (C-15), 26.1 and 26.5 (C-12 and C-11), 30.4 and 30.9 (C-7 and C-6), 37.8 and 39.0 (C-8 and C-9), 50.3 and 51.4 (C-14 and C-13), 55.2 (3-OMe), 96.6 (C-16), 111.4 and 111.7 (C-14^1 and C-2), 113.3 (C-4), 126.7 (C-1), 131.9 (C-10), 137.3 (C-5), 157.6 (C-3), 169.1 and 170.2 (2 x OCOCH3) (Found : C, 69.3; H, 7.3%; *M*$^+$, 414. $C_{24}H_{30}O_6$ requires C, 69.3; H, 7.3%; *M*, 414), followed by starting material (40 mg).

(17^{2}S)-17α,14-(*Epoxymethano*)-3-*methoxy*-17^2-*methylestra*-1,3,5(10)-*trien*-17β-*ol* (**44**)

Methyl-lithium (1.4 M; 1.4 ml, 2.05 mmol) was added dropwise under nitrogen to the 14α-formyl-17-ketone (**40**)(157 mg, 0.5 mmol) in dry tetrahydrofuran (10 ml) at 0 °C. Saturated aqueous ammonium chloride was added after 4 h. Standard work-up (chloroform) afforded a crude product (150 mg). Chromatography [ethyl acetate-hexane (1:1)] on silica gel (7 g) afforded starting material (**40**)(10%), followed by (17^{2}S)-17α,14-(*epoxymethano*)-3-*methoxy*-17^2-*methylestra*-1,3,5(10)-*trien*-17β-*ol* (**44**)(140 mg, 85%), m.p. 150-155 °C (from ethyl acetate-methanol); [α]$_D$ +77° (*c* 1.1); v_{max} 3374 (OH) cm^{-1}; δ_H(200 MHz) 0.96 (3H, d, *J* 0.7 Hz, 13β-Me), 1.23 (3H, d, *J* 6.3 Hz, 14^1-CH_3), 2.6-2.9 (2H, m, 6-H_2), 3.74 (3H, s, 3-OMe), 4.55 (1H, dq, *J* 3 x 6.2 and 2.2 Hz, 14^1-H), 6.6 (1H, d, *J* 2.8 Hz, 4-H), 6.69 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.18 (1H, d, *J* 8.6 Hz, 1-H); δ_C(50.1 MHz) 15.5 and 18.8 (14^2-H and C-18), 21.3 (C-16), 25.1 (C-15), 25.6 and 25.7 (C-12 and C-13), 31.1 (C-7), 33.6 (C-5), 37.6 (C-8), 40.6 (C-9), 48.5 (C-14), 50.7 (C-13), 55.1 (3-OMe), 73.2 (C-17), 109.5 (C-O), 111.7 (C-2), 113.7 (C-4), 127.0 (C-1), 137.4 (C-5), 132.6 (C-10), and 157.4 (C-3) (Found : C, 76.5; H, 8.3%; *M*$^+$, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.5%; *M*, 328).

Hydroboration of 3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol (**39**)

Borane-tetrahydrofuran (1 M; 16.5 ml) was added dropwise under nitrogen to the hydroxy olefin (**39**)[containing ca 10% of (**45**)](727 mg, 2.3 mmol) in dry tetrahydrofuran (15 ml) at <10 °C. After 48 h at 25 °C, the reaction was cooled to 0 °C and hydrogen peroxide (4 M; 3 ml) and sodium hydroxide (4 M; 3 ml) were added simultaneously. Water was added after 2 h. Standard work-up (ethyl acetate) afforded the crude product (800 mg). Chromatography [ethyl acetate-chloroform (1:19) → (1:1)] on silica gel (90 g) afforded (17^1R)-3-methoxy-14,17α-ethano-16α,17^1-cycloestra-1,3,5(10)-trien-17β-ol (**45**)(70 mg, 10%), m.p. 127-131 °C (from benzene-hexane); $[\alpha]_D$ +100° (c 1.0) [lit.,[32] m.p. 133-134 °C; $[\alpha]_D$ +104° (c 1.0)]; δ(200 MHz) 0.9 (3H, s, 13β-Me), 1.03 and 1.28 (each 1H, ddd, J 6.1, 1.5 and 1.2 Hz, 16- and 17^1-H), 1.45 and 1.49 (each 1H, dd, J 10.0 and 1.2 Hz, 15α- and endo 17^2-H), 1.54 (1H, s, exch; by D_2O, 17-OH), 1.77 and 1.84 (each 1H, dt, J 10.0, 2 x 1.5 Hz, 15β- and exo 17^2-H), 2.28 (1H, m, 9α-H), 2.8 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.6 (1H, d, J 2.8 Hz, 4-H), 6.71 (1H, dd, J 8.6 and 2.8 Hz, 2-H), and 7.28 (1H, d, J 8.6 Hz, 1-H) (Found : C, 81,2; H, 8.5%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.5%; M, 310), 3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol (**46**)(16 mg, 2%), m.p. 115-118 °C (from methanol); $[\alpha]_D$ +48° (c 1.1) [lit.,[32] m.p. 120-121 °C; $[\alpha]_D$ +46° (c 0.99)]; v_{max} 3598 (OH) cm^{-1}; δ(200 MHz) 0.9 (3H, s, 13β-Me), 2.69-2.9 (2H, m, 6-H_2) 3.74 (3H, s, 3-OMe), 6.62 (1H, d, J 2.4 Hz, 4-H), 6.67 (2H, dd, J 8.6 and 2.4 Hz, 2-H), and 7.2 (1H, d, J 8.6 Hz, 1-H) (Found : C, 80.4; H, 9.0%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; M, 312), (17^1R)-3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-17β,17^1-diol (**47**)(56 mg, 7%), m.p. 200-205 °C (from ethyl acetate-hexane); $[\alpha]_D$ +36° (c 1.0); v_{max} 3605 (OH) cm^{-1}; δ(200 MHz) 0.89 (3H, s, 13β-Me), 2.64 (1H, m, 9α-H), 2.7-2.9 (2H, m, 6-H_2), 3.74 (3H, s, 3-OMe), 3.79 obsc. (1H, dd, J 8.4 and 3.1 Hz, 17^1-H), 6.6 (1H, d, J 2.6 Hz, 4-H), 6.7 (1H, dd, J 8.6 and 2.6 Hz, 2-H), and 7.2 (1H, d, J 8.6 Hz, 1-H) (Found : C, 76.6; H, 8.6%; M^+, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%; M, 328), (17^2S)-3-methoxy-14,17α-

