SYNTHESIS AND SELECTIVE REACTIVITY OF 14β-FORMYL 19-NORSTEROIDS

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To Fiona

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ABSTRACT

A synthetic route to 3-methoxy-16-methyl-14,17α-ethanoestra-1,3,5(10)-triene-15,16,17β-triol 17β-acetate was devised, based upon cycloaddition of a dienophilic 'propyne equivalent' to 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate. The dienophile chosen for this purpose, methyl propiolate, reacted with the diene regio- and stereoselectively to give methyl 17β-acetoxy-3-methoxy-14,17α-ethenoestra-1,3,5(10),15-tetraene-16-carboxylate. The resulting cycloadduct was chemoselectively hydrogenated to give methyl 17β-acetoxy-3-methoxy-14,17α-ethanoestra-1,3,5(10),15-tetraene-16-carboxylate. Attempted 1,2-reduction of this compound was unsuccessful and an indirect synthetic sequence to key intermediates for oxidative cleavage to 14β-formyl 19-norsteroids was undertaken. *cis*-Dihydroxylation of the dihydrocycloadduct gave an isomeric mixture of the 15α,16α- and 15β,16β-diols, which were protected via acetonide formation. Sequential reduction of the ester functionality, chemoselective mesylation of the 16^1-hydroxy group of the resultant 16^1-hydroxymethyl 17-alcohols, and reduction of the 16^1-mesylate, gave the isomeric 16-methyl 15,16-acetonides. 17-Acetylation followed by diol deprotection gave the desired 3-methoxy-16-methyl-14,17α-ethanoestra-1,3,5(10)-triene-15,16,17β-triol 17β-acetates. A more direct and efficient route entailed conjugate addition of thiophenol to the dihydrocycloadduct to give methyl 17β-acetoxy-3-methoxy-15α-phenylthio-14,17α-ethanoestra-1,3,5(10)-triene-16β-carboxylate. Reductive deoxygenation of the functionality on C(16) gave the 16β-methyl 15α-phenylthio intermediate, the corresponding sulfoxide of which underwent smooth thermal elimination to yield the key intermediate, 3-methoxy-16-methyl-14,17α-ethanoestra-1,3,5(10),15-tetraen-17β-ol. This hydroxy olefin, and the corresponding 17-acetate, underwent *cis*-dihydroxylation to give the desired 16-methyl 15,16-diols in superior overall yields. These intermediates underwent oxidative cleavage to give 17α-acetoxy-3-methoxy-20-oxo-19-nor-14β-pregna-1,3,5(10)-triene-14-carbaldehyde. This strategy and related adaptations led to the synthesis of a variety of 17-substituted 14β-formyl 19-norsteroids, including the 14β-formyl analogue of estrone. Chemoselective

reaction of this compound led to the synthesis of 14β-hydroxymethyl- and 14β-vinyl analogues of estradiol. Intramolecular aldol condensation of 17α-acetoxy-3-methoxy-20-oxo-19-nor-14β-pregna-1,3,5(10)-triene-14-carbaldehyde gave 17α-hydroxy-3-methoxy-14,17β-prop-17^2-eno-14β-estra-1,3,5(10)-triene-17^1-one, which was converted into a novel bridged hormone analogue, (17^1S)-14β,17β-prop-17^2-eno-14β-estra-1,3,5(10)-triene-3,17α,17^1-triol. Further, it was shown that the 14β,17β-prop-17^2-eno 17α,17^1-diol underwent 16(16 → 17^1)*abeo* rearrangement to 3-methoxy-14,17α-ethano-17a-homoestra-1,3,5(10),15-tetraen-17a-one, which, on reduction, gave the corresponding 17a-homoestradiol analogues. Hormone analogues that were synthesised during this investigation were subjected to biological evaluation, and the results and structure activity implications reported.

CONTENTS

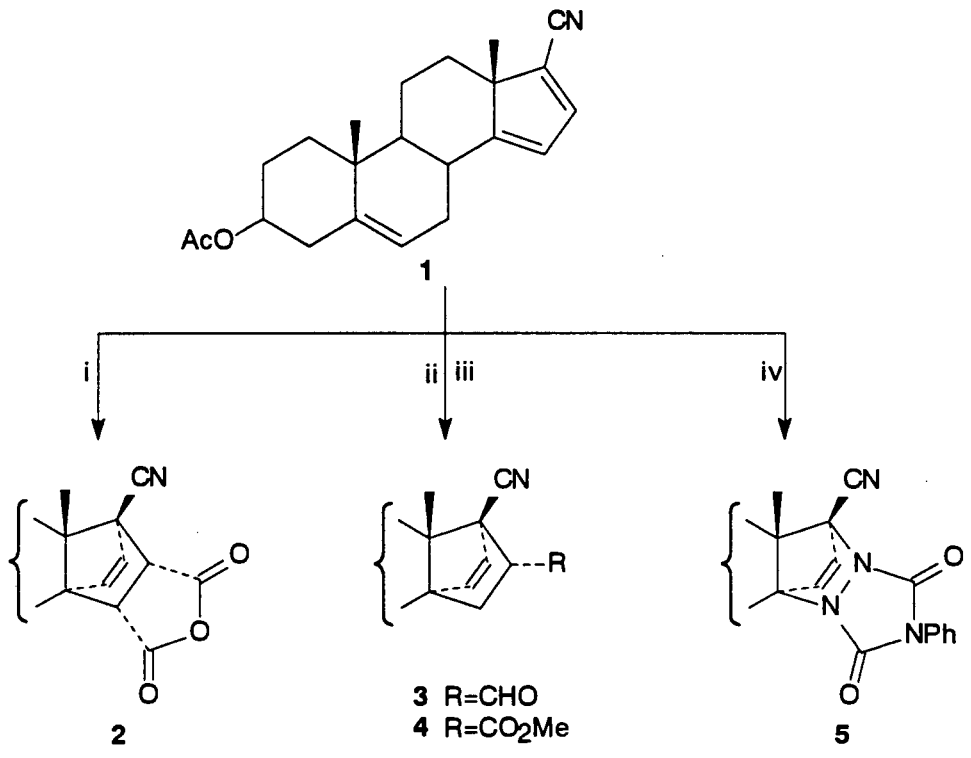
CHAPTER 1

Introduction

The elucidation of the structures and common structural relationships of the sex hormones and later the adrenocortical hormones,[1] led to numerous attempts to synthesise structurally modified hormone analogues with enhanced or altered physiological activity compared to that manifested by the naturally occurring parent hormones.[2] An estimated 100 000 steroid and steroid-like structures have been prepared for this purpose, with the emphasis on small variations in functional groups rather than modification of the parent skeleton.

Cycloaddition-mediated Synthesis of Ring D-bridged Steroids. Modifications of ring D using cycloaddition reactions to steroidal ring D dienes were first reported in 1965 by Solo *et al.*[3]

Scheme 1-1

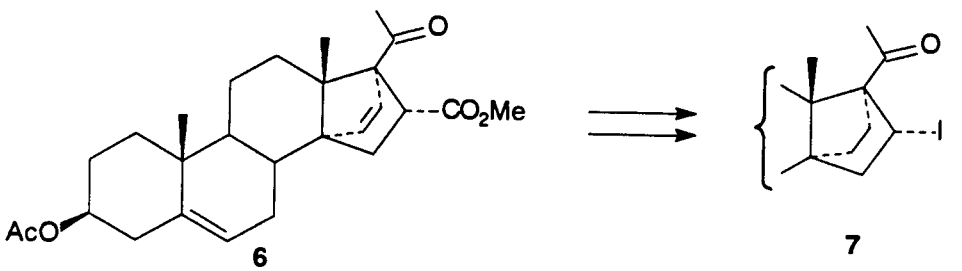


Reagents: (i) Molten maleic anhydride, 100°C. (ii) Acrolein 105°C. (iii) Methyl acrylate 115°C. (iv) 4-Phenyl-1,2,4-triazoline-3,5-dione 20°C.

17α-Substituted progesterone and testosterone derivatives were known to possess enhanced biological activity[4] and it was reasoned that the stereochemistry of ring D with a 14,17-bridge would correspond closely to the stereochemistry of one of the rotamers of 17α-alkyl or 17α-*O*-acyl derivatives, and could thus also be candidates for enhanced activity. Accordingly, 3β-acetoxyandrosta-5,14,16-triene-17-carbonitrile (**1**) was reacted with various dienophiles (Scheme 1-1) to give the 14,17-cycloadducts formulated as (**2**), (**3**) (**4**) and (**5**).

At the outset, the stereochemical assignments of the cycloadducts were based on examination of Dreiding stereomodels, which suggested that the β-face of the ring D diene is less sterically hindered than the α-face. This observation was supported by the knowledge that catalytic hydrogenation of these systems occurs by attack from the β-face.[5] When unsymmetrical dienophiles were used, it was further assumed that 'head-to-head' approach of dienophile and *endo*-orientation of the substituent would be favoured. These assumptions proved valid when the X-ray crystal strucuture of 16α-iodo-20-oxo-14α,17α-ethanopregn-5-en-3β-yl acetate (**7**), derived with retention of configuration from the corresponding methyl acrylate cycloadduct (**6**) (Scheme 1-2), was determined.[6] The stereo- and regiochemical outcome of this and related Diels-Alder cycloadditions is consistent with predictions based upon frontier molecular orbital theory.[7]

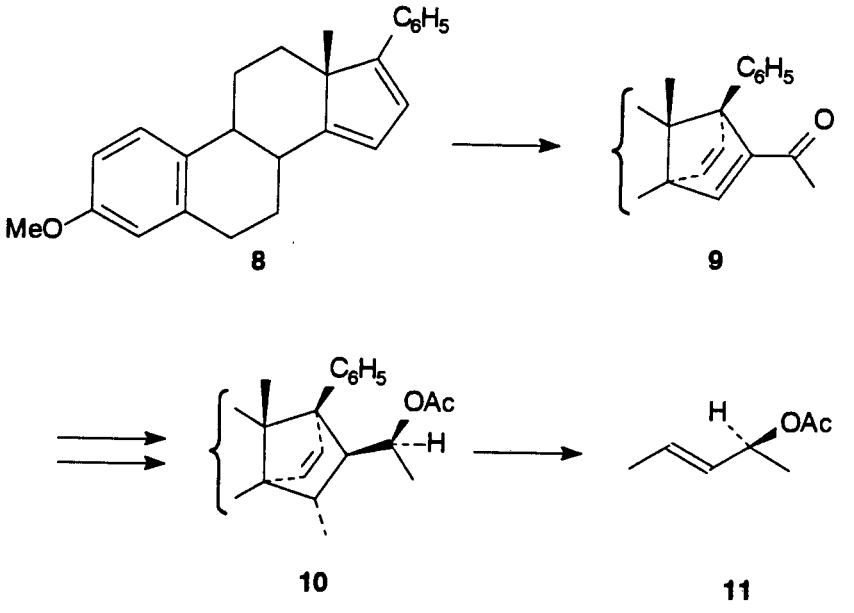
Scheme 1-2



Thus, Solo and his co-workers extended the range of cycloaddition reactions to 14,17-steroidal dienes,[8,9,10,11,12] and laid the foundations for extensive exploitation of cycloaddition methodology for the construction of steroidal ring D bridged systems, both in order to synthesise novel hormone analogues and as intermediates in asymmetric synthesis. The latter application is exemplified by the use of the steroid nucleus as a chiral template in reaction sequences involving cycloaddition, diastereoselective modification and cycloreversion, leading to enantiocontrolled syntheses of homochiral compounds.[13] For example, the steroidal ring D diene was effectively used as a chiral template in the synthesis of optically pure pent-3-en-2-yl acetate (**11**).[14] The key step in the synthesis was the cycloaddition of butynone to the steroidal diene (**8**) to give exclusively the cycloadduct (**9**)

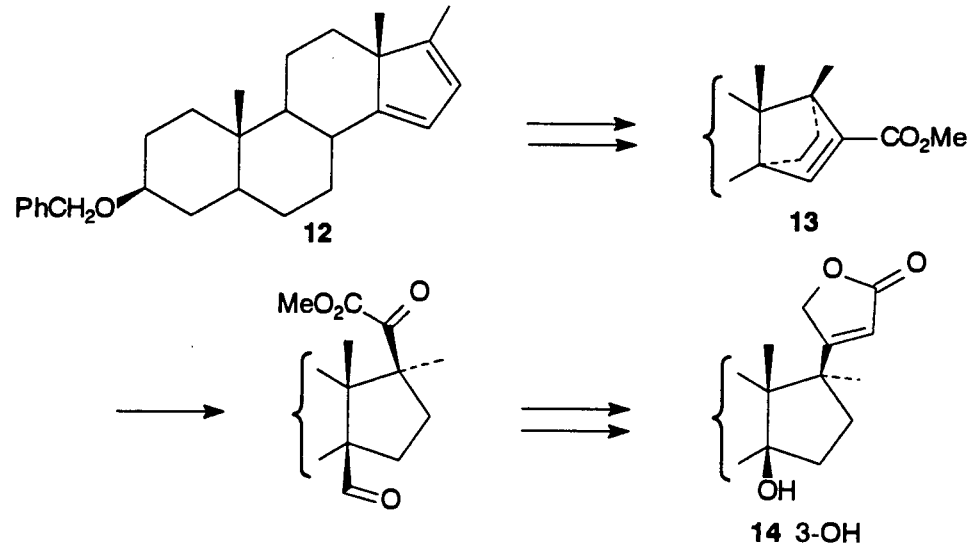
(94%), which was subsequently transformed into the compound (**10**) via conjugate addition, reduction and acetylation. Thermal retro-Diels-Alder reaction afforded the optically pure acetate (**11**) (Scheme 1-3).

Scheme 1-3



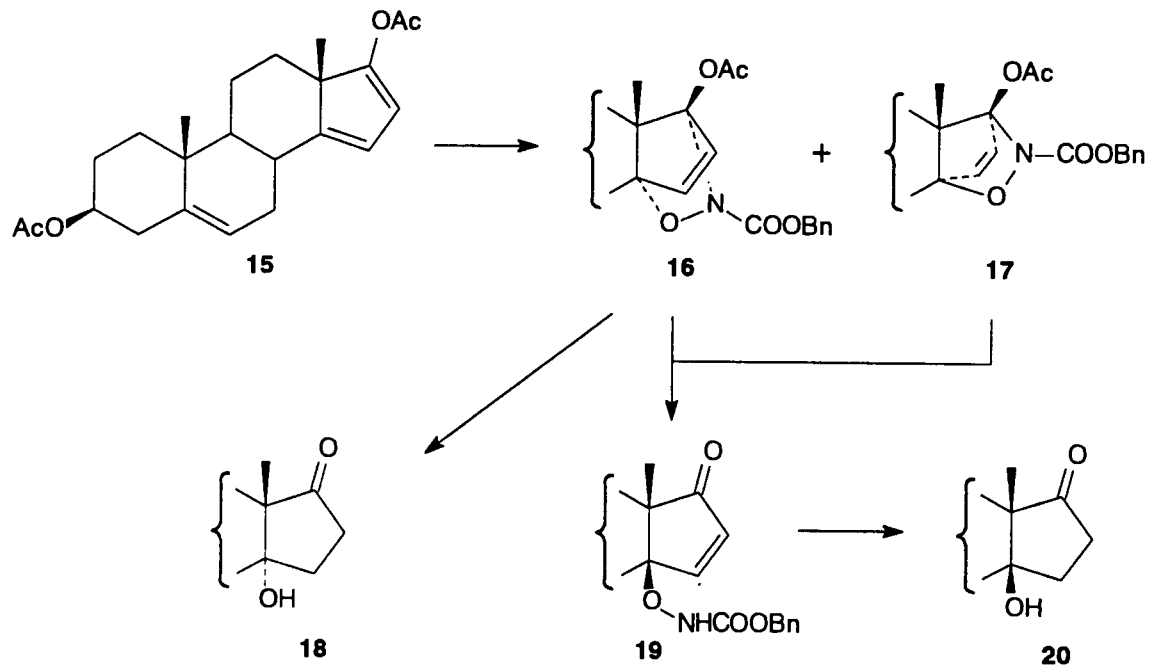
Cycloaddition methodology has also been used as an indirect method for the introduction of functionality at C(14) and C(17) of steroid systems. Wiesner *et al.*[15] used such an approach in the synthesis of the 17α-methyl analogue of digitoxigenin for investigation of structure-activity-toxicity relationships. The diene (**12**) (readily obtained via 1,2-methylation of the Δ^{15}-17-one and subsequent dehydration) underwent cycloaddition with ethyl propiolate to give a single cycloadduct (75%), which was chemoselectively hydrogenated to the unsaturated ester (**13**). Oxidative cleavage of (**13**), followed by several subsequent transformations, gave the 17α-methyl digitoxigenin (**14**) (Scheme 1-4), thus effecting stereocontrolled introduction of functionality at C(17).

Scheme 1-4



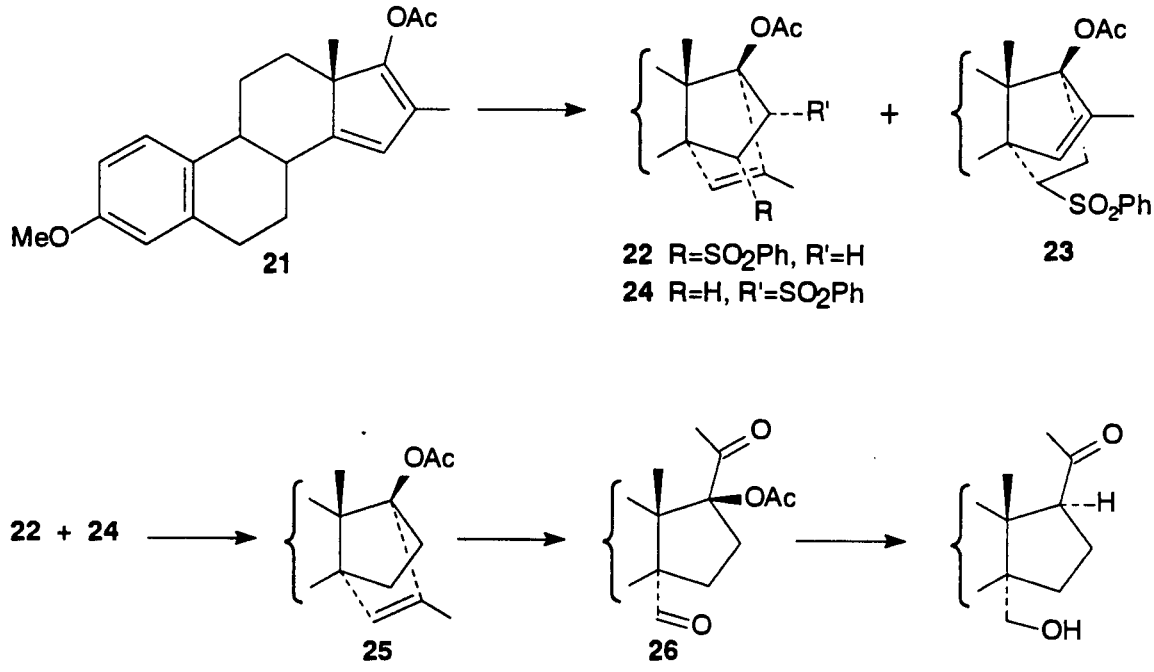
Heterocycloaddition provided the basis for a novel approach to the stereoselective synthesis of 14α- and 14β-hydroxy compounds in the androstane series.[16] The dienyl acetate (**15**) was treated with the hetero-dienophile, benzyl nitrosoformate, to yield two stereoisomeric cycloadducts (**16**) (78%) and (**17**) (22%) (Scheme 1-5), the major component being the α-adduct (**16**) in marked contrast to the expected β-face selectivity. The major cycloadduct was recovered in high yields, and hydrogenated to give the 14α-hydroxy androstane (**18**). Alternatively, methanolysis of the total reaction mixture gave the common intermediate (**19**), and subsequent hydrogenation gave the 14β-hydroxy androstane (**20**) in high yield.

Scheme 1-5



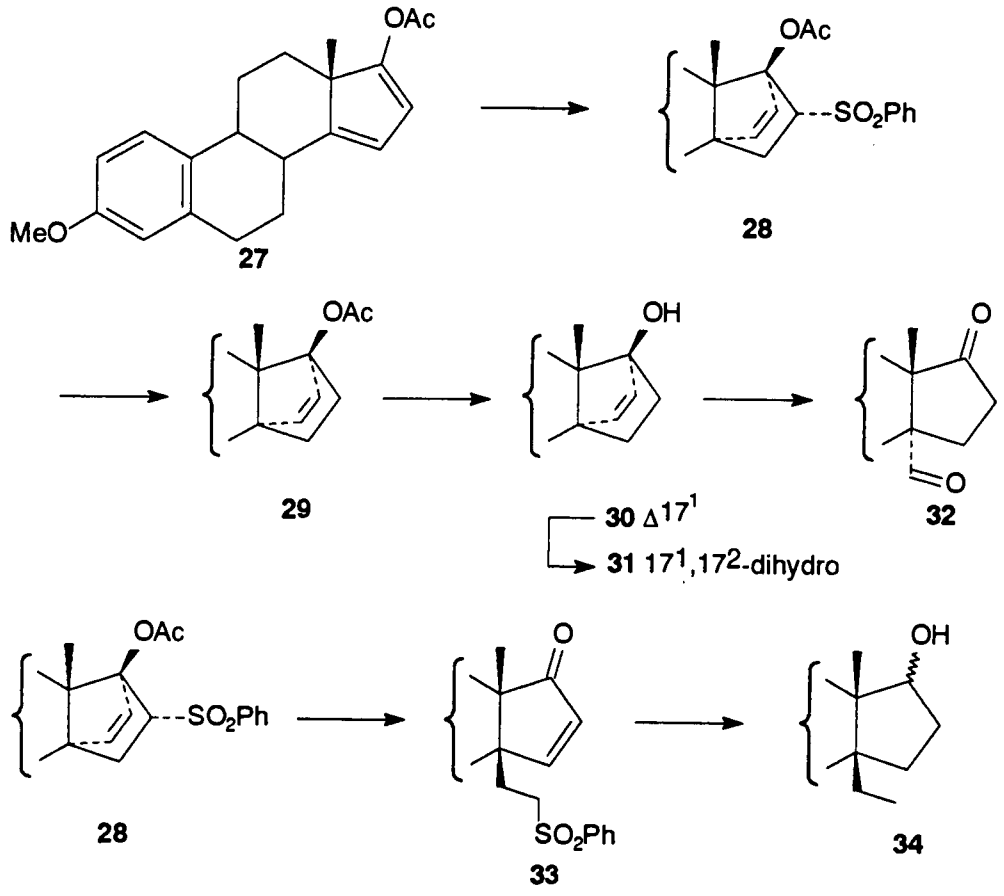
In the study targeted at 14α-functionalised analogues of 19-norprogesterone,[17] it was found that the stereo- and regioselectivity of the cycloaddition to steroidal 14,17-dienes is diminished by the presence of a 16-methyl group on the diene. Cycloaddition of phenyl vinyl sulfone[18] to the 16-methyl-14,17-dienyl acetate (**21**) afforded three 14,17-cycloadducts (**22**), (**23**) and (**24**) (Scheme 1-6); the two major products (**22**) and (**24**) (each *ca.* 37%) were regioisomers derived from *endo* addition on the β-face, whereas the minor product (**23**) (*ca.* 14%) was the *endo* isomer of *meta*-directed attack on the α-face. The two major components (**22**) and (**24**) were converted into a common intermediate (**25**), which was oxidatively cleaved to the 14α-formyl 20-ketone (**26**). This intermediate was subsequently converted into 14α-hydroxymethyl- and 14α-formyl analogues of 19-norprogesterone.

Scheme 1-6



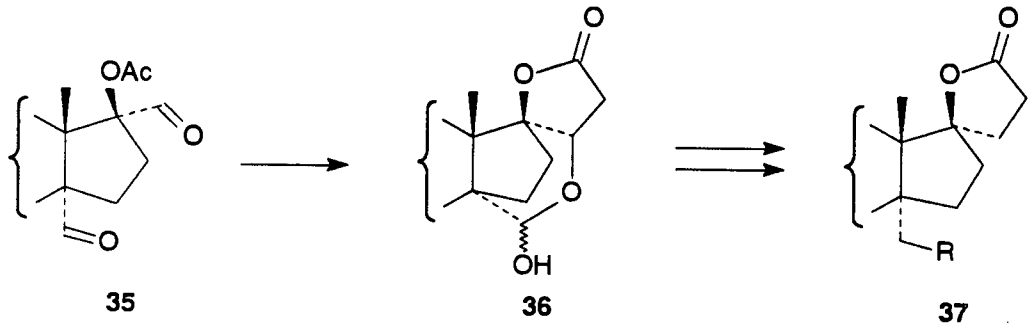
A similar strategy has been reported for the synthesis of 14α-functionalised 19-norsteroids,[19] thus cycloaddition of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**27**) and phenyl vinyl sulfone yielded the cycloadduct (**28**) exclusively (92%) (Scheme 1-7). The cycloadduct (**28**) was reductively desulfonylated to the 14α,17α-etheno compound (**29**). Double oxidative cleavage of the hydroxy olefin (**30**) afforded the 14α-formyl 17-ketone (**32**) which was then converted into various 14α-functionalised hormone analogues. The cycloadduct (**28**) was also used in the synthesis of 14β-ethyl-19-norsteroids[20] where it underwent an efficient retrograde reaction in the presence of alkali to give the 14β-(2-phenylsulfonylethyl)-Δ^{15}-17-ketone (**33**), which was readily converted into 14β-ethyl analogues of estradiol and 19-nortestosterone (**34**) (Scheme 1-7).

Scheme 1-7



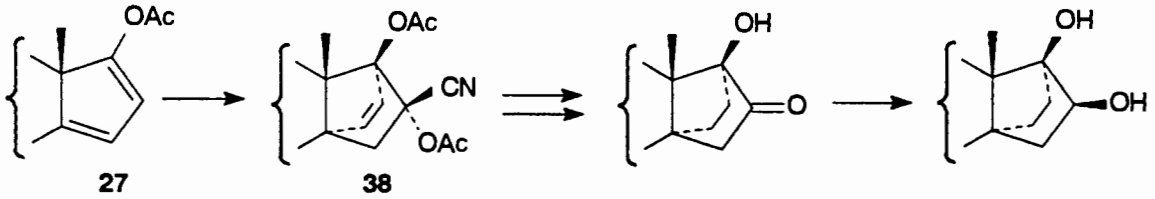
In order to further the synthetic and structure-activity studies of aldosterone antagonists, the synthesis of 14-functionalised 17-spirolactones[21] was effected using the 14α-formyl 20-ketone (**35**). Thus, base-mediated reaction of the 17α-acetyl 17β-acetate (**35**) gave the intermediate (**36**) arising from intramolecular ester enolate condensation of 17,17-functionality accompanied by 14,20-hemiacetal formation. The latter functionality underwent reductive cleavage and β-elimination, leading eventually to 14α-functionalised 17-spirolactones (**37**) (Scheme 1-8).

Scheme 1-8



In view of the high level of oral estrogenicity associated with the structural analogues (**30**) and (**31**) of estradiol (Scheme 1.7), it was of great interest to synthesise the corresponding 16α-hydroxy compounds as analogues of estriol. The latter compound is implicated in the metabolism of estradiol and functions as an important short-lived estrogen. Access to bridged estriol analogues was planned via cycloaddition of a ketene equivalent to the steroidal ring D diene, allowing manipulation and reduction of the cycloadduct to the target compound.[17] Thus, cycloaddition of 2-acetoxyacrylonitrile to the diene (**27**) gave the cycloadduct (**38**) in 81% yield (Scheme 1-9). Alkaline hydrolysis gave the 14α,17α-etheno 16-ketone, and hydrogenation gave the 14α,17α-ethano 16-ketone, both of which underwent stereoselective reduction of the 16-ketone to the undesired 16β-hydroxy 17-alcohols. Other methods of reduction and attempted inversion at C(16) were unsuccessful, emphasising the impracticality of this route to the desired bridged analogues of estriol.

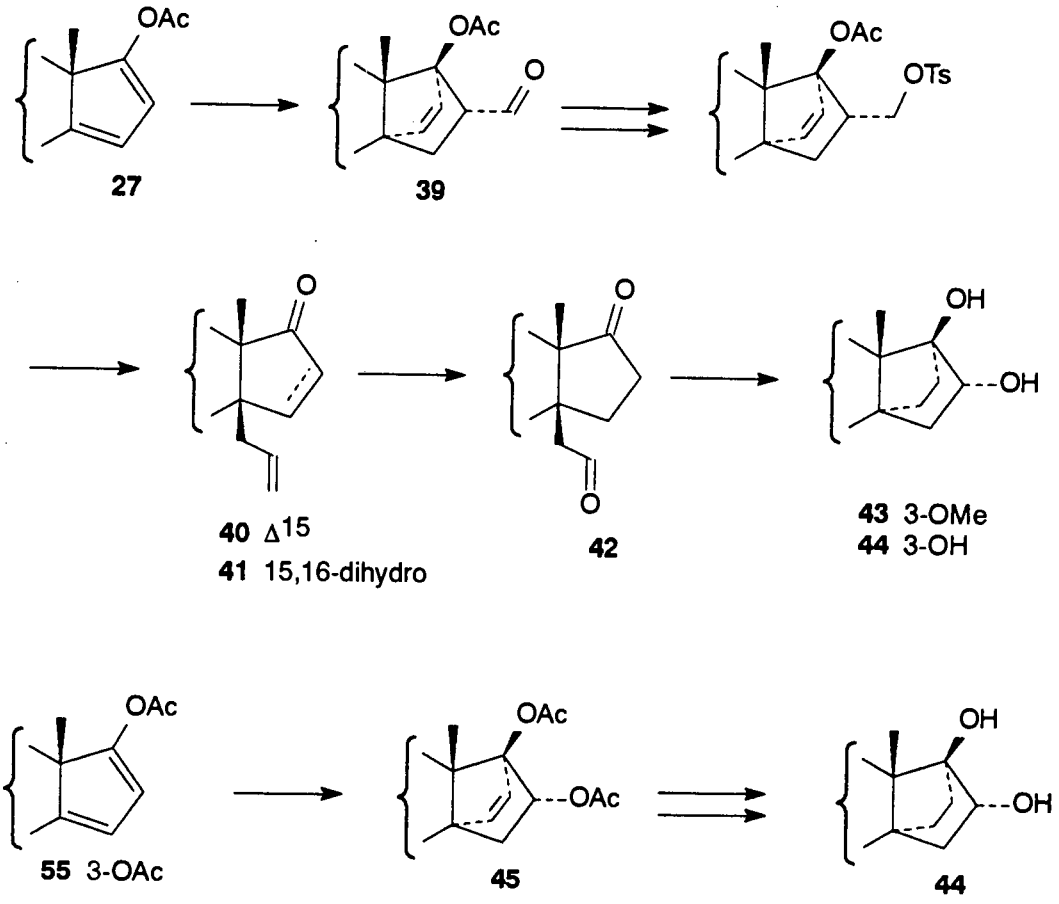
Scheme 1-9



27 **38**

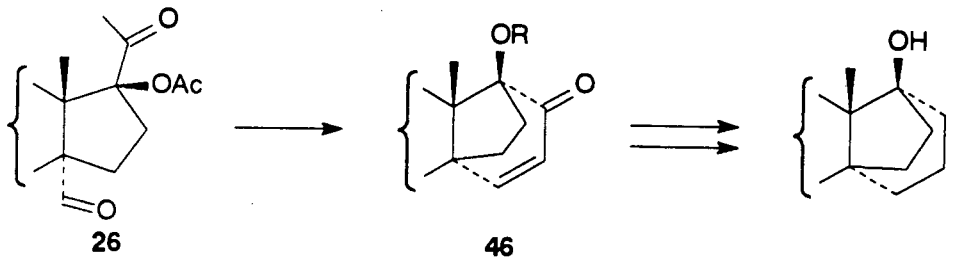
An alternative approach was investigated in which indirect stereocontrol could be achieved at C(16).[23] Thus cycloaddition of acrolein to the 14,17-diene (**27**) gave one cycloadduct (**39**) in 83% yield (Scheme 1-10). Subsequent reduction, tosylation and Wharton fragmentation yielded the allyl enone (**40**). Ozonolysis of the derived allyl ketone (**41**) gave the 14β-formylmethyl 17-ketone (**42**), intramolecular reductive coupling of which gave the desired 14α,17α-ethano 16α,17β-diol (**43**) (71%). This stereochemical outcome was rationalised in terms of significant *si*-face selectivity of the 14^1-formyl group during cyclisation. Deprotection of (**43**) gave the sought-after 16α-hydroxy estriol analogue (**44**). In a more recent development, a more direct approach to this hormone analogue involves cycloaddition of vinyl acetate to the diene (**55**) to give the cycloadduct (**45**) in 53 % yield,[24] which was readily converted into the estriol analogue (**44**).

