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CHEMISTRY

by

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SUMMARY

Studies have been conducted in synthesising bridged analogues of estradiol in which the ring D hydroxy group is displaced from the 17-position. The aim was to explore the possible rotational equivalence between such analogues and estradiol.

The synthetic routes investigated were based upon cycloaddition to 3-methoxyestra-1,3,5(10),14,16-pentaene. In the first phase of the project, two approaches for the synthesis of this diene were explored. The first entailed the vinylogous Shapiro elimination of the tosylhydrazone of 3-methoxyestra-1,3,5(10),15-tetraen-17-one to give the 14,16-diene. The second involved conversion of 3-methoxyestra-1,3,5(10),15-tetraen-17-one into the corresponding dienyl triflate, followed by palladium(0) mediated deoxygenation to afford the 14,16-diene. Of these two methods, only the latter was successful, as the tosylhydrazone of 3-methoxyestra-1,3,5(10),15-tetraen-17-one could not be synthesised.

In the second phase of the work, cycloaddition of 2-chloroacrylonitrile to the 14,16-diene, followed by alkaline hydrolysis afforded 3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-15-one and 3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-16-one, with the 15-ketone as the major isomer. Treatment of these ketones with L-Selectride® afforded 3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-15β-ol and 3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-16β-ol. Standard deprotection afforded the corresponding diols which were submitted for biological evaluation.

An approach towards the corresponding α-alcohols which was investigated is based upon the Baeyer-Villiger oxidation of 16α-acetyl-3-methoxy-14,17α-ethenoestra-1,3,5(10)-triene. This compound was obtained as the minor product of the boron trifluoride mediated reaction between the 14,16-diene and methyl vinyl ketone (MVK). The major compound was formulated 16α-acetyl-3-methoxy-17β-3′-oxobutyl-14,17α-ethenoestra-1,3,5(10)-triene, on the basis of the available spectral data. Reaction of MVK and the 14,16-diene under thermal conditions afforded the desired 16α-acetyl compound as the major product. Attempts to perform the peracid mediated insertion of oxygen were unsuccessful.

The final phase of the work was aimed at the synthesis of α-bridge oxygenated compounds. Cycloaddition of phenyl vinyl sulfone to the 14,16-diene afforded 3-methoxy-16α-phenylsulfonyl-14,17α-ethenoestra-1,3,5(10)-triene, as well as 3-methoxy-15α-phenylsulfonyl-14,17α-ethenoestra-1,3,5(10)-triene as a minor component. Hydroboration of the 16α-sulfone gave (17^2S)-3-methoxy-16α-phenylsulfonyl-14,17α-ethenoestra-1,3,5(10)-trien-17^2-ol and (17^1R)-3-methoxy-16α-phenylsulfonyl-14,17α-ethenoestra-1,3,5(10)-trien-17^1-ol as a separable mixture. Treatment of the alcohols with magnesium in methanol followed by standard deprotection afforded the corresponding diols, which were submitted for biological evaluation.

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Chapter 1

Introduction

An important class of compounds found in living organisms is the steroid family. These are molecules sharing a common feature, namely a structure based on the tetracyclic ring system shown in Figure 1.1. Many mammalian steroids function as hormones and are divided into two main classes: the sex hormones, responsible for maturation and reproduction; and the adrenocortical hormones, responsible for the regulation of a wide variety of metabolic processes.

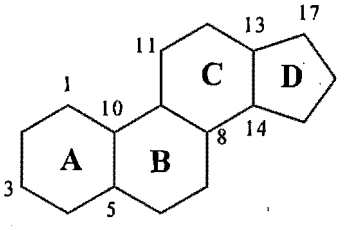


Figure 1.1

The female sex hormones have been and continue to be extensively studied. These hormones and their analogues have been used successfully in a wide range of medical applications such as birth control, hormone replacement therapy in postmenopausal women, and management of postmenopausal breast cancer.[1] The steroidal female sex hormones may be divided into two classes, i.e. the estrogens and the progestins. Estrogenic hormones are important substances responsible for the development of secondary female sex characteristics, and for regulation of the menstrual cycle.[2] The steroidal estrogens which have been known for the longest time are estrone, estradiol, estriol, equilin, and equilenin (Figure 1.2).[3] These were first isolated in the early 1930's from the urine of pregnant mares.[3] The most abundant of these hormones in humans are estradiol, estrone and estriol, and are synthesised in the ovaries from cholesterol in a multistep reaction sequence culminating in aromatisation via the action of the enzyme aromatase.[4]

The biochemical action of estrogens arises from their interaction with estrogen receptors.[7] Until recently, crystal structure data for the estradiol – estrogen recptor complex have been unavailable, and the mode of receptor binding as well as the nature of the receptor have been inferred from binding affinity data of numerous estradiol analogues. By making systematic variations of functional groups around the periphery of the estradiol skeleton, the influence of specific structural features upon binding sites may be quantified.[8] A recent review describes a general model for the estradiol – estrogen receptor complex, based on such data.[9] An important deduction made from binding affinity studies is that binding of the hormone to the receptor occurs via a strong hydrogen bond between the receptor and the phenolic 3-hydroxy group, and interaction of the 17-hydroxy group with the receptor induces the biological response.[10]

The availability of crystal structure data for other nuclear receptors (the superfamily to which the estrogen receptor belongs) led to the formulation of a three dimensional molecular model of the human estrogen receptor ligand binding domain.[11] Prior to this, the crystal structure of the ligand binding domain of the estrogen receptor in complex with estradiol had been published.[12] It was shown that the ring A and ring D hydroxy groups are involved in direct hydrogen bonds and the remainder of the estradiol molecule participates in a number of hydrophobic contacts, consistent with the models proposed previously. It is clear that analysis of the crystal structure in conjunction with the vast amount of binding affinity data available will lead to a greatly improved understanding of the binding of ligands to the estrogen receptor, and thus facilitate the design of estradiol analogues.

The work carried out in this project is part of a broad investigation into the structure activity relationships of ring D bridged estradiol analogues. The investigation was prompted by the discovery that 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol (Figure 1.4) is an orally active estrogen, with biological activity similar or superior to 17α-ethynylestradiol.[13] Since then, a number of other ring D bridged estradiol analogues have been synthesised .[14-17] In this thesis, the synthesis of further bridged analogues of estradiol is described. The precise nature of these analogues is discussed in the following chapter.

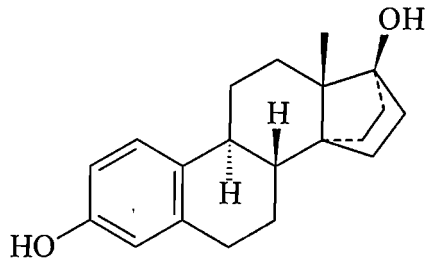


Figure 1.4: 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol

Chapter 2

Objectives and Approach

The overall objective of this investigation was to synthesise bridged analogues of estradiol, using 14,17α-ethanoestra-1,3,5(10)-trien-3-ol as a template for locating the ring D hydroxy group in a variety of new locations (Figure 2.1). The 14,17α-ethano bridge adds another degree of freedom for the attachment of a polar partner for receptor binding.

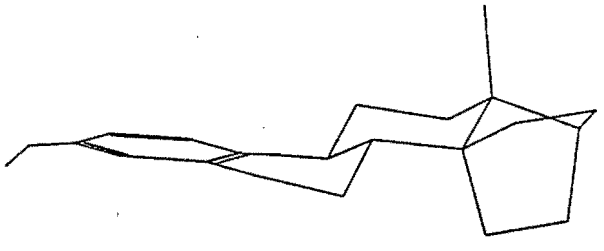


Figure 2.1: 14,17α-ethanoestra-1,3,5(10)-trien-3-ol

Such analogues are characterised by a possible "rotational equivalence" to estradiol, in that rotation of these hormones may lead to spatial relationships between the terminal hydroxy groups similar to that present in estradiol. An example is shown in Figure 2.2, in which estradiol and the 17-deoxy-17^1-alcohol are superimposed to obtain the best possible correspondence between the terminal hydroxy groups. Rotation clearly alters the spatial characteristics of the hydrophobic tetracyclic template within the estrogen receptor cavity, and it is thus possible that these analogues will have altered estrogenic activity, relative to estradiol

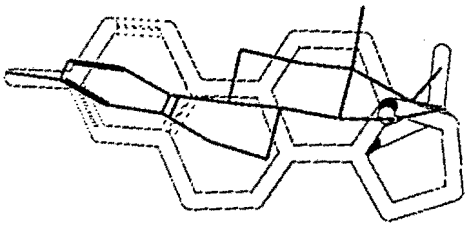
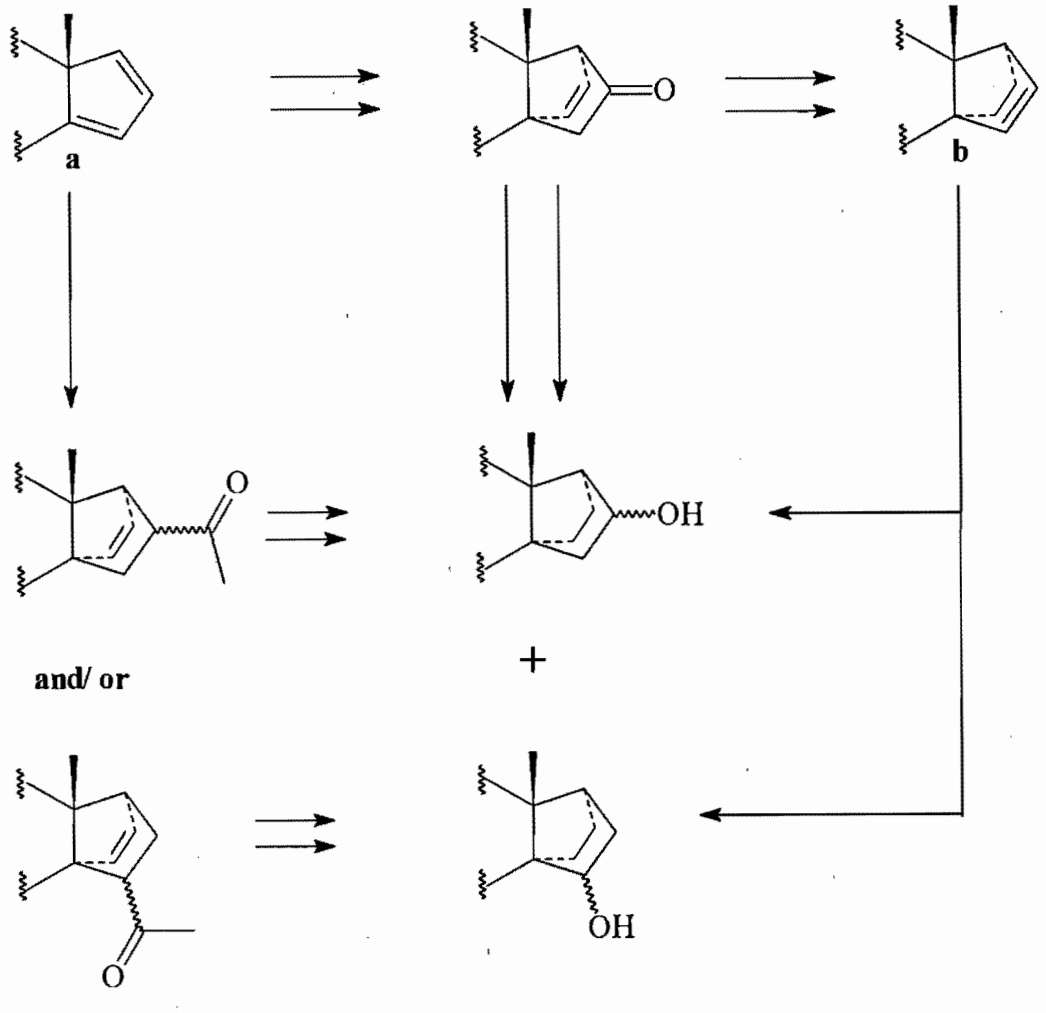


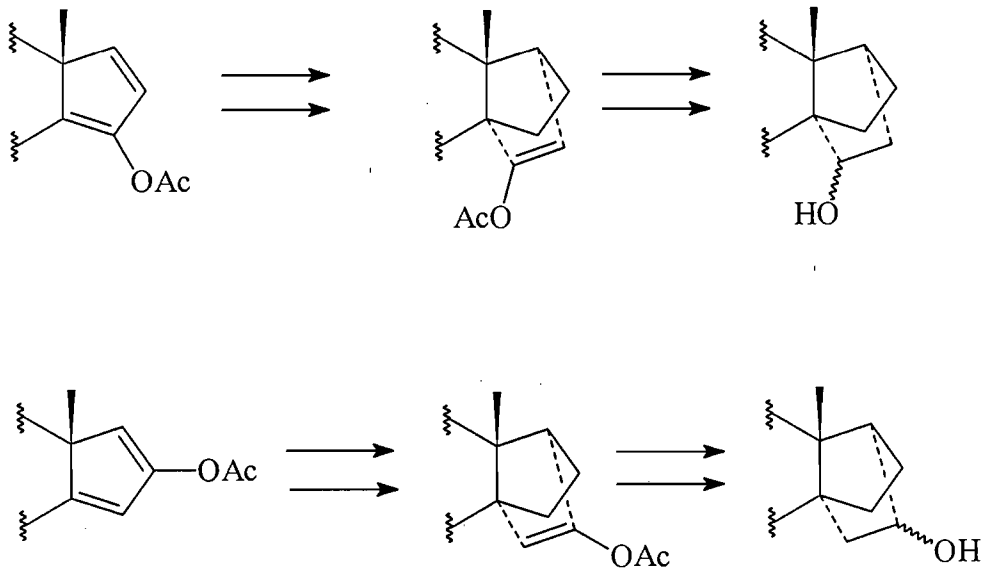
Figure 2.2: 3-Dimensional view of estradiol and a bridged rotational analogue

Locating the hydroxy group at all possible positions on ring D of the template shown in Figure 2.1 affords a total of eight possible diastereomeric compounds, with potentially varying degrees of rotational equivalence. It was planned to synthesise all of these hormones, and compare their relative binding affinity data. Analogues bearing functionality on the β-bridge are expected to be accessible via cycloaddition of a ketene equivalent to 3-methoxyestra-1,3,5(10),14,16-pentaene **a** (Scheme 2.1). Hydride reduction of the resulting ketone(s) would afford the corresponding alcohol(s). Alternatively, hydroboration of the olefin **b** would also afford β-bridge alcohols. Another practical approach to stereodefined introduction of a bridged hydroxy group entails cycloaddition of methyl vinyl ketone to diene **a**, followed by the Baeyer Villiger reaction, resulting in the stereoselective insertion of oxygen (Scheme 2.1).



Scheme 2.1

It is expected that oxygen could be introduced onto the α-bridge via hydroboration of the residual olefinic bond resulting from cycloaddition to the 14,16-diene **a**. Bridge-oxygenated intermediates can also be envisaged by cycloaddition to C(15)- and C(16)-oxygenated dienyl systems (Scheme 2.2). This would afford intermediates bearing built-in oxygen functionality as masked carbonyl groups. Reduction of the ketones obtained from deprotection of these groups is expected to give access to the corresponding bridge-hydroxylated compounds.



Scheme 2.2

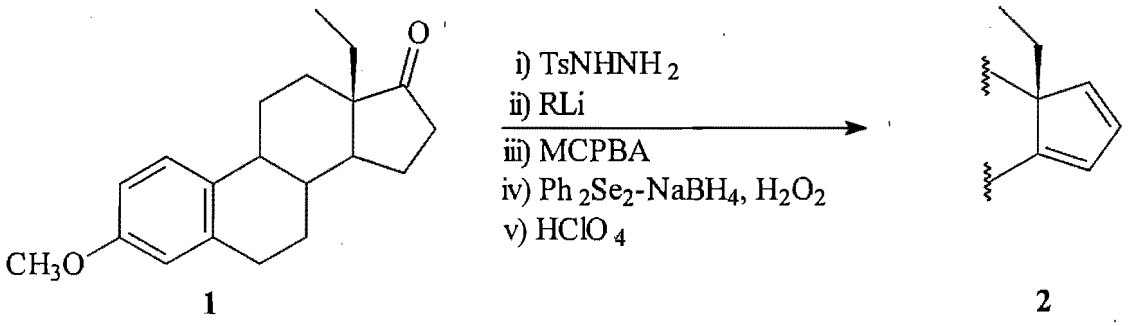
The first phase of the work was devoted to the development of an efficient synthesis of the diene **a**, and will be discussed in the next chapter.

Chapter 3

Discussion

3.1 Synthesis of 3-methoxyestra-1,3,5(10),14,16-pentaene.

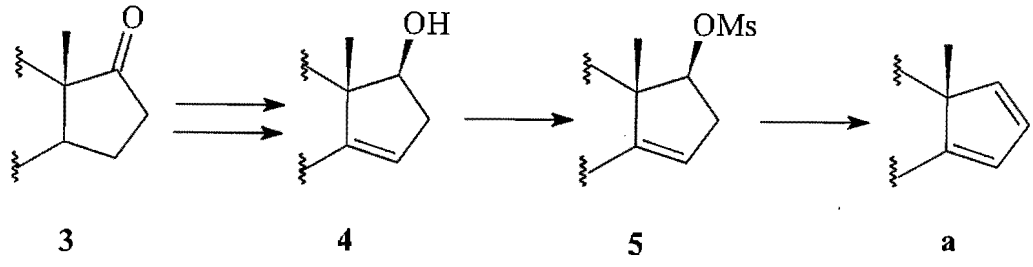
A method for the synthesis of steroidal 14,16-dienes has been described by Hofmeister.[18] In that work, 3-methoxy-18a-homoestra-1,3,5(10)-trien-17-one **1** was converted via sequential Shapiro elimination of the derived p-tosylhydrazone into the Δ^{16}-compound and hence, the corresponding 16α,17α-epoxide. Treatment of the epoxide with sodium phenylselenide, followed by hydrogen peroxide, afforded the Δ^{15}-17α-alcohol which was dehydrated with aqueous perchloric acid to give the 14,16-diene **2** in an overall yield of 24% (Scheme 3.1).



1 **2**

Scheme 3.1

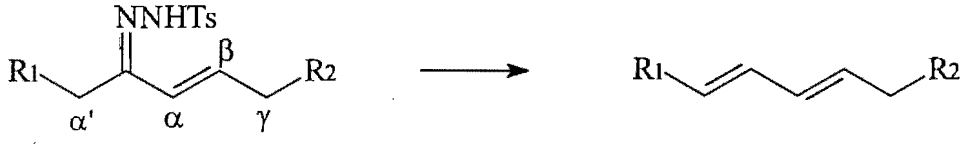
A subsequent attempt to apply this reaction sequence to estrone 3-methyl ether **3** was reported to give a very poor yield of the 14,16-diene **a**.[19] Accordingly, these authors investigated alternative approaches based upon the intermediacy of the Δ^{14}-17-alcohol **4** ,[20] which is readily prepared in good yields from estrone 3-methyl ether **3** (Scheme 3.2). Treatment of the alcohol **4** with methanesulfonyl chloride yielded the Δ^{14}-17β-mesylate **5**. Subsequent reaction with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in refluxing dimethylformamide afforded the diene **a**. This constitutes a six step synthesis of the diene **a** from estrone 3-methyl ether **3** in 36% overall yield.



Scheme 3.2

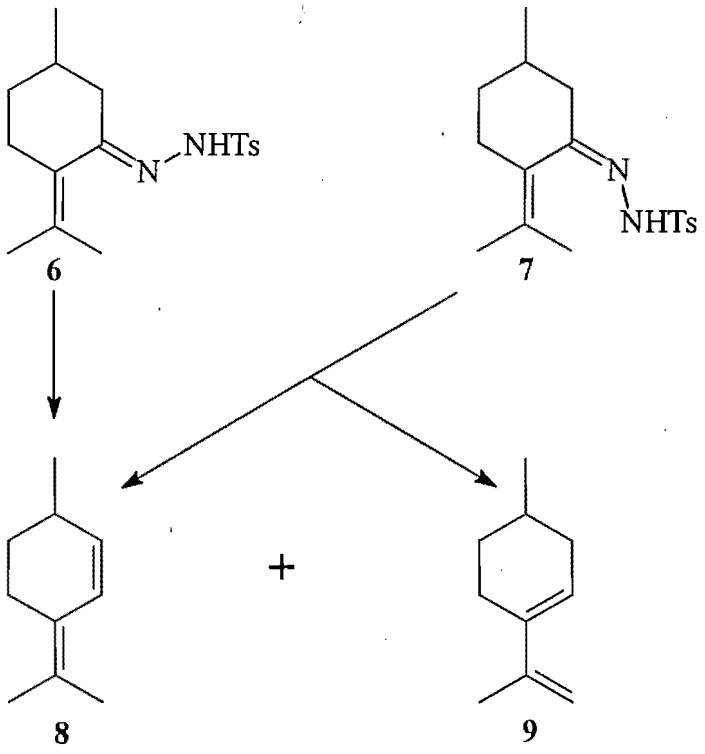
The foregoing literature methods are characterised by multi-step reaction sequences, and modest overall yields. Accordingly, it was decided to explore the scope for developing a more direct approach for preparing the 14,16-diene **a**.

The Shapiro reaction is the alkyllithium-mediated decomposition of ketone arenesulfonylhydrazones and is a method for the conversion of ketones to alkenes.[21] The synthesis of conjugated dienes using the Shapiro reaction was first reported by Shapiro *et al.* in 1968.[22] It was found that the reaction of methyllithium with the tosylhydrazones of α,β-unsaturated ketones afforded conjugated dienes in good to excellent yields (Scheme 3.3).



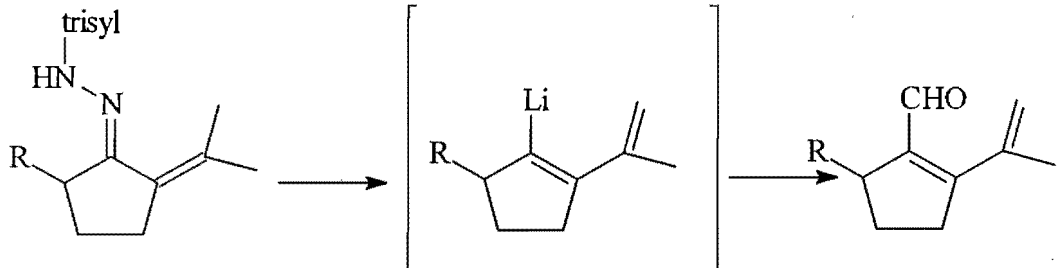
Scheme 3.3

In all the cases studied, it was found that the elimination involved only the α'-proton, and that isomerisation of the original double bond did not occur. The first known reaction in which elimination occured via abstraction of the γ-proton was reported by Dauben *et al.*[23] Studies on the isomeric pulegone tosylhydrazones **6** and **7** showed that the regioselectivity of proton abstraction is dependent on the geometry of the tosylhydrazone grouping (Scheme 3.4). The relative proportions of the dienes **8** and **9** were demonstrated to be solvent dependent, with tetrahydrofuran affording the highest yield of the diene **9** (9:1).



Scheme 3.4

Recent work by Caille *et al.* also demonstrated the feasibility of diene synthesis via abstraction of the γ-proton of α,β-unsaturated hydrazones.[24] Arenesulfonylhydrazones of α,β-unsaturated cyclopentanones such as isopropylidene cyclopentanones **10** and **11** were treated with *sec*-butyllithium to give an intermediate 1,4-lithiodiene which was trapped with dimethylformamide (DMF) to give aldehydes **12** and **13** (Scheme 3.5).

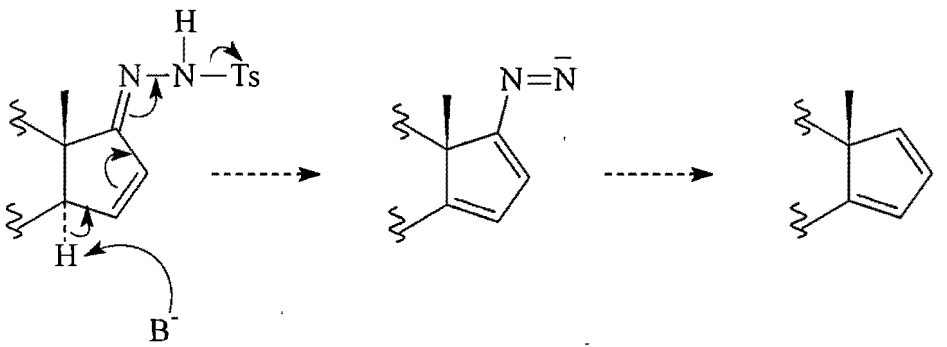


10: R=CH_3
11: R=H

12: R=CH_3
13: R=H

Scheme 3.5

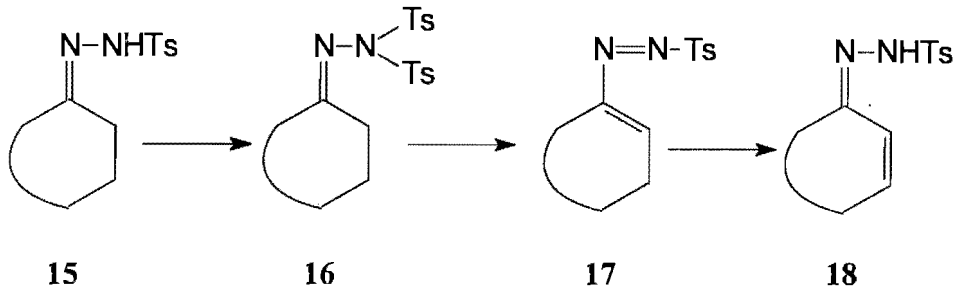
It was speculated that if the α,β-unsaturated tosylhydrazone **14** is accessible, it may be possible to synthesise the diene **a** under the conditions of the Shapiro reaction (Scheme 3.6). A favourable feature of compound **14** is that there is only one acidic proton available, as the α'-position is blocked. Various methods for the synthesis of α,β-unsaturated tosylhydrazones have been reported in the literature. The most obvious method of reacting an α,β-unsaturated ketone with toluene-*p*-sulfonylhydrazide has limited applicability, as competitive conjugate addition occurs unless the β-substituent is sufficiently bulky to prevent this process.[25] Monitoring (TLC) of small scale experiments in which 3-methoxyestra-1,3,5(10),15-tetraen-17-one was reacted with toluene-*p*-sulfonylhydrazide in the presence of catalytic trifluoroacetic acid indicated a complex mixture of products, with no clear major product, and the reaction was not investigated further. Alternative methods for the synthesis of α,β-unsaturated tosylhydrazones have been developed, which do not proceed via α,β-unsaturated ketones. These methods were investigated and are described here.



