STEREOSELECTIVE REACTIONS OF 16-METHYLENE 19-NORSTEROIDS

by

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Submitted in accordance with the requirements

for the degree of

MASTER OF SCIENCE

in the subject of

CHEMISTRY

at the

UNIVERSITY OF CAPE TOWN

Supervisor: Professor J. R. Bull

SEPTEMBER 1991

Acknowledgements.

I would like to express my appreciation to all those who have made the production of this thesis possible, and in particular to the following:

Professor J. R. Bull, for his continual guidance, encouragement and advice throughout this study;

my colleagues, especially Dr. D. Gammon, A. Jardine, E. Sturrock, C. Grundler, M. Loedolff, J. Rahmdohr, and S. Heggie for their many helpful discussions;

G. Benincasa, for the microanalysis and mass spectroscopy;

M. Nair, for n.m.r. spectra and her patience in complying with all my requests; and

my parents, for their support.

Finally, I would like to thank the Foundation for Research and Development and the University of Cape Town for their financial support.

Summary

The influence of the 17-substituent upon epoxidation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one and the derived 17ß-hydroxy and 17ß-acetoxy compounds was investigated. Alkaline hydrogen peroxide epoxidation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one occurred in good yields, but poor stereoselectivity was obtained due to mechanistic considerations. Poor stereoselectivity was also obtained for the peracid epoxidation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17ß-ol, due to the pseudo-equatorial position of the 17ß-hydroxyl group. However, excellent stereoselectivity was obtained using Sharpless conditions (vanadium catalyst), which gave only the epoxide *syn* to the hydroxyl group, in good yields. Surprisingly, peracid epoxidation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17ß-yl acetate favoured equatorial attack resulting in a 2:1 ratio of the (16*R*)- and (16*S*)-epoxide isomers, instead of the expected axial approach by the peracid.

The configuration of the epoxide isomers could not be unambiguously assigned by spectroscopic and mechanistic considerations, therefore chemical correlation reactions were used to confirm the assignments. Interconversion reactions of the resulting epoxides gave the relative configuration of each isomer. Comparison between the major product obtained from *cis*-hydroxylation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one and the acid mediated opening of the major epoxidation product to the diol, indicated the configuration based on steric reasons. Conclusive evidence was obtained by treating each diol obtained from the reduction of (16*R*)- and (16*S*)-spiro[3-methoxyestra-1,3,5(10)-trien-17-one-16,2'oxirane] with sodium periodate. No reaction was found for the 16α,17ß-diol, as expected in a *trans*-diol.

It was found that attempted epoxidation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one and the derived 17ß-acetate with dimethyldioxirane gave poor yields of epoxides due to a competing oxygen insertion reaction at C-9. A model study using 3-methoxy estrone as substrate confirmed that oxygen insertion occurred.

A suitable route to the D-homo steroids using the epoxide products, was investigated. It was found that the most efficient method was obtained by the reduction of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one to the 17ß-alcohol, followed by Sharpless epoxidation and further reduction to the 16ß,17ß-diol. Oxidative cleavage, followed by base condensation gave 3-methoxy-17a-homoestra-1,3,5(10),16-tetraen-16-one in 67-87% yield This compound gave only one isomer on treatment with alkaline hydrogen peroxide which afforded the Δ^{16} 17a-ol on Wharton rearrangement.

Attempts to synthesise 16-functionalised Δ^{15} 17-ketones from the epoxidation and hydroxylation products of the 16-methylene analogues were unsuccessful. Michael addition with benzyl alcohol or thiophenol were successful, but subsequent attempts to trap the enolate with trimethylsilyl chloride failed, as ß-elimination was found to be a competing reaction. Preliminary investigations with 3-methoxy-16-methoxymethylestra-1,3,5(10)-trien-17-one indicated that dehydrosilylation occurred to give the 16-methoxymethylene compound instead of the desired Δ^{15} 17-ketone. Further attempts at direct isomerisation of the 16-methylene 17-ketone and the 17ß-acetoxy derivative using sulphinyl benzenesulphonamide were also unsuccessful.

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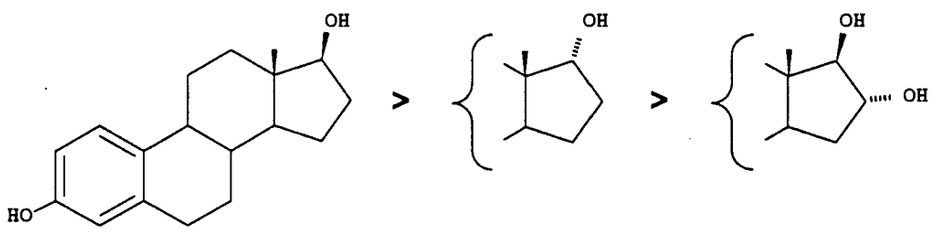
1.1 INTRODUCTION

The quest for highly potent estradiol analogues which exhibit a minimum of side effects has prompted numerous studies of the structure-activity relationships of the estrogen receptor in an attempt to elucidate its structure.[1,2] Various modifications of estrone have been carried out and the measurement of the affinity of these products towards the estrogen receptor have contributed towards the 'mapping' of the spatial demands of the receptor. It has been found that the activity of the estrogen agonists or antagonists is associated very strongly with the structure of ring D.[1] Binding of the molecule onto the estrogen receptor, as well as the activity exhibited by the molecule, decreases sharply when compared to estra-1,3,5(10)-triene-3,17ß-diol (estradiol) (**1**), if no 17ß-hydroxy group is present. Binding is also decreased if the hydroxyl group is inverted to the 17α-position (**2**), or if an extra hydroxyl group is introduced at the 16-position as in estra-1,3,5(10)-triene-3,16α,17ß-triol (estriol) (**3**) (*fig.* 1).[2] It has been shown that although the estrogen receptor is very tolerant of small non-polar substituents at the 16α-position of the estrone molecule, more polar groups cause a decrease in activity.[3]

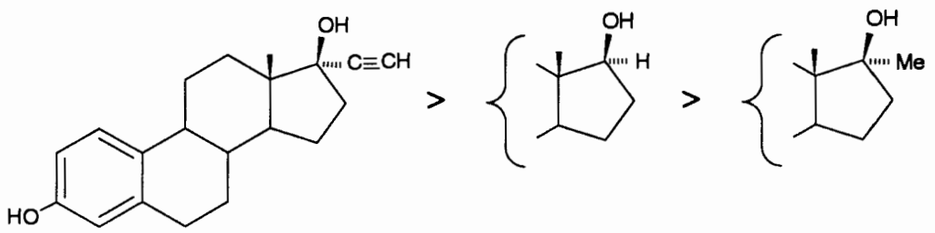


(1) Estradiol (2) (3) Estriol

Fig. 1. Comparison between the binding affinities with the estrogen receptor of estradiol and some analogues.

The 17α-alkyl substituent in estradiol analogues is of particular interest as it has been shown to influence binding affinities to the estrogen receptor. Binding affinity may be only slightly decreased such as when a 17α-methyl substituent is present (*fig.* 2), or

even greatly increased such as in 19-nor-17α-pregn-1,3,5(10)-trien-20-yne-3,17ß-diol (ethynylestradiol) (**4**) which exhibits a greatly increased oral estrogenic activity, and is used worldwide in replacement therapy and in oral contraceptives.[4,5]



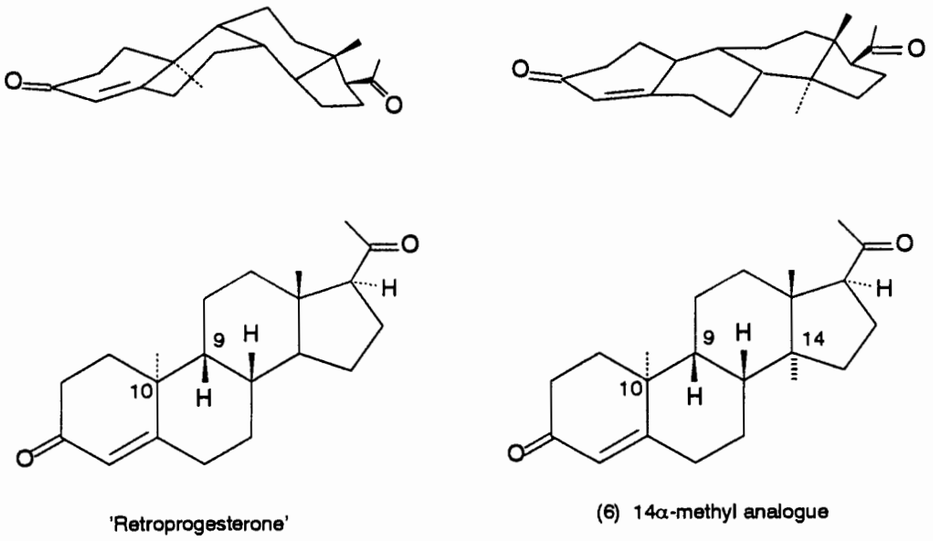
(4) Ethynylestradiol (1) Estradiol (5)

Fig. 2. Comparison between binding affinities of compounds bearing different 17α-substituents.

The research programme at the University of Cape Town, on estrogen analogues, originated from an unrelated investigation into structure-activity relationships of backbone-modified 19-norpregnane derivatives. In 1960, Reerink *et al.*[6] published the first of a series of papers in the which the unexpectedly high gestagenic activity of 9ß,10α-pregn-4-ene-3,20-dione ('retroprogesterone') and derived 9ß,10α-steroids was reported. Subsequent speculation on the reason for these findings included the hypothesis[7] that retroprogesterone undergoes conformational deformation during interaction with the gestagen receptor, in order to generate a skeletal 'template' which more closely resembles that of progesterone.

Attempts to exploit this concept in deliberate synthesis of progesterone analogues disposed toward appropriate conformational deformation, led Bull *et al.*[8-10] to investigate the synthesis of 14α-methyl steroids. It was recognised[8] that incorporation of a 14α-methyl group, together with 9ß,10α-configuration, in 19-norsteroids, would lead to steric interactions similar to those present in retroprogesterone, and hence, to the possibility of synthesising new 'conformational analogues' of progesterone with

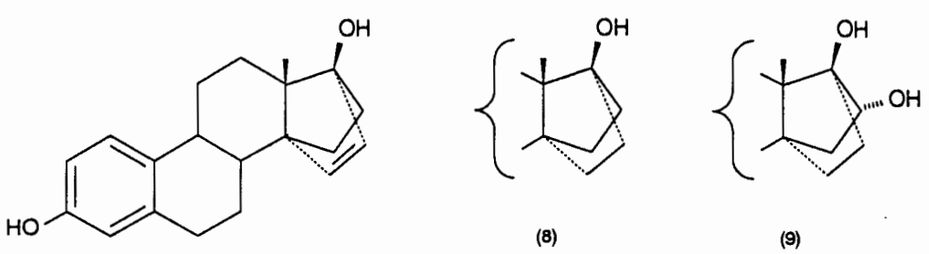
comparable or higher affinity for the gestagen receptor. Recent results[11] have confirmed that 14α-methyl-19-nor-9ß,10α-pregnan-4-ene-3,20-dione (*fig.* 3) adopts a ground state conformation in which rings B and C are non-chairlike, and the resultant conformation bears a spatial resemblance to that of progesterone.



'Retroprogesterone' (6) 14α-methyl analogue

Fig. 3. Comparison of conformations between retroprogesterone and the 14α-methyl analogue (**6**)

As part of the programme to develop a new synthetic approach to 14α-methyl-19-norsteroids, the cycloaddition of ethylene equivalents to ring D dienes was investigated.[12,13]

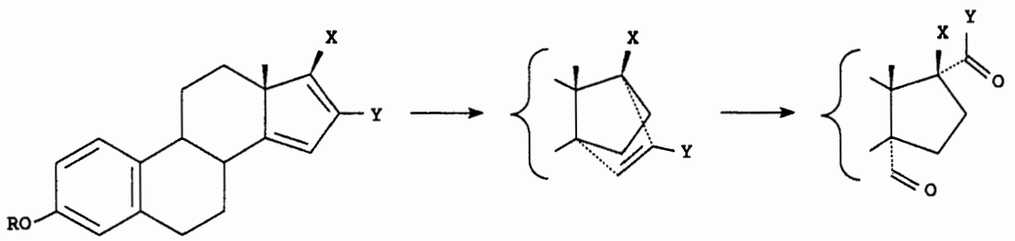


(7) (8) (9)

It has been shown that 14,17α-ethenoestra-1,3,5(10)-triene-3,17ß-diol (**7**) and the derived products (**8**) and (**9**) display oral estrogenicity.[14] In certain compounds of this series, this property is comparable or superior to that of ethynylestradiol (**4**).

Oxidative cleavage of the residual olefinic bond in the cycloadduct has been found to be a versatile method of synthesising 14α-alkyl steroids.[12,13,15] Depending on the substituents on the D ring of the starting diene, the 14- and 17-substitution pattern could be varied, thus giving rise to a wide variety of compounds (scheme 1).

Scheme 1

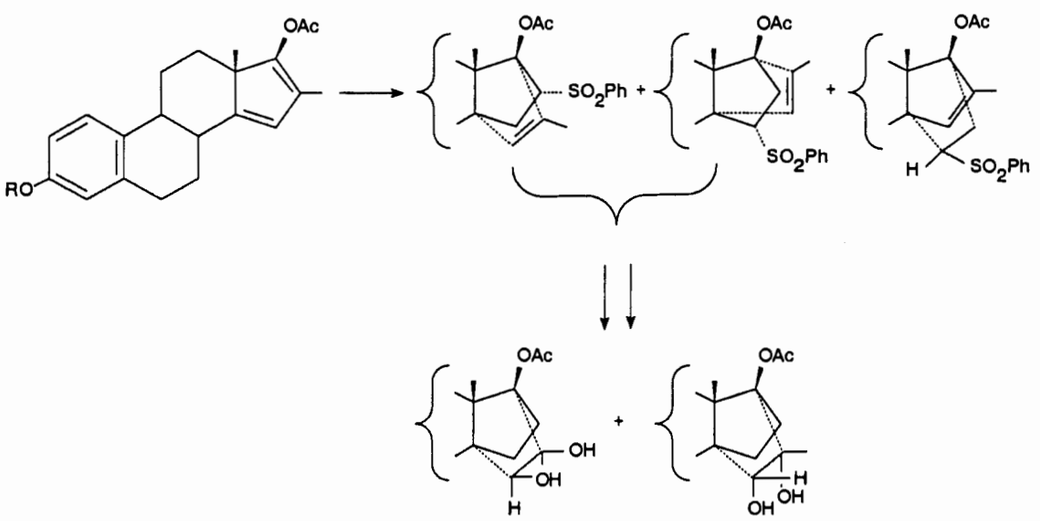


The influence of a 16-functionalised substituent upon cycloaddition and subsequent cleavage products, and the resultant hormonal activity displayed by these compounds would be of interest as it would provide further insights into the structure-activity relationship.

That a substituent in the 16-position influences cycloaddition was found by Bull[15] who has reported that presence of a 16-methyl substituent in the Diels-Alder reaction of 3-methoxy-16-methylestra-1,3,5(10),14,16-pentaen-17-yl acetate with phenyl vinyl sulphone decreased the reactivity of the 14,16-diene and suppressed the usual *ortho*-regioselectivity, giving three products instead of the highly selective reactions found in similar compounds lacking the methyl group[13] (scheme 2). Differences in

stereoselectivity were noted in compounds with or without the 16-methyl group in the hydroxylation step of the reaction sequence.

Scheme 2

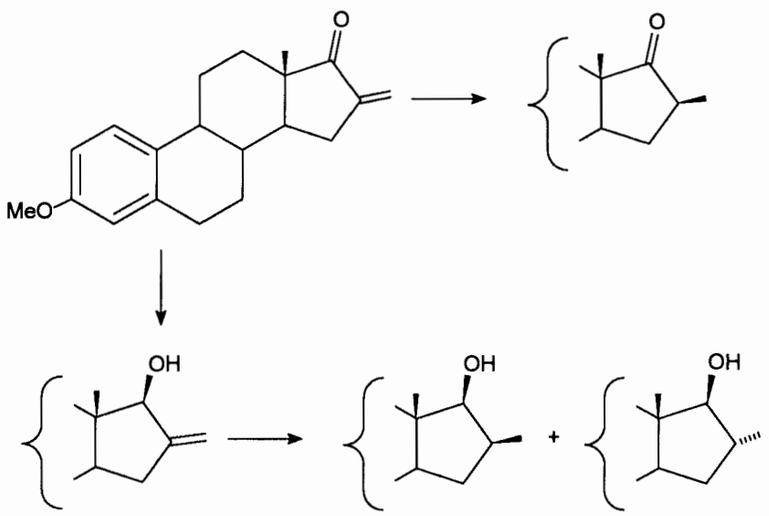


Steroidal 16-methylene 17-ketones offer an excellent source of compounds having 16-functionalised substituents, as the ring D functionality could be exploited through both *cis*- and Michael addition, thus enabling a wide variety of substituents to be introduced, which could provide useful substrates for cycloaddition studies. Although the synthesis of 16-methylene steroids has been well documented,[3,16-23] their reactions have been reported mostly in the patent literature, and have been limited mainly to hydrogenation reactions.[16-20, 24-29]

Hydrogenation of the 16-methylene functionality[20,24-27] is a favoured method of introducing a 16ß-methyl group. This method is stereoselective and therefore superior to direct alkylation which results in epimeric mixtures and dialkylated products. The conversion of 16-methylene to 16ß-methyl in the estrone series[16,17,20,26] has been reported in good yields, although it was found[25] that the 16α-methyl isomer was also formed during hydrogenation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17ß-ol

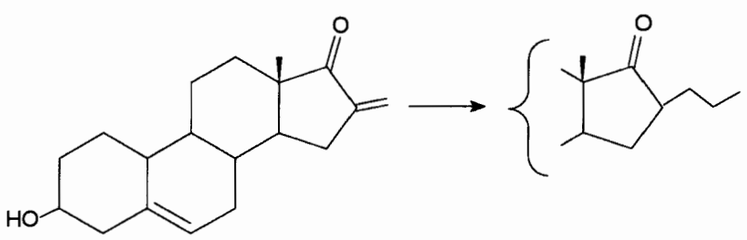
(scheme 3). No yields or ratios of isomers were given. Similar hydrogenation reactions were undertaken in the androstane series.[26]

Scheme 3



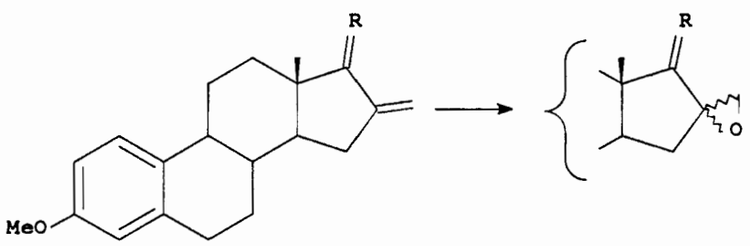
Few other reactions have been reported for the 16-methylene steroids. Trehan[30] reported the reaction of 3-hydroxy-16-methylene-androst-5-en-17-one with triethylborane to give the 16-propyl product in 70,9% yield (scheme 4). No stereochemistry of the 16-alkyl group was given.

Scheme 4



Epoxidation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one with alkaline hydrogen peroxide, which gave a mixture of epoxide isomers (scheme 5) has been reported in the patent literature.[18,19,28] An isomeric mixture was also obtained on epoxidation of the 17ß-acetoxy analogue with benzoyl peroxide. No yields or ratio of isomers formed were given.

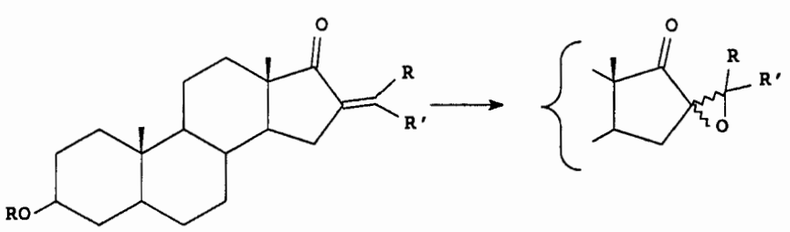
Scheme 5



R = O
R = β-OAc, α-H

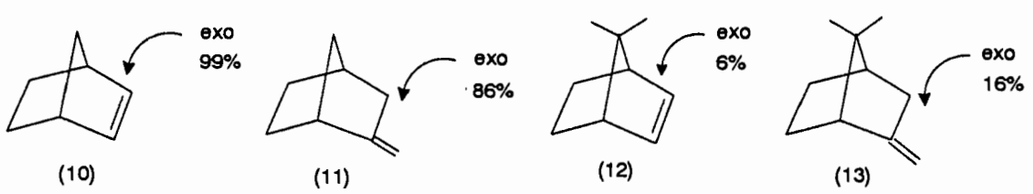
Epoxidation of 16-alkylidene and 16-arylidene steroids with trifluoroperacetic acid has been reported by Marples and Chagonda[31] as part of their investigation of steroidal α,ß-unsaturated δ-lactones (scheme 6). They reported that α-epoxidation predominated in both the alkylidene and arylidene series, but little evidence is given in support of the stereochemical assignment.

Scheme 6



To our knowledge, no systematic investigation of *cis*-additions to steroidal 16-methylene compounds has been reported. However, there have been numerous reports of addition to olefinic bonds exocyclic to ring systems.[32-39] In particular, attention has been given to studies of alkylidene or arylidene cycloalkanes, and to methylenecyclohexanes and methylenebicyclo[2.2.1]heptanes. Many of these investigations were conducted to explore mechanistic and stereochemical aspects of the reactivity of exocyclic double bonds and to examine the influence of neighbouring groups. Some of the investigations relevant to the subject of our work are discussed below.

It has been reported by Brown *et al.*[33] that the epoxidation of exocyclic methylene groups is influenced by steric effects, but to a considerably lesser extent than in the analogous endocyclic olefins. Thus treatment of bicyclo[2.2.1]hept-2-ene (**10**) with *m*-chloroperbenzoic acid in dichloromethane followed by reduction of the epoxide product with lithium in ethylenediamine gave 99% of the *exo*-isomer whereas 2-methylenebicyclo[2.2.1]heptane (**11**) showed a slight decrease in selectivity to give 86% of the *exo*-product. As expected, the presence of the bridge substituents in 7,7-dimethylbicyclo[2.2.1]hept-2-ene (**12**) resulted in stereoreversal of epoxidation, to give highly selective *endo*-attack (94%). Again, epoxidation of the corresponding exocyclic model olefin (**13**) displayed a small loss of stereoselectivity to 84%.



(10) (11) (12) (13)

The discovery by Henbest[40] that cyclic allylic alcohols assisted peracid epoxidation to form epoxides principally *syn* to the hydroxyl group, gave rise to a new stereoselective method of epoxidation. Henbest did note, however, that large steric effects could

hinder this directing effect. He found that corresponding ethers and esters reacted at slower rates and did not undergo preferential *syn* attack. The mechanism he proposed therefore, involved a transition state where hydrogen bonding between the allylic alcohol and the peracid occurred (*fig.* 4).

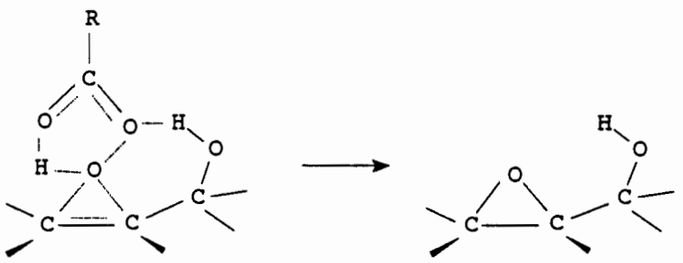
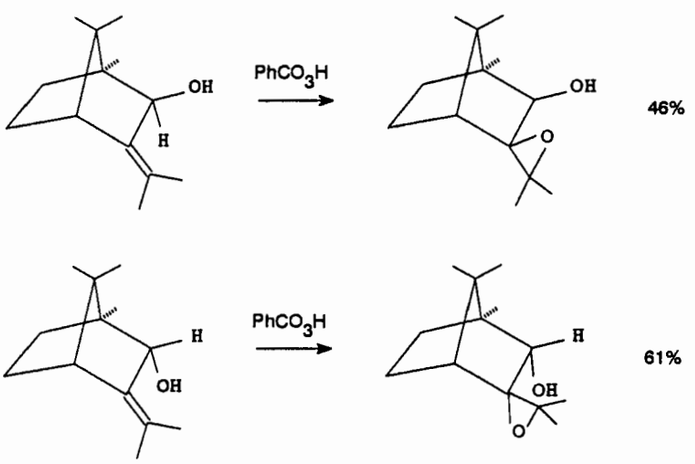


Fig. 4. Transition state proposed by Henbest showing hydrogen bonding between alcohol and peracid.