Scheme 1-10



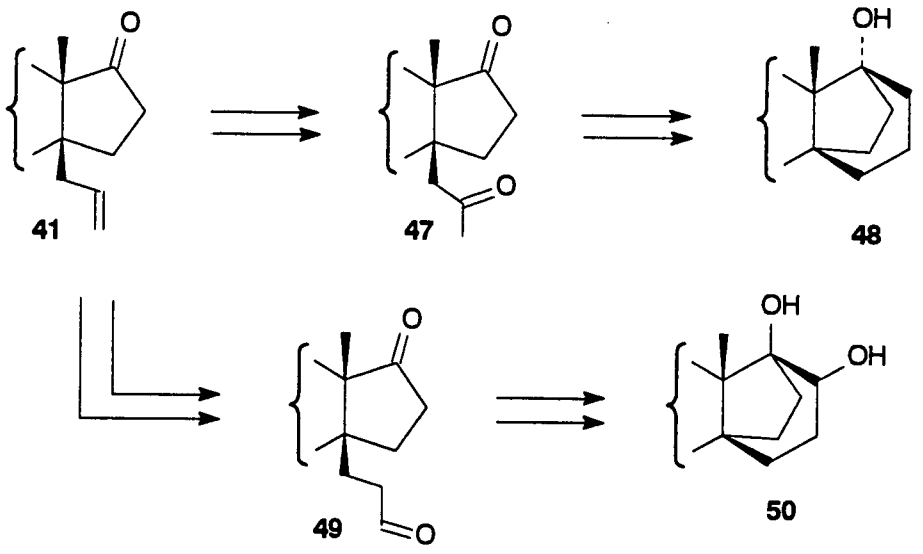
During the foregoing studies, it was demonstrated that the 14α,17α-ethano bridge imparts powerful oral estrogenicity to estradiol analogues,[25,26] and an obvious extension of this structure-activity study entails the synthesis of selectively expanded ring D bridged analogues. The availability of the 14α-formyl 20-ketone (**26**) provided ready access to the 14α,17α-propano series of analogues. Thus, intramolecular aldol condensation of (**26**) gave the 14α,17α-propeno compound (**46**),[27] functional group simplification of which gave access to a range of 14α,17α-propano- and propenoestradiol analogues (Scheme 1-11).

Scheme 1-11



Using a different approach, the 14β,17β-propanoestradiol analogues were synthesised[28] by manipulation of the allyl ketone (**41**),[23] which underwent Wacker oxidation to the 14β-acetonyl 17-ketone (**47**) (Scheme 1-12). Base-mediated intramolecular aldol condensation of (**47**) and subsequent functional group modifications yielded 14β,17β-propano analogues (**48**). Terminal functionalisation of the allyl ketone (**41**) gave an intermediate (**49**) for reductive cyclisation to 17α,17[1]-diol analogues (**50**).

Scheme 1-12



The foregoing discussion highlights the versatility of the cycloaddition reaction to steroidal ring D dienes for the stereocontrolled synthesis of steroid hormone analogues. For the most part, the key reaction is stereo- and regioselective, allowing ready access to a range of 14- and 17-functionalised steroids in a predictable manner.

Structure-activity of Estrogens and Estrogen Analogues. The most important naturally occurring estrogens are estrone (**51**), estradiol (**52**) and estriol (**53**) (Figure 1-1); estrone is the major estrogen found in the blood, estradiol the main secretory product of the ovary, and estriol the most abundant estrogen excreted in urine.[29] The biogenesis of the estrogens proceeds generally by the pathway (simplified here): cholesterol → progesterone → 17α-hydroxyprogesterone → androst-4-ene-3,17-dione → 17β-estradiol → estrone → estriol,[30] with these transformations taking place mainly in the liver. The principle uses of estrogens in medicine are to control post-menopausal symptoms, including osteoporosis;

estrogen therapy has also been applied to menstrual irregularities, the treatment of prostatic carcinoma, suppression of lactation and ovulation, and fertility control. Estrogen therapy is also under investigation in the treatment of coronary thrombosis, hemostasis and palliative treatment of breast and genital cancer in women.[29]

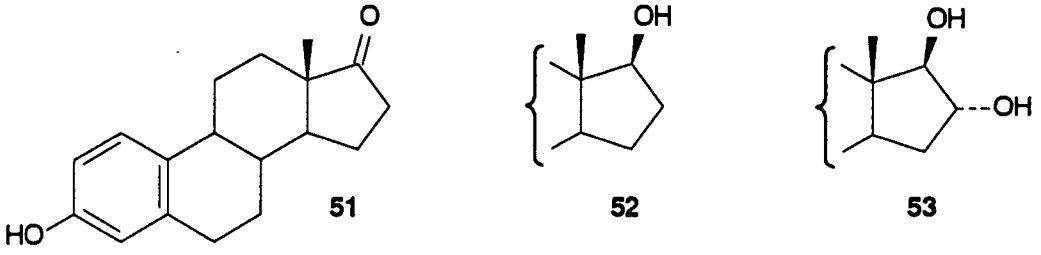


Figure 1-1 Estrone, Estradiol and Estriol.

The three naturally occurring estrogens, estrone, estradiol, and estriol are all orally inactive. The synthesis of the first orally active estrogen, 17α-ethynylestradiol (**54**) (Figure 1-2), in 1938,[31] marked the beginning of systematic investigations into the structure-activity relationships of steroidal hormones and analogues.

The binding of a biologically active steroid to the binding site of the receptor is the first important step in the chain of events that culminates in the appropriate physiological response. The biological activity of a hormone or hormone analogue is determined by the concentration of the hormone-receptor complex at the site of action and by the intrinsic activity of the complex; the concentration of the hormone-receptor complex depends upon the availability of the hormone at the site of action and its affinity for the receptor.[32] Although complete amino acid sequences for steroid hormone receptors have been determined, X-ray crystal structure determination has so far been impossible.[33] Accordingly, elucidation of the structural requirements which facilitate binding of the hormone to the receptor provides an indirect probe for the properties of the binding region.

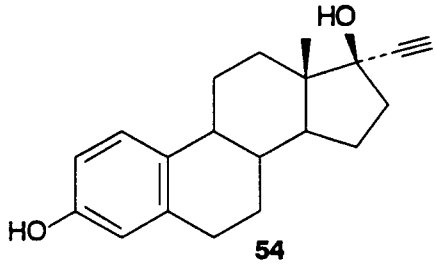


Figure 1-2 Ethynylestradiol

Binding of the substrate to the receptor is largely determined by hydrogen bonds, and the steroid-receptor complex is stabilised by other forces, for example van der Waal's interactions.[33] Removal of the C(3) and/or C(17) substituents results in drastic loss of affinity for the receptor, and it is known that the phenolic ring facilitates interaction with the estrogen receptor[34] by playing an anchor role in receptor binding.[35]

Thus, binding studies are concerned with four aspects:[33] the structural requirements for ligand binding; identification of ligands to be used as probes to detect the receptor; comparison of ligands of different potency, and the design of ligands for use as potential analogues.

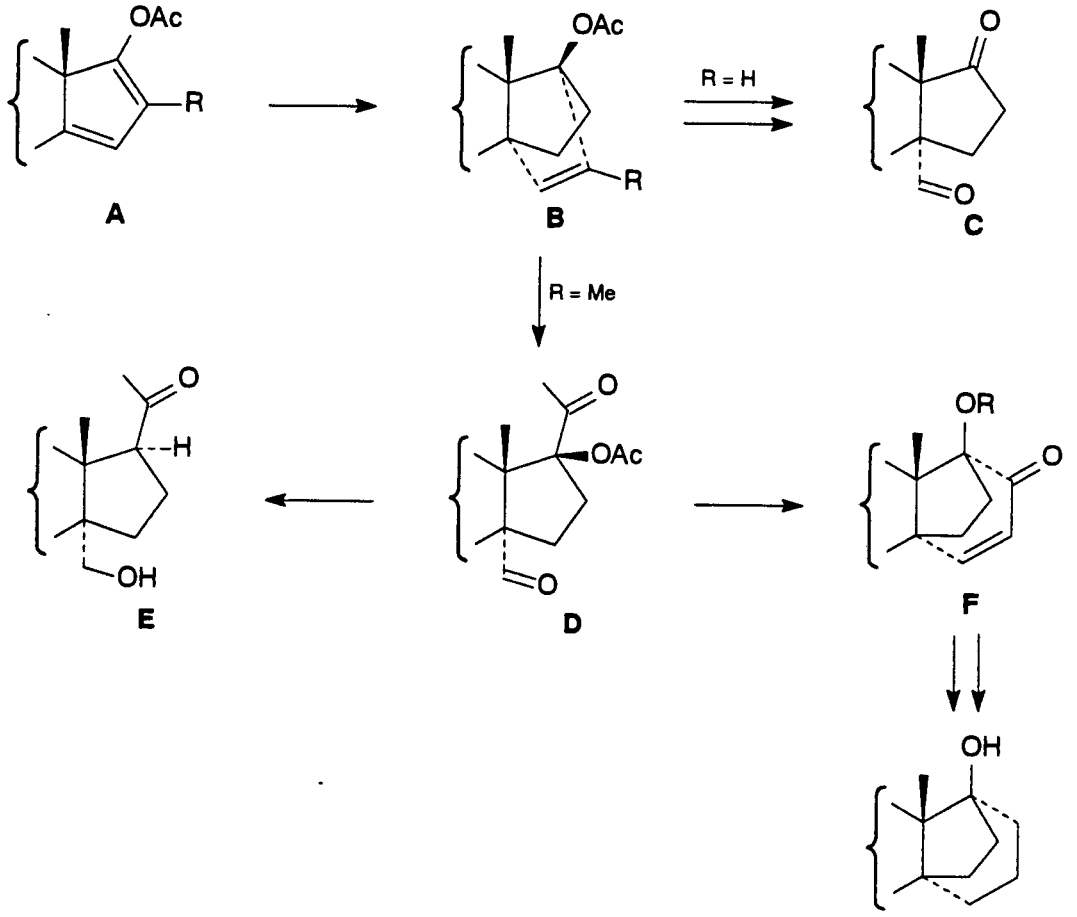
The main metabolic pathways of the estrogens involve modifications of functionalisation on rings A and D and appropriate substitution at these sites can be expected to influence the activity of the hormone analogue. Investigations conducted in these laboratories are concerned with ring D modifications of estrogens involving bridge formation and functionalisation at C(14) in order to impart oral estrogenicity and enhanced activity to the analogues.

In order to design target hormone analogues, it was necessary to investigate the structure-activity patterns which have already emerged for estradiol analogues. Thus, the 14α,17α-ethanoestradiol and estriol analogues all exhibited enhanced oral estrogenicity; 14α,17α-propano- and 14α,17α-(prop-17^2-eno)estra-1,3,5(10)-triene-3,17β-diol both proved to be potent estrogens, while the 17^1-hydroxy 14,17α-propanoestradiol analogues displayed low affinity for the estrogen receptor.

Objectives of This Study. Successful entry into 14α-functionalised steroidal systems has been gained by initial introduction of a bridge on the D-ring of the steroid via cycloaddition of an ethylene equivalent to the diene (**A**) to give the cycloadduct (**B**) (Scheme 1-13).[17,19] Depending on the nature of 16-substitution (R) in the diene, the derived α-bridge olefin (**B**) undergoes double oxidative cleavage at C(15)-C(16) and C(16)-C(17) (for R=H) to give the 14α-formyl 17-ketone (**C**),[19] or simple oxidative cleavage at C(15)-C(16) (for R=Me) to give the 14α-formyl 20-ketone (**D**).[17] The formyl ketone (**C**) provides an entry into a range of 14α-functionalised estradiol and estriol derivatives, while the 14α-formyl 20-ketone (**D**) serves as an intermediate for two synthetic sequences. One of these sequences involves initial reductive deacetoxylation of (**D**) to give the 14α-hydroxymethyl 20-ketone (**E**) which gives access to 14α-functionalised 19-norprogesterone analogues;[17]

the second sequence involves intramolecular aldol condensation of (**D**) to give the 14α,17α-propeno bridged compound (**F**), which enabled synthesis of 14α,17α-propano bridged estradiol analogues for biological evaluation.[27]

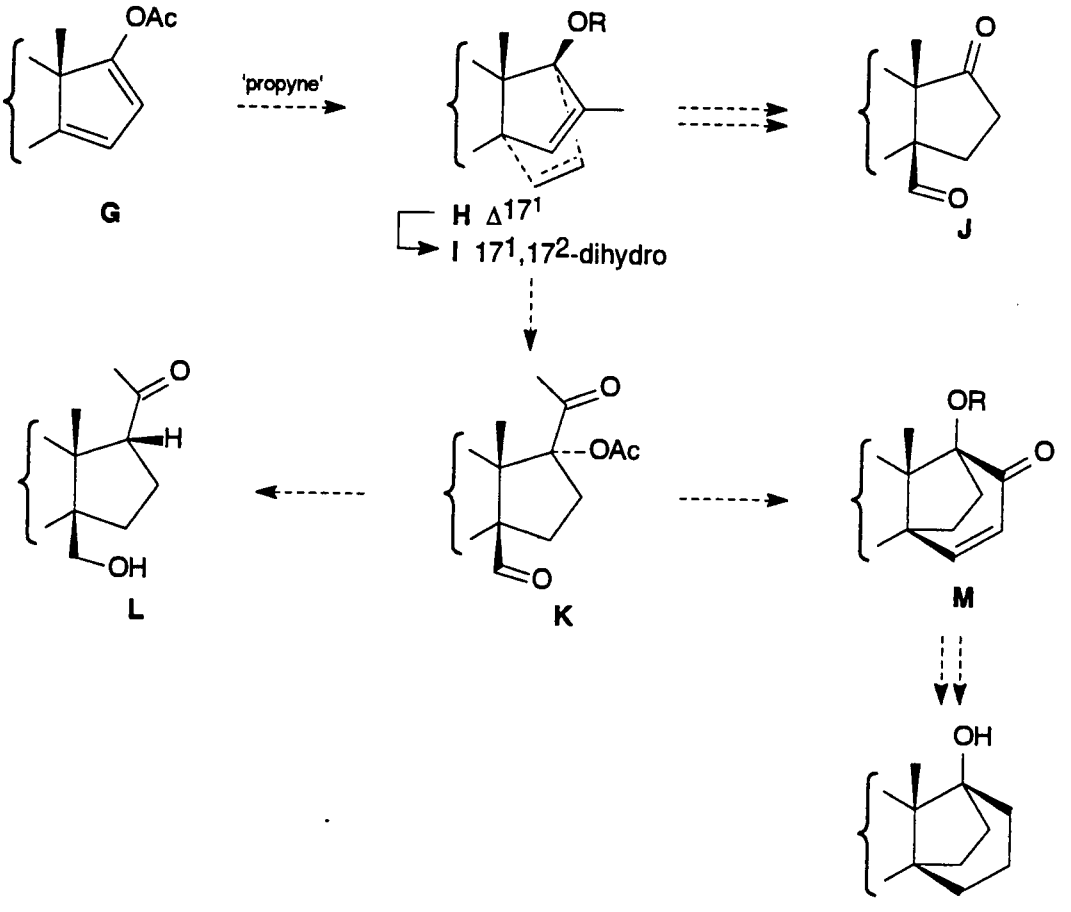
Scheme 1-13



In the light of the success of the foregoing approaches to 14α-functionalised 19-norsteroids, a complementary synthetic sequence was envisaged to the 14β-functionalised 19-norsteroids (Scheme 1-14). Thus cycloaddition of a 'propyne equivalent' to the diene (**G**) would be expected to give the cycloadduct (**H**). Chemoselective hydrogenation of this cycloadduct was expected to result in the key intermediate, the 16-methyl Δ^{15} compound (**I**). This compound could then either be subjected to double oxidative cleavage to give the 14β-formyl 17-ketone (**J**) allowing access to 14β-functionalised estradiols and estriols, or to oxidative cleavage of only the C(15)-C(16) bond to give the 14β-formyl 20-ketone (**K**), which would make two sequences available for investigation. The first of these would be reductive deacetoxylation to give the 14β-hydroxymethyl 19-norprogesterone derivative (**L**), and the second to proceed via intramolecular cyclisation of the 14β-formyl 20-ketone (**K**) to give the 14β,17β-propeno compound (**M**). This compound would serve as an

alternative intermediate for the synthesis of 14β,17β-propanoestradiols and of analogues selectively functionalised on the β-bridge.

Scheme 1-14



CHAPTER 2

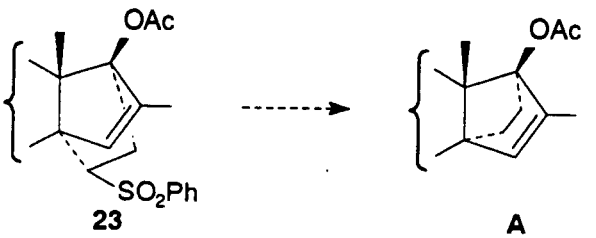
Synthesis of 3-Methoxy-16-methyl-14,17α-ethanoestra-1,3,5(10)-triene-15,16,17β-triol 17-Acetates

2.1 Cycloaddition of Phenyl Vinyl Sulfone to 3-Methoxy-16-methylestra-1,3,5(10),14,16-pentaen-17-yl Acetate.

At the outset of the project, it was decided that the availability of (17^2R)-3-methoxy-16-methyl-17^2-phenylsulfonyl-14,17α-ethanoestra-1,3,5(10),15-tetraen-17β-yl acetate would provide an opportunity to conduct a feasibility study on the preparation and reactions of key intermediates in the proposed synthetic approach to 14β-formyl 19-norsteroids and the derived 14β,17β-propano-19-norsteroids.

The phenylsulfonyl compound (**23**) was available as a minor cycloadduct (14%) in the reaction of 3-methoxy-16-methylestra-1,3,5(10),14,16-pentaen-17-yl acetate with phenyl vinyl sulfone (see Schemes 1-6 and 1-13). Previous studies have demonstrated that the two major cycloadducts of this reaction undergo reductive desulfonylation to a common intermediate for further elaboration into 14α-formyl 19-norsteroids[36,17] and hence, into 14α,17α-propano analogues of estradiol.

Scheme 2.1-1

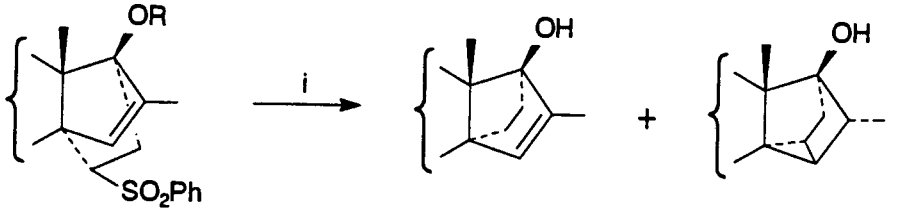


23 **A**

It was reasoned that reductive desulfonylation of the minor product (**23**) could provide ready access to the key intermediate (**A**) (Scheme 2.1-1) for similar elaboration of the isomeric series. However, attempts at reductive desulfonylation of both the 17β-acetate (**23**) and the derived 17-alcohol (**56**) under a variety of conditions proved disappointing (Scheme 2.1-2).[37] In a typical experiment, treatment of (**56**) with magnesium in methanol, followed by chromatography of the product, furnished crystalline material (82%) which appeared to be homogeneous on TLC, but displayed NMR signals consistent with the presence of the desired product (**57**) [δ 0.83 (3H, d, *J* 0.6 Hz, 13β-Me), 1.71 (3H, d, *J* 1.7,

16-Me), 3.76 (3H, s, 3-OMe), 5.62 (1H, d, *J* 1.7 Hz, 15-H)], and a product formulated as the 15,17^2-cyclo compound (**58**) [δ 0.9 (3H, s, 13β-Me), 0.92 (3H, d, *J* 6.8 Hz, 16α-Me), 3.76 (3H, s, 3-OMe)]. The proportions of these components were estimated as *ca.* 1:2. The derived acetylation products were also inseparable, and attempts to improve the yield of the desired product (**57**) through variation in the conditions of reductive desulfonylation were fruitless; for example, treatment of (**23**) with sodium in liquid ammonia gave similar proportions of the reaction products.

Scheme 2.1-2



23 R=Ac
56 R=H

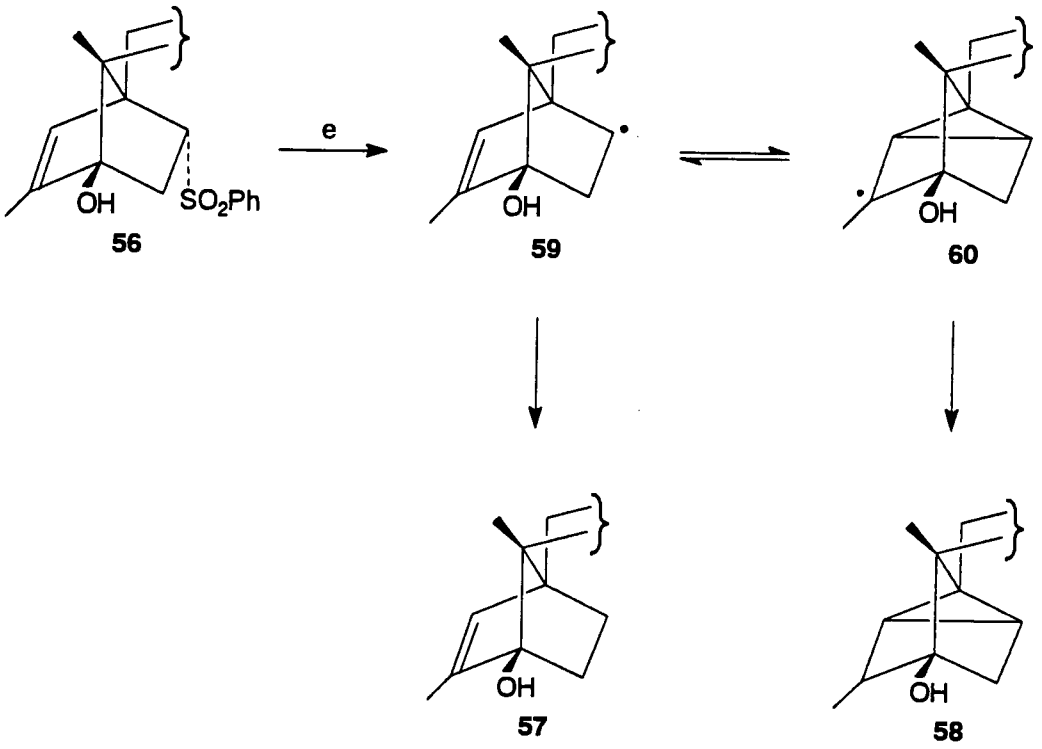
57

58

Reagents: (i) Mg, MeOH, 50°C, 23h.

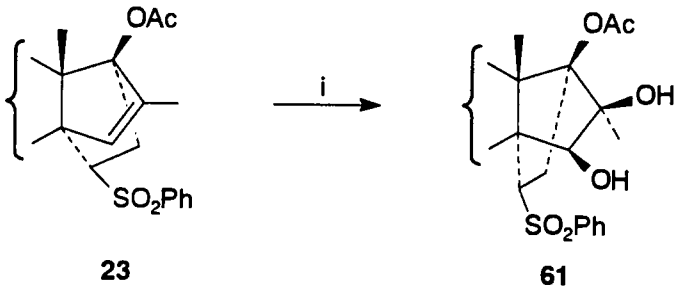
Formation of the 15,17^2-cyclo compound (**58**) is presumed to arise from olefinic bond participation during reductive desulfonylation, in a process which is analogous to those observed during similar reaction of structurally related substrates.[38,39] It is notable that the amounts of product arising from these interfering reactions are sensitive to the nature of the substrate, and we are unable to explain why it occurs as a favoured pathway in this instance, other than to speculate that, in the reductive desulfonylation of (**56**) (Scheme 2.1-3), the longevity of the initial radical species (**59**) may be influenced by the steric environment of the reactive site. If this environment is crowded enough to prevent rapid protonation of the initial radical on (**59**), then the rearrangement pathway to (**60**) and (**58**) would be favoured, while unhindered protonation of (**59**) would give (**57**).

Scheme 2.1-3 Olefinic Bond Participation during Reductive Desulfonylation.



Since the overall strategy for exploiting this starting material (**23**) entailed potentiation of the Δ^{15}-bond for oxidative cleavage, it was reasoned that the reductive desulfonylation step could be postponed to a more convenient point in the overall reaction sequence. Direct ozonolysis of the cycloadduct (**23**) was not considered as a option, owing to the poor results obtained in the isomeric series,[19] and a stepwise oxidative cleavage pathway was adopted. Thus, treatment of the compound (**23**) with osmium tetroxide in pyridine at 20°C gave a single product, the 15β,16β-diol (**61**), in 84% yield (Scheme 2.1-4).

Scheme 2.1-4

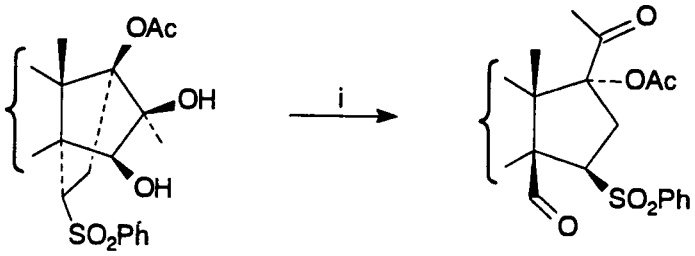


Reagents: (i) OsO_4, pyridine, 20°C, 168h.

This gratifying stereoselectivity can probably be ascribed to the steric bulk of the 17^2-phenylsulfonyl group, which completely inhibits *endo*-addition of the reagent. The structural assignment of the diol (**61**) was supported by the NMR evidence, which revealed the signal for the 15α-proton as a sharp singlet (after D_2O exchange) at δ 4.95, and a corresponding signal at δ 3.99 (dd, *J* 12.1 and 5.5 Hz) for the 17^2-proton. The absence of additional coupling in these signals excluded the alternative configurational assignment at C(15) in which a four-bond W-coupling would be expected.

Sodium periodate cleavage of the diol (**61**) resulted in efficient conversion into 17α-acetoxy-3-methoxy-15β-phenylsulfonyl-20-oxo-19-nor-14β-pregna-1,3,5(10)-triene-14-carbaldehyde (**62**) (Scheme 2.1-5), the structure of which was evident from absorption bands at ν_{max} 1737 (17α-OAc) and 1714 (14^1 and 20-CO) cm^{-1} in the infrared spectrum, and signals in the NMR spectrum [δ 2.03 and 2.07 (each 3H, s, 14^1- and 20-Me), 4.28 (1H, dd, *J* 11.3 and 9.8 Hz, 15α-H), and 10.29 (1H, s, 14^1-H)].

Scheme 2.1-5

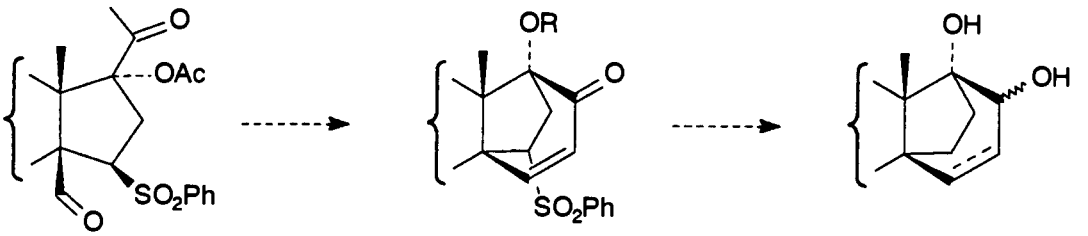


61 **62**

Reagents: (i) $NaIO_4$, EtOH, 20°C, 3.5h.

It seemed reasonable to expect that the 17β-acetyl 14β-carbaldehyde (**62**) would undergo intramolecular aldol closure, since the array of interacting functionality is analogous to that of the isomeric series in which a 17α-acetyl 14α-carbaldehyde was successfully cyclised.[27] Furthermore, it was hoped that the expected product might be amenable to functional group simplification in one step through reductive desulfonylation with concomitant reduction of the bridged enone structure (Scheme 2.1-6).

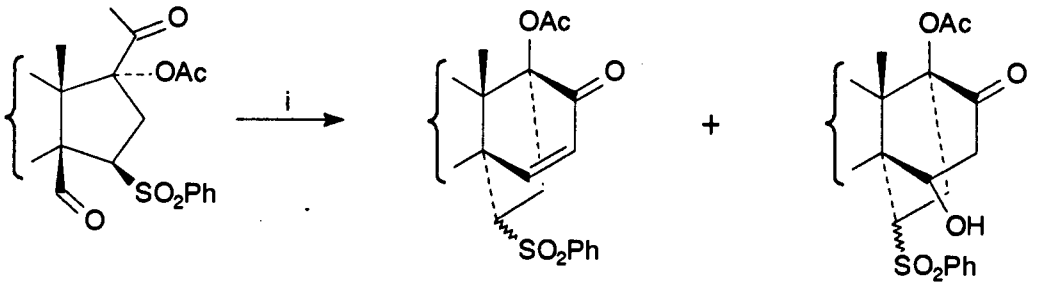
Scheme 2.1-6



62

However, treatment of the acetyl carbaldehyde (**62**) with refluxing M hydrochloric acid in tetrahydrofuran gave rise to a complex mixture which failed to simplify on more prolonged reaction. Chromatography yielded two major fractions, each of which comprised inseparable mixtures of isomers (Scheme 2.1-7).