ethanoestra-1,3,5(10)-*triene*-17β,17^2-*diol* (**48**)(74 mg, 10%), m.p. 91-96 °C (from ethyl acetate-hexane); $[\alpha]_D$ +33° (*c* 0.7); ν_{max} 3601 (OH) cm^{-1}; δ(200 MHz) 0.91 (3H, s, 13β-Me), 2.8-2.9 (2H, m, 6-H_2), 3.4 (1H, dt, *J* 2 x 11.4 and 5.3 Hz, 9α-H), 3.77 (3H, s, 3-OMe), 4.15 (1H, dd, *J* 8.2 and 4.6 Hz, 17^2-H), 6.6 (1H, d, *J* 2.8 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found : C, 76.5; H, 8.6%; M^+, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%; *M*, 328), followed by an inseparable mixture (411 mg, 55%)(*ca* 1:1 by ^{1}H n.m.r.) of (17^1*S*)-3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-17β,17^1-diol (**49**) and (17^2*R*)-3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-17β,17^2-diol (**50**)(see later for characterisation of the pure components).

Periodate cleavage of the diol isomers (**47-50**)

Aqueous metaperiodate (6%; 14 ml) was added to the total diol mixture (**47-50**) (204 mg, 0.6 mmol) in absolute ethanol (20 ml) at 25 °C. Water was added after 10 h. Standard work-up (ethyl acetate) afforded the crude product (205 mg). Chromatography [ethyl acetate-hexane (1:4) → (2:3) → (3:2)] on silica gel (50 g) afforded 14α-*formylmethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**51**)(103 mg, 53%), m.p. 122-127 °C decomp. (from methanol); $[\alpha]_D$ +112° (*c* 1.1); ν_{max} 1734 and 1713 (C=O) cm^{-1}; δ(200 MHz) 1.04 (3H, s, 13β-Me), 2.69-2.9 (2H, m, 6-H_2), 3.74 (3H, s, 3-OMe), 6.69 (1H, d, *J* 2.8 Hz, 4-H), 6.7 (1H, dd, *J* 8.8 and 2.8 Hz, 2-H), 7.2 (1H, d, *J* 8.8 Hz, 1-H), and 9.87 (1H, dd, *J* 3.5 and 2.8 Hz, 14^2-H) (Found : C, 77.0; H, 8.0%; M^+, 326. $C_{21}H_{26}O_3$ requires C, 77.3; H, 8.0%; *M*, 326), followed by (17^2*S*)-3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-17β,17^2-diol (**48**) (22 mg, 11%), and (17^2R)-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-17β,17^2-*diol* (**50**)(30 mg, 15%), m.p. 179-181 °C (from ethyl acetate-hexane); ν_{max} 3347 (OH) cm^{-1}; δ(200 MHz) 0.89 (3H, s, 13β-Me), 2.6-2.8 (2H, m, 6-H_2), 3.7 (3H, s, 3-OMe), 4.6 (1H, br.ddd, *J* 10.2, *ca* 2, and *ca* 0.8 Hz, 17^2-H), 6.6 (1H, d, *J* 2.8 Hz, 4-H), 6.8 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.15 (1H, d, *J* 8.6 Hz, 1-H) (Found : C, 76.5; H, 8.6%; M^+, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%; *M*, 328).