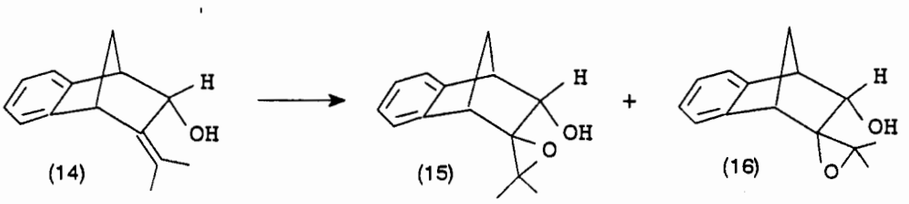
Since then, numerous reports[32] have been published investigating the stereoselectivity of this method. Katsuhara[34] has reported that epoxidation of epimeric isopropylideneborneol gave only the epoxides bearing a *syn* relationship to the hydroxyl group (scheme 7).

Scheme 7



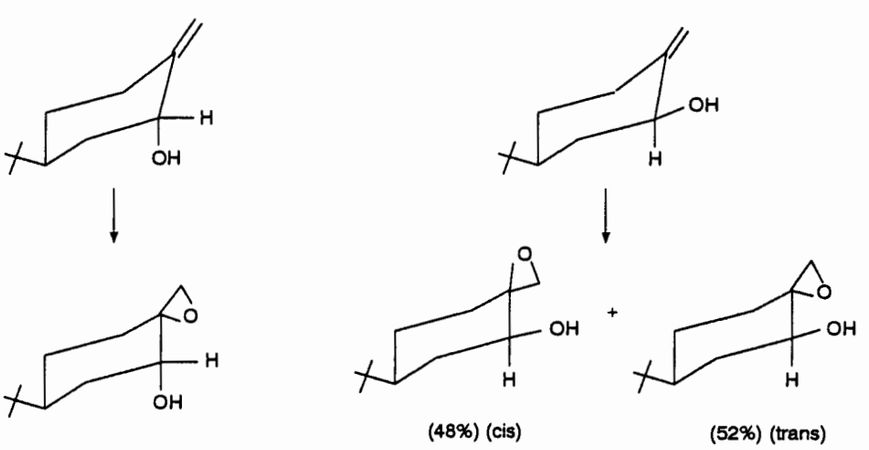
By contrast, Lee[35] found that steric and hydroxyl-directing effects competed with one another. Thus epoxidation of 2α-hydroxy-3-methylene-1,2,3,4-tetrahydro-1,4-methanonaphthalene (**14**) gave the isomeric epoxides (**15**) and (**16**) in about equal amounts (scheme 8).

Scheme 8



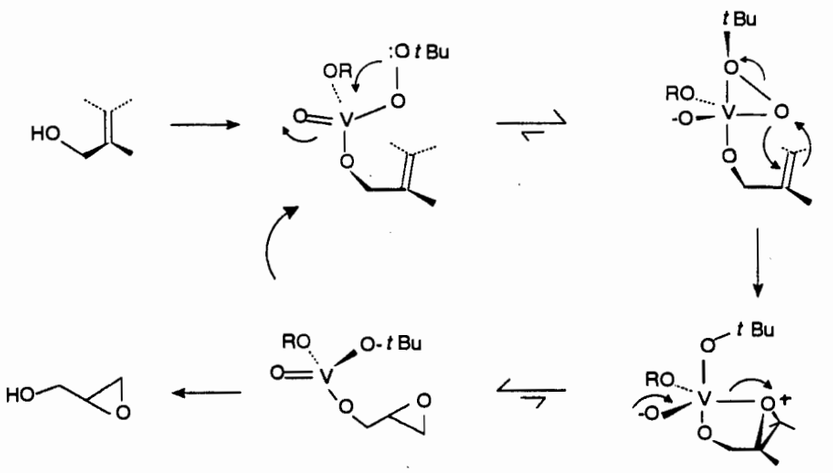
Chautemps[36] has reported that if the allylic hydroxyl group is axial to the exocyclic methylene group, the epoxide *syn* to the alcohol is exclusively obtained when *cis*-5*t*-butyl-2-methylenecyclohexanol is treated with *p*-nitroperbenzoic acid. If the hydroxyl group is equatorial, then the double bond and the C-OH bond eclipse one another, and no notable stereodirecting effect occurs. It is noted that the equatorial alcohol isomer is epoxidised about twice as fast as the axial alcohol isomer (scheme 9).

Scheme 9



The excellent stereoselectivity of *t*-butylhydroperoxide and vanadium catalysts reported by Sharpless[41,42] has enabled highly stereoselective epoxidations to be carried out in good yields. He found that allylic alcohols were epoxidised considerably faster with this reagent than the corresponding alkenes. In comparison, peracid epoxidation of unhindered allylic alcohols was nearly twice as slow as that of the corresponding alkenes.[40] The proposed mechanism is given in scheme 10.

Scheme 10

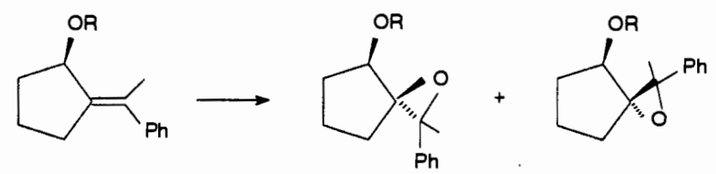


Sharpless subsequently reported titanium-catalysed asymmetric epoxidation in the presence of chiral ligands.[43] This will not be discussed here, as we are only concerned with diastereoselectivity.

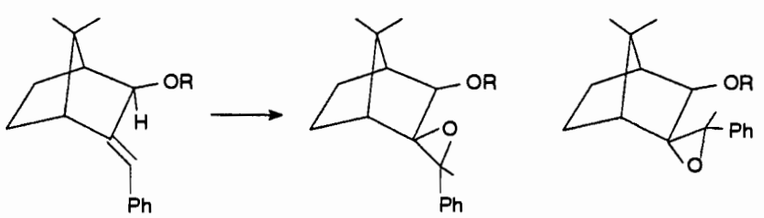
Investigations by Rao[37] comparing the peracid and Sharpless methods, showed that poor stereoselectivity was obtained using either method, in the epoxidation of 2-*trans*-benzylidene-4*t*-butylcyclohexan-1-ol. Epoxidation of 2-*trans*-benzylidene-cyclopentanol (**17**), however, was stereoselective giving greater than 95% of the *cis*-epoxy alcohol with either method, this being ascribed to the lack of steric interference and the favourable dihedral angle of 60° between the C-OH bond and the plane of the

double bond. The much more hindered olefin (**19**) gave only the epoxide *anti* to the hydroxyl group (>97%) with *m*-chloroperbenzoic acid, but exclusively the epoxide *syn* to the hydroxyl group (>99%) with the *t*-butyl hydroperoxide-vanadium catalyst (scheme 11). It is suggested that the steric hindrance is large enough to suppress the weak hydroxyl assistance to the peracid, but that the stronger assistance assistance given to the hydroperoxide-vanadium reagent is able to overcome these steric effects. A mixture of epoxy isomers (60:40) was obtained when an acetoxy group was the α-substituent (**18**), with the *cis*-epoxy acetate being the more favoured. Steric effects again dominated the peracid epoxidation of (**20**) to give exclusively the epoxide *anti* to the acetoxy group.

Scheme 11



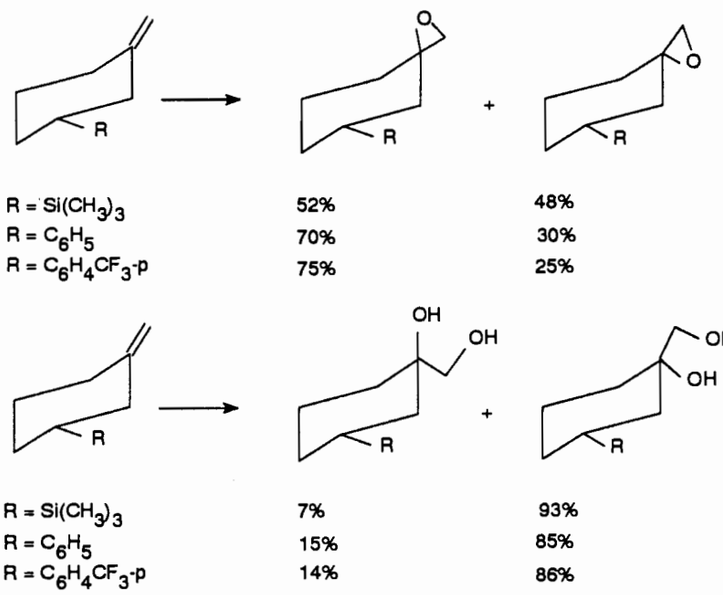
(17) R = H (mcpba)	95%	5%
R = H (Sharpless)	99%	<1%
(18) R = Ac (mcpba)	60%	40%



(19) R = H (mcpba)	<3%	>97%
R = H (Sharpless)	>99%	<1%
(20) R = Ac (mcpba)	0%	100%

Cieplak *et al.*[38] reported that an increase of the relative proportion of axial attack in a number of different reactions including osmylation and peracid epoxidation, was found when electronegative substituents were present at C-3 of methylenecyclohexane. Some representative results are given in scheme 12.

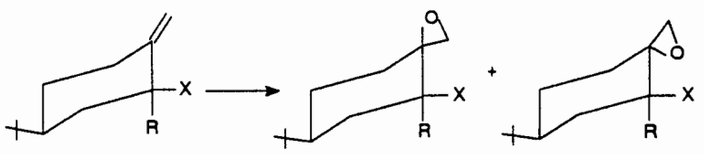
Scheme 12



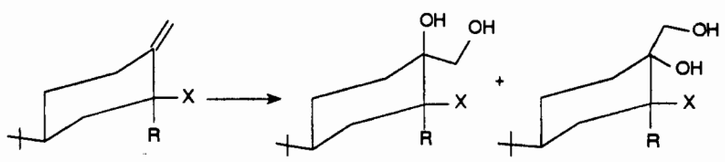
He therefore proposed a new model which attributes stereoelectronic control in cyclohexane-based systems to electron donation into the vacant σ^* orbital associated with the incipient bond in the transition state complex.

In the light of this work, Vedejs[39] investigated the epoxidation and osmylation of 4-*t*-butylmethylenecyclohexane derivatives to determine if a similar pattern of σ,σ^* interactions occur. Representative results are given in scheme 13.

Scheme 13



R = OH, X = H	60%	40%
R = H, X = OH	11%	89%
R = OCH_3, X = CH_3	88%	12%
R = CH_3, X = OCH_3	83%	17%
R = OAc, X = H	75%	25%



R = OH, X = H	<5%	95%
R = H, X = OH	33%	67%
R = OCH_3, X = CH_3	20%	80%
R = CH_3, X = OCH_3	90%	10%
R = OAc, X = H	8%	92%

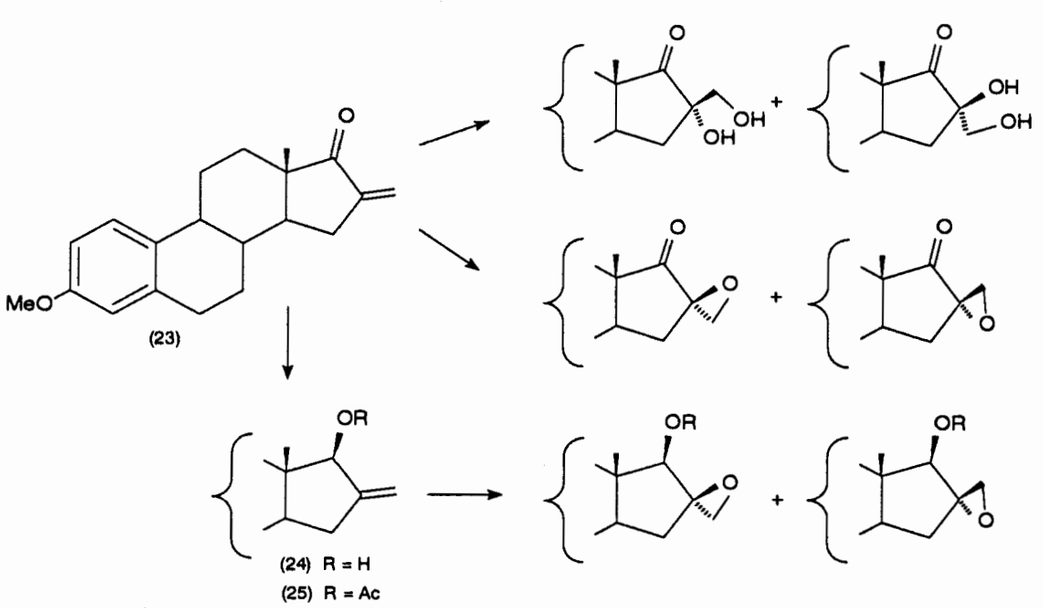
His investigations gave similar results to those of Chautemp[36] and Rao.[44,45] The small difference found in the direction of epoxidation when the methoxy and methyl positions were reversed indicated that no significant σ,σ^* interactions occurred. No real trends were observed and it was therefore concluded that hyperconjugative interactions may be important in controlling stereochemistry when no steric bias is present, but that other variables, such as transition state geometry become more important when hetereoatoms are present.

1.2 OBJECTIVES

In view of our interest in developing synthetic routes to 16-alkyl and 16-functionalised-alkyl 19-norsteroids for cycloaddition and related studies, we set out to examine the scope for exploiting the chemistry of the readily available 17-functionalised 16-methylene steroids. For this purpose, 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one (**23**) and the derived 17ß-hydroxy (**24**) and 17ß-acetoxy (**25**) compounds were chosen as model systems. Although it would have been highly desirable to carry out a companion study on the corresponding 17α-hydroxy and 17α-acetoxy compounds, they have not been reported in the literature, and an attempt to prepare the compounds proved unsuccessful.

In the first instance, the plan was to epoxidise the model compounds under a variety of conditions and to determine the influence of 17-functionality upon the stereoselectivity of epoxidation (scheme 14).

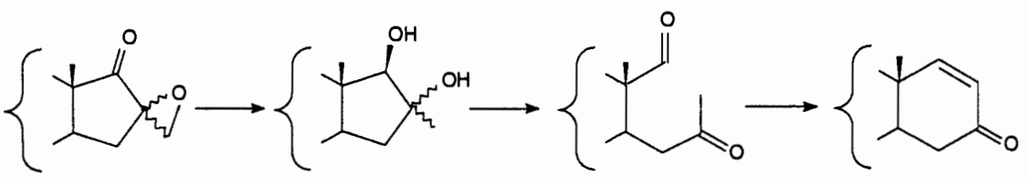
Scheme 14



It was further planned to corroborate configurational assignments, based upon mechanistic and spectroscopic grounds, with the aid of correlation reactions and complementary *cis*-hydroxylation of the methylene ketone (**23**).

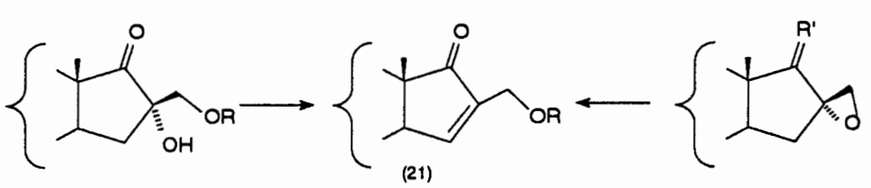
These epoxidation products could then be used in the synthesis of D-homo analogues. The proposed route would include the reduction of the epoxide, followed by cleavage and condensation to give 3-methoxy-17a-homoestra-1,3,5(10),17-tetraen-16-one which can then undergo further modifications (scheme 15).

Scheme 15



The products obtained from *cis* addition would also be used to explore direct or indirect routes to the formation of 16-functionalised Δ^{15} 17-ketones, which could then be converted to the 17-acetoxy-14,16-dienes for cycloaddition studies. For example, selective acetylation of the hydroxylation products followed by dehydration could be expected to give the Δ^{15} 17-ketone (scheme 16). An alternative option for consideration was base-mediated rearrangment of selected epoxide products to form the allylic alcohol.

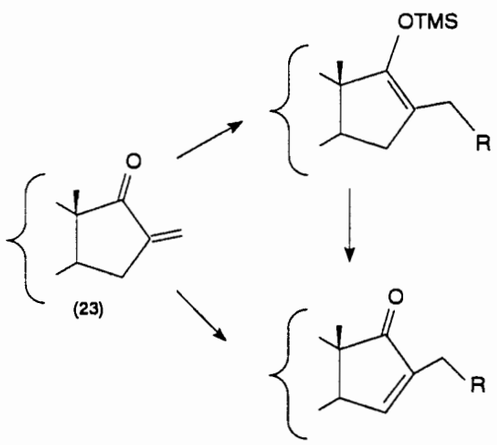
Scheme 16



(21)

Alternative synthetic routes to the 16-hydroxymethyl Δ^{15} 17-ketones (**21**) (or 16^{1}-protected derivatives) that could be considered, were through Michael addition to the 16-methylene 17-ketone followed by trapping of the intermediate enolate and direct or indirect dehydrogenation. Hence it was planned to carry out a complementary investigation of this approach, and to examine the scope for applying analogous procedures to the formal isomerisation of the methylene ketone into the corresponding 16-methyl-Δ^{15} 17-ketone (scheme 17).

Scheme 17



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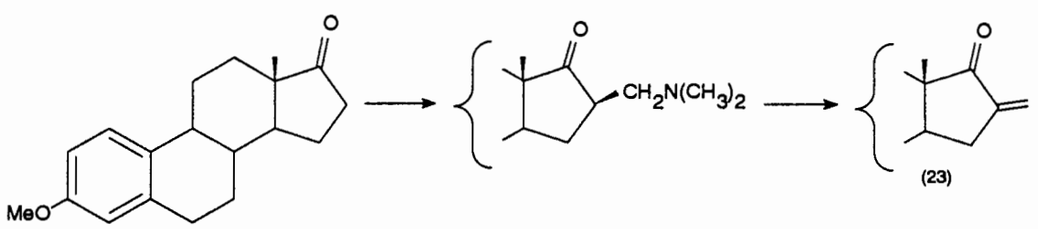
2. Discussion

2.1. Preparation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one and derived 17ß-OR compounds.

The methylene ketone (**23**) was synthesised by the α-methylenation method reported by González *et al.*[20] Thus, 3-methoxyestra-1,3,5(10)-trien-17-one was treated with freshly prepared dimethylmethyleneimmonium chloride in dry acetonitrile and refluxed for 20 h. Alkaline work up gave the crude Mannich base which was refluxed without further purification in acetic anhydride for 2 h to give 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one (**23**) (98%) (scheme 18).

Scheme 18



Spectroscopic data were consistent with the structure. An infrared band at 1722 cm^{-1} agreed with that expected for an a,ß-unsaturated carbonyl in a five-membered ring, and another band at 1638 cm^{-1} was consistent with the 16-methylene group. The methylene protons in the proton n.m.r. spectrum were represented by two triplets of doublets at 5,42 and 6,1 ppm as was also found by González,[20] although we found coupling constants of 2,8 and 1,4 Hz instead of the reported 3 and 2,2 Hz he obtained on a Varian HA 100. These five-peak signals probably arise from geminal coupling between the methylenic protons of 2,8 Hz and long range coupling of 1,4 Hz with the 15α- and 15ß-protons suggesting that the dihedral angles between the plane of the methylene group

and each 15-proton is similar (*fig.* 5). This long range coupling can be seen in the 15α-H signal which appears at 2,68 ppm as a triplet of doublets of doublets showing a coupling constant of 1,4 Hz together with a geminal coupling of 13 Hz and vicinal coupling of 6,1 Hz with the 14α-H.

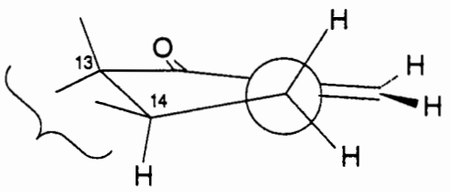
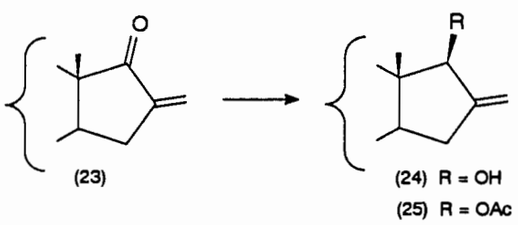


Fig. 5. Newman projection along the C(15)-C(16) bond.

Treatment of the methylene ketone (**23**) in tetrahydrofuran with lithium aluminium hydride for 1,5 h at 0°C gave 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17ß-ol (**24**) as the only product (96%) (scheme 19). The assignment of the stereochemistry of the 17ß-alcohol was assumed since reduction of a steroidal 17-ketone normally yields the 17ß-hydroxy group. This assignment was confirmed by the presence of a broad singlet obtained for the 17-H after D_2O exchange, suggesting long range coupling with the methylene protons which appear as broad quartet-like signals. Consideration of molecular models show the 17α-H as nearly orthogonal to the plane of the double bond, which is favourable for long range coupling through sp^2 centres.[46]

Scheme 19



Acetylation of the methylene alcohol (**24**) with pyridine and acetic anhydride for 19 h at 25°C gave 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17ß-yl acetate (**25**) (94%). Spectroscopic data were consistent with the structure. The 17α-H again appeared as a broad quartet-like signal (*J ca.* 2,3 Hz) caused by coupling with the allylic protons, thus confirming the stereochemical assignment of the 17-position.

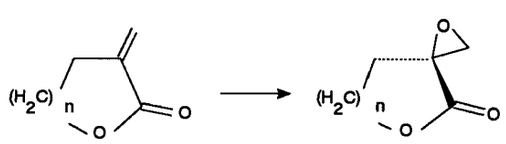
These three compounds were used as substrates for *cis*-addition experiments.

2.2. *cis*-Addition studies

2.2.1 Epoxidation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one (23)

At the outset, it was of interest to ascertain whether the 16-methylene 17-ketone (**23**) would undergo reaction with a peracid. Although it was recognised that α,ß-unsaturated carbonyl compounds do not normally undergo epoxidation under these conditions, it was considered possible that the obligatory *s-Z* conformation of the functionality in a rigid five-membered ring might result in unusual reactivity. Alkylidene and arylidene 17-oxo-steroids have been epoxidised with trifluoroperacetic acid in moderate to good yields.[31] *m*-Chloroperbenzoic acid was used to epoxidise 2-isopropylidene pentanone in 70% yield.[47] The methylene ketone (**23**) differs in that it is less nucleophilic as there are less electron donating substituents on the olefinic bond. Epoxidation of α-methylene lactones has however, been reported[48] with *m*-chloroperbenzoic acid and 2,6-di-*t*-butylphenol at elevated temperatures (scheme 20) in good yields.

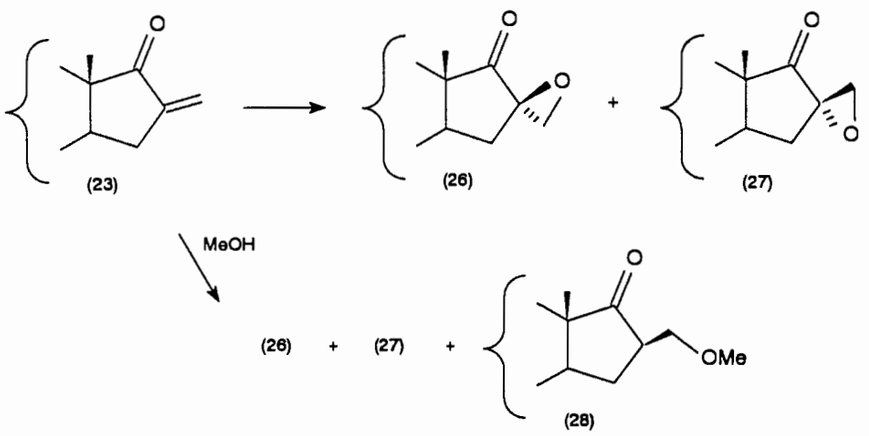
Scheme 20



In the event, treatment of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one (**23**) in dichloromethane with *m*-chloroperbenzoic acid at 25°C for 24 h gave no reaction. Furthermore, there was no evidence of Baeyer-Villiger oxidation products.

The reaction was then carried out under conventional conditions, using alkaline hydrogen peroxide in dioxane. After 45 h at 20°C, a separable mixture of the isomeric spiro-oxirane (**26**) (27%) and (**27**) (35%) was obtained (scheme 21).