Scheme 2.1-7



62 **63, 64** 15ξ **65, 66** 15ξ

Reagents: (i) 1M HCl, THF, 80°C, 22h.

The least polar mixture (*ca.* 2:3) (**63**) + (**64**) (41%) showed the expected infrared absorption for the 17α-acetoxy group and enone functionality, but several NMR signals displayed doubling [δ 0.84 and 0.97 (each 3H, s, 13β-Me), 2.09 and 2.16 (each 3H, s, 17α-OAc), 6.35 and 7.35 (each 1H, d, *J* 9.8 Hz, 17^2-H), 6.45 and 7.80 (each 1H, d, *J* 9.8 Hz, 17^3-H)], and the signals for the 15-protons appeared as a complex signal at δ 4.41. It was surmised that the material must indeed have the expected gross structure of intramolecular aldol condensation, and that the only possible explanation for the isomeric mixture is partial epimerisation at C(15) during the reaction.

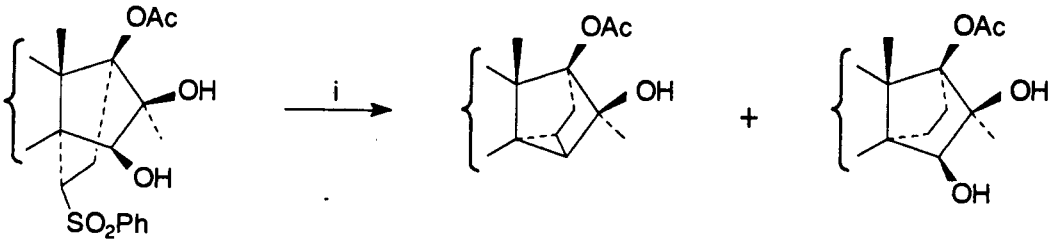
The second, more polar fraction (37%) (*ca.* 1:4) displayed spectroscopic properties consistent with the intermediate structures of aldol condensation (**65**) and (**66**). Diagnostic

infrared absorption bands at ν_{max} 3527 (OH), 1745 (OAc) and 1727 (CO) cm^{-1} supported this interpretation. Again, the material displayed doubling of several NMR signals indicating an isomeric mixture [δ 1.15 and 1.24 (each 3H, s, 13β-Me) and 2.07 and 2.17 (each 3H, s, 17β-OAc)]. The lower field signals for the minor epimer were not discernable, but signals for the major epimer supported this structural assignment [δ4.18 (1H, dd, *J* 11.0 and 6.9 Hz, 15-H), 5.17 (1H, dd, *J* 7.8 and 4.5 Hz, 17^3-H)].

Treatment of the carbaldehyde (**62**) with KOH in methanol was also unsuccessful for our purposes and gave similar results to those discussed above.

Although the foregoing results confirmed the viability of the overall strategy, it was clear that complications arising from the presence of the phenylsulfonyl group detracted from this approach to the desired objectives. This was further demonstrated in an attempt to conduct reductive desulfonylation upon the diol (**61**). Surprisingly, treatment of (**61**) with samarium(II) iodide[40] and hexamethylphosphoric triamide in tetrahydrofuran at -20°C furnished two products formulated as the 15α,17^2-cyclo compound (**67**) (31%) and the diol (**68**) (30%) (Scheme 2.1-8).

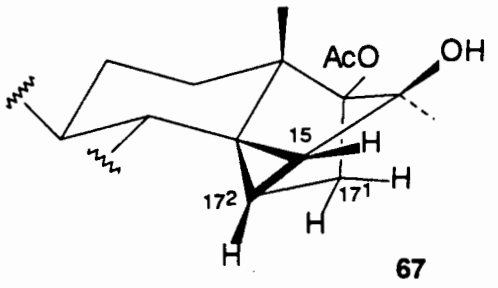
Scheme 2.1-8



61 **67** **68**

Reagents: (i) SmI_2, HMPA, THF, -20°C, 4h.

Spectroscopic and analytical data confirmed that the more polar compound (**68**) was the product of reductive desulfonylation, whereas the less polar product (**67**) was assigned the 15α,17^2-cyclo structure. Evidence in support of a tricyclo[2.2.1.$0^{2,6}$]heptanoid structure included NMR data comparable to those observed in related systems.[19] With the aid of COSY (see Appendix) and HETCOR spectra it was possible to correlate the four-proton spin system associated with C(15), C(17^1) and C(17^2) (Figure 2.1-1).



67

Proton	δ (ppm)	Coupling constants	
15-H	1.55	$J_{15\beta,\ 17^2}$	6.2 Hz
17^2-H	1.09	$J_{17^2,\ 17^1 endo}$	0 Hz
17^1-H_{exo}	2.58	$J_{17^2,\ 17^1 exo}$	1.1 Hz
17^1-H_{endo}	1.83	$J_{17^1 endo,\ 17^1 exo}$	11.4 Hz

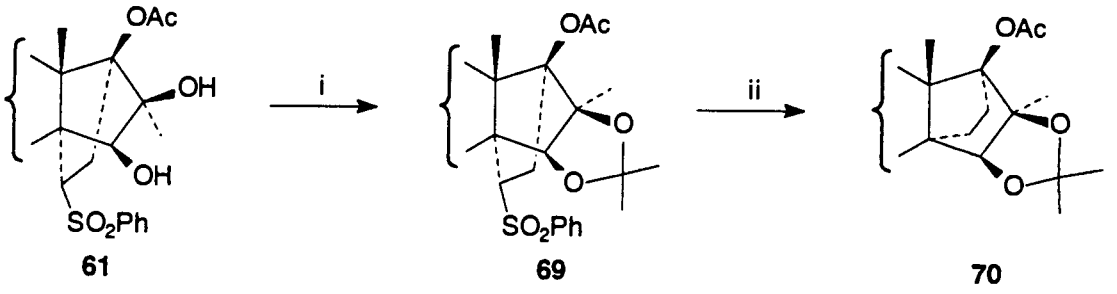
Figure 2.1-1 Diagnostic ^{1}H NMR Properties of the Ring D-bridged Compound (**67**).

The apparent participation by a hydroxy group during reductive desulfonylation of diols does not appear to have any precedent, and it can only be assumed that one electron transfer to the C(17^1)-S bond is followed by radical-mediated bond formation to C(15) with concomitant breakage of the C(15)-O bond, perhaps promoted by the intermediacy of an Sm^{3+} alkoxy species.[41] Participation reactions during reductive desulfonylation of related bicyclo[2.2.1]hept-2-enoid systems have been observed,[19,37,38] and it is concluded that these bicyclo systems may be particularly prone to transannular reaction when the intermediate radical species is sufficiently hindered to inhibit immediate capture by hydrogen.

The structural assignment of the diol (**68**), the second product of reductive desulfonylation of (**61**), was also supported by spectroscopic data. The NMR signal for the 15α-proton of (**68**) occurred, as expected, as a doublet at δ 3.61 (*J* 4.7 Hz) and as a singlet on D_2O exchange, and the 16-methyl singlet appeared at δ 1.49. This compound will be studied further in the following chapters.

In order to demonstrate the participation of the free 15-hydroxy group in the foregoing reaction, the diol was converted into the corresponding 15β,16β-acetonide (**69**), treatment of which with samarium(II) iodide and hexamethylphosphoric triamide in tetrahydrofuran at -20°C resulted in smooth conversion into the expected product 15β,16β-isopropylidenedioxy-3-methoxy-16α-methyl-14,17α-ethanoestra-1,3,5(10)-trien-17β-yl acetate (**70**) (70%) (Scheme 2.1-9).

Scheme 2.1-9



Reagents: $HClO_4$, acetone, 20°C, 5h. (ii) SmI_2, HMPA, THF, -20°C, 1.5h.

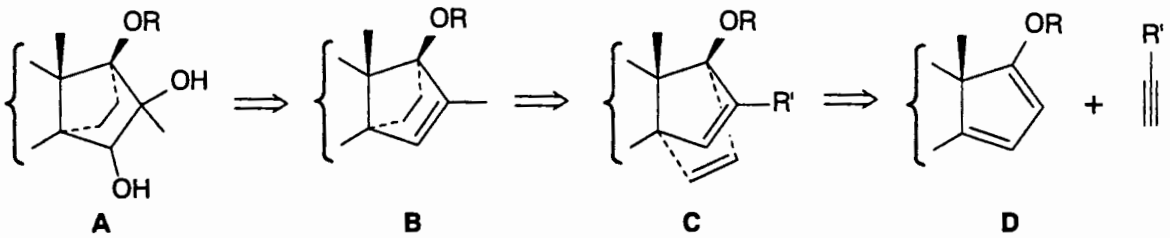
The absence, in the NMR spectrum of (**70**), of the characteristic low-field multiplet (δ 7.5 - 7.9) for the aromatic protons of the phenylsulfonyl moeity, indicated successful reductive desulfonylation. Other confirmatory signals for the structural assignment of (**70**) were the signals for the isopropylidenedioxy-methyl groups at δ 1.43 and 1.52, that for the 16α-methyl protons at δ 1.64, and the singlet at δ 3.89 for the 15α-proton.

The foregoing experiments provided for valuable insights into the problems which might be expected in developing synthetic routes to 14β-formyl 19-norsteroids and the derived products of interest. However, they also confirm that a synthetic strategy based upon the limited availability of the cycloadduct (**23**) was impractical: the overall yield of (**70**) from the olefin (**23**) was 50%, but from the dienyl acetate (**27**), the yield was 7%. Accordingly, the challenge remained to devise an alternative strategy targeted at stereo- and regiocontrolled synthesis of the key intermediates 3-methoxy-16-methyl-14,17α-ethanoestra-1,3,5(10),15-tetraen-17β-ol or 3-methoxy-16-methyl-14,17α-ethanoestra-1,3,5(10)-triene-15,16,17β-triol 17-acetate, for oxidative cleavage and further elaboration into the desired products.

2.2 Cycloaddition of Methyl Propiolate to 3-Methoxyestra-1,3,5(10),14,16-pentaen-17-yl Acetate.

2.2.1 Cycloaddition and Attempted 1,2-Reduction of the Dihydrocycloadduct. A retrosynthetic analysis of the primary targets (**A**) and (**B**) (Scheme 2.2-1) shows that the conceptual approach based upon cycloaddition of a propyne equivalent (R'=Me) to the dienyl acetate (**D**) would lead to a bicyclo[2.2.1]hepta-1,5-dienoid structure (**C**) in which an essential prerequisite for further development would be chemoselective differentiation of the olefinic bonds. A further prerequisite is that the propyne equivalent should contain functionality R', which would potentiate the dienophile for cycloaddition, but could then be readily converted into a methyl group at an appropriate stage in the synthetic sequence.

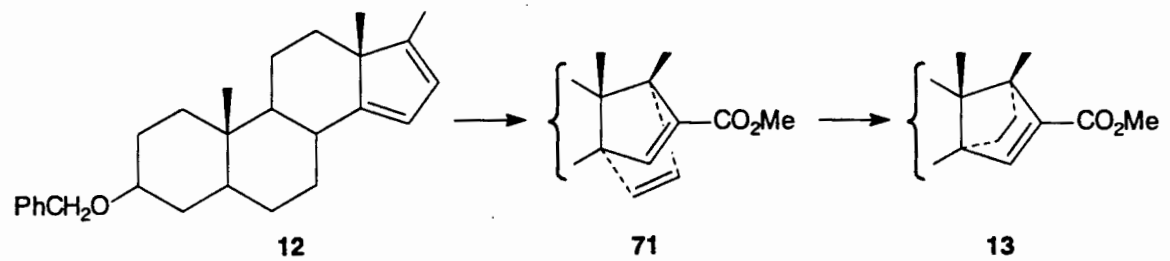
Scheme 2.2-1



Esters of propiolic acid have been used in cycloaddition reactions to steroidal 14,16-dienes.[12] Wiesner *et al.*[15] have shown that treatment of the 17-methyl-14,16-diene (**12**) with ethyl propiolate gave the cycloadduct (**71**) in 75% yield (Scheme 2.2-2).

Furthermore, it was shown that the cycloadduct (**71**) undergoes chemoselective hydrogenation of the isolated double bond to give the unsaturated ester (**13**).

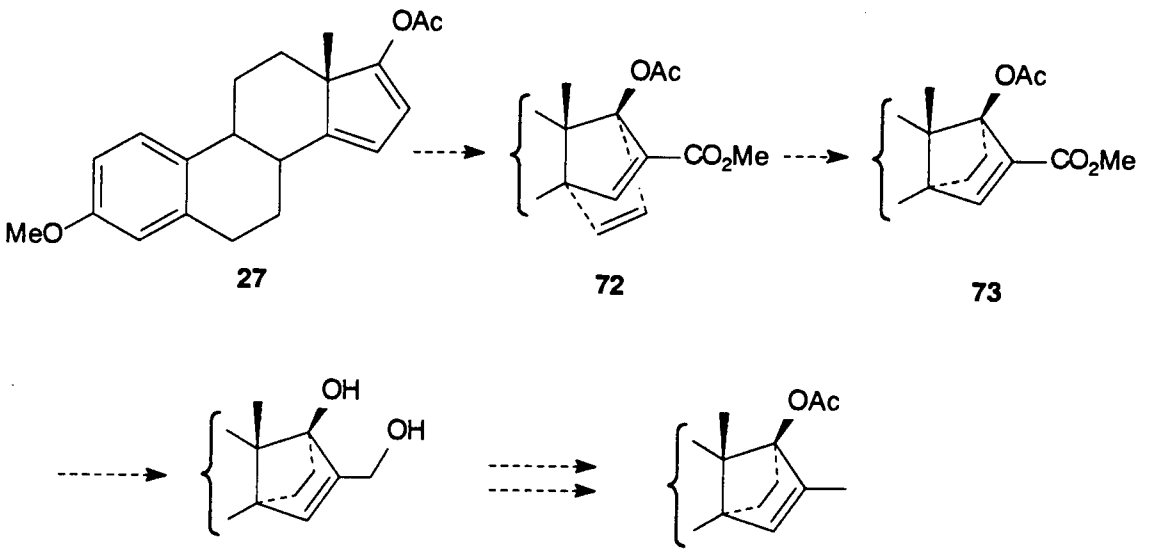
Scheme 2.2-2



Based on these results, the synthetic strategy adopted for this work entailed cycloaddition of methyl propiolate to the diene (**27**), followed by chemoselective hydrogenation leading to an intermediate in which the most direct route to the 16-methyl

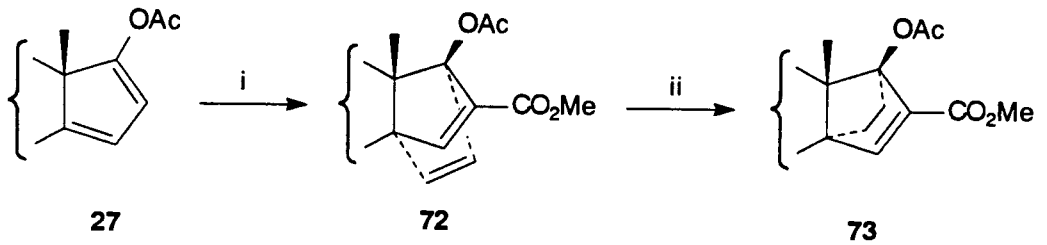
olefin (**B**) appears to require chemoselective 1,2-reduction of the ester (**73**), and potentiation of the resultant primary alcohol, followed by deoxygenation via an appropriate reductive process (Scheme 2.2-3).

Scheme 2.2-3



Thus, treatment of the dienyl acetate (**27**) with methyl propiolate in benzene at 100°C in a sealed tube for 23 h gave the cycloadduct (**72**) in high yield (85%) (Scheme 2.2-4).

Scheme 2.2-4



Reagents: (i) HC≡CCO$_2$Me, benzene, 100°C sealed tube, 23h. (ii) Pd-C, H_2, 25°C, 3h.

Although conclusive proof of the stereo- and regiochemical assignment was lacking, there is sufficient analogy to assign the structure of cycloadduct (**72**) with confidence.[6] Spectroscopic evidence for the introduced functionalities was apparent from two carbonyl absorption bands in the infrared spectrum at ν_{max} 1740 and 1710 cm^{-1}, and the expected signals in the NMR spectrum [δ 3.69 (3H, s, 16-CO$_2$Me), 6.58 and 7.05 (each 1H, d, *J* 5.6 Hz, 17^1- and 17^2-H), and 7.44 (1H, s, 15-H)]. In the ^{13}C-spectrum of the diene (**72**), the

signal for C(13) occurred at δ 88.3, which is markedly deshielded compared with the expected value (*ca.* δ 60). It is documented that in norbornadiene systems, the signal for C(7) (Figure 2.2-1) is deshielded by *ca.* 25 ppm when compared with the signals for C(1) and C(4).[42,43] This deshielding effect is attributed to the interaction of the π-orbitals of the two double bonds, with the sigma orbitals of the C(1)-C(7) and C(4)-C(7) bonds, which leads to a low-lying π^* orbital, causing electron withdrawal from C(7) (Figure 2.2-1). As ring D of the diene (**72**) can be viewed as a norbornadienoid system, the aforementioned interactions would account for the deshielding of C(13) (Figure 2.2-1).

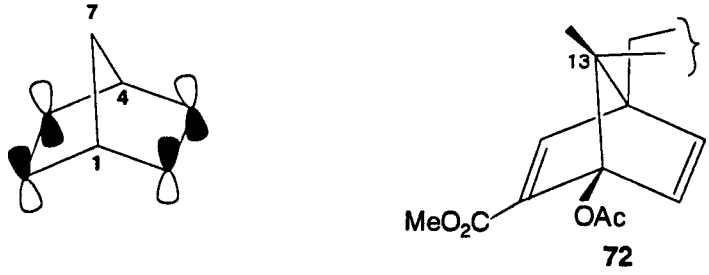


Figure 2.2-1 Deshielding Effects in Norbornadienoid Systems.

This deshielding effect is apparent in the signal for C(13) for all the 15,17[1]-dienes synthesised in this study, and will be highlighted at the relevant stages of discussion.

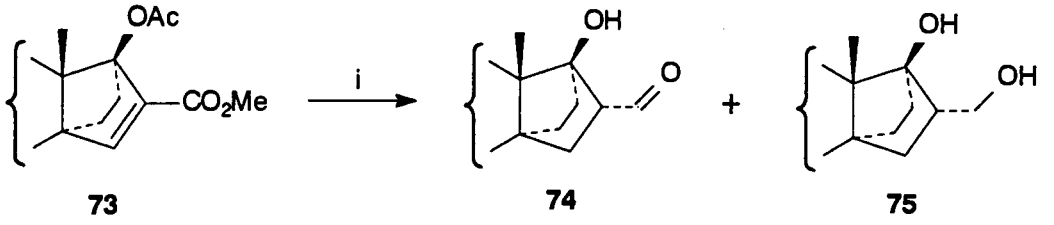
The next reaction in the proposed synthetic sequence was chemoselective hydrogenation of the diene (**72**). This was achieved by treatment of the cycloadduct (**72**) with palladium on carbon in ethyl acetate under hydrogen, to give the desired product of chemoselective hydrogenation, methyl 17β-acetoxy-3-methoxy-14,17α-ethanoestra-1,3,5(10),15-tetraene-16-carboxylate (**73**) (83%) (Scheme 2.2-4).

The structural assignment of (**73**) was supported by the appropriate signals in the NMR spectrum [δ 0.95 (3H, s, 13β-Me), 2.09 (3H, s, 17β-OAc), 3.71 (3H, s, 16-CO_2Me), 6.91 (1H, s, 15-H)].

At this stage, transformation of the 16-ester functionality to a 16-methyl group was required, as discussed previously (Scheme 2.2-3). Although the most direct method of achieving this transformation would be a single step reduction of ester to methyl, the more controlled three-step approach was adopted. Many accounts of selective 1,2-reduction of α,β-unsaturated esters to allylic alcohols are documented, using a variety of reagents.[44] However, despite this wealth of precedent, reaction of the ester (**73**) with a number of available reductants was unsuccessful for our purposes. In a typical reaction, the compound (**73**) was treated with lithium aluminium hydride in tetrahydrofuran at 80°C for 20 h, after which time the reaction was incomplete. Chromatography yielded the starting ester (**73**) (40%) followed by two products (Scheme 2.2-5), the less polar of which was formulated as the 16α-aldehyde (**74**) (11%). Spectroscopic evidence which supported this structural

assignment included signals in the NMR spectrum at δ 1.04 (13β-Me), 3.77 (3-OMe) and 9.72 (16-CHO). The more polar of the two products was formulated as the 16α-hydroxymethyl compound (**75**) (28%), which was verified by direct correlation with an authentic sample.[23]

Scheme 2.2-5



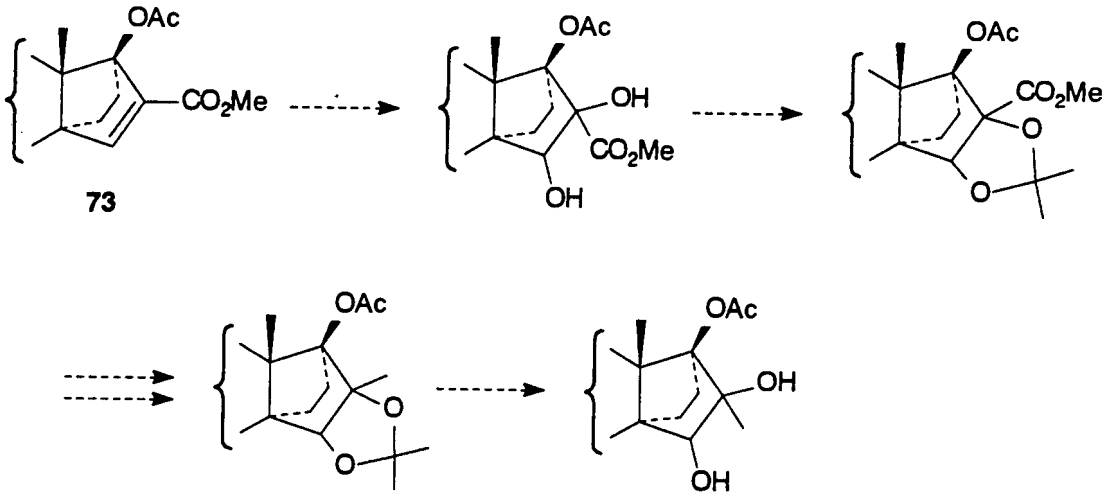
73 **74** **75**

Reagents: (i) LAH, THF, 80°C, 20h.

Although the foregoing experiments afforded insight into the reactivity of the cycloadduct (**72**) and the α,β-unsaturated ester (**73**), it was clear that reduction of the ester functionality was not viable at this stage of the synthetic sequence as the presence of the 15-olefin was essential for synthesis of the target compounds. Accordingly an alternative sequence was sought which would retain the ester moeity until a more convenient opportunity for reduction was reached.

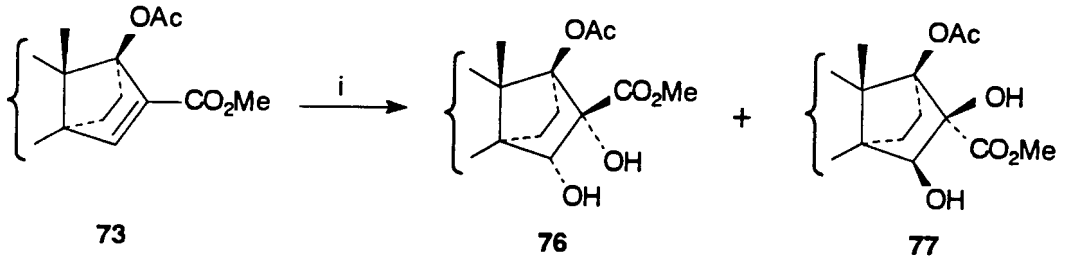
2.2.2 Dihydroxylation-Reduction of the Dihydrocycloadduct. The failure of the α,β-unsaturated system of (**73**) to undergo regioselective 1,2 reduction necessitated an alternative approach to the desired diol intermediate (Scheme 2.2-6). It was reasoned that dihydroxylation of the dihydrocycloadduct (**73**) could be performed as the initial step and that protection of the glycol moiety would facilitate deoxygenation of the 16-ester via stepwise reduction, mesylation of the resultant 16-hydroxymethyl group and reductive deoxygenation. Appropriate manipulation of the residual ring D functionality would then restore the desired 17β-acetoxy 15,16-diol structure. It was recognised however, that the synthetic efficiency of this pathway would be influenced by the stereoselectivity of dihydroxylation; the ideal result would be highly stereoselective formation of a single 15,16-diastereomer.

Scheme 2.2-6



Reaction of (**73**) with osmium tetroxide in pyridine for 48 h, followed by chromatography of the resultant product mixture, resulted in the 15α,16α-diol (**76**) (65%) followed by the 15β,16β-diol (**77**) (27%) (Scheme 2.2-7). For large scale preparations, it was found that catalytic dihydroxylations, using 4-methylmorpholine-4-oxide monohydrate as secondary oxidant,[45] were preferred both in terms of cost and toxicity of large amounts of osmium tetroxide. In the dihydroxylation carried out here, the catalytic reaction was slower than the stoichiometric reaction and resulted in slightly lower yields, but the stereochemical outcome was comparable, in accordance with results reported elsewhere.[46,19] Thus, treatment of the olefin (**73**) with 1.3 mol% osmium tetroxide, 4-methylmorpholine-4-oxide monohydrate in tetrahydrofuran and water, followed by chromatography, gave the starting olefin (**73**) (10%), 15α,16α-diol (**76**) (68%) and 15β,16β-diol (**77**) (19%).

Scheme 2.2-7



Reagents: (i) OsO_4, pyridine, 20°C, 48h OR OsO_4, NMMO, THF, H_2O, 20°C, 168h.

The structural and stereochemical assignments of the diols (**76**) and (**77**) were confirmed by NMR spectroscopy, thus the spectrum for the 15α,16α-diol (**76**) displayed characteristic signals at δ 2.14 (17β-OAc) and 3.73 (16β-CO_2Me) and the signal for the 15β-proton appeared at δ 4.42 as a doublet (after D_2O exchange) with a coupling of 1.5 Hz. This was ascribed to a four-bond W-coupling[47] between the 15β- and 17^2_{exo}-protons (bold lines in Figure 2.2-2).

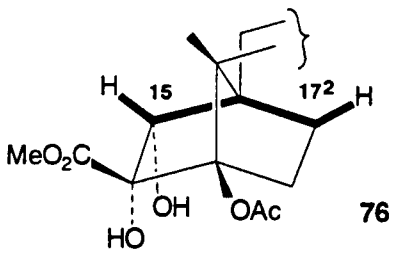


Figure 2.2-2 W-Coupling Between 15- and 17^2-Protons on the Diol (**76**)

It has been postulated that these long range proton-proton couplings are due to the overlap and interaction of the rear orbital lobes of the carbon atoms bearing the protons in question.[103] W-couplings are useful in assigning stereochemistry in these bridged systems and have been thus used previously.[17,19]

The NMR spectrum of the 15β,16β-diol (**77**) showed a similar array of signals to that for (**76**), however, the signal for the 15α-proton appeared as a singlet (after D_2O exchange) at δ 4.11, thus confirming the reliability of this method of isomer differentiation.

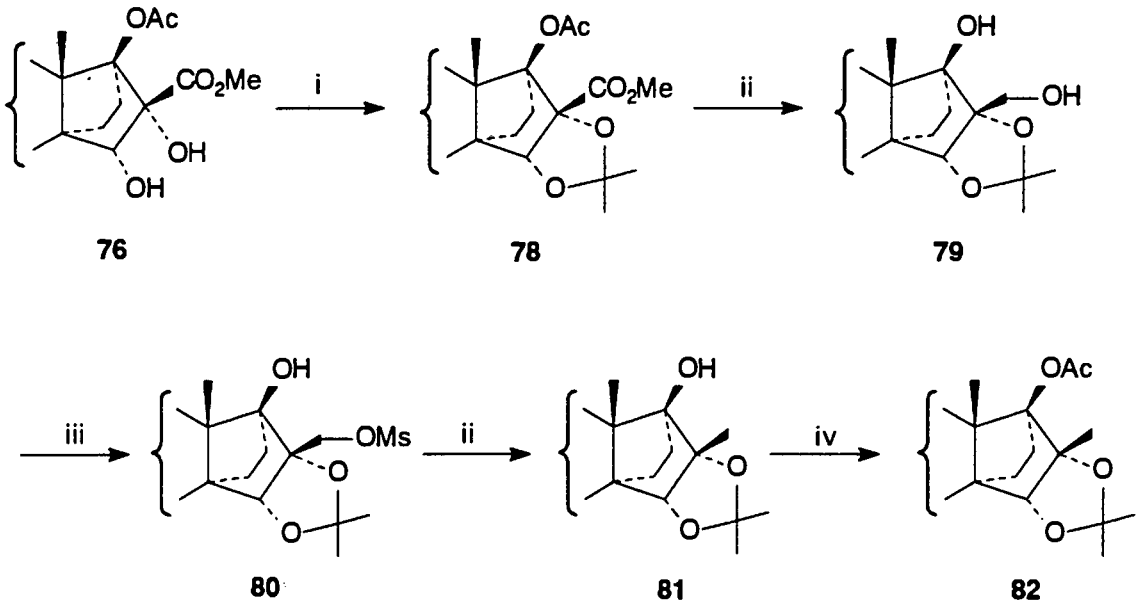
The stereochemical outcome of dihydroxylation was not of key importance in the synthetic sequence, as both diols could eventually be converted to a common intermediate; however the results are interesting as part of a larger selectivity study, which will be discussed in Chapter 5. Nevertheless, the presence of the two isomers was a practical hindrance as individual treatment of the isomers was necessary until a point of convergence was reached. The reaction sequence for the major isomer (**76**) is described in detail, but it is shown (see later) that both diol isomers (**76**) and (**77**) follow a similar reaction course.

Treatment of the diol (**76**) with perchloric acid in acetone at 20°C gave the 15α,16α-isopropylidenedioxy compound (**78**) in good yield (85%) (Scheme 2.2-8). This structural assignment was supported by spectroscopic evidence, the most noticeable of which were the signals for the acetonide methyl protons in the NMR spectrum which appeared as singlets at δ 1.35 and 1.61, and the signal for the 15β-proton at δ 5.0 (d, *J* 1.1 Hz).