Oxidation of the (17^1*S*)- and (17^2*R*)-diol isomers (**49** + **50**)

8 M-Chromic acid was diluted to *ca* 1 M and added dropwise to the mixture of 17β,17^1- and 17β,17^2-diols (**49** + **50**) (140 mg, 0.43 mmol) in acetone (15 ml) at 0 °C. Saturated aqueous sodium metabisulphite was added after 1 h. Standard work-up (ethyl acetate) afforded a crude product (125 mg). Chromatography [ethyl acetate-chloroform (1:9) → (3:7) → (6:4)] on silica gel (15 g) afforded 14α-formylmethyl-3-methoxyestra-1,3,5(10)-trien-17-one (**51**)(6 mg, 4%), 17β-*hydroxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17^1-*one* (**52**)(23 mg, 17%), m.p. 153-158 °C (from ethyl acetate-hexane); $[\alpha]_D$ +74° (*c* 0.5); ν_{max} 3597 (OH) and 1742 (C=O) cm^{-1}; δ(200 MHz) 1.12 (3H, s, 13β-Me), 2.7-2.9 (2H, m, 6-H$_2$), 3.76 (3H, s, 3-OMe), 6.6 (1H, d, *J* 2.8 Hz, 4-H), 6.7 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.2 (1H, d, *J* 8.5 Hz, 1-H) (Found : C, 77.1; H, 8.0%; *M*$^+$, 326. $C_{21}H_{26}O_3$ requires C, 77.3; H, 8.0%; *M*, 326), 17β-*hydroxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17^2-*one* (**53**)(44 mg, 31%), m.p. 186-189 °C (from acetone-methanol); $[\alpha]_D$ +101° (*c* 1.0); ν_{max} 3597 (OH) and 1735 (C=O) cm^{-1}; δ(200 MHz) 1.01 (3H, s, 13β-Me), 2.7-2.9 (2H, m, 6-H$_2$), 3.78 (3H, s, 3-OMe), 6.6 (1H, d, *J* 2.8 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found : C, 77.0; H, 8.0%; *M*$^+$, 326. $C_{21}H_{26}O_3$ requires C, 77.3; H, 8.0%; *M*, 326), and (17^1S)-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-17β,17^1-*diol* (**49**)(44 mg, 30%), m.p. 214-218 °C (from methanol); $[\alpha]_D$ +48° (*c* 1.1); ν_{max} 3347 (OH) cm^{-1}; δ(200 MHz) 0.93 (3H, s, 13β-Me), 1.0 (1H, dd, *J* 13.6 and 4.0 Hz, 12α-H), 2.7-2.9 (2H, m, 6-H$_2$), 3.74 (3H, s, 3-OMe), 4.3 br. (1H, ddd, *J* 10.7, 4.0, and *ca* 1.5 Hz, 17^1-H), 6.6 (1H, d, *J* 2.6 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H), and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found : C, 76.5; H, 8.6%; *M*$^+$, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%; *M*, 328).

(17^{1}R)-14,17α-*Ethanoestra*-1,3,5(10)-*triene*-3,17β,17^1-*triol* (**54**)

Diisobutylaluminium hydride (DIBAH) (20%; 2.1 ml, 2.7 mmol) was added under nitrogen to a stirring solution of the (17^1*S*)-diol (**47**)(70 mg, 0.22 mmol) in anhydrous toluene (4 ml) at 25 °C. The reaction mixture was refluxed for 72 h, cooled to 0 °C, and hydrochloric acid (10%; 5 ml) was added dropwise. Standard work-up (ethyl acetate) afforded a crude product (70 mg). Chromatography [ethyl acetate-hexane (1:1)] on silica gel (7 g) afforded (17^{1}R)-14,17α-*ethanoestra*-1,3,5(10)-*triene*-3,17β,17^1-*triol* (**54**)(44 mg, 64%), m.p. 240-244 °C (from methanol); $[\alpha]_D$ +12° (*c* 0.5 in methanol) (Found : C, 76.3; H, 8.4%; *M*$^+$, 314. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.4%; *M*, 314).

Hydroboration of the 3-*Methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*yl acetate* (**55**)

Borane-dimethyl sulphide (1.4 ml, 14 mmol) was added under nirogen to the acetoxy olefin (**55**)[containing (**56**)](502 mg, 1.4 mmol) in dry tetrahydrofuran (21 ml) at 25 °C. The reaction mixture was refluxed for 24 h, cooled to 0 °C, and sodium hydroxide (4 M; 2 ml) and hydrogen peroxide (30%; 2 ml) were added simultaneously. The mixture was stirred for 2 h, then water was added. Standard work-up (ethyl acetate) afforded a crude product (510 mg). Chromatography [ethyl acetate-hexane (1:9) → (1:4) → (2:3) → (3:2)] on silica gel (50 g) afforded starting material (**55**)(15 mg, 3%), (17^1*R*)-3-methoxy-14,17α-ethano-16α,17^1-cycloestra-1,3,5(10)-trien-17β-ol (**45**)(36 mg, 8%), m.p. 131-134 °C (from benzene-hexane) (lit.,^{32} m.p. 133-134 °C) (Found : C, 81.3; H, 8.5%; *M*$^+$, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; *M*, 310), 3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol (**46**)(49 mg, 11%), m.p. 120-122 °C (from methanol) (lit.,^{32} m.p. 120.5-121 °C) (Found : C, 80.5; H, 9.2%; *M*$^+$, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; *M*, 312), and (17^{1}S)-17β-*ethoxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17^1-*ol* (**57**)(58 mg, 12%), m.p. 168-173 °C (from methanol); $[\alpha]_D$ +39° (*c* 1.0);