Scheme 21



This reaction has been described previously, but the patent literature source[18,19,28] gave no details of isomer proportions and reasons for stereochemical assignments. Accordingly, we attempted to confirm assignments with the aid of spectroscopy but no conclusive assignments could be made. The 16^1-protons of the two isomers differed in that they occurred as two doublets at 2,97 and 3,12 ppm in the major isomer (**27**), but as a doublet at 2,95 ppm and a doublet of doublets at 3,2 ppm in the minor isomer (**26**). The neighbouring proton causing this small long range coupling of *ca.* 0,5 Hz was not evident in a COSY spectrum of (**26**) and no obvious reason for this coupling could be seen from inspection of molecular models.

The reaction was found to be slow in tetrahydrofuran, taking 5 days to reach completion, with no improvement in yield. In order to improve solubility of the reagents, a 1:1 mixture of tetrahydrofuran and methanol was used. However, the use of methanol as co-solvent resulted in 1,4-addition of the methoxide anion to form the 16ß-methoxymethyl ketone (**28**) (29%) together with a *ca.* 1:1 mixture of epoxy ketones (**26**) and (**27**) (35%) (scheme 21). The structure of (**28**) was assigned from spectroscopic data. The presence of a three proton singlet at 3,3 ppm in the proton n.m.r. spectrum indicates the presence of a methoxy group. The signal representing the 16^1-protons was a complex multiplet and could not be used to assign the stereochemistry of the $-CH_2OCH_3$ group. This group was tentatively assigned to the ß-position based on the complex signal for the 16-H found at 2,75 ppm. Due to signal overlap, only eleven peaks could be seen, instead of the theoretical twelve (assuming that the 16-H couples equally to each 16^1-proton). Based on a coupling constant of 1,74 Hz which could be clearly seen on each side of the multiplet, the other coupling constants were assigned (*fig.* 6). Thus a large coupling constant of *ca.* 9,4 Hz is due to the vicinal coupling between the pseudo-axial 15ß-H and a pseudo-axial 16α-H. Smaller vicinal coupling of *ca.* 5,4 Hz is found between the 16^1-protons and the 16α-H. Coupling between the pseudo-equatorial 15α-H and the pseudo-axial 16α-H gave the smallest coupling constant of 1,74 Hz. Calculated signals based on these values showed

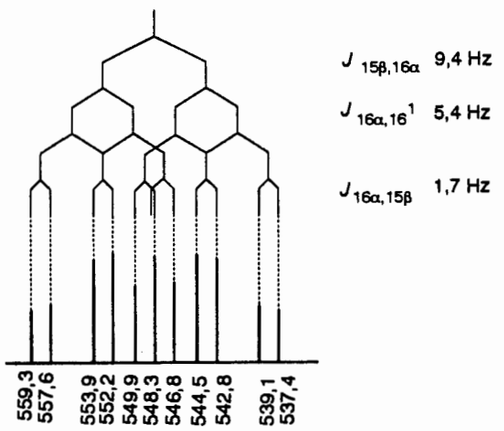


Fig. 6. Calculated values based on J values of 9,4, 2 x 5,4 and 1,7 Hz

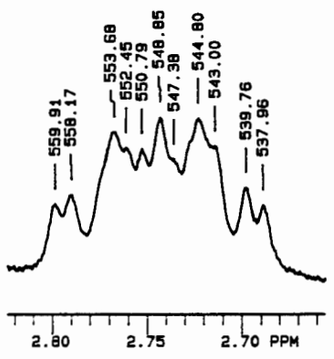


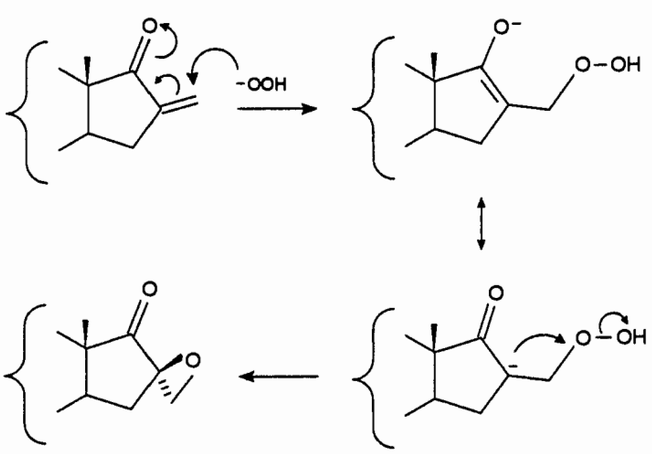
Fig. 7. N.m.r. spectrum of the 16α-H

good agreement with those found in the n.m.r. spectrum (*fig.* 7). If the 16-proton were in the pseudo-equatorial position, then no large diaxial coupling should be seen. In order to demonstrate the origin of this by-product, the methylene ketone (**23**) in tetrahydrofuran was treated with methanolic sodium methoxide at 20°C for 3 h which gave the identical compound (**28**) (65%).

The best solvent system for epoxidation was a 1:1 mixture of tetrahydrofuran and *t*-butyl alcohol which gave a mixture of epoxide isomers in 80-92% yields within 4 h at 20°C. The tetrahydrofuran was used as co-solvent in order to improve solubility of the steroid and to prevent the reaction mixture from solidifying at 0°C during initial addition of the hydrogen peroxide.

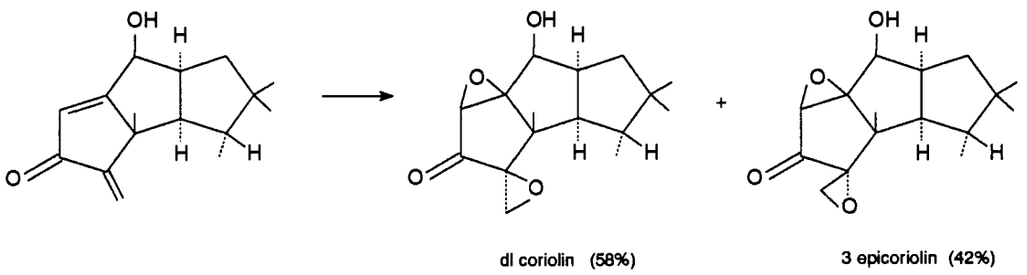
Stereoselectivity was poor with the ratio of α:ß epoxide isomers being 4:5. The accepted mechanism[49] is based upon a nucleophilic attack by the hydroperoxy anion upon the terminus of the α,ß-unsaturated carbonyl system (scheme 22) Thus steric effects from the ring system are minimised. The possibility of rotation about the exocyclic carbon-carbon bond in the reaction intermediate, which would negate any stereoselectivity of hydroperoxide addition, cannot be excluded.[32]

Scheme 22



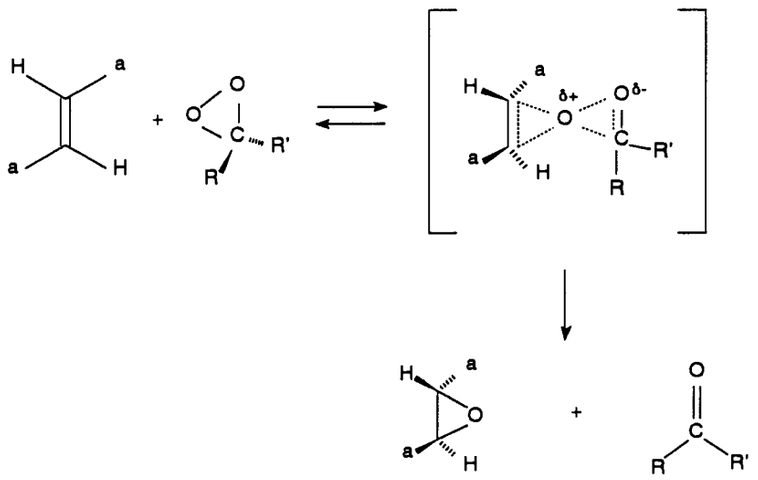
Poor stereoselectivity with alkaline hydrogen peroxide epoxidation was found by Danishefsky *et al.*[50] in the total synthesis of dl-coriolin (scheme 23).

Scheme 23



cis-Addition of the methylene ketone (**23**) was attempted using dimethyldioxirane, which was reported to epoxidise electron deficient double bonds in good yields.[51-55] Dimethyldioxirane epoxidation is thought to take place via a butterfly intermediate[51] in a similar fashion to peracid epoxidation (scheme 24).

Scheme 24



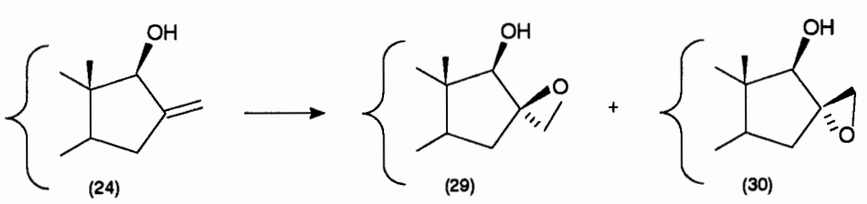
Accordingly, the methylene ketone (**23**) in dichloromethane was treated with an acetone solution of dimethyldioxirane[56] in small portions over 3 days to give a mixture of

epoxides (*ca.* 4:5) (26%). Low yields were obtained due to competing side reactions which will be discussed in section 2.2.6.

2.2.2 Epoxidation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17ß-ol (24)

Epoxidation of the methylene alcohol (**24**) was first attempted by addition of *m*-chloroperbenzoic acid to the methylene alcohol (**24**) at -10°C in dichloromethane, followed by two further additions at 20°C over a total of 2 h to give an isomeric epoxide mixture of (**29**) and (**30**) (40 and 14% respectively) (scheme 25). An improvement in yield was obtained when the reaction was repeated in tetrahydrofuran, but with concomitant decrease in stereoselectivity. Thus 52% of (**29**) and 40% of (**30**) was obtained after treating the methylene alcohol (**24**) in tetrahydrofuran with *m*-chloroperbenzoic acid for 16 h at 20°C.

Scheme 25



Assignment of stereochemistry of the epoxide isomers could not be made conclusively from spectroscopic data. The large difference in R_f values suggested that intramolecular hydrogen bonding may occur in the less polar major isomer (**29**). Inspection of molecular models suggested that weak intramolecular hydrogen bonding could occur in the 16ß-epoxide isomer. The O-H stretch band in the infrared spectrum of each isomer was sharp, but the band was slightly lower in the major isomer (**29**) at 3 523 cm^{-1}, compared to 3 608 cm^{-1} found in the minor isomer (**30**). No conclusive evidence could be found in the proton n.m.r. spectra. A coupling constant of 9,3 Hz

was found between the 17ß-OH and the 17α-H for the major isomer (**29**), compared to 5,8 Hz found in the minor isomer (**30**). The 16^1-protons appeared as two doublets in both isomers with geminal coupling between the 16^1-protons being slightly smaller in the major isomer (**29**) (*J* 4,8 Hz) than the minor isomer (**30**) (*J* 5,88 Hz).

It was assumed that the main product of epoxidation is the (16*R*)-spiro[3-methoxyestra-1,3,5(10)-trien-17ß-ol-16,2'-oxirane], on the basis of the well known[40] directing effect of the hydroxy group (*fig.* 8).

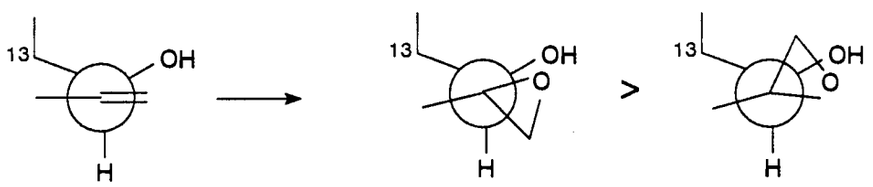


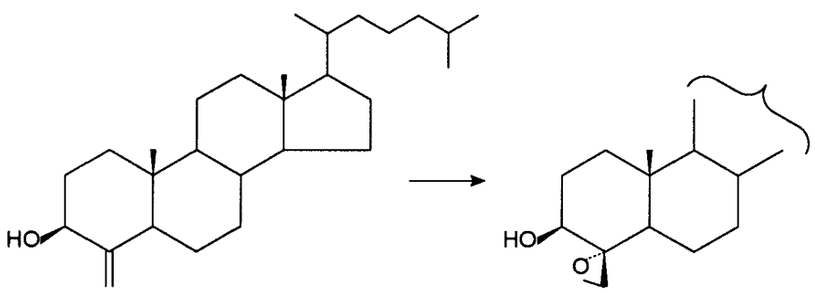
Fig. 8. Newman projection along the C(16)-C(17) bond.

However, the stereoselectivity of the reaction was modest, suggesting that the hydroxy-directing effect of epoxidation is not dominant in this case due to its pseudo-equatorial orientation.[36] Accordingly, the assignments based on this evidence are not conclusive, but were subsequently proved by further reactions and correlation experiments.

In an attempt to obtain further insight into the stereoselectivity of the process, epoxidation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17ß-ol (**24**) was also carried out under Sharpless conditions. It is known that epoxidation of allylic alcohols in the presence of *t*-butyl hydroperoxide and vanadium catalyst is not only greatly accelerated, but that *syn*-epoxidation predominates strongly, even for substrates which fail to display the expected stereoselectivity in the presence of peracids.[37,41,42] However, a recent report by Robinson *et al.*,[57] has shown that this pattern of stereoselectivity is not entirely reliable as a prediction, since epoxidation of

4-methylene-5a-cholestan-3ß-ol with either *m*-chloroperbenzoic acid or enantioselective Sharpless conditions (titanium catalyst) gave exclusively the *anti* isomer (scheme 26).

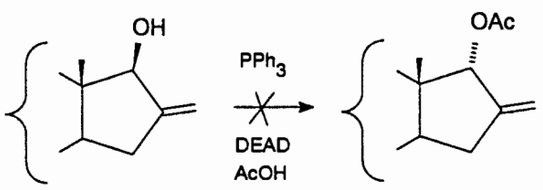
Scheme 26



Accordingly, it could not be assumed that Sharpless epoxidation of the methylene alcohol (**24**) would provide unambiguous evidence of a directing effect in this case. In the event, epoxidation of (**24**) with *t*-butyl hydroperoxide and vanadyl acetylacetonate in benzene at 25°C for 15 min gave a single product (**29**) (85%) corresponding to the major product of the peracid epoxidation.

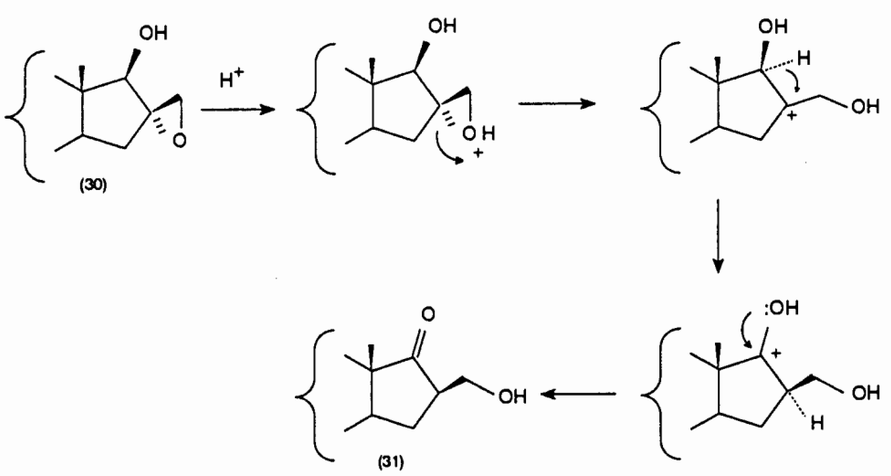
It was recognised that comparative experiments on the corresponding 16-methylene 17α-alcohol would be desirable, in order to demonstrate the expected stronger directing effect associated with a pseudoaxial 17α-hydroxy group. An attempt was made to carry out an inversion of the methylene alcohol (**24**) using Mitsunobu[58] conditions (scheme 27). Although it has been reported that the steroidal 17ß-OH is difficult to invert to the α-position,[58] it was hoped that the methylene group sufficiently "flattened" the D-ring to allow approach of the reagent. Thus, the methylene alcohol (**24**) was treated with triphenylphosphine, diethylazodicarboxylate and glacial acetic acid in dry benzene, and refluxed for 5 days, but resulted only in incomplete esterification to form the 17ß-acetate (**25**) (45%; conversion yield = 75%). This was confirmed by melting point and mixed melting point.

Scheme 27



The epoxy alcohol (**30**) was labile, and rearranged on prolonged exposure to silica gel, to form 16ß-hydroxymethyl-1,3,5(10)-trien-17-one. This rearrangement was achieved deliberately by exposing a solution of the epoxide in dry tetrahydrofuran to toluene-*p*-sulphonic acid for 1 h at 20°C, which gave a 60% yield of the rearranged product (**31**) (scheme 28).

Scheme 28



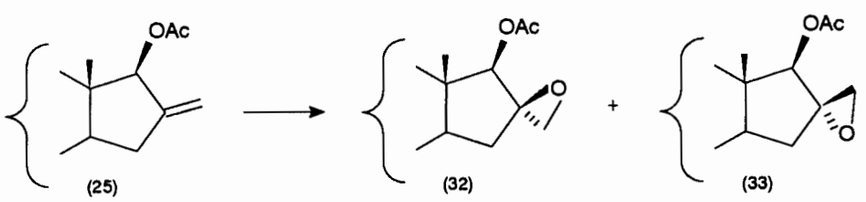
Spectroscopic data were consistent for this structure. A strong carbonyl band in the infrared spectrum at 1724 cm^{-1}, and a signal at 222,6 ppm in the C^{13} n.m.r. spectrum indicated the presence of a ketone. Overlapping signals of the 16^{1}-protons in the proton n.m.r. when run in $CDCl_3$ were resolved into two doublets of doublets at 3,47 and 3,72 respectively, in C_6D_6. Both signals show a geminal coupling constant of 10,6 Hz. The

upfield signal has a vicinal coupling of 5,8 Hz, whereas the vicinal coupling in the downfield signal is slightly smaller at 5,2 Hz indicating a similar angle between the 16^1-protons and the 16α-H. This clear coupling suggests that hydrogen bonding between the hydroxyl group and the carbonyl is taking place, preventing rotation of the 16-side chain. The signal for the 16α-H was obscured and therefore could not be compared with that of the analogous compound (**28**). As further proof of the structure of the rearranged product (**31**), it was dehydrated to the methylene ketone (**23**) by refluxing with dilute hydrochloric acid in benzene for 22 h in 82% yield.

2.2.3 Epoxidation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17ß-yl acetate (25)

Epoxidation of the 17ß-acetate (**25**) with *m*-chloroperbenzoic acid in dry dichloromethane for 2 days at 20°C gave poor yields (40%) of the epoxide isomers (**32** and **33**) (scheme 29), with apparently poor stereoselectivity, the ratio of (**32**):(**33**) being 1,2:1. Ratios were calculated from integrals of the signals for the 17α-H, the 13ß-methyl and the 16^1-epoxide protons in the proton n.m.r. spectrum.

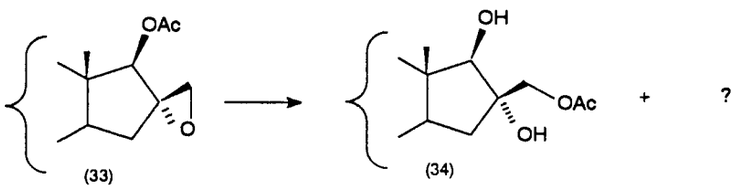
Scheme 29



An improvement in yield (90%) and stereoselectivity (ratio of (**32**):(**33**) is 2:1) was obtained using tetrahydrofuran as solvent. However, reactivity was decreased as the reaction needed 3 days to go to completion. The epoxide isomers had very similar R_f

values, and prolonged chromatography on silica gel in an attempt to obtain separation, was found to decrease the yield of the more labile α-epoxy acetate (**33**). Two, more polar products were formed, being 16ß-acetoxymethylestra-1,3,5(10)-triene-16α,17ß-diol (**34**) and an as yet unidentified more polar product (scheme 30).

Scheme 30

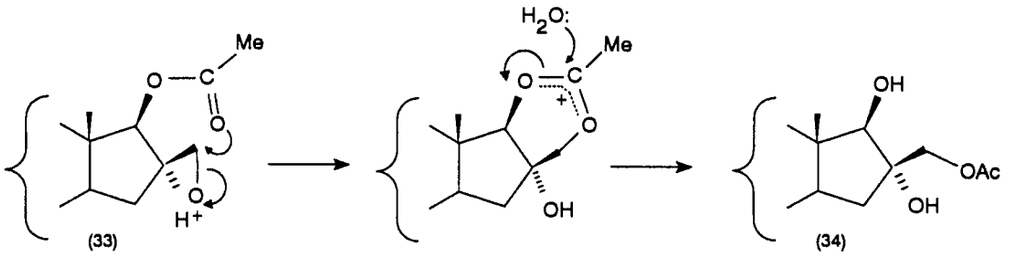


Spectroscopic data for (**34**) were consistent with the assigned structure. A molecular ion of 374, instead of 356 for the epoxy acetate, indicates an addition of a water molecule. The infrared spectrum showed a broad band centered at 3500 cm^{-1}, suggesting the presence of hydrogen bonding, and a strong carbonyl band at 1734 cm^{-1}, indicating that the acetoxy methyl is still present. This is supported by the proton n.m.r. evidence which showed the presence of an acetoxy group as a 3-proton singlet at 2,1 ppm. Two signals at 2,4 and 3,2 ppm disappeared on D_2O exchange. That one of the hydroxyl groups is secondary is indicated by one of the signals at 2,4 ppm showing coupling (*J* 8,1 Hz) with a single proton neighbour at 3,42 ppm which simplifies from a doublet to a singlet on D_2O exchange. This is very similar to the signals for the 17ß-OH and the 17α-H found in the α-epoxy alcohol (**30**). An AB system integrating for two protons at 4,03 and 4,11 ppm was assigned to the 16^1-protons adjacent to an acetoxy group.

The decomposition of the α-epoxy acetate (**33**) to the 16ß-acetoxymethyl-16α,17ß-diol (**34**) is probably initiated by the acidic silica gel, and is assisted by the acetoxy group

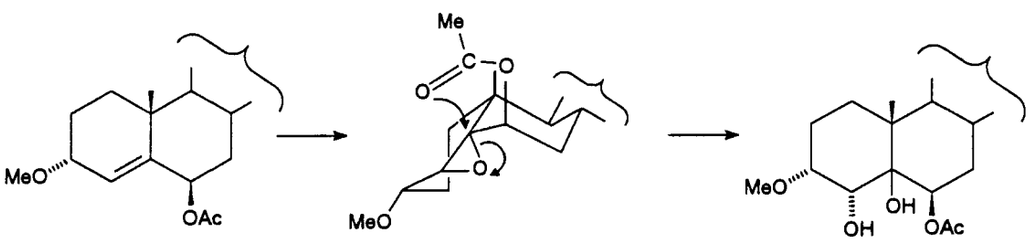
anti to the epoxide to form the acetoxonium ion. Nucleophilic attack by water results in the more stable primary acetate[59] being formed (scheme 31).

Scheme 31



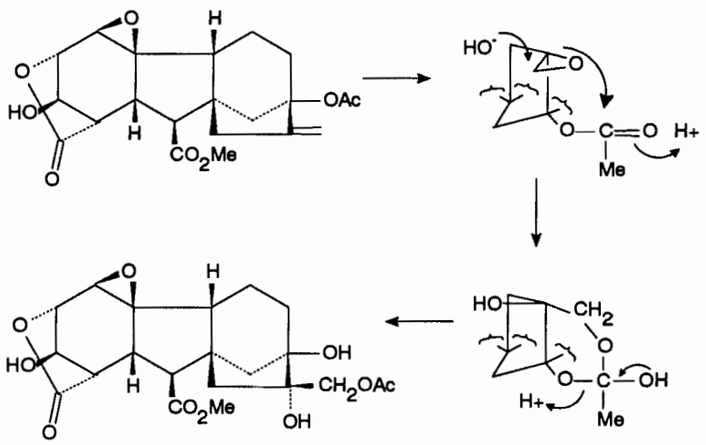
Morrison[60] has reported an analogous rearrangement on treatment of 6ß-acetoxy-3α-methoxycholest-4-ene with *m*-chloroperbenzoic acid. Although the 4ß,5ß-epoxide was the major product, small amounts of 6ß-acetoxy-3α-methoxy-5ß-cholestane-4α,5-diol were obtained, its presence being explained by acid-catalysed cleavage of the 4,5-epoxide with participation of the adjacent *trans*-axial acetoxy group. (scheme 32)

Scheme 32



It was also reported[61] that the rearrangement of the epoxidation product of the 3,13-diacetate of methyl gibberellate resulted in the migration of the acetoxy group from C-13 to C-16, with the inversion of configuration at C-16 (scheme 33).