Treatment of the ester (**78**) with lithium aluminium hydride in tetrahydrofuran at 25°C for 3 h, reduced both the 16- and 17-ester functionalities, to give the diol (**79**). The signals for the 16^1-methylene protons of (**79**) appeared in the NMR spectrum as an AB multiplet at

δ 3.79 and 4.32 (each d, *J* 11.9 Hz, after D_2O exchange), and the signal for the 15β-proton appeared at δ 4.22 (d, *J* 1.2 Hz).

Scheme 2.2-8



Reagents: (i) $HClO_4$, acetone, 20°C, 2h. (ii) LAH, THF, 25°C. (iii) MsCl, pyridine, 0°C, 1.5h. (iv) Ac_2O, TsOH, THF, 20°C, 1h.

Potentiation of the 16^1-hydroxy group on (**79**) was necessary for reductive deoxygenation; accordingly treatment of the diol (**79**) with methanesulfonyl chloride in pyridine at 0°C for 1.5 h gave the mesyloxy derivative (**80**) chemoselectively and quantitatively. The signal for the mesyloxy-methyl protons of (**80**) occurred in the NMR spectrum at δ 3.05 as expected; the signals for the 16^1-protons occurred as doublets (*J* 11.1 Hz) at δ 4.45 and 4.75, and the signal for the 15β-proton appeared at δ 4.60 (d, *J* 1.4 Hz).

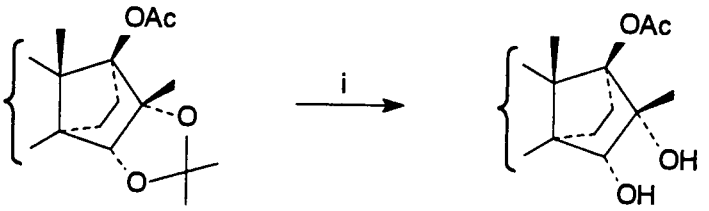
Hydride reduction of the mesyloxy compound (**80**) gave the 16β-methyl compound (**81**) in high yield (89%), the structural assignment of which was supported by spectroscopic evidence; in partial NMR data [δ 0.94 (3H, d, *J* 0.8 Hz; 13β-Me), 1.45 and 1.54 (each 3H, s, CMe_2), 1.63 (3H, s, 16β-Me), 4.22 (1H, d, *J* 1.6 Hz, 15β-H)].

Reacetylation of the 17-hydroxy group on (**81**) was necessary to ensure selective 15,16-diol cleavage at a later stage, and the presence of the acetate was essential for reductive deacetoxylation of the cleavage product. Accordingly, treatment of the 17-alcohol (**81**) with acetic anhydride and toluene-*p*-sulfonic acid in tetrahydrofuran at 20°C for 1 h gave the 17-acetate (**82**) (73%). The presence of the acetate functionality was represented

by the usual spectroscopic signals: in the infrared spectrum by an absorption band at ν_{max} 1735 cm^{-1} and in the NMR spectrum by the singlet at δ 2.05 (3H, s).

With the acetate (**82**) in hand, deprotection of the diol moeity was expected to give the key intermediate in this synthetic sequence. Accordingly, reaction of the acetonide (**82**) with iodine in refluxing methanol[48] gave 3-methoxy-16β-methyl-14,17α-ethanoestra-1,3,5(10)-triene-15α,16α,17β-triol 17-acetate (**83**) (79%) (Scheme 2.2-9). The overall yield of (**83**) from the dienyl acetate (**27**) was 20%.

Scheme 2.2-9

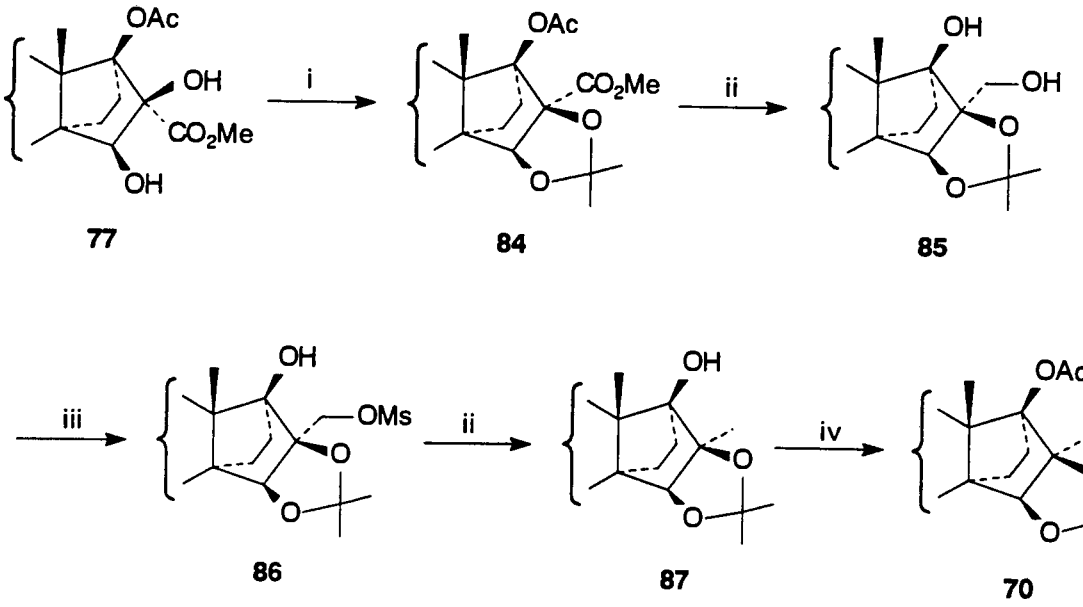


82 **83**

Reagents: (i) I_2, MeOH, 82°C, 5.5h.

Conversion of the minor product of dihydroxylation, the 15β,16β-diol (**77**), into the 16-methyl-15β,16β-diol (**68**) involved a parallel series of reactions (Scheme 2.2-10) to the foregoing experiments, starting with treatment of the diol (**77**) with perchloric acid in acetone to give the acetonide (**84**).

Scheme 2.2-10



77 **84** **85**

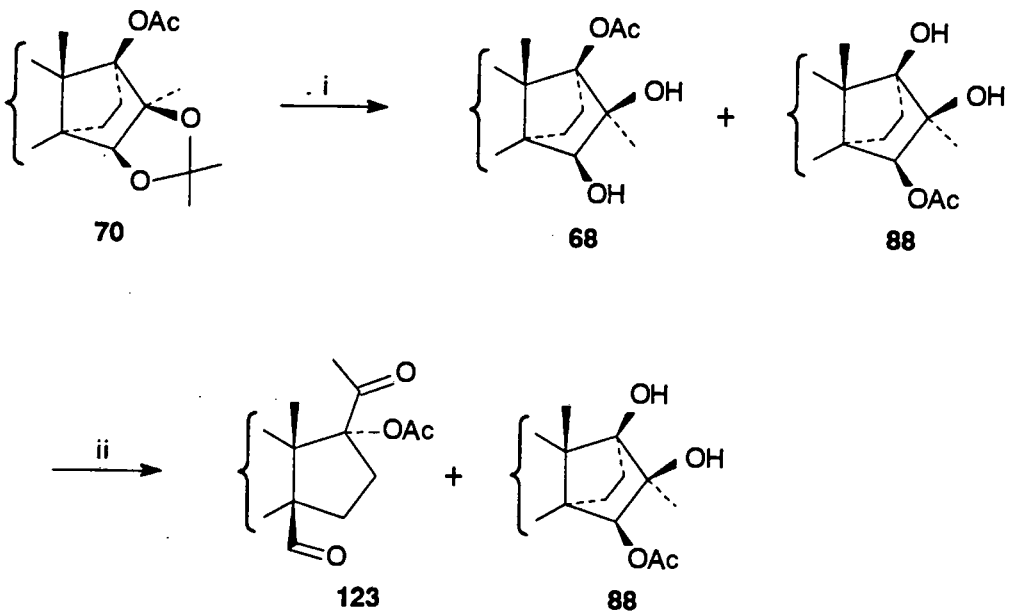
86 **87** **70**

Reagents: (i) $HClO_4$, acetone, 20°C, 1.5h. (ii) LAH, THF, 25°C. (iii) MsCl, pyridine, 0°C, 1.5h. (iv) Ac_2O, TsOH, THF, 20°C, 24h.

The 16-ester group was reduced to the 16-methyl group via reduction to the diol (**85**), potentiation of the primary alcohol by mesylation to (**86**), and finally treatment of (**86**) with lithium aluminium hydride to give the 16α-methyl compound (**87**). It was necessary to acetylate the 17-hydroxy group on (**87**) for the reasons discussed above, accordingly treatment of (**87**) with acetic anhydride and toluene-*p*-sulfonic acid in tetrahydrofuran gave the acetate (**70**). The structural assignments for this series of compounds were supported by the expected spectroscopic evidence.

As before, deprotection of the 15β,16β-diol moeity was necessary in order to furnish the target 15β,16β-diol; however, treatment of the 15β,16β-isopropylidenedioxy compound (**70**) with iodine in methanol and tetrahydrofuran at 80°C, gave an inseparable mixture of products, formulated as the 15β,16β-diol 17-acetate (**68**) and the 16β,17β-diol 15-acetate (**88**) (*ca.* 1.8:1) (Scheme 2.2-11). The structural assignments and product distribution were verified when the mixture of (**68**) and (**88**) was treated with aqueous sodium periodate in ethanol at 20°C, and subsequent chromatography yielded the product of C(15)-C(16) bond cleavage (**123**) (56%) (see Chapter 3) followed by the 16β,17β-diol 15-acetate (**88**). Cleavage of the latter diol by periodate was evidently inhibited by greater steric hindrance and obligatory participation of a bridgehead hydroxy group in the reaction.

Scheme 2.2-11

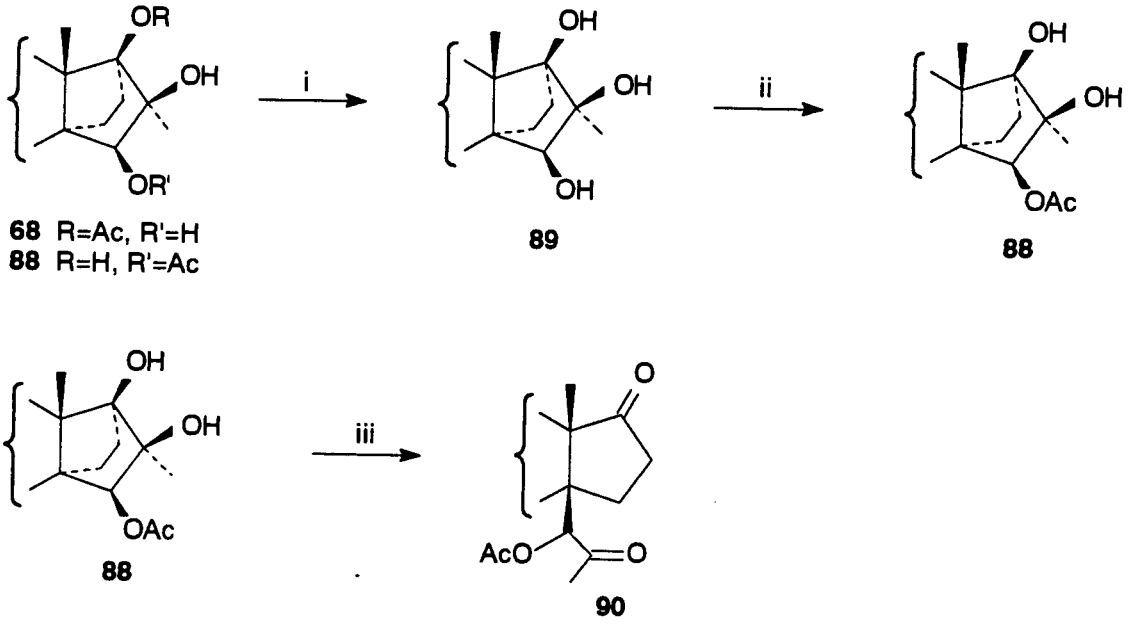


Reagents: (i) I_2, MeOH, THF, 80°C, 3.5h. (ii) $NaIO_4$, EtOH, 20°C, 24h.

The structural assignment of (**88**) was supported by several spectroscopic features, including the infrared absorption bands at ν_{max} 3597 (OH) and 1721 (OAc) cm^{-1}, and

signals in the NMR spectrum at δ 1.48 (s, 16α-Me), 2.05 (s, 15β-OAc), and 4.45 (s, 15α-H). The latter signal is clearly more deshielded than that for the 15α-proton of the 15β,16β-diol (**68**), which occurs as a singlet at δ 3.61. The structure of (**88**) was further verified by treatment of the mixture of diols (**68**) and (**88**) with lithium aluminium hydride in tetrahydrofuran at 25°C to give one common product, formulated as the 15β,16β,17β-triol (**89**) which, when reacted under acetylation conditions (acetic anhydride, toluene-*p*-sulfonic acid, tetrahydrofuran, 25°C), gave the product (**88**) chemoselectively (Scheme 2.2-12).

Scheme 2.2-12

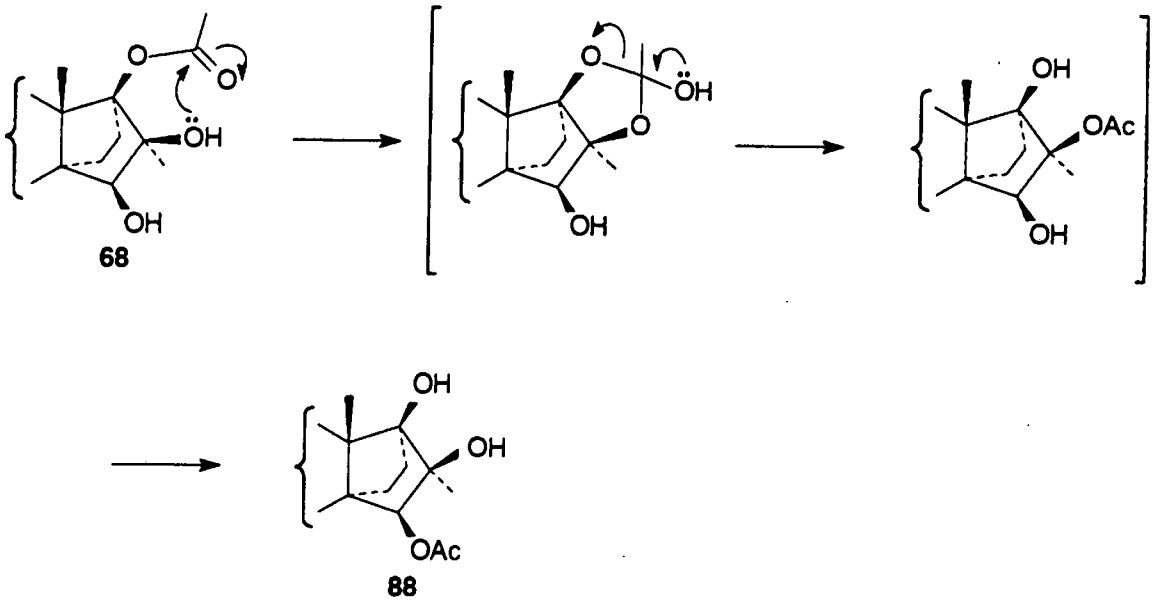


Reagents: (i) LAH, THF, 25°C, 1.25h. (ii) Ac_2O, TsOH, THF, 25°C, 20h. (iii) LTA, benzene, 20°C, 5min.

The 16β, 17β-diol (**88**) was easily cleaved by treatment with lead tetraacetate in benzene at 20°C, to give the cleavage product (**90**) quantitatively, the structural assignment of which was supported by infrared absorption bands (ν_{max} 1735 and 1725br cm^{-1}), and signals in the NMR spectrum [δ 1.98 (s, 14^1-OAc), 2.37 (s, 14^2-Me), 4.77 (s, 14^1-H)].

It was concluded that during the attempted deprotection of the isopropylidenedioxy compound (**70**), the free diol underwent stepwise transacetylation from the tertiary acetate on (**68**) to the primary acetate on (**88**) (Scheme 2.2-13).

Scheme 2.2-13



Transacetylations are not uncommon in 1,2-diol monoacetates in carbohydrate[49] and steroidal systems,[50,51,52] and depend on the stereochemical relationship between the groups involved. In accordance with the findings of Schneider *et al.*[50] transacetylation occurs in the 16β,17β-diol 17-acetate (**68**) but not in the 16α,17β-diol 17-acetate (**83**). This result can be analysed in terms of conformational transmission; thus for compound (**68**), the transition state of transacetylation necessitates a *cis*-fused dioxabicyclopentanoid system [bold lines in intermediate (**a**), Figure 2.2-3], while for (**83**), a *trans*-fused dioxabicyclopentanoid system [intermediate (**b**)] would be invoked; the latter being too strained for facile transacetylation.

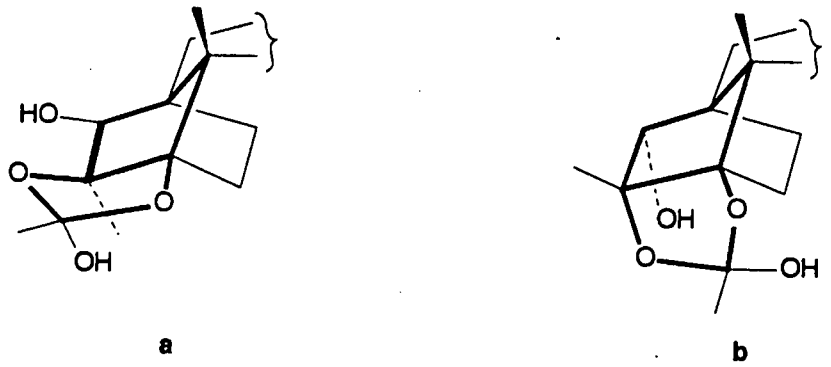


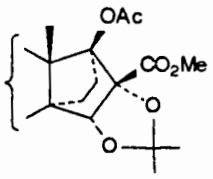
Figure 2.2-3 Transition States for Potential Transacetylation.

Although the targets in this section of the overall synthetic sequence were reached, the multistep nature of the transformations, and the necessity to react the diols separately,

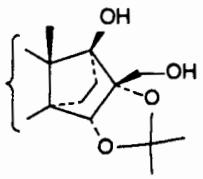
detracted from the usefulness of this approach; also the interference of the transacetylation reaction decreased the overall yields dramatically [the triol (**89**) was obtained in an overall yield of 7.4% from the dienyl acetate (**27**)].

2.2.3 Differentiation of NMR Signals for 16-Methyl- and Isopropylidenedioxy-methyl Protons. For both the 15α,16α- and 15β,16β-series of compounds studied in this chapter, derivatives were synthesised with three apparently indistinguishable methyl groups *viz.* the 16- methyl- and 15,16-isopropylidenedioxy-methyl groups. Accordingly, an attempt was made to assign the signals for these groups in the ^{1}H NMR spectrum of the relevant compounds. The assignments for the compounds in the 15α,16α-series are summarised in Table 2.2-1 and the rationale behind these assignments will be discussed in detail.

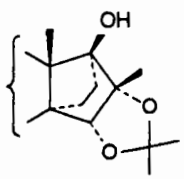
Table 2.2-1 ^{1}H NMR Chemical Shifts for Ring D Methyl Protons of (**78**), (**79**), (**81**), (**82**).



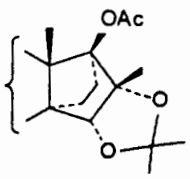
78



79



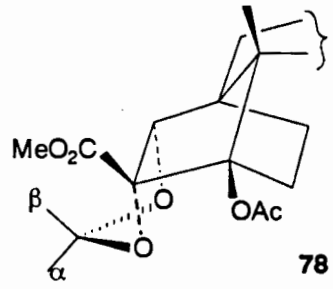
81



82

Chemical Shifts (δ)

Compound	**78**	**79**	**81**	**82**
13β-Me	0.95	0.92	0.94	0.99
16β-Me			1.63	1.59
α-acetonide-Me	1.61	1.61	1.54	1.56
β-acetonide-Me	1.35	1.48	1.45	1.46



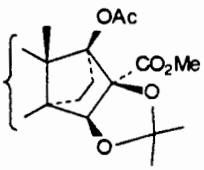
78

Figure 2.2-4 Proximity of Acetonide Methyl Groups to C(16)-Functionality on Compound (**78**).

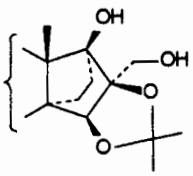
Examination of a model of the ester (**78**) (Figure 2.2-4) revealed that the β-acetonide-methyl group might be affected by a change in the functionality on C(16), whereas the α-acetonide methyl group would not experience this effect. On reduction of the ester to give the diol (**79**), only one of the two signals for these methyl groups experienced a change in chemical shift (δ 1.35 → δ 1.48), and these signals were thus assigned to the β-acetonide methyl group. For the compound (**81**), the signal at δ 1.63 was positively assigned to the 16-methyl group, by inspection of the HMBC[1] spectrum of (**81**), which revealed cross-peaks between this signal and the signals for C(15), C(16) and C(17). The α-acetonide-methyl group should not be affected to a large extent by transformation to (**81**), thus the signal at δ 1.54 was assigned to this group.

Acetylation at C(17) is known to have a slight shielding effect on the 16β-methyl group, accordingly, the signal at δ 1.59 in the spectrum of (**82**) was assigned to this group; also this transformation should not affect either α- or β-acetonide-methyl groups and inspection of the table reveals that these signals can be assigned on this basis.

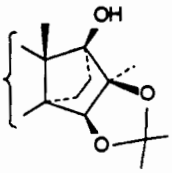
Table 2.2-2 ^{1}H NMR Chemical Shifts for Ring D Methyl Protons of (**84**), (**85**), (**87**), (**70**), and (**69**).



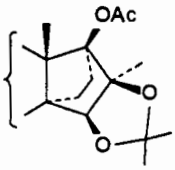
84



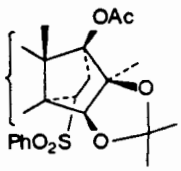
85



87



70

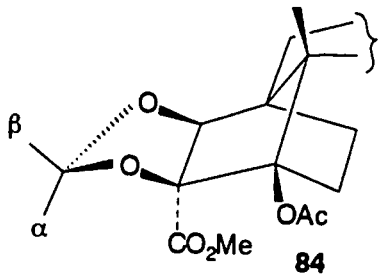


69

Chemical Shifts (δ)

Compound	**84**	**85**	**87**	**70**	**69**
13β-Me	1.24	1.30	1.26	1.33	1.44
16α-Me			1.50	1.64	1.93
α-acetonide-Me	1.35	1.40	1.43	1.43	1.48
β-acetonide-Me	1.55	1.55	1.54	1.52	1.55

[1]HMBC (heteronuclear multiple bond coherence) is a 2D NMR technique which correlates protons and carbon atoms through two- and three-bond interactions.



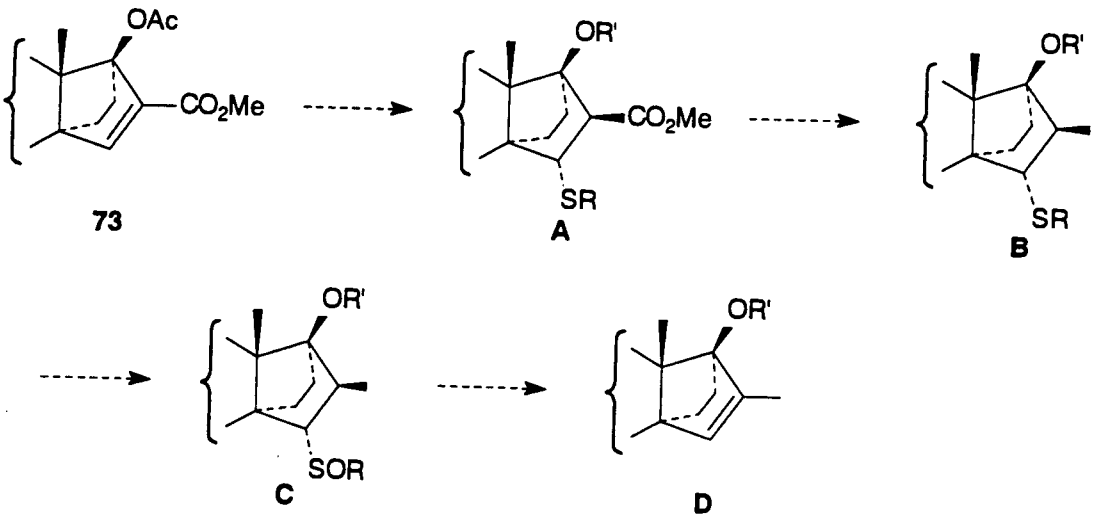
84

Figure 2.2-5 Proximity of Acetonide Methyl Groups to C(16)-Functionality on Compound (**84**).

For the 15β,16β-series of compounds, a similar strategy was adopted. A long-range HETCOR (see footnote on HMBC) spectrum of (**70**) made positive assignment of the signal at δ 1.64 to the 16-methyl protons possible [cross-peaks to signals for C(15), C(16) and C(17)], and it was again possible to trace the effects of functional group transformations on the signal for the α-acetonide methyl protons (Table 2.2-2 and Figure 2.2-5). In this way, it was also appropriate to include the phenylsulfone (**69**) (see Chapter 2.1) in this analysis, and the deshielding effect of the phenylsulfonyl group on the 16α-methyl protons was highlighted.

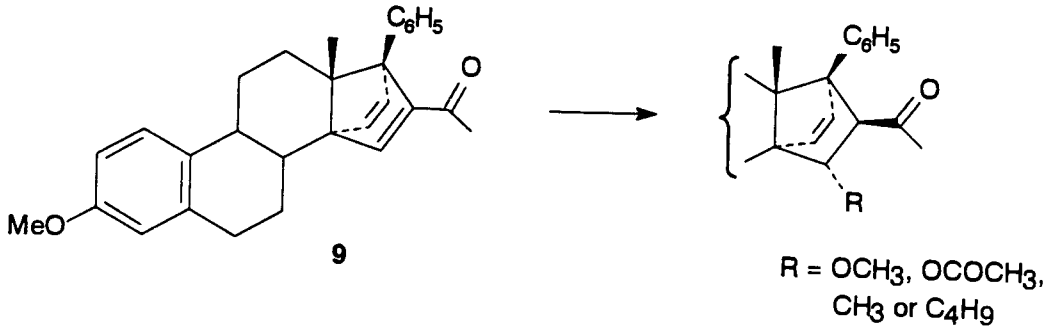
2.2.4 Synthesis and Dihydroxylation of 3-Methoxy-16-methyl-14,17α-ethanoestra-1,3,5(10),15-tetraen-17β-ol. Although the work outlined in the foregoing chapters resulted in successful synthesis of the key intermediates for the envisaged synthetic strategy, the need to modify the dihydroxylation products separately, detracted from the overall efficiency and elegance of the approach. Accordingly, consideration was given to an alternative method for modifying the unsaturated ester (**73**). The plan which was adopted entailed conjugate addition of a thiolate to the ester (**73**), followed by reductive conversion of the product to a 16-methyl intermediate (**B**), from which the derived sulfoxide (**C**) could be prepared for dehydrosulfinylation to give (**D**) (Scheme 2.2-14).

Scheme 2.2-14



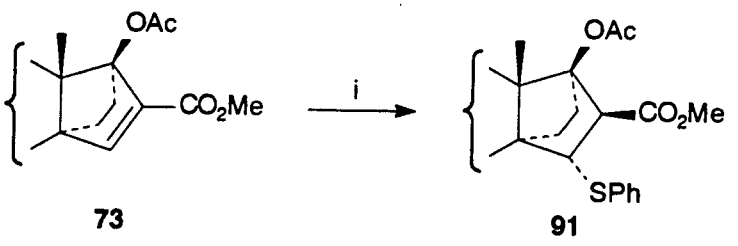
The success of this approach depended critically upon stereoselective conjugate addition of the thiolate as indicated in Scheme 2.2-14, since this would ensure the obligatory orientation of functionality for *syn*-elimination of the sulfoxide. We were encouraged in this expectation by the results reported by Winterfeldt[13,14] on conjugate addition of various nucleophiles to the unsaturated ketone (**9**), in which it was shown that the derived products are indeed of the appropriate configuration (Scheme 2.2-15).

Scheme 2.2-15



Accordingly, the reactivity of the unsaturated ester (**73**) towards thiophenol was investigated. Treatment of (**73**) with thiophenol and a catalytic amount of diisopropylamine at 20°C for 48 h gave only one product (98%) (Scheme 2.2-16), which was assigned the structure 15α-phenylthio-16β-carboxylate (**91**), according to the analogy discussed above.

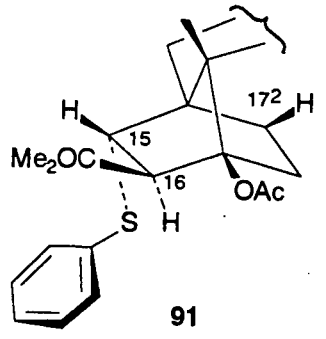
Scheme 2.2-16



73 91

Reagents: (i) Diisopropylamine, thiophenol, 20°C, 48h.

The structural assignment of the product (**91**) was supported by spectroscopic evidence. The introduction of the phenylthio group on C(15) resulted in two absorption bands at ν_{max} 1599 and 1571 cm^{-1} in the infrared spectrum, which remained in evidence throughout the series containing this group. For compound (**91**), there was also a strong absorption band at ν_{max} 1734 cm^{-1} for the ester carbonyl groups. In the NMR spectrum, the signal for the acetyl methyl protons appeared at δ 2.02, and that for the ester methyl group at δ 3.53. The signal for the 16α-proton occurred at δ 3.82 as a doublet (*J* 5.6 Hz), while the signal for the 15β-proton occurred as a doublet of doublets (*J* 5.6 and 2.5 Hz) at δ 3.36, as expected for a methine proton α to a sulfide group.[53] The W-coupling (2.5 Hz) of the 15β-proton to the 17^2-*exo* proton confirmed the stereochemical assignment at C(15). Confirmation of the *trans*-relationship between protons on C(15) and C(16) came from the coupling constant between these protons (5.6 Hz), thereby excluding both an *endo-endo*- and an *exo-exo*-relationship[54] (Figure 2.2-6). The chemical shift for the 16α-proton (δ 3.53) is more deshielded than expected for a proton adjacent to an ester group; accordingly, the functional array on the α-face of ring D invites speculation on the deshielding effect of the phenylsulfenyl group on this proton (Figure 2.2-6).