ν_{max} 3445 (OH) cm^{-1}; δ(200 MHz) 0.98 (3H, s, 13β-Me), 1.03 (1H, dd, *J* 13.6 and 3.8 Hz, 12α-H), 1.17 (3H, t, *J* 7.0 Hz, $OCH_2C\underline{H}_3$), 2.7-2.9 (2H, m, 6-H_2), 2 x 3.62 (each q, *J* 3 x 7.0 Hz, $OC\underline{H}_2CH_3$), 3.75 (3H, s, 3-OMe), 4.6 (1H, ddd, *J* 10.5, 3.6 and 1.2 Hz, 17^1-H), 6.6 (1H, d, *J* 2.8 Hz, 1-H), 6.72 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.2 (1H, d, *J* 8.5 Hz, 1-H) (Found : C, 74.0; H, 7.6%; $\underline{M}^+$, 356. $C_{22}H_{28}O_4$ requires C, 74.2; H, 7.8%; *M*, 356), followed by (17^1*R*)- and (17^2*S*)-diols (**47**) and (**48**)(27 mg, 6%), and then the (17^1*S*)- and (17^2*R*)-diols (**49**) and (**50**)(117 mg, 26%).

17β-*Allyloxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene* (**59**)

Sodium hydride (50%; 231 mg, 4.8 mmol) was added under nitrogen to the hydroxy olefin (**39**)[containing (**45**)](500 mg, 1.6 mmol) in 1,2-dimethoxyethane (20 ml) at 25 °C. The mixture was refluxed for 2 h, then allyl bromide (0.45 ml, 4.8 mmol) was added. After a further 15 min refluxing, saturated aqueous ammonium chloride was added. Standard work-up (ethyl acetate) afforded the crude product (570 mg). Chromatography [toluene] on silica gel (75 g) afforded (17^1R)-17β-*allyloxy*-3-*methoxy*-14,17α-*ethano*-16α,17^1-*cycloestra*-1,3,5(10)-*triene* (**58**)(152 mg, 27%), m.p. 115-118 °C (from toluene-hexane); $[\alpha]_D$ +78° (*c* 1.0); ν_{max} 2939 and 2862 cm^{-1}; δ(200 MHz) 0.94 (3H, s, 13β-Me), 2.7-2.9 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.05 (2H, br.d, *J* 5.2 Hz and $\underline{W}_{\frac{1}{2}}$ *ca* 4.8 Hz, 1'-H_2), 5.11 (1H, ddd, *J* 10.3, 2.8 and 1.6 Hz, 3'-H_{cis}), 5.25 (1H, ddd, *J* 17.3, 3.5, and 1.6 Hz, 3'-H_{trans}), 5.9 (1H, m, *J* 17.3, 10.3, and 2 x 5.2 Hz, 2'-H), 6.6 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H), and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found : C, 82.0; H, 8.5%; $\underline{M}^+$, 350. $C_{24}H_{30}O_2$ requires C, 82.3; H, 8.6%; *M*, 350), 17β-*allyloxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene* (**59**)(366 mg, 66%), m.p. 120-122 °C (from ethyl acetate-methanol); $[\alpha]_D$ +86° (*c* 1.0); ν_{max} 3119, 3014, 1853, and 1421 cm^{-1}; δ(200 MHz) 0.92 (3H, s, 13β-Me), 2.7-2.9 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 4.15 (2H, br.d, *J* 5.3 Hz and $\underline{W}_{\frac{1}{2}}$ *ca* 4.8 Hz, 1'-H_2), 5.15 (1H, ddd, *J* 10.3, 2.7, and 1.5 Hz, 3'-H_{cis}), 5.3 (1H, ddd, *J* 17.3, 3.3 and 1.5 Hz, 3'-H_{trans}), 5.91 (1H, d, *J* 6.2 Hz, 17^1-H), 6.0 obsc. (1H, m, *J* *ca* 17.3, *ca* 10.3, and 2 x *ca* 5.3 Hz, 2'-H), 6.1 (1H, d, *J* 6.2 Hz, 17^2-H), 6.62 (1H, d, *J* 2.6 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H), and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found : C, 81.9; H, 8.6%; M^+, 350. $C_{24}H_{30}O_2$ requires C, 82.3; H, 8.6%; *M*, 350).