Scheme 33



Attempts to epoxidise the methylene acetate (**25**) with dimethyldioxirane gave poor yields (*ca.* 30%) due to competing side reactions. This reaction is discussed in section 2.2.6.

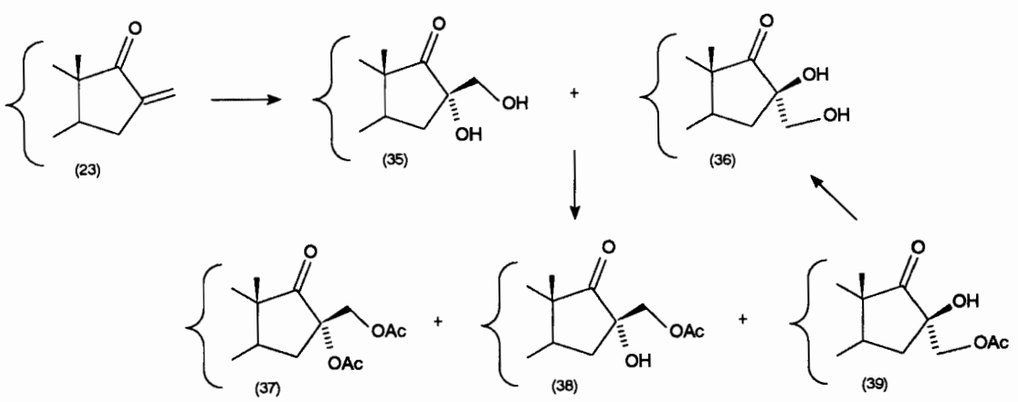
2.2.4 Hydroxylation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one (23).

The foregoing experiments on the epoxidation of the 16-methylene compounds (**23**), (**24**) and (**25**) revealed certain trends in epoxidation which were not entirely consistent with steric or stereoelectronic expectations. Furthermore, the configurational assignments could not be unequivocally established with the aid of spectroscopic data. It was therefore considered necessary to carry out a series of correlation reactions and further transformations in an attempt to establish the relationships between the isomers. For this purpose, a comparative study of the *cis*-hydroxylation of the methylene ketone (**23**) was undertaken. It was expected that hydroxylation with osmium tetroxide using 4-methylmorpholine-4-oxide monohydrate as co-oxidant would lead mainly to α-attack. This expectation was based primarily on steric considerations.

The methylene ketone (**23**) was treated with osmium tetroxide and 4-methylmorpholine-4-oxide-monohydrate in aqueous tetrahydrofuran[13] for 22 h at 25°C to give an inseparable mixture of diols (**35** and **36**) in excellent yields (97%). A pure sample of the major isomer (**35**) was obtained by crystallisation of the total hydroxylation product. Although the mixture (**35** and **36**) was chromatographically inseparable, acetylation gave a separable mixture of 16^1-acetates (**38**) and (**39**), accompanied by small amounts of a diacetate (**37**) (4%). Relative stereochemistry of the diacetate (**37**) was established by further acetylation of the monoacetate (**38**), which yielded an identical compound.

Hydrolysis of the minor isomer (**39**) with methanolic potassium hydroxide for 10 min at 20°C gave the minor diol (**36**) in excellent yield (97%) (scheme 34).

Scheme 34



The n.m.r. spectrum of each diol showed two exchangable signals which disappeared in D_2O wash. These signals appeared as broad singlets at 2,3 and 2,98 ppm in the major isomer (**35**). The 16^1-protons were found as a two-proton broad doublet at 3,7 ppm, which simplified to a singlet after D_2O exchange. The signal for the 16ß-hydroxy

group of the minor isomer (**36**) appeared as a broad singlet at 3,5 ppm, with the $16^1\alpha$-hydroxyl group appearing as a doublet of doublets (*J* 10 and 2,4 Hz) at 2,77 ppm, showing coupling with the 16^1-protons. The signal for the 16^1-protons was partially overlapped by the large 3-methoxy singlet and the 16ß-hydroxyl group. On D_2O exchange, the signals resolved into two doublets (*J* 11,8 Hz), which suggested that intramolecular hydrogen bonding ocurred between the 16α-hydroxymethyl group and the 17-ketone. Examination of molecular models showed that steric hindrance of the 15-protons and the 13ß-methyl group would prevent a favourable orientation for hydrogen bonding in the 16ß-hydroxymethyl isomer (**35**) whereas this does not occur in the 16α-hydroxymethyl isomer (**36**).

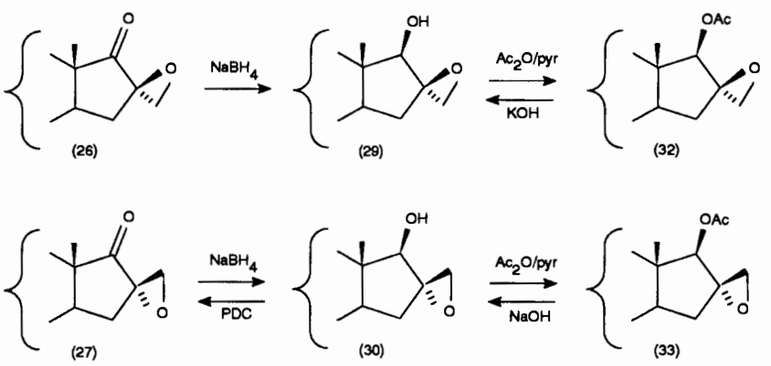
The n.m.r spectra for the 16^1-acetates (**38**) and (**39**) were as expected. The appearance of a set of two well spaced doublets for the 16^1-protons with a geminal coupling of 11,5 and 11,8 Hz for (**38**) and (**39**) respectively, indicated that rotation of the 16-sidechain was restricted. The 16^1-protons appeared as an AB system in the case of the diacetylated product (**37**) due to a more homogenous environment. Geminal coupling (*J* 11,7 Hz) was very similar to that of the mono-acetates.

2.2.5 Stereochemical assignments.

With the experimental results in hand, an attempt was made to confirm tentative assignments of configuration to the epoxidation and hydroxylation products.

In the first place, the self-consistency of the assignments was established by appropriate interconversions of 17-functionality (scheme 35).

Scheme 35



Thus, the major epoxy ketone (**27**) underwent reduction in the presence of sodium borohydride to give the minor product (**30**) derived from the epoxidation of the methylene alcohol (**24**). Furthermore, acetylation of (**30**) in acetic anhydride and pyridine gave a product (**33**) identical to the minor product obtained from the epoxidation of the 17ß-acetoxy 16-methylene compound (**25**).

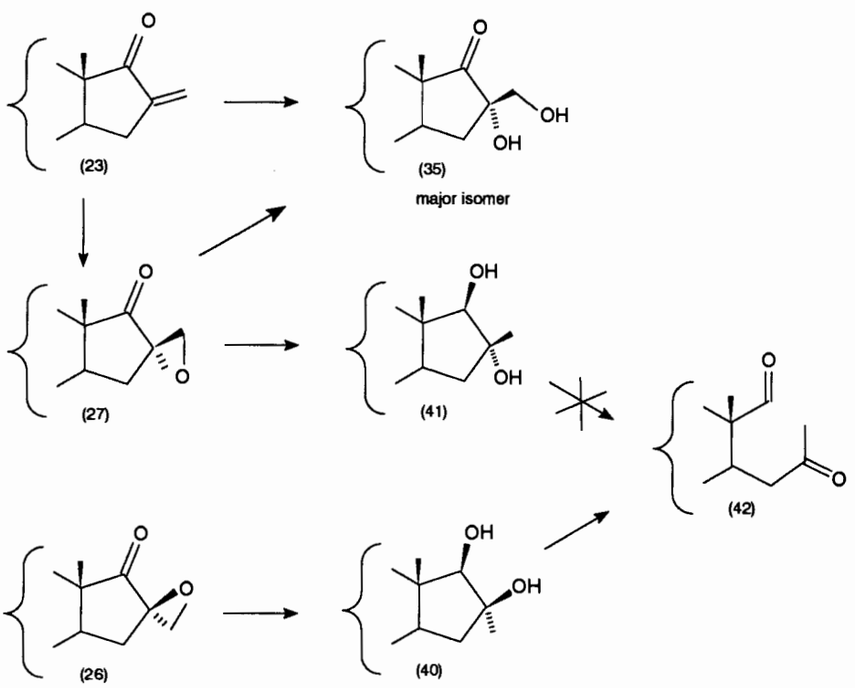
Hydrolysis of (**33**) with methanolic sodium hydroxide gave the epoxy alcohol (**30**) in 98% yield. This product was oxidised with pyridinium dichlorochromate in dry dichloromethane using the method of Corey[62] to give the epoxy ketone (**27**).

Similarly, reduction of the minor epoxy ketone (**26**) gave the major product (**29**) obtained from the epoxidation of the methylene alcohol (**24**). Acetylation of the epoxy alcohol (**29**) with acetic anhydride in pyridine gave a product corresponding to the major 17ß-acetoxy epoxide (**32**). Treatment with methanolic potassium hydroxide gave the epoxy alcohol (**29**). All compounds were verified using t.l.c., melting points and mixed melting points.

The relationship between the epoxidation and hydroxylation products was confirmed by acid-mediated hydration of the epoxy ketone (**27**) using the procedure by Meakins *et*

al.,[63] to give a dihydroxy ketone (**35**) identical with the major product obtained from *cis*-hydroxylation of the methylene ketone (**23**) (scheme 36).

Scheme 36



Having established the relative stereochemical assignments of the series, the most convincing evidence of the given assignments was obtained as follows:

Lithium aluminium hydride reduction of (**26**) gave a 16-methyl 16,17-diol (**40**), whereas similar treatment of (**27**) gave an isomeric 16-methyl 16,17-diol (**41**). The precedent of sodium borohydride reduction of (**26**) and (**27**) (see scheme 35) supported the assignment of a 17ß-hydroxy group in both cases.

The *cis*-relationship of the hydroxy groups in (**40**) was confirmed by rapid and efficient oxidative cleavage in the presence of sodium periodate at 25°C for 1 h to give 3-methoxy-16-methyl-16-oxo-16,17-secoestra-1,3,5(10)-trien-17-al (**42**) in 80% yield.

On the other hand, treatment of the *trans*-diol (**41**) with sodium periodate at 25°C for 3 days gave no reaction. Spectroscopic data were consistent with that expected for the cleavage product. A one-proton singlet at 9,35 ppm and a 3-proton singlet at 2,16 ppm in the proton n.m.r. spectrum confirmed the presence of the aldehyde proton and the 16-methyl group respectively.

Once the stereochemistry of the epoxy isomers was unambiguously assigned, a few trends in the proton n.m.r. spectra of the epoxides and hydroxylation products and their derivatives emerged (table 1).

The signal for the 13ß-methyl was found to be usually more downfield for the ß-epoxides than the α-epoxides except for the epoxy alcohols. Marples[31] reported that the 13ß-methyl signal of the ß-epoxide obtained from the epoxidation of 16-benzylidene-17-ketone appeared at 1,08 ppm, whereas that of the α-epoxide was at 0,92 ppm. However, the inverse occurred on epoxidation of 3ß-acetoxy-16-(*s*-butylidene)-5α-androstan-17-one as the 13ß-methyl of the ß-epoxide gave a signal at 0,91 ppm, whereas that of the α-isomer occurred at 0,98 ppm. The stereochemistry of the epoxidation products of other substrates was not given and therefore could not be used as a comparison.

The 16^1-protons of the epoxides gave the typical two doublet signals of a spiro 1,1-disubstituted oxirane, except for the ß-epoxy ketone (**26**) which showed a doublet of doublets for the downfield signal at 3,18 ppm, indicating a very small long-range coupling of 0,5 Hz. The geminal coupling constants of the 16^1-protons were similar for each of the three groups of epoxide isomers, and no trends could be deduced from the chemical shifts of the signals.

A clear pattern emerged concerning the 15-protons of the epoxide isomers. It was found that the 15α-H was shifted downfield in the ß-epoxide isomers and usually had a

Table 1 Comparison of proton n.m.r. data of some ring D protons.

Signal	Epoxy ketones		Epoxy alcohols		Epoxy acetates		16,16[1]-Diols		Hydroxy Acetates		16,17-Diols	
	(24) R	(25) S	(27) R	(28) S	(30) R	(31) S	(36) R*	(35) S*	(39) R*	(38) S*	(40) R*	(41) S*
13ß-Me (ppm)	1,08	1,06	0,84	0,90	1,01	0,91	1,11	0,99	1,06	0,99	0,85	0,77
16-CH_2	2 d	2 d	2 d	2 d	2 d	2 d	2 d**	s**	2 d	2 d	s***	s***
(ppm)	2,95	2,97	2,78	2,68	2,75	2,70	3,55	3,7	4,0	4,1	1,35	1,33
	3,20	3,12	2,93	3,14	2,76	2,97	3,72	-	4,36	4,3	-	-
J (Hz)	6,81	6,3	4,8	5,88	5,3	5,2	11,8	-	11,8	11,5	-	-
15α-H	dd	-	dd	-	dd	-	dd	-	dd	-	dd	-
(ppm)	2,17	-	2,15	-	2,10	-	2,13	-	2,26	-	1,94	-
$J_{15\alpha,15ß}$	12,7	-	14	-	13,3	-	13	-	12,8	-	12,8	-
$J_{15\alpha,141}$	5,9	-	7,2	-	7,1	-	5,8	-	5,1	-	6,8	-
15ß-H	-	-	-	-	t	-	t	-	t	-	-	-
(ppm)	-	-	-	-	1,73	-	1,82	-	1,78	-	-	-
$J_{15ß,15\alpha}$	-	-	-	-	13,3	-	13	-	12,8	-	-	-

* Given for comparative purposes only.
** After D_2O exchange.
*** 16-methyl

distinct doublet of doublets pattern consisting of a large geminal coupling of *ca.* 14 Hz and a further coupling to the 14α-H of about 6 Hz. The 15ß-proton could usually be found further upfield as a triplet as the larger *trans*-axial coupling constant is similar to the large geminal coupling. The α-epoxide isomers showed complex overlapping multiplets, and no clear assignment could be made.

2.2.6 Reactions with dimethyldioxirane.

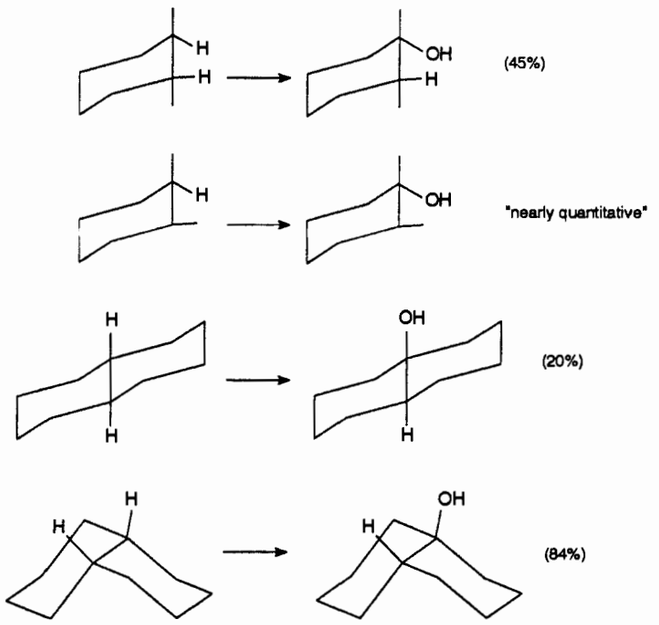
Dimethyldioxirane has been reported to epoxidise electron deficient olefins in good yields.[51-55] We therefore investigated the stereoselectivity and reactivity of dimethyldioxirane epoxidation upon the methylene ketone (**23**) and the 17ß-acetoxy 16-methylene compound (**25**).

Dimethyldioxirane in acetone solution was prepared according to the method by Adam *et al.*[56] and gave on average 0,08M solutions in 2% yield. Thus a stirred solution of the methylene ketone (**23**) in dichloromethane was treated with small additions of dimethyldioxirane in acetone solution at 25°C over 2 days to give a complex reaction mixture, comprising of starting material (6%), and a *ca.* 1:1 mixture of epoxy ketones (**26** and **27**) (16%), together with a more polar product (**43**) (22%) and other minor products (scheme 37). Ratios and yields of products depended on reaction times and the amount of dimethyldioxirane added, as the epoxides and compound (**43**) degenerated into more polar products with longer reaction times and a higher concentration of reagent. Decreasing the temperature to 0°C slowed the reaction considerably, and did not noticably favour epoxidation over oxygen insertion.

Compound (**43**) could not be obtained analytically pure in our hands but is suspected to be 9α-hydroxy-3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one which dehydrates to 16-methylene-estra-1,3,5(10),9(11)-tetraen-17-one (**44**) (scheme 37).

substrate:reagent ratio (scheme 38). Investigation of oxidation rates of benzylic protons showed that tertiary C-H bonds are more prone to oxidation than the secondary or primary counterparts.[64]

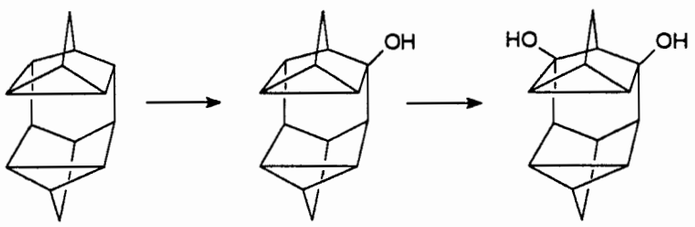
Scheme 38



Investigation of the mechanism indicated that the breaking of the C-H bond was the rate determining step, and that the C-H bond may not be completely cleaved in the transition state.[64]

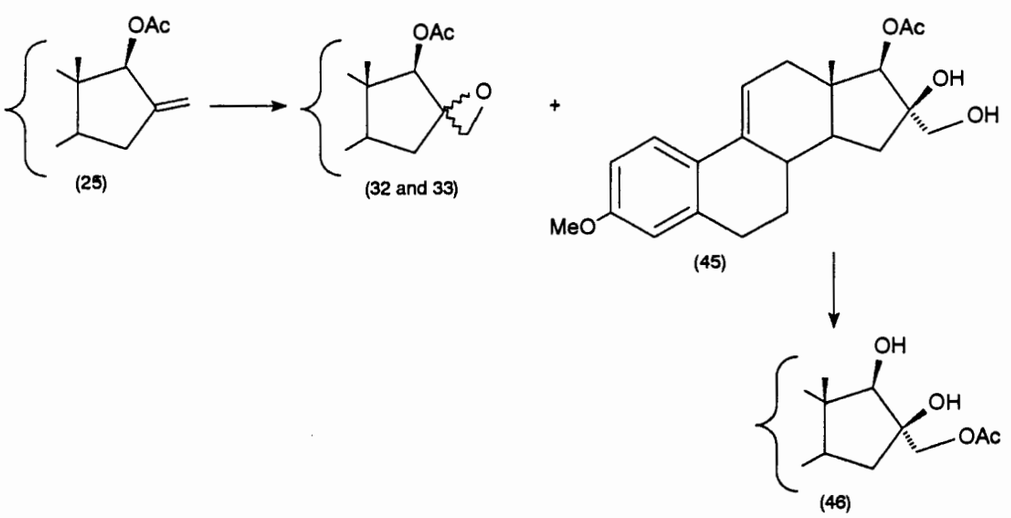
This preference for insertion into tertiary benzylic C-H bonds supports our proposal that insertion occurred at C-9 in the steroid skeleton. Insertion into a tertiary C-H bond was also reported by Eaton *et al.*,[65] who found that treatment of the head to head dimer of norbornadiene (binor-s) with dimethyldioxirane gave the 1-ol (scheme 39). Further exposure to dimethyldioxirane formed the symmetrical 1,9-diol.

Scheme 39



Treatment of the 17ß-acetoxy 16-methylene compound (**25**) with dimethyldioxirane over 2 days at 25°C gave a similarly complex mixture comprising of starting material (**25**) (22%), a mixture of epoxides (**32** and **33**) (30%) and an impure compound (**45**) (28%), together with minor products (scheme 40).

Scheme 40



Again the yields of the products depended on length of reaction and amount of dioxirane. Interestingly, the ratio of S:R-epoxides obtained was 9:1 which was the reverse of that obtained with *m*-chloroperbenzoic acid.

Attempts at purification of the more polar compound (**45**) failed in our hands but is suspected to be impure 16ß-hydroxy-16α-hydroxymethyl-3-methoxyestra-1,3,5(10),9(11)-tetraen-17-yl acetate. This assignment is supported by a one-proton multiplet at 6,1 ppm, and a downfield shift of 1-H to 7,5 ppm. Evidence for hydroxyl functionality was given by a sharp band at 3 599 cm^{-1}. The absence of the methylene protons indicated that epoxidation had occurred with subsequent ring opening as the 16^1-protons occur as doublets (*J* 11,3 Hz) at 3,48 and 3,58 ppm. This is very similar to that found in the diol (**36**) (see table 2).

Table 2. Comparison of ^1H n.m.r. data of some ring D protons

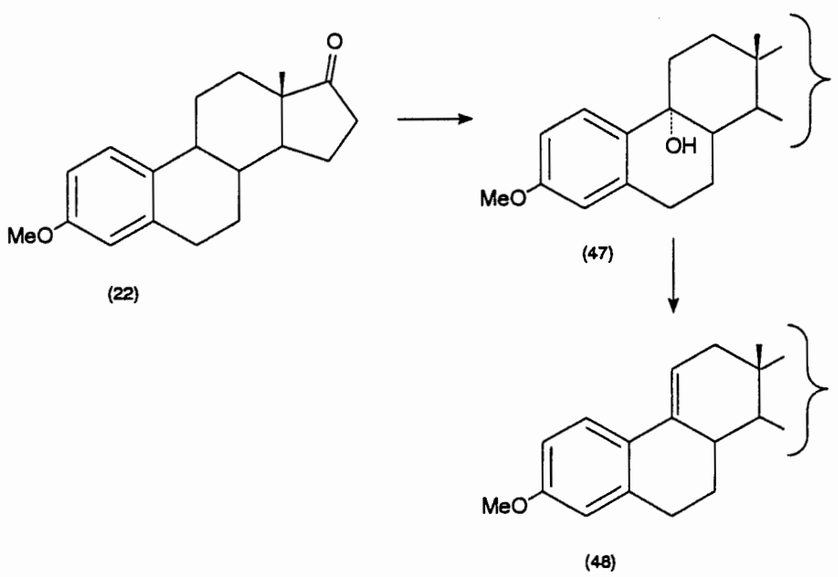
Signal	(**45**)	16ß-hydroxy 16α-hydroxymethyl compound (**36**)
16-CH_2 (ppm)	3,48 3,58	3,55 3,72
$J_{16^1,16^1}$	11,3 Hz	11,8 Hz
15α-H	dd	dd
(ppm)	2,5	2,13
$J_{15\alpha,15ß}$	13,4 Hz	13 Hz
$J_{15\alpha,14\alpha}$	7,2 Hz	5,8 Hz
15ß-H	t	t
(ppm)	1,71	1,82
$J_{15\alpha,15ß}$	13,4 Hz	13 Hz

We have found that the 15α- and 15ß-protons in compounds having a 16^1α-carbon sidechain or a 16ß-heteroatom, tend to be visible as distinct multiplets, whereas they are obscured in compounds having a 16^1ß-carbon sidechain. Accordingly, the stereochemical assignment of (**45**) is based on the presence of a triplet (*J* 13,4 Hz) at 1,71 ppm and a doublet of doublets (*J* 13,4 and 7,4 Hz) at 2,5 ppm. A molecular ion of 372 and a M^+-18 signal is consistent with the structural assignment.

The minor compound (**46**) found together with (**45**) is likely due to transacetylation occuring from the 17ß-position to the more favourable the 16^1-position (scheme 40). This is supported by an upfield shift of the 13ß-methyl to 0,8 ppm due to the presence of a 17ß-hydroxyl group. The 16^1-protons have shifted downfield to 4,1 ppm indicating the presence of a neighbouring acetoxy group. Transacetylation from the 17ß-position to the 16^1-position has been previously reported.[59]

In order to verify that oxygen insertion at the 9α-H does occur, model studies were undertaken using estrone methyl ether (**22**) as substrate. It was found that a complex reaction mixture occurred if large excesses of dioxirane were used. Hence estrone methyl ether (**22**) was treated with 0,3 equiv of dimethyldioxirane in small portions over 2 days to give a single product (**47**) (20%) and starting material (**22**) (77%). This compound could not be obtained analytically pure in our hands, but evidence from proton n.m.r. and mass spectra suggests that the product is 9α-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (**47**) together with 3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (**48**) (scheme 41).

Scheme 41



The mass spectrum showed a molecular ion of 300 and a signal at M^+-18. The proton n.m.r. spectrum corresponded well with literature values for these compounds (table 3).