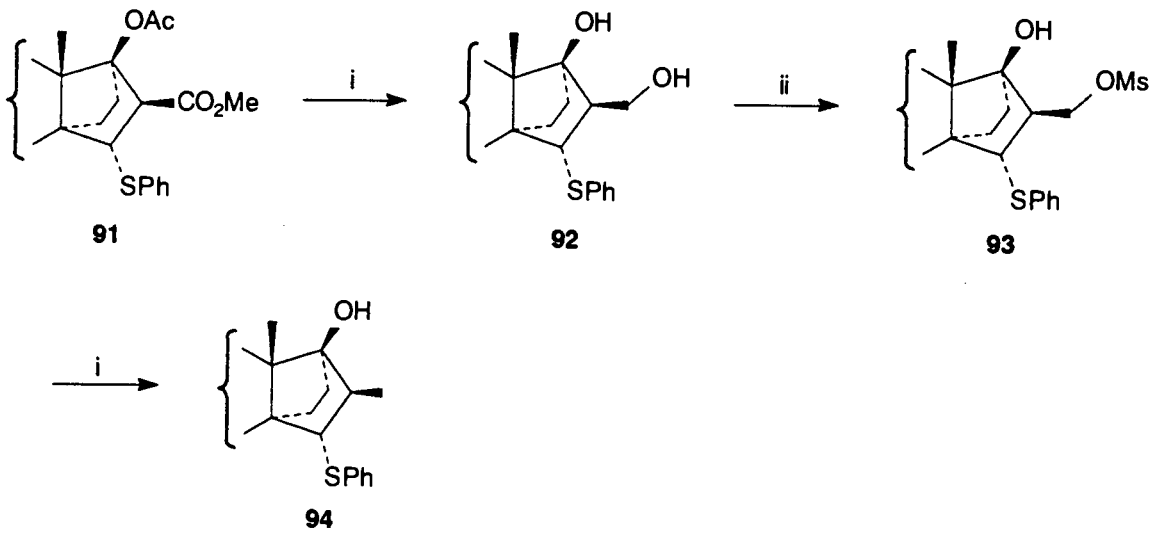


91

Figure 2.2-6 W-Coupling, and Functional Group Array on Phenylthio Compound (**91**).

The ester functionality of (**91**) was transformed to the 16β-methyl group according to expectation (Scheme 2.2-17), starting with treatment of the ester (**91**) with lithium aluminium hydride in tetrahydrofuran at 20°C to give the diol (**92**) quantitatively. The NMR spectrum of (**92**) was not conclusive, as the signal for the 15-proton was obscured by that for the 6-protons (δ 2.74), and the signals for the 16^1-protons appeared as a multiplet at δ 3.80. Confidence in this structural assignment was, however, restored by microanalytical data of (**92**), and subsequent chemistry thereof.

Scheme 2.2-17

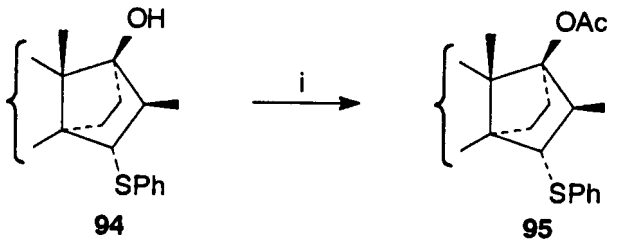


Reagents: (i) LAH, THF, 20°C. (ii) MsCl, pyridine, 0°C, 1h.

The diol (**92**) was chemoselectively potentiated for reductive deoxygenation by reaction with methanesulfonyl chloride in pyridine at 0°C to give the 16β-(methanesulfonyloxy)methyl compound (**93**) (81%), which was immediately treated with lithium aluminium hydride in tetrahydrofuran at 20°C, to give the 16β-methyl 15α-phenylthio compound (**94**) in high yield (96%). Spectroscopic evidence supported this structural assignment. In the NMR spectrum, the signal for the 16β-methyl group appeared at δ 0.90 as a doublet (*J* 7.2 Hz), and that for the 15β-proton at δ 2.84 as a doublet (*J* 5.6 Hz). The signal for the 15β-proton does not show evidence of long-range coupling, possibly due to distortion arising from the 1,3-*exo,syn*-relationship between the 16β- and 13β-methyl groups, which could perturb the exact arrangement necessary for W-coupling.

The acetate (**95**) was synthesised for further characterisation purposes by reaction of the alcohol (**94**) with acetic anhydride and dimethylaminopyridine in pyridine at 20°C (Scheme 2.2-18).

Scheme 2.2-18

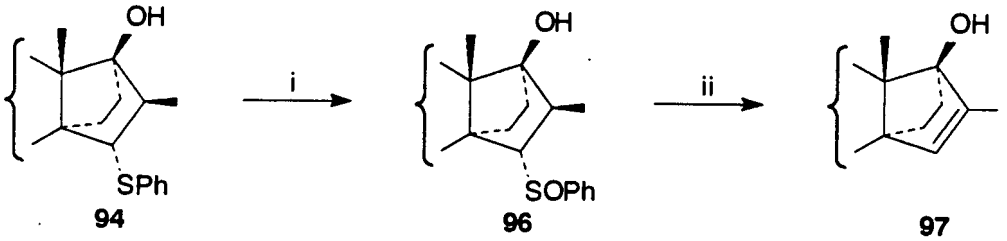


94 **95**

Reagents: (i) Ac_2O, DMAP, pyridine, 20°C, 71h.

At this point in the synthetic sequence, regeneration of the 15-olefin was planned via dehydrosulfinylation. The dehydrosulfinylation sequence involves oxidation of the phenylthio group followed by thermolysis of the derived sulfoxide. The oxidation of sulfides to sulfoxides is a facile transformation for which many reagents have been successfully employed,[55] and the thermal instability of the resulting sulfoxides has been recognised for many years[56] and extensively utilised in organic synthesis. Accordingly, the sulfide (**94**) was treated with aqueous sodium metaperiodate[57,58] in ethanol at 20°C to give the 15α-sulfoxide (**96**) (Scheme 2.2-19). Sulfoxides are known to be highly polar derivatives,[55] and the sulfoxide (**96**) was no exception; it is a highly insoluble, powdery solid, which was not fully characterised, with structural confirmation coming from successful subsequent transformations.

Scheme 2.2-19



94 **96** **97**

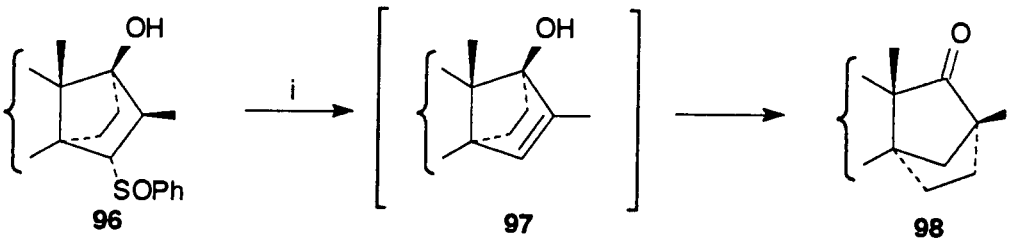
Reagents: (i) $NaIO_4$, EtOH, THF, 20°C, 24h. (ii) Triethylamine, benzene, 115°C sealed tube, 16h.

In order to effect *cis*-elimination of the sulfoxide, the compound (**96**) was heated with triethylamine and benzene in a sealed tube at 115°C to give 3-methoxy-16-methyl-14,17α-ethanoestra-1,3,5(10),15-tetraen-17β-ol (**97**) quantitatively (Scheme 2.2-19). This structural assignment was supported by spectroscopic evidence: a broad absorption band at ν_{max} 3598 cm^{-1} in the infrared spectrum indicated the presence of the 17-hydroxy group,

and in the NMR spectrum the signal for the 16-methyl group appeared at δ 1.73 as a doublet (*J* 1.6 Hz) due to the long-range allylic coupling[59] with the 15-proton. Correspondingly, the signal for the 15-proton appeared at δ 5.62 as a quartet (*J* 3x1.6 Hz).

The thermolysis of the sulfoxide (**96**) was attempted in the absence of triethylamine (Scheme 2.2-20) and the resultant product of rearrangement (**98**) highlighted the need for a reagent to trap the benzenesulfenic acid formed as a byproduct during the elimination.[60]

Scheme 2.2-20

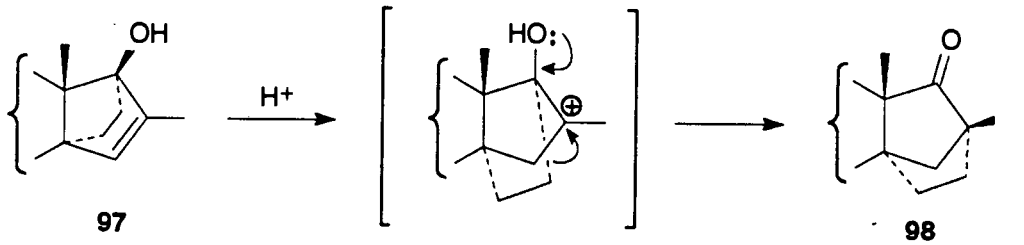


96 **97** **98**

Reagents: (i) Benzene, 115°C sealed tube, 16h.

This type of acid-mediated 17(17[1] → 16)*abeo*-rearrangement has been investigated[37] and the resulting ketone (**98**) was correlated directly with an authentic sample obtained from an unrelated synthetic sequence.[37] The mechanism of this rearrangement involves carbocation formation at C(16), followed by C(17[1])-C(17) bond migration to C(16), to give the 16β-methyl-14α,16α-ethano 17-ketone (**98**) (Scheme 2.2-21).

Scheme 2.2-21

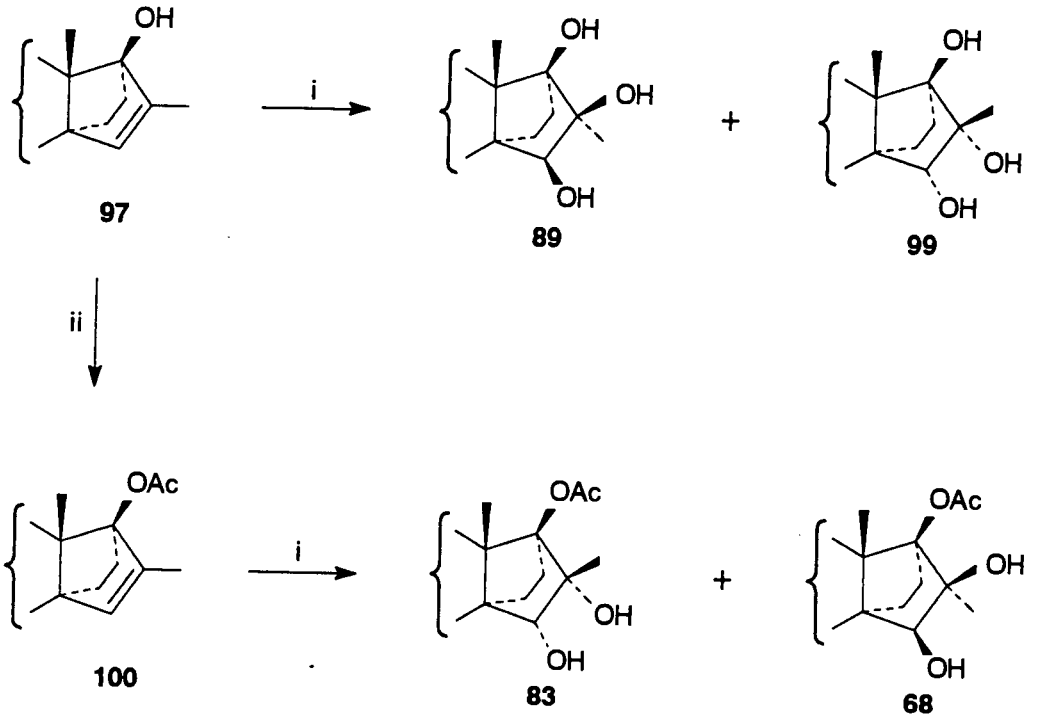


97 **98**

With the key intermediate (**97**) in hand, it was possible to undertake dihydroxylation of (**97**) to give 15,16,17-triols, as well as acetylation of (**97**) and dihydroxylation of the resultant acetate to give 15,16-diol 17-acetates. Accordingly, the hydroxy olefin (**97**) was treated with osmium tetroxide in pyridine at 20°C and the resultant mixture chromatographed to give the 15β,16β,17β-triol (**89**) (50%), followed by the 15α,16α,17β-triol (**99**) (40%) (Scheme 2.2-22). The triol (**89**) had been characterised previously (Chapter

2.2.2) and could be directly correlated, however, the triols could also be differentiated by spectroscopic data: in the NMR spectrum of the 15α,16α,17β-triol (**99**), the signal for the 15β-proton appeared at δ 3.72 as a doublet (after D_2O exchange) with W-coupling of 1.3 Hz, confirming the stereochemistry at C(15) and thus C(16) whereas the signal for the 15α-proton on (**89**) appeared at δ 3.60 as a singlet (after D_2O exchange).

Scheme 2.2-22



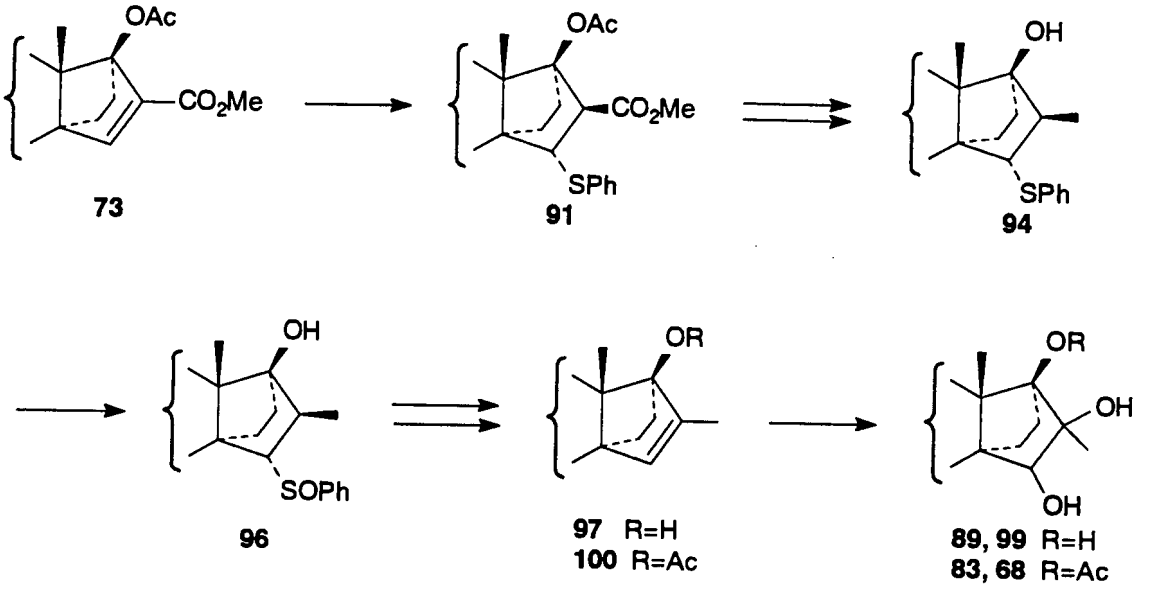
Reagents: (i) OsO_4, pyridine, 20°C. (ii) Ac_2O, DMAP, pyridine, 20°C, 22h.

The hydroxy olefin (**97**) was treated with acetic anhydride in pyridine at 20°C to give the acetoxy olefin (**100**) (97%) (Scheme 2.2-22). The spectroscopic evidence for successful acetylation included the absorption band at ν_{max} 1729 cm^{-1} for the acetoxy carbonyl group in the infrared spectrum, and the singlet at δ 2.10 for the acetoxy methyl protons in the NMR spectrum. The signal for the 15-proton on (**100**) once again revealed long range allylic coupling [δ 5.67 (1H, q, *J* 3x1.5 Hz)] to the16-methyl protons [δ 1.74 (3H, d, *J* 1.5 Hz)].

The acetoxy olefin (**100**) was treated with osmium tetroxide in pyridine at 20°C and the resultant mixture chromatographed to give the 15α,16α-diol (**83**) (63%), followed by the 15β,16β-diol (**68**) (29%) (Scheme 2.2-22). Both the diols (**83**) and (**68**) had been previously characterised (Chapter 2.2.2), and it was therefore a simple task to identify them, both by physical correlation and spectroscopic comparison.

In summary, the synthetic sequence discussed in this chapter (Scheme 2.2-23) was gratifyingly successful, with high yields at each transformation, resulting in high overall yields of triols (**89**) and (**99**) from the ester (**73**) (51%), and diols (**83**) and (**68**) from the ester (**73**) (53%).

Scheme 2.2-23

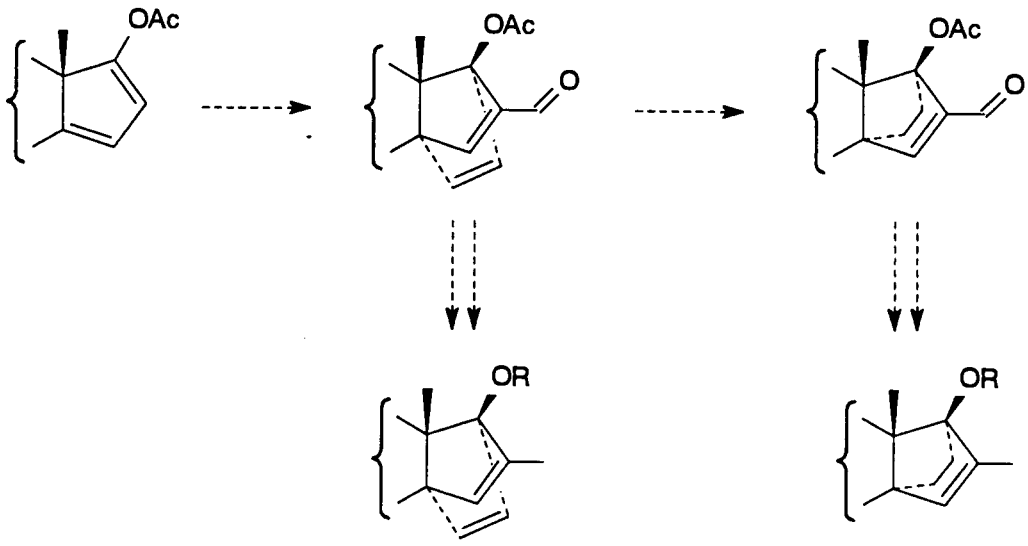


2.3 Cycloaddition of Propynal to 3-Methoxyestra-1,3,5(10),14,16-pentaen-17-yl Acetate.

During the investigation described in the foregoing chapters, a complementary study was conducted on alternative dienophilic propyne equivalents or precursors, in search of functionality which could be converted more directly into a 16-methyl group on the resultant cycloadducts. The failure of the 16-carbomethoxy group on compound (**73**) to respond to attempted 1,2-reduction necessitated the multistep (albeit efficient) synthetic routes we have described.

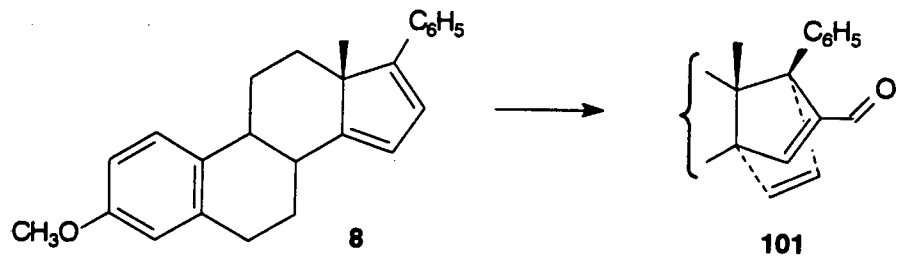
An attractive alternative to methyl propiolate as dienophile appeared to be propynal. It was reasoned that the 16-formyl group on the cycloadduct (Scheme 2.3-1) would be more amenable to direct deoxygenation to the corresponding methyl group, or that regioselective 1,2-reduction would give an intermediate for controlled reductive deoxygenation. In either event, this approach would also provide scope for examining the chemoselectivity of reactions to the olefinic bonds of the bicyclo[2.2.1]heptadienoid structures, possibly leading to new unsaturated analogues of the compounds already prepared.

Scheme 2.3-1



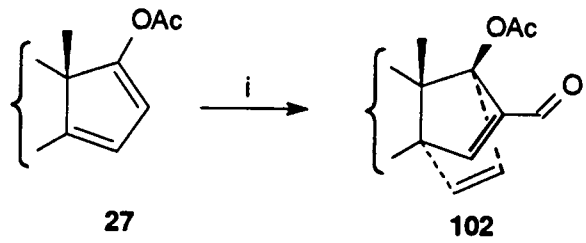
We were encouraged to attempt this cycloaddition by reports in the literature that propynal is easily prepared in the laboratory,[61] and has been successfully used as a dienophile with steroidal diene systems, both in ring-B[62] and ring-D,[14] and with[62] or without[63] Lewis acid catalysis. For example, the diene (**8**) was reacted with propynal to give the cycloadduct (**101**) in high yield (Scheme 2.3-2).[14]

Scheme 2.3-2



For the cycloaddition of propynal to the diene (**27**), the method of choice was heating the diene (**27**), propynal and benzene at 80°C in a sealed tube for 39 h, to give exclusively the cycloadduct (**102**) (89%) (Scheme 2.3-3).

Scheme 2.3-3



Reagents: (i) Propynal, benzene, 80°C sealed tube, 39h.

The regio- and stereochemical assignments were based on precedent discussed previously.[6] The cycloadduct (**102**) displayed several diagnostic spectroscopic features, including an ultraviolet absorption band at λ_{max} 207 nm (ε 15649) as expected for an α,β-unsaturated aldehyde chromophore,[64] and characteristic infrared absorption bands at ν_{max} 1743 cm^{-1} and 1669 cm^{-1} for the acetyl carbonyl and aldehydic carbonyl groups. The NMR signals for the three vinylic protons on (**102**) were present. The signals for the 17^1 and 17^2-protons appeared as doublets (*J* 5.6 Hz) at δ 6.60 and 7.09, and the signal for the 15-proton appeared as a singlet at δ 7.61. In the ^{13}C spectrum of the aldehyde (**102**), the signal for C(15) occurred at δ 161.5, while those for C(17^1) and C(17^2) occurred at δ 141.1 and 138.5. The signal for C(13) is highly deshielded by the π-orbitals of the 15- and 17^1-olefinic bonds and appeared at δ 88.4.[42,43]

Contrary to expectations, the aldehyde (**102**) did not provide ready access to the desired intermediates. In the first instance, deoxygenation via thioketal formation was envisaged; however, attempted thioketalisation under a variety of conditions[65,66,67] was unsuccessful, resulting in complex mixtures of products. Attempts at differentiation of the

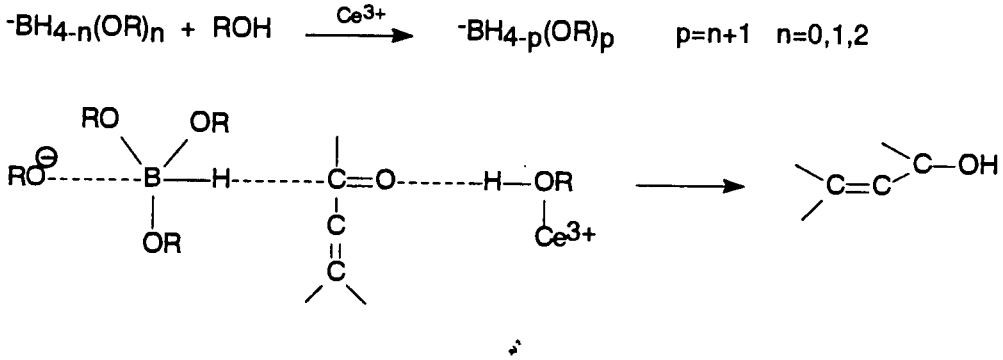
ring-D olefinic bonds through chemoselective dihydroxylation or hydrogenation were also unsuccessful, and resulted in intractable mixtures of products.

In the light of the success of conjugate addition of thiophenol to the unsaturated ester (**73**), the aldehyde (**102**) was treated with thiophenol, resulting once again in intractible mixtures of products.

Cerium(III)-mediated sodium borohydride reduction[68] was attempted on the aldehyde (**102**) in the hope of achieving selective 1,2-reduction. Luche *et al.*[69] have studied the mechanistic and stereochemical aspects of this reaction: sodium borohydride, being a nucleophilic reagent, causes reduction by attack at the centre of lowest electron density. Reduction of enones by sodium borohydride alone, invariably yields mixtures of saturated and unsaturated alcohols. Addition of cerium(III) chloride to the reaction medium promotes 1,2-reduction to give exclusively the allylic alcohols.

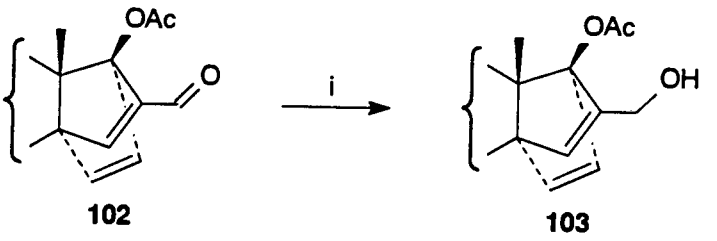
The authors[69] propose that the cerium^{3+} species catalyses the decomposition of BH_4^- by the solvent, to form the alkoxyborohydrides which act as the reducing agent. They deduced from the 'hard and soft acids and bases' theory that the substitution of hydrides by alkoxy groups on the boron anion (BH_4^-) increases the 'hardness' of the reductant. The carbonyl carbon is the 'hard' site of the conjugate enone system, and therefore attack is enhanced at this position (Scheme 2.3-4).

Scheme 2.3-4 Mechanism of Cerium^{3+}-Mediated 1,2-Reduction of Enones.



This methodology has been used in the synthesis of many natural products, where the 1,2-selectivity was necessary for unsaturated ketones[70,71,72,73] and aldehydes.[74] For our purposes, treatment of the aldehyde (**102**) with sodium borohydride and cerium(III) chloride in dichloromethane and methanol at -78°C for 30 min gave the allylic alcohol (**103**) in 75% yield (Scheme 2.3-5).

Scheme 2.3-5



102 **103**

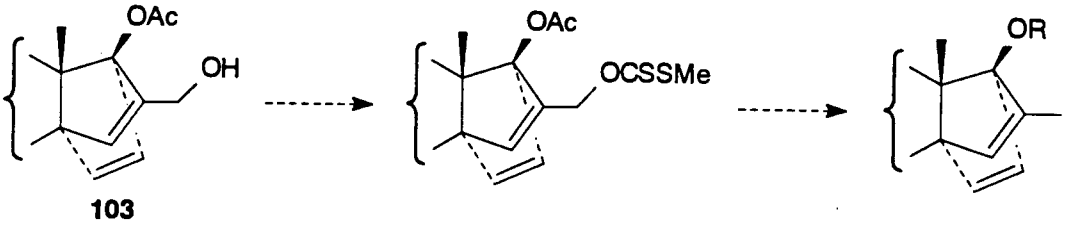
Reagents: (i) $CeCl_3.7H_2O$, $NaBH_4$, MeOH, CH_2Cl_2, -78°C, 30min.

Spectroscopic data of (**103**) supported this structural assignment. the NMR signals for the 16^1-protons each appear at δ 4.15 and 4.25, each as a doublet of doublets (*J* 13.6 and 1.2 Hz) in which the geminal coupling is accompanied by allylic coupling to the 15-proton. Correspondingly, the signal for the 15-proton appears at δ 6.47 as a triplet (*J* 2x1.2 Hz).

With the alcohol (**103**) in hand, it seemed reasonable to expect facile reductive deoxygenation of either the tosyloxy- or mesyloxy derivative; however, neither derivative could be successfully synthesised. Direct deoxygenation of the alcohol (**103**) was then attempted using a system designed for the one-pot deoxygenation of aliphatic-[75] and allylic alcohols.[76] Thus, treatment of the allylic alcohol (**103**) with chlorotrimethylsilane, sodium iodide and zinc gave intractable mixtures of products. It was also impossible to achieve chemoselective hydrogenation of the alcohol (**103**).

Another option which seemed reasonable was to prepare a xanthate derivative of the alcohol (**103**) (Scheme 2.3-6), which could subsequently be reduced to the 16-methyl diene.

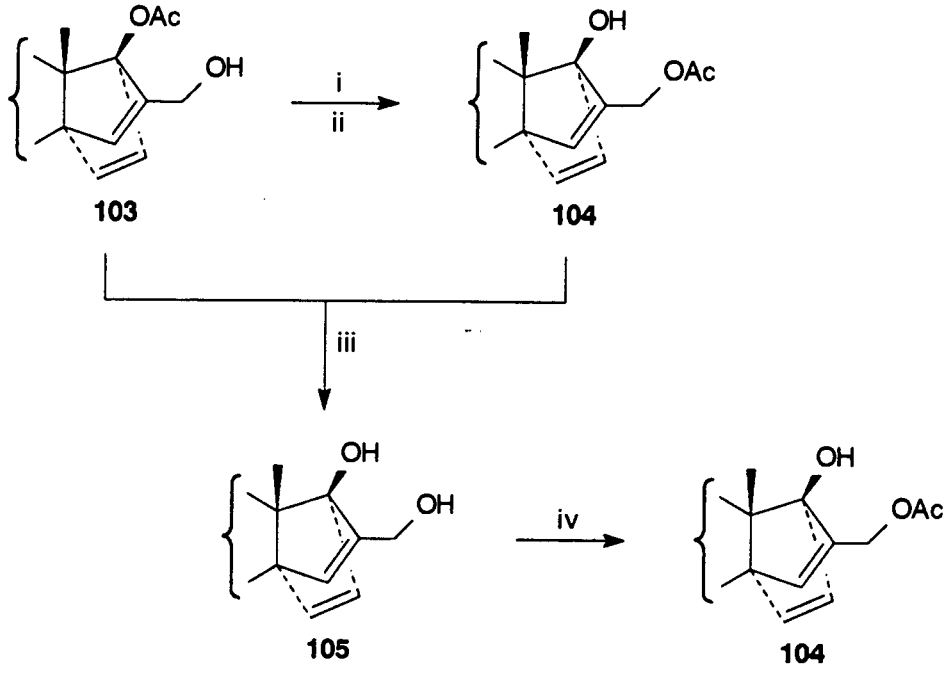
Scheme 2.3-6



103

However, treatment of the alcohol (**103**) with carbon disulfide, 1,5-diazabicyclo-[4.3.0]non-5-ene and methyl iodide[77] did not give the desired xanthate, but rather, a complex mixture of products, followed by the product of transacetylation (**104**) (22%) (Scheme 2.3-7).