14 **a**

Scheme 3.6

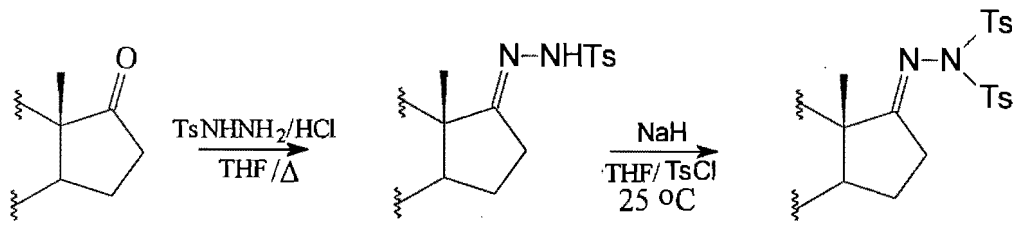
A recent report by Magnus and Roe describes the synthesis of α,β-unsaturated tosylhydrazones from saturated ketones via *N,N*-bis-tosylhydrazone derivatives.[26] That work was part of an investigation into a shortened synthetic route to 2-lithiodienes for subsequent treatment with an electrophile. The tosylhydrazone of a saturated ketone **15** was treated with sodium hydride and tosyl chloride to afford the *N,N*-bis-tosylhydrazone **16**. Treatment of this product with 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) yielded the tosylazoalkene **17**, via elimination of toluene-*p*-sulfinic acid. The tosylazoalkene **17** then tautomerised to the more stable α,β-unsaturated tosylhydrazone **18** (Scheme 3.7).



15 **16** **17** **18**

Scheme 3.7

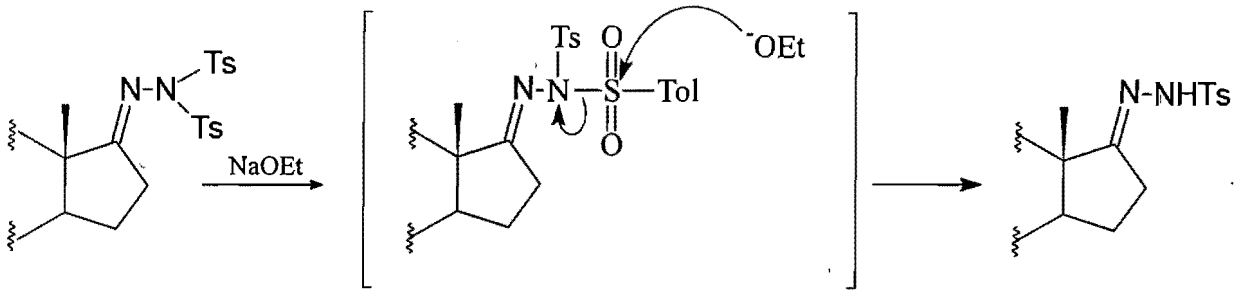
Attempts were made to apply this method to the synthesis of the α,β-unsaturated tosylhydrazone **14**. The tosylhydrazone of estrone 3-methyl ether **19** was synthesised quantitatively from **3**. Treatment of this product with sodium hydride and toluene-*p*-sulfonyl chloride in tetrahydrofuran (THF) resulted in slow conversion (88h) to the *N,N*-bis-tosylhydrazone **20**, but in excellent yield (95%) (Scheme 3.8). Spectroscopic and microanalytical evidence confirmed that the addition of a second tosyl group had occurred. The ^{1}H NMR spectrum displayed a six proton singlet at δ 2.40 which was assigned to the methyl protons of the two tosyl groups.



3 **19** **20**

Scheme 3.8

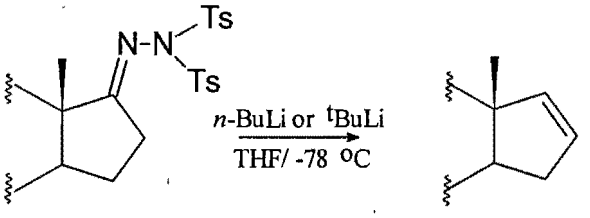
Disappointingly, the attempted elimination of toluene-*p*-sulfinic acid from the *N,N*-bis-tosylhydrazone to form the corresponding α,β-unsaturated tosylhydrazone was unsuccessful. Using the conditions employed by Magnus and Roe, *viz.* treatment of the *N,N*-bis-tosylhydrazone **20** with DBU in chlorobenzene or THF at room temperature, failed to result in a reaction. Heating caused extensive decomposition, as described by Magnus and Roe. The *N,N*-bis-tosylhydrazone **20** was reacted with other bases in an attempt to achieve the desired elimination reaction. Treatment of **20** with sodium ethoxide at room temperature afforded the tosylhydrazone **19** (Scheme 3.9). This result may be a consequence of nucleophilic attack by the ethoxide anion on the tosyl sulfur atom.



20 19

Scheme 3.9

The reaction of **20** with n-butyllithium in tetrahydrofuran at –78 °C afforded 3-methoxyestra-1,3,5(10),16-tetraene **21** in 60% yield. The mechanism may be analogous to that of the previous case, in which nucleophilic attack by the *n*-butyllithium anion on the tosyl sulfur atom affords the anion of the tosyl hydrazone, and subsequent conventional Shapiro elimination intervenes. The *N,N*-bis-tosylhydrazone **20** was reacted with the non-nucleophilic base *t*-butyllithium in an attempt to prevent the initial nucleophilic attack on the tosyl group, but this too led to the formation of the olefin **21**.



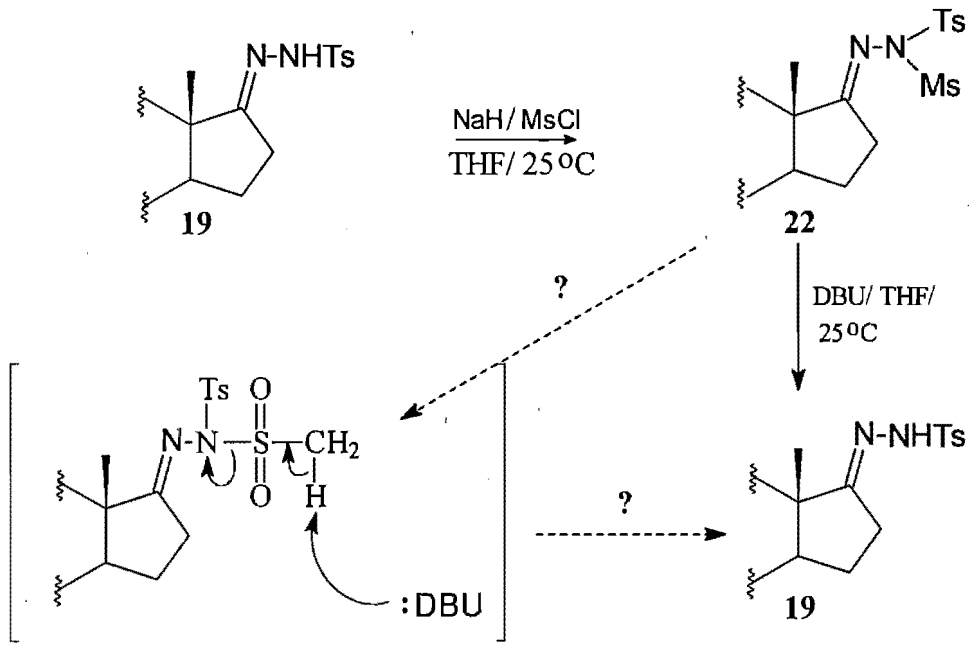
20 21

Scheme 3.10

It is possible that DBU-mediated abstraction of the proton alpha to the hydrazone is impeded by the steric bulk of the geminal *N,N*-ditosyl grouping, although there is no clear difference between the steric environment of the α-protons in **20** and the examples reported in the literature. In an attempt to overcome this problem, a *N*-methanesulfonyl-*N*-tosylhydrazone **22** was synthesised by reacting the tosylhydrazone **19** with methanesulfonyl chloride. (Scheme 3.11). The ^{1}H NMR spectrum of this compound displayed a three proton singlet at δ 2.83, which confirmed the presence of a mesyl group. The microanalytical data was consistent with the assigned structure.

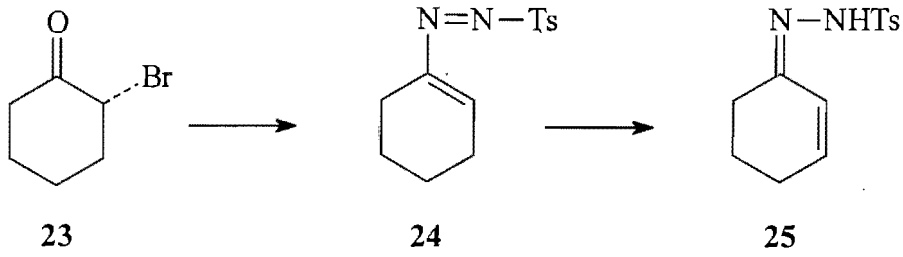
However, treatment of **22** with DBU afforded the tosylhydrazone **19** in 73% yield, shown by direct

comparison with authentic material (Scheme 3.11). This reaction was not investigated further, as it did not lead to the desired product, but it is possible to speculate on the mechanism of this transformation. Proton abstraction under the influence of a lone pair of electrons on DBU may result in loss of the mesyl group, as shown in Scheme 3.11.



Scheme 3.11

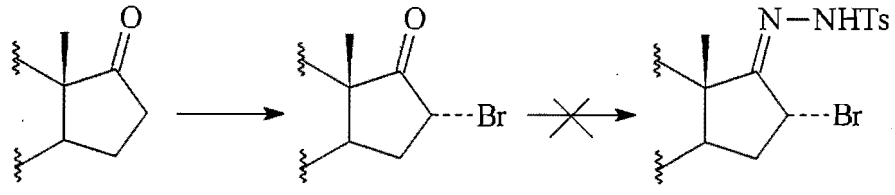
Attention was turned to indirect methods for preparing the Δ^{15}-17-tosylhydrazone **14**. One such approach is suggested by work reported by Caglioti *et al.*,[27] in which it was shown that reaction of toluene-*p*-sulfonylhydrazine with α-bromocyclohexanone **23** affords the tosylazoalkene **24** after basic work-up (Scheme 3.12). This product may be isomerised to the α,β-unsaturated tosylhydrazone **25** upon treatment with triethylamine.[28] This method has been employed by Lightner *et al.* to synthesise the α,β-unsaturated tosylhydrazone of 3-methylcyclohexanone,[29] as the reaction of 3-methylcyclohex-2-enone with toluene-*p*-sulfonylhydrazine leads to the conjugate addition product.



23 **24** **25**

Scheme 3.12

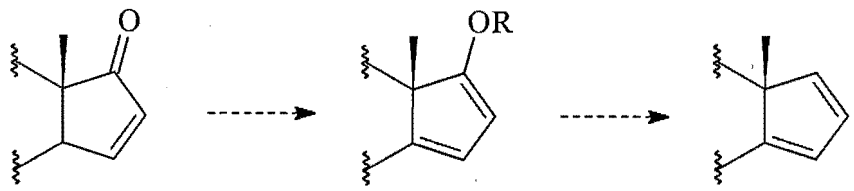
Attempts to apply this method to the synthesis of the α,β-unsaturated tosylhydrazone **14** were unsuccessful. The bromoketone **26** was readily prepared from estrone 3-methyl ether **3** by reaction of **3** with copper (II) bromide (Scheme 3.13).[30] However, treatment of **26** with toluene-*p*-sulfonylhydrazine failed to lead to the desired bromotosylhydrazone **27**. It is not unreasonable to assume that approach of the reagent to the 17-ketone is sterically impeded by the 13β-methyl group and the 16α-bromo substituent.



3 **26** **27**

Scheme 3.13

A second approach to the synthesis of the 14,16-diene **a** that was studied involved the use of enolate trapping. The synthesis of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate **28** (see appendix for structure of **28**) is a convenient three step synthesis of a 14,16-diene from estrone 3-methyl ether **3**.[30] This method of diene synthesis prompted us to investigate the possibility of trapping the dienolate of 3-methoxyestra-1,3,5(10),15-tetraen-17-one and performing a deoxygenation of the derived intermediate (Scheme 3.14).

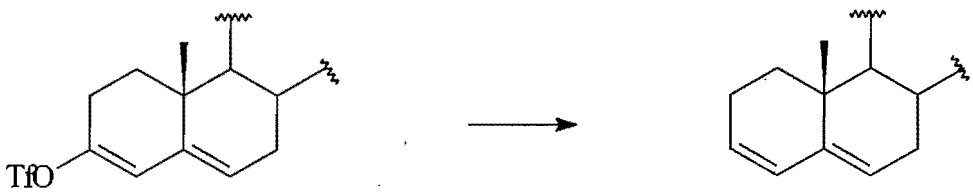


a

Scheme 3.14

The direct deoxygenation of the dienyl acetate **28** was considered, but the only precedent for this approach appears to be work reported by Nelson *et al.*[31] Vinyl acetates were deoxygenated using iron pentacarbonyl, but in poor yield. For example, 3-methoxyestra-1,3,5(10),16-tetraen-17-yl acetate was deoxygenated to afford the corresponding olefin in 35% yield. No subsequent improvements or modifications on this reaction were found in the literature.

The deoxygenation of ketones to olefins via enol trifluoromethanesulfonates (triflates) was first reported by Cacchi *et al.*[32] The enolates of ketones were trapped with triflic anhydride to afford enol triflates, according to the method of Stang.[33] Treatment of the enol triflates with formic acid in the presence of palladium(0) catalysts afforded the corresponding olefins in good yield. Dienyl triflates could also be synthesised from the corresponding enones and undergo deoxygenation to yield dienes without reported overreduction (Scheme 3.15).

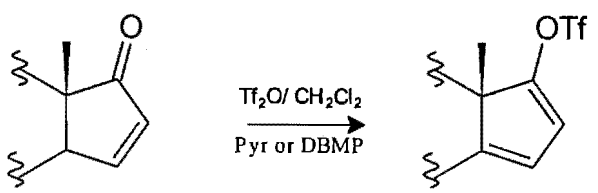


Scheme 3.15

An application of this method of diene synthesis may be found in work reported by Dolle et al.,[34] in which various derivatives of ergosterol were synthesised.

In the light of these results, it was expected that the diene **a** could be successfully synthesised via

this method. The Δ^{15}-17-ketone **29** was treated with triflic anhydride in dichloromethane in the presence of pyridine at 25 °C for 90h to afford the dienyl triflate **30** in 70% yield (Scheme 3.16). The product displayed spectroscopic and analytical properties consistent with the assigned structure. The noteworthy feature of the ^{1}H NMR spectrum is the diagnostic presence of signals for 15-H and 16-H at δ 6.15 (d, *J* 2.7 Hz) and δ 5.86 (dd, *J* 2.7 and 1.6 Hz) respectively. The splitting pattern of the 15-H signal is compatible with coupling between 15-H and 16-H, and a smaller allylic coupling between 15-H and 8β-H. The chemical shift and coupling constant values of these signals in **30** correlate well with those obtained for the dienyl acetate **28**. [35]



29 **30**

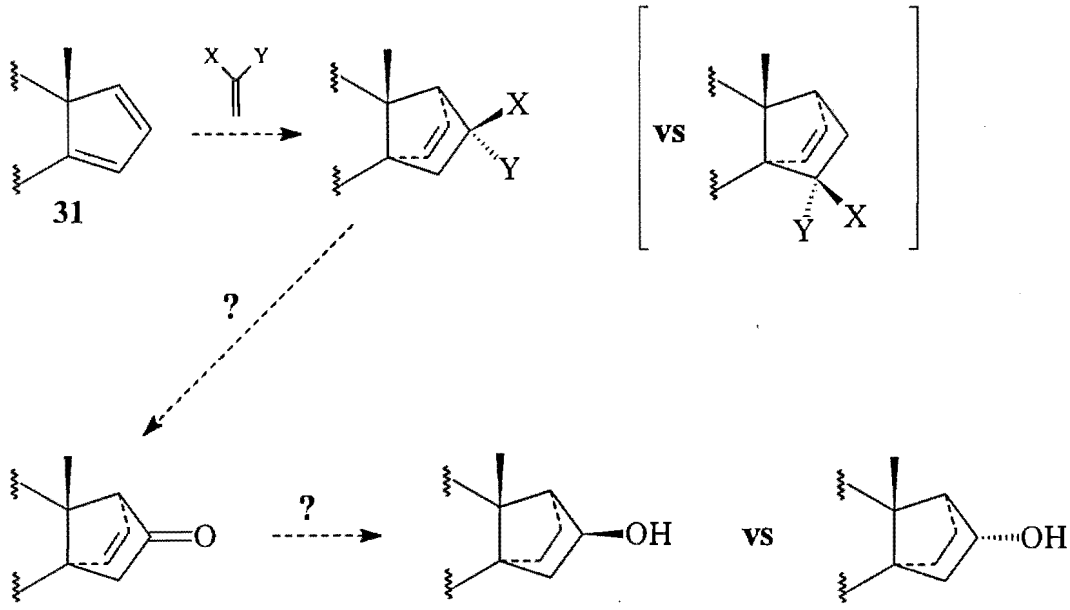
Scheme 3.16

An improvement in the yield of this reaction to 90% was achieved by using di-*t*-butyl-4-methyl pyridine (DBMP) in place of pyridine. This sterically hindered base is thought to be effective because it acts only as an acid scavenger without forming salts with triflic anhydride.[33] The use of an alternative sterically hindered base was also investigated. Ethyldiisopropylamine (Hünig's base) was used in the triflation reaction and found to be superior to pyridine, in that it resulted in a faster reaction time and a homogeneous reaction mixture, but gave only a marginal improvement in the yield.

Initially, the deoxygenation of the dienyl triflate **30** was performed under the conditions reported in the literature.[32,34] The dienyl triflate **30** was treated with excess formic acid in the presence of triethylamine, triphenylphosphine, and catalytic palladium(II) acetate, and afforded the diene **31** in 39% yield, as well as a product of overreduction, *viz.* 3-methoxyestra-1,3,5(10),14-tetraene **32** in 28% yield (Scheme 3.17).

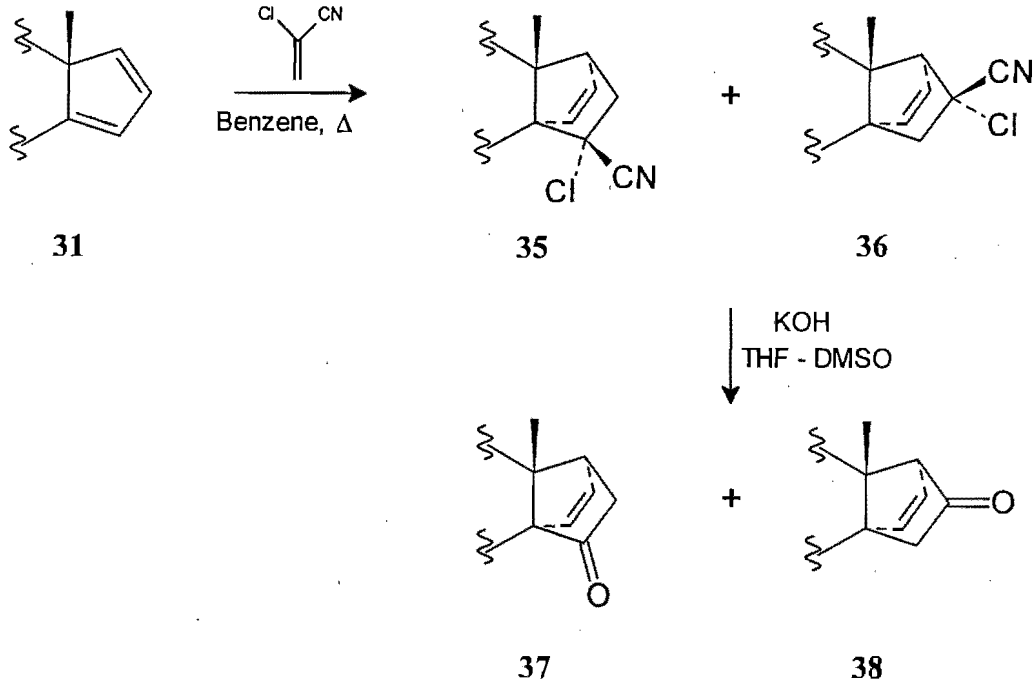
3.2 Synthesis of β-Bridge Oxygenated Analogues

The second phase of this investigation entailed cycloadddition of a ketene equivalent to the 14,16-diene **31** in order to introduce β-bridge oxygen functionality at C-16 and/or C-15 (Scheme 3.19). This approach is well precedented in the analogous study by Grundler,[37] on cycloaddition mediated approaches to 14α,17α-etheno analogues of estriol. In that work, it was shown that cycloaddition of 2-chloroacrylonitrile and 2-acetoxyacrylonitrile with the dienyl acetate **28** proceeded with high stereo- and regioselectivity to give 16-substituted adducts.



Scheme 3.19

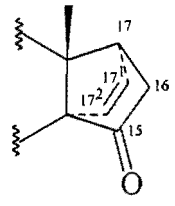
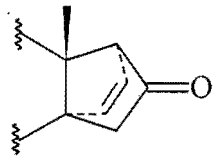
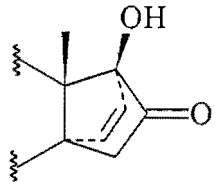
The ketene equivalent employed in this study was 2-chloroacrylonitrile. As no extensive investigation into the reactivity of the 14,16-diene **31** with various ketene equivalents was performed, it cannot be claimed that this reagent was the most suitable, but it served our purposes nonetheless. The cycloaddition of 2-chloroacrylonitrile to the 14,16- diene **31** was carried out in dry benzene in a sealed tube at 90°C and afforded an inseparable mixture of cycloadducts **35** and **36** as an oil in a total yield of 68% (Scheme 3.20).The reaction was slow (two weeks) and required the addition of further 2-chloroacrylonitrile at intervals during the reaction. Raising the temperature above 100 °C led to extensive decomposition of the diene. The ^{1}H NMR spectrum of the mixture **35** and **36** displayed the signals for 17^1- and 17^2-H as a multiplet (δ6.15 – 6.38)



Scheme 3.20

The mixture was treated with potassium hydroxide in THF/DMSO/water (1:1:1) at 80 °C for 45 h to afford the ketones **37** and **38** in 48 and 21% yield respectively (Scheme 14).[38] No reaction was observed at room temperature and at elevated temperatures, the conversion was slow. Temperatures above 100 °C led to diminished yields of the ketones **37** and **38**. The analytical and spectroscopic data of these compounds were in accordance with the proposed structures. The cycloaddition of 2-chloroacrylonitrile to the diene **31** was assumed to be β-face selective, on the basis of results obtained for cycloadditions to the dienyl acetate **28**. The regiochemistry of each ketone was assigned with the aid of the available spectral data, which are summarised in Table 3.1. The corresponding signals of 17β-hydroxy-3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-16-one **39** (recorded in deuteriochloroform) are shown for comparative purposes.[37]

Table 3.1: Assignments and coupling constants of the ring D protons of the ketones **37**, **38** and **39***

	 **37**	 **38**	 **39**
15α-H	–	δ 1.71 (dd, *J* 16.0 and 0.6 Hz)	δ 2.20 (d, *J* 16.9 Hz)
15β-H	–	δ 1.58 (dd, *J* 16.0 and 0.9 Hz)	δ 2.00 (dd, *J* 16.9 and 0.9 Hz)
16α-H	δ 1.66 (d, *J* 16.5 Hz)	–	–
16β-H	δ 1.96 (ddd, *J* 16.5, 3.0 and 0.9 Hz)	–	–
17β-H	δ 2.23 (td, *J* 2 x 3.0 and 0.8 Hz)	δ 2.64 (d, *J* 3.4 Hz)	–
17^1-H	δ 5.97 (ddd, *J* 5.7, 3.0 and 0.9 Hz)	δ 5.61 (dd, *J* 5.8 and 3.4 Hz)	δ 6.43 (d, *J* 6.0 Hz)
17^2-H	δ 5.63 (d, *J* 5.7 Hz)	δ 5.97 (d, *J* 5.8 Hz)	δ 5.83 (dt, *J* 6.0 and 2 x 0.9 Hz)

*Spectra of **37** and **38** recorded in deuteriobenzene. Spectrum of **39** recorded in deuteriochloroform

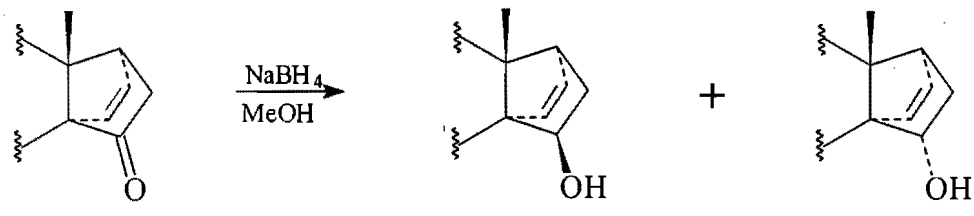
Initially the ^{1}H NMR spectra of both the 15- and 16- ketones were recorded in deuteriochloroform. In the case of the minor isomer **38**, key signals required to confirm the assigned regiochemistry could not be observed. These were the signals for 17-H, 15α-H, and 15β-H. A two proton singlet at δ 1.98 was tentatively assigned as the 15α- and 15β-H resonance, on the basis of the two protons having identical chemical shifts, giving rise to a degenerate spin system. The ^{1}H NMR spectrum was recorded in deuteriobenzene to achieve greater dispersion of signals. The signals for 15α-H and 15β-H resonated at δ 1.58 (dd, *J* 16.0 and 0.9 Hz) and 1.71 (dd, *J* 16.0 and 0.6 Hz), the splitting pattern of each signal consistent with a large geminal coupling between the respective protons. There is no obvious coupling partner for the small (0.6 Hz) coupling observed in the signal for 15α-H and no visible correlation peak in the COSY spectrum. The isolated AB system regiodefines this

compound as the 16-ketone **38**.