Table 3. Comparison of ^{1}H n.m.r. data of the mixture with reported values.

Signals of mixture (ppm)	9α-hydroxy compound (**47**)*	9(11)-ene compound (**48**)**
0,90 (s)	0,90 (s)	-
0,92 (s)	-	0,94 (s)
6,13 (m)	-	6,13 (m)
6,6 (d) *J* 2,7 Hz	-	6,61 (d) *J* 2,6 Hz
6,65 (d) *J* 2,7 Hz	6,66 (d) *J* 2,5 Hz	-
6,71 (dd)	-	6,72 (dd)
J 8,9 and 2,7 Hz	-	*J* 8,8 and 2,9 Hz
6,75 (dd)	6,76 (dd)	-
J 8,8 and 2,7 Hz	*J* 8,9 and 2,5 Hz	-
7,45 (d) *J* 8,8 Hz	7,45 (d) *J* 8,9 Hz	-
7,52 (d) *J* 8,9 Hz	-	7,52 (d) *J* 8,8 Hz

* lit.,[66] (270 MHz) 9α-*hydroxy*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one*

** lit.,[66] (270 MHz) 3-*methoxyestra*-1,3,5(10),9(11)-*tetraen*-17-*one*

On treating the mixture with toluene-*p*-sulphonic acid in dry tetrahydrofuran at 25°C for 1 h, the pure dehydrated product (**48**) was obtained (77%) which was identical to an authentic sample synthesised using the method by Collins and Sjövall.[67] Thus estrone was treated with 2,3-dichloro-5,6-dicyanobenzoquinone in dry methanol for 1 h at 25°C to give 3-hydroxyestra-1,3,5(10),9(11)-tetraen-17-one (**49**) which was then treated with dimethyl sulphate under alkaline conditions to give the tetraene (**48**) (88%).

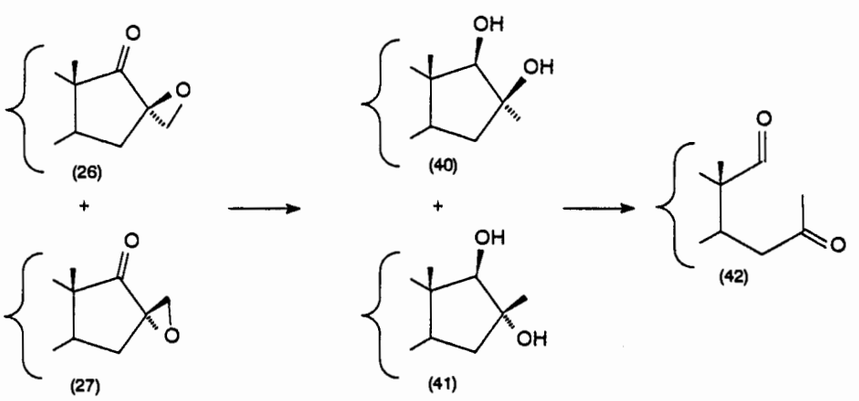
2.3 Synthesis of D-homo steroid analogues

2.3.1 Formation of 3-methoxy-16-methyl-16-oxo-16,17-secoestra-1,3,5(10)-trien-17-al (42)

The reduction of the epoxy ketones (**26** and **27**) and the cleavage of the 16α-methyl-16ß,17ß-diol (**40**) to give 3-methoxy-16-methyl-16-oxo-16,17-secoestra-1,3,5(10)-trien-17-al (**42**) previously discussed in section 2.2.5, provided a useful starting point for the synthesis of D-homo steroids. As only the 16ß,17ß-diol (**40**) underwent oxidative cleavage with sodium periodate, alternative reagents and routes were investigated.

Reduction of the mixture of epoxy ketones (**26** and **27**) obtained from epoxidation of the methylene ketone (**23**), rather than treating each epoxide individually, was the preferred method as the isomeric diols (**40** and **41**) were easily separable by flash chromatography, whereas repeated chromatography was necessary to separate the epoxy ketones, which would make this route lengthy and more expensive. Thus the mixture of epoxy ketones (**26** and **27**) was treated with lithium aluminium hydride for 5 h at 25°C to give the 16ß,17ß-diol (**40**) (35%) and the 16α,17ß-diol (**41**) (53%) (scheme 42).

Scheme 42



As discussed previously, the 16ß,17ß-diol (**40**) was easily cleaved with sodium periodate, whereas the 16α,17ß-diol (**41**) did not react due to the inability to form the cyclic intermediate. Although lead tetraacetate can cleave *cis*-diols through a similar cyclic intermediate,[49] its ability to cleave many *trans*-axial diols has led to a different mechanism being suggested for these cases (*fig.* 9).

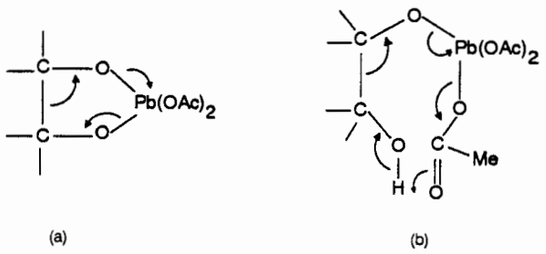


Fig. 9. The two different transition states for cleavage of (a) *cis*-glycols and (b) *trans*-glycols.

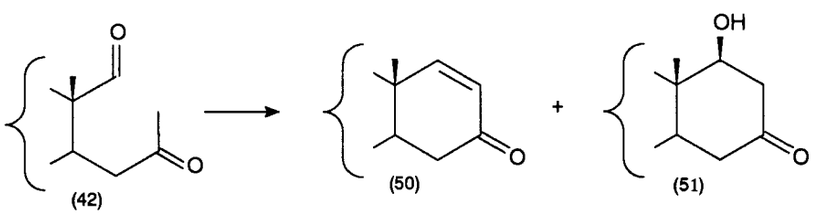
Thus the 16α,17ß-diol (**41**) was treated with lead tetraacetate in dry benzene for 1 h at 25°C to give the cleavage product (**42**) in moderate yields (55-62%). Cleavage occurred within 40 min upon treating the 16ß,17ß-diol (**40**) under the same conditions and gave excellent yields. (95%). As the stereochemistry would be destroyed during cleavage, and in order to reduce chromatography to a minimum, cleavage of the mixture of diols (**38** and **39**) was attempted using lead tetraacetate, but only moderate yields of 55-65% could be obtained.

The overall yield was improved by the addition of an extra step in the sequence. Thus, reduction of the methylene ketone (**23**) to the methylene alcohol (**24**), followed by Sharpless epoxidation using *t*-butyl hydroperoxide and vanadyl acetylacetonate gave the (16*R*)-epoxy alcohol (**29**). Further reduction with lithium aluminium hydride followed by treatment with sodium periodate or lead tetraacetate gave the cleavage product (**42**) in 67-80% yield, compared with 32-50% obtained when either or both epoxy ketones are used.

2.3.2 Condensation of 3-methoxy-16-methyl-16-oxo-16,17-secoestra-1,3,5(10)-trien-17-al (42)

Condensation of the cleavage product (**42**) was first attempted with 2% methanolic sodium hydroxide at 25°C for 15 min to give 3-methoxy-17a-homoestra-1,3,5(10),17-tetraen-16-one (**50**) (35%) and 17aß-hydroxy-3-methoxy-17a-homoestra-1,3,5(10)-trien-16-one (**51**) (50%) (scheme 43).

Scheme 43



Spectroscopic data were consistent for that expected in each compound. The proton n.m.r. of the α,ß-unsaturated ketone (**50**) showed two doublets (*J* 9,8 Hz) at 5,9 and 6,8 ppm assigned to 17-H and 17a-H respectively. The signal for 15α-H appeared as a doublet of doublets at 2,8 ppm with a large geminal coupling of 17,5 Hz and smaller J_{ae} of 3,7 Hz due to coupling with the axial 14α-H. The 15ß-proton also appeared as a doublet of doublets at 2,2 ppm due to the geminal coupling with the 15α-H (*J* 17,5 Hz) and the *trans*-diaxial coupling with the 14α-H (*J* 14 Hz). The geminal coupling is large as the 15ß-proton lies approximately in the plane of the carbonyl double bond.

The stereochemistry assigned to the 17aß-hydroxy 16-ketone (**51**) is based on the 17aα-proton signal (dd, *J* 11,4 and 5,6 Hz) at 3,58 ppm. This large coupling constant suggests an antiperiplanar relationship with the 17ß-proton (*fig.* 10).

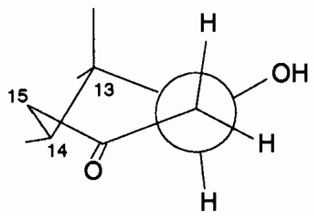


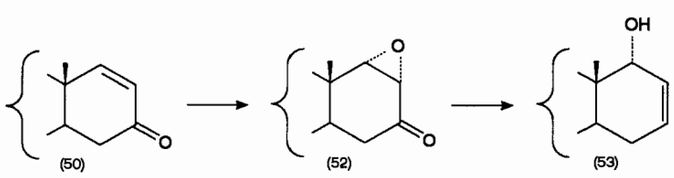
Fig. 10 Newman projection along the C(17)-C(17a) bond showing relative positions of the 17a- and 17-protons.

Treatment of the cleavage product (**42**) with potassium *t*-butoxide at 20°C for 20 min gave an improved yield of the α,ß-unsaturated ketone (**50**) (62%) and a mixture of the 17a-hydroxy 16-ketone (**51**) and an unidentified compound (38%). It was found that refluxing the cleavage product (**42**) in tetrahydrofuran with potassium *t*-butoxide for 1 h, gave the α,ß-unsaturated ketone (**50**) in 88% yield.

2.3.3 Epoxidation of 3-methoxy-17a-homoestra-1,3,5(10),17-tetraen-16-one (50) and Wharton rearrangement.

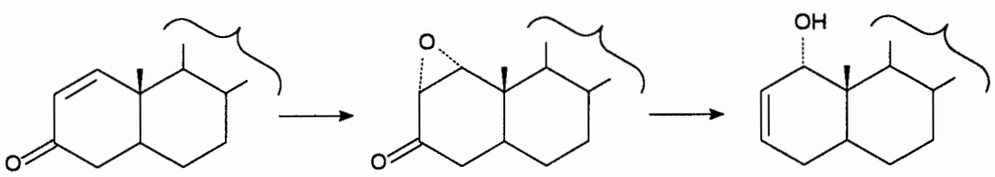
Addition of hydrogen peroxide to the α,ß-unsaturated ketone (**50**) in a 1:1 mixture of tetrahydrofuran and *t*-butyl alcohol under alkaline conditions, over 3 h at 25°C gave 3-methoxy-17α,17aα-epoxy-17a-homoestra-1,3,5(10)-trien-16-one (**52**) (88%) (scheme 44).

Scheme 44



The stereochemical assignment of the epoxide ring is tentative. The ß-face is sterically crowded near the terminus of the α,ß-unsaturated system by the 13ß-methyl, hence epoxidation is likely to occur at the α-face. Similar α-face epoxidation was reported in cholest-1-en-3-one[69] (scheme 45).

Scheme 45



Wharton rearrangement[68] of the epoxy ketone (**52**) was achieved with hydrazine hydrate and acetic acid in *t*-butyl alcohol at 20°C for 10 min to give the Δ^{16} 17a-ol (**53**) (scheme 44). Only moderate yields were obtained (40%) and reaction conditions need to be further optimised. A similar rearrangement[69] obtained by refluxing 1α,2α-oxidocholestan-3-one in hydrazine gave the Δ^{2}-cholesten-1α-ol in 57% yield (scheme 45).

Spectroscopic data for the Δ^{16} 17a-ol (**53**) were consistent for the assigned structure. The stereochemistry of the 17aα-hydroxyl group was deduced from its starting material as it could not be unambiguously assigned from the proton n.m.r. as both the 16- and 17-protons appeared as a multiplet at 5,87 ppm. The 17aß-proton appeared as a broad multiplet after D_2O exchange.

2.4 Attempted routes to 16-functionalised Δ^{15} 17-ketones

The products obtained from epoxidation and *cis*-hydroxylation were used to explore routes to 16-functionalised Δ^{15} 17-ketones, which could then be converted to the 17ß-acetoxy 14,16-dienes for cycloaddition studies.

2.4.1 Attempted dehydration of 16ß-acetoxymethyl-16α-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (38)

The first route investigated was the attempted dehydration of the 16ß-acetoxymethyl 16α-hydroxy 17-ketone (**38**). Thus treatment of (**38**) with freshly distilled thionyl chloride in dry pyridine at -10°C for 1,5 h gave an unidentified inseparable 1:1 isomeric mixture (2%) and starting material (95%). Proton n.m.r. of the isomeric mixture showed doubling of signals for the acetoxy group, 13ß-methyl, and the 16^1-protons. The lack of an olefinic signal indicated that no dehydration had occurred. Increasing the proportion of pyridine and varying the temperature did not result in increased yields.

No dehydration occurred on treatment of the 16ß-acetoxy methyl 16α-hydroxy 17-ketone (**38**) with ferric chloride on silica gel for 5 h at 25°C using the method of Keinan and Mazur.[70]

As the Δ^{15} 17-ketone was not obtained, this route was discarded.

2.4.2 . Attempted base- and acid-mediated rearrangements of epoxy ketone (27) and epoxy alcohol (29)

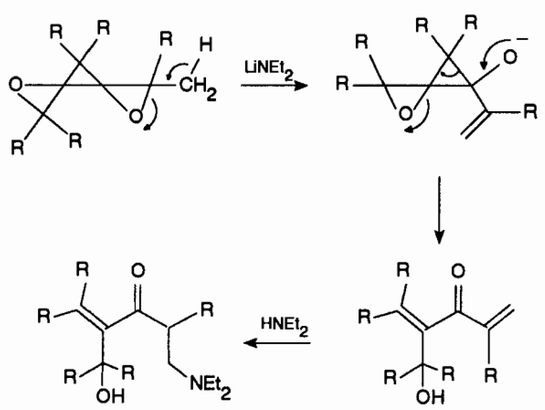
Base mediated rearrangement of an epoxide into an allylic alcohol has been well documented,[71-75] although few examples exist for spiro-epoxides or epoxides next to a functional group, due to an increased likelihood of competing side reactions resulting

from nucleophilic attack by the base and the anticipated reactivity of the functional group under these reaction conditions.

The formation of allylic alcohols with lithium amide bases in relatively non-polar solvents appears to proceed predominantly by a ß-elimination pathway. Thus, in the epoxy ketone (**27**), only the 15-protons should eliminate to form the 16-hydroxymethyl Δ^{15} 17-ketone. As lithium diethylamide is regarded as the reagent of choice[74] for promoting ß-eliminations, the epoxy ketone (**27**) was treated with lithium diethylamide at -10°C for 4 h. As no reaction occurred, the reaction was allowed to warm up to room temperature and stirred for a further 12 h, but this resulted in a complex reaction mixture, from which only a minor unidentified product (**54**) (2%) was isolated. The proton n.m.r. spectrum of (**54**) showed an addition of a CH_2CH_3 group attached to a heteroatom, suggesting that the epoxide had undergone nucleophilic attack by the base. A suitable microanalysis was not obtained due to insufficient material. Two broad singlets, each integrating for one proton, at 6,4 and 7,2 ppm in the proton n.m.r. and a band at 1 647 cm^{-1} in the infrared spectrum indicate that unsaturation has occurred.

Michael addition by diethylamine has been reported[76] on treatment of a diepoxide with lithium diethylamide (scheme 46).

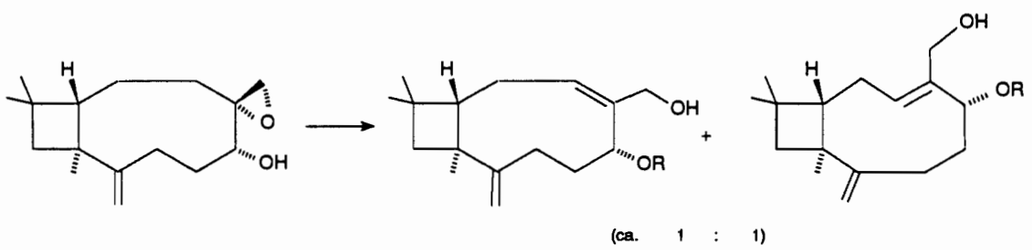
Scheme 46



In order to decrease the possibility of nucleophilic attack, reactions with different bases such as lithium diisopropylamide and a mixture of lithium diisopropylamide and potassium *t*-butoxide[77] were attempted, but only complex reaction mixtures were obtained.

Hoffmann and Vogt[78] reported the successful isomerisation of a spiro-oxirane α to a hydroxyl group in an eight-membered ring, to an allylic alcohol using lithium diisopropylamide in 66% yield (scheme 47).

Scheme 47



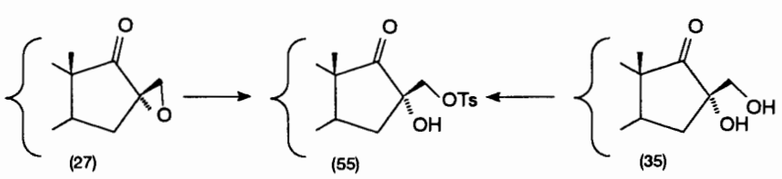
However, treatment of the epoxy alcohol (**29**) with lithium diisopropylamide at 20°C for 12 h gave a complex reaction mixture, and therefore this method was abandoned.

Lewis acid treatment of epoxy ketones is known to result in rearrangements. An exploratory reaction treating the epoxy ketone (**27**) with boron trifluoride-etherate gave five major products together with some minor products, thus the reaction was not investigated further.

Treating the epoxy ketone (**27**) with toluene-*p*-sulphonic acid gave a single product (**55**) in quantitative yield. Spectroscopic data suggested that the product was 16α-hydroxy-3-methoxy-16ß-tosyloxymethylestra-1,3,5(10)-trien-17-one formed by protonation of

the epoxide followed by nucleophilic attack of the tosyloxy group. Purification using either silica gel or alumina could not be used, as the product reverted back to the epoxide (**27**). An authentic sample was prepared by treating 16α-hydroxy-16ß-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17-one (**35**) with toluene-*p*-sulphonyl chloride for 5 days at 4°C, which was identical by n.m.r. to that formed by acid treatment of the epoxy ketone (scheme 48).

Scheme 48



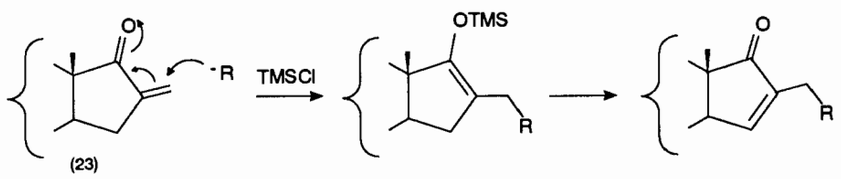
Nucleophilic addition of toluene-*p*-sulphonic acid to epoxides is known to occur and was first reported by Criegee and Stanger.[79] To our knowledge, no examples of this reaction with spiro-oxiranes have been reported.

As the desired Δ^{15} 17-ketone could not be synthesised by the foregoing methods, the methylene ketone (**23**) was then used to explore other routes.

2.4.3 Attempted enolation of a 16-functionalised 17-ketone and dehydrosilylation to the Δ^{15} 17-ketone.

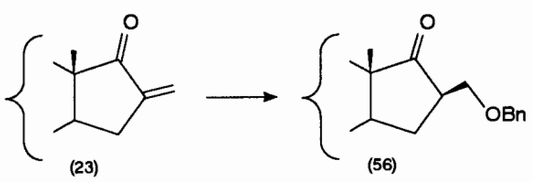
An alternative approach to the desired objective was based upon the evident ease of Michael addition of alcoholates to the 16-methylene 17-ketone (**23**). It was expected that the derived 16-alkoxymethyl 17-ketone could be converted into the corresponding silyl enol ether for dehydrosilylation[80] to a 16-alkoxymethyl Δ^{15} 17-ketone. Conceivably, the first two steps could be combined in a Michael addition-trapping sequence (scheme 49).

Scheme 49



The benzyloxy anion was chosen as the nucleophile, as the benzyl group could be removed later by hydrogenolysis under neutral conditions. Accordingly, the methylene ketone (**23**) was treated with a mixture of sodium hydride and benzyl alcohol at 0°C and then stirred for 2 h at 20°C to give 16ß-benzyloxy-3-methoxyestra-1,3,5(10)-trien-17-one (**56**) (76%) and starting material (**23**) (11%) (scheme 50).

Scheme 50

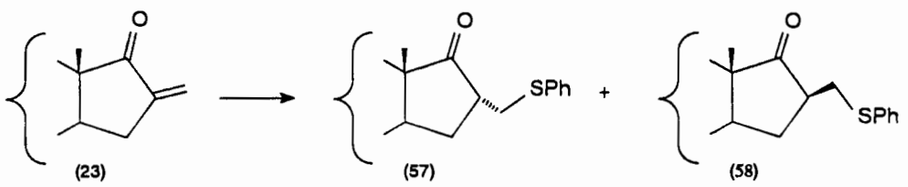


Spectroscopic data were consistent with that expected for the compound (**56**). The stereochemical assignment at the 16-position was tentative and is based on the absence of a distinct 15α-H signal in the proton n.m.r. The 16ß-benzyloxy compound (**56**) was then treated with sodium hydride in benzene for 1 h at 20°C, followed by quenching with trimethylsilyl chloride. Partial elimination occurred to give the methylene ketone (**23**) (40%) and starting material (**56**) (30%), together with more polar products. No silylated intermediate was formed.

Thiophenol was then chosen as the nucleophile. Accordingly, the methylene ketone (**23**) was treated with thiophenol and tetrabutylammonium fluoride using the method of Kuwajima[81] which gave a 1:1 isomeric mixture of 3-methoxy-16α-

phenylthiomethylestra-1,3,5(10)-trien-17-one (**57**) and 3-methoxy-16ß-phenylthiomethylestra-1,3,5(10)-trien-17-one (**58**) (98%) which could only be separated by repeated chromatography (scheme 51). Stereochemical assignment was based on the 15α-H doublet of doublets (*J* 12,6 and 5,3 Hz) at 2,08 ppm found in compound (**57**), which was absent in compound (**58**).

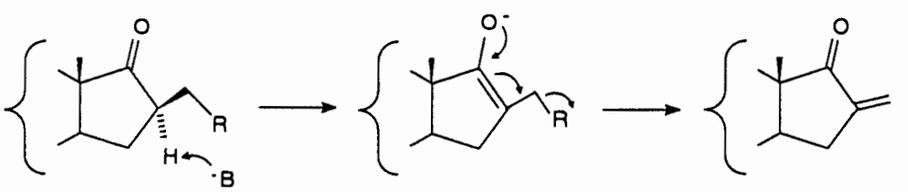
Scheme 51



Treatment of the 16ß-phenylthiomethyl 17-ketone (**58**) with lithium diisopropylamide in tetrahydrofuran for 1 h at 25°C, followed by quenching with trimethylsilyl chloride, again resulted in partial elimination to give the methylene ketone (**23**) (20%) and starting material (**58**) (20%).

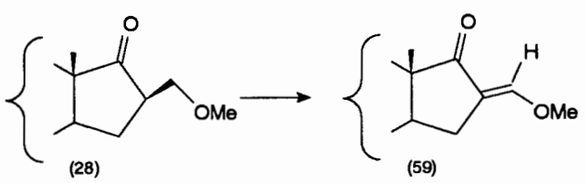
The failure to trap the enolate intermediate in the foregoing reactions suggests that silylation is slow, owing possibly to steric hindrance, thus allowing competing ß-elimination to interfere (scheme 52).

Scheme 52



As a comparison, the 16ß-methoxymethyl 17-ketone (**28**) was treated with lithium diisopropylamide for 80 min at 20°C, and quenched with trimethylsilyl chloride to give a single product. This was then treated with palladium acetate[80] in acetonitrile and refluxed for 22 h to give starting material (**28**) (48%) and 3-methoxy-16-methoxymethylene-estra-1,3,5(10)-trien-17-one (**59**) (40%) (scheme 53).

Scheme 53



Evidence for this structure (**59**) is given by a downfield shift of the 16^1-methoxy group to 3,84 ppm suggesting a vinylic position. The 16^1-proton signal appeared as a 1H doublet of doublets (*J* 2,57 and 1,6 Hz) at 7,2 ppm, coupled with the 15α-H signal found at 2,66 ppm (ddd, *J* 14,9, 6,2 and 1,6 Hz).

Further work will be necessary to find conditions for efficient enolate trapping of the Michael addition products reported here, and to verify the apparent dehydrosilylation toward the 16^1- rather than the 15-position.