Scheme 2.3-7



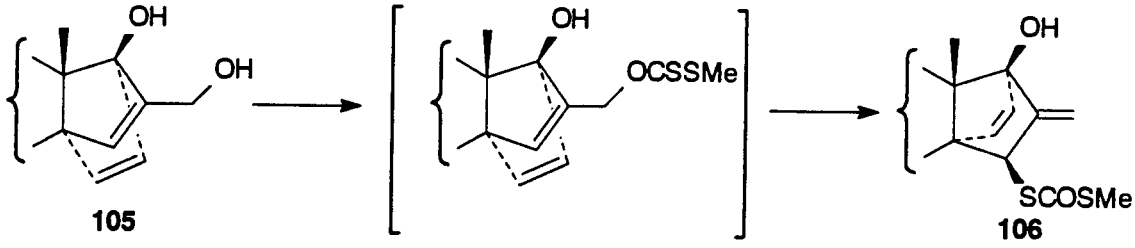
Reagents: (i) CS_2, DBN, DMF, 25°C, 30min. (ii) MeI, 25°C, 40 min. (iii) M KOH, THF, 25°C. (iv) Ac_2O, pyridine, 20°C, 4h.

Transacetylation was evident from the NMR spectrum of the allylic acetate (**104**). The signals for the 16^1-protons underwent a typical downfield shift of acetylation compared with those for the 16^1-alcohol (**103**), and appeared at δ 4.70 and 4.85 (each dd, *J* 12.7 and 1.1 Hz). The signal for the 15-proton appeared as a broad singlet at δ 6.57. The structure of the allylic acetate (**104**) was further verified by hydrolysis of both the 16^1-acetate (**104**) and 17-acetate (**103**) to a common diol (**105**), followed by chemoselective acetylation to give the 16^1-acetate (**104**) (Scheme 2.3-7).

In the light of this transacetylation, which could account for some of the difficulties experienced in earlier transformations, further reactions were performed on the diol (**105**). Attempted reductive deoxygenation of the diol (**105**) was unsuccessful and neither selective mesylation nor tosylation of the compound (**105**) could be achieved. Reaction with methanesulfonyl chloride in pyridine gave intractable mixtures of products, while no reaction was observed after prolonged treatment with toluene-*p*-sulfonyl chloride in pyridine.

Treatment of the diol (**105**) under conditions for xanthate formation, led to a non-crystalline rearrangement product formulated as *S*-methyl 17β-hydroxy-16-methylene-14,17α-ethenoestra-1,3,5(10)-triene-15-dithiocarbonate (**106**) (73%) (Scheme 2.3-8).

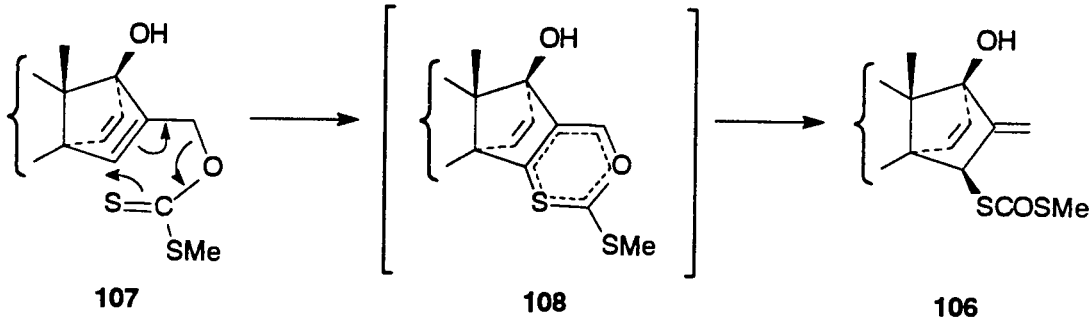
Scheme 2.3-8



Reagents: (i) CS_2, DBN, DMF, 0°C, 30min. (ii) MeI, 0°C, 15min.

Spectroscopic features which led to the conclusion that rearrangement to the thiocarbonate (**106**) had taken place, included a carbonyl absorption band at ν_{max} 1731 cm^{-1} in the infrared spectrum, a singlet in the NMR spectrum at δ 2.36 for the 15-thiocarbonate methyl protons, and signals for the two exo-methylene protons at δ 5.19 and 5.29 (each dd, *J* 1.8 and 0.4 Hz). The signal for the 15-proton appeared at δ 4.69 (t, *J* 2x1.8 Hz) and coupling between the 15- and 16^1-protons was confirmed by a crosspeak between these signals in the COSY spectrum. In the ^{13}C spectrum, the signal for the carbonyl carbon appeared at δ 190.6, for C(16^1) at δ 106.7, for C(16) at δ 156.2, and for C(15) at δ 51.8.

Scheme 2.3-9



The [3,3]-sigmatropic rearrangement of allylic xanthates is a well-known rearrangement pathway for allylic xanthates.[79] The mechanism of the reaction has been studied in detail,[80] and the reaction has been successfully applied synthetically.[78,81,82,83,84]

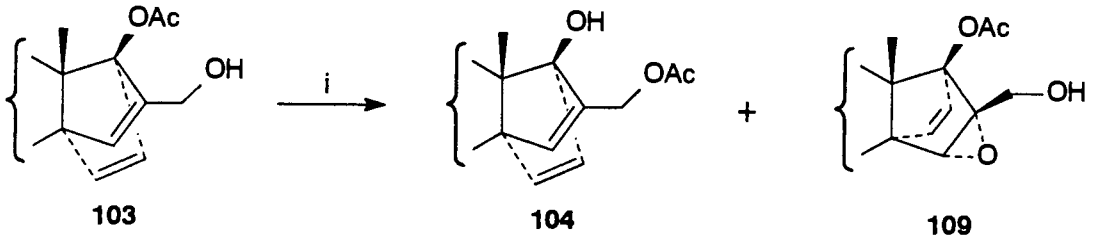
This transformation is known to be highly stereoselective,[78] however, the stereochemistry at C(15) of the dithiocarbonate (**106**) was difficult to assign with certainty. Examination of models of the xanthate (**107**) and the cyclic intermediate (**108**) (Scheme 2.3-9) revealed that both faces of the Δ^{15} bond are stereoelectronically equivalent, and the only steric impedance could arise from the 13β-methyl group on the *exo*-face. However, the magnitude of the long-range allylic coupling between the 16^1-methylene- and 15-protons

(1.8 Hz) indicates that the angle between the plane containing the olefinic protons and the C-H bond of the allylic carbon atom is approaching 90°.[59] Accordingly *exo*-approach of the xanthate group is proposed, to give an *endo*-proton on C(15).

With the thiocarbonate (**106**) in hand, the possibility existed for further manipulation to target compounds, or other structural variants. Ueno *et al.*[85] illustrated a method for the synthesis of terminal olefins, by reaction of thiocarbonates with tributyltin hydride. However, prolonged reaction of the thiocarbonate (**106**) with tributyltin hydride and α,α'-azobisisobutyronitrile in refluxing benzene was unsuccessful at removing the dithiocarbonate moeity, as was attempted desulfurisation using samarium(II) iodide / hexamethylphosphoric triamide at low and elevated temperatures; only starting material was isolated in both cases.

In the light of the failure of the diol (**105**) to undergo reductive deoxygenation, it was of interest to ascertain whether some other approach to chemoselective differentiation of the olefinic bonds in (**103**) could lead to intermediates more suitable to this purpose. Since chemoselective dihydroxylation of (**103**) had failed, the scope for chemoselective epoxidation was examined. Allylic alcohols are especially reactive towards epoxidation by *tert*-butyl hydroperoxide in the presence of vanadium catalysts, and many examples are available of the impressive stereoselectivity of these reactions.[86] This selectivity is attributed to the rate enhancement (*ca.* 10^3 times faster than the parent olefin) of epoxidation of allylic alcohols. However, treatment of the allylic alcohol (**103**) with *tert*-butyl hydroperoxide and vanadyl acetylacetonate in toluene, gave the product of transacetylation (**104**) (38%), followed by the product formulated as 15,16α-epoxy-16β-hydroxymethyl-3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate (**109**) (30%) (Scheme 2.3-10). The approach of the reagent was assumed to be *endo*, as this approach is supposedly favoured in these bicyclo[2.2.1]heptenoid systems,[a3.13] allowing assignment of the 15α,16α-epoxide moeity.

Scheme 2.3-10



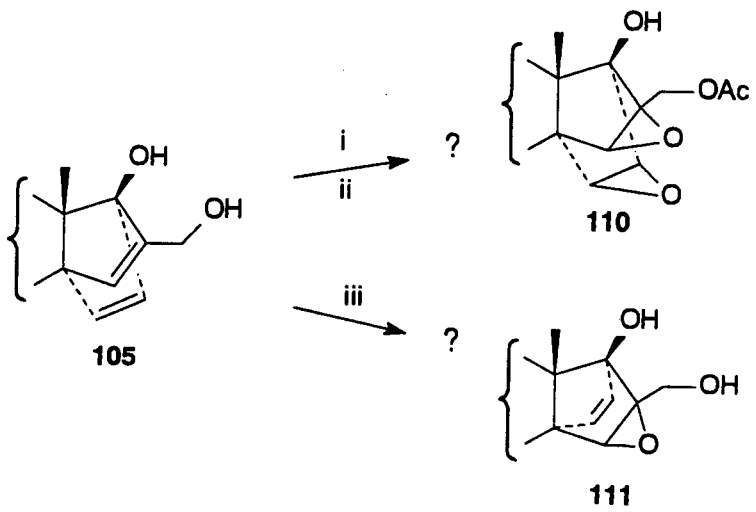
103 **104** **109**

Reagents: (i) *t*-BuOOH, $VO(acac)_2$, toluene, 20°C, 19h.

The analytical and spectroscopic data for the epoxide (**109**) supported this structural assignment, with the signal for the 15-proton in the NMR spectrum appearing as a singlet at δ 3.52, the signals for the 16^1-protons at δ 3.90 and 4.09 (each d, *J* 13.0 Hz), and signals for the etheno bridge protons at δ 5.90 and 6.14 (each 1H, d, *J* 5.6 Hz).

Once again, the interference of transacetylation led us to attempt the foregoing reaction on the diol (**105**). Treatment of the diol (**105**) with *tert*-butyl hydroperoxide and vanadyl acetylacetonate in toluene, gave a non-crystalline product of identical Rf to the starting diol, which was mono-acetylated due to difficulties experienced with its purification. The resultant acetate was initially thought to be the diepoxide (**110**) (Scheme 2.3-11); however, close examination of spectroscopic data revealed that these data did not support this structural assignment. The infrared spectrum showed two absorption bands at ν_{max} 3501 and 1746 cm^{-1}, and the NMR spectrum displayed signals inconsistent with attempted structural assignments: [δ 1.08 (3H, s, 13β-Me), 2.05 (3H, s, OAc), 3.39 (1H, dd, *J* 3.4 and 1.8 Hz), 3.78 (3H, s, 3-OMe), 3.89 (1H, d, *J* 12.0 Hz, disp. on D_2O exch.), 4.12 (1H, dt → t on D_2O exch., *J* 2x1.9 Hz), 4.18 (1H, dd, *J* 3.4 and 1.9 Hz), 4.52 and 4.64 (each 1H, d, *J* 11.8 Hz)]. The diepoxide (**110**) would be expected to display a singlet at *ca.* δ 3.50 for the 15-proton, and doublets at this chemical shift for both 17^1- and 17^2-protons.

Scheme 2.3-11



Reagents: (i) *t*-BuOOH, $VO(acac)_2$, toluene, 25°C, 4.5h. (ii) Ac_2O, pyridine, 25°C, 3h. (iii) *t*-BuOOH, $VO(acac)_2$, $CHCl_3$, 0°C, 50min.

A similar problem was encountered on attempted selective epoxidation of the diol (**105**), thus treatment of the diol (**105**) with *tert*-butyl hydroperoxide and vanadyl acetylacetonate in chloroform at 0°C gave a complex mixture having Rf identical to that of starting material, followed by an unidentifiable compound (33%). Examination of analytical

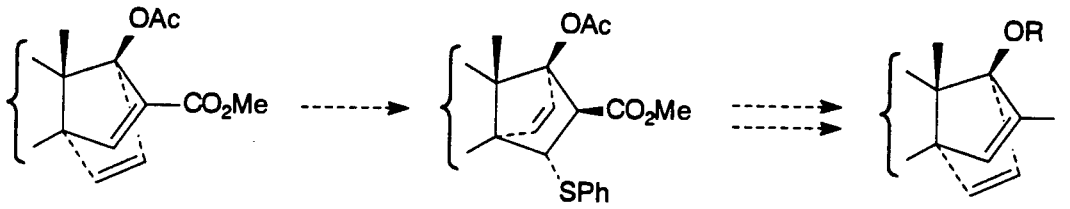
data (M^+ 354.1813) led us to suspect the presence of the mono-epoxide (**111**) (Scheme 2.3-11), however, the NMR spectrum displayed signals inconsistent with this structural assignment: [δ 1.13 (3H, s, 13β-Me), 3.78 (3H, s, 3-OMe), 3.98 and 4.10 (each 1H, d, *J* 12.0 Hz), 4.62 (1H, t, 1.2 Hz), 5.94 (1H, dt, *J* 5.7 and 2x1.1 Hz), 6.67 (1H, obsc d, *J* 5.7 Hz)]. The monoepoxide (**111**) would be expected to display a singlet at *ca.* δ 3.50 for the 15-proton, and a deshielded doublet for each of the 17^1- and 17^2-protons.

From the results obtained in this chapter, we concluded that the propynal cycloadduct and its derivatives do not give ready access to key intermediates in the overall synthetic sequence, nor do they facilitate chemoselective investigations of these bicyclo[2.2.1]-heptadienoid systems. This route was therefore abandoned.

2.4 Synthesis of 3-Methoxy-16-methyl-14,17α-ethenoestra-1,3,5(10),15-tetraen-17β-ol.

The success of the route to the 16-methyl olefin (**97**) (Chapter 2.2.4) via conjugate addition of thiophenol to the olefin (**73**), initiated the plan for a similar synthetic sequence upon the cycloadduct (**72**), in the hope that the corresponding 16-methyl diene could be prepared (Scheme 2.4-1).

Scheme 2.4-1



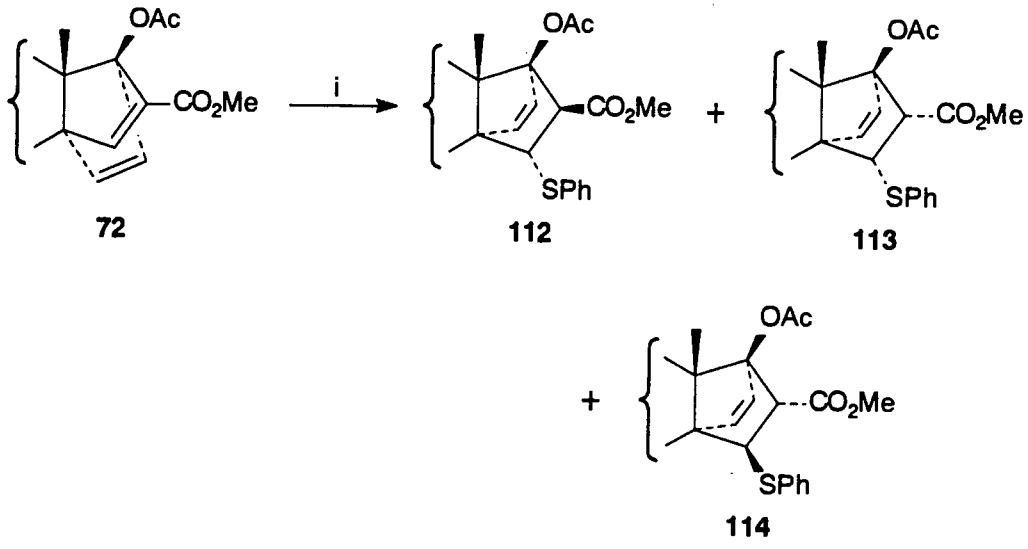
72

However, this reaction sequence was attended by complications. In the first place, conjugate addition of thiophenol to the cycloadduct (**72**) failed to proceed stereoselectively as in the case of the dihydrocycloadduct (**73**). Thus treatment of (**72**) with thiophenol at 20°C, followed by chromatography of the reaction mixture gave a major product (**112**) (60%), followed by an inseparable chromatographic fraction (36%), which was clearly a mixture (Scheme 2.4-2).

The major product was formulated as methyl 17β-acetoxy-3-methoxy-15α-phenylthio-14,17α-ethenoestra-1,3,5(10)-triene-16β-carboxylate (**112**) on the basis of spectroscopic data. Thus, in the NMR spectrum of the phenylsulfide (**112**), the signals for the 15β- and 16α-protons appeared at δ 3.44 and 2.45 (each d, *J* 4.5 Hz). The magnitude of this coupling indicated the *trans*-relationship between these protons, and the stereochemistry at C(15) and C(16) was assumed from the results obtained in Chapter 2.2.4.

The more polar fraction from column chromatography was shown by spectroscopy to be a mixture of two compounds (*ca.* 1:2.5) formulated as the 15α,16α-functionalised compound (**113**) and the 15β,16α-functionalised compound (**114**) (Scheme 2.4-2). The NMR spectrum of the mixture displayed doubling of key signals indicating the presence of an isomeric mxture [0.79 and 1.30 (each s, 13β-Me), 1.69 and 1.71 (each s, 17β-OAc), 3.35 and 3.40 (each s, 16-CO_2Me), 3.39 and 3.42 (each s, 3-OMe)]. The doublets at δ 3.76 and 3.84 (*J* 4.8 Hz) were assigned to the 15α- and 16β-protons of (**114**), and the doublets at δ 3.88 and 2.44 (*J* 9.2 Hz), to the 15β- and 16β-protons of (**113**).

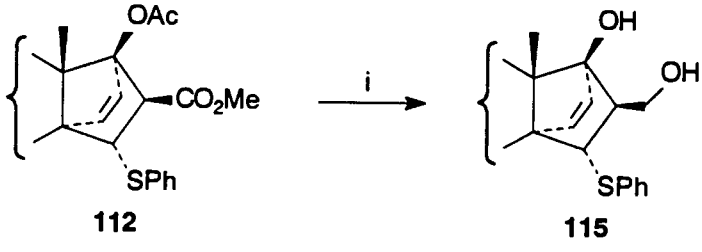
Scheme 2.4-2



Reagents: (i) Diisopropylamine, thiophenol, 20°C, 22h.

The major product of conjugate addition, the 15α-phenylsulfide (**112**), was treated with lithium aluminium hydride in tetrahydrofuran for 1 h, to give a poor yield (48%) of the expected diol (**115**) (Scheme 2.4-3), the NMR spectrum of which showed the expected signals. After D_2O exchange, the signals for the 16^1-protons appeared as a doublet of doublets at δ 3.46 (*J* 10.7 and 4.6 Hz) and a triplet at δ 4.15 (*J* 2x10.7 Hz), and the signal for the 15β-proton appeared as a doublet at δ 3.38 (*J* 5.1 Hz).

Scheme 2.4-3

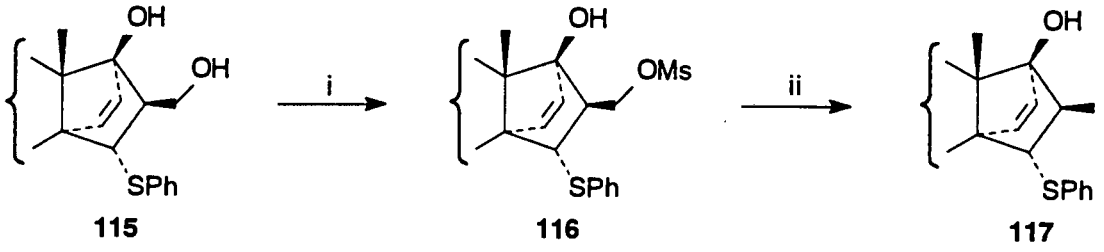


Reagents: (i) LAH, THF, 20°C, 1h.

Potentiation and elimination of the 16^1-functionality on the diol (**115**) proceeded smoothly, and was achieved as before (Scheme 2.4-4). Thus, reaction of the diol (**115**) with methanesulfonyl chloride in pyridine gave the intermediate 16^1-mesylate (**116**), which was not characterised, but immediately reduced with lithium aluminium hydride to give non-

crystalline 3-methoxy-16β-methyl-15α-phenylthio-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol (**117**). The conversion from the diol (**115**) to the 16-methyl compound (**117**) proceeded in good yield (73%), in contrast to the previous steps. The structural assignment of the 16-methyl compound (**117**) was supported by analytical and spectroscopic data.

Scheme 2.4-4

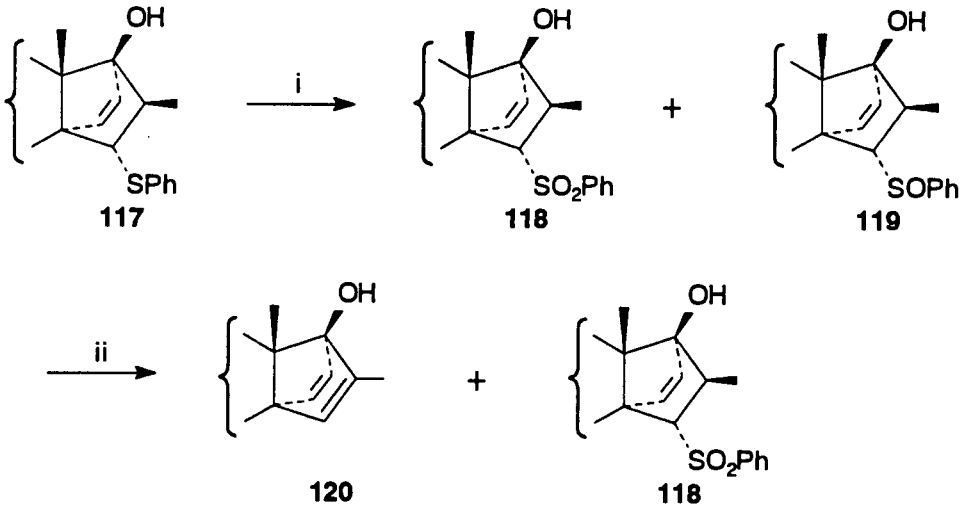


115 **116** **117**

Reagents: (i) MsCl, pyridine, 0°C, 1h. (ii) LAH, THF, 20°C, 12h.

The reaction sequence was then completed unexceptionally through oxidative elimination of the thiophenol group. In this case, oxidation of the phenylsulfide (**117**) gave a mixture of the desired intermediate sulfoxide (**119**), accompanied by the product (**118**) of overoxidation (Scheme 2.4-5). The crude mixture was not separated or characterised, but immediately subjected to conditions for thermal elimination to give the readily separable mixture of the expected 16-methyl diene (**120**) (42%) and the residual sulfone (**118**) (22%).

Scheme 2.4-5



117 **118** **119**

120 **118**

Reagents: (i) Aq. $NaIO_4$, EtOH, 20°C, 16h. (ii) Triethylamine, benzene, 120°C sealed tube, 16h.

The structural assignment of the 16-methyl diene (**120**) was supported by spectroscopic data. The signals in the NMR spectrum for the vinyl protons appeared as expected [δ 6.50 (d, *J* 5.6 Hz, 17^1-H), 6.60 (dd, *J* 5.6 and 0.9 Hz, 17^2-H), 6.06 (q, *J* 3 x 1.9 Hz, 15-H)], and

the signal for the 16-methyl protons appeared as a doublet at δ 1.83 (*J* 1.9 Hz). The familiar deshielding of C(13) by the two ring-D olefinic bonds was once again illustrated in the ^{13}C spectrum of the diene (**120**), where the signal for C(13) appeared at δ 84.9.[42,43] The structural assignment of the sulfone (**118**) followed from analytical and spectroscopic data, including the NMR signals [δ 0.44 (d, *J* 7.2 Hz, 16β-Me), 3.09 (d, *J* 5.4 Hz, 15β-H), 6.08 (d, *J* 6.1 Hz, 17^2-H), 6.20 (d, *J* 6.1 Hz, 17^1-H)].

Although the foregoing route did lead to the successful synthesis of the 16-methyl diene (**120**), the overall yield (8%) from dienyl acetate (**27**) was inadequate for further exploration of the chemoselective reactivity of the respective olefinic bonds, and further work was discontinued.

CHAPTER 3

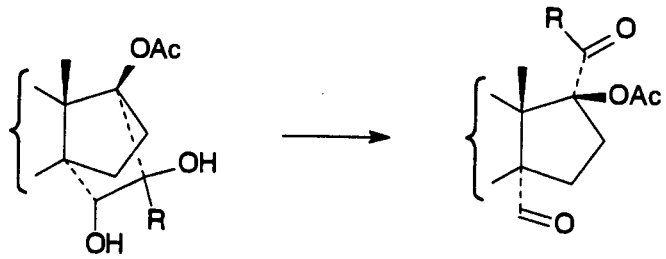
Synthesis and Reactions of 14β-Formyl 19-Norsteroids

3.1 Oxidative Cleavage Routes to 19-Norpregna-1,3,5(10)-triene-14β-carbaldehyde.

The successful completion of synthetic routes to the 16-methyl 15,16-diols (**68**) and (**83**), and the derived triols (**89**) and (**99**), set the scene for an investigation into oxidative cleavage, leading to 14β-formyl 19-norsteroids.

A synthetic route to 14α-functionalised-alkyl systems has been described[19] using oxidative cleavage of α-bridged diols (Scheme 3.1-1), and extension of this methodology to include a 17^1-methyl group (as in **122**)[17] provided entry into 14α-functionalised 19-norpregna-1,3,5(10)-trienes (**26**).

Scheme 3.1-1

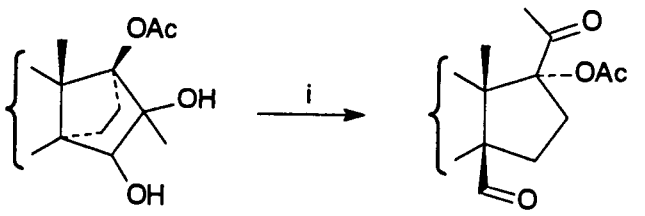


121 R=H
122 R=Me

35 R=H
26 R=Me

Accordingly, the analogous reaction of the β-bridged diols was examined. When (**83**) and (**68**) were treated, individually or as a mixture, with aqueous sodium periodate in ethanol, 17α-acetoxy-3-methoxy-20-oxo-19-nor-14β-pregna-1,3,5(10)-triene-14-carbaldehyde (**123**) was obtained in high yield (95%) (Scheme 3.1-2). This compound was an essential intermediate for much of the subsequent work in this study, and the structural assignment was supported by spectroscopic evidence. The infrared spectrum displayed absorption bands at ν_{max} 1731 (OAc and 20-CO) and 1711 (14^1-CO) cm^{-1}, and the NMR spectrum displayed signals for the two acetyl methyl groups [δ 2.04 and 2.15 (each 3H, s)] and for the aldehydic proton [δ 9.67 (1H, s)] (see Appendix for NMR spectra).

Scheme 3.1-2



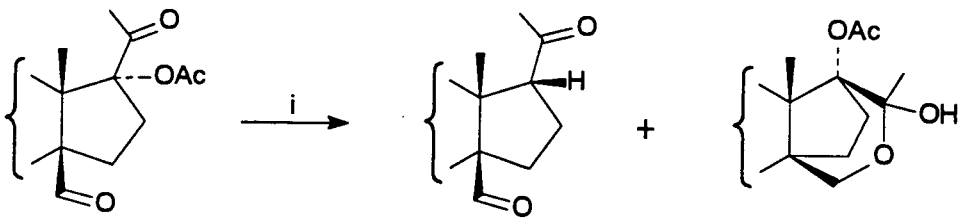
83 15α,16α-OH
68 15β,16β-OH

123

Reagents: (i) $NaIO_4$, EtOH, 20°C, 4h.

Further elaboration of the carbaldehyde (**123**) into 19-norpregnatriene derivatives required deacetoxylation at C(17). Molander and Hahn[87] found that instantaneous reduction of a broad spectrum of α-heterosubstituted ketones could be achieved with samarium(II) iodide under mild conditions and in high yields. The optimum conditions for their experiments were found to be samarium(II) iodide at -78°C in tetrahydrofuran and methanol. The optimum conditions for complete reaction of the carbaldehyde (**123**), following numerous experimental variations of solvent, temperature and concentration of reagent, were found to be treatment with samarium(II) iodide in tetrahydrofuran at 0°C for 15 h (Scheme 3.1-3). The two products which were isolated after chromatography, were formulated as 3-methoxy-20-oxo-19-nor-14β,17α-pregna-1,3,5(10)-triene-14-carbaldehyde (**124**) (18%), and the lactol (**125**) (48%), which had Rf identical to that of the starting material (**123**).

Scheme 3.1-3



123 **124** **125**

Reagents: (i) SmI_2, THF, 0°C, 15h.

The structure of the carbaldehyde (**124**) was evident from appropriate spectroscopic features, including an infrared absorption band at ν_{max} 1705br cm^{-1}, and the expected NMR signals [δ 2.12 (s, 20-Me), 2.71 (t, *J* 2x9.6 Hz, 17β-H), 9.62 (1H, d, *J* 1.3 Hz, 14β-CHO)]. The stereochemical assignment at C(17) was based on analogy; it is documented[88,89,90] that for 14β-substituted 19-norsteroids (Figure 3.1-1), an α-proton on C(17) couples to the 16-protons with one small (*J ca.* 3 Hz) and one large (*J ca.* 8 Hz) coupling. A β-proton on C(17) on the other hand, experiences two large couplings (*J ca.* 8 Hz) to the adjacent protons. Figure 3.1-1 shows a Newman projection of these systems viewed down the C(16) → C(17) bond, illustrating the difference in torsion angle between the 17α- and β-protons, and the 16-protons. The 17α-proton has torsion angles of *ca.* 10° and 100°, whereas the 17β-proton has angles of *ca.* 10° and 170°. According to the vicinal Karplus correlation between dihedral angle of vicinal protons and their coupling constant (*J*),[53] the stereochemical assignment at C(17) of the carbaldehyde (**124**) is thus justified.

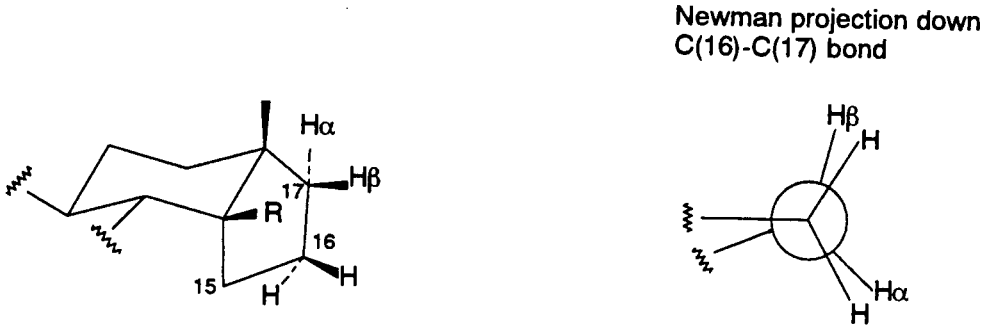
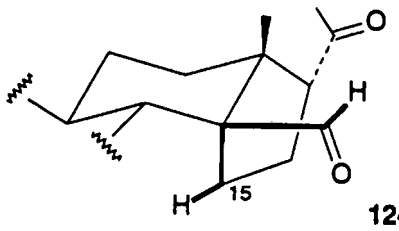


Figure 3.1-1 The Relationship between 17- and 16-Protons on 14β-Substituted 19-Norsteroids.