The ^{1}H NMR spectrum of the 15-ketone **37** was recorded in deuteriobenzene to allow a comparison of chemical shifts with those obtained for 16-ketone **38**. This also allowed the assignment of key signals, such as that for 16β-H which was partially obscured in the spectrum recorded in deuteriochloroform. The signals for 17^{1}-H and 17^{2}-H resonated at δ 5.97 (ddd, *J* 5.7, 3.0 and 0.9 Hz) and δ 5.63 (d, *J* 5.7 Hz) respectively. The splitting pattern of the 17^{1}-H resonance is compatible with couplings to 17^{2}-H and 17β-H, as well as a small long range coupling to 16β-H (*J* 0.9 Hz). The 16α-H resonated at δ 1.66 as a doublet (*J* 16.5 Hz), indicating its orthogonality to 17-H. The coupling of 17-H to 16β-H provided conclusive evidence of the regiochemistry of **37**.

3.2.1 Reduction of the ketones 37 and 38

As both ketones were desired in the context of this project, the lack of regioselectivity in the cycloaddition of 2-chloroacrylonitrile to the 14,16-diene **31** was advantageous. With the ketones **37** and **38** in hand, it was obvious that hydride reduction of these ketones would lead to some of the desired targets of this project. Initially, the 15-ketone **37** was reacted with sodium borohydride in methanol-THF at 0 °C to afford the 15β-alcohol **40** and the 15α-alcohol **41** in 71 and 8% yield respectively (Scheme 3.21).



37 **40** **41**

Scheme 3.21

Unfortunately, the signal for 15-H in the ^{1}H NMR spectrum of the major compound **40** was poorly resolved, and no coupling information could be obtained. It was possible, however, to assign the structure of the minor isomer on the basis of its ^{1}H NMR spectrum. The signal for 16β-H at δ 2.63 (ddd, *J* 12.8, 7.5 and 3.8 Hz) was assigned on the basis of its muliplicity, and, specifically, its coupling to 17-H (*J* 3.8 Hz) which defines the orientation as *exo*. The magnitude of the vicinal coupling between 16β-H and 15-H (*J* 7.5 Hz) indicates a syn relationship between the respective protons. This implies that the orientation of 15-H is *exo* and hence the 15-hydroxy group must be *endo*. The coupling data for the ring D protons are summarised in Figure 3.1.

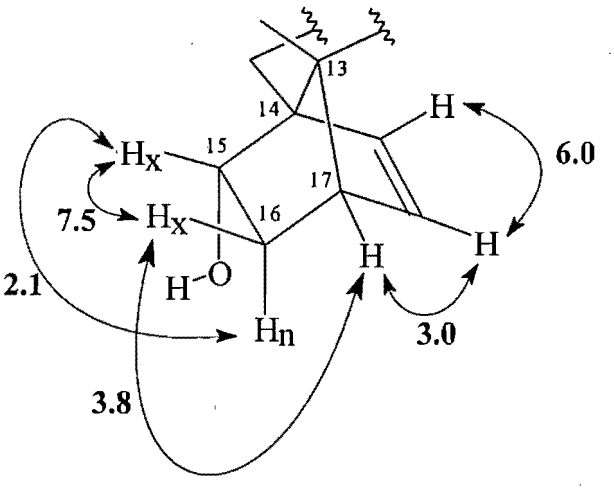
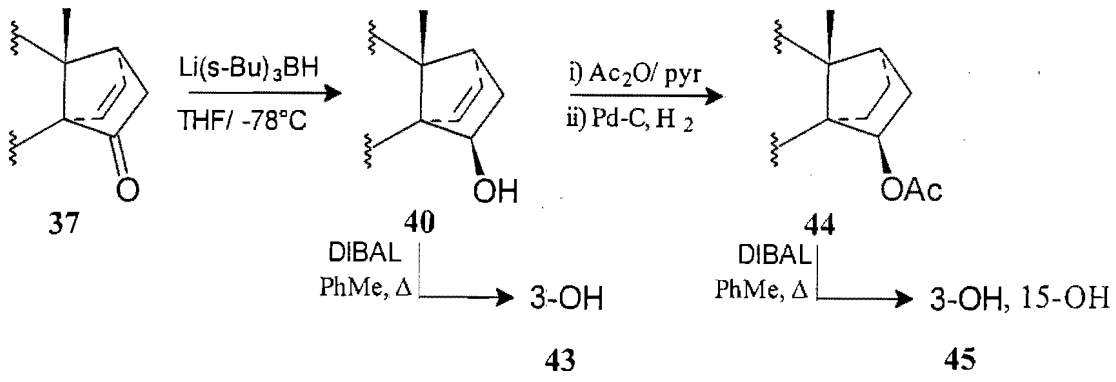


Figure 3.1: Coupling Constants for Ring D Protons for the Alcohol **41**

The stereoselectivity of this reaction is consistent with the findings of Brown and Deck in their study on the hydride reduction of bicyclic ketones,[39] in which it was found that hydride reduction of camphor yielded the corresponding *exo*-alcohol as the major isomer as a result of the steric shielding afforded by the 7-methyl group.

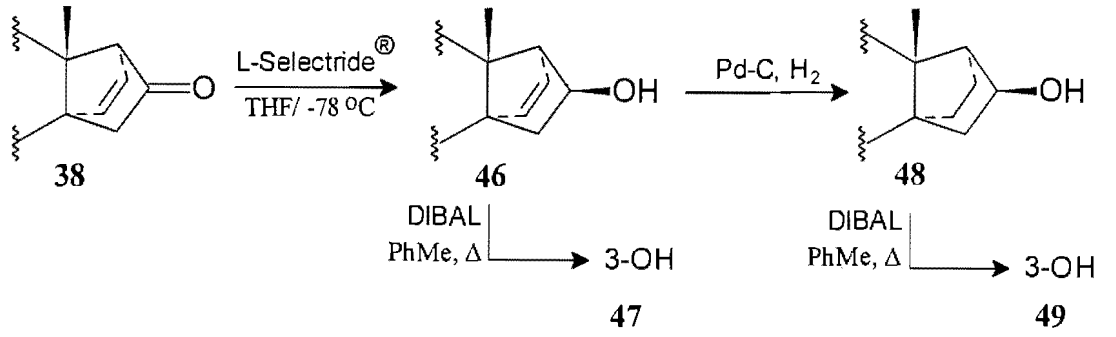
Although both isomers were desired in this project, the yield of the minor isomer was too low for this to be synthetically viable process. It was decided to utilise a reaction that would yield the major 15β-alcohol **40** exclusively. The use of lithium tri-sec-butylborohydride (L-Selectride®) for the stereoselective reduction of ketones was first reported by Brown and Krishnamurthy.[40] It was found that treatment of camphor with L-Selectride® afforded the corresponding *exo*-alcohol in an isomeric purity of 99.6%. The excellent stereoselectivity of this reagent can be attributed to the size of the alkyl substitution on boron. It was expected that similar high stereoselectivity could be obtained for the L-Selectride®-mediated reduction of the ketones **37** and **38**. The 15-ketone **37** was treated with L-Selectride® in THF at -78 °C to afford the 15β-alcohol **40** in 83% yield (Scheme 3.22). A portion of this material was converted into the acetate **42** by treating the 15β-alcohol with acetic anhydride in pyridine in order to facilitate characterisation. Treatment of the 15β-alcohol with diisobutyl aluminium hydride in refluxing toluene for 24 afforded the diol **43** in 93% yield (Scheme 3.22). Catalytic hydrogenation of the acetate **42** proceeded smoothly to give 17^1,17^2-dihydro compound **44** (Scheme 3.22). The product displayed spectroscopic and analytical properties consistent with the assigned structure. The signal for 15β-OCOCH_3 resonated at δ 1.98 (s), and 15α-H resonated at δ 4.87 (dd, *J* 6.7 and 3.7 Hz). This compound was deprotected at C-3 and C-17

by reaction with diisobutylaluminium hydride in refluxing toluene for 24 hours to yield the diol **45** in 90% yield. (Scheme 3.22).



Scheme 3.22

A similar sequence of reactions was performed on the 16-ketone **38** to obtain the corresponding estradiol analogues. (Scheme 3.23). The ketone **38** was treated with L-Selectride® in THF at –78 °C to afford the 16β-alcohol **46** in 94% yield. The 16α-H resonated at δ 3.98 (dd, *J* 7.5 and 2.8 Hz), the splitting pattern confirming the orthogonality to 17-H, thus supporting the assigned stereochemistry. Standard deprotection of the methyl ether with di-isobutylaluminium hydride gave the diol **47** in 92% yield. Catalytic hydrogenation of the 16β-alcohol **46** afforded the ethano compound **48** which was deprotected with di-isobutylaluminium hydride to afford the diol **49** in good yield. The four 17-deoxy bridged analogues of estradiol were submitted for biological evaluation. The results of the biological tests on the analogues synthesised in this work will be discussed later.

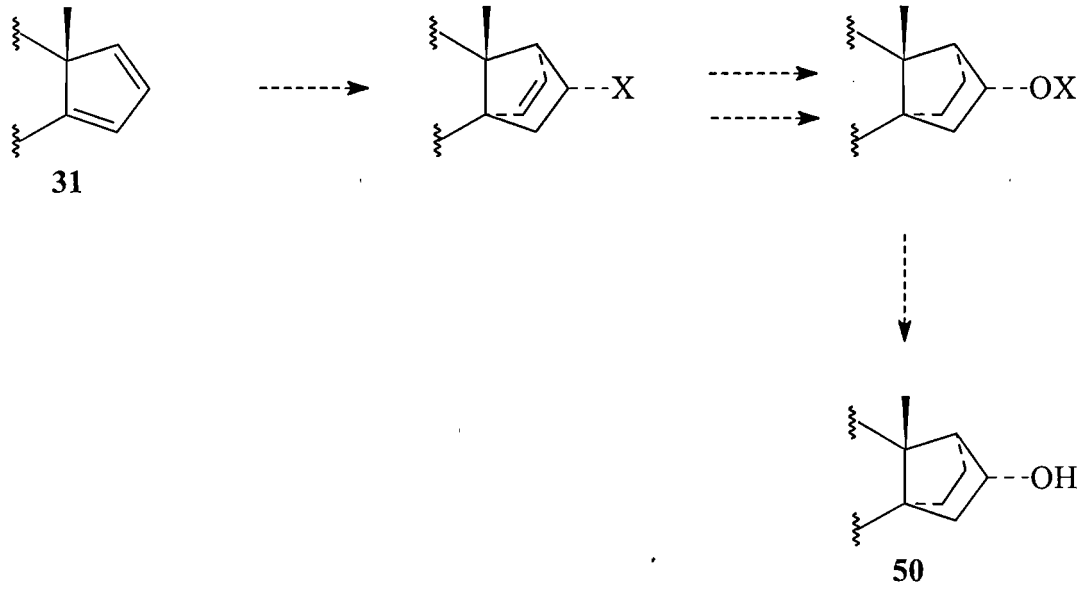


Scheme 3.23

There are various methods for the synthesis of the corresponding *endo*-alcohols in this series. The most straightforward method is most likely hydride reduction of the appropriate ketone (**37** or **38**), followed by recycling of the major *exo*-isomer via oxidation to the starting ketone. It is possible that sufficient quantities of the *endo*-alcohols could be obtained for biological testing via repetition of this sequence.

A more elegant possibility is inversion of the major *exo*-alcohols. A well known reaction which leads to the inversion of configuration at a secondary carbinol centre is the Mitsunobu reaction.[41] The reaction involves treatment of the alcohol with a carboxylic acid, such as *p*-nitrobenzoic acid, triphenylphosphine, and diethyl azodicarboxylate (DEAD). The primary product is an ester, which may be saponified with aqueous base to afford the inverted alcohol. This reaction was not attempted in this investigation, and further work is required to determine the viability of this route.

A possible route to the *endo*-isomers of the alcohols **45** and **49** that was investigated in this project is described here. It was recognised that since cycloaddition to the diene **31** is generally *endo*-selective, insertion of oxygen into the bond between the electron withdrawing group of the dienophile and the steroid would lead to the corresponding *endo*-alcohol after further functional group modification (Scheme 3.24).

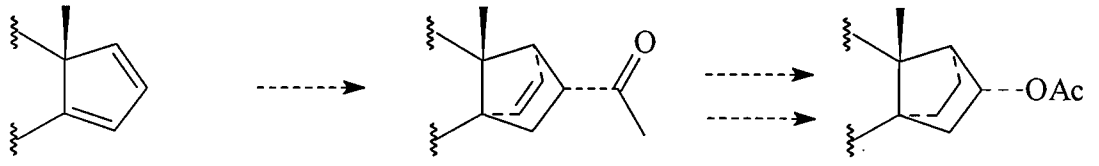


31 **50**

Scheme 3.24

A well known reaction of this type is the Baeyer – Villiger reaction, which is the oxidation of ketones with organic peroxy acids, hydrogen peroxide, or alkyl hydroperoxides to give esters or

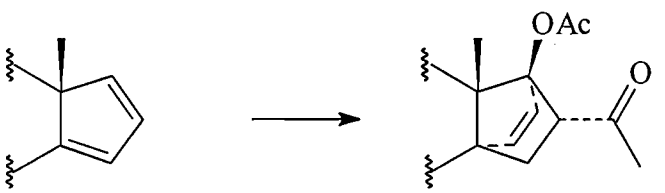
lactones. [42] The cycloadduct arising from the cycloaddition of methyl vinyl ketone to the diene **31** would provide a suitable substrate for Baeyer – Villiger oxidation, and thus lead to the desired α-alcohol **50** (Scheme 3.25).



31

Scheme 3.25

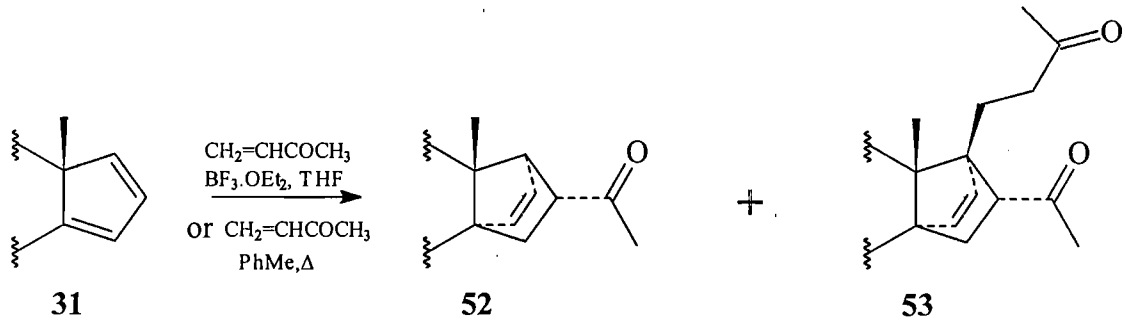
The cycloaddition of methyl vinyl ketone to the 14,16-dienyl acetate **28** has been reported previously.[43] In that work, the cycloaddition was performed under both thermal and Lewis acid catalysed conditions. The thermal reaction afforded the cycloadduct **51** in 74% yield, whilst the optimised Lewis acid catalysed reaction afforded **51** in 94% yield (Scheme 3.26).



28 **51**

Scheme 3.26

It was thus decided to perform the cycloaddition of methyl vinyl ketone to the diene **31** under similar Lewis acid catalysed conditions. The reaction of **31** with methyl vinyl ketone in anhydrous tetrahydrofuran at 25 °C in the presence of $BF_3.Et_2O$ for 24 h gave a separable mixture of products (Scheme 3.27). The minor component **52** (31%) analysed for a conventional cycloadduct, whereas the major product **53** (53%) had an empirical formula $C_{27}H_{34}O_3$, consistent with the formal addition of two methyl vinyl ketone equivalents to the diene. It was suspected that the Lewis acid catalyst might have been responsible for a non-pericyclic process. Accordingly, an uncatalysed reaction was performed, in which the diene **31** in toluene was reacted with methyl vinyl ketone at 120 °C (sealed tube) for 9h. This resulted in a greatly improved yield of the cycloadduct **52** (67%), but the unwanted product **53** was also formed under these conditions, although in much lower yield (17%).

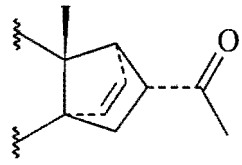
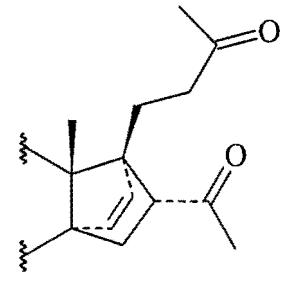


31 **52** **53**

Scheme 3.27

The structures of the products were assigned in accordance with the expectation that β-face cycloaddition had occurred. Analysis of the ^{1}H NMR spectrum of the conventional cycloadduct **52** confirmed the assigned structure. The signal for 16β-H occurred at δ 3.23 (dt, *J* 7.6 and 2 x 3.9 Hz). The multiplicity of this signal is compatible with a large *exo-exo* coupling between 16β-H and 15β-H, and smaller couplings to 15α-H and 17β-H. The coupling to 17β-H thus locates the functional group at C-16 and in an *endo*-orientation. Most of the signals in the ^{1}H NMR spectrum of this compound could be assigned with the aid of the corresponding COSY plot, which is shown in Figure 3.2. The signals for the aromatic protons, which occurred in the lower field region, exhibited no coupling with any of the high field signals, and have been excluded from the figure for clarity. All the ^{1}H NMR data for **52** are displayed in Table 3.2.

Table 3.2: ^{1}H NMR Data* for the cycloadducts **52** and **53**

	 **52**	 **53**
1-H	7.21 (d, *J* 8.5 Hz)	7.20 (d, *J*, 8.7 Hz)
2-H	6.72 (dd, *J* 8.5 and 2.8 Hz)	6.71 (dd, *J* 8.7 and 2.8 Hz)
4-H	6.64 (d, *J* 2.8 Hz)	6.64 (d, *J* 2.8 Hz)
6-H_2	2.86 (m)	2.85 (m)
7α-H	?	1.64 (m)
7β-H	1.92 (dddd, *J* 12.7, 5.3, and 2 x 2.6 Hz)	1.86 (m)
8β-H	1.42 (td, *J* 2 x 11.4 and 3.4 Hz)	1.44 (td, *J* 2 x 11.5 and 2.2 Hz)
9α-H	2.46 (td, *J* 2 x 11.4 and 3.7 Hz)	2.47 (td, *J* 2 x 11.5 and 3.8 Hz)
11α-H	2.19 (dq, *J* 13.7 and 3 x 3.7 Hz)	2.20 (dq, *J* 13.7 and 3 x 4.0 Hz)
11β-H	?	1.33 (ddd, *J* 3 x 13.0 and 3.9 Hz)
12α-H	?	?
12β-H	1.87 (dt, *J* 12.8 and 2 x 3.2 Hz)	1.11 (dt, *J* 12.6 and 2 x 3.2 Hz)
15α-H	1.72 (dd, *J* 12.0 and 3.9 Hz)	1.37 (dd, *J* 11.7 and 4.8 Hz)
15β-H	1.55 (dd, *J* 12.0 and 7.6 Hz)	1.98 (dd, *J* 11.7 and 9.4 Hz)
16β-H	3.23 (dt, *J* 7.6 and 2 x 3.9)	3.06 (dd, *J* 9.4 and 4.8 Hz)
17-H	2.92 (dt, *J* 2 x 3.9 and 0.9 Hz)	–
17^{1}-H	5.77 (dd, *J* 5.9 and 3.9 Hz)	5.94 (d, *J* 5.9 Hz)**
17^{2}-H	6.11 (d, *J* 5.9 Hz)	6.02 (d, *J* 5.9 Hz)**
13β-Me	0.96 (s)	0.87 (s)
3-OMe	3.78 (s)	3.77 (s)
COCH_3	2.14 (s)	2.05 (s); 2.15 (s)
1′-H_2	–	1.83 and 2.08 (each ddd, *J* 14.6, 10.0, 5.8)
2′-H_2	–	2.60 (m)

* ^{1}H NMR data reported as chemical shift (in ppm), multiplicity and J values (in Hz)
** Interchangeable

The assigned structure of the second compound **53** is consistent with the mass spectral, microanalytical, and NMR spectral data. It was possible to assign fully the 400 MHz ^{1}H NMR spectrum with the aid of COSY, HETCOR, DEPT, and ^{13}C data. It was assumed that β-face and 1,2-regioselective cycloaddition had occurred, and that *endo*-stereoselectivity was operative. The high field region of the ^{1}H NMR spectrum together with the corresponding COSY plot is shown in Figure 3.3. All the assignments for the protons are displayed in Table **3.2**. Substitution at C-17 was indicated by the pattern of signals associated with 17^{1}-H and 17^{2}-H at δ 5.94 and δ 6.02 (each d, *J* 5.9 Hz). Since neither of these signals displayed additional coupling, it was inferred that a bridgehead proton must be absent. The presence of two acyl groups was confirmed by two methyl singlets in the ^{1}H NMR spectrum at δ 2.05 and δ 2.15, and by two resonances in the ^{13}C NMR spectrum at δ 208.9 and δ 210.2, which were assigned to the carbonyl carbons. The signal for 16β-H resonated at δ 3.06 (dd, *J* 9.4 and 4.8 Hz), the splitting pattern compatible with a large *exo-exo* coupling to 15β-H, and a smaller *exo-endo* coupling to 15α-H, and confirming the absence of a proton at C-17. The signal for 15β-H resonated at δ 1.98 (dd, *J* 11.7 and 9.4 Hz) and was shown clearly to couple to 16β-H by a crosspeak in the COSY spectrum. The COSY spectrum also allowed the assignment of the 15α-H resonance at δ 1.37 (dd, *J* 11.7 and 4.8 Hz). All the ring A, B, C, and D protons and the corresponding ^{13}C resonances were assigned using the available spectral data. This allowed the identification and assignment of the proton and ^{13}C resonances of the oxobutyl side-chain at C-17. A multiplet at δ 2.60 which integrated for two protons was assigned to 2′-H_2. The chemical shift value is in agreement with the 'usual' value of δ 2.4 for methylene protons alpha to a carbonyl group.[44] A crosspeak in the HETCOR spectrum between this signal and a ^{13}C resonance at δ 40.9 (t) allowed the assignment of the C-2' signal. The COSY spectrum showed the 2′-protons to couple to a proton that resonated at δ 2.08 (ddd, *J* 14.6, 10.0, and 5.8 Hz), and to a proton at δ 1.83 (dd, *J* 14.6, 10.0, and 5.8 Hz). These two protons were also seen to couple to each other in the COSY spectrum, and were thus assigned as the 1′-H_2 resonances. The splitting pattern of each signal is consistent with a large geminal coupling between the 1′-protons, and smaller antiperiplanar (*J* 10 Hz) and synclinal (*J* 5.8 Hz) couplings to the 2′-protons.[44] The HETCOR spectrum showed the protons at δ 1.83 and δ 2.08 to be bonded to the same carbon, which resonated at δ 21.7 (t). This signal was thus assigned to C-1′.

It should be noted that the data do not lead to a unique assignment of the structure of this compound and are also consistent with the structure of the 15-regioisomer.