Hydroboration of 17β-*Allyloxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene* (**59**)

Borane-tetrahydrofuran (1 M; 0.8 ml, 0.8 mmol) was added dropwise under nitrogen to the allyl ether (**59**)(216 mg, 0.62 mmol) in dry tetrahydrofuran (12 ml). The reaction was heated to 45 °C and then brought up to reflux. After 48 h, the mixture was cooled to 0 °C, and sodium hydroxide (4 M; 1 ml) and hydrogen peroxide (30%; 1 ml) were added simultaneously. Water was added after stirring for 1 h at 25 °C. Standard work-up (ethyl acetate) afforded a crude product (260 mg). Chromatography [ethyl acetate-hexane (1:19) → (1:9) → (2:3)] on silica gel (28 g) afforded (2'-*R*/*S*)-17β-(2-*hydroxypropoxy*)-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene* (**60 + 61**)(24 mg, 11%), m.p. 90-125 °C (from ethyl acetate-hexane); ν_{max} 3579 cm^{-1}; δ(200 MHz) 0.92 (s, 13β-Me), 1.17 (d, *J* 6.4 Hz, 2'-CH_3), 2.7-2.9 (m, 6-H_2), 3.4 (m, 2'-H), 3.6 (ddd, *J* 9.2, 3.0, and 2.1 Hz, 1'-H), 3.78 (s, 3-OMe), 3.95 (m, 1'-H), 6.0 and 6.1 (each d, *J* 6.1 Hz, 17^1- and 17^2-H), 6.6 (d, *J* 2.8 Hz, 4-H), 6.72 (dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.2 (d, *J* 8.6 Hz, 1-H) (Found : C, 78.0; H, 8.5%; M^+, 368. $C_{24}H_{32}O_3$ requires C, 78.3; H, 8.7%; *M*, 368), 17β-(3-*hydroxypropoxy*)-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene* (**62**)(96 mg, 42%), m.p. 75-79 °C (from ethyl acetate-hexane); $[\alpha]_D$ +80° (*c* 1.0); ν_{max} 3505 (OH), 2929, and 2397 cm^{-1}; δ(200 MHz) 0.92 (3H, s, 13β-Me), 1.85 (2H, m, 2'-H), 3.78 (3H, s, 3-OMe), 3.82 (4H, m, 1'- and 3'-H), 6.05 and 6.15 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.62 (1H, d, *J* 2.6 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H), and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found : C, 77.9; H, 8.7%; M^+, 368. $C_{24}H_{32}O_3$ requires C, 78.2; H, 8.7%; *M*, 368), (17^1R)-17β-(3-*hydroxypropoxy*)-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17^1-*ol* (**63**)(7 mg, 3%), m.p. 125-130 °C (from ethyl acetate-hexane);

$[\alpha]_D$ +9° (*c* 0.7); ν_{max} 3402 cm^{-1}; δ(200 MHz) 0.92 (3H, s, 13β-Me), 1.82 (2H, m, 2'-H), 2.64 (1H, m, 9α-H), 2.7-2.9 (2H, m, 6-H_2), 3.6 (4H, m, 1'- and 3'-H), 3.77 (3H, s, 3-OMe), 4.1 (1H, dd, *J* 8.4 and 2.7 Hz, 17^1-H), 6.6 (1H, d, *J* 2.5 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.5 Hz, 2-H), and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found : C, 75.0; H, 8.8%; M^+, 386. $C_{24}H_{34}O_4$ requires C, 74.6; H, 8.9%; *M*, 386), (17^2S)-17β-(3-*hydroxypropoxy*)-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17^2-*ol* (**64**)(13 mg, 5%), m.p. 107-111 °C (from ethyl acetate-hexane); ν_{max} 3400 cm^{-1}; δ(200 MHz) 0.92 (3H, s, 13β-Me), 1.81 (2H, m, 2'-H), 2.7-2.9 (2H, m, 6-H_2), 3.4 (1H, dt, *J* 12.2, 10.5 and 4.9 Hz, 9α-H), 3.69 (4H, m, 1'- and 3'-H), 3.77 (3H, s, 3-OMe), 4.12 (1H, dd, *J* 8.5 and 4.6 Hz, 17^2-H), 6.6 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.6 Hz, 2-H), and 7.2 (1H, d, *J* 8.4 Hz, 1-H) (Found : C, 74.2; H, 8.8%; M^+, 386. $C_{24}H_{34}O_4$ requires C, 74.6; H, 8.9%; *M*, 386), followed by an inseparable mixture (*ca* 2:1) of (17^1S)-17β-(3-*hydroxypropoxy*)-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17^1-*ol* (**65**) and (17^2R)-17β-(3-*hydroxypropoxy*)-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17^2-*ol* (**66**)(21 mg, 9%), m.p. 120-130 °C (from ethyl acetate-hexane); ν_{max} 3607 and 3485 cm^{-1}; δ(200 MHz) 0.96 and 0.98 (each s, 13β-Me), 1.13 (dd, *J* 13.5 and 4.0 Hz, 12α-H of (**65**)), 1.8 (m, 2'-H), 2.7-2.9 (m, 6-H_2), 3.6 and 3.78 (m, 1'- and 3'-H), 3.77 (s, 3-OMe), 4.6 br. (ddd, *J* 10.5, 3.6, and *ca* 1.5 Hz, 17^1-H of (**65**)), 4.73 (br.ddd, *J* 10.5, *ca* 2.1, and *ca* 0.7 Hz, 17^2-H of (**66**)), 6.6 (d, *J* 2.7 Hz, 4-H), 6.72 (dd, *J* 8.6 and 2.7 Hz, 2-H), 7.2 and 7.23 (each d, *J* 8.6 Hz, 1-H) (Found : C, 74.4; H, 8.7%; M^+, 386. $C_{24}H_{34}O_4$ requires C, 74.6; H, 8.9%; *M*, 386).