The NMR signal for the aldehydic proton, which appeared as a doublet with a typically small long-range coupling constant (*J* 1.3 Hz), provided insight into the preferred conformation of the 14-substituent, as the 14^1-proton was most likely W-coupled to the 15α-proton (Figure 3.1-2). However, the presence of the 14-carbonyl group precludes definite conformational assignments as the influence of this group on long-range coupling effects is not well understood.

The clarity of the signal for the 17-proton, and the coupling between the 14^1- and 15-protons, enabled assignment of the signals for C(15) and C(16) in the ^{13}C NMR spectrum of (**124**), by investigation of the crosspeaks in the COSY and HETCOR spectra. These two signals are usually difficult to distinguish from those for other secondary carbon centres in the ^{13}C spectrum.

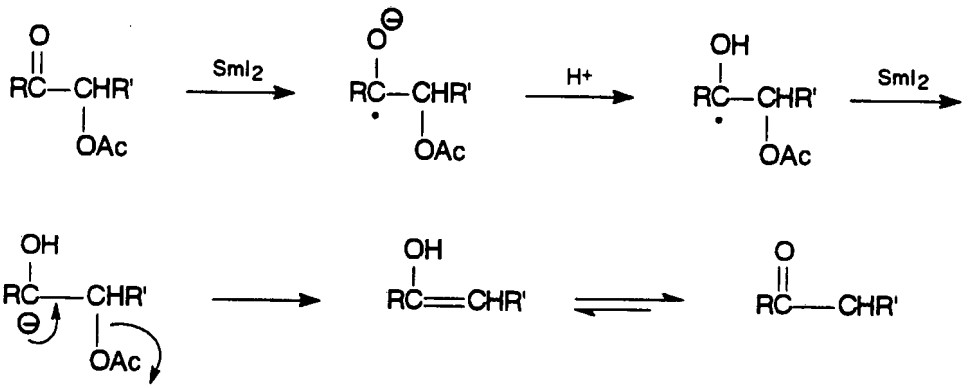


124

Figure 3.1-2 Preferred Conformation of the 14β-Formyl 20-Ketone (**124**).

The mechanism proposed[87] for this type of deacetoxylation by samarium(II) iodide, involves initial generation of a ketyl radical (Scheme 3.1-4), followed by rapid protonation of the anion. Further reduction by the second equivalent of samarium(II) iodide produces a carbanion, inducing elimination of the acetoxy group, followed by tautomerisation to give the ketone.

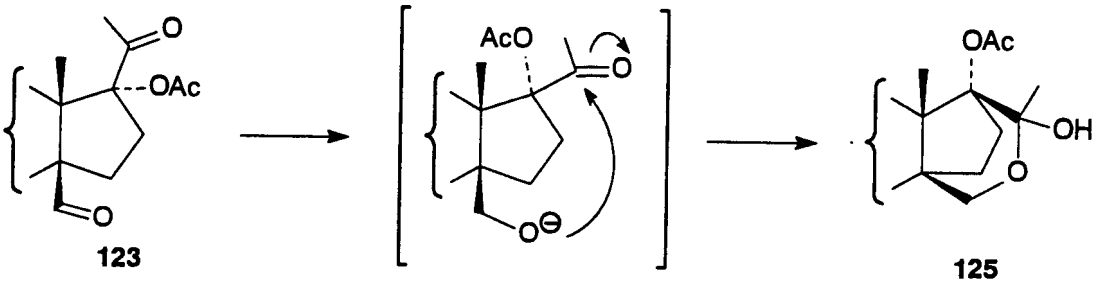
Scheme 3.1-4 Mechanism of Samarium(II) Iodide Mediated Deacetoxylation.



The lactol (**125**) was the more polar product of reaction with samarium(II) iodide, and is the result of initial reduction of the exposed aldehyde on the starting carbaldehyde (**123**), followed by hemiacetal formation and protonation (Scheme 3.1-5) to give the cyclised product (**125**).

The NMR spectrum of the lactol (**125**) displayed signals consistent with this structural assignment [δ 1.34 (s, 20-Me), 2.12 (s, 17α-OAc), 3.40 (d, *J* 7.3 Hz, 14^1-H*endo*), 3.74 (dd, *J* 7.3 and 2.1 Hz, 14^1-H*exo*)]. Examination of a model of the lactol (**125**) revealed that the 14^1*exo*- and 15α-protons are appropriately orientated for long-range W-coupling.

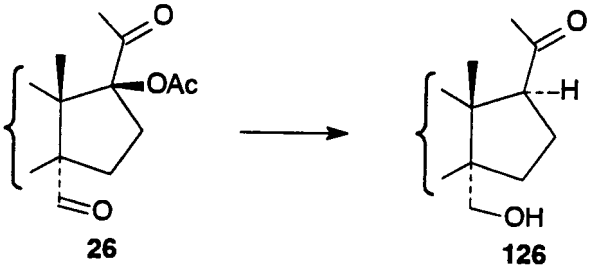
Scheme 3.1-5



Failure of the foregoing approach to yield the product of deacetoxylation in reasonable yield resulted in consideration of an alternative method.

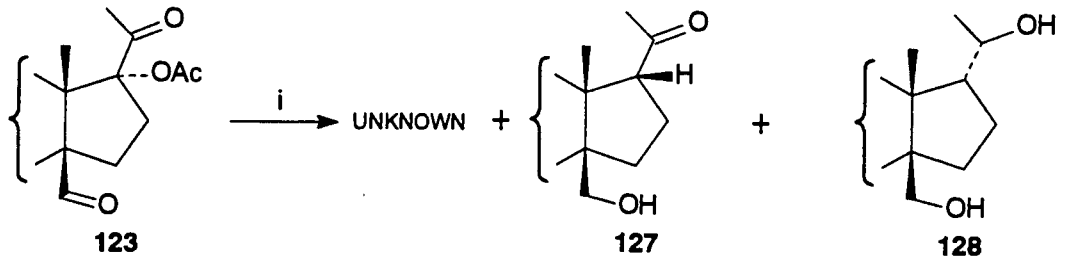
Part of a study towards 14α-functionalised 19-norsteroids[17] involved the reductive deacetoxylation of the carbaldehyde (**26**) by calcium in liquid ammonia (Scheme 3.1-6) to give the product (**126**) in high yield. An added advantage of this result was that reduction of the 14-aldehyde gave attendant differentiation of functionality at C(14[1]) and C(20).

Scheme 3.1-6



Reaction of the carbaldehyde (**123**) with calcium in liquid ammonia at -78°C for 20 min resulted in a mixture of three separable products (Scheme 3.1-7). The structure of the first product eluted from chromatography (*ca.* 16%) was impossible to assign, although the absence of an appropriate signal in the NMR spectrum indicated that deacetoxylation had occurred. Other significant signals in the NMR spectrum were a singlet at δ 2.20 (3H), a triplet at δ 3.05 (1H, *J* 2x9.9 Hz) and a doublet at δ 4.14 (1H, *J* 6.1 Hz → singlet on D_2O exchange). The accurate mass determination gave a molecular ion peaks at 340.2020 which is consistent with $C_{22}H_{28}O_3$.

Scheme 3.1-7



Reagents: (i) Ca-NH_3, -78°C, 20min.

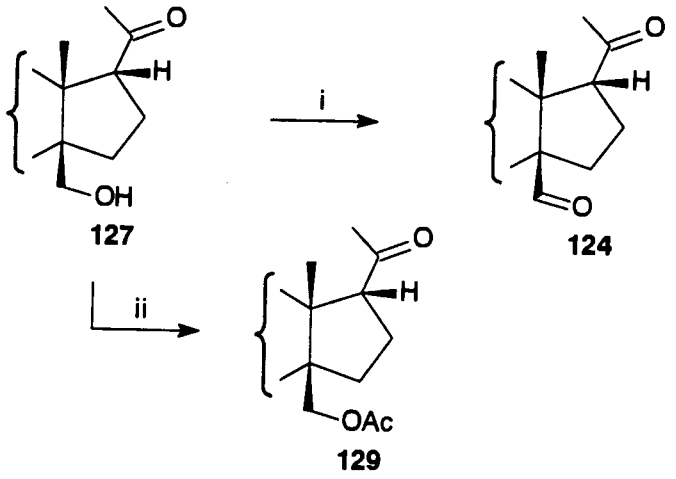
The second eluted product was non-crystalline 14-hydroxymethyl-3-methoxy-19-nor-14β,17α-pregna-1,3,5(10)-trien-20-one (**127**) (46%). This structural assignment was supported by spectroscopic evidence. The signal in the NMR spectrum for the acetyl methyl group appeared, as expected, as a singlet at δ 2.17, and the signal for the 17β-proton appeared at δ 3.22 (t, *J* 2x8.8 Hz) thus the 17α-acetyl stereochemistry could be assigned with confidence. Reduction at C(14^1) was evident from the signals for the 14^1-protons at δ 3.62 and 3.82 (each d, *J* 11.7 Hz).

The third compound was the product of over-reduction (**128**) (12%), the structure of which was verified spectroscopically. In the NMR spectrum, the signal for the 20-methyl protons appeared at δ 1.16 (d, *J* 6.3 Hz), and the corresponding signal for the 20-proton appeared partially obscured at δ 3.83, with the 6.3 Hz coupling visible. The 14^1-protons appeared at δ 3.58 and 3.82 (each d, *J* 12.0 Hz on D_2O exchange).

In order to verify the structure of both the 14^1-aldehyde (**124**) and 14^1-alcohol (**127**), the alcohol was oxidised under Dess-Martin conditions (Scheme 3.1-8), to give the aldehyde, which had spectroscopic data identical to that of (**124**).

Both the aldehyde (**124**) and the alcohol (**127**) were non-crystalline; accordingly further verification of structure was obtained by acetylation of the alcohol (**127**) to give the crystalline acetate (**129**) (75%) (Scheme 3.1-8), which was fully characterised. The spectroscopic characteristics of the acetate (**129**) were similar to those of the alcohol (**127**), the obvious differences being the signals in the infrared (ν_{max} 1718 cm^{-1}) and NMR (δ 2.04, 3H, s) spectra for the acetate group. The 17β-proton appeared in the NMR spectrum at δ 3.14 (dd, *J* 8.8 and 8.6 Hz) and the signals for the 14^1-protons were slightly deshielded at δ 4.08 and 4.20 (each d, *J* 12.3 Hz).

Scheme 3.1-8



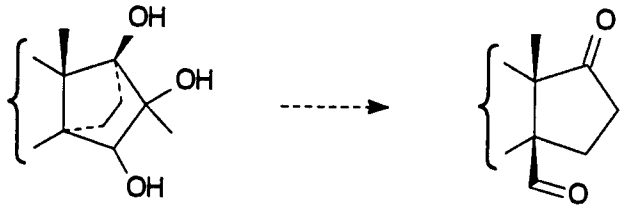
Reagents: (i) 1,1,1-triacetoxy-2,1-benzoxiodol-3(3H)-one, CH_2Cl_2, 20°C, 10min. (ii) Ac_2O, pyridine, 20°C, 6h.

Further synthetic modification of the alcohol (**127**) was not taken to its natural conclusion, that is Birch reduction of ring-A to give the 19-norprogesterone analogue, as insufficient material was available for this purpose. The investigation of the foregoing series of compounds provided insight into the reactivity of these systems, and target compounds, albeit in low yield, were synthesised. However, the selectivity of the attempted reactions was poor under the conditions described in this work. It is evident that further work on these approaches to 14β-functionalised 19-norpregna-1,3,5(10)-triene systems and their 19-norprogesterone analogues will be necessary in order to achieve a practical synthesis of the target compounds. The scarcity of starting material resulted in termination of this investigation.

3.2 Oxidative Cleavage Routes to Estrone 14β-Carbaldehyde.

Successful oxidative cleavage of the 15,16-diols (**68**) and (**83**) to the 19-norpregnatriene derivatives in the previous chapter invited extension of this methodology to double oxidative cleavage of the triols (**89**) and (**99**) to give the formyl ketone (**144**) (Scheme 3.2-1). This methodology was successfully utilised by Bull *et al.*[19] to synthesise the 14α-formyl analogues of estrone (see Scheme 1-13).

Scheme 3.2-1



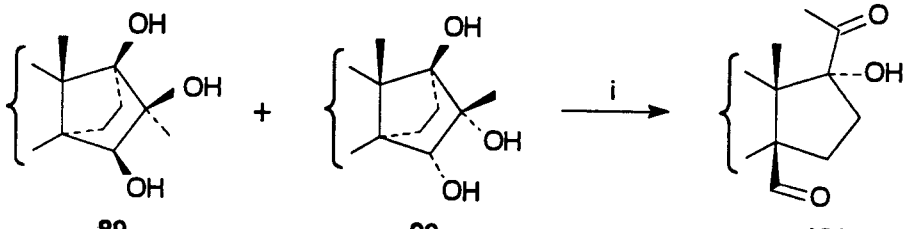
89 15β,16β-OH
99 15α,16α-OH

144

However, treatment of the triols (**89**) and (**99**) (individually or as a mixture) with excess aqueous sodium metaperiodate in ethanol at 20°C for 2 h gave quantitative yields of the α-hydroxy-ketone (**131**) (Scheme 3.2-2). The compound (**131**) displayed the familiar spectroscopic features of these systems: a broad infrared absorption band at ν_{max}1708 cm^{-1}, and the expected NMR signals [δ 1.11 (s, 13β-Me), 2.21 (s, 20-Me), 3.17 (s, 3-OMe) and 9.62 (s, 14β-CHO)].

The reaction had obviously been arrested after initial cleavage of the 15,16-diol, with no hydration of the 20-ketone occurring to enable further cleavage, even after extended reaction times.

Scheme 3.2-2

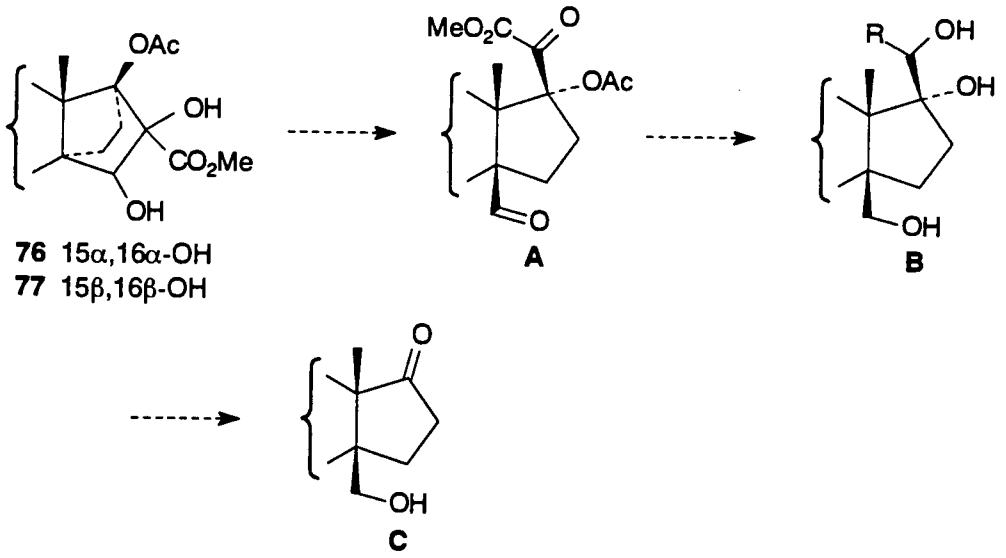


89 **99** **131**

Reagents: (i) $NaIO_4$, EtOH, 20°C, 2h.

In principle, it should be unnecessary to use advanced intermediates such as the triols (**89**) and (**99**), since their precursors could serve as well if C(16) and its attached ligands are to be lost during oxidative cleavage. Accordingly, a reaction sequence was envisaged (Scheme 3.2-3) utilising the diols (**76**) and (**77**) (see Chapter 2.2) for oxidative cleavage to the formyl ketone (**A**), followed by reduction to the triol (**B**) and cleavage to the 14β-hydroxymethyl ketone (**C**).

Scheme 3.2-3

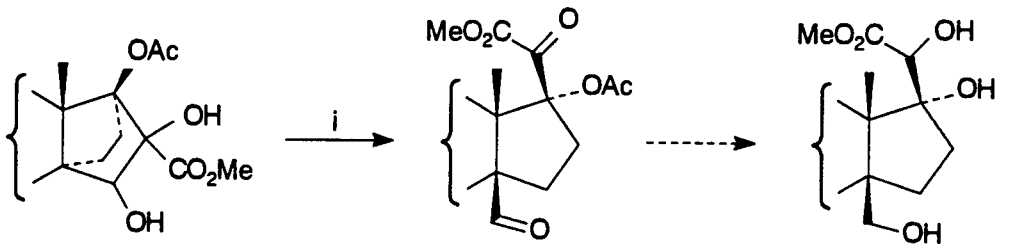


76 15α,16α-OH
77 15β,16β-OH

A **B** **C**

Synthetically, this route would be advantageous as the starting diols were obtained in high yield, and could immediately be converted to a common intermediate. Accordingly, the diols (**76**) and (**77**) (individually or as a mixture) were treated with aqueous sodium periodate in ethanol for 30 min at 20°C to give high yields (*ca.* 90%) of methyl 17-acetoxy-14-formyl-3-methoxy-20-oxo-19-nor-14β-pregna-1,3,5(10)-trien-20-oate (**132**) (Scheme 3.2-4). This structural assignment was supported by the infrared absorption bands (ν_{max} 1740, 1725, and 1715 cm^{-1}) and by signals in the NMR spectrum of the 14β-formyl 20-ketone (**132**) [δ 2.10 (s, 17α-OAc), 3.76 (s, 20-CO_2Me), and 9.65 (s, 14β-CHO)].

Scheme 3.2-4



76 15α,16α-OH
77 15β,16β-OH

132

D

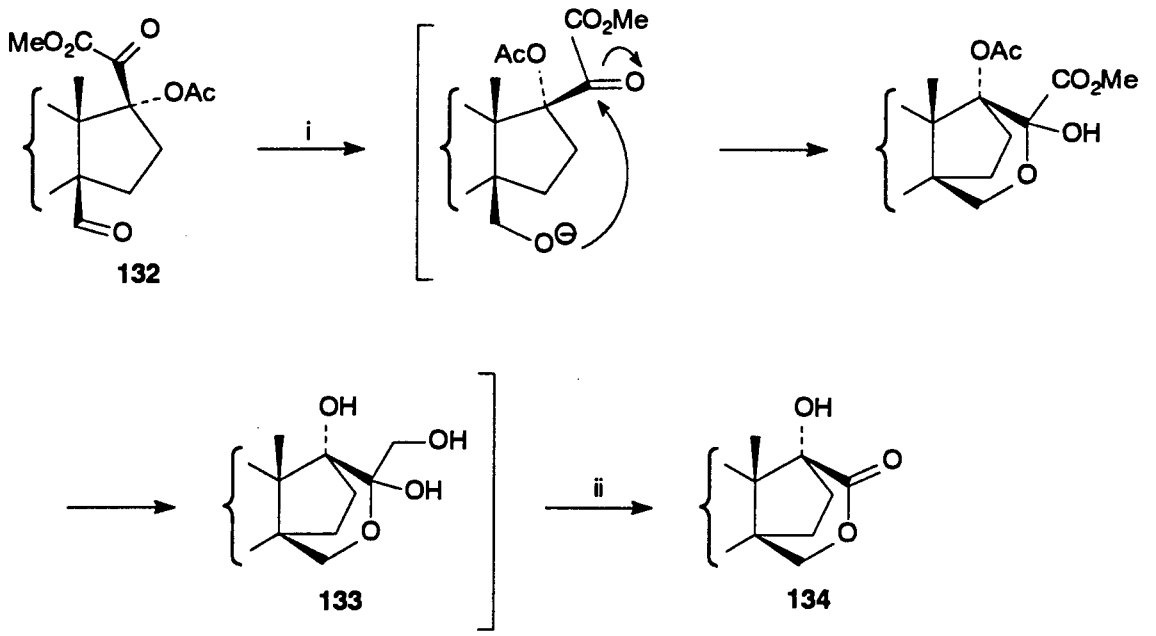
Reagents: (i) $NaIO_4$, EtOH, 20°C, 30min.

The most conservative manipulation of the dicarbonyl compound (**132**) would be chemoselective reduction to retain the methyl ester functionality while reducing the other susceptible ring D functionalities, to give the triol (**D**) (Scheme 3.2-4). However, treatment of the formyl ketone (**132**) with sodium borohydride or L-Selectride® led to complex mixtures which were not simplified by subsequent reaction with periodate or lead tetraacetate.

An alternative reductive approach was then adopted. Thus, treatment of the formyl ketone (**132**) with lithium aluminium hydride in refluxing tetrahydrofuran for 4 h gave a highly polar product, presumed to be the triol (**133**) (Scheme 3.2-5), the high polarity of which precluded adequate characterisation. Subsequent periodate treatment of this compound (**133**) furnished a product formulated as the δ-lactone (**134**) (56% from **132**). The infrared spectrum of the lactone (**134**) displayed absorption bands at ν_{max} 3521 and 1726 cm^{-1}, consistent with an α-hydroxy δ-lactone structure, and the ^1H NMR spectrum showed multiplets at δ 4.15 (dd, *J* 10.7 and 1.9 Hz), and 4.37 (d, *J* 10.7 Hz) consistent with the 14^1-protons; the geminal coupling of the 14^1_{exo}-proton is accompanied by the smaller W-coupling to the 15α-proton, which is typical of the four-bond couplings frequently encountered in these bridged systems.

From this result, it was concluded that initial reduction of the 14^1-aldehyde had taken place, being intercepted as a 14^1,20-hemiacetal. Further reduction at C(21) and C(17) gave the highly polar presumed intermediate (**133**), which underwent selective periodate cleavage of the C(20)-C(21) bond to give (**134**) (Scheme 3.2-5).

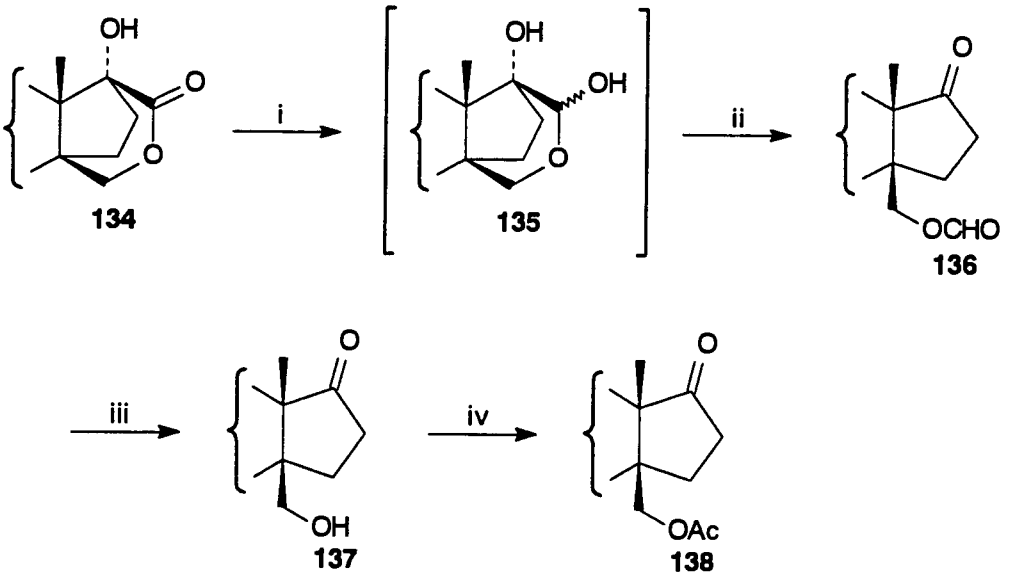
Scheme 3.2-5



Reagents: (i) LAH, THF, 80°C, 4h. (ii) $NaIO_4$, EtOH, 20°C, 10h.

Further evidence for the structure of the δ-lactone (**134**) was obtained through a reductive-oxidative cleavage reaction sequence. Thus, (**134**) was treated with lithium aluminium hydride at 20°C and no attempt was made to isolate or characterise the presumed lactol intermediate (**135**), but the total reaction product was treated with lead tetraacetate to give the 14β-formyloxymethyl 17-ketone (**136**) (70%) (Scheme 3.2-6). Several spectroscopic features of this product supported the proposed structural assignment, including the infrared absorption band at ν_{max} 1724 cm^{-1}, and NMR signals at δ 4.03 and 4.36 (each d, *J* 11.4 Hz, 14^1-H_2), and 8.01 (s, 14^1-OCHO).

Scheme 3.2-6

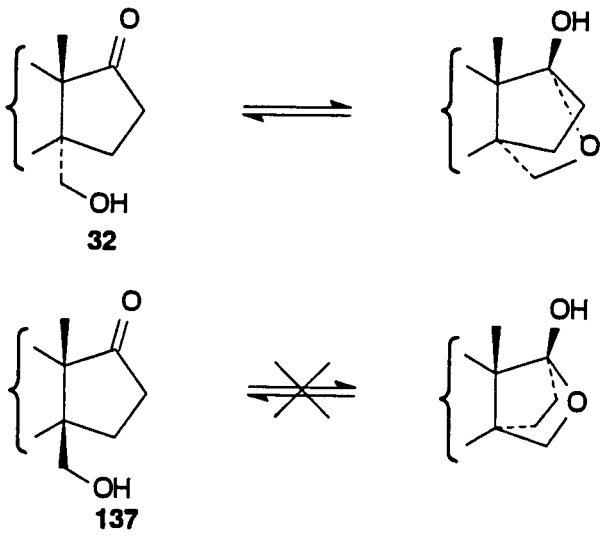


Reagents: (i) LAH, THF, 20°C, 2h. (ii) LTA, THF, 25°C, 20min. (iii) M KOH in MeOH, THF, 25°C, 5min. (iv) Ac_2O, DMAP, pyridine, 20°C, 2h.

Alkaline hydrolysis of the formyloxymethyl ketone (**136**) gave 14-hydroxymethyl-3-methoxy-14β-estra-1,3,5(10)-trien-17-one (**137**) in high yield (95%) (Scheme 3.2-6). The spectroscopic features of the hydroxymethyl ketone (**137**) which supported this structural assignment were the infrared absorption bands (ν_{max} 3434 and 1724 cm^{-1}) for the hydroxy- and carbonyl groups, and the NMR signals for the 14^1-protons. Both protons coupled to the 14^1-hydroxy group prior to D_2O exchange, and the signals therefore appeared at δ 3.57 and 3.88 as doublets of doublets with geminal coupling of 10.4 Hz and exchangeable couplings of 3.1 and 3.8 Hz. After D_2O exchange, the signal at δ 3.88 was a doublet as expected, but the signal at δ 3.57 remained a doublet of doublets, now with smaller coupling of 0.9 Hz. This implied that prior to D_2O exchange, the latter coupling was not resolved, and became visible thereafter. This coupling was attributed to W-coupling between one of the 14^1-protons and the 15α-proton. Unlike the 14α-hydroxymethyl ketone (**32**),[19] there was no sign of hemiacetal formation for the 14β-hydroxymethyl ketone (**137**) (Scheme 3.2-7), attributed to conformational differences favouring or disfavouring intramolecular closure.

The acetate (**138**) was synthesised for further characterisation purposes (Scheme 3.2-6), and the structural assignment was supported by analytical and spectroscopic data.

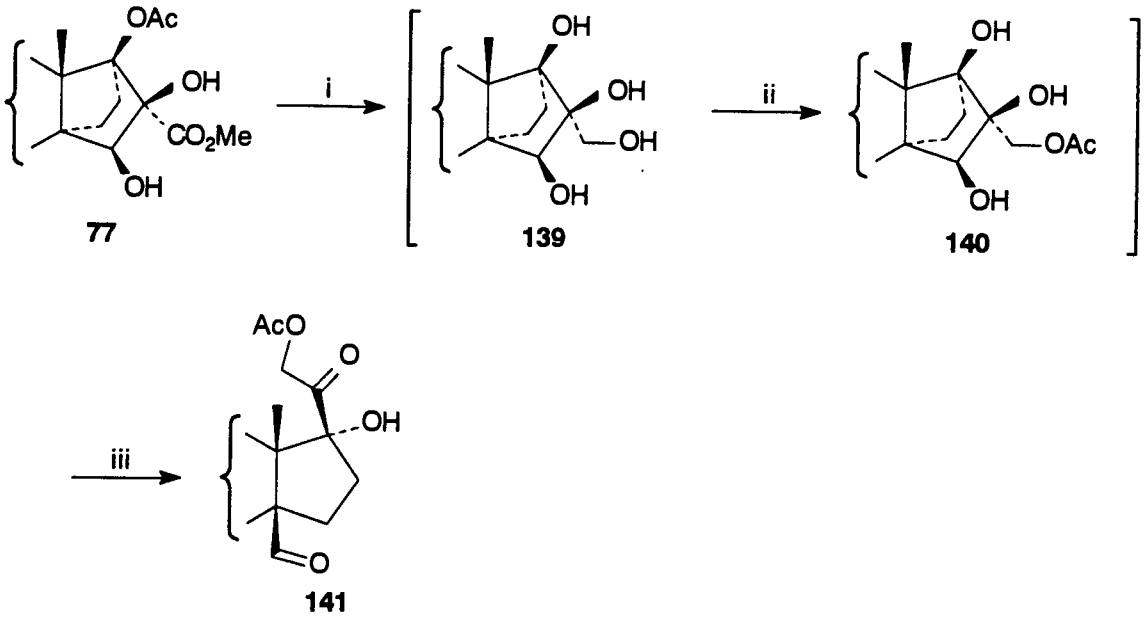
Scheme 3.2-7



The number of steps involved in the conversion of the 14β-formyl 20-ketone (**132**) to the14β-hydroxymethyl ketone (**137**) detracted from its utility, as did the low yield of the transformation to the δ-lactone (**134**). Accordingly, an alternative approach was sought.

Investigation of the effect of altering the functionality on C(17) after initial cleavage was considered. The diol (**77**) was exhaustively reduced to give a highly polar product assumed to be the tetraol (**139**) (Scheme 3.2-8) which could not be characterised. Brief treatment of this intermediate with acetic anhydride in pyridine at 20°C was conducted in the hope of achieving chemoselective protection of the primary 16[1]-hydroxy group. Our expectation, based on previous results, was that the intermediate would then undergo chemoselective cleavage at C(15)-C(16). The crude product (**140**) was also highly polar, and was thus not isolated and characterised, but subjected to periodate cleavage to give a gratifyingly high yield of the expected product (**141**) (83% from **77**). This multistep sequence was repeated for the conversion of the 15α,16α-diol (**76**) to the product (**141**) (80%). The structure of (**141**) followed from the infrared absorption bands at ν_{max} 3519, 1745, 1728 and 1715 cm^{-1} for the hydroxy- and carbonyl groups, and the appearance in the ^1H NMR spectrum of an AB multiplet at δ 4.86 and 5.41 (each d, *J* 17.9 Hz, 21-H_2), and a singlet at δ 9.60 for the 14-formyl proton.