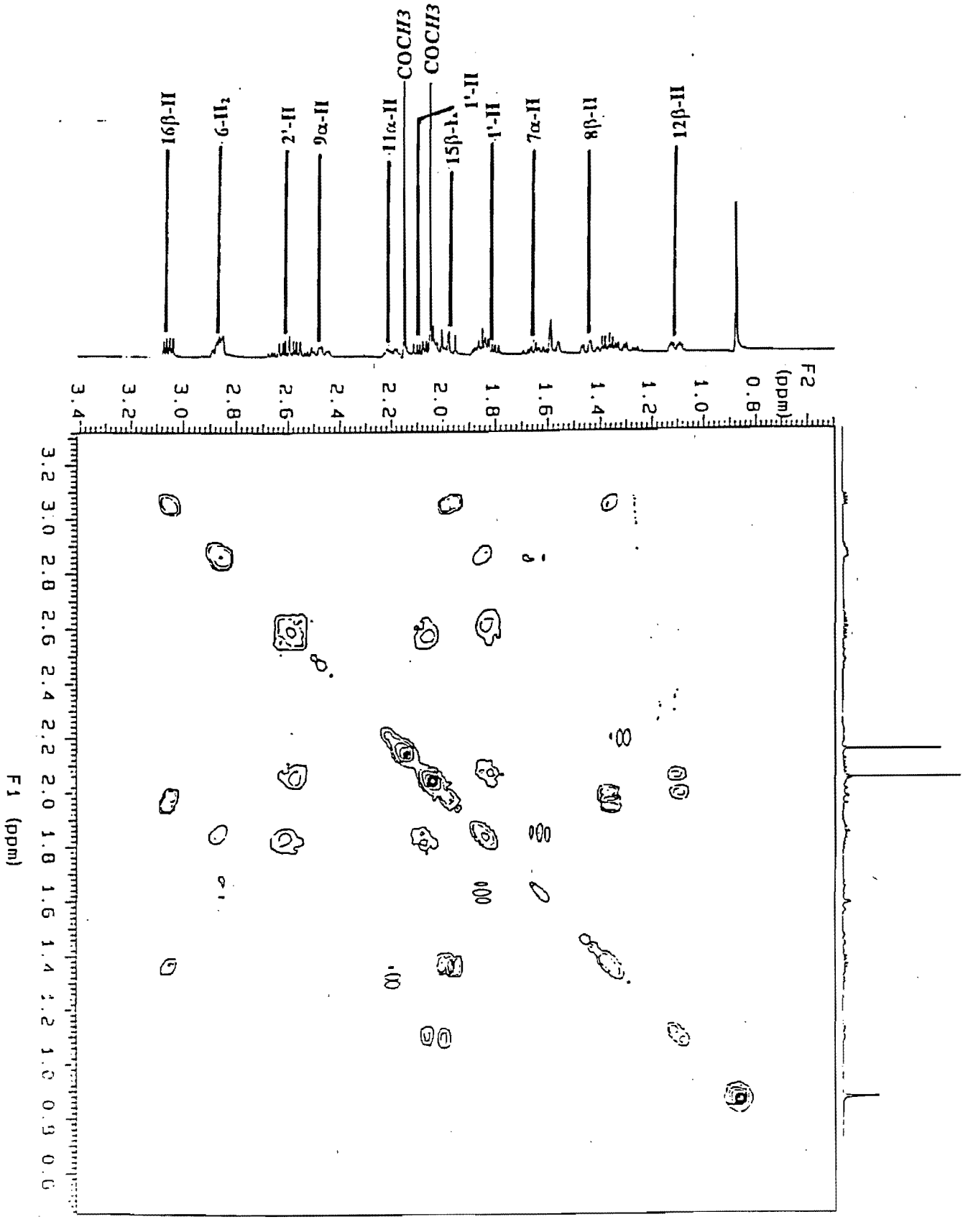
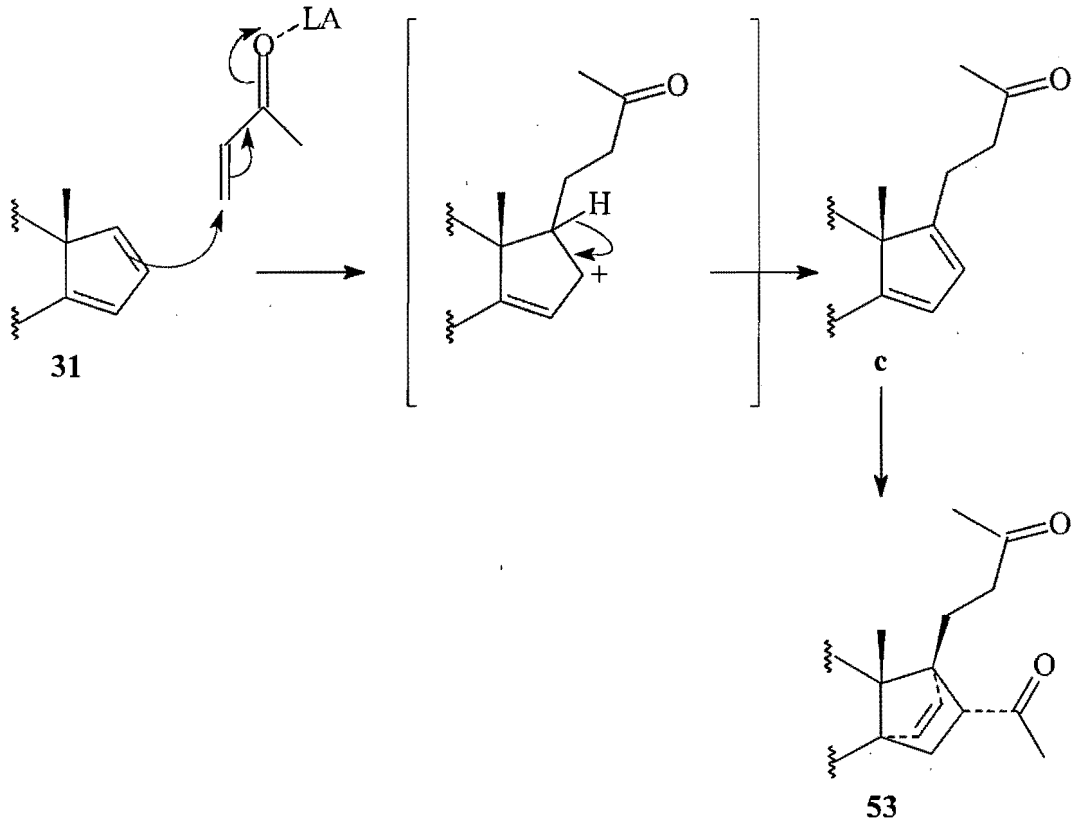


Figure 3.3: Highfield Region of COSY Spectrum of the Cycloadduct **54**

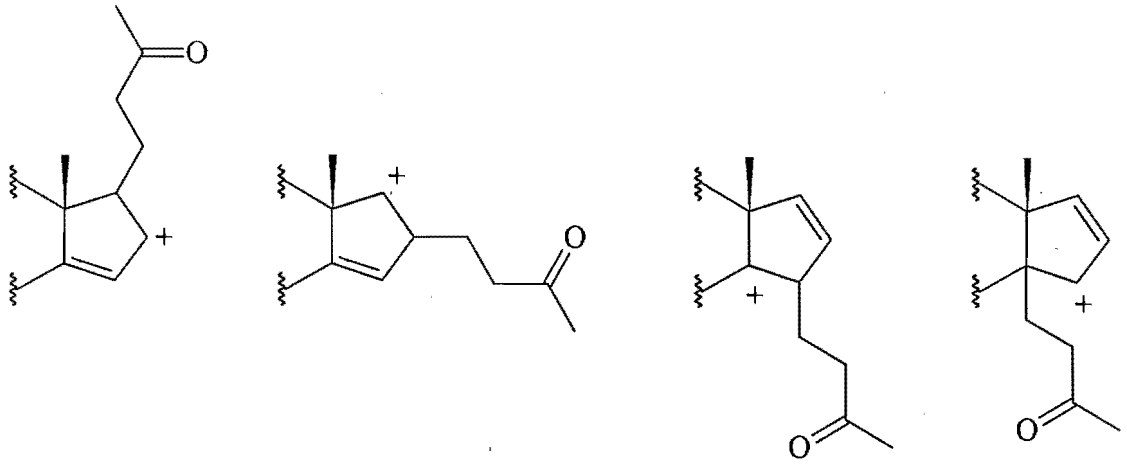
A possible mechanism for the formation of this compound is shown in Scheme 3.28. It is proposed that the diene **31** undergoes a nucleophilic 1,4-addition to methyl vinyl ketone, which is activated via complexation to the Lewis acid (LA). Loss of a proton affords the diene **c**, which reacts with a second unit of methyl vinyl ketone to afford the cycloadduct **53**. This mechanism, however, does not account for the formation of **53** under thermal conditions, although the reaction may also be mediated by traces of acid in the reaction medium.

The intermediate diene **c** is an obligatory intermediate in the proposed reaction pathway, but it was not isolated, nor was its presence observed during the course of the reaction. Further investigation, especially into the use of temperature control and stoichiometric addition of reagents, is required to provide confirmation of this mechanism.



Scheme 3.28

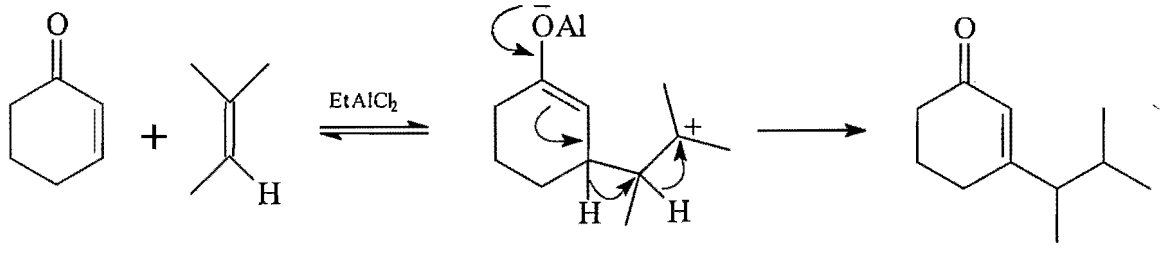
The regioselectivity of the 1,4-addition of the diene **31** to MVK can be rationalised in terms of the relative stabilities of the possible intermediate carbocations **54**, **55**, **56**, and **57** (Scheme 3.29). The allylic carbocations **54** and **57** are expected to be the most stable of the four possible intermediates. Of these two, only **54** can undergo a loss of a proton to afford a diene.



54 55 56 57

Scheme 3.29

This type of reaction, in which an alkene undergoes a Lewis acid induced conjugate addition to an α,β-unsaturated ketone has been reported by Snider *et al.*[45] In that work, 2-cyclohexenone **58** was reacted with 2-methyl-2-butene **59** in the presence of ethylaluminium dichloride to afford intermediate **60** (Scheme 3.30). Intermediate **60** yielded the final product **61** via a 1,2-hydride shift (Scheme **3.30**). The 1,2-hydride shift pathway is possible for the allylic carbocation intermediate **54**, but it is reasonable to assume that regeneration of a diene system is favoured, as no product corresponding to a 1,2-hydride shift reaction was observed.

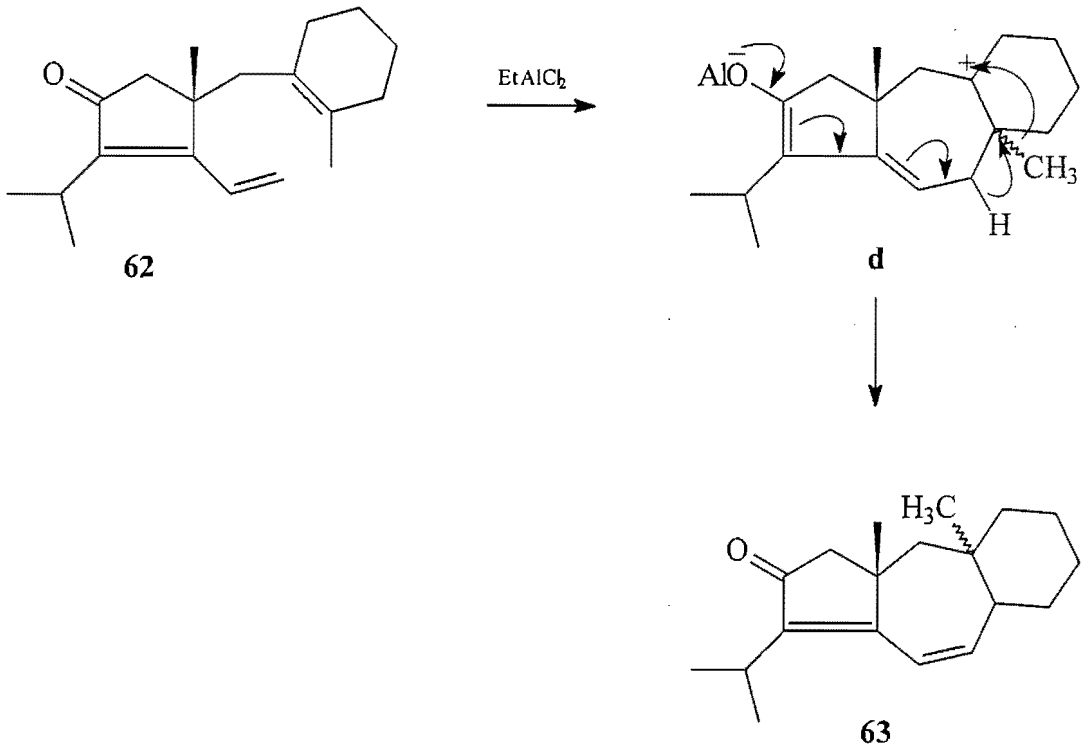


58 59 60 61

Scheme 3.30

The reaction described above has been used as a method for the construction of polycyclic compounds. In recent work by Majetich *et al.*[46] it was found that the trienone **62** cyclised in the presence of ethylaluminium dichloride to afford the tricyclic dienone **63**, via the pathway shown in

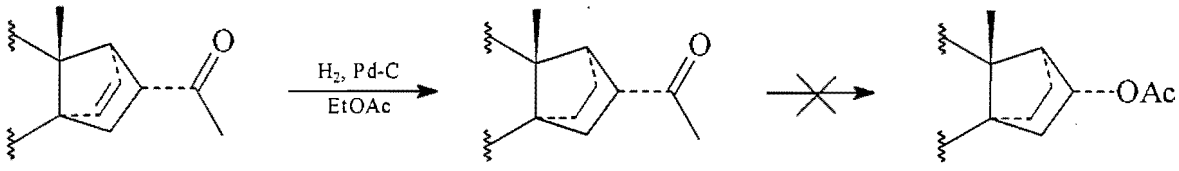
Scheme 3.31. The noteworthy feature of this reaction is that the alkene reacts with a conjugated dienone. The reaction mechanism is analogous to that described by Snider *et al.*[45] The zwitterion **d** formed as a result of Lewis acid-promoted ring closure undergoes an alkyl shift, followed by a 1,2-hydride shift to afford the final product **63**.



62 **d** **63**

Scheme 3.31

With the cycloadduct **52** accessible in acceptable yields from the thermal reaction between the diene **31** and methyl vinyl ketone, attention was turned to transforming **52** into the desired endo-alcohol via the Baeyer – Villiger reaction. Hydrogenation of the cycloadduct **52** in the presence of catalytic palladium on carbon proceeded smoothly to afford the ethano compound **64** in excellent yield (Scheme 3.32). The product displayed spectroscopic and analytical properties consistent with the assigned structure.



52 **64**

Scheme 3.32

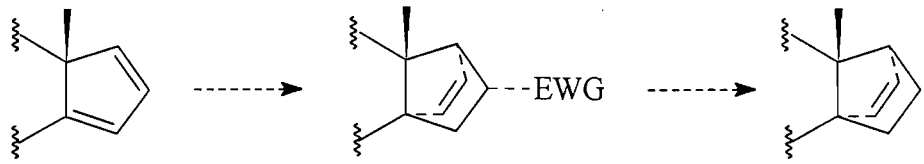
Initially, the oxidation was attempted using trifluoroperoxyacetic acid (TFPAA). This reagent was prepared by combining trifluoroacetic anhydride and the hydrogen bonded adduct urea-hydrogen peroxide (UHP), as reported by Heaney *et al.*[47] The advantage of this method is that it does not involve the use of 'high test' (>85%) aqueous hydrogen peroxide to prepare high strength trifluoroperoxyacetic acid. The UHP adduct is used as an alternative source of hydrogen peroxide. It was shown that the trifluoroacetic acid – UHP system could be used to perform efficient Baeyer – Villiger oxidations, such as the oxidation of methyl *t*-butyl ketone to *t*-butyl acetate.

The reaction was performed via the addition of the ketone **64** to a solution of UHP, trifluoroacetic anhydride, and disodium hydrogen phosphate in dichloromethane at 0 °C. After 5h at 0 °C, a mixture of products had formed (TLC), but a large quantity of starting ketone remained. The reaction mixture was allowed to warm to 25 °C, and the starting ketone was consumed within a period of 2h. TLC analysis indicated that the residue after work-up was a complex mixture. A similar result was obtained when MCPBA was added to a solution of the ketone **64** and sodium carbonate in dichloromethane. The complexity of the mixture precluded isolation of any pure products, and hence, attempted optimisation of the desired reaction.

3.3 Synthesis of α-Bridge Functionalised Rotational Analogues

The next phase of the investigation was directed at introducing oxygen functionality on the α-bridge of the template shown in Figure 2.1. The oxygenation of the α-bridge of the analogous 3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol **65** (see appendix for structure of **65**) has been studied previously with the aim of synthesising new bridged – oxygenated analogues of estriol.[48,49] In work reported by Bull *et al.*,[49] it was shown that oxygen could be introduced onto the α-bridge of **65** via hydroboration. Loedolff investigated an alternative approach,[48] aimed at the regioselective introduction of oxygen onto the α-bridge. That approach entailed cycloaddition to C(16), C(17)- and C(15), C(17)-dioxygenated dienyl systems.

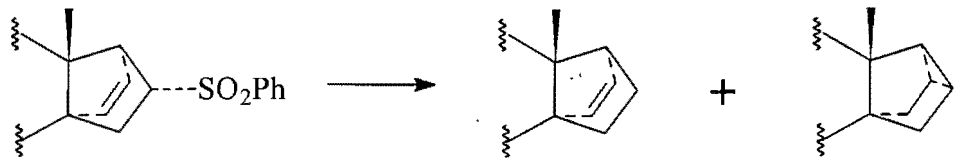
The approach adopted in this investigation was analogous to that employed by Bull *et al.*[49] The plan entailed cycloaddition of an ethylene equivalent to the 14,16-diene **31**, followed by removal of the electron withdrawing group (EWG) of the dienophile to afford the etheno-bridged compound **e** (Scheme 3.33).



31 **e**

Scheme 3.33

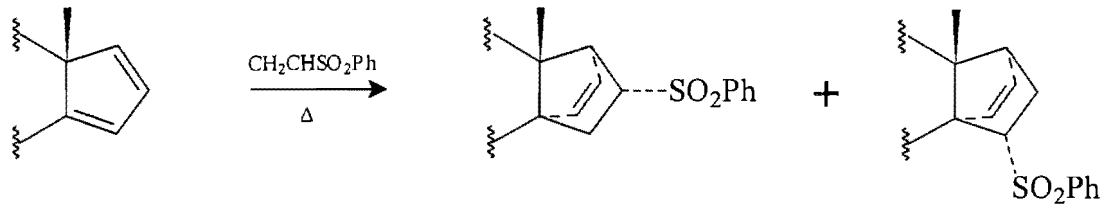
The ethylene equivalent used in the synthesis of the bridged hydroxy compound **65** is phenyl vinyl sulfone (PVS).[35] The reaction of the diene **31** with PVS, and the subsequent removal of the phenylsulfonyl group has been studied previously by Thomson.[50] It was found that olefinic bond participation was the major reaction pathway (Scheme 3.34). The cycloadduct **66** was treated with sodium amalgam in methanol-tetrahydrofuran at –20 °C to afford a *ca* 1:9 mixture of **67** and **68**. Treatment of **66** with magnesium in methanol at 50 °C afforded a *ca* 1:3 mixture of **67** and **68**.



66 67 68

Scheme 3.34

It was therefore clear that reductive desulfonylation of the cycloadduct **66** would not provide an efficient route to further bridged analogues of estradiol. In order to gain quick access to some of these analogues, it was decided to perform a hydroboration reaction on the cycloadduct **66** and desulfonylate the resulting alcohols, thus eliminating the possibility of olefinic bond participation.[50] The 14,16-diene **31** was reacted with phenyl vinyl sulfone in toluene at 145 °C (sealed tube) for 78 h to afford, after chromatography, a crystalline fraction in 76% yield. It was initially assumed that this was a single compound, *viz.* the 16α-sulfone **66** , as reported by Thomson.[50] However, subsequent hydroboration of this material and analysis of the products of this reaction revealed that it also contained significant amounts of the 15α-sulfone **69** (Scheme 3.35). The product distribution of the hydroboration reaction showed that **66** and **69** were present in a ratio of *ca* 3:1.



31 66 69

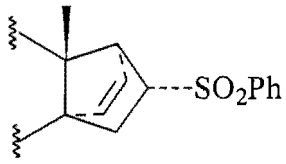
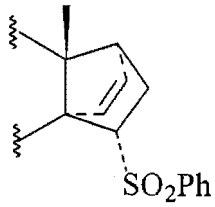
Scheme 3.35

Careful chromatography of the residue obtained in the cycloaddition of phenyl vinyl sulfone to the diene **31** allowed partial separation of this mixture, and sufficient quantities of the 15α-sulfone **69** were obtained to perform a complete characterisation of this compound. Mass spectral. microanaytical, and NMR spectral data were consistent with the assigned structure. The signals for the ring D protons are summarised in Table **3.3**. The corresponding signals for the 16α-sulfone are included for comparative purposes. The splitting pattern of the signal for 15β-H is compatible with

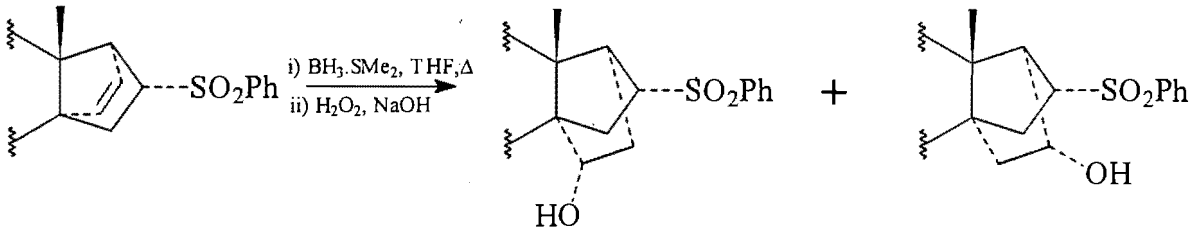
one large *exo-exo* coupling, between 15β-H and 16β-H, and a smaller *exo-endo* coupling between 15β-H and 16α-H. A triplet (*J* 3.4 Hz) was observed at δ 2.40, which was assigned to 17β-H. The reciprocal coupling was observed in the signal for 17^1-H (δ 6.12, dd, *J* 5.8 and 3.4 Hz) and in the signal for 16β-H (δ 2.01, ddd, *J* 12.9, 9.0 and 3.4 Hz).

An interesting feature of the ^{1}H NMR spectrum is the downfield shift of the signal for 7β-H from δ 1.86 in the 16α-sulfone **66**,[50] to δ 3.10 in the corresponding 15α-isomer **69**. The 7α-H signal exhibits a smaller, but notable downfield shift from δ 1.69 in the case of the 16α-sulfone **66**,[50] to δ 1.84. This downfield shift can be attributed to anisotropic deshielding of the 7α- and 7β-protons, arising from their proximity to the oxygens of the 15α-sulfonyl group. This provides further evidence of substitution at C-15. From the ^{1}H NMR evidence, it can be assumed that the assigned regio- and stereochemistry is correct.

Table 3.3: Ring D Proton Assignments and Coupling Data for the Sulfones **66** and **69**

	 **66**	 **69**
15α-H	1.79 (dd, *J* 12.3 and 4.6 Hz)	–
15β-H	1.85 (dd, *J* 12.3 and 8.5 Hz)	3.66 (dd, *J* 9.0 and 5.4 Hz)
16α-H	–	1.19 (dd, *J* 12.9 and 5.4 Hz)
16β-H	3.84 (ddd, *J* 8.5, 4.6 and 3.0 Hz)	2.01 (ddd, *J* 12.9, 9.0 and 3.4 Hz)
17β-H	2.81 (t, *J* 3.0 Hz)	2.40 (t, *J* 3.4 Hz)
17^1-H	6.10 (dd, *J* 5.9 and 3.0 Hz)	6.12 (dd, *J* 5.8 and 3.4 Hz)
17^2-H	6.22 (d, *J* 5.9 Hz)	6.21 (d, *J* 5.8 Hz)

Treatment of the 16α-sulfone **66** with borane-dimethylsulfide in tetrahydrofuran at 70 °C for 6 h followed by oxidative work-up afforded the hydroxy compounds **70** and **71** in 33 and 44% yield respectively (Scheme 3.36).

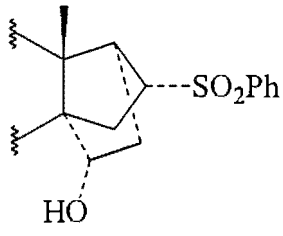
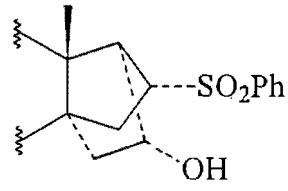


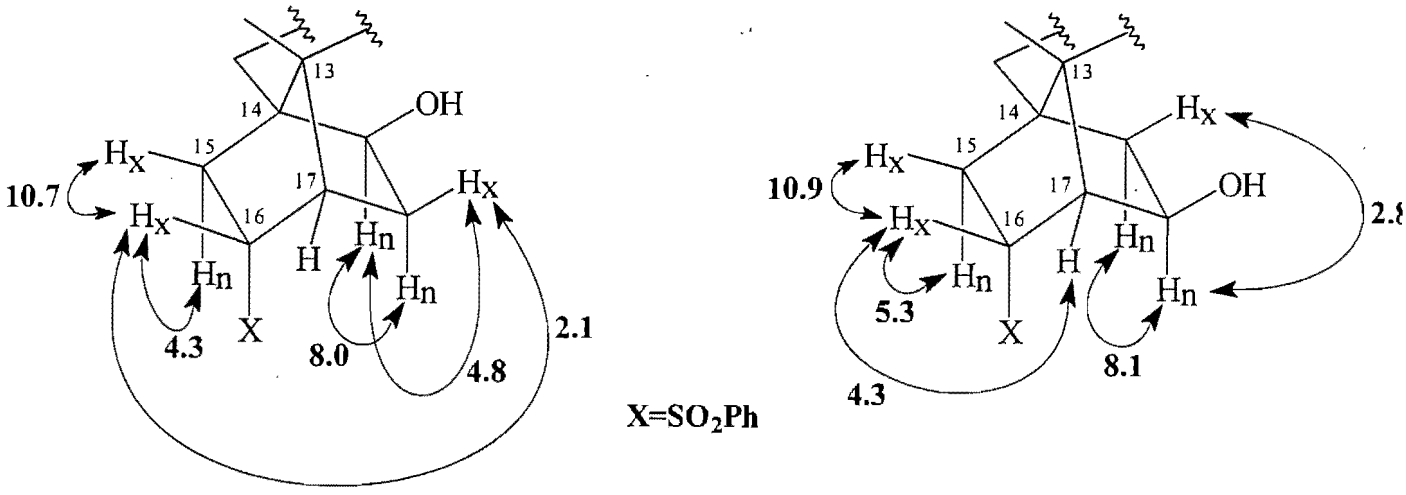
66 **70** **71**

Scheme 3.36

The compounds were readily differentiated with the aid of ^{1}H NMR spectroscopy. The data are summarised in Table 3.4. The ^{1}H NMR spectrum of the 17^2-*exo*-hydroxy-16α-sulfone **70** was characterised by a large downfield shift of the signal for the 9α-proton. This implied that the orientation of the hydroxy group was *exo*, and was located at C-17^2, in accordance with previous observations of this type.[35,50] A general feature which was observed in the ^{1}H NMR spectra of the hydroboration products was the downfield shift of the *endo*-proton in a 1,3 relationship with the sulfonyl group, arising from anisotropic deshielding. In the case of the 17^2-*exo*-hydroxy-16α-sulfone **70**, the 17^1-*endo*-H resonated at δ 2.94 (dd, *J* 13.8 and 8.0 Hz). The reciprocal vicinal coupling was observed in the signal for the 17^2-proton, which resonated at δ 4.37 (dd, *J* 8.0 and 4.8 Hz).The couplings between the ring D protons of **70** are summarised in Figure 3.4.