Hydroboration of 17β-(3-*Hydroxypropoxy*)-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*ol* (**62**)

Borane-tetrahydrofuran (1 M; 1.5 ml, 1.5 mmol) was added under nitrogen to the hydroxypropyl compound (**62**)(93 mg, 0.25 mmol) in tetrahydrofuran (4 ml) at 0 °C. After stirring for 48 h at 25 °C, the reaction was cooled to 0 °C, and hydrogen peroxide (30%; 1 ml) and sodium hydroxide (4 M; 1 ml) were added simultaneously. Water was added after 2 h at 25 °C. Standard work-up (ethyl acetate) afforded the crude product (90 mg). Chromatography [ethyl acetate hexane (2:3)] on silica gel (9 g) afforded starting material (**62**) (3 mg, 3%), the (17^1*S*)-alcohol (**63**)(18 mg, 19%), the (17^2*S*)-alcohol (**64**)(14 mg, 15%), and an inseparable mixture (40 mg, 42%)(*ca* 2:1) of the (17^1*R*)-alcohol (**65**) and the (17^2*R*)-alcohol (**66**).

3-*Methoxy*-17β-*methoxyethoxymethoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene* (**67**)

Sodium hydride (50%; 184 mg, 3.84 mmol) was added under nitrogen to the hydroxy olefin (**39**)[containing (**45**)](400 mg, 1.28 mmol) in 1,2-dimethoxyethane (15 ml) at 25 °C. The mixture was refluxed for 2 h, then methoxyethoxymethyl chloride (MEMCl) (0.45 ml, 3.84 mmol) was added and reflux was continued for 5 h, then saturated aqueous ammonium chloride was added. Standard work-up (ethyl acetate) afforded a crude product (450 mg). Chromatography [ethyl acetate-hexane (1:9)] on silica gel (60 g) afforded an inseparable mixture of 3-*methoxy*-17β-*methoxyethoxymethoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene* (**67**) and (17^1R)-3-*methoxy*-17β-*methoxyethoxymethoxy*-14,17α-*ethano*-16α,17^2-*cycloestra*-1,3,5(10)-*triene* (**68**)(260 mg, 50%); δ(200 MHz) 0.91 and 0.92 (each s, 13β-Me), 2.7-2.9 (m, 6-H_2), 3.40 and 3.41 (each s, 5'-CH_3), 3.58 and 3.7 (m, 3'- and 4'-H), 3.78 (s, 3-OMe), 4.78 and 4.90 (each s, 1'-H), 6.0 and 6.2 (each d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.61 (d, *J* 2.6 Hz, 4-H), 6.72 (dd, *J* 8.6 and 2.6 Hz, 2-H), and 7.2 (d, *J* 8.6 Hz, 1-H) (Found : C, 75.2; H, 8.6%; M^+, 398. $C_{25}H_{34}O_4$ requires C, 75.4; H, 8.5%; *M*, 398), followed by an inseparable mixture of starting material (**39**)[containing (**45**)](86 mg, 22%).

Hydroboration of the 17β-*Methoxyethoxymethoxy derivatives* (**67 + 68**)