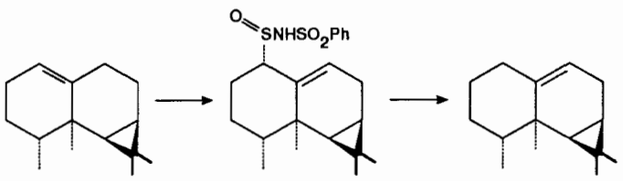
2.4.4 Attempted direct isomerisation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one (23) using sulphinyl benzenesulphonamide.

The 16-methyl Δ^{15} 17-ketone has been previously synthesised by a four step procedure,[15] namely methylenation, catalytic hydrogenation, bromination and dehydrobromination. A more elegant method involving only two steps would be methylenation followed by direct isomerisation of the exocyclic double bond. Such

isomerisation has been reported[82] for 2-methylenecyclopentanone using rhodium trichloride as catalyst. However, attempts to isomerise the 16-methylene 17-ketone (**23**) with rhodium trichloride using a ratio of 2:1 of substrate to catalyst,[83] have resulted in low yields (30%) of the desired product.

Recent reports[84-87] show that a two step isomerisation based on an ene reaction with sulphinyl benzenesulphonamide followed by catalytic desulphuration has been successfully used in a variety of compounds (scheme 54).

Scheme 54



Thus, sulphinyl benzenesulphonamide was prepared by refluxing a solution of benzene sulphonamide in benzene with thionyl chloride for five days according to a prescribed method.[88] Treatment of the methylene ketone (**23**) with the reagent using temperatures ranging from 0°C to 80°C (refluxing benzene) failed to give any of the desired ene adducts. Similar treatment of the 17ß-acetoxy 16-methylene compound also only gave starting material.

Sharpless[89] has reported that the ene reaction with N-sulphinylsulphonamides are reversible under mild conditions. Standing in moist air at room temperature was found to cause decomposition of the adduct. In our case, strict measures were taken to ensure the exclusion of water, hence it is concluded that the isomerisation is not favourable. MM2 calculations show that the energy states of the two isomers are very similar, although the 16–methyl Δ^{15} 17-ketone isomer is more stable with a total energy of

194 kJ.mol^{-1} and a heat of formation of 251 kJ.mol^{-1}, compared to a total energy of 200 kJ.mol^{-1} and a heat of formation of 260 kJ.mol^{-1} for the 16-methylene ketone (**23**).[90]

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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. 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 deuterio-chloroform unless otherwise stated. Mass spectra were recorded on a VG micromass 16F mass spectrometer at 70 eV, and an ion source temperature of between 160-220°C. Optical rotations were determined in chloroform 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), together with spraying with a solution of ammonium ceric sulphate, followed by heating the plate at 150°C for 5-10 min.

Column chromatography was carried out using silica gel (Merck Kieselgel 60, 70-230 mesh, or with Merck Kieselgel 60, 230-400 mesh, when flash chromatography was performed). 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 indicator.

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

Dichloromethane: Distilled from phosphorus pentoxide.

Benzene: Initial fraction from distillation discarded and then dried over sodium and distilled from sodium.

3-*Methoxy*-16-*methylene-estra*-1,3,5(10)-*trien*-17-*one* (**23**)

A solution of acetyl chloride (2,5 ml; 35,2 mmol) in dry ether (35 ml) was added dropwise to stirred N,N,N',N'-tetramethyldiaminomethane (45 ml) at 0°C. After 30 min, the white precipitate which formed was rapidly filtered off and suspended in dry acetonitrile (45 ml). Estrone 3-methyl ether (**22**) (5 g; 17,6 mmol) was added and the reaction mixture was stirred at 80°C for 20 h. The solvent was removed under reduced pressure and the residue was made alkaline with aqueous 2M-sodium hydroxide. The mixture was extracted with ether (2 x 75 ml) and the extract was dried (Na_2SO_4) and concentrated to give a yellow oil (5,94 g), which was dissolved in acetic anhydride (35 ml) and stirred at 140°C for 2 h. Saturated aqueous sodium hydrogen carbonate was added carefully to the cooled mixture, which was stirred for a further 0,5 h, then extracted with chloroform (3 x 80 ml), dried ($MgSO_4$) and evaporated to yield a yellow semi-crystalline product (5,1 g; 98%). The product was recrystallised twice from benzene to yield the methylene ketone (**23**), m.p. 122-124°C; $[\alpha]_D$ +114° (*c* 1,1) (lit.,[22] 120-122°C; lit.,[19] $[\alpha]_D$ +113°); ν_{max} 1722 and 1638 cm^{-1}; δ_H 0,93 (3H, s, 13ß-Me), 2,68 (1H, ddt, *J* 15,5, 6,1, and 1,4 Hz, 15α-H), 2,90 (2H, m, 6-H_2), 3,78 (3H, s, 3-OMe), 5,42 and 6,1 (each 1H, dt, *J* 2,8 and 2 x 1,4 Hz, 16-CH_2), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H) (Found: C, 80,8; H, 8,1%; M^+, 296. $C_{20}H_{24}O_2$ requires C, 81,0; H, 8,2%; *M*, 296).

3-*Methoxy*-16-*methylene-estra*-1,3,5(10)-*trien*-17ß-*ol* (**24**)

Lithium aluminium hydride (0,58 g; 15,26 mmol) was added in small portions with stirring to the ketone (**23**) (0,9 g; 3 mmol) in dry tetrahydrofuran (25 ml) at 0°C under nitrogen. After 1,5 h at 0°C, saturated aqueous ammonium chloride was added, and the mixture was extracted with chloroform (3 x 20 ml). The extract was washed with brine, dried (Na_2SO_4), and evaporated to give a crystalline residue (0,87 g; 96%) which was recrystallised twice from chloroform-hexane to give the 16-methylene 17ß-alcohol (**24**), m.p. 132-135°C; $[\alpha]_D$ -11° (*c* 1,0) (lit.,[91] m.p. 132-135°C; $[\alpha]_D$ -12°); δ_H 0,71 (3H, s, 13ß-Me), 2,86 (2H, m, 6-H_2), 3,78 (3H, s, 3-OMe), 3,98 (1H, br. d, *J ca* 6 Hz → br. s

$W_{1/2}$ 10 Hz on D_2O exch., 17α-H), 5,07 and 5,18 (each 1H, q, *J* 3 x 2,2 Hz, 16-CH_2), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H) (Found: C, 80,2; H, 8,5%; M^+, 298. $C_{20}H_{26}O_2$ requires C, 80,5; H, 8,8%; *M*, 298).

3-*Methoxy*-16-*methylene-estra*-1,3,5(10)-*trien*-17ß-*yl acetate* (**25**)

The alcohol (**24**) (1,6 g; 5 mmol) was treated with acetic anhydride (4 ml) in dry pyridine (50ml) at 20°C for 19 h. Water (20 ml) was added and the mixture was treated carefully with saturated aqueous sodium hydrogen carbonate. The resultant precipitate was filtered and washed with water to yield the 17ß-acetate (**25**) (1,72 g, 94%), m.p. 123-126°C (from aqueous methanol); $[\alpha]_D$ -26° (*c* 1,0) (lit.,[91] m.p. 124-127°C; $[\alpha]_D$ -27°); δ_H 0,78 (3H, s, 13ß-Me), 2,15 (3H, s, OAc), 2,83 (2H, m, 6-H_2), 3,77 (3H, s, 3-OMe), 4,94 and 5,05 (each 1H, q, *J* 3 x 2,3 Hz, 16-CH_2), 5,26 (1H, br. q, *J* 3 x 2,3 Hz, 17α-H), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H) (Found: C, 77,3; H, 8,3%; M^+, 340. $C_{22}H_{28}O_3$ requires C, 77,6; H, 8,3%; *M*, 340).

Epoxidation of 3-*methoxy*-16-*methylene-estra*-1,3,5(10)-*trien*-17-*one* (**23**)

a) Aqueous 4M-sodium hydroxide was added dropwise to the methylene ketone (**23**) (100 mg; 0,33 mmol) in dioxane (20 ml) at 0°C followed by the dropwise addition of hydrogen peroxide (0,5 ml, 30%). The heterogeneous mixture was allowed to warm up to 20°C and was stirred for 45 h. Water was added and the mixture was extracted with ethyl acetate (3 x 15 ml). The extract was dried (Na_2SO_4), and concentrated to give a product (82 mg) which was adsorbed on silica gel (9 g). Elution with ethyl acetate-toluene (1:49) gave (16R)-*spiro*[3-*methoxyestra*-1,3,5,(10)-*trien*-17-*one*-16,2'-*oxirane*] (**26**) (29 mg; 27%), m.p. 141-144°C (from dichloromethane-methanol) (lit.,[28] m.p. 142-143°C); $[\alpha]_D$ +140° (*c* 1,1); ν_{max} 1747 cm^{-1}; δ_H 1,07 (3H, s, 13ß-Me), 2,17 (1H, dd, *J* 12,7 and 5,9 Hz, 15α-H), 2,90 (2H, m, 6-H_2), 2,95 (1H, d, *J* 6,8 Hz, 16-CH), 3,20 (1H,

dd, *J* 6,8 and 0,7 Hz, 16-CH), 3,79 (3H, s, 3-OMe), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H); δ_C 14,0 (C-18), 25,6 (C-11)*, 26,7 (C-12)*, 27,5 (C-7), 29,4 (C-6), 31,6 (C-15), 37,6 (C-8), 43,9 (C-9), 45,5 (C-14), 47,8 (C-13), 53,3 (C-16^1), 55,1 (3-OMe), 59,6 (C-16), 111,5 (C-2), 113,8 (C-4), 126,1 (C-1), 131,5 (C-10), 137,4 (C-5), 157,6 (C-3), and 215,3 (C-17) (Found: C, 76,9; H, 7,8%; M^+, 312. $C_{20}H_{24}O_3$ requires C, 76,9; H, 7,7%; *M*, 312). Further elution yielded the (16S)-*spiro*[3-*methoxyestra*-1,3,5(10)-*trien*-17-*one*-16,2'-*oxirane*] (**27**) (37 mg; 35%), m.p. 164-166°C (from methanol); $[\alpha]_D$ +150° (*c* 1,0) (lit.,[18] m.p. 169-173°C; $[\alpha]_D$ +161°); δ_H 1,06 (3H, s, 13ß-Me), 2,90 (2H, m, 6-H_2), 2,97 and 3,13 (each 1H, d, *J* 6,3 Hz, 16-CH_2), 3,78 (3H, s, 3-OMe), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H); δ_C 14,1 (C-18), 25,5 (C-11)*, 26,5 (C-12)*, 28,1 (C-7), 29,4 (C-6), 31,2 (C-15), 38,0 (C-8), 43,6 (C-9), 48,0 (C-14), 48,4 (C-13), 51,5 (C-16^1), 55,1 (3-OMe), 59,4 (C-16), 111,5 (C-2), 113,8 (C-4), 126,1 (C-1), 131,6 (C-10), 137,5 (C-5), 157,6 (C-3), and 215,4 (C-17) (Found: C, 76,6; H, 7,8%; M^+, 312. $C_{20}H_{24}O_3$ requires C, 76,9; H, 7,7%; *M*, 312).

b) Hydrogen peroxide (30%, 3 ml) was added dropwise over 10 min to a stirred mixture of methylene ketone (**23**) (155 mg, 0,49 mmol) and a 4M-sodium hydroxide (0,2 ml) in tetrahydrofuran (5 ml) and *t*-butyl alcohol (5 ml) at 0°C. After 1 h, more hydrogen peroxide (2 ml) was added and the mixture was stirred for another 2 h at 20°C. Saturated aqueous sodium sulphite was slowly added to the cooled mixture, followed by saturated aqueous ammonium chloride. The mixture was extracted with chloroform (4 x 20 ml) and the extract was washed with brine, dried ($MgSO_4$), and concentrated to give an oil (145 mg, 89%). Flash chromatography of the oil on silica gel (8 g) with ethyl acetate-toluene

* Denotes that assignment is uncertain.

(1:49) as eluent yielded a mixture of the epoxy ketones (**26**) and (**27**) (140 mg, 86%).

c) Hydrogen peroxide (30%, 10 ml) was added dropwise over 30 min to a stirred solution of the ketone (**23**) (1 g; 3,38 mmol) in tetrahydrofuran (25 ml), methanol (20 ml) and aqueous 4M-sodium hydroxide (0,4 ml) at 0°C. After 1,5 h, water was added and the mixture was extracted with ethyl acetate (3 x 30 ml). The organic phase was washed successively with aqueous ferrous sulphate, water, and brine, dried ($MgSO_4$), and concentrated to give a residue (0,778 g), which was chromatographed on silica gel (80 g) and eluted with ethyl acetate-hexane (15:85), to yield 3-*methoxy*-16ß-*methoxymethylestra*-1,3,5(10)-*trien*-17-one (**28**) (0,29 g), m.p. 124-128°C (from chloroform-methanol); $[\alpha]_D$ +102° (*c* 0,9); δ_H 0,94 (3H, s, 13ß-Me), 2,74 (1H, dddd, *J* 9,4, 2 x 5,4, and 1,7 Hz, 16α-H), 3,33 (3H, s, 16^1-OMe), 3,54 - 3,6 (2H, m, 16-CH_2), 3,78 (3H, s, 3-OMe), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H) (Found: C, 76,9; H, 8,7%; M^+, 328. $C_{21}H_{28}O_3$ requires C, 76,8; H, 8,6%; *M*, 328). Further elution with ethyl acetate-hexane (20:80) yielded mixed fractions (0,34 g), followed by the (16*S*)-epoxy ketone (**27**) (84 mg) m.p.165-168°C (from methanol).

3-*Methoxy*-16*β*-*methoxymethylestra*-1,3,5(10)-*trien*-17-*one* (**28**)

A mixture of methanolic sodium methoxide (0,4M; 10 ml) and the methylene ketone (**23**) (23 mg; 0,08 mmol) in tetrahydrofuran (1 ml) was stirred at 20°C for 3 h. Saturated aqueous ammonium chloride was added, and the mixture was extracted with chloroform (3 x 10 ml). The extract was washed with brine, dried ($MgSO_4$), and concentrated to give an oil (50 mg) which was chromatographed on silica gel (2 g) with ethyl acetate-toluene (1:49) to give starting material (5 mg; 20%) followed by the 16ß-methoxymethyl ketone (**28**) (16,2 mg; 65%), m.p. 124-127°C.

Epoxidation of 3-*methoxy*-16-*methylene-estra*-1,3,5(10)-*trien*-17ß-*ol* (**24**)

a) *m*-Chloroperbenzoic acid (75%) (204 mg; 0,89 mmol) in dry dichloromethane (6 ml) was added dropwise to a stirred mixture of the methylene alcohol (**24**) (200 mg; 0,67 mmol) and sodium hydrogen carbonate (25 mg) in dry dichoromethane (6 ml) at -10°C. Two further portions of *m*-chloroperbenzoic acid (50 mg) were added at 30 min intervals, and after 2h saturated aqueous sodium hydrogen carbonate was added. The mixture was extracted with dichloromethane (3 x 10 ml), and the extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield a clear oil. Flash chromatography on silica gel (12 g) with ethyl acetate-toluene (1:9) gave (16R)-*spiro*[3-*methoxyestra*-1,3,5(10)-*trien*-17ß-*ol*-16,2'-*oxirane*] (**29**) (88 mg; 40%), m.p. 136-140°C (from chloroform-hexane); $[\alpha]_D$ +59° (*c* 1,0); ν_{max} 3523 cm^{-1}; δ_H 0,84 (3H, s, 13ß-Me), 2,08 (1H, d, *J* 9,3 Hz, exch. by D_2O, 17ß-OH), 2,15 (1H, dd, *J* 14,0 and 7,2 Hz, 15α-H), 2,78 and 2,92 (each 1H, d, *J* 4,8 Hz, 16-CH_2), 2,87 (2H, m, 6-H_2), 3,59 (1H, d, *J* 9,3 Hz → s on D_2O exch., 17α-H), 3,78 (3H, s, 3-OMe), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H) (Found: C, 76,4; H, 8,3%; M^+ 314. $C_{20}H_{26}O_3$ requires C, 76,4; H, 8,3%; *M*, 314). Further elution yielded (16*S*)-*spiro*[3-*methoxyestra*-1,3,5,(10)-*trien*-17ß-*ol*-16,2'-*oxirane*] (**30**) (31 mg; 14%), m.p. 145-162°C decomp. (from dichloromethane-hexane); $[\alpha]_D$ +32° (*c* 1,1); ν_{max} 3608 cm^{-1}; δ_H 0,90 (3H, s, 13ß-Me), 1,68 (1H, d, *J* 5,8 Hz, exch. by D_2O, 17ß-OH), 2,67 and 3,14 (each 1H, d, *J* 5,2 Hz, 16-CH_2), 2,87 (2H, m, 6-CH_2), 3,77 (3H, s, OMe), 3,82 (1H, d, *J* 5,8 Hz, → s on D_2O exch., 17α-H), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H); δ_C 12,2 (C-18), 25,9 (C-11), 27,3 (C-7), 29,6 (C-6), 30,8 (C-15), 36,5 (C-12), 38,1 (C-8), 43,8 (C-9), 43,9 (C-13), 46,8 (C-14), 50,3 (C-16[1]), 55,2 (3-OMe), 66,4 (C-16), 82,0 (C17), 111,5 (C-4), 113,8 (C-2), 126,1 (C-1), 132,3 (C-10), 137,7 (C-5), and 157,5 (C-3) (Found: C, 76,6; H 8,6%; M^+ 314. $C_{20}H_{26}O_3$ requires C, 76,4; H, 8,3%; *M*, 314).

b) *m*-Chloroperbenzoic acid (147 mg; 0,68 mmol) was added in two portions to the 17ß-hydroxy 16-methylene compound (**24**) (59 mg; 0,2 mmol) in dry tetrahydrofuran (5 ml) while stirring under nitrogen at 0°C. The reaction was allowed to warm to 20°C and after 16 h, saturated aqueous sodium sulphite and saturated aqueous sodium hydrogen carbonate were added. The mixture was extracted with chloroform (3 x 10 ml) and the extract was dried ($MgSO_4$), and concentrated to give a clear oil (67 mg). Flash chromatography on silica gel (3,5 g) using ethyl acetate-toluene (1:49) as eluent gave starting material (**24**) (1,3 mg; 2%) followed by the (16*R*)-epoxy 17ß-alcohol (**29**) (32,6 mg; 52%), m.p. 135-140°C (from dichloromethane-hexane). Further elution with ethyl acetate-toluene (1:9) gave the (16*S*)-epoxy 17ß-alcohol (**30**) (25,2 mg; 40%), m.p. 145-152°C.

c) *t*-Butyl hydroperoxide (0,1 ml; 80% solution) was added to a stirred solution of vanadyl acetylacetonate (5,5 mg; 0,02mmol) and the methylene alcohol (**24**) (49 mg, 0,16 mmol) in dry benzene (2 ml) at 25°C. Saturated aqueous sodium sulfite was added after 15 min, and the mixture was extracted with chloroform (3 x 15 ml). The organic phase was dried ($MgSO_4$), and concentrated to give a yellow oil (53 mg). Flash chromatography on silica gel (4 g) eluting with ethyl acetate-toluene (1: 20) gave epoxy alcohol (**29**) (44 mg; 85%), m.p. 135-140°C.

Acid catalysed rearrangement of (16S)-*spiro*[3-*methoxyestra*-1,3,5(10)-*trien*-17ß-*ol*-16,2'-*oxirane*] (**30**)

A mixture of epoxy alcohol (**30**) (31 mg; 0,01 mmol) and toluene-*p*-sulphonic acid (15 mg; 0,08 mmol) in tetrahydrofuran (3 ml) was stirred under nitrogen at 20°C for 1 h. Saturated aqueous sodium hydrogen carbonate was added and the mixture was extracted with chloroform (3 x 8 ml), and the extract was dried ($MgSO_4$), and concentrated to give an oil. Chromatography on silica gel (4 g) with ethyl acetate-toluene (1:5) as eluent gave 16ß-*hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one*

(**31**) (20 mg; 64%), m.p. 138-142°C (from dichloromethane-hexane); $[\alpha]_D$ +141° (*c* 1,0); ν_{max} 3 616, 1724 cm^{-1}; δ_H (C_6D_6) 0,68 (3H, s, 13ß-H), 2,72 (2H, m, 6-H_2), 3,42 (3H, s, 3-OMe), 3,48 (1H, dd, *J* 10,7 and 5,8 Hz; 16^1-H), 3,73 (1H, dd, *J* 10,7 and 5,0 Hz, 16^1-H), 6,70 (1H, d, *J* 2,7 Hz, 4-H), 6,78 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,09 (1H, d, *J* 8,5 Hz, 1-H); δ_C 13,6 (13ß-Me), 25,1 (C-11)*, 25,9 (C-15)*, 26,8 (C-7), 29,6 (C-6), 31,8 (C-12)*, 37,8 (C-8), 44,0 (C-9), 48,6 (C-13), 49,1 (C-14), 51,4 (C-16^1), 55,20 (3-OMe), 62,9 (C-16), 111,6 (C-2), 113,9 (C-4), 126,2 (C-1), 131,9 (C-10), 137,69 (C-5), 157,61 (C-3), and 222,7 (C-17) (Found: C, 75,9; H, 8,2%; M^+, 314. $C_{20}H_{26}O_3$ requires C, 76,4; H, 8,3%; *M* 314).

ß-Elimination of 16ß-*hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**31**)

The 16ß-hydroxymethyl ketone (**31**) (13 mg; 0,04 mmol) and dilute hydrochloric acid (0,2 ml) in tetrahydrofuran (1 ml) was refluxed for 22 h and then was allowed to cool. Saturated aqueous sodium hydrogen carbonate was added and the mixture was extracted with chloroform (3 x 5 ml). The extract was dried ($MgSO_4$), and concentrated to give a crystalline residue (10 mg; 82%). Recrystallisation from benzene gave the 16-methylene 17-ketone (**23**), m.p. 122-124°C, mixed m.p. 122-125°C.

Attempted Mitsunobu reaction of the 16-*methylene* 17ß-*alcohol* (**24**).

Triphenylphosphine (190 mg; 0,72 mmol) and diethylazodicarboxylate (0,11 ml) were added sequentially to a mixture of 16-methylene 17ß-alcohol (**24**) (86 mg; 0,29 mmol) and glacial acetic acid (0,08 ml; 1,45 mmol) in dry benzene (5 ml). The mixture was refluxed for 5 days under nitrogen, then saturated aqueous sodium hydrogen carbonate was added to the cooled solution, and the mixture was extracted with chloroform (3 x 15 ml). The extract was dried ($MgSO_4$), and concentrated to give an oil (444 mg) which was chromatographed on silica gel (20 g) eluting with toluene to give the 17ß-acetoxy 16-methylene compound (**25**) (44 mg; 45%), m.p. 124-127°C (from chloroform-methanol) (mixed m.p. 123-127°C), followed by starting material (34 mg; 40%).