Table 3.4: Selected ^{1}H NMR Data for the Compounds **70** and **71**

	 **70**	 **71**
9α-H	3.51 (td, *J* 2 x 12.1 and 5.0 Hz)	Obsc.
16β-H	3.61 (dddd, *J* 10.7, 2 x 4.3 and 2.1 Hz)	3.60 (ddd, *J* 10.9, 5.3, and 4.3 Hz)
17β-H	2.25 (t, *J* 4.3 Hz)	2.45 (d, *J* 4.3 Hz)
17^1-*endo*-H	2.94 (dd, *J* 13.8 and 8.1 Hz)	5.05 (dd, *J* 8.1 and 2.8 Hz)
17^2-*endo*-H	4.37 (dd, *J* 8.0 and 4.8 Hz)	?

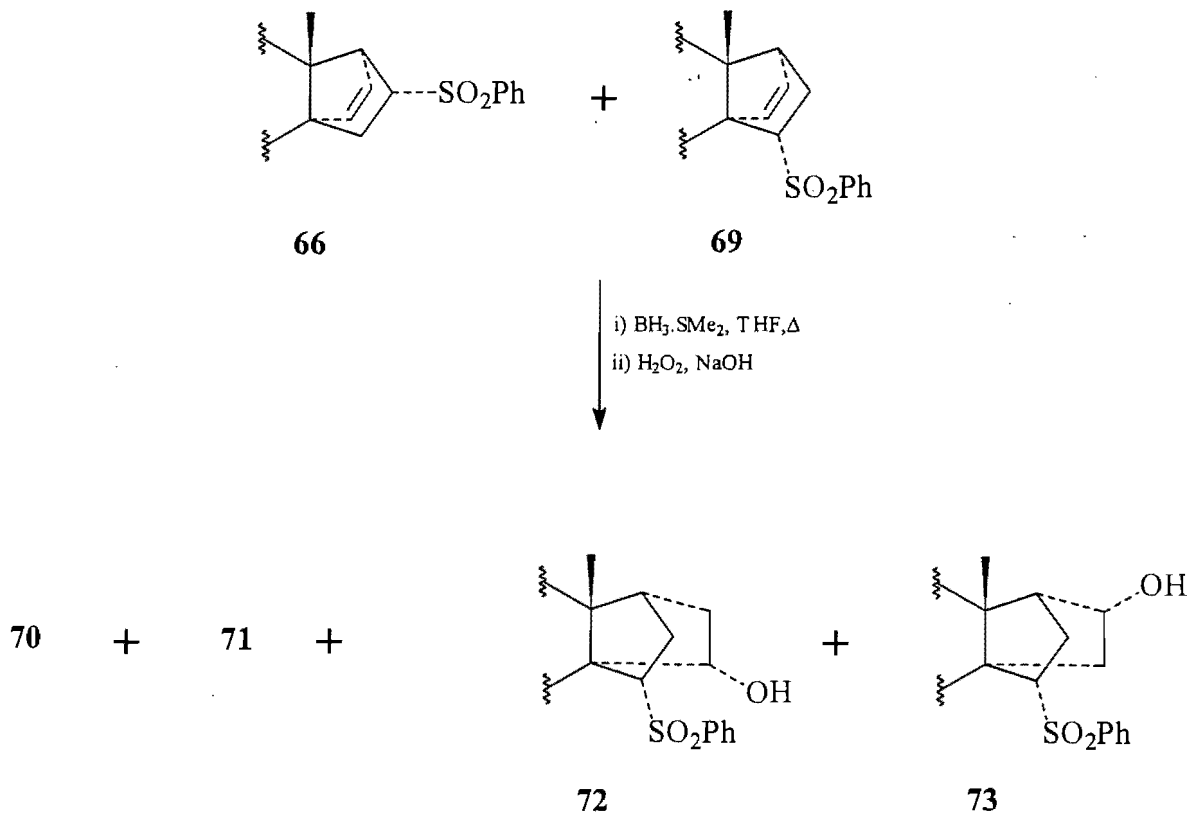


70 **71**

Figure 3.4: Coupling Constants for Ring D Protons for the Alcohols **70** and **71**

The key signal in the ^{1}H NMR spectrum of the (17^{1}R)-16α-sulfone **71** which established the location and orientation of the hydroxy group was the resonance for 17β-H. This occurred as a doublet (*J* 4.3 Hz) at δ 2.45, consistent with coupling to 16β-H. The absence of coupling to 17^1-*exo*-H indicated that the hydroxy group is located at C-17^1 in an *exo*-orientation. The 17^1-H, which is in a 1,3-relationship with the sulfonyl group, resonated downfield at δ 5.05 (dd, *J* 8.1 and 2.8 Hz). The signal for 16β-H resonated at δ 3.60 (ddd, *J* 10.9, 5.3 and 4.3 Hz), the splitting pattern consistent with vicinal couplings to 15α-H, 15β-H and 17β-H. A doublet of doublets at δ 1.98 (*J* 12.6 and 5.3 Hz) was assigned to15α-H by means of a crosspeak to 16β-H in the COSY spectrum. The coupling data are summarised in Figure 3.4.

Initially, the hydroboration reaction was performed on the mixture of sulfones, and that experiment is described here. Treatment of the mixture of sulfones **66** and **69** with borane-dimethyl sulfide followed by oxidative work-up afforded the compounds **70** and **71**, in 25 and 34% yield respectively, as well as the products of hydroboration-oxidation of the 15α-sulfone **69**, *viz.* the 17^2-*exo*-hydroxy-15α-sulfone **72** and the 17^1-*exo*-hydroxy-15α-sulfone **75**, in 7 and 11% yield respectively (Scheme 3.37).



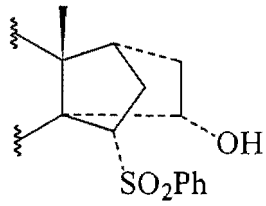
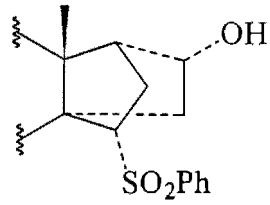
Scheme 3.37

The structures of **72** and **73** were assigned using arguments similar to those used for **70** and **71**. The essential ^{1}H NMR spectral data of both compounds are summarised in Table 3.5. The ^{1}H NMR spectrum of the 17^2-*exo*-hydroxy-15α-sulfone **72** displayed a large downfield shift of the signal for the 9α-proton, suggesting that the orientation of the hydroxy group is *exo* and located at C-17^2. Anisotropic deshielding by the phenylsulfonyl group results in a downfield shift of the 17^2-*endo* resonance, from the 'usual' region (δ3.9),[44] to δ 5.45. This implies that the sulfonyl group is located at C-15 and in an *endo* orientation. Confirmation of this initial assignment of the regio- and stereochemistry of this compound was provided by the multiplicities of key diagnostic signals. The coupling data of **72** are summarised in Figure 3.5.

The assigned structure of the 17^1-*exo*-hydroxy-15α-sulfone **73** followed directly from an analysis of its ^{1}H NMR spectrum. The 17^1-H resonated δ 4.13 as a doublet of doublets (*J* 8.1 and 3.4 Hz). The chemical shift of this signal suggested that the proton alpha to the hydroxy group is not in a 1,3 relationship with the sulfonyl group, as in the case of the 17^2-*exo*-hydroxy-15α-sulfone **72**. The signal for 15β displayed long range coupling to 17^2-*exo*-H, in addition to the coupling to 16α-H and

16β-H. This long range coupling eliminates the possibility of 17^2-*endo*-substitution. The possibility of 17^1-*endo* substitution is also excluded, because no long range coupling was observed in the signal for the proton alpha to the hydroxy group. No downfield shift for the 9α-H was observed, providing further evidence for the hydroxy group not being located at C-17^2 in an *exo*-orientation.

Table 3.5: Selected ^{1}H NMR Data for **72** and **73**

	 **72**	 **73**
9α-H	3.41 (td, *J* 2 x 11.4 and 4.9 Hz)	?
15β-H	3.08 (dd, *J* 11.0 and 7.3 Hz)	3.16 (ddd, *J* 10.6, 6.1 and 2.2 Hz)
16α-H	1.39 (dd, *J* 13.2 and 7.3 Hz)	1.36 (dd, *J* 13.6 and 6.1 Hz)
17^1-*endo*-H	2.06 (dd, *J* 12.9 and 8.0 Hz)	4.13 (dd, *J* 8.1 and 3.4 Hz)
17^2-*endo*-H	5.45 (dd, *J* 8.0 and 4.2 Hz)	3.10 (dd, *J* 14.4 and 8.1 Hz)

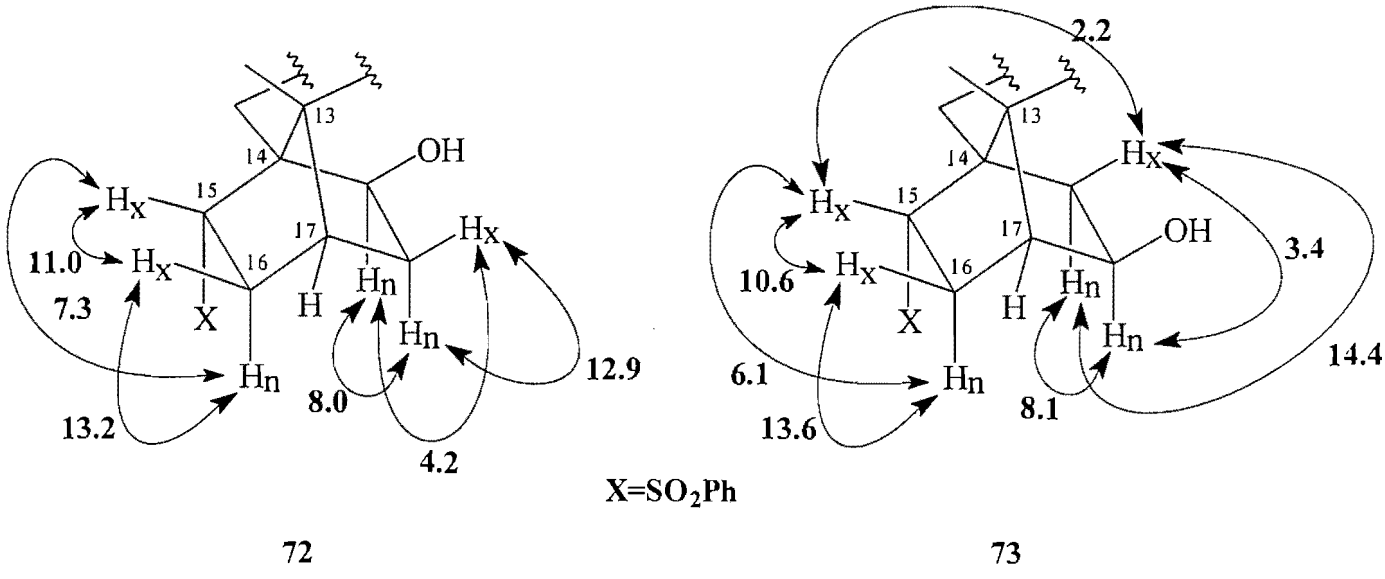
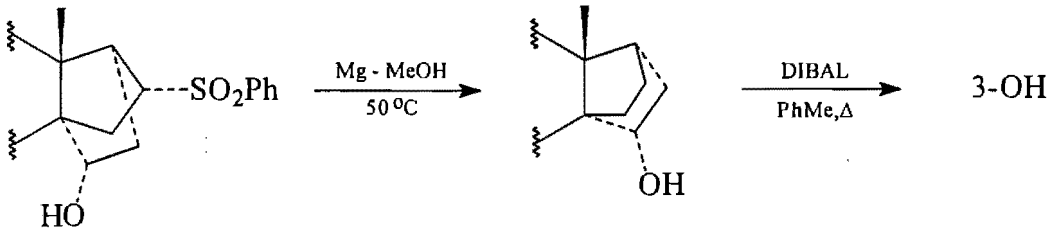


Figure 3.5: Coupling Constants for Ring D Protons for the Alcohols **72** and **73**

The stereochemical outcome of the foregoing reaction is unsurprising when one considers the steric bulk of the phenylsulfonyl group. Approach by the reagent to the *endo*-face of the olefinic bond is impeded by steric shielding which the phenylsulfonyl group provides, resulting in borane adding to the less hindered *exo*-face. In the absence of the phenylsulfonyl group, as shown in earlier work,[49] all possible isomers are obtained.

The two products of hydroboration of the 16α-sulfone **66** were used in subsequent transformations to obtain new analogues of estradiol. The 17^2-*exo*-hydroxy-16α-sulfone **70** was treated with activated magnesium in methanol at 50 °C for 7 h to afford the (17^2S)-alcohol **74** in 77% yield.[51] (Scheme 3.38). Comparison of the ^{1}H NMR spectrum of this compound with that of the 17^2-*exo*-hydroxy-16α-sulfone **70** serves to illustrate some of the observations made earlier. Apart from the obvious absence of the aromatic protons of the phenyl sulfonyl group, the downfield shift of the signal for 17^1-endo-H, thought to be a consequence of anisotropic deshielding by the phenylsulfonyl group was not observed. In addition, the signal for 17^2-H exhibited a small upfield shift from δ 4.37 to δ 4.04, implying that the sulfonyl group has a slight deshielding effect on this proton. The alcohol **74** was treated with diisobutylaluminium hydride in refluxing toluene for 15 h to afford the bridged estradiol analogue **75** in 91% yield (Scheme 3.38). The product displayed mass spectral and microanalytical characteristics consistent with the assigned structure.

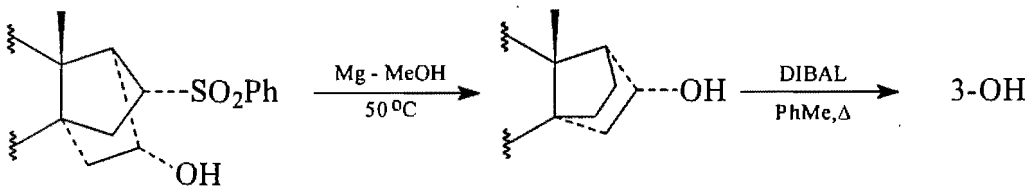


70 **74** **75**

Scheme 3.38

The 17^1-*exo*-hydroxy-16α-sulfone **71** was converted into the bridged estradiol analogue **77** via a similar sequence of reactions. Treatment of **71** with activated magnesium in methanol at 50 °C for 6 h afforded the (17^1R)-alcohol **76** in 84% yield (Scheme 3.39). Analytical and spectroscopic data were in accordance with the proposed structure. The outstanding feature of the ^{1}H NMR spectrum is the upfield shift of the 17^1-H from δ 5.05 in the case of the 16α-sulfone **71**, to δ 3.93. The reaction sequence was completed by treating the alcohol **76** with diisobutylaluminium hydride in refluxing

toluene for 18 h to yield the diol 77 in 85% yield (Scheme 3.39). The product displayed mass spectral and microanalytical characteristics consistent with the assigned structure.



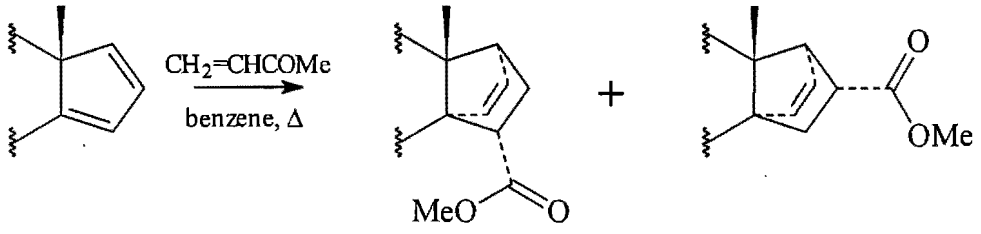
71 **76** **77**

Scheme 3.39

As the hydroboration of the cycloadduct **66** yielded only two of the possible four alcohols, further work is required for the synthesis of the 17^1- and 17^2-*endo*-alcohols. An option for future consideration is hydroboration of the etheno compound **e** (Scheme 3.33) which is likely to afford all possible alcohols, based on analogy with the reaction reported by Bull *et al.*[49]

3.4 Other Cycloaddition Reactions of the 14,16-diene 31

The cycloadditions of methyl acrylate and acrolein to the diene **31** were briefly studied to compare the outcome of these reactions with other cycloadditions to **31**, and to determine whether a clear trend exists in the regio- and stereoselectivity of these reactions. Treatment of the diene **31** with methyl acrylate in benzene at 90 °C (sealed tube) for 96 h furnished a chromatographically inseparable mixture (78%, ~3:1 by ^{1}H NMR) of two cycloadducts (Scheme 3.40).

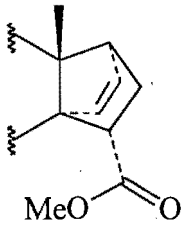
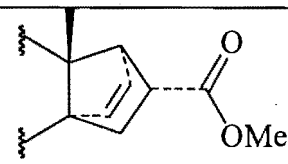


31 **78** **79**

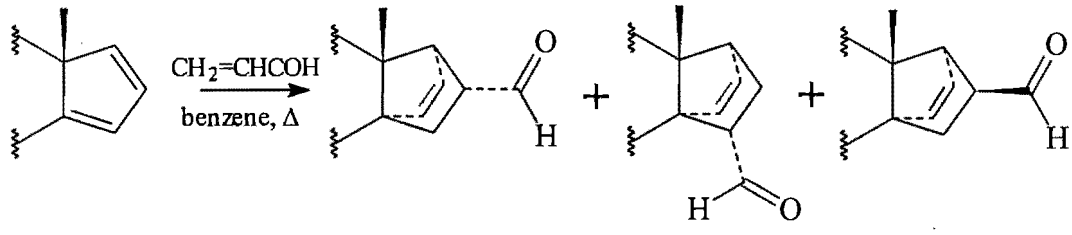
Scheme 3.40

The structure of the major component **78** was inferred from a ^{1}H NMR signal at δ 3.22 (ddd, *J* 7.9 and 2 x 3.9 Hz), which was assigned to the proton α- to the 16α-methoxycarbonyl group, on the basis of multiplicity consonant with *exo* – bridgehead coupling to 17-H (*J* 3.9 Hz), as well as the neighbouring 15α- and 15β-protons. The comparable signal of the minor component **79** appeared at δ 3.43 (dd, *J* 9.6 and 3.7 Hz). It may be argued that this is consistent with any one of the three other possible cycloadducts arising from β-face cycloaddition, since the proton α- to a 16β-methoxycarbonyl substituent would be expected to occupy a near-orthogonal relationship (J ~0 Hz) with 17-H, and either of the 15-substituted compounds could also account for the observed signal multiplicity. The ^{1}H NMR spectral data assigned to the respective components of the cycloadduct mixture are summarised in Table 3.6.

Table 3.6: Selected ^{1}H NMR Data for the Components **78** and **79**

	 **78**	 **79**
15β-H	3.43 (dd, *J* 9.6 and 3.7 Hz)	-
16β-H		3.22 (ddd, *J* 7.9 and 2 x 3.9 Hz)
17^1-H	6.20 (dd, *J* 5.9 and 3.0 Hz)	5.85 (dd, *J* 5.7 and 2.8 Hz)
17^2-H	6.11 (d, *J* 5.9 Hz)	6.13 (d, *J* 5.7 Hz)

Reaction of the 14,16-diene **31** with acrolein in benzene in a sealed tube at 90 °C afforded an inseparable mixture of three cycloadducts in 61% yield (Scheme 3.41).

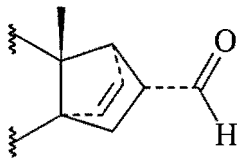
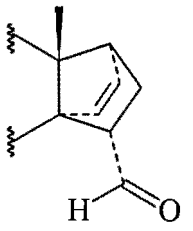
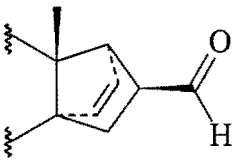


31 **80** **81** **82**

Scheme 3.41

The ^{1}H NMR spectrum of this mixture showed that the ratio of **80**, **81** and **82** was *ca* 2:2:1. The structures were assigned using arguments similar to those used in the assignment of the methyl acrylate cycloadducts. The data are summarised in Table 3.7.

Table 3.7: Selected ^{1}H NMR Data for the Components **80**, **81**, and **82**

	 **80**	 **81**	 **82**
15β-H		3.14 (ddd, *J* 5.4 and 3.6 Hz)	
16α-H			3.71 (dt, *J* 8.9 and 2 x 3.4 Hz)
16β-H	3.55 (dddd, *J* 7.8, 2 x 3.8 and 1.6 Hz)		
17^1-H	6.28 (dd, *J* 5.8 and 3.0 Hz)	6.57 (dd, *J* 6.1 and 3.0 Hz)	6.61 (dd, *J* 5.8 and 3.0 Hz)
CO*H*	9.96 (d, *J* 1.6 Hz)	9.72 (d, *J* 5.3 Hz)	9.84 (d, *J* 3.5 Hz)

A comparison of the results of the cycloadditions performed in this study with cycloadditions to steroidal 14,16-dienes bearing functionality at C-17 highlights the important regiodirecting rôle of the C-17 substituent. Cycloadditions to 17-substituted 14,16-dienes generally proceed with a high degree of regio- and stereoselectivity, whereas no such regioselectivity has hitherto been observed in cycloadditions to the diene **31**. This difference in regioselectivity is exemplified in the cycloaddition of phenyl vinyl sulfone to the dienyl acetate **28** , and to the diene **31**. In the former case, a single regioisomer is obtained, whereas in the latter, both the 15- and 16-isomers are produced.

Chapter 4

Binding Affinity Studies*

The bridged analogues **43**, **45**, **47**, **49**, **75**, and **77** were submitted for receptor binding assay. The affinities were determined by the method of competitive binding.[8] The affinity of the hormone analogue for the receptor is measured in terms of the 'competition factor' (CF) which is defined as the ratio of the concentration of the test sample (C_{test}) and that of the reference substance (C_{ref}) required for 50% competition.[8]

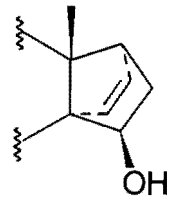
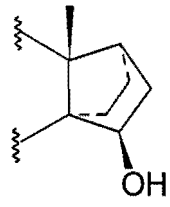
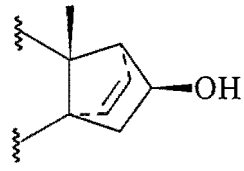
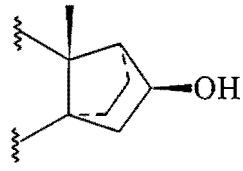
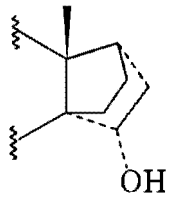
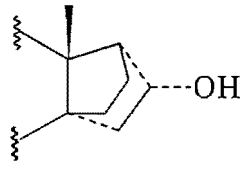
$$CF = \frac{C_{test} \text{ at 50\% competition}}{C_{ref} \text{ at 50\% competion}}$$

Estradiol is taken as the reference substance and thus has a CF value of unity. Hormone analogues with competion factors in the region of untiy are regarded as highly competitive, whereas analogues with competition factors of less than unity are potentially more active than estradiol.

The competition factors of the analogues synthesised in this work are given in Table 4.1. The analogues **43**, **45**, **47**, and **49** were submitted for biological testing prior to the publication of a report which describes the cloning of a new estradiol receptor subtype that appears to be expressed at high levels in some tissues (prostate and ovary).[52] This subtype has been labelled ER-β to distinguish it from the estradiol receptor subtypes cloned previously, which are now referred to as ER-α. The competition factors of the analogues **75** and **77** have been determined for both estradiol receptor subtypes.

*Kindly performed at the laboratories of Schering AG (Berlin)

Table 4.1: Competition factors of the bridged estradiol analogues **43**, **45**, **47**, **49**, **75**, and **77**

 **43**	182
 **45**	No competition
 **47**	12.1
 **49**	32.4
 **75**	(ER-α) 13.0; (ER-β) 140
 **77**	(ER-α) 7.65; (ER-β) 23

All the analogues display moderate to very weak competition, but it is remarkable that in spite of the displacement of the important 17β-hydroxy group, competition is still observed. Of particular interest is **75**, which appears to be subtype selective. Analogues such as this have the potential to target tumours located in specific tissues, such as breast and uterine tissues, without affecting the function of others, such as ovary.

It is obvious that in order to make a definitive statement concerning the rotational equivalence of estradiol analogues, binding affinity data for a much larger number of bridged analogues are required. These include the *endo*-isomers of the compounds synthesised in this work, as well as compounds with different types of ring D bridges, such as analogues bearing a 14,16-ethano bridge. The results obtained in this work do indicate that displacement of the ring D hydroxy group from the 17-position does not result in complete loss of binding affinity.

EXPERIMENTAL

Melting points were determined on a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Optical rotations were determined in chloroform, unless otherwise specified, using a Perkin-Elmer 141 polarimeter, and are recorded in units of 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded in chloroform solutions using a Perkin-Elmer 983 infrared spectrometer or a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Proton nuclear magnetic resonance spectra were recorded, unless specified, as deuteriochloroform solutions using tetramethylsilane as an internal standard on a Varian VXR-200 (200 MHz) or a Varian Unity Spectrometer (400 MHz). Carbon-13 nuclear magnetic resonance spectra were recorded on the same instruments at 50 or 100 MHz (using tetramethylsilane as an internal standard). Elemental analyses were performed using a Fisons EA 1108 CHNS-O instrument. Mass spectra were recorded on a VG micromass 16F spectrometer operating at 70 eV with an accelerating voltage of 4 kV. Accurate masses were determined on a VG-70E spectrometer at the Cape Technikon.

All reactions were monitored by thin-layer chromatography using aluminium backed silica gel 60 F_{254} plates. The plates were visualised by spraying with cerium(IV) ammonium sulfate in 8 mol dm^{-3} sulfuric acid and baking at 200°C. Column chromatography was carried out on silica gel (Merck Kieselgel 60: 70-230 mesh for gravity and 230-400 mesh for flash chromatography).

All solvents used were dried by the appropriate technique[53].