Borane-tetrahydrofuran (1 *M*; 2.7 ml, 2.7 mmol) was added dropwise under nitrogen to the 17β-MEMO compounds **(67 + 68)** (213 mg, 0.54 mmol) in tetrahydrofuran (10 ml) at 25 °C. After 72 h at 25 °C, the reaction was cooled to 0 °C, and hydrogen peroxide (30%; 2 ml) and sodium hydroxide (4 *M*; 2 ml) were added simultaneously. Chromatography [ethyl acetate-toluene (1:4)] on silica gel (33 g) afforded (17^{1}R)-3-*methoxy*-17β-*methoxyethoxymethoxy*-14,17α-*ethano*-16α,17^1-*cycloestra*-1,3,5(10)-*triene* **(68)** (65 mg, 30%), m.p. 57-59 °C (from ethyl acetate-hexane); $[\alpha]_D$ +69° (*c* 1.0); v_{max} 3402, 1710, and 1155 cm^{-1}; δ(200 MHz) 0.92 (3H, s, 13β-Me), 2.8-2.9 (2H, m, 6-H$_2$), 3.4 (3H, s, 5'-H), 3.49-3.8 (4H, m, 3'- and 4'-H), 3.77 (3H, s, 3-OMe), 4.78 (2H, s, 1'-H), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found : C, 75.1; H, 8.6%; *M*$^+$, 398. C$_{25}$H$_{34}$O$_4$ requires C, 75.4; H, 8.5%; *M*, 398), followed by an inseparable mixture (58 mg,26%)(*ca* 2:3) of (17^{1}S)-3-*methoxy*-17β-*methoxyethoxymethoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17^1-*ol* **(69)** and (17^{1}R)-3-*methoxy*-17β-*methoxyethoxymethoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17^1-*ol* **(70)**, m.p. 50-80 °C (from ethyl acetate-hexane); v_{max} 3497 and 3373 cm^{-1}; δ(200 MHz) 0.92 and 0.94 (each s, 3-OMe), 1.15 (dd, *J* 13.5 and 3.9 Hz, 12α-H of **(69)**), 2.28 (m, 9α-H), 2.7-2.9 (m, 6-H$_2$), 3.4 (s, 5'-CH$_3$), 3.6-4.0 (m, 3'-H, 4'-H, and 17^1-H of **(69)**), 3.77 (s, 3-OMe), 4.35 (ddd, *J* 10.4, 3.8, and *ca* 1.2 Hz, 17^1-H of **(70)**), 4.78-4.9 (m, 1'-H), 6.6 (d, *J* 2.6 Hz, 4-H), 6.72 (dd, *J* 8.6 and 2.6 Hz, 2-H), and 7.2 (d, *J* 8.6 Hz, 1-H) (Found : C, 71.8; H, 8.5%; *M*$^+$, 416. C$_{25}$H$_{36}$O$_5$ requires C, 72.1; H, 8.7%; *M*, 416), (17^{2}S)-3-*methoxy*-17β-*methoxyethoxymethoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17^2-*ol* **(71)** (40 mg; 18%); v_{max} 3611 (OH) cm^{-1}; δ(200 MHz) 0.93 (3H, s, 13β-Me), 2.4 (1H, m, 9α-H), 2.7-2.9 (2H, m, 6-H$_2$), 3.4 (3H, s, 5'-H), 3.58-3.74 (4H, m, 3'- and 4'-H), 3.77 (3H, s, 3-OMe), 4.12 (1H, dd, *J* 8.6 and 4.7 Hz, 17^2-H), 4.83 (2H, s, 1'-H), 6.62 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H), and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found : C, 71.8; H, 8.8%; *M*$^+$, 416. C$_{25}$H$_{36}$O$_5$ requires C, 72.2; H, 8.7%; *M*, 416), and (17^{2}R)-3-*methoxy*-17β-*methoxyethoxymethoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17^2-*ol* **(72)** (17 mg, 8%); v_{max} 3609 (OH) cm^{-1}; δ(200 MHz) 0.97 (3H, s, 13β-Me), 2.7-2.9 (2H, m, 6-H_2), 3.39 (3H, s, 5'-CH_3), 3.53-3.72 (4H, m, 3'- and 4'-H), 3.77 (3H, s, 3-OMe), 4.71 (1H, br.ddd, J 10.9, ca 2, and ca 0.8 Hz, 17^2-H), 4.78 (2H, s, 1'-H), 6.6 (1H, d, J 2.6 Hz, 4-H), 6.71 (1H, dd, J 8.4 and 2.6 Hz, 2-H), and 7.2 (1H, d, J 8.4 Hz, 1-H) (Found : C, 71.7; H, 8.5%; M^+, 416. $C_{25}H_{36}O_5$ requires C, 72.1; H, 8.7%; M, 416).

Difficulty was encountered in the attempted purification and recrystallisation of the foregoing MEM derivatives (**68-72**) owing to their lability; accordingly the products have not all been fully characterised.

Attempted hydroboration of 16α-Phenylsulphonyl-14,17α-etheno-3-methoxyestra-1,3,5(10)-trien-17β-yl-acetate (**73**)

Borane-tetrahydrofuran (1 M; 3.6 ml, 3.6 mmol) was added under nitrogen to the sulphone derivative (**73**)(300 mg, 0.61 mmol) in tetrahydrofuran (10 ml) at 0 °C. After 72 h at 25 °C, the reaction was cooled to 0 °C, and water (1 ml) and sodium perborate (154 mg, 3.05 mmol) were added sequentially. After 5 h of stirring at 25 °C, standard work-up (ethyl acetate) afforded a crude product (310 mg). Chromatography [ethyl acetate-hexane (3:7) - (9:1)] on silca gel (30 g) afforded an inseparable mixture of starting material and an unknown compound (63 mg), followed by 3-methoxy-16α-phenylsulphonyl-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol (**74**)(86 mg, 32%), m.p. 193-196 °C (from chloroform-methanol); $[\alpha]_D$ +90° (c 1.1); v_{max} 3527 cm^{-1}; δ(200 MHz) 0.90 (3H, s, 13β-Me), 2.79-2.9 (2H, m, 6-H_2), 3.6 (1H, m, 16β-H), 3.77 (3H, s, 3-OMe), 6.21 and 6.24 (each 1H, d, J 6.2 Hz, 17^1- and 17^2-H), 6.61 (1H, d, J 2.8 Hz, 4-H), 6.68 (1H, dd, J 8.6 and 2.8 Hz, 2-H), 7.15 (1H, d, J 8.6 Hz, 1-H), 7.56 (2H, m, m-H x 2 of $PhSO_2$), 7.64 (1H, m, p-H of $PhSO_2$), and 7.89 (2H, σ-H x 2 of $PhSO_2$) (Found : C, 71.9; H, 6.7%; M^+, 450. $C_{27}H_{30}O_4S$ requires C, 72.0; H, 6.7%; M, 450), followed by an intractable mixture (70 mg).