Epoxidation of 3-*methoxy*-16-*methylene-estra*-1,3,5(10)-*trien*-17ß-*yl acetate* (**25**)

m-Chloroperbenzoic acid (335 mg; 1,9 mmol) was added in small portions over 3 days to the 17ß-acetoxy 16-methylene compound (**25**) (100 mg; 0,29 mmol) in tetrahydrofuran (8 ml) with stirring under N_2 at 20°C. Saturated aqueous sodium sulfite and saturated aqueous sodium hydrogen carbonate were added sequentially, and the mixture was extracted with chloroform (3 x 10 ml). The organic phase was dried ($MgSO_4$), and concentrated to give a crystalline residue (130 mg) which was chromatographed on silica gel (10 g). Elution with toluene gave starting material (1,5 mg; 2%). Further elution with ethyl acetate-toluene (1:49) gave (16S)-*spiro*[17ß-*acetoxy*-3-*methoxyestra*-1,3,5(10)-*triene*-16,2'-*oxirane*] (**33**) (15 mg; 14%) m.p. 160-168°C decomp. (from chloroform-hexane); $[\alpha]_D$ -32° (*c* 1,0); ν_{max} 1737 cm^{-1}; δ_H 0,91 (3H, s, 13ß-Me), 2,07 (3H, s, 17ß-OAc), 2,7 and 3,0 (each 1H, d, *J* 5,2Hz, 16-CH_2), 2,87 (2H, m, 6-H_2), 3,77 (3H, s, 3-OMe), 5,07 (1H, s, 17α-H), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H) (Found: C, 73,7; H, 7,9%; M^+, 356. $C_{22}H_{28}O_4$ requires C, 74,1; H, 7,9%; *M*, 356). Further elution gave (16R)-*spiro*[17ß-*acetoxy*-3-*methoxyestra*-1,3,5(10)-*triene*-16,2'-*oxirane*] (**32**) (63 mg; 60%), m.p. 134-140°C (from chloroform-hexane); $[\alpha]_D$ +42° (*c* 1,0); ν_{max} 1728 cm^{-1}; δ_H 1,01 (3H, s, 13ß-Me), 1,73 (1H, t, *J* 2 x 13,3 Hz, 15ß-H), 2,10 (1H, dd, *J* 13,3 and 7,1 Hz, 15α-H), 2,10 (3H, s, 17ß-OAc), 3,78 (3H, s, 3-OMe), 2,75 and 2,76 (each 1H, d, *J* 5,3 Hz, 16-CH_2), 2,88 (2H, m 6-H_2), 4,95 (1H, s, 17α-H), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H) (Found: C, 74,0; H, 7,8%; M^+, 356. $C_{22}H_{28}O_4$ requires C, 74,1; H, 7,9%; *M*, 356).

cis-Hydroxylation of 3-*methoxy*-16-*methylene-estra*-1,3,5(10)-*trien*-17-*one* (**23**)

Osmium tetroxide (250 mg; 0,98 mmol) was added to a solution of methylene ketone (**23**) (3,0 g; 10,15 mmol) and 4-methylmorpholine-4-oxide monohydrate (2,67 g; 19,68 mmol) in tetrahydrofuran (73 ml) and water (7,3 ml) under nitrogen, and the mixture was stirred at 20°C for 22 h. Water (4 ml) was added, followed by sodium disulphite (2 g). The reaction mixture was stirred for 45 min then extracted with ethyl

acetate (3 x 35 ml). The organic phase was washed with brine, dried ($MgSO_4$), and concentrated to yield plate-like crystals (3,3 g; 99%). The product appeared to be homogeneous (t.l.c.) but subsequent experiments revealed that it comprised a mixture (*ca* 6:1) of the isomers (**35**) and (**36**). Crystallisation of the total product from methanol afforded 16α-*hydroxy*-16ß-*hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**35**), m.p. 154-157°C; $[\alpha]_D$ +168° (*c* 1,1); ν_{max} 3545 and 1733 cm^{-1}; δ_H 0,99 (3H, s, 13ß-Me), 2,30 and 2,98 (each 1H, s, exch. by D_2O, 16α- and 16^1-OH), 2,90 (2H, m, 6-H_2), 3,7 (2H, d, *J* 4,3 Hz → s on D_2O exch., 16-CH_2), 3,78 (3H, s, 3-OMe), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H) (Found: C, 72,4; H, 8,1%; M^+, 330. $C_{20}H_{26}O_4$ requires C, 72,7; H, 7,9%; *M*, 330).

Acetylation of the hydroxylation product (**35**) *and* (**36**)

The total hydroxylation product (**35** + **36**) (3,3 g; 0,01 mol) (see previous experiment) was treated with acetic anhydride (5 ml) in dry pyridine (8 ml) at 20°C for 40 min. An excess of saturated aqueous sodium hydrogen carbonate was slowly added and the mixture was stirred for 30 min, then extracted with chloroform (3 x 35 ml). The extract was washed with brine, dried (Na_2SO_4), and the solvent removed under reduced pressure to give a crystalline residue. Chromatography of the crude product with ethyl acetate-toluene (1:19) yielded 16α-*acetoxy*-16ß-*acetoxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**37**) (178 mg; 4%), m.p. 107-109°C (from chloroform-methanol); $[\alpha]_D$ +132° (*c* 0,9); δ_H 0,99 (3H, s, 13ß-Me), 2,15 and 2,17 (each 3H, s, 16α-OAc and 16ß-CH_2OAc), 2,87 (2H, m, 6-H_2), 3,8 (3H, s, 3-OMe), 4,38 and 4,45 (each 1H, d, *J* 11,7 Hz, 16-CH_2), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H) (Found: C, 69,3; H, 7,2%; M^+, 414. $C_{24}H_{30}O_6$ requires C, 69,5; H, 7,3%; *M*, 414). Further elution with ethyl acetate-toluene (1:9) gave 16ß-*acetoxymethyl*-16α-*hydroxy*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**38**) (2,79 g; 74%), m.p. 140-143°C (from chloroform-hexane); $[\alpha]_D$ +174° (*c* 1,1); ν_{max} 3552 and 1743 cm^{-1}; δ_H 0,99 (3H, s, 13ß-Me), 2,07 (3H, s, 16^1-OAc), 2,69 (1H, s, exch. by D_2O, 16α-OH), 2,88 (2H, m, 6-H_2), 3,75 (3H, s, 3-OMe), 4,1 and 4,3 (each

1H, d, *J* 11,5 Hz, 16-CH_2), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H); δ_C 13,4 (C-18), 20,7 ($COCH_3$), 25,7 (C-11), 26,5 (C-7), 29,5 (C-6), 32,0 (C-12)*, 32,8 (C-15)*, 37,7 (C-8), 43,8 (C-9), 46,1 (C-14), 48,6 (C-13), 55,2 (3-OMe), 67,2 (C-16^1), 77,2 (C-16), 111,6 (C-2), 113,9 (C-4), 126,2 (C-1), 131,7 (C-10), 137,6 (C-5), 157,6 (C-3), 170,5 ($COCH_3$), and 218,0 (C-17) (Found: C, 70,5; H, 7,6%; M^+, 372. $C_{22}H_{28}O_5$ requires C, 70,9; H, 7,6%; *M*, 372). Further elution yielded 16α-*acetoxymethyl*-16ß-*hydroxy*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**39**) (450 mg, 12%), m.p. 139-141°C (from dichloromethane-hexane); $[\alpha]_D$ +80° (*c* 1,1); ν_{max} 3554 and 1743 cm^{-1}; δ_H 1,06 (3H, s, 13ß-Me), 1,78 (1H, t, *J* 2 x 12,8 Hz, 15ß-H), 2,11 (3H, s, 16^1-OAc), 2,26 (1H, dd, *J* 12,8 and 5,1 Hz, 15α-H), 2,90 (2H, m, 6-H_2), 3,79 (3H, s, 3-OMe), 4,0 and 4,36 (each 1H, d, *J* 11,8 Hz, 16α-CH_2), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 4-H) (Found: C, 70,6; H, 7,4%; M^+, 372. $C_{22}H_{28}O_5$ requires C, 70,9; H, 7,6%; *M*, 372).

16ß-*Hydroxy*-16α-*hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**36**)

The 16α-acetoxymethyl-16ß-hydroxy ketone (**39**) (256 mg; 0,69 mmol) was stirred in methanolic potassium hydroxide (3%; 10 ml) at 20°C under nitrogen for 10 min. Saturated aqueous ammonium chloride was added and the mixture was extracted with chloroform (3 x 15 ml). The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue with ethyl acetate-toluene (1:1) gave the diol (**36**) (222 mg; 97%), m.p. 143-146°C (from dichloromethane-hexane); $[\alpha]_D$ +109° (*c* 1,1); ν_{max} 3544 and 1728 cm^{-1}; δ_H 1,11 (3H, s, 13ß-Me), 1,82 (1H, t, *J* 2 x 13 Hz, 15ß-H), 2,13 (1H, dd, *J* 13 and 5,8 Hz, 15α-H), 2,77 (1H, dd, *J* 8,9 and 2,4 Hz, exch. by D_2O, 16^1-OH), 3,5 (1H, s, exch. by D_2O, 16ß-OH), 3,65 (2H, m, simplifying to AB quartet on D_2O exch., *J* 11,8 Hz, 16α-CH_2), 3,78 (3H, s, 3-OMe), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H) (Found: C, 72,8; H, 7,8%; M^+, 330. $C_{20}H_{26}O_4$ requires C, 72,7; H, 7,9%; *M*, 330).

Interconversions of the spiro-oxiranes

a) *Reduction of epoxy ketone* (**26**). Sodium borohydride (7,6 mg; 0,2 mmol) was added to (16*R*)-epoxy ketone (**26**) (50 mg; 0,16 mmol) suspended in dry ethanol (5 ml) at 20°C under nitrogen. After 1 h, ice and water were added and the mixture was extracted with chloroform (3 x 20 ml) and the extract was washed with brine, dried ($MgSO_4$), and concentrated to give a crystalline residue (48 mg; 96%). Recrystallisation from dichloromethane-hexane gave the (16*R*)-epoxy 17ß-alcohol (**29**), m.p. 136-140°C.

b) *Reduction of epoxy ketone* (**27**). Sodium borohydride (30 mg; 0,79 mmol) was added to (16*S*)-epoxy ketone (**27**) (229 mg; 0,73 mmol) suspended in dry ethanol (15 ml) at 20°C under nitrogen. After 1 h, ice and water were added and the mixture was extracted with chloroform (3 x 20 ml) and the extract was washed with brine, dried ($MgSO_4$), and concentrated to give a crystalline residue (230 mg). Recrystallisation from dichloromethane-hexane gave the (16*S*)-epoxy 17ß-alcohol (**30**) (202 mg; 88%), m.p. 145-152°C.

c) *Oxidation* 17ß-*hydroxy epoxide* (**30**). A mixture of (16*S*)-epoxy 17ß-alcohol (**30**) (69 mg; 0,21 mmol) and pyridinium dichlorochromate (240 mg; 0,65 mmol) in dry dichloromethane (5 ml) was stirred at 20°C under nitrogen for 60 h. The mixture was then filtered through celite and the filtrate was washed with water, dried ($MgSO_4$), and concentrated to give a brown residue which was chromatagraphed on silica gel (4,5 g) eluting with ethyl acetate-toluene (1:99) to give the (16*S*)-epoxy ketone (**27**) (40,2 mg; 59%) m.p. 162-165°C (from chloroform-hexane).

d) *Acetylation of* 17ß-*hydroxy epoxide* (**30**). The (16*S*)-epoxy 17ß-alcohol (**30**) (25 mg; 0,8 mmol) was treated with acetic anhydride (1 ml) and pyridine (1 ml) for 24 h. Saturated aqueous ammonium chloride and dilute hydrochloric acid were added and the mixture was extracted with chloroform (3 x 10 ml). The extract was washed

with brine, dried ($MgSO_4$), and concentrated to give a crystalline residue (30 mg). Recrystallisation from dichloromethane-methanol gave the (16*S*)-epoxy 17ß-acetate (**33**), m.p. 159-165°C (from chloroform-hexane).

e) *Acetylation of* 17ß-*hydroxy epoxide* (**29**). The (16*R*)-epoxy 17ß-alcohol (**29**) (60 mg; 0,19 mmol) was treated with acetic anhydride (1,5 ml) in pyridine (2 ml). After 24 h, saturated aqueous ammonium chloride was added and the mixture was extracted with chloroform (3 x 10 ml). The extract was washed with brine, dried ($MgSO_4$), and concentrated to give a brown crystalline residue which was chromatographed on silica gel (2 g) eluting with ethyl acetate-toluene (1:19), which gave the (16*R*)-epoxy 17ß-acetate (**32**) (51 mg; 74%), m.p. 135-140°C (from chloroform-hexane).

f) *Hydrolysis of* 17*β-acetoxy epoxide* (**32**). The (16*R*)-epoxy 17ß-acetate (**32**) (78 mg; 0,22 mg) in 3% methanolic potassium hydroxide (5 ml) was stirred for 40 min, then aqueous ammonium chloride was added. The mixture was extracted with chloroform (3 x 5 ml) and the extract was dried ($MgSO_4$), and concentrated to give an oil. Flash chromatography on silica gel (1 g) gave the (16*R*)-epoxy-17ß-alcohol (**29**) (43 mg; 64%), m.p. 136-140°C (from chloroform-hexane).

g) *Hydrolysis of* 17*β-epoxy acetate* (**33**). The (16*S*)-epoxy 17ß-acetate (**33**) (65 mg; 0,18 mmol) was dissolved in 3% methanolic sodium hydroxide (5 ml) and stirred at 20°C for 30 min. Saturated aqueous ammonium chloride was added and the mixture was extracted with chloroform (3 x 10 ml). The extract was dried ($MgSO_4$), and concentrated to give (16*S*)-epoxy 17ß-alcohol (**30**) (57 mg; 98%), m.p. 146-157°C (from dichloromethane-hexane); mixed m.p. 146-160°C.

Acid mediated hydrolysis of epoxy ketone (**27**)

Perchloric acid (70%; 0,2 ml) was added dropwise to the epoxy ketone (**27**) in ethyl methyl ketone (2 ml) and was stirred at 20°C for 3 h. Saturated aqueous sodium

hydrogen carbonate was added and the mixture was extracted with chloroform (3 x 10 ml), dried ($MgSO_4$), and concentrated to give a brown oil (120 mg). Flash chromatography on silica gel (5 g) eluting with ethyl acetate-toluene (3:7) gave the diol (**35**) (34 mg; 37%), m.p. 150-155°C; mixed m.p. 150-155°C.

Reduction of (16R)-*spiro*[3-*methoxyestra*-1,3,5(10)-*trien*-17-*one*-16,2'-*oxirane*] (**26**)
Lithium aluminium hydride (15 mg; 0,39 mmol) was added in small portions to a stirred solution of the epoxy ketone (**26**) (50 mg; 0,16 mmol) in tetrahydrofuran (3 ml) at 0°C under nitrogen. After 1 h, ethyl acetate was added and the reaction was stirred for a further 15 min, then saturated aqueous ammonium chloride was added. The mixture was extracted with chloroform (3 x 10 ml), and the extract was washed with brine, dried ($MgSO_4$), and concentrated to give an oil which was chromatographed on silica gel (4 g). Elution with ethyl acetate-toluene (1:5) gave 16α-*methyl*-3-*methoxyestra*-1,3,5(10)-*triene*-16ß,17ß-*diol* (**40**) (48 mg; 96%), m.p. 168-172°C (from dichloromethane-hexane), (lit.,[92] 171-174°C); $[\alpha]_D$ +61° (*c* 0,9); ν_{max} 3613 cm^{-1}; δ_H 0,85 (3H, s, 13ß-Me), 1,35 (3H, s, 16α-Me), 2,0 (1H, s, exch. by D_2O, 16ß-OH) 2,4 (1H, d, *J* 8,7 Hz, exch. by D_2O, 17ß-OH), 2,83 (2H, m, 6-H_2), 3,16 (1H, d, *J* 8,7 Hz, 17α-H), 3,77 (3H, s, 3-OMe), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H) (Found: C, 76,1; H, 9,0%; M^+, 316. $C_{20}H_{28}O_3$ requires C, 75,9; H, 8,9%; *M*, 316).

Reduction of (16S)-*spiro*[3-*methoxyestra*-1,3,5(10)-*trien*-17-*one*-16,2'-*oxirane*] (**27**)
Lithium aluminium hydride (14 mg; 0,34 mmol) was added in small portions to a stirred solution of the epoxy ketone (**27**) (51 mg; 0,16 mmol) in tetrahydrofuran (3 ml) at 0°C under nitrogen. After 40 min, ethyl acetate was added and the reaction was stirred for a further 20 min, then saturated aqueous ammonium chloride was added. The mixture was extracted with chloroform (3 x 10 ml), and the extract was washed with brine, dried ($MgSO_4$), and concentrated to give an oil which was chromatographed on silica gel (3,5 g). Elution with ethyl acetate-toluene (1:5) gave the (16*S*)-epoxy 17ß-alcohol

(**30**) (7 mg; 13%), m.p. 145-150°C, followed by 16ß-*methyl*-3-*methoxyestra*-1,3,5(10)-*triene*-16α,17ß-*diol* (**41**) (42 mg; 82%), m.p. 84-86°C (from benzene), (lit.[18] 85-90°C, 123-7°C, 151-3°C); $[\alpha]_D$ +68° (*c* 0,9); ν_{max} 3683 and 3595 cm^{-1}; δ_H 0,77 (3H, s, 13ß-Me), 1,33 (3H, s, 16ß-Me), 1,64 (1H, br s, $W_{½}$ 7,5 Hz, exch. by D_2O, OH), 2,85 (2H, m, 6-H_2), 3,63 (1H, s, 17α-H), 3,77 (3H, s, 3-OMe), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H) (Found: C, 71,9; H, 9,0%; M^+, 316. $C_{20}H_{28}O_3$ requires *M*, 316. $C_{20}H_{28}O_3.H_2O$ requires C, 71,8; H, 9,0%).

Reduction of epoxy ketone isomers (**26**) and (**27**)

Lithium aluminium hydride (120 mg, 3,1 mmol) was added in small portions to a stirred solution of isomeric epoxy ketones (**26**) and (**27**) (126 mg, 0,4 mmol) in tetrahydrofuran (10 ml) at 0°C. The mixture was stirred for 5 h, then ethyl acetate was added and stirred for another 1 h. Water and saturated aqueous ammonium chloride were added and the mixture was extracted with chloroform (4 x 10 ml). The extract was filtered through sintered glass to remove emulsion and the organic phase was washed with brine, dried ($MgSO_4$), and concentrated to give an oil (140 mg). Flash chromatography on silica gel (7 g) with ethyl acetate-toluene (1:5) as eluent yielded 3-*methoxy*-16α-*methylestra*-1,3,5(10)-*triene*-16ß,17ß-*diol* (**38**) (45 mg; 35%) m.p. 168-172°C (from ethyl acetate-hexane). Further elution gave 3-*methoxy*-16ß-*methylestra*-1,3,5(10)-*triene*-16α,17ß-*diol* (**41**) (67 mg, 53%) m.p. 84-86°C (from benzene).

Reduction of (16R)-*spiro*[3-*methoxyestra*-1,3,5(10)-*trien*-17ß-*ol*-16,2'-*oxirane* (**29**)

Lithium aluminium hydride (110 mg; 2,9 mmol) was added in small portions to a stirred solution of the epoxy 17ß-alcohol (**29**) (358 mg; 1,4 mmol) in dry tetrahydrofuran (15 ml) at 0°C under nitrogen. The reaction was allowed to warm to 20°C and was stirred for 18 h. Water and saturated aqueous ammonium chloride were added, and the mixture was filtered and extracted with chloroform (3 x 25 ml). The extract was

washed with brine, dried ($MgSO_4$) and concentrated to give the 16ß,17ß-diol (**38**) (350 mg; 97%), m.p. 168-172°C (from dichloromethane-hexane).

Cleavage of the 16α-*methyl* 16ß,17ß-*diol* (**40**) *with sodium periodate*

Aqueous sodium periodate (6%; 0,5 ml) was slowly added to a stirred solution of 16ß,17ß-diol (**40**) (50 mg; 0,15 mmol) in methanol (5 ml). After 30 min, water was added, and the mixture was extracted with chloroform (4 x 15 ml). The extract was washed with brine, dried ($MgSO_4$), and concentrated to give an oil (54 mg). Flash chromatography on silica gel (3 g) eluting with ethyl acetate-toluene (1:19) gave 3-*methoxy*-16-*methyl*-16-*oxo*-16,17-*secoestra*-1,3,5(10)-*trien*-17-*al* (**42**) (40 mg; 80%) (oil) $[\alpha]_D$ +55° (*c* 1,04) (lit.[19] +65°); ν_{max} 1717 cm^{-1}; δ_H 1,02 (3H, s, 13ß-Me), 1,86 (1H, dt, *J* 13,2 and 3,5 Hz, 14α-H), 2,16 (3H, s, $COCH_3$), 3,76 (3H, s 3-OMe), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), 7,2 (1H, d, *J* 8,5 Hz, 1-H), and 9,35 (1H, s, CHO) (Found: M^+, 314. $C_{20}H_{26}O_3$ requires *M*, 314). Further elution gave starting material (2 mg; 4%).

Attempted cleavage of the 16ß-*methyl* 16α,17ß-*diol* (**41**) *with sodium periodate*

A mixture of aqueous sodium periodate (6%; 3 ml) and the 16α,17ß-diol (**41**) (5 mg; 0,02 mmol) in methanol (0,5 ml) was stirred at 20°C for 3 days. Water was added and the mixture was extracted with chloroform (3 x 5 ml), dried ($MgSO_4$), and concentrated to give a starting material (**41**) (4 mg), m.p. 80-85°C (from benzene).

Cleavage of 16ß,17ß- *diol* (**40**) *with lead tetraacetate*

Lead tetraacetate (68 mg; 0,15 mmol) was added to a stirred solution of 16ß,17ß-diol (**40**) (40 mg; 0,13 mmol) in dry benzene (2 ml) at 20°C. After 40 min, water and saturated aqueous sodium hydrogen carbonate were added, and the mixture was extracted with chloroform (2 x 10 ml), filtered and re-extracted (2 x 10 ml). The organic phase was washed with brine, dried ($MgSO_4$), and concentrated to give an oil

(50 mg) which was chromatographed on silica gel (3 g) to give the 16,17-seco compound (**42**) as an oil (40 mg; 99%).

Cleavage of 16α,17ß-*diol* (**41**) *with lead tetraacetate*

Lead tetraacetate (120mg; 0,27 mmol) was added to a stirred solution of the 16α,17ß-diol (**41**) (63 mg; 0,2 mmol) in dry benzene (5 ml) under nitrogen. After 1 h, water was added and the mixture was extracted with chloroform (3 x 10 ml), and the extract was dried ($MgSO_4$), and concentrated to give an oil (54,7 mg). Flash chromatography on silica gel (5 g) using ethyl acetate-toluene (1:99) as eluent gave the 16,17-seco product (**42**) as an oil (35 mg; 56%).

Cleavage of the 16ß,17ß- *and* 16α,17ß-*diols* (**40** and **41**)

Lead tetraacetate (453 mg; 1,02 mmol) was added to a stirred solution of diols (**40** and **41**) (290 mg; 0,9 mmol) in dry benzene (5 ml) and the mixture was stirred for 10 min at 20°C. Water and saturated aqueous sodium hydrogen carbonate were added and the mixture was extracted with chloroform (3 x 15 ml), filtered to remove the emulsion and re-extracted. The organic phase was dried ($MgSO_4$), and concentrated to give an oil (283 mg). Flash chromatography on silica gel (15 g) using ethyl actate-toluene (1:49) as eluent gave the 16,17-seco compound (**42**) (160 mg; 55%) as an oil.

Preparation of dimethyldioxirane.[56]

A gentle stream of nitrogen was passed through a vigorously stirred mixture of oxone (25 g), sodium hydrogen carbonate (12 g), water (20 ml) and acetone (13 ml) for 30 min at 25°C, then a vacuum (water aspirator) was applied for the next 40 min. A pale yellow solution of dimethyldioxirane was collected in a receiving flask at -78°C (10 ml; 0,08M, 2%). The solution was dried over molecular sieves, and was then used for the following three experiments.

Treatment of 3-*methoxy*-16-*methylene-estra*-1,3,5(10)-*trien*-17-*one* (**23**) *with dimethyldioxirane*

Dimethyldioxirane in acetone solution (0,08M; 4 ml; 0,32 mmol) was added in 3 portions to a stirred solution of the methylene ketone (**23**) (41 mg; 0,14 mmol) in dry dichloromethane at 20°C under nitrogen for 36 h, then saturated aqueous sodium sulphite was added. The mixture was extracted with chloroform (3 x 5 ml), and the extract was dried ($MgSO_4$), and concentrated to give a yellow oil which was chromatographed on silica gel (5 g). Elution with ethyl acetate-toluene (1:49) gave starting material (**23**) (2,6 mg; 6%), followed by a 1:1 mixture (n.m.r.) of epoxy ketones (**26** and **27**) (6,8 mg; 16%). Further elution with ethyl acetate-toluene (1:9) gave impure 9α-hydroxy-3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one (**43**) (18,8 mg; 22%), ν_{max} 3599 and 1638 cm^{-1}; (Found: M^+, 314. $C_{20}H_{26}O_3$ requires *M*, 314). Further elution gave a mixture of four compounds (11 mg).

Treatment of 3-*methoxy*-16-*methylene-estra*-1,3,5(10)-*trien*-17ß-*yl acetate* (**25**) *with dimethyldioxirane*

Dimethyldioxirane in acetone solution (0,08M; 7 ml; 0,56 mmol) was added in five portions to a stirred solution of the 17ß-acetoxy 16-methylene compound (**25**) (64,7 mg; 0,19 mmol) over 36 h at 25°C under nitrogen, then saturated aqueous sodium sulphite was added. The mixture was extracted with chloroform (3 x 5 ml), and the extract was dried ($MgSO_4$), and concentrated to give an oil. Chromatography on silica gel (5 g), eluting with ethyl acetate-toluene (1:99), gave starting material (**25**) (14,6 mg; 22%), followed by a 1:9 mixture (n.m.r.) of epoxides (**32** and **33**) (20 mg; 30%). Further elution with ethyl acetate-toluene (1:9) gave a mixture of products (13 mg; 19%), followed by impure 16ß-hydroxy-16α-hydroxymethyl-3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (**45**) (40 mg; 50%), ν_{max} 3599 cm^{-1}; δ_H 1,01 (3H, s, 13ß-Me), 1,71 (1H, t, *J* 13,4 Hz, 15ß-H), 2,1 (1H, dd, *J* 13,4 and 7,4 Hz, 15α-H), 2,20 (3H, s, 17ß-Ac), 2,84 (2H, m, 6-H_2), 3,47 and 3,52 (each 1H, d, *J* 11,3, 16-CH_2), 3,78 (3H, s, 3-OMe), 4,61 (1H, s, 17α-H), 6,09 (1H, m, 11-H), 6,6 (1H, d, *J* 2,7 Hz, 4-H), 6,71 (1H, dd, *J* 8,9 and

(1H, dd, *J* 8,9 and 2,7 Hz, 2-H), and 7,50 (1H, d, *J* 8,9 Hz, 1-H) (Found: M^+, 372. $C_{22}H_{28}O_5$ requires *M*, 372).