3-Methoxy-17-toluene-*p*-sulfonylhydrazono-estra-1,3,5(10)-triene 19

The 17-ketone **3** (641 mg, 2.26 mmol) and toluene-*p*-sulfonylhydrazide (588 mg, 3.16 mmol) were combined in tetrahydrofuran (10 cm^3) along with 20 μl concentrated HCl. The solution was stirred under reflux under nitrogen for 90 min. The solvent was evaporated and a yellow solid isolated (1.22 g). Purification through flash chromatography on silica gel (50 g) with ethyl acetate - toluene (1:9) as eluent afforded the tosylhydrazone **19** (1.01 g, 99%), m.p. 194 - 196 °C (from ethyl acetate) (lit.,[54] m.p. 194-196 °C).

17-[*N*,*N*-bis(toluene-*p*-sulfonyl)]hydrazono-3-methoxyestra-1,3,5(10)-triene 20

Sodium hydride (60% dispersion in mineral oil, 188 mg, 4.70 mmol) was suspended in tetrahydrofuran (5 cm^3) at 0 °C under nitrogen and the tosylhydrazone **19** (1.01 g, 2.24 mmol) dissolved in tetrahydrofuran (8 cm^3) was added. After 15 min, toluene-*p*-sulfonyl chloride (2.07 g, 10.9 mmol) was added and the mixture stirred at 25 °C under nitrogen for 88 h. The reaction was quenched by the addition of water (15 cm^3). The mixture was extracted with dichloromethane (3 x 30 cm^3) and the organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure to yield a residue (3.86 g). The residue was purified through flash chromatography on silica gel (70 g) with ethyl acetate - toluene (1:19) as eluent to give the bis-tosylhydrazone **20** (1.29 g, 95 %), m.p. 212 - 215 °C (from ethyl acetate); $[\alpha]_D$ +53 (*c* 0.8); (Found: C, 65.4; H, 6.2; S, 10.7%. $C_{33}H_{38}N_2O_5S_2$ requires C, 65.3; H, 6.3; S, 10.6%); δ_H(200 MHz) 1.04 (3 H, s, 13β-Me), 2.40 (6 H, s, tosyl-Me), 2.90 (4 H, m, 6-H_2 and 16-H_2), 3.79 (3 H, s, 3-OMe), 6.64 (1 H, d, *J* 2.7 Hz, 4-H), 6.74 (1 H, dd, *J* 8.5 and 2.7 Hz, 2-H), 7.16 (4 H, d, *J* 8.3 Hz, *m*-tosyl-H), 7.26 (1 H, d, *J* 8.5 Hz, 1-H), and 7.58 (4H, d, *J* 8.3 Hz, *o*-tosyl-H)

Treatment of the bis-tosylhydrazone 20 with sodium ethoxide

Sodium (150 mg, 6.52 mmol) was dissolved in ethanol (4 cm^3) and the *bis*-tosylhydrazone **20** (198 mg, 0.33mmol) dissolved in dry dichloromethane (4cm^3) was added at 0 °C. The mixture was stirred at 25 °C under nitrogen for 8 h. The solvent was evaporated under reduced pressure and water (10 cm^3) added. The mixture was extracted with dichloromethane (3 x 20 cm^3) and the combined organic layers were washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to yield a crude product (162 mg). The crude material was recrystallised from ethyl acetate to yield the mono-tosylhydrazone **19** (80 mg, 54%) m.p. 194 - 196 (lit.,[54] 194 - 196); δ_H(200 MHz) 0.81 (3 H, s, 13β-Me), 2.43 (3 H, s, tosyl-Me), 2.85 (2 H, m, 6α- and 6β-H), 3.77 (3 H, s, 3-OMe), 6.44 (1 H, d, *J* 2.7 Hz, 4-H), 6.72 (1 H, dd, *J* 8.7 and 2.7 Hz, 2-H), 7.20 (1 H, d, *J* 8.7 Hz, 1-H), 7.32 (2 H, d, *J* 8.2 Hz, *o*-tosyl-H), and 7.86 (2 H, d, *J* 8.2 Hz, *m*-tosyl-H).

3-Methoxyestra-1,3,5(10),16-tetraene 21

(*a*) *n*-Butyllithium (2.5 M solution in hexanes,0.60 cm^3, 1.59 mmol) was added dropwise to a stirred solution of the *bis*-tosylhydrazone **20** (320 mg, 0.53 mmol) in tetrahydrofuran (4 cm^3) at -78 °C under nitrogen. The mixture was allowed to warm to room temperature and stirred under nitrogen for 2h. Ice water (5 cm^3) was added and the mixture was extracted with ethyl acetate (3 x 15 cm^3). The combined organic extract was washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to yield a residue (150 mg). The residue was purified through flash chromatography on silica gel (10 g) with ethyl acetate - hexane (3:97) as eluent to give the olefin **21** (85 mg, 60%), mp 70 - 72 °C (lit.,[54] mp 69 - 70 °C); (Found: M^+ 268. $C_{19}H_{24}O$ requires *M* 268); δ_H (200 MHz) 0.81 (3 H, s, 13β-Me), 2.90 (2 H, m, 6α- and 6β-H), 3.79 (3 H, s, 3-OMe), 5.76 (1 H, ddd, *J* 5.7, 2.9 and 1.5 Hz, 16-H), 5.93 (1 H, ddd, *J* 5.7, 2.2, and 0.9 Hz, 17-H), 6.65 (1 H, d, *J* 2.7 Hz, 4-H), 6.72 (1 H, dd, *J* 8.4 and 2.7 Hz, 2-H), and 7.22 (1 H, d, *J* 8.4 Hz, 1-H).

(*b*) *t*-Butyllithium (1.7 M solution in pentanes, 1.1 cm^3 , 1.88 mmol) was added dropwise to a stirred solution of **20** (380 mg, 0.63 mmol) in tetrahydrofuran (5 cm^3) at -78 °C under nitrogen. The mixture was allowed to warm to 25 °C and stirred under nitrogen for 1.5 h. Work-up as in

the preceding experiment yielded a residue (184 mg). The residue was purified by flash chromatography on silica gel (10 g) with ethyl acetate - hexane (3:97) as eluent to give **21** (124 mg, 74%).

17-(*N*-methanesulfonyl-*N*-toluene-*p*-sulfony)lhydrazono-3-methoxyestra-1,3,5(10)-triene 22

The tosylhydrazone of estrone 3-methyl ether **19** (164 mg, 0.36 mmol) and sodium hydride (60% dispersion in mineral oil, 70 mg, 2.92 mmol) were combined in tetrahydrofuran (3 cm^3), and the mixture stirred at 0 °C under nitrogen for 20 min. Methanesulfonyl chloride (0.15 cm^3, 1.81 mmol) was added and the mixture was stirred at 25 °C under nitrogen for 48 h. Water (5 cm^3) was added and the mixture was extracted with ethyl acetate (3 x 10 cm^3). The combined organic extract was washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to yield a residue (240 mg). The residue was chromatographed on silica gel (20 g) with ethyl acetate - toluene (1:9) as eluent to yield the N-*methanesulfonyl*-N-*tosylhydrazone* **22** (172 mg, 90%), mp 175 - 178 °C (from chloroform - methanol); $[\alpha]_D$ +63° (c 1.0); (Found: C, 61.3; H, 6.6; N, 5.3; S, 11.9%. $C_{27}H_{34}N_2O_5S_2$ requires C,61.1; H, 6.4; N 5.3; S, 12.1%) δ_H (200 MHz) 1.02 (3 H, s 13β-Me), 2.46 (3 H, s, tosyl-Me), 2.83 (3 H, s, mesyl-Me), 2.84 (2 H, m, 6α- and 6β-H), 3.78 (3 H, s, 3-OMe), 6.62 (1 H, d, *J* 2.8 Hz, 4-H), 6.71 (1 H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.20 (1 H, d, *J* 8.6 Hz, 1-H), 7.38 (2 H, d, *J* 8.0 Hz, 3- and 5-tosyl-H), and 7.85 (2 H, d, *J* 8.0 Hz, 2- and 6-tosyl-H).

Treatment of the Methanesulfonyltosylhydrazone 22 with DBU

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.15 cm^3, 1.06 mmol) was added to a solution of **22** (190 mg, 0.36 mmol) in tetrahydrofuran (3 cm^3) and the mixture was stirred at 25 °C under nitrogen for 48 h. Saturated aqueous ammonium chloride (5 cm^3) was added and the mixture was extracted with ethyl acetate (3 x 10 cm^3). The combined organic extract washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to yield a residue (140 mg). Purification of the residue through flash chromatography on silica gel (10 g) with ethyl acetate

- toluene (1:9) as eluent afforded the tosylhydrazone **19** (125 mg, 73%), which was identical to a sample prepared previously.

3-Methoxyestra-1,3,5(10),14,16-pentaen-17-yl Trifluoromethanesulfonate 30

a) The Δ^{15}-ketone **29** (130 mg, 0.46 mmol) was dissolved in anhydrous dichloromethane (2 cm^3). Dry pyridine (0.15 cm^3, 1.38 mmol) and triflic anhydride (0.25 cm^3, 1.38 mmol) were added and the solution was stirred at 25 °C under nitrogen for 90 h. The reaction was quenched by the addition of sat. aq. sodium carbonate (5 cm^3). The mixture was extracted with dichloromethane (3 x 15 cm^3) and the combined organic layers were separated, washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to yield a residue (236 mg). Flash chromatography of the residue on silica gel (10 g) with ethyl acetate - hexane (3:97) as eluent afforded the dienyl triflate **30** (134mg, 70%), m.p. 98 - 101 °C (from ethyl acetate - methanol); $[\alpha]_D$ +213° (*c* 1.0); (Found: C, 58.0; H, 5.2; S, 7.9%; M^+, 414. $C_{20}H_{21}F_3O_4S$ requires C, 58.0; H, 5.1; S, 7.7%; *M*, 414); δ_H (200 MHz) 1.18 (3 H, s, 13β-Me), 2.95 (2 H, m, 6α- and 6β-H), 3.79 (3 H, s, 3-OMe), 5.86 (1 H, dd, *J* 2.7 and 1.6 Hz, 15-H), 6.15 (1 H, d, *J* 2.7 Hz, 16-H), 6.68 (1 H, d, *J* 2.9 Hz, 4-H), 6.74 (1 H, dd, *J* 8.5 and 2.9 Hz, 2-H), and 7.22 (1 H, d, *J* 8.5 Hz, 1-H).

b) 2,6-Di-*t*-butyl-4-methylpyridine (1.27 g, 6.21 mmol) in dry dichloromethane (6 cm^3) was added to the Δ^{15}-17-ketone **29** (1.75 g, 6.21 mmol), followed by trifluoromethanesulfonic anhydride (1.6 cm^3, 9.31 mmol). The mixture was stirred at 25 °C for 1h under nitrogen. Work-up as described in the preceding reaction afforded a residue (3.85 g). The residue was purified through flash chromatography on silica gel (130 g) with ethyl acetate - hexane (3:97) as eluent to give the *dienyl triflate* **30** (2.46 g, 90%).

c) To a solution of the Δ^{15}-ketone **29** (751 mg, 2.66 mmol) and ethyldiisopropylamine (0.5 cm^3, 2.87 mmol) in anhydrous dichloromethane (8 cm^3) was added triflic anhydride (0.9 cm^3, 5.30 mmol). The resulting mixture was stirred for 5 h at 25 °C in an atmosphere of nitrogen.

The reaction was quenched by the addition of water (10 cm^3) and the mixture was extracted with dichloromethane (4 x 20 cm^3). The combined organic extract was washed (dil. aq. HCl, brine), dried ($MgSO_4$), and evaporated to yield a residue (1.56 g). The residue was purified through flash chromatography on silica gel (50 g) with toluene - hexane (1:1) as eluent to give the dienyl triflate **30** (781 mg, 71%).

3-Methoxyestra-1,3,5(10),14,16-pentaene 31

a) To a mixture of the dienyl triflate **30** (285 mg, 0.68 mmol), triethylamine (0.30 cm^3, 2.06 mmol), palladium acetate (8 mg, 0.034 mmol), triphenylphosphine (90 mg, 0.34 mmol), and dimethylformamide (6 cm^3) was added formic acid (0.25 cm^3, 5.50 mmol). The mixture was stirred at 25 °C under nitrogen for 16h. Water (15 cm^3) was added and the mixture was extracted with ethyl acetate (3 x 20 cm^3) The organic layer was separated, filtered through Celite, washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to yield a residue (458 mg). The residue was purified through flash chromatography on silica gel (10 g) with ethyl acetate - hexane (3:97) as eluent to give a mixture of two compounds (134 mg, 74%). The mixture was rechromatographed on silica gel (30 g) with toluene - hexane (3:70) as eluent to give 3-methoxyestra-1,3,5(10),14-tetraene **32**, (70 mg, 39%), mp 64 - 67 °C (from ethyl acetate - hexane) (lit.,[54] 65 - 67 °C); (Found: M^+ 268. $C_{19}H_{24}O$ requires *M*, 268); δ_H(200 MHz) 1.07 (3 H, s, 13β-Me), 2.90 (2 H, m, 6α- and 6β-H), 3.80 (3 H, s, 3-OMe), 5.25 (1 H, dd, *J* 4.3 and 2.1 Hz, 15-H), 6.65 (1 H, d, *J* 2.7 Hz, 4-H), 6.74 (1 H, dd, *J* 8.5 and 2.7 Hz, 2-H), and 7.25 (1H, d, *J* 8.5 Hz, 1-H); followed by 3-methoxyestra-1.3.5(10),14,16-pentaene **31** (50 mg, 28%), m.p. 96 -97 °C (from ethyl acetate) (lit.,[19] m.p. 97 -98.5 °C); (Found: M^+ 266. $C_{19}H_{22}O$ requires *M*, 266); δ_H(200 MHz) 1.08 (3 H, s, 13β-Me), 2.95 (2 H, m, 6α- and 6β-H), 3.80 (3 H, s, 3-OMe), 5.92 (1 H, d, *J* 1.6 Hz, 15-H), 6.37 (1 H, dd, *J* 5.3 and 1.6 Hz, 16-H), 6.40 (1 H, d, *J* 5.3 Hz, 17-H), 6.74 (2 H, m, 4- and 2-H), and 7.26 (1 H, d, *J* 8.3 Hz, 1-H)

(b) To a mixture of the dienyl triflate **30** (1.0 g, 2.43 mmol), triethylamine (5 cm^3, 36.4 mmol), palladium acetate (27 mg, 0.12 mmol), triphenylphosphine (319 mg, 1.22 mmol), and dry THF (10 cm^3) was added formic acid (0.10 cm^3, 2.43 mmol). The mixture was refluxed under nitrogen for 30 min. Work-up as before afforded a residue (1.45 g). The residue was purified

through flash chromatography on silica gel (35 g) with ethyl acetate - hexane (3:97) as eluent to give the diene **31** (440 mg, 69%).

c) The preceding experiment was repeated on the dienyl triflate **30** (1.0 g, 2.43 mmol), with tributylamine (8.5 cm^3, 35.7 mmol) in place of triethylamine, to give the diene **31** (485 mg, 75%).

Cycloaddition of 2-Chloroacrylonitrile to the Diene 31

A solution of the diene **31** (206 mg, 0.77 mmol) and 2-chloroacrylonitrile (0.30 cm^3, 3.87 mmol) in benzene (3 cm^3) was heated in sealed tube at 90 °C for two weeks. Further aliquots (0.1 cm^3) of 2-chloroacrylonitrile were added at intervals of five days. The reaction mixture was concentrated under reduced pressure and the resulting residue was chromatographed on silica gel (30 g) with ethyl acetate - toluene (1:9) as eluent. This gave starting material (16 mg, 7%), followed by an inseparable mixture of cycloadducts (185 mg, 68%) as an oil; δ_H(200 MHz) 1.10 (s, 13β-Me), 1.18 (s, 13β-Me), 3.78 (s, 3-OMe), 6.15 – 6.38 (m, 17^1-H and 17^2-H), 6.63 (d, *J* 2.9 Hz, 4-H), 6.74 (dd, *J* 8.6 and 2.9 Hz, 2-H), and 7.20 (d, *J* 8.6 Hz, 1-H).

Alkaline Treatment of the Cycloadducts 35 and 36

To a solution of the cycloadducts **35** and **36** (462 mg, 1.31 mmol) in tetrahydrofuran (2 cm^3), dimethyl sulfoxide (2 cm^3) and water (2 cm^3) was added potassium hydroxide (520 mg, 9.27 mmol). The mixture was stirred at 80 °C for 45 h under nitrogen. Sat. aq. ammonium chloride (10 cm^3) was added and the mixture was extracted with dichloromethane (3 x 15 cm^3). The combined organic extract was washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to yield a residue (540 mg). Chromatography of the residue on silica gel (52 g) with ethyl acetate - toluene (1:99) as eluent afforded 3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-15-*one* **37** (194 mg, 48%), m.p. 124-126 °C (from ethyl acetate); $[\alpha]_D$ -283 (*c* 0.8); (Found: C, 82.1; H, 8.0%; M^+ 308. $C_{21}H_{24}O_2$ requires C, 81.8; H, 7.8%; *M*, 308); ν_{max} /cm^{-1} 1729; δ_H(200 MHz) 1.05 (3 H, s, 13β-Me), 1.98 (1 H, d, *J* 16.5 Hz, 16α-H), 2.90 (3 H, m, 6α-, 6β- and 17-H), 3.78 (3 H, s, 3-OMe), 5.90 (1 H, J 5.6 Hz, 17^2-H), 6.52 (1 H, dd, *J* 5.6 and 2.9 Hz, 17^1-H),

6.67 (1 H, d, *J* 2.7 Hz, 4-H), 6.71 (1 H, dd, *J* 8.5 and 2.7 Hz, 2-H), and 7.20 (1 H, d, *J* 8.5 Hz, 1-H); δ_H (400 MHz; C_6D_6) 0.72 (3 H, s, 13β-Me), 1.66 (1 H, d, *J* 16.5 Hz, 16α-H), 1.96 (1 H, ddd, *J* 16.5, 3.0 and 0.9 Hz, 16β-H), 2.23 (1 H, td, J 2 x 3.0 and 0.8, 17-H) 2.84 (2 H, m, 6α– and 6β-H), 3.35 (3 H, s, 3-OMe), 5.63 (1 H, d, *J* 5.7 Hz, 17^2-H), 5.97 (1 H, ddd, *J* 5.7, 3.0 and 0.9 Hz, 17^1-H), 6.58 (1 H, d, *J* 3.0 Hz, 4-H), 6.76 (1 H, dd, *J* 8.8 and 3.0 Hz, 2-H), and 7.06 (1 H, d, *J* 8.8 Hz, 1-H); δ_C (100 MHz, C_6D_6) 17.3 (13β-Me), 24.5 (C-7), 26.9 (C-12), 28.8 (C-11), 30.4 (C6), 35.6 (C-8), 37.6 (C-16), 40.1 (C-9), 49.0 (C-17), 54.7 (3-OMe), 60.0 and 68.0 (C-13 and C-14), 112.3 (C-2), 114.0 (C-4), 127.1 (C-1), 130.0 ($C-17^2$), 132.0 (C-10), 138.4 (C-5), 142.1 ($C-17^1$), 158.3 (C-3), and 213.1 (C-15). This was followed by 3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-16-*one* **38** (86 mg, 21%), m.p. 115-117 °C (from ethyl acetate - methanol); $[\alpha]_D$ +564 (*c* 0.8); (Found C, 82.2; H, 8.0%; M^+ 308. $C_{21}H_{24}O_2$ requires C, 81.8; H, 7.8%; *M*, 308); ν_{max} /cm^{-1} 1736; δ_H(200 MHz) 1.09 (3 H, s, 13β-Me), 1.98 (2 H, s, 15α- and 15β-H), 2.90 (3 H, m, 6α-,6β- and 17-H), 3.78 (3 H, s, 3-OMe), 5.98 (1 H, dd, *J* 5.7 and 3.6 Hz, 17^1-H), 6.50 (1 H, d, *J* 5.7 Hz, 17^2-H), 6.65 (1 H, d, *J* 2.2 Hz, 4-H), 6.74 (1 H, dd, *J* 8.6 and 2.2 Hz, 2-H), and 7.26 (1 H, d, *J* 8.6 Hz, 1-H); δ_H (400 MHz; C_6D_6) 0.76 (3 H, s, 13β-Me), 1.58 (1 H, dd, *J* 16.0 and 0.6 Hz 15β-H), 1.71 (1 H, dd, *J* 16.0 and 0.9 Hz 15α-H)2.56 (2 H, m, 6α- and 6β-H), 2.64 (1 H, d, *J* 3.4 Hz, 17-H), 3.38 (3 H, s, 3-OMe), 5.61 (1 H, dd, *J* 5.8 and 3.4 Hz, 17^1-H), 5.97 (1 H, d, *J* 5.8 Hz, 17^2-H), 6.65 (1 H, d, *J* 2.8 Hz, 4-H), 6.75 (1 H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.07 (1 H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz; C_6D_6) 17.4 (13β-Me), 25.2 (C-7), 26.5 (C-12), 28.5 (C-11), 30.1 (C-6), 37.3 (C-15), 37.9 (C-8), 39.7 (C-9), 54.5 (3-OMe), 57.6 and 59.4 (C-13 and C-14), 67.2 (C-17), 111.9 (C-2), 113.9 (C-4), 126.9 ($C-17^1$), 127.3 (C-1), 131.9 (C-10), 137.6 (C-5), 143.5 ($C-17^2$), 158.1 (C-3), and 211.9 (C-16).

Treatment of the 15-ketone 37 with sodium borohydride

A solution of the 15-ketone **37** (202 mg, 0.65 mmol) in methanol (4 cm^3) and tetrahydrofuran (10 cm^3) at 0 °C was treated with sodium borohydride (74 mg, 1.95 mmol). After 1 h, the reaction was incomplete (TLC). A further aliquot of sodium borohydride (80 mg, 2.11 mmol) was added and the mixture was allowed to warm to room temperature and stirred for a further 2 h. Water was added and the mixture was extracted with ethyl acetate (3 x 20 cm^3). The combined organic extract was washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to yield a residue. The residue was chromatographed on silica gel (20 g) with ethyl

acetate -hexane (3:17) as eluent to afford the 15β-alcohol **40** (142 mg, 71%), (Found: M^+ 310. $C_{21}H_{26}O_2$ requires *M*, 310), δ_H(200 MHz) 1.22 (3 H, s, 13β-Me), 2.80 (2 H, m, 6α- and 6β-H), 3.79 (3 H, s, 3OMe), 5.88 (1 H, d, *J* 5.8 Hz, 17^2-H), 6.05 (1 H, dd, *J* 5.8 and 2.6 Hz, 17^1-H), 6.65 (1 H, d, *J* 2.8 Hz, 4-H), 6.75 (1 H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.24 (1 H, d, *J* 8.6 Hz, 1-H); followed by 3-*methoxy*-14,17α–*ethanoestra*-1,3,5(10)-*trien*-15α–*ol* **41** (15 mg, 8%); mp 134 - 137 °C (from ethyl acetate); (Found: M^+, 310. $C_{21}H_{26}O_2$ requires *M*, 310); δ_H (400 MHz) 0.89 (3 H, s, 13β-Me), 1.58 (1 H, br. s, exch. by D_20, 15α-OH), 2.63 (1 H, ddd, *J* 12.8, 7.5 and 3.8 Hz, 16β-H), 2.92 (2 H, m, 6α- and 6β-H), 3.78 (3 H, s, 3-OMe), 4.32 (1 H, ddd, *J* 9.9, 7.5 and 2.4 Hz, 15β-H; exch. by D_20, 1 H, dd, *J* 7.5 and 2.1 Hz, 15β-H), 6.04 (1 H, d, *J* 6.0 Hz, 17^2-H), 6.36 (1 H, dd, *J* 6.0 and 3.0 Hz, 17^1-H), 6.67 (1 H, d, *J* 2.8 Hz, 4-H), 6.71 (1 H, dd, *J* 8.5 and 2.8 Hz, 2-H), 7.21 (1 H, d, *J* 8.5 Hz, 1-H).

Treatment of the 15-ketone 37 with L-Selectride®

Lithium tri-*sec*-butylborohydride (1.0M) in tetrahydrofuran (4.0 cm^3, 4.00 mmol) was added dropwise to a solution of the 15-ketone **37** (310 mg, 1.01 mmol) in tetrahydrofuran (6 cm^3) at -78 °C under nitrogen. After 30 min, the reaction mixture was allowed to warm to 0 °C and stirred for a further 30 min. Water (10 cm^3) was added and the mixture was extracted with ethyl acetate (3 x 15 cm^3). The combined organic extract was washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to yield a residue (560 mg). Chromatography of the residue on silica gel (30 g) with ethyl acetate - toluene (5:95) as eluent gave 3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-15β-*ol* **40** (260 mg, 83%) as an oil. A portion of this material (176 mg, 0.57 mmol) and acetic anhydride (0.2 cm^3, 2.30 mmol) in anhydrous pyridine was stirred at 25 °C under nitrogen for 16h. Water was added and the mixture was extracted with ethyl acetate (3 x 15 cm^3). The combined organic extract was washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to yield a residue (212 mg). The residue was chromatographed on silica gel (20 g) with ethyl acetate - toluene (1:49) as eluent to afford the acetate **42** (160 mg, 80%) m.p. 118 - 121 °C (from ethyl acetate); $[\alpha]_D$ 66 (*c* 0.8); (Found: C, 78.3; H 8.4%; M^+, 352. $C_{23}H_{28}O_3$ requires C, 78.4; H, 8.0%; *M*, 352); ν_{max} /cm^{-1} 1731; δ_H (400 MHz) 1.23 (3 H, s, 13β-Me), 2.02 (3 H, s, 15β-OAc), 2.85 (2 H, m, 6α- and 6β-H), 3.78 (3 H, s, 3-OMe), 4.77 (1 H, dd, *J* 7.3 and 2.8 Hz, 15α-H), 5.90 (1 H, d, *J* 5.8 Hz, 17^2-H), 6.12 (1 H, ddd, *J* 5.8, 3.0 and 0.9 Hz, 17^1-H), 6.65 (1 H, d, *J* 2.8 Hz, 4-H), 6.72 (1 H, dd, *J*

8.5 and 2.8 Hz, 2-H), 7.24 (1 H, d, *J* 8.5 Hz, 1-H); δ_C (100 MHz) 18.2 (q, C-18), 21.2 (q, 15β-OCO*C*H$_3$), 24.7 (t, C-7), 27.1 (t, C-12), 30.3 (t, C-6), 31.4 and 34.4 (each t, C-11 and C-16), 34.9 (d, C-8), 39.8 (d, C-9), 50.7 (d, C-17), 55.2 (q, 3-OMe), 57.3 and 61.0 (each s, C-13 and C-14), 74.7 (d, C-15), 111.6 (d, C-12), 113.7 (d, C-4), 126.9 (d, C-1), 133.0 (s, C-10), 133.5 (d, C-17^2), 138.1 (s, C-5), 138.4 (d, C-17^1),157.4 (s, C-3), 170.9 (s, 15β-O*C*OCH$_3$)

14,17α-Ethenoestra-1,3,5(10)-triene-3,15β-diol 43

Diisobutyl aluminium hydride (1.5M) in toluene (0.7 cm^3, 1.08 mmol) was added to a stirred solution of the 15β-alcohol **40** (83 mg, 0.27 mmol) in anhydrous toluene (5 cm^3) under nitrogen and the mixture was refluxed for 24 h. Hydrochloric acid (10%, 10 cm^3) was added and the mixture was extracted with ethyl acetate (3 x 15 cm^3). The combined organic extract was washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to yield a residue (89 mg). The residue was chromatographed on silica gel (10 g) with ethyl acetate - toluene as eluent (1:19) to afford the diol **43** (73 mg, 93%), m.p. 151 - 157 °C; $[\alpha]_D$ 148 (*c* 0.9 in THF); (Found: M$^+$, 296.177. $C_{20}H_{24}O_2$ requires *M*, 296.178); ν_{max} /cm^{-1} 3474 and 3324.