REFERENCES

1. H. Laurent, D. Bittler, H. Hofmeister, K. Nickolson, K. Petzoldt, and R. Weichert, J. Steroid. Biochem., 1983, 19, 771.

2. J. A. Cella and C. M. Kagawa, J. Am. Chem. Soc., 1957, 79, 4808.

3. H. J. Hess, J. Org. Chem., 1962, 27, 1096.

4. H. G. Lehmann, Angew. Chem. Int. Ed. Engl., 1965, 4, 783.

5a. L. M. Steer, PhD Thesis, University of South Africa, 1987.

b. J. R. Bull and L. M. Steer, Tetrahedron, 1990, 46, in press.

6. T. C. Miller, J. Org. Chem., 1969, 34, 3829.

7. S .F. Martin, Synthesis, 1979, 633, and references cited.

8. S. Danishefsky, K. Nagasawa and Nai Wang, J. Org. Chem., 1975, 40, 1989.

9. S. G. Levine, J. Am. Chem. Soc., 1958, 80, 6150.

10. C. W. Marshall, T. H. Kritchevsky, S. Lieberman, and T. F. Gallagher, J. Am. Chem. Soc., 1948, 70, 1837.

11. F. A. Cutler jr, J. F. Fisher, and J. M. Chemerda, J. Org. Chem., 1959, 24, 1626.

12. A. H. Soloway, W. J. Considine, D. K. Fukushima and T. F. Gallagher, J. Am. Chem. Soc., 1954, 76, 2941.

13. G. Wittig and M. Schlosser, Chem. Ber., 1961, 94, 1373.

14. D. W. Moore, J. Chem. Phys., 1961, 32, 1470.

15. E. J. Corey and M. A. Tius, Tetrahedron Lett., 1980, 21, 3535.

16. G. R. Pettit, B. Green, G. L. Dunn, and P. Sunder-Plassman, *J. Org. Chem.*, 1970, *35*, 1385.

17. Chang-Yon Byon and M. Gut, *J. Org. Chem.*, 1980, *45*, 4404.

18. N. L. Wendler,"Molecular Rearrangements", P. de Mayo, Ed., John Wiley and Sons, New York, 1964, Part 2, a) pp 1020-1022, b) pp 1114-1121.

19. D. N. Kirk and M. A. Wilson, *J. Chem. Soc.* (*C*), 1971, 414.

20. C. L. Hewett, S. G. Gibson, I. M. Gilbert, J. Redpath, and D. S. Savage, *J. Chem. Soc.*, *Perkin Trans.* *1*, 1973, 1967.

21. D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms", Elsevier, Amsterdam, 1968, a) pp 269-272, b) pp 294-301.

22. C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, 1968, *33*, 2789.

23. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, *87*, 1353.

24. K. Ponsold, M. Hueber, R. Schnabel, and J. Strecke, *Arzneim.-Forsch.* (Drug Res.), 1974, *24*, 896.

25. D. S. Crumrine, M. L. Curtin, and H. Iwamura, *J. Org. Chem.*, 1990, *55*, 1076.

26. F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, 1957, *79*, 5029.

27. R. Kanojia, S. Rovinsky, and I. Scheer, *J. Chem. Soc.*, *Chem. Commun.*, 1971, 1579.

28. V. V. Jejorova *et al*. Patent Application: Czech. CS 225,014 (*Chem. Abs.* 1986, *105*, 60810k); Synthesis of 14-substituted 17β-hydroxymethyl compounds have been reported.

29. A. M. Krubiner and E. P. Oliveto, J. Org. Chem., 1966, 31, 24.

30. E. J. Corey and J. W. Suggs, Tetrahedron Lett., 1975, 2647.

31. M. Huebner and K. Ponsold, Z. Chem., 1981, 21(6), 220.

32. J. R. Bull and R. I. Thompson, J. Chem. Soc., Perkin Trans. 1, 1990, 241.

33. J. L. Marshall, S. R. Walter, M. Barfield, A. P. Marchand, N. W. Marchand, and A. L. Segre, Tetrahedron, 1976, 32, 537.

34. J. R. Bull, J. Floor, and M. Sefton, J. Chem. Soc., Perkin Trans. 1, 1987, 37.

35. H. C. Brown and J. H. Kawakami, J. Am. Chem. Soc., 1970, 92, 1990.

36. H. C. Brown and E. Negishi, Tetrahedron, 1977, 33, 2331.

37. T. Harada, Y. Matsuda, J. Uchimura and A. Oku, J. Chem. Soc. Chem. Commun., 1989, 1429.

38. L. N. Mander and G. L. Patrick, Tetrahedron Lett., 1990, 31, 423.