Treatment of 3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**22**) *with dimethyldioxirane.*

Dimethyldioxirane (9 ml) (0,08M; 0,7 mmol) was added over 2 days to a stirred solution of estrone 3-methyl ether (**22**) (537 mg; 1,89 mmol) in dichloromethane (15 ml) at 25°C under nitrogen. Saturated aqueous sodium sulphite was added and the mixture was extracted with chloroform (3 x 15 ml). The extract was dried ($MgSO_4$), and concentrated to give a crystalline residue (562 mg). Flash chromatography on silica gel (30 g) using ethyl acetate-toluene (1:49) as eluent gave starting material (412 mg; 77%). Further elution with ethyl acetate-toluene (1:9) gave impure 9α-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (**47**) together with 3-methoxyestra-1,3,5(10),9(11)-trien-17-one (**48**) (112 mg; 20%); δ_H 0,90 [3H, s, 13ß-Me of (**47**)], 0,92 [3H, s, 13ß-Me of (**48**)], 3,77 (3H, s, 3-OMe), 6,13 [1H, m, 11-H of (**47**)], 6,6 [1H, d, *J* 2,7 Hz, 4-H of (**48**)], 6,65 [1H, d, *J* 2,7 Hz, 4-H of (**47**)], 6,71 [1H, dd, *J* 8,9 and 2,7 Hz, 2-H of (**48**)], 6,75 [1H, dd, *J* 8,8 and 2,7 Hz, 2-H of (**47**)], 7,45 [1H, d, *J* 8,8 Hz, 1-H of (**47**)] and 7,52 [1H, d, *J* 8,9 Hz, 1-H of (**48**)] (Found: M^+, 300. $C_{19}H_{24}O_3$ requires *M*, 300).

3-Methoxyestra-1,3,5(10),9(11)-*tetraen*-17-*one* (**48**)

a) A mixture of toluene-*p*-sulphonic acid (30 mg; 0,15 mmol) and impure 9α-hydroxy estrone methyl ether (**47**) (31 mg; 0,10 mmol) in dry benzene (6 ml) was stirred for 12 h at 20°C. Saturated aqueous sodium hydrogen carbonate was added and the mixture was extracted with chloroform (3 x 10 ml). The extract was washed with brine, dried ($MgSO_4$), and concentrated to give a yellow crystalline residue (29 mg), which was chromatographed on silica gel (3 g) eluting with ethyl acetate-toluene (1:99) to give 3-*methoxyestra*-1,3,5(10),9(11)-*tetraen*-17-*one* (**48**) (22,5 mg; 77%), m.p. 141-142°C (from dichloromethane-methanol); $[\alpha]_D$ +291° (*c* 0,9) (lit.,[93] 142,5-144°C, $[\alpha]_D$ +290,9°); ν_{max} 1731 and 1621 cm^{-1}; δ_H 0,93 (3H, s, 13ß-Me), 2,90 (2H, m, 6-H_2), 3,78 (3H, s, 3-OMe), 6,13 (1H, m, 11-H), 6,6 (1H, d, *J* 2,8 Hz, 4-H), 6,75 (1H, dd, *J* 8,7 and

2,8 Hz, 2-H), and 7,65 (1H, d, *J* 8,7 Hz, 1-H) (Found: C, 80,9; H, 7,8%; M^+, 282. $C_{19}H_{22}O_2$ requires C, 80,8; H, 7,9%; *M*, 282).

b) A solution of 2,3-dichloro-5,6,-dicyanobenzoquinone (844 mg; 3,72 mmol) in dry methanol (15 ml) was added dropwise to a stirred solution of estrone (941 mg; 3,49 mmol) in dry methanol (110 ml) at 20°C under nitrogen. After 30 min, the deep red-green colour had changed to light yellow and the mixture was stirred for a further 45 min. The methanol was removed under reduced pressure and the residue was triturated with hot chloroform (30 ml), and left to stand overnight. Activated charcoal was added, and after brief stirring, the mixture was filtered through celite. The filtrate was evaporated and the residue was triturated with hot ethyl acetate (20 ml), allowed to cool to room temperature, then filtered. The filtrate was washed with cold ethyl acetate to give crude 3-hydroxyestra-1,3,5(10),9(11)-tetraen-17-one (**49**) (471,2 mg; 50%) m.p. 259-262°C (from ethyl acetate), (lit.,[67] 260-263°C). Concentration of the filtrate gave additional, less pure material (390 mg; 41%). Dimethyl sulphate (0,15 ml) was added dropwise to a stirred solution of recrystallised (**49**) (391 mg; 1,45 mmol) in methanol (15 ml) and aqueous potassium hydroxide (7%; 2 ml) at 0°C under nitrogen. After simultaneous dropwise addition of dimethyl sulphate (2,5 ml) and potassium hydroxide (1,67 g) in water (2,2 ml), the alkaline mixture was stirred for 10 min, and then additional dimethyl sulphate (0,44 ml) and potassium hydroxide (0,4 g) in water (0,4 ml) were added. The stirred mixture was allowed to warm up to 20°C, then was heated under reflux for 1 h. Most of the methanol was removed under reduced pressure, and the mixture was extracted with dichloromethane (3 x 15 ml). The extract was washed with a 1:1 mixture of methanol and 40% aqueous potassium hydroxide, then water, and dried ($MgSO_4$), and concentrated to give a grey crystalline residue (376 mg). Flash chromatography on silica gel (20 g) using dichloromethane as eluent gave 3-*methoxyestra*-1,3,5(10),9(11)-*tetraen*-17-*one* (**48**) (355 mg; 86%), m.p. 141-142°C (from dichloromethane-methanol).

Condensation of 3-*methoxy*-16-*methyl*-16-*oxo*-16,17-*secoestra*-1,3,5(10)-*trien*-17-*al* (**42**)

a) A mixture of the 16,17-seco compound (**42**) (40 mg; 0,13 mmol) and 2% methanolic sodium hydroxide (1 ml) was stirred at 25°C for 1 h, then saturated aqueous ammonium chloride was added. The mixture was extracted with chloroform (3 x 10 ml), and the extract was washed with brine, dried ($MgSO_4$), and concentrated to give an oil. Chromatography on silica gel (4,5 g), using ethyl acetate-toluene as eluent (1:49) gave 3-*methoxy*-17a-*homo*-1,3,5(10),17-*estratetraen*-16-*one* (**50**) (13 mg; 35%) m.p. 143-146°C (from chloroform-methanol) (lit.,[19] 147°C; lit.,[94] 138-139°C); $[\alpha]_D$ +118° (*c* 1,1); ν_{max} 1669 cm^{-1}; δ_H 1,07 (3H, s, 13ß-Me), 2,20 (1H, dd, *J* 17,4 and 14 Hz, 15ß-H), 2,66 (1H, dd, *J* 17,4 and 3,7 Hz, 15α-H), 2,84 (2H, m, 6-H_2), 3,77 (3H, s, 3-OMe), 5,88 (1H, d, *J* 9,9 Hz, 17-H), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), 6,80 (1H, d, *J* 9,9 Hz, 17α-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H) (Found: C, 80,9; H, 8,0%; M^+, 296. $C_{20}H_{24}O_2$ requires C, 81,0; H, 8,2%; *M*, 296). Further elution with ethyl acetate-toluene (1:9) gave 17aß-*hydroxy*-3-*methoxy*-17a-*homoestra*-1,3,5(10)-*trien*-16-*one* (**51**) (20 mg; 50%), m.p. 143-145°C (from benzene); $[\alpha]_D$ +58° (*c* 1,2); ν_{max} 3 609 and 1709 cm^{-1}; δ_H 1,02 (3H, s, 13ß-Me), 1,62 (1H, br.s; exch. by D_20, 17a-H), 2,65 (1H, ddd, *J* 15,3, 5,5 and 1,4 Hz), 2,84 (2H, m, 6-H_2), 3,6 (1H, dd, *J* 11,4 and 5,6 Hz, 17aα-H), 3,77 (3H, s, 3-OMe), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H) (Found: C, 76,7; H, 8,3%; M^+, 314. $C_{20}H_{26}O_3$ requires C, 76,4; H, 8,3%; *M*, 314).

b) Sublimed potassium-*t*-butoxide (66 mg; 0,59 mmol) was added to a stirred solution of 16,17-seco compound (**42**) (150 mg; 0,48 mmol) in dry tetrahydrofuran (5 ml) and the mixture was refluxed for 1h. After cooling, saturated aqueous ammonium chloride and water were added, and the mixture was extracted with chloroform (3 x 15 ml), dried ($MgSO_4$), and concentrated to give a semi-crystalline residue (137 mg). Chromatography on silica gel (14 g) with ethyl acetate-toluene

(1:49) as eluent gave the α,ß-unsaturated ketone (**50**) (115 mg; 81%) m.p. 143-146°C (from chloroform-methanol)

3-*methoxy*-17α,17aα-*epoxy*-17a-*homoestra*-1,3,5(10)-*trien*-16-*one* (**52**)

Hydrogen peroxide (30%, 2 ml) was added dropwise to a stirred solution of a,ß-unsaturated ketone (**50**) (48 mg, 0,16 mmol) and 10M sodium hydroxide (0,1 ml) in tetrahydrofuran (4 ml) and *t*-butyl alcohol (4 ml) at 0°C. The mixture was allowed to warm slowly to 20°C and, after 3h the mixture was cooled to 0°C and saturated aqueous sodium sulphite and ammonium chloride were added sequentially. The mixture was extracted with chloroform (3 x 10 ml), and the extract was dried ($MgSO_4$), and concentrated to give a semicrystalline residue (51 mg). Recrystallisation from chloroform-methanol gave the epoxy ketone (**52**) (45 mg; 88%), m.p. 138-140°C (lit.,[95] 142-146°C); $[\alpha]_D$ -28° (*c* 1,2); ν_{max} 1703 cm^{-1}; δ_H 0,93 (3H, s, 13ß-Me), 3,23 and 3,26 (each 1H, d, *J* 4,2 Hz, 17α- and 17aα-H) 3,77 (3H, s, 3-OMe), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H, d, *J* 8,5 Hz, 1-H) (Found: C, 77,1; H, 7,6%; M^+, 312. $C_{20}H_{24}O_3$ requires C, 76,9; H, 7,7%; *M*, 312).

Wharton rearrangement of epoxy ketone (**52**)

Hydrazine hydrate (0,5 ml) and acetic acid (0,1 ml; 5 M) was added to a stirred solution of epoxy ketone (**53**) (80 mg; 0,25 mmol) in *t*-butyl alcohol (5 ml) at 20°C. Saturated aqueous sodium hydrogen carbonate was added after 10 min and the mixture was extracted with chloroform (3 x 15 ml). The extract was washed with brine, dried ($MgSO_4$), and concentrated to give a foam (89 mg). Flash chromatography on silica gel (6g) eluting with ethyl acetate-toluene (1:49) gave 3-*methoxy*-17a-*homo-estra*-1,3,5(10),16-*tetraen*-17aα-*ol* (**53**) (30,8 mg; 41%) m.p. 125-129°C (chloroform-hexane); $[\alpha]_D$ -82° (*c* 0,9); ν_{max} 3603, 1742 and 1694 cm^{-1}; δ_H 0,79 (3H, s 13ß-Me), 1,42 (1H, s, 17α-OH), 3,50 (1H, m, 17α-H), 3,78 (3H, s, 3-OMe), 5,88 (2H, m, 16-, and 17-H), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), and 7,2 (1H,

d, *J* 8,5 Hz, 1-H) (Found: C, 80,2; H, 8,8%; M^+, 298; $C_{20}H_{26}O_2$ requires C, 80,5; H, 8,8%; *M*, 298).

Attempted dehydration of 16*β-acetoxymethyl*-16*α-hydroxy ketone* (**36**)

Thionyl chloride (0,5 ml; 7 mmol) was added dropwise to a stirred solution of the 16ß-acetoxymethyl 16α-hydroxy ketone (**36**) (285,6 mg; 0,76 mmol) in pyridine (15 ml) under nitrogen at -10°C. Ice and water were added after 1 h, and the mixture was extracted with chloroform (3 x 15 ml). The extract was washed with dilute hydrochloric acid and brine, dried ($MgSO_4$), and concentrated to give a semi-crystalline residue (348 mg) which was chromatagraphed on silica gel (35 g) using ethyl acetate-toluene as eluent (1:49). An inseparable mixture of isomers (6 mg; 2%) was obtained followed by starting material (272 mg; 95%), m.p. 140-143°C confirmed by mixed melting point.

Attempted rearrangment of epoxy ketone (**27**) *with toluene*-p-*sulphonic acid*

A mixture of the epoxy ketone (**27**) (71 mg; 0,22 mmol) and toluene-*p*-sulphonic acid (76 mg; 0,4 mmol) in dry benzene (5 ml) was refluxed for 1 h. After cooling, water and saturated aqueous sodium hydrogen carbonate were added and the mixture was extracted with chloroform (3 x 10 ml), washed with brine, dried ($MgSO_4$), and concentrated to give 16α-hydroxy-3-methoxy-16ß-tosyloxymethylestra-1,3,5(10)-trien-17-one (**55**) as a light brown oil (104 mg, 100%); ν_{max} 3545, 1742, 1364, 1174 cm^{-1}; δ_H 0,89 (3H, s, 13ß-Me), 2,42 (3H, s, Ts-Me), 2,57 (1H, br. s, exch. by D_2O, 16α-OH), 2,89 (2H, m, 6-H_2), 3,74 (3H, s, 3-OMe), 4,02 (2H, s, 16ß-CH_2), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), 7,2 (1H, d, *J* 8,5 Hz, 1-H), 7,32 (2H, d, *J* 8,3 Hz, 3'- and 5'-H), and 7,75 (2H, d, *J* 8,3 Hz, 2'- and 6'-H). Attempts to purify the compound by chromatography failed as reversion to starting material occurred (t.l.c. and mixed melting point).

Tosylation of 16α-*hydroxy*-16ß-*hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**35**)

Toluene-*p*-sulfonyl chloride (103 mg; 0,54 mmol) was added to a stirred solution of the diol (**35**) (167 mg; 0,5 mmol) in pyridine (5 ml) at 0°C. After 5 days at 4°C, ice and saturated aqueous ammonium chloride were added and the mixture was extracted with chloroform (3 x 10 ml), washed with brine, dried ($MgSO_4$), and concentrated to give a light brown oil (262 mg). N.m.r. was identical to that of (**56**).

16ß-*Benzyloxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**57**)

A suspension of sodium hydride (112 mg; 2 mmol) in benzyl alcohol (5 ml) was stirred for 15 min, then added dropwise to a stirred solution of methylene ketone (**23**) (116 mg; 0,33 mmol) in benzene (5 ml) at 0°C under nitrogen. The mixture was allowed to warm to 20°C and was stirred for another 2 h, then cold water was added. The mixture was extracted with chloroform (3 x 10 ml), and the extract was washed with brine, dried ($MgSO_4$), and concentrated to give a yellow oil. Flash chromatography on silica gel (9 g) using ethyl acetate-toluene (1:99) as eluent gave starting material (12 mg; 11%), followed by 16ß-*benzyloxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**57**) (120 mg; 76%), m.p. 105-108°C (from dichloromethane-methanol); $[\alpha]_D$ +118° (*c* 0,9); ν_{max} 1 730 cm^{-1}; δ_H 0,89 (3H, s, 3ß-Me), 2,89 (2H, m, 6-H_2),3,7 (2H, m, 16^1-H_2), 3,77 (3H, s, 3-OMe), 4,50 (2H, s, PhCH_2), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), 7,2 (1H, d, *J* 8,5 Hz, 1-H), and 7,3 (5H, m, Ph) (Found: C, 79,9; H, 7,8%; M^+, 404. $C_{27}H_{32}O_3$ requires C, 80,2; H, 8,0%; *M*, 404).

Attempted enolisation of 16ß-*benzyloxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**56**)

A mixture of sodium hydride (12 mg; 0,25 mmol) and the 16ß-benzyloxymethyl ketone (**56**) (58 mg; 0,14 mmol) in tetrahydrofuran (5 ml) was stirred at 20°C under nitrogen for 1 h. The mixture was cooled to 0°C and trimethylsilyl chloride (0,3 ml) was added, and the mixture was stirred for a further 15 min. Cold water was added and the mixture

was extracted with chloroform (3 x 10 ml). The extract was dried ($MgSO_4$), and concentrated to give an oil which was chromatographed on silica gel (7 g). Elution with ethyl acetate-toluene (1:49) gave the methylene ketone (**23**) (17 mg; 40%). Further elution with ethyl acetate-toluene (1:20) gave starting material (**57**) (16 mg; 30%). Further elution with ethyl acetate-toluene (1:5) gave a polar mixture of products (10 mg).

Phenylthiolation of 3-*methoxy*-16-*methylene-estra*-1,3,5(10)-*trien*-17-*one* (**23**)

Thiophenol (0,1 ml) and tetrabutylammonium fluoride (0,05 ml) were added sequentially to a stirred solution of methylene ketone (**23**) (146 mg; 0,49 mmol) in dry tetrahydrofuran (6 ml) at 20°C. Water was added after 5 h and the mixture was extracted with chloroform (3 x 15 ml). The extract was washed with brine, dried ($MgSO_4$), and concentrated to give an oil which was adsorbed onto coarse silica. Flash chromatography (10 g silica) with hexane as eluent removed the diphenyl disulphinide and further elution with toluene gave a semi-crystalline residue (196 mg, 98%). Repeated chromatography yielded 3-*methoxy*-16α-*phenylthiomethylestra*-1,3,5(10)-*trien*-17-*one* (**57**) as an oil, ν_{max} 1 732 cm^{-1}; δ_H 0,92 (3H, s, 13ß-Me), 2,08 (1H, dd, *J* 12,6 and 5,3 Hz, 15α-H), 2,72 (2H, m, 16-CH_2), 2,88 (2H, m, 6-H_2), 3,45 (1H, m, 16ß-H), 3,77 (3H, s, 3-OMe), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), 7,2 (1H, d, *J* 8,5 Hz, 1-H), and 7,12-7,4 (5H, m, SPh) (Found: M^+, 406. $C_{26}H_{30}O_2S$ requires *M*, 406). Further elution yielded 3-*methoxy*-16ß-*phenylthiomethylestra*-1,3,5(10)-*trien*-17-*one* (**58**), m.p. 126-127°C (from dichloromethane-methanol); $[\alpha]_D$ +213° (*c* 1,0); ν_{max} 1 731 cm^{-1}; δ_H 0,90 (3H, s, 13ß-Me), 2,88 (2H, m, 6-H_2), 3,58 (1H, dd, *J* 12,9 and 3,3 Hz, 16^1-H), 3,78 (3H, s, 3-OMe), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,5 and 2,7 Hz, 2-H), 7,2 (1H, d, *J* 8,5 Hz, 1-H), and 7,12-7,4 (5H, m, SPh); δ_C 14,1 (13ß-Me), 25,8 (C-11), 26,7 (C-15), 28,4 (C-7), 29,6 (C-6), 31,8 (C-12), 35,9 (C-16^1), 37,8 (C-8), 44,0 (C-9), 48,5 (C-16), 48,5 (C-14), 48,7 (C-13), 55,2 (3-OMe), 111,5 (C-2), 113,8 (C-4), 126,2 (C-1), 126,2, 128,9, 129,1, 129,3, and 129 (C-2', 3', 4', 5', and 6'), 131,9 (C-10), 135,6 (C-1'), 137,7 (C-5),

157,6 (C-3), and 220,0 (C-17) (Found: C, 76,8; H, 7,6%; M^+, 406. $C_{26}H_{30}O_2S$ requires C, 76,8; H, 7,4%; *M*, 406).

Attempted enolation of 3-*methoxy*-16ß-*phenylthiomethylesta*-1,3,5(10)-*trien*-17-*one* (**58**)

n-Butyllithium (0,8 ml; 1,28 mmol) was added to a stirred solution of diisopropylamine (0,3 ml; 2,1 mmol) in tetrahydrofuran (3 ml) at 0°C under nitrogen. After 30 min, the mixture was cooled to -78°C, then a solution of the 16ß-thiophenylmethyl ketone (**58**) (56 mg; 0,13 mmol) in tetrahydrofuran (3 ml) was added and the mixture was stirred for 1 h at 0°C. Trimethylsilyl chloride (0,1 ml) was added and the mixture was stirred for another hour at 0°C, then saturated aqueous sodium hydrogen carbonate was added. The mixture was extracted with chloroform (3 x 10ml), and the extract was washed with brine, dried ($MgSO_4$), and concentrated to give a yellow oil smelling strongly of thiophenol. Chromatography on silica gel (13 g) and eluting with ethyl acetate-toluene (1:99) gave starting material (**59**) (11 mg; 20%) followed by methylene ketone (**23**) (10 mg; 25%).

Attempted enolation and dehydrosilylation of 3-*methoxy*-16ß-*methoxymethylestra*-1,3,5(10)-*trien*-17-*one* (**23**)

n-Butyllithium (0,5 ml; 0,8 mmol) was added slowly to a stirred solution of diisopropylamine (0,2 ml; 1,4 mmol) in tetrahydrofuran (5 ml) at 0°C under nitrogen and the mixture was stirred for a further 30 min, then cooled to -78°C. A solution of the 16ß-methoxymethyl 17-ketone (**23**) (20 mg; 0,06 mg) in tetrahydrofuran (5 ml) was added and the mixture was slowly warmed to 20°C. After 80 min, the mixture was cooled to 0°C, and trimethylsilyl chloride (0,2 ml) was added and the mixture was stirred for another 15 min. Saturated aqueous ammonium chloride and ice were added, and the mixture was extracted with chloroform (3 x 8 ml). The extract was dried ($MgSO_4$), and concentrated to give a yellow crystalline residue (38 mg) which was dissolved in acetonitrile (2 ml) and refluxed with palladium acetate (18 mg; 0,08 mmol)

for 22 h under nitrogen. The mixture was cooled, then filtered, and washed with chloroform to give an oil (33 mg) which was chromatographed on silica gel (5 g). Elution with ethyl acetate-toluene (1:49) gave starting material (**23**) (9,6 mg, 48%), followed by 3-*methoxy*-16-*methoxymethylene-estra*-1,3,5(10)-*trien*-17-*one* (**59**) (8 mg; 40%), m.p. 150-153°C (from dichloromethane-methanol); ν_{max} 1 709 and 1633 cm^{-1}; δ_H 0,90 (3H, s, 13ß-Me), 2,66 (1H, ddd, *J* 14,9, 6,2 and 1,6 Hz, 15α-H), 2,88 (2H, m, 6-H_2), 3,77 (3H, s, 3-OMe), 3,84 (3H, s, 16^1-Me), 6,64 (1H, d, *J* 2,7 Hz, 4-H), 6,73 (1H, dd, *J* 8,3 and 2,7 Hz, 2-H), 7,2 (1H, d, *J* 8,3 Hz, 1-H), and 7,2 (1H, dd, *J* 2,57 and 1,6 Hz, 16^1-H) (Found: M^+ 326. $C_{21}H_{26}O_3$ requires *M*, 326).

Attempted isomerisation of 3-*methoxy*-16-*methylene-estra*-1,3,5(10)-*trien*-17-*one* (**23**)

The methylene ketone (**23**) (111 mg; 0,37 mmol) was added to a stirred solution of sulphinyl benzenesulphonamide (77 mg; 0,38 mmol) in dry tetrahydrofuran (5 ml) at 0°C. The mixture was refluxed for 3 days, then cooled and filtered through celite. The filtrate was concentrated to give a yellow residue which was chromatographed on silica gel (10 g) eluting with toluene to give starting material (100 mg; 90%), m.p. 122-124°C (from benzene).

Attempted isomerisation of 3-*methoxy*-16-*methylene-estra*-1,3,5(10)-*trien*-17ß-*yl acetate* (**25**)

The 17ß-acetoxy 16-methylene compound (**25**) (64 mg; 0,19 mmol) was added to a stirred solution of sulphinyl benzene sulphonamide (50 mg; 0,24 mmol) in dry benzene (5 ml) and the mixture was refluxed for 3 days. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (7 g) to give starting material (53 mg; 82%), m.p. 123-126°C.

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