3-Methoxy-14,17α-ethanoestra-1,3,5(10)-trien-15β-yl acetate 44

A solution of the 15β-acetate **42** (142 mg, 0.40 mmol) in ethyl acetate (5 cm^3) was hydrogenated in the presence of palladium on charcoal (10%, 55 mg) at 25 °C and atmospheric pressure for 8 h. The catalyst was removed by filtration through Celite and then washed with ethyl acetate. The combined organic phase was evaporated under reduced pressure to afford a residue (152 mg). The residue was chromatographed on silica gel (20g) with ethyl acetate - toluene (1:49) as eluent to afford the 15β-acetate **44** (140 mg, 98%), m.p. 96 - 99 °C (from ethyl acetate - methanol); $[\alpha]_D$ 10 (*c* 0.9); (Found: C, 77.5; H, 8.7%; M$^+$, 354. $C_{23}H_{30}O_3$ requires C, 77.9; H, 8.5%; *M*, 354); ν_{max} /cm^{-1} 1731; δ_H (200 MHz) 1.07 (3 H, s, 13β-Me), 1.98 (3 H, s, 15β-OAc), 2.82 (2 H, m, 6α- and 6β-H), 3.78 (3 H, s, 3-OMe), 4.87 (1 H, dd, *J* 6.7 and 3.7 Hz, 15α-H), 6.64 (1 H, d, *J* 2.8 Hz, 4-H), 6.73 (1 H, dd, *J* 8.4 and 2.8 Hz, 2-H), 7.22 (1 H, d, *J* 8.4 Hz, 1-H).

14,17α-Ethanoestra-1,3,5(10)-triene-3,15β-diol 45

Diisobutyl aluminium hydride (1.5M) in toluene (1.5 cm^3, 2.25 mmol) was added to a stirred solution of the 15β-acetate **44** (142 mg, 0.40 mmol) in anhydrous toluene (7 cm^3) under nitrogen and the mixture was refluxed for 18 h. Hydrochloric acid (10%, 15 cm^3) was added and the mixture was extracted with ethyl acetate (3 x 20 cm^3). The combined organic extract was washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to yield a residue (126 mg). The residue was chromatographed on silica gel (10 g) with ethyl acetate - toluene (1:19) as eluent to yield the diol **45** as a colourless foam (107 mg, 90%), $[\alpha]_D$ 26 (*c* 1.0 in THF); (Found: M^+; 298.193.$C_{20}H_{26}O_2$ requires *M*, 298.193); ν_{max} / cm^{-1} 3473 br.

3-Methoxy-14,17α-ethenoestra-1,3,5(10)-trien-16β-ol 46

Lithium tri-*sec*-butylborohydride (1.0M) in THF (4.0 cm^3, 4.00 mmol) was added dropwise to a solution of the 16-ketone **38** (316 mg, 1.03 mmol) in tetrahydrofuran (8 cm^3) at -78 °C under nitrogen. After 30 min, the reaction mixture was allowed to warm to 0 °C and stirred for a further 30 min. Water (10 cm^3) was added and the mixture was extracted with ethyl acetate (3 x 20 cm^3). The combined organic extract was washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to yield a residue (620 mg). Chromatography of the residue on silica gel (30 g) with ethyl acetate - toluene (1:19) as eluent gave the 16β-alcohol **46** (298 mg, 94%), m.p. 142 - 145 °C (from ethyl acetate); $[\alpha]_D$ 148 (*c* 0.8); (Found: C, 81.2; H, 8.8%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; *M*, 310); ν_{max} /cm^{-1} 3487; δ_H (400 MHz) 1.23 (3 H, s, 13β-Me), 2.47 (1 H, d, *J* 3.3 Hz, 17-H), 2.85 (2 H, m, 6α- and 6β-H), 3.77 (3 H, s, 3-OMe), 3.98 (1 H, dd, *J* 7.5 and 2.8 Hz, 16α-H), 5.92 (1 H, dd, *J* 5.8 and 3.3 Hz, 17^1-H), 6.02 (1 H, d, *J* 5.8 Hz, 17^2-H), 6.62 (1 H, d, *J* 2.8 Hz, 4-H), 6.72 (1 H, dd. *J* 8.6 and 2.8 Hz, 2-H), 7.21 (1 H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 17.7 (q, C-18), 25.3 (t, C-7), 26.9 and 31.0 (each t, C-11 and C-12), 30.3 (t, C-6), 35.9 (t,C-15), 38.7 and 39.4 (each d, C-8 and C-9), 55.2 (q, 3-OMe), 57.0 and 58.6 (each s, C-13 and C-14), 59.2 (d, C-17), 76.5 (d, C-16), 111.7 (d, C-2), 113.7 (d, C-4), 127.1 (d,C-1), 132.6 (d, $C-17^1$), 132.8 (s, C-10), 138.0 (s, C-5), 138.7 (d, $C-17^2$), 157.3 (s, C-3)

14,17α-Ethenoestra-1,3,5(10)-triene-3,16β-diol 47

Diisobutyl aluminium hydride (1.5M) in toluene (1.8 cm^3, 2.7 mmol) was added to a stirred solution of the 16β-alcohol **46** (92 mg, 0.30 mmol) in anhydrous toluene (5 cm^3) under nitrogen and the mixture was refluxed for 24 h. Hydrochloric acid (10%, 10 cm^3) was added and the mixture was extracted with ethyl acetate (3 x 15 cm^3). The combined organic extract was washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to yield a crystalline residue (103 mg). The residue was recystallised from methanol to give the diol **47** (80 mg, 92%), m.p. 200 - 203 °C; $[\alpha]_D$ 179 (*c* 1.0 in tetrahydrofuran); (Found: C,81.2; H, 8.8%; M^+ 296. $C_{20}H_{24}O_2$ requires C, 81.3; H, 8.4%; *M* 296); ν_{max} /cm^{-1} 3450 and 3320.

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

A solution of the 16β-alcohol **46** (173 mg, 0.56 mmol) in ethyl acetate (5 cm^3) was hydrogenated in the presence of palladium on charcoal (10%, 60 mg) at 25 °C and atmospheric pressure for 16 h. The catalyst was removed by filtration through Celite and then washed with ethyl acetate. The combined organic phase was evaporated under reduced pressure to afford a residue (173 mg). Chromatography of the residue on silica gel (20g) with ethyl acetate - toluene (5:95) as eluent afforded 3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-16β-*ol* **48** (170 mg, 97%) as a non-crystalline residue. A portion of this material (82 mg, 0.26 mmol) and acetic anhydride (0.1 cm^3, 2.1 mmol) in dry pyridine (4 cm^3) was stirred at 25 °C under nitrogen. After 16 h, the reaction was incomplete (TLC). 4-Dimethylaminopyridine (5 mg) was added and the mixture was stirred for a further 5h. Water (5 cm^3) was added and after 15 min the mixture was extracted with ethyl acetate (3 x 15 cm^3). The combined organic extract was washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to yield a residue. The residue was chromatographed on silica gel (10 g) with ethyl acetate - toluene (5:95) as eluent to yield 3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-16β-*yl acetate* as a colourless foam (90 mg, 97%) $[\alpha]_D$ 58 (*c* 0.9); ν_{max} /cm^{-1} 1711; (Found: M^+, 354.219. $C_{23}H_{30}O_3$ requires 354.219);.δ_H (200 MHz) 1.05 (3 H, s, 13β-Me), 2.02 (3 H, s, 16β-OAc), 2.85 (2 H, m, 6α- and 6β-H), 3.78 (3 H, s, 3-OMe), 4.72 (1 H, dd, *J* 8.0 and 3.9 Hz, 16α-H), 6.62 (1 H, d, *J* 2.6 Hz, 4-H), 6.72 (1 H, dd, *J* 8.5 and 2.6 Hz, 2-H), 7.22 (1 H, d, *J* 8.5 Hz, 1-H).

14,17α-Ethanoestra-1,3,5(10)-triene-3,16β-diol 49

Diisobutyl aluminium hydride (1.5M) in toluene (1.0 cm^3, 1.5 mmol) was added to a stirred solution of the 16β-alcohol **48** (80 mg, 0.26 mmol) in anhydrous toluene (5 cm^3) under nitrogen and the mixture was refluxed for 24 h. Hydrochloric acid (10%, 10 cm^3) was added and the mixture was extracted with ethyl acetate (3 x 15 cm^3). The combined organic extract was washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure to yield a residue (145 mg). The residue was chromatographed on silica gel (10 g) with ethyl acetate - toluene (1:19) as eluent to yield the diol **49** (70 mg, 92%), m.p. 217 - 220 °C; $[\alpha]_D$ 32 (*c* 0.9 in THF); (Found: C,80.2; H, 8.5%; M^+ 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.7%; *M* 298); ν_{max} /cm^{-1} 3440 and 3320.

Cycloaddition of Methyl Vinyl Ketone to the 14,16-diene 31

a) The 14,16-diene **31** (510 mg, 1.92 mmol) and methyl vinyl ketone (0.8 cm^3, 9.59 mmol) were combined in anhydrous tetrahydrofuran (5 cm^3) and stirred in an atmosphere of nitrogen at 0 °C. To this mixture was added borontrifluoride-diethylether (0.1 cm^3, 0.77 mmol) with stirring.The reaction mixture was allowed to warm to 25 °C and stirred for a further 24 h in an atmosphere of nitrogen. Water (10 cm^3) was added and the mixture was extracted with ethyl acetate (3 x 20 cm^3). The combined organic extract was washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to yield a residue (782 mg). Chromatography of the residue on silica gel (60 g) with ethyl acetate toluene (1:19) as eluent afforded 16α-*acetyl*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene* **52** (200 mg, 31%); mp 189 - 191 °C (from ethyl acetate); $[\alpha]_D$ 212 (*c* 1.2); (Found: C, 82.4; H, 8.4%; M^+, 336. $C_{23}H_{28}O_2$ requires C, 82.1; H, 8.3%; *M*, 336); ν_{max}/cm^{-1} 1712 (CO) ; δ_H(400 MHz) 0.96 (3 H, s, 13β-Me), 1.87 (1 H, dt, *J* 12.8 and 2 x 3.2 Hz, 12β-H), 1.42 (1 H, td, *J* 2 x 11.4 and 2.5 Hz, 8β-H), 1.92 (1 H, dddd, *J* 12.7, 5.3, and 2 x 2.6 Hz, 7β-H), 2.14 (3 H, s, $COCH_3$), 2.19 (1 H, dq, *J* 13.7 and 3 x 3.7 Hz, 11α-H), 2.46 (1 H, td, *J* 2 x 11.4 and 3.7 Hz, 9α-H), 2.86 (2 H, m, 6-H_2), 2.92 (1 H, dt, *J* 2 x 3.9 and 0.9 Hz, 17β-H), 3.23 (1 H, dt, *J* 7.6 and 2 x 3.9 Hz, 16β-H), 3.78 (3 H, s, 3-OMe), 5.77 (1 H, dd, *J* 5.9 and 3.9 Hz, 17^1-H), 6.11 (1 H, d, *J* 5.9 Hz, 17^2-H), 6.64 (1 H, d, *J* 2.8 Hz,

4-H), 6.72 (1 H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.21 (1 H, d, *J* 8.5 Hz, 1-H); δ_C(100 MHz) 17.6 (q, C-18), 25.2 (t, C-7), 27.3 (t, C-11), 28.7 (t, C-15), 29.0 (q, $COCH_3$), 29.2 (t, C-12), 30.4 (t, C-6), 39.2 (d, C-8), 40.0 (d, C-9), 53.5 (d, C-17), 55.2 (q, 3-OMe), 55.4 (d, C-16), 57.8 and 59.4 (each s, C-13 and C-14), 111.7 (d, C-2), 113.7 (d, C-4), 127.0 (d, C-1), 129.5 and 137.6 (each d, C-17^1 and C-17^2), 132.6 (s, C-10), 138.0 (s, C-5), 157.4 (s, C-3), and 209.1 (s, *C*OCH3). This was followed by 16α-*acetyl*-3-*methoxy*-17β-3′-*oxobutyl*-14,17α-*ethenoestra*-1,3,5(10)-*triene* **53** (417 mg, 53%), mp 91 - 92 °C (from ethyl acetate - methanol), $[\alpha]_D$ +122° (*c* 1.3); (Found: C, 79.6; H, 8.8%, M^+ 406. $C_{27}H_{34}O_3$ requires C, 79.8; H, 8.4%; *M* 406); ν_{max}/cm^{-1} 2712 (CO); δ_H (400 MHz) 1.11 (1 H, dt, *J* 12.6 and 2 x 3.2 Hz, 12β-H), 1.33 (1 H, dddd, *J* 3 x 13.0 and 3.9 Hz, 11β-H), 1.37 (1 H, dd, *J* 11.7 and 4.8 Hz, 15α-H), 1.44 (1 H, td, *J* 2 x 11.5 and 2.2 Hz, 8β-H), 1.64 (1 H, m, 7α-H), 1.83 (1 H, ddd, *J* 14.6, 10.0, and 5.8 Hz, 1′-H), 1.86 (1 H, m, 7β-H), 1.98 (1 H, dd, *J* 11.7 and 9.4 Hz, 15β-H), 2.05 (3 H, s, $COCH_3$), 2.08 (1 H, ddd, *J* 14.6, 10.0, and 5.8 Hz, 1′-H), 2.15 (3 H, s, $COCH_3$), 2.20 (1 H, dq, *J* 13.0 and 3 x 4.0 Hz, 11α-H), 2.47 (1 H, td, *J* 2 x 11.5 and 3.8 Hz, 9α-H), 2.60 (2 H, m. 2′-H_2), 2.85 (2 H, m, 6α- and 6β-H), 3.06 (1 H, dd, *J* 9.4 and 4.8 Hz, 16β-H), 3.77 (3 H, s, 3-OMe), 5.94 and 6.02 (each 1 H, d, *J* 5.9 Hz, 17^1- and 17^2-H), 6.64 (1 H, d, *J* 2.8 Hz, 4-H), 6.71 (1 H, dd, *J* 8.7 and 2.8 Hz, 2-H), and 7.20 (1 H, d, *J* 8.7 Hz, 1-H); δC(100 MHz) 15.2 (q, C-18), 21.7 (t, C-1′), 24.9 (t, C-7), 27.3 (t, C-11), 29.4 (t, C-12), 29.9 (q, $COCH_3$), 30.2 (t, C-6), 30.7 (q, $COCH_3$), 34.1 (t, C-15), 39.3 (d, C-8), 39.9 (d, C-9), 40.9 (t, C-2′), 55.2 (q, 3-OMe), 58.1 (d, C-16), 59.6, 60.3, and 61.4 (each s, C-13, C-14, and C-17), 111.7 (d, C-2), 113.7 (d, C-4), 126.9 (d, C-1), 132.4 (s, C-10), 134.4 and 134.5 (each d, C-17^1 and C-17^2), 137.9 (s, C-5), 157.4 (s, C-3), 208.9 and 210.2 (each s, *C*OCH3).

b) A mixture of the 14,16-diene **31** (350 mg, 1.31 mmol) and methyl vinyl ketone (0.5 cm^3, 6.58 mmol) in anhydrous toluene (1 cm^3) was heated in a sealed tube at 125 °C for 9 h. The reaction mixture was concentrated under reduced pressure to yield a crystalline residue (515 mg). Chromatography of the residue on silica gel (35 g) with ethyl acetate - toluene (1:19) as eluent afforded the ketone **52** (300 mg, 67%). Elution with ethyl acetate - toluene (3:7) gave the dione **53** (95 mg, 17%).

3-Methoxy-16α-acetyl-14,17α-ethanoestra-1,3,5(10)-triene 64

A solution of the 14,17α-etheno compound **52** (152 mg, 0.45 mmol) in ethyl acetate (2 cm^3) was hydrogenated in the presence of palladium on charcoal (10%, 65 mg) at 25 °C and atmospheric pressure. The catalyst was removed by filtration, washed with ethyl acetate, and the organic phase was concentrated under reduced pressure to give the 14,17α-*ethano* compound **64** as a crystalline residue (152 mg, 99%), mp 170 - 173 °C (from ethyl acetate), $[\alpha]_D$ +75 (*c* 1.2 in $CHCl_3$); (Found: C, 82.1; H, 9.2%; M^+, 338. $C_{23}H_{30}O_2$ requires C, 81.7; H, 8.9%; *M*, 338); ν_{max}/cm^{-1} 1715; δ_H(200 MHz) 1.00 (3 H, s, 13β-H), 2.13 (3 H, s, $COCH_3$), 2.84 (2 H, m, 6-H_2), 3.15 (1 H, dddd, *J* 10.7, 2 x 4.2, and 2.3 Hz, 16β-H), 3.77 (3 H, s, 3-OMe), 6.64 (1 H, d, *J* 2.7 Hz, 4-H), 6.74 (1 H, dd, *J* 8.5 and 2.7 Hz, 2-H), and 7.22 (1 H, d, *J* 8.5 Hz, 1-H).

Attempted Baeyer-Villiger Oxidation of the 14,17α-Etheno Ketone 64

a) To a solution of urea-hydrogen peroxide (UHP) (289 mg, 3.08 mmol) and disodium hydrogen phosphate (152 mg, 1.08 mmol) in dichloromethane (2 cm^3) at 0 °C under nitrogen was added trifluoroacetic anhydride (0.1 cm^3, 0.77 mmol). The resulting solution was stirred at 0 °C for 5 min, followed by the dropwise addition of the 14,17α-ethano ketone **64** (104 mg, 0.31 mmol) in dichloromethane (1 cm^3). The reaction mixture was stirred at 0 °C for 5 h, and then at 25 °C for 2 h. A saturated solution of sodium hydrogen carbonate was added and the mixture was extracted with dichloromethane (4 x 15 cm^3). The combined organic layers were washed (water), dried ($MgSO_4$), and evaporated to yield a residue (124 mg) which TLC analysis indicated was a complex mixture.

b) To a solution of the 14,17α-ethano ketone **64** (52 mg, 0.15 mmol) and sodium carbonate (127 mg, 1.2 mmol) in dichloromethane (2 cm^3) was added *m*-chloroperbenzoic acid (64% pure, 124 mg, 0.46 mmol). The reaction mixture was stirred at 25 °C for 52 h. Aqueous 5% sodium thiosulfate (10 cm^3) was added and the mixture was extracted with dichloromethane (4 x 20 cm^3). The combined organic extract was washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to afford a residue which TLC analysis indicated was a complex mixture.

Cycloaddition of Phenyl Vinyl Sulfone to the Diene 31

A solution of the diene **31** (338 mg, 1.27 mmol) and phenyl vinyl sulfone (260 mg, 1.55 mmol) in anhydrous toluene (0.8 cm^3) was heated in a sealed tube purged with nitrogen at 145 °C for 78h. The mixture was cooled to room temperature and chromatographed directly on silica gel (50 g), with ethyl acetate - toluene (1:19) as eluent. This afforded starting material (17 mg, 5%), followed by a mixture of cycloadducts (418 mg, 76%). The mixture was recrystallised from ethyl acetate to yield the 16α-sulfone **66** (205 mg, 37%); mp 186 - 188 °C (lit.,[50] 186 - 187 °C); δ_H(200 MHz) 0.86 (3 H, s, 13β-Me), 1.41 (1 H, m, 8β-H), 2.51 (1 H, m, 9α-H), 2.86 (3 H, m, 17β-H and 6-H_2), 3.77 (3 H, s, 3-OMe), 3.86 (1 H, ddd, *J* 8.0, 4.9, and 3.2 Hz, 16β-H) 6.12 (1 H, dd, *J* 5.7 and and 2.8 Hz, 17^1-H), 6.24 (1 H, d, *J* 5.7 Hz, 17^2-H), 6.62 (1 H, d, *J* 2.6 Hz, 4-H), 6.70 (1 H, dd, *J* 8.5 and 2.6 Hz, 2-H), 7.17 (1 H, d, *J* 8.5 Hz, 1-H), and 7.50 - 7.92 (5 H, m, $SO_2C_6H_5$); δ_C(50 MHz) 17.4 (q, C-18), 25.3 (t, C-7), 27.0 (t, C-11), 28.5 (t, C-12), 30.2 (t, C-6), 31.1 (t, C-15), 38.9 (d, C-8), 39.9 (d, C-9), 54.3 (d, C-17), 55.2 (q, 3-OMe), 58.8 and 60.0 (each s, C-13 and C-14), 66.2 (d, C-16), 111.7 (d, C-2), 113.6 (d, C-4), 126.8 (d, C-1), 127.8 (d, C-2′ and C-6′), 129.1 (d, C-3′ and C-5′), 129.9 and 136.5 (each d, $C\text{-}17^1$ and $C\text{-}17^2$) 132.0 (s, C-10), 133.2 (d, C-4′), 137.7 (s, C-5), 140.7 (s, C-1′, and 157.4 (s, C-3). The mother liquor material (210 mg) was chromatographed on silica gel (30 g) with ethyl acetate - hexane (1:9) as eluent to give 3-*methoxy*-15α-*phenylsulfonyl*-14,17α-*ethenoestra*-1,3,5(10)-*triene* **69** (55 mg, 10%); mp 142 - 146 °C (from ethyl acetate); $[\alpha]_D$ 63 (c 1.0); (Found: C, 75.1; H, 6.9; S, 7.1%; M^+, 434. $C_{27}H_{30}O_3S$ requires C, 75.3; H, 6.9; S, 7.4%; *M*, 434); ν_{max}/cm^{-1} 1317 and 1145 ; δ_H (400 MHz; $CDCl_3$) 0.92 (3 H, s, 13β-Me), 1.75 (1 H, td, *J* 2 x 11.1 and 2.0 Hz, 8β-H), 1.84 (1 H, dddd, *J* 12.1, 2 x 10.9, and 5.6 Hz, 7α-H), 2.01 (1 H, ddd, *J* 12.9, 9.0, and 3.4 Hz, 16β-H), 2.40 (1 H, t, *J* 3.4 Hz, 17β-H), 2.55 (1 H, m, 9α-H), 2.97 (2 H, m, 6α- and 6β-H), 3.10 (1 H, dddt, *J* 12.1, 5.7, and 2 x 2.8 Hz, 7β-H), 3.66 (1 H, dd, *J* 9.0 and 5.4 Hz, 15β-H), 3.79 (3 H, s, 3-OMe), 6.12 (1 H, dd, *J* 5.8 and 3.4 Hz, 17^1-H), 6.21 (1 H, d, *J* 5.8 Hz, 17^2-H), 6.67 (1 H, d, *J* 3.0 Hz, 4-H), 6.71 (1 H, dd, *J* 8.6 and 3.0 Hz, 2-H), 7.21 (1 H, d, *J* 8.6 Hz, 1-H), and 7.50 – 7.82 (5 H, m, $SO_2C_6H_5$); δ_C (100 MHz; $CDCl_3$) 18.1 (q, C-18), 26.6, 28.8, 30.1, 30.5, and 34.8 (each t, C-6, C-7, C-11, C-12, and C-16), 39.4 and 41.0 (each d, C-8 and C-9), 49.5 (d, C-17), 55.2 (q, 3-OMe) 61.2 (s, C-13), 65.6 (s, C-14), 68.4 (d, C-15), 111.7 (d, C-2), 113.3 (d, C-4), 126.9 (d, C-1), 127.9 (C-2′ and C-6′),

129.0 (d, C-3′ and C-5′), 132.3 and 132.4 (each d, C-17^1 and C-17^2), 132.9 (d, C-4′), 134.5 (s, C-10), 138.6 (s, C-5), 141.6 (s, C-1′), and 157.5 (s, C-3).

Hydroboration of the Cycloadducts 66 and 69

a) To a solution of the sulfones **66** and **69** (409 mg, 0.94 mmol) in dry tetrahydrofuran (4 cm^3) was added borane-dimethyl sulfide (10 M in THF, 0.5 cm^3, 5 mmol). The mixture was stirred at 70 °C under nitrogen for 6 h. After cooling to room temperature, aq. NaOH (4 M, 4 cm^3) was added, followed by aq. hydrogen peroxide (30%, 5 cm^3), and the mixture was stirred for a further 4 h. Water (30 cm^3) was added and the mixture was extracted with ethyl acetate (3 x 20 cm^3). The combined organic extract was washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to yield a residue (395 mg). The residue was chromatographed on silica gel (55 g) with ethyl acetate - toluene (1:9) as eluent to afford (17^{2}S)-3-*methoxy*-15α-*phenylsulfonyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17^2-*ol* **72** (28 mg, 7%); mp 245 - 247 °C (from ethyl acetate); $[\alpha]_D$ -6 (*c* 1.1); (Found C, 71.7; H, 7.2%; M$^+$, 452. $C_{27}H_{32}O_4S$ requires C, 71.7; H, 7.1%, *M*, 452); ν_{max}/cm^{-1} 3573; δ_H(400 MHz) 0.88 (3 H, s, 13β-H), 1.39 (1 H, dd, *J* 13.2 and 7.3 Hz, 16α-H) 2.06 (1 H, dd, *J* 12.9 and 8.0 Hz, 17^1-*endo*-H), 2.95 (2 H, m, 6α- and 6β-H), 3.02 (1 H, dddt, *J* 10.1, 5.2, and 2 x 2.7 Hz, 7β-H), 3.08 (1 H, dd, *J* 11.0 and 7.3 Hz, 15β-H), 3.41 (1 H, td, *J* 2 x 11.4 and 4.9 Hz, 9α-H), 3.79 (3 H, s, 3-OMe), 5.45 (1 H, dd, *J* 8.0 and 4.2 Hz, 17^2-H), 6.68 (1 H, d, *J* 2.8 Hz, 4-H), 6.72 (1 H, dd, *J* 8.5 and 2.8 Hz, 2-H), 7.16 (1 H, d, *J* 8.5 Hz, 1-H), and 7.58 – 7.84 (5H, m, $SO_2C_6H_5$); δ_C(100 MHz) 18.6 (q, C-18), 25.1, 26.6. 30.4, 30.7, 35.2, and 41.0 (each t, C-6, C-7, C-11, C-12, C-16, and C-17^1), 39.4 and 40.7 (each d, C-8 and C-9), 42.1 (d, C-17), 52.0 (s, C-13), 55.2 (q, 3-OMe), 61.6 (s, C-14), 68.0 (d, C-15), 70.8 (d, C-17^2), 111.1 (d, C-2), 113.5 (d, C-4), 125.3 (d, C-1), 127.8 (d, C-2′ and C-6′), 129.1 (d, C-3′ and C-5′), 133.2 (d, C-4′), 135.3 (s, C-10), 138.6 (s, C-5), 141.4 (s, C-1′), and 157.4 (s, C-3); followed by (17^{2}S)-3-*methoxy*-16α-*phenylsulfonyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17^2-*ol* **70** (108 mg, 25%); mp 216 - 219 °C (from ethyl acetate); $[\alpha]_D$ 28 (*c* 1.3); (Found: C, 71.5; H, 7.4; S 7.1%; M$^+$ 452. $C_{27}H_{32}O_4S$ requires C, 71.7; H, 7.1; S, 7.1%; *M* 452); ν_{max}/cm^{-1} 3609, 1316, and 1148; δ_H(400 MHz) 0.67 (3 H, s, 13β-Me), 2.25 (1 H, t, *J* 4.3 Hz, 17β-H), 2.88 (2 H, m, 6α- and 6β-H), 2.94 (1 H, dd, *J* 13.8 and 8.1 Hz, 17^1-*endo*-H), 3.51 (1 H, td, *J* 2 x 12.1 and 5.0 Hz, 9α-H), 3.61 (1 H, dddd, *J* 10.7, 2 x 4.3, and 2.1 Hz, 16β-H),

3.76 (3 H, s, 3-OMe) 4.37 (1 H, dt, *J* 8.0 and 2 x 4.8 Hz, → dd, *J* 8.0 and 4.8 Hz on D_2O exch., 17^2-H), 6.63 (1 H, d, *J* 2.9 Hz, 4-H), 6.70 (1 H, dd, *J* 8.6 and 2.9 Hz, 2-H), 7.16 (1 H, d, *J* 8.6 Hz, 1-H), and 7.28 - 7.90 (5H, m, $SO_2C_6H_5$); δ_C(100 MHz) 17.2 (q, C-18), 24.5, 25.9, 28.2, 30.0, 34.1, and 34.4 (each t, C-6, C-7, C-11, C-12, C-15, and C-17^1), 37.0 and 41.1 (each d, C-8 and C-9), 46.4 (d, C-17), 49.9 and 53.2 (each s, C-13 and C-14), 55.2 (q, 3-OMe), 65.0 (d, C-16), 77.8 (d, C-17^2), 111.3 (d, C-2), 113.7 (d, C-4), 125.8 (d, C-1), 127.7 (d, C-2′ and C-6′), 129.3 (d, C-3′ and C-5′), 133.4 (d, C-4′), 134.6 (s, C-10), 137.4 (s, C-5), 140.7 (s, C-1′), and 157.2 (s, C-3); followed by (17^1R)-3-*methoxy*-16α-*phenylsulfonyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17^1-*ol* **71** (147 mg, 34%), mp 188 - 189 °C (from ethyl acetate); $[\alpha]_D$ -16 (*c* 0.9); (Found: C, 71.8; H, 7.1; S 6.9%; M^+, 452. $C_{27}H_{32}O_4S$ requires C, 71.7; H, 7.1; S, 7.1%; *M* 452); ν_{max}/cm^{-1} 3618 δ_H(400 MHz) 0.86 (3 H, s, 13β-Me), 1.98 (1 H, dd, *J* 12.6 and 5.3 Hz, 15α-H), 2.45 (1 H, d, *J* 4.3 Hz, 17β-H), 2.72 (2 H, m, 12α- and 9α-H), 2.84 (2 H, m, 6α- and 6β-H), 3.60 (1 H, ddd, *J* 10.9, 5.3, and 4.3 Hz, 16β-H), 3.76 (3 H, s, 3-OMe) 5.05 (1 H, dd, *J* 8.1 and 2.8 Hz, 17^1-H), 6.61 (1 H, d, *J* 2.8 Hz, 4-H), 6.71 (1 H, dd, *J* 8.5 and 2.8 Hz, 2-H), 7.20 (1 H, d, *J* 8.5 Hz, 1-H), and 7.58 – 7.90 (5H, m, $SO_2C_6H_5$); δ_C(100 MHz) 16.7 (q, C-18), 25.3, 26.5, 29.6, 30.1, 34.0, and 40.1 (each t, C-6, C-7, C-11, C-12, C-15, and C-17^2), 37.0 and 40.2 (each d, C-8 and C-9), 49.6 and 52.0 (each s, C-13 and C-14), 55.2 (q, 3-OMe), 56.2 (d, C-17), 63.5 (d, C-16), 77.3 (d, C-17^1), 111.6 (d, C-2), 113.7 (d, C-4), 126.6 (d, C-1), 127.7 (d, C-2′ and C-6′), 129.4 (d, C-3′and C-5′), 132.8 (s, C-10), 133.5 (d, C-4′), 137.5 (s, C-5), 141.0 (s, C-1′), and 157.2 (s, C-3); followed by (17^1R)-3-*methoxy*-15α-*phenylsulfonyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17^1-*ol* **73** (48 mg, 11%) as a glass; $[\alpha]_D$ 24 (*c* 1.1); (Found: M^+, 452.2013. $C_{27}H_{32}O_4S$ requires *M*, 452.2019); δ_H(400 MHz) 0.92 (3 H, s, 13β-Me), 1.36 (1 H, dd, *J* 13.6 and 6.1 Hz, 16α-H), 2.95 (2 H, m, 6α- and 6β-H), 3.10 (1 H, dd, *J* 14.4 and 8.2 Hz, 17^2-*endo*-H), 3.16 (1 H, ddd, *J* 10.6, 6.1, and 2.2 Hz, 15β-H) 3.79 (3 H, s, 3-OMe), 4.13 (1 H, dd, *J* 8.1 and 3.4 Hz, 17^1-H), 6.66 (1 H, d, *J* 2.4 Hz, 4-H), 6.72 (1 H, dd, *J* 8.6 and 2.7 Hz, 2-H), 7.22 (1 H, d, *J* 8.6 Hz, 1-H), and 7.58 – 7.85 (5 H, m, $SO_2C_6H_5$).

b) The 16α-sulfone **66** (415 mg, 0.96 mmol) was reacted with borane-dimethyl sulfide (10 M solution, 0.50 cm^3, 5.0 mmol) in tetrahydrofuran (5 cm^3) according to the procedure described above. The residue (439 mg) after work-up was chromatographed on silica gel (50 g) with ethyl acetate - toluene (1:9) as eluent to afford the (17^2S)-16α-sulfone **70** (145 mg, 33%), followed by the (17^1R)-16α-sulfone **71** (190 mg, 44%).

(17^{2}S)-3-Methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17^2-ol 74

Activated magnesium turnings (150 mg, 6.21 mmol) were added to a solution of the (17^{2}S)-16α-sulfone **70** (104 mg, 0.23 mmol) in absolute methanol (5 cm^3), and the mixture was stirred at 50 °C for 1 h. Further magnesium turnings (162 mg) were added and the solution was stirred at 50 °C for a further 6 h. After cooling the reaction mixture to 0 °C, the reaction was quenched by the addition of concentrated hydrochloric acid (4 cm^3), and the methanol was removed under reduced pressure. The residue was extracted with chloroform (4 x 20 cm^3) and the combined organic extract was washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to yield a residue (89 mg). The residue was chromatographed on silica gel (70 g) with ethyl acetate - toluene (1:19) as eluent to give the (17^{2}S)-*alcohol* **74** (55 mg, 77%); mp 94 -96 °C (from hexane); $[\alpha]_D$ 64 (*c* 1.1); (Found: C, 80.4; H, 9.6%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.8; H, 9.0%; *M*, 312); ν_{max}/cm^{-1} 3614; δ_H(400 MHz) 0.89 (3 H, s, 13β-Me), 2.14 (1 H, td, *J* 2x 13.0 and 4.1 Hz, 8β-H), 2.90 (2 H, m, 6-H_2), 3.38 (1 H, td, J 2 x 11.7 and 5.1 Hz, 9α-H), 3.77 (3 H, s, 3-OMe), 4.04 (1 H, dd, *J* 8.2 and 4.5 Hz, 17^2-H), 6.64 (1 H, d, *J* 2.7 Hz, 4-H), 6.71 (1 H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.20 (1 H, d, *J* 8.6 Hz, 1-H); δ_C(100 MHz) 17.8 (q, C-18), 24.9, 26.3, 28.7, 29.6, 30.4, and 31.5 (each t, C-6, C-7, C-11, C-12, C-15, and C-16), 37.8 and 41.2 (each d, C-8 and C-9), 41.0 (t, C-17^1), 42.9 (d, C-17), 47.2 (s, C-13), 51.8 (s, C-14), 55.2 (q, 3-OMe), 79.6 (d, C-17^2), 111.2 (d, C-2), 113.8 (d, C-4), 126.0 (d, C-1), 135.2 (s, C-10), 137.8 (s, C-5), and 157.2 (s, C-3).

(17²S)-14,17α-Ethanoestra-1,3,5(10)-triene-3,17²-diol 75

To a stirred solution of the (17²S)-alcohol **74** (77 mg, 0.25 mmol) in anhydrous toluene (5 cm^3) was added diisobutyl aluminium hydride (1.5 M) in toluene (0.7 cm^3, 1.08 mmol). The reaction mixture was refluxed under nitrogen for 15 h. The reaction was quenched by the addition of hydrochloric acid (10%, 10 cm^3) and the mixture was extracted with ethyl acetate (3 x 15 cm^3). The combined organic extract was washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to yield a residue (88 mg). The residue was chromatographed on silica gel (10 g) with ethyl acetate - toluene as eluent to yield the *diol* **75** (66 mg, 91%); mp 142 - 145 °C (from $CHCl_3$); $[\alpha]_D$ 56 (*c* 1.0); (Found: C, 80.4; H, 8.9%; M^+, 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.7%; *M*, 298);

(17¹R)-3-Methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17¹-ol 76

To a vigorously stirred solution of the (17¹R)-16α-sulfone **71** (100 mg, 0.22 mmol) in methanol (5 cm^3) was added activated magnesium turnings (145 mg, 6.0 mmol). The mixture was stirred at 50 °C for 1 h, after which further magnesium turnings were added (160 mg). The solution was stirred for a further 5 h at 50 °C. Cooling of the reaction mixture to 0 °C was followed by the addition of concentrated hydrochloric acid (5 cm^3), and the methanol was removed under reduced pressure. The residue was extracted with chloroform (4 x 15 cm^3), and the combined organic extract was washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to yield a residue (74 mg). Chromatography of the residue on silica gel (10 g) with ethyl acetate - toluene (1:9) as eluent afforded the (17¹R)-*alcohol* **76** (58 mg, 84%); mp 122 - 124 °C (from ethyl acetate - hexane); $[\alpha]_D$ 33 (*c* 1.1); (Found: C, 81.2; H, 9.1%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.8; H, 9.1%; *M*, 312); ν_{max}/cm^{-1} 3618; δ_H(400 MHz;) 0.90 (3 H, s, 13β-Me), 2.70 (1 H, td, *J* 2 x 11.3 and 4.2 Hz, 9α-H), 2.84 (2 H, m, 6-H_2), 3.78 (3 H, s, 3-OMe), 3.93 (1 H, dd, *J* 8.2 and 3.1 Hz, 17¹-H), 6.63 (1 H, d, *J* 2.8 Hz, 4-H), 6.72 (1 H, dd, *J* 8.4 and 2.8 Hz, 2-H), and 7.24 (1 H, d, *J* 8.4 Hz, 1-H); δ_C(100 MHz) 17.1 (q, C-18), 25.5, 26.8, 30.2, 30.4, and 31.4 (each t, C-6, C-7, C-11, C-12, C-15, and C-16), 37.7 and 40.4 (each d, C-8 and C-9), 41.0 (t, C-17²), 47.0 (s, C-13), 50.1 (s, C-14), 52.9 (d, C-17), 55.2 (q, 3-OMe), 76.0 (d, C-17¹), 111.5 (d, C-2), 113.7 (d, C-4), 126.7 (d, C-1), 133.5 (s, C-10), 137.8 (s, C-5), and 157.3 (s, C-3).

(17[1]R)-14,17α-Ethanoestra-1,3,5(10)-triene-3,17[1]-diol 77

A stirred solution of the (17[1]R)-alcohol **76** (103 mg, 0.33 mmol) in anhydrous toluene (5 cm^3) was treated with diisobutyl aluminium hydride (1.5 M solution in toluene, 1.1 cm^3, 1.65 mmol). The resulting mixture was refluxed under nitrogen for 18 h. Hydrochloric acid (10%, 15 cm^3) was added and the reaction mixture was extracted with ethyl acetate (3 x 20 cm^3). The organic extracts were combined and washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure to yield a residue. Chromatography of the residue on silica gel (10 g) with ethyl acetate - toluene (1:9) as eluent afforded the 3,17[1]R-*diol* **77** (84 mg, 85%); mp 238 - 241 °C (from tetrahydrofuran); $[\alpha]_D$ 30 (*c* 1.1 in tetrahydrofuran); (Found: C, 80.6; H, 8.8; M^+, 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.7; *M*, 298); ν_{max}/cm^{-1} 3494 br.

Cycloaddition of Methyl Acrylate to the 14,16-Diene 31

A solution of the diene **31** (105 mg, 0.39 mmol) and methyl acrylate (0.20 cm^3 2.22 mmol) in anhydrous benzene was purged with nitrogen and heated in a sealed tube at 90 °C. A further aliquot of methyl acrylate (0.20 cm^3) was added after 48 h. After 96 h, the cooled reaction mixture was concentrated under reduced pressure and chromatographed on silica gel (15 g) with ethyl acetate -toluene (1:99) as eluent to afford the diene **31** (8 mg, 8%) followed by an inseparable two component mixture of cycloadducts **78** and **79** (108 mg, 78%), (Found: M^+ 352. $C_{23}H_{28}O_3$ requires *M*, 352); δ_H (200 MHz) 0.92 (s, 13β-Me), 3.22 (ddd, *J* 7.9 and 2 x 3.9 Hz, 16β-H), 3.43 (dd, *J* 9.6 and 3.7 Hz, 15β-H), 3.62 (s, -COOCH_3), 3.64 (s, -COOCH_3), 3.78 (s, 3-OMe), 5.85 (dd, *J* 5.7 and 2.8 Hz, 17[1]-H), 6.11 (d, *J* 5.9 Hz, 17[2]-H), 6.13 (d, *J* 5.7 Hz, 17[2]-H), 6.20 (dd, *J* 5.9 and 3.9 Hz, 17[2]-H), 6.64 (d, *J* 2.8 Hz, 4-H), 6.70 (dd, *J* 6.5 and 2.8 Hz, 2-H), 7.24 (d, *J* 8.5 Hz, 1-H).

Cycloaddition of Acrolein to the 14,16-Diene 31

A solution of the diene **31** (158 mg, 0.59 mmol) and acrolein (0.20 cm^3 3.00 mmol) in anhydrous benzene was purged with nitrogen and heated in a sealed tube at 90 °C. Further aliquots of acrolein (each 0.1 cm^3) were added after 64, 80 and 96 h. After 115 h, the cooled reaction mixture was concentrated under reduced pressure and chromatographed on silica gel (20 g) with ethyl acetate -toluene (1:19) as eluent to afford the diene **31** (25 mg, 16%) followed by an inseparable three component mixture of cycloadducts **80**, **81** and **82** (117 mg, 61%), (Found: M^+, 322. $C_{22}H_{26}O_2$ requires *M*, 322); δ_H (400 MHz) 1.31 (s, 13β-Me), 3.14 (ddd, *J* 8.8, 5.4 and 3.6 Hz), 3.55 (dddd, *J* 7.8, 2 x 3.8 and 1.6 Hz), 3.71 (dt, *J* 8.9 and 2 x 3.4 Hz), 4.14 (s, 3-OMe), 6.28 (dd, *J* 5.8 and 3.0 Hz, 17^1-H), 6.48 (m, 17^2-H), 6.57 (dd, *J* 6.1 and 3.0 Hz, 17^1-H), 6.61 (dd, *J* 5.8 and 3.0 Hz, 17^1-H), 7.01 (m, 4-H), 7.08 (m, 2-H), 7.58 (m, 1-H), 9.72 (d, *J* 5.3 Hz, -CO*H*), 9.84 (d, *J* 3.5, -CO*H*), 9.96 (d, *J* 0.8 Hz, -CO*H*).

References

1. P.C. Ruenitz, in *Burger's Medicinal Chemistry and Drug Discovery*, 5th Ed., Ed. M.E. Wolff, vol. 4, Wiley-Interscience, New York, 1997, p 554
2. P.A. Cole and C.H. Robinson, in *Molecular Structure and Biological Activity of Steroids*, Eds. M. Bohl and W.L. Duax, CRC Press, Boca Raton, 1992, P 230
3. P.Morand and J. Lyall, *Chem. Rev.*, 1968, **68**, 85
4. P.C. Ruenitz, in *Burger's Medicinal Chemistry and Drug Discovery*, 5th Ed., Ed. M.E. Wolff, vol. 4, Wiley-Interscience, New York, 1997, p 555
5. D. Lednicer and L.A. Mischer, in *The Organic Chemistry of Drug Synthesis*, Wiley-Interscience, New York, 1977, p 161
6. J. Salmon, D. Couissediere, C. Cousty, and J.P. Raynaud, *J. Steroid Biochem.*, 1983, **18**, 565
7. P.C. Ruenitz, in *Burger's Medicinal Chemistry and Drug Discovery*, 5th Ed., Ed. M.E. Wolff, vol. 4, Wiley-Interscience, New York, 1997, p 558
8. K.Lubke, E. Schillinger, and M. Topert, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 741
9. G.M. Anstead, K.E. Carlson, and J.A. Katzenellenbogen, *Steroids*, 1997, **62**, 268
10. W.L Duax, in *Molecular Structure and Biological Activity of Steroids*, Eds. M.Bohl and W.L. Duax, CRC Press, Boca Raton, 1992, pp2 – 11
11. J.Wurtz, U. Egner, N. Heinrich, D. Moras, and A. Mueller-Fahrnow, *J. Med. Chem.*, 1998, **41**, 1803
12. A..M. Brzozowski, A.C.W. Pike, Z. Dauter, R.E. Hubbard, T.Bonn, O. Engström, L. Öhman, G.L. Greene, J. Gustafsson, and M. Carlquist, *Nature*, 1997, **389**, 753
13. J.R. Bull, R.I. Thomson, H.Laurent, H.G. Schröeder, and R. Wiechert, Ger. Offen., *DE*, 3 628 189 (1988) (*Chem. Abstr.*, 1988, **109**, 129451w)
14. J.R. Bull, C. Grundler, H.Laurent, R. Bohlmann, and A. Müller-Fahrnow, *Tetrahedron*, 1994, **50**, 6347
15. J.R.Bull, P.G. Mountford, G.Kirsch, G. Neef, A. Müller-Fahrnow, and R. Wiechert, *Tetrahedron*, 1994, **50**, 6363
16. J.R. Bull, L.M.Steer, and K. Jaworski, *Synlett*, 1994, 709
17. J.R. Bull and P.G. Mountford, *Synlett*, 1994, 711
18. H. Hofmeister, K. Annen, G. Cleve, H. Laurent, and R. Wiechert, *Liebigs Ann. Chem.*, 1981, 1973

19. J.R. Bull and M.A. Sefton, *S. Afr. J. Chem.*, 1985, **38**, 73

20. G.H. Rasmusson and G.E. Arth, *Steroids*, 1973, **22**, 107

21. W.G. Dauben, M.E. Lorber, N.D. Vietmeyer, R.H. Shapiro, J.H. Duncan, and K. Tomer, *J. Am. Chem Soc.*, 1968, **90**, 4762

22. R.H. Shapiro, J.H. Duncan, K. Tomer, W.G. Dauben, M.E. Lorber, and N.D. Vietmeyer, *J. Am. Chem. Soc.*, 1968, **90**, 4762

23. W.G. Dauben, G.T. Rivers, W.T. Zimmerman, N.C. Yang, B. Kim, and J. Yang, *Tetrahedron Lett.*, 1976, 2951

24. J.C. Caille, M. Farnier, and R.Guilard, *Can. J. Chem,* 1986, **64**, 824

25. W. Kirmse and L. Ruetz, *Liebigs Ann. Chem.*, 1969, **30**, 726

26. P. Magnus and M.B. Roe, *Tetrahedron Lett.*, 1995, **36**, 5479

27. L. Caglioti, P. Grasselli, F. Morlacchi, , and G. Rosini, *Chem. Ind.(London)*, 1968, 25

28. A.Dondini, G. Rossini, G. Mossa, and L. Caglioti, *J. Chem. Soc. (B)*, 1968, 1404

29. D.A. Lightner, T.D. Bouman, J.K. Gawronski, K. Gawronska, J. Chappuis, B.V. Crist, and A.E. Hansen, *J. Am. Chem. Soc.*, 1981, **103**, 5314

30. D.K. Philips, P.P. Wickham. G.O. Pots, and A. Arnold, *J. Med. Chem.*, 1968, **11**, 924

31. S.J. Nelson, G. Detre, and M. Tanabe, *Tetrahedron Lett.*, 1973, 447

32. S. Cacchi, E. Morera, and G. Ortar, *Tetrahedron Lett.*, 1984, **25**, 4821

33. P. Stang and W. Treptow, *Synthesis*, 1980, 283

34. R.E. Dolle, S.J. Schmidt, and L.I. Kruse, *Tetrahedron Lett.*, 1988, **29**, 1581

35. J.R. Bull and R.I. Thomson, *J. Chem. Soc., Perkin Trans. 1*,1990, 241

36. N.A. Cortese and R.F. Heck, *J. Org. Chem.*, 1978, **43**, 3985

37. C. Grundler, PhD Thesis, University of Cape Town, 1992

38. P.K. Freeman, D.M. Balls, and D.J. Brown, *J. Org Chem.*, 1968, **33**, 2211

39. H.C. Brown and H.R. Deck, *J. Am. Chem. Soc.*, 1965, **87**, 5620

40. H.C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.* 1972, **94**, 7159

41. O. Mitsunobu, *Synthesis*, 1981, 1

42. G.R. Krow, in *Comprehensive Organic Synthesis*, ed. B.M. Trost and I Fleming, Pergamon Press, Oxford, 1991, vol. 7, P 671

43. E.S. Sickle, PhD Thesis, University of Cape Town, 1997

44. D.H. Williams and I Fleming, *Spectroscopic Methods in Organic Chemistry*, second ed., McGraw-Hill, London, 1973, P 81

45 B.B. Snider, D.J. Rodini, and J. van Stralen, *J. Am. Chem. Soc.*, 1980, **102**, 5872

46. G Majetich and V. Khetani, *Tetrahedron Lett.*, 1990, **31**, 2243

47. M.S. Cooper, H. Heaney, A.J. Newbold, and W.R. Sanderson, *Synlett*, 1990, 533

48. M.C. Loedolff, MSc Thesis, University of Cape Town, 1991

49. J.R. Bull, P.D. de Koning, C. Hoadley, and K. Reddie, *S. Afr. J. Chem.*, 1998, **51**, 186

50. J.R. Bull and R.I. Thomson, *S. Afr. J. Chem.*, 1991, **44**, 87

51. A.C. Brown and L.A. Carpino, *J. Org. Chem.*, 1985, **50**, 1749

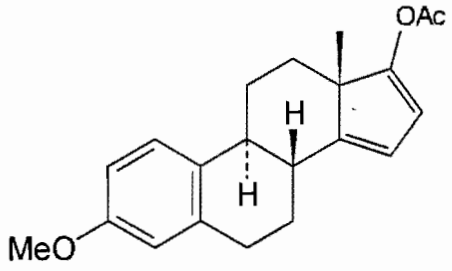
52. G.G. Kuiper, E. Enmark, M.Pelto-Huiko, S. Nilsson, J.A. Gustafsson, *Proc. Natl. Acad. Sci. USA.*, 1996, **93**, 5925

53. D.D. Perrin and W.L.F. Armarego, *Purification of Laboratory Chemicals*, 3rd Ed., Pergamon, Oxford, 1988

54. S.A. Sakek, S.M. Shaw, W.V. Kessler, and G.C. Wolf, *J.Org. Chem.*, 1981, **46**, 3259

Appendix

Structures not Illustrated in Chapter 3



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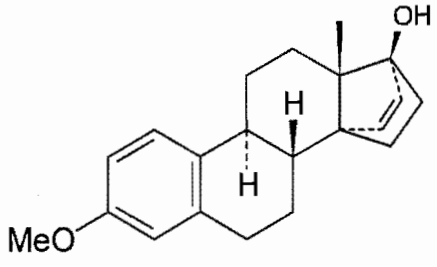

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