Scheme 3.2-8



Reagents: (i) LAH, THF, 80°C, 2.5h. (ii) Ac_2O, pyridine, 20°C, 1.5h. (iii) $NaIO_4$, EtOH, 20°C, 15h.

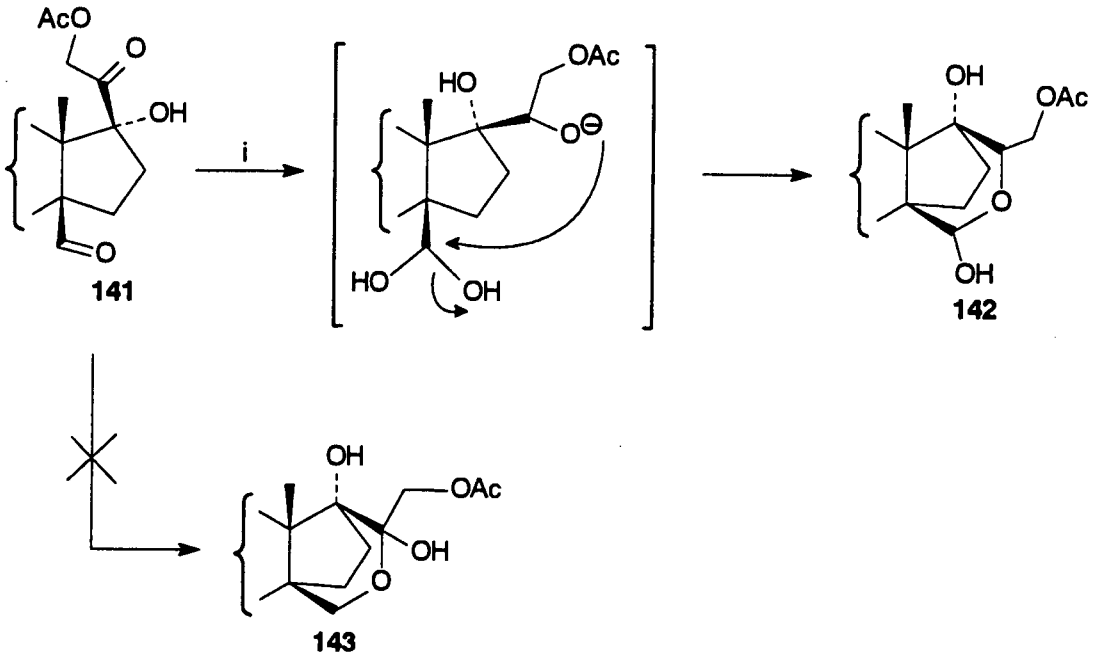
Attempted cleavage of the hydroxy ketone moeity on (**141**) confirmed the difficulty of hydration of 20-ketones in these systems. Reaction with lead tetraacetate or sodium bismuthate in phosphoric- and acetic acid gave multiple intractable mixtures of products, and no reaction was observed on treatment of (**141**) with sodium metaperiodate.

In view of the unexpected success of the reaction sequence up to this point, further degradation of the 14β-formyl 20-ketone (**141**) to the target 14β-formyl 17-ketone or the 14β-hydroxymethyl compound was considered, and sodium borohydride treatment in order to generate an intermediate with a 20-hydroxy group for subsequent oxidative cleavage, seemed to be a reasonable option. However treatment of the formyl ketone (**141**) with sodium borohydride in tetrahydrofuran and water at 0°C gave a product (**142**) formulated as the hemiacetal (Scheme 3.2-9) and leading to the conclusion that chemoselectivity of the reduction was unexpectedly reversed when compared with that observed for the α-oxo ester (**132**).

The structure of the hemiacetal (**142**) was formulated on the basis of distinctive spectroscopic properties. In the NMR spectrum an ABX multiplet at δ 4.09 (dd, *J* 11.6 and 7.0 Hz), 4.29 (dd, *J* 7.0 and 2.6 Hz) and 4.50 (dd, *J* 11.6 and 2.6 Hz) could be uniquely assigned to the protons at C(20) and C(21), whereas the signal for the 14^1-proton appeared as a singlet (on D_2O exchange) at δ 5.01. The alternative structure of chemoselective 14^1 reduction and hemiacetal formation (**143**) could not be reconciled with this data.

This reaction outcome invites speculation upon possible survival of the 14β-aldehyde as a hydrate, thereby promoting chemoselective reduction at C(20) and subsequent intramolecular hemiacetal formation (Scheme 3.2-9).

Scheme 3.2-9

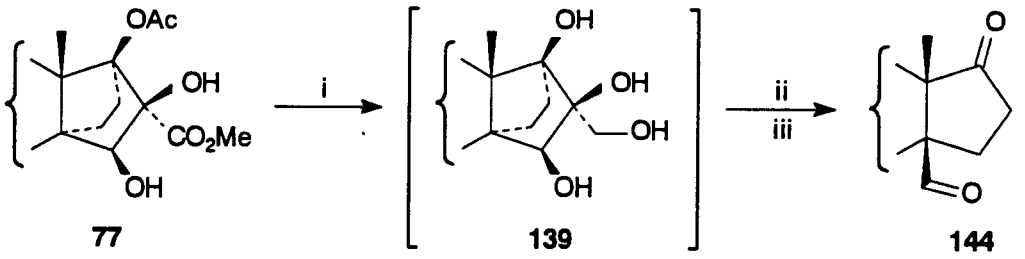


Reagents: (i) $NaBH_4$, THF, H_2O, 0°C, 15min.

This part of the investigation provided interesting insight into the reactivity of the compounds studied, but did not lead to the desired products, accordingly, another approach was attempted, again using the tetraol intermediate (**139**).

Treatment of the tetraol (**139**) with lead tetraacetate gave the 17-oxo 14β-carbaldehyde (**144**) in low yield (57% from **77**), accompanied by intractable polar material. However, treatment of (**139**) with sodium metaperiodate gave an indeterminate product which, when treated with lead tetraacetate, furnished the 14β-formyl 17-ketone (**144**) in high yield (80% from **77**) (Scheme 3.2-10). This result was also achieved using the 15α,16α-diol (**76**).

Scheme 3.2-10



Reagents: (i) LAH, THF, 80°C, 2.5h. (ii) $NaIO_4$, EtOH, 20°C, 16h. (iii) LTA, THF, 20°C, 15min.

The structure of the formyl ketone (**144**) followed from two infrared absorption bands (ν_{max} 1735 and 1715 cm^{-1}), and from the expected NMR signals. The ^1H NMR spectrum of (**144**) was readily resolved and assigned, based on analogy[21] and connectivities in the COSY spectrum (see Appendix), and selected signals are tabulated (Table 3.2-1) for clarity (see Chapter 7.1 for details of NMR data capture).

Table 3.2-1 Selected Signals from the NMR Spectrum of (**144**).

Proton	δ (ppm)	Multiplicity	*J* (Hz)
12α	1.65	td	2x14.2 and 3.3
15α	2.0	dtd	13.5, 2x10.0 and 1.3
8β	2.12	td	2x11.2 and 2.8
15β	2.16	obsc.	
11α	2.41	dq	12.9 and 3x3.5
16-H_2	2.54	m	
9α	2.66	td	2x11.2 and 3.5
6	2.85	ddd	16.9, 5.9 and 2.5
6	2.90-3.0	m	
14^1	9.62	d	1.3

Based on previous cleavage results, it was concluded that, with periodate treatment of the tetraol (**139**), preferential oxidative cleavage of (**139**) occurs either at C(15)-C(16) or C(16)-C(16^1), to result in one or more α-hydroxy ketones which resisted further reaction in the presence of periodate, but responded to lead tetraacetate.

The reason for the low yields obtained from direct treatment of (**139**) with lead tetraacetate was not immediately obvious; however, it could be postulated that this treatment led to less discriminate initial cleavage, resulting in intermediates which were less amenable to further cleavage.

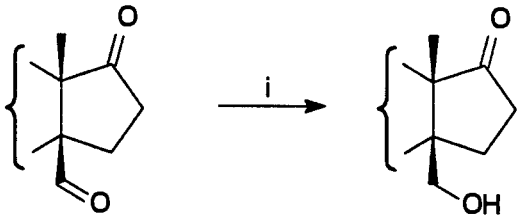
The high overall yield of formyl ketone (**144**) made this an attractive synthetic sequence and enabled extensive studies to be performed on (**144**).

3.3 Chemoselective Reactions of Estrone 14β-Carbaldehyde.

The foregoing successful and efficient synthesis of the 14β-formyl 17-ketone (**144**) facilitated the investigation of the chemoselective reactivity of this compound. The reactivity of the isomeric 14α-formyl 17-ketone (**32**) has been extensively studied[19] with a view to synthesis of 19-norsteroids having ring D modified functionality, and transformation of the 14β-formyl ketone (**144**) would allow comparison of the properties of the isomeric series of 14-chain extended hormone analogues.

The obvious point of departure for this investigation was to determine the chemoselectivity of reduction of the compound (**144**). Thus, treatment of (**144**) with lithium tri(sec-butyl)borohydride in tetrahydrofuran at 0°C (Scheme 3.3-1), gave the 14β-hydroxymethyl 17-ketone (**137**) (94%), characterised in Chapter 3.2.

Scheme 3.3-1



144 **137**

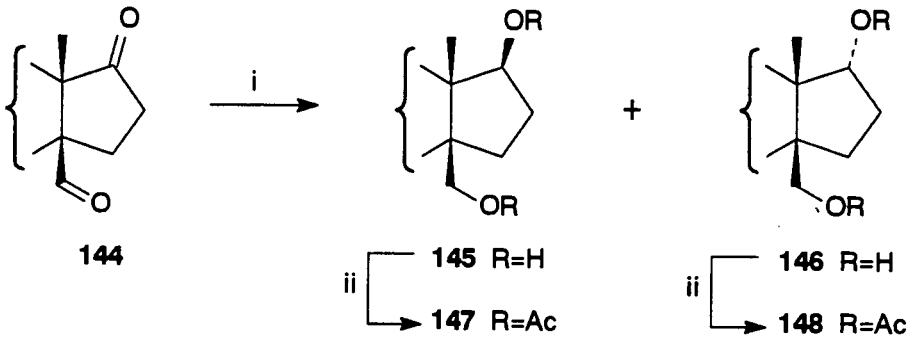
Reagents: (i) L-Selectride, THF, 0°C, 15min.

Prior to further investigation of the chemoselectivity of (**144**), this compound [or the 14β-hydroxymethyl 17-ketone (**137**)] was reduced under forcing conditions, to give a separable 1:1 mixture of the 14[1],17β- and 14[1],17α-diols (**145**) and (**146**) (Scheme 3.3-2). The NMR spectra of diols (**145**) and (**146**) were examined for distinguishing signals, unfortunately, those between δ3.60 and 4.30 for the 17-protons, were obscured in both cases by the signal for the 3-methoxy group. Consequently, the 14[1],17β- and 14[1],17α-diacetates (**147**) and (**148**) were synthesised (Scheme 3.3-2), and the spectroscopic characteristics of these compounds will be discussed.

The stereochemical assignments at C(17) of (**147**) and (**148**) were based on the distinguishing NMR signals for the 17-protons (see Chapter 3.1). For the 14[1],17β-diacetate (**147**), the signal for the 17α-proton appeared at δ 4.78 as a doublet of doublets with couplings of 8.0 and 2.3 Hz, while that for the 17β-proton of (**148**) appeared at δ 5.14 as a doublet of doublets with couplings of 9.3 and 7.9 Hz.

The remainder of the spectroscopic features of (**147**) and (**148**) were very similar, and will be discussed only for (**147**). The presence of the acetate groups was verified by the infrared absorption band at ν_{max} 1718 cm^{-1}, and singlets at δ 1.97 and 2.0 in the NMR spectrum. The signals for the 14^1-protons appeared as an AB multiplet (*J* 11.9 Hz) at δ 4.16 and 4.36. It was interesting to note that the long-range coupling between the 14^1-proton and 15α-proton (see compound **137**) is no longer present for either the diols (**145**) and (**146**) or the acetates (**147**) and (**148**).

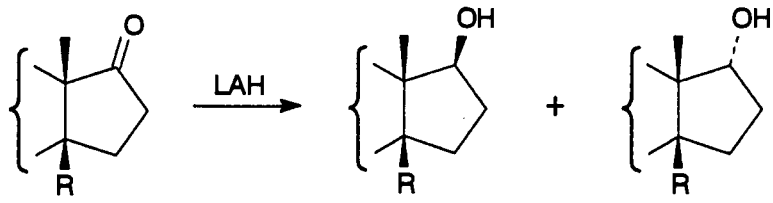
Scheme 3.3-2



Reagents: (i) LAH, THF, 20°C, 30min. (ii) Ac_2O, DMAP, pyridine, 20°C, *ca.*1h.

The stereochemical outcome of reduction of the 14β-hydroxymethyl 17-ketone (**137**) was significant when compared to the reduction of other 14β-functionalised 17-ketones (Scheme 3.3-3). Hydride reduction of the 14β-H-[91] and 14β-hydroxy ketones[90] (**149**) and (**150**), gave exclusively the 17α-alcohols, while reduction of the 14β-methyl-[88] and 14β-ethyl ketones[20] (**151**) and (**152**) gave 1:1 ratios of the corresponding 17α- and 17β-alcohols. Thus it can be postulated that the 14β-methyl and ethyl groups sterically hinder approach of the reagent from the β-face, and there is no evidence of participation by the hydroxy group on the hydroxymethyl ketone (**137**) to overcome this steric impedance.

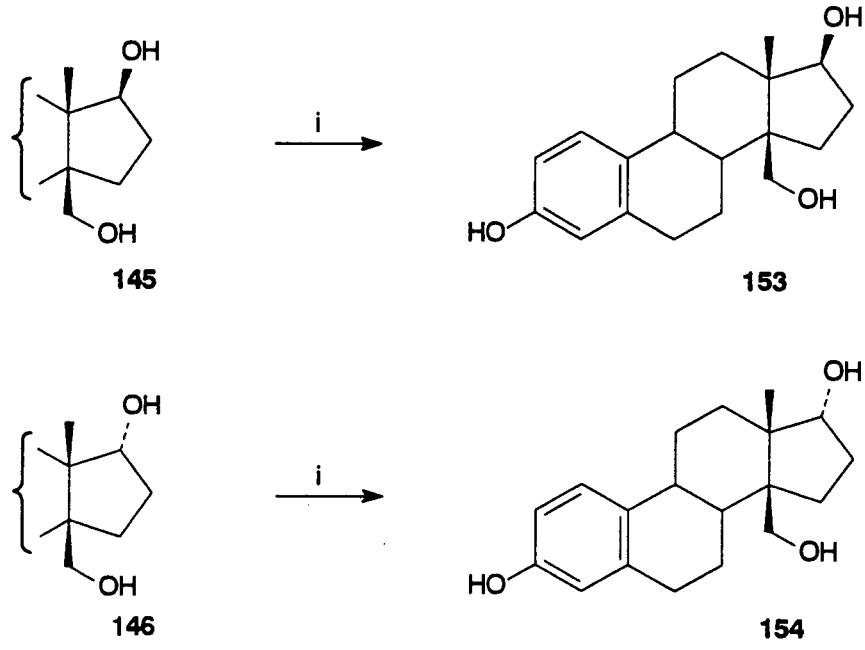
Scheme 3.3-3



149	R=H	0 : 100
150	R=OH	0 : 100
151	R=Me	50 : 50
152	R=Et	50 : 50
137	R=CH_2OH	50 : 50

In order to convert the diols (**145**) and (**146**) to 14β-hydroxymethyl analogues of estradiol, it was necessary to deprotect at C(3). Although many methods are available for the cleavage of aryl alkyl ethers,[92] experience has proved that in steroidal systems[93] diisobutylaluminium hydride in refluxing toluene is often the method of choice. Accordingly, the diols (**145**) and (**146**) were treated with diisobutylaluminium hydride (Scheme 3.3-4) to give 14-hydroxymethyl-14β-estra-1,3,5(10)-triene-3,17β-diol (**153**) (92%) and 14-hydroxymethyl-14β-estra-1,3,5(10)-triene-3,17α-diol (**154**) (88%), which have been subjected to biological evaluation (see Chapter 6).

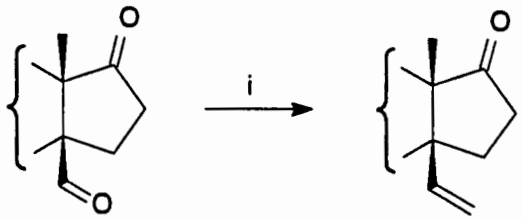
Scheme 3.3-4



Reagents: (i) DIBAH, toluene, 120°C, *ca.*48h.

Having demonstrated the chemoselectivity of hydride reduction of the formyl ketone (**144**), the possibility of exploiting this selectivity towards the synthesis of other 14β-substituted estradiol analogues was investigated. Thus, treatment of the formyl ketone (**144**) with methyltriphenylphosphonium bromide and *n*-butyllithium in tetrahydrofuran, gave 3-methoxy-14-vinyl-14β-estra-1,3,5(10)-trien-17-one (**155**) (Scheme 3.3-5). Unfortunately, the yield of this reaction could not be improved beyond 50%, even with variation of reaction conditions; however, starting material was recovered and could be recycled.

Scheme 3.3-5



144 **155**

Reagents: (i) $Me(PPh_3)Br$, BuLi, THF, 20°C, 17h.

The structure of the 14β-vinyl 17-ketone (**155**) was verified by investigation of the spectroscopic features of this compound. Retention of the 17-carbonyl group was obvious from the infrared absorption band at ν_{max} 1726 cm^{-1}. Many of the signals at high field in the NMR spectrum, which are usually obscured, were readily resolved in the spectrum of (**155**), and could be assigned with the aid of the COSY spectrum (see Appendix). The 14β-vinyl substituent was clearly represented in the ^1H NMR spectrum and these signals are tabulated for clarity (Table 3.3-1).

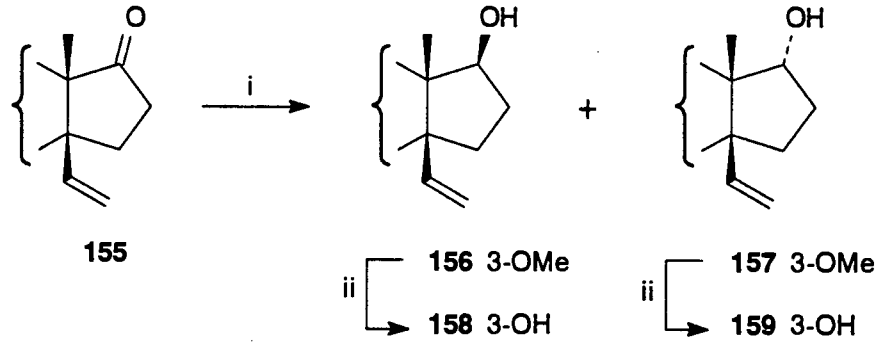
The long-range W-coupling between the 14^1-proton and the 15α-proton was again apparent in (**155**) (*J* 1.1 Hz). The clarity of the ^1H spectrum enabled complete assignment of the ^{13}C spectrum, with the aid of COSY and HETCOR spectra.

Table 3.3-1 ^1H NMR Signals for Ring D Olefinic Protons on Compound (**155**).

Proton	δ (ppm)	Multiplicity	*J* (Hz)
14^1	5.60	ddd	17.6, 11.0 and 1.1
14^2*trans*	4.99	dd	17.6 and 0.8
14^2*cis*	5.61	dd	11.0 and 0.8

The vinyl ketone (**155**) was reduced with lithium aluminium hydride in tetrahydrofuran, to give 1:2.3 ratio of 17β- and 17α-alcohols (**156**) and (**157**) (Scheme 3.3-6). In contrast to the trend of 17-hydride reduction discussed previously, the 14β-vinyl group does not contribute as strongly as the 14β-methyl or hydroxymethyl groups to β-face impedance of hydride approach, for reasons which are not immediately apparent.

Scheme 3.3-6



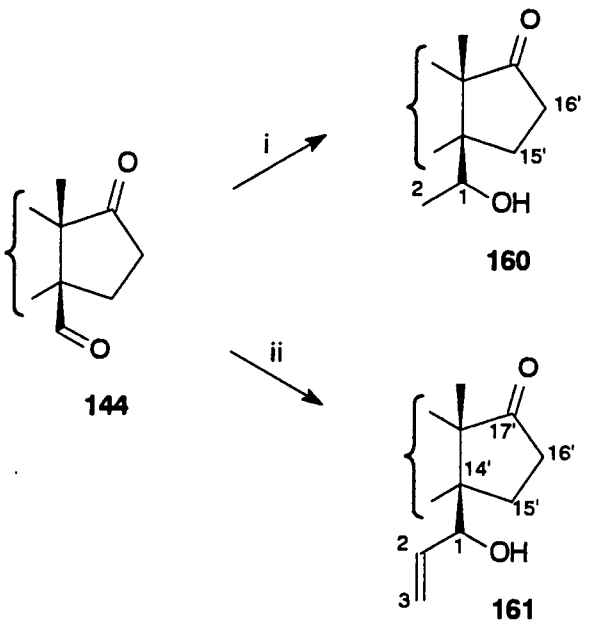
Reagents: (i) LAH, THF, 20°C, 25min. (ii) DIBAH, toluene, 120°C, 26h.

Once again, the stereochemistry at C(17) was assigned by inspection of the NMR spectra of the isomers (**156**) and (**157**). The signal for the 17α-proton on (**156**) appeared in the NMR spectrum at δ 3.57 as a doublet of doublets (after D_2O exchange) with couplings of 7.4 and 1.3 Hz; the signal for the 17β-proton on (**157**) appeared as a triplet with *J* 2x9.6 Hz. The pattern of signals for the 14-vinyl protons for both (**156**) and (**157**) was similar to that for the 17-ketone (**155**), with the W-coupling of the 14^1-proton still present [*J* 0.8 Hz for (**156**) and 1.1 Hz for (**157**)].

The alcohols (**156**) and (**157**) were deprotected using diisobutylaluminium hydride in toluene to give 14-vinyl-14β-estra-1,3,5(10)-triene-3,17β-diol (**158**) (99%) and 14-vinyl-14β-estra-1,3,5(10)-triene-3,17α-diol (**159**) (97%) (Scheme 3.3-6). The analytical data for these estradiol analogues agreed with the structural assignments, accordingly, they were subjected to biological evaluation (see Chapter 6).

With the chemoselectivity of reactions of the formyl ketone (**144**) now well established, further alkylations were attempted on this compound, initially to ascertain the diastereoselectivity of nucleophilic attack at C(14^1), but also to investigate alternative methods for homologation of the 14-chain, and to overcome the rather poor Wittig reaction. Thus, treatment of (**144**) with methylmagnesium iodide at 0°C gave (1*R*)-1-(3-methoxy-17-oxo-14β-estra-1,3,5(10)-trien-14-yl)ethanol (**160**) in high yield (95%) (Scheme 3.3-7), while reaction with allylmagnesium bromide at 0°C gave (1*R*)-1-(3-methoxy-17-oxo-14β-estra-1,3,5 (10)-trien-14-yl)prop-2-enol (**161**) (71%).

Scheme 3.3-7



Reagents: (i) MeMgI, THF, 0°C, 5min. (ii) CH_2:CHMgBr, THF, 0°C, 20min.

The gross structural assignments of (**160**) and (**161**) were verified by several spectroscopic features in the NMR spectra. For (**160**), the 1-methyl protons (see Scheme 3.3-7 for numbering) were represented by a doublet at δ 1.29 (*J* 6.9 Hz), and the signal for the 1-proton occurred at δ 4.22 as a quartet (*J* 3x6.9 Hz) after D_2O exchange.

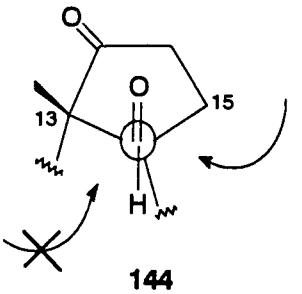
For (**161**), the signals in the NMR spectrum for the 1-, 2- and 3-protons displayed a clear pattern of couplings, which are tabulated (Table 3.3-2) for ease of inspection.

Table 3.3-2 ^{1}H NMR Signals for the 1-, 2-, and 3-Protons on Compound (**161**).

Proton	δ (ppm)	Multiplicity	*J* (Hz)
1-H	4.47	br d	8.3, (1.5) and (1.0)
2-H	6.15	ddd	18.5, 10.2 and 8.3
3-H*cis*	5.16	ddd	10.2, 1.5 and 1.0
3-H*trans*	5.22	dt	18.5, and 2x1.5

Unfortunately, the long-range allylic couplings between the 3-protons and the 1-proton were only visible in the signals for the 3-protons, showing the magnitudes to be 1.5 and 1.0 Hz.

The stereochemistry at C(1) of (**160**) and (**161**) could not be unambiguously assigned; however, as only one diastereomer was obtained for each reaction, strong preference for nucleophilic addition to one face of the 14^1-carbonyl group of (**144**) must exist. The long range coupling of the 14^1- and 15α-protons on (**144**) discussed previously, suggested a preferred conformation of the 14-formyl group. Examination of the model of (**144**) in this conformation, represented by the Newman projection viewed down the C(14^1)-C(14) bond in Figure 3.3-1, showed clearly that steric impedance to reagent approach from the pro-*S* face by the 13β-methyl group was likely, and this would result in preferred *re*-addition of the nucleophile, and resultant 1*R* configuration of the product.



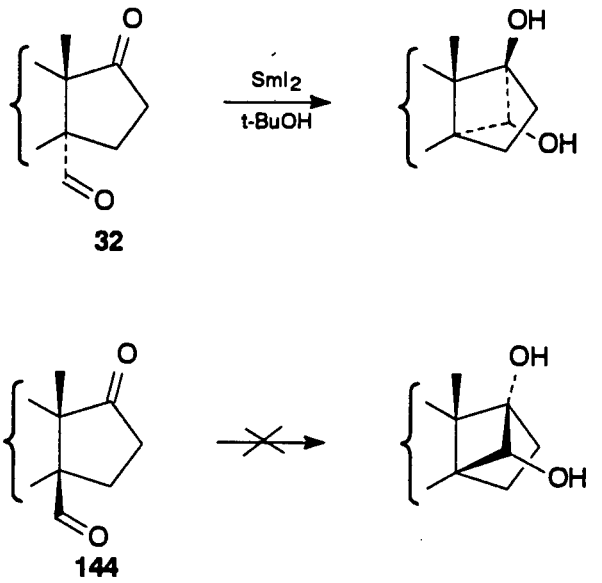
144

Figure 3.3-1 Newman Projection Viewed down the C(14)-C(14) bond of (**144**), Showing the Preferred Direction of Reagent Approach.

The foregoing reactions demonstrated the diastereoselectivity of nucleophilic attack on the 14β-formyl group on (**144**), but the products (**160**) and (**161**) were resistant to derivatisation. Neither tosyloxy- nor mesyloxy derivatives could be made from (**160**) or (**161**), and these possible routes to 14β-alkyl analogues were abandoned.

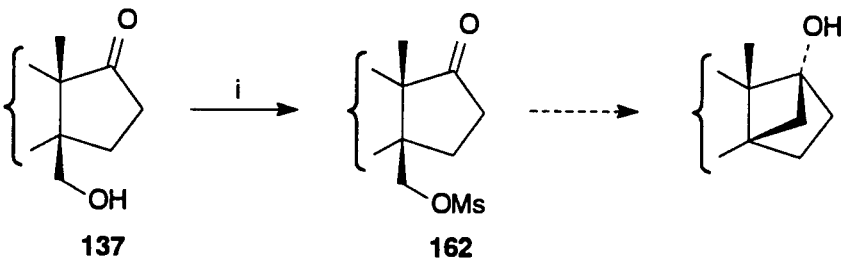
Recent work in these laboratories has demonstrated that the 14α-formyl 17-ketone (**32**) undergoes intramolecular coupling to give 14α,17α-methanoestriol analogues,[94] and an analogous reaction for the 14β-formyl 17-ketone was envisaged (Scheme 3.3-8), with the view to preparing a novel ring D bridged analogue of estriol. However, treatment of the formyl ketone (**144**) with samarium(II) iodide[95,96] and *t*-butanol, at a range of temperatures, gave the hydroxymethyl ketone (**137**) in small amounts, and intractable mixtures of products, without any evidence of an intramolecular reductive coupling product.

Scheme 3.3-8



The next option was to synthesise the mesyloxy derivative (**162**) of the hydroxymethyl ketone (**137**), in order to attempt a reductive trapping to give the 14β,17β-methano bridged derivatives. Accordingly, reaction of (**137**) with methanesulfonyl chloride in pyridine for 1.5 h gave the mesyloxy compound (**162**) in good yield (82%) (Scheme 3.3-9). The compound (**162**) was non-crystalline, and thus only partially characterised; however, the spectroscopic features were consistent with the structural assignment.

Scheme 3.3-9



Reagents: (i) MsCl, pyridine, 20°C, 1.5h.

Further reaction of the mesyloxy compound (**162**), however, was unsuccessful; treatment with samarium(II) iodide at a variety of temperatures gave intractable mixtures of products, and reaction with sodium iodide and diisopropylethylamine in acetone, at

temperatures from 0°C to 80°C for extended periods of time, gave no reaction, and starting material was recovered. No further attempts were made to cyclise this series of compounds.

In summary, synthesis of the 14β-formyl 17-ketone (**144**) allowed access to a range of 14β-substituted estradiol analogues, via chemoselective reaction of the 14β-formyl group. Although manipulation of the 14β-alkyl derivatives was limited, the diastereoselectivity of nucleophilic addition to the 14β-formyl group was illustrated.

CHAPTER 4

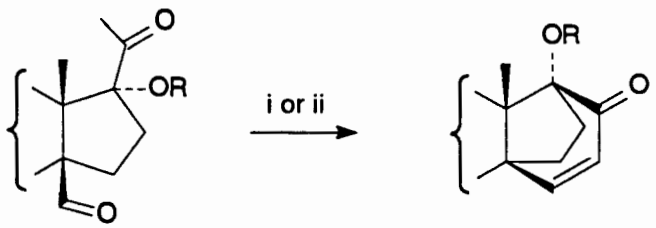
Synthesis of Ring D Bridged Estradiol Analogues

4.1 Intramolecular Cyclisation Route to 14β,17β-Propenoestradiols.

One of the original objectives in this study was to investigate the intramolecular aldol condensation of 17α-acetoxy-3-methoxy-20-oxo-19-nor-14β-pregna-1,3,5(10)-triene-14-carbaldehyde (**123**) as a possible pathway to 14β,17β-propanoestradiols and to analogues bearing additional functionality on the propano bridge. The 17α-acetyl 14α-carbaldehyde (see Scheme 1-13) was successfully cyclised to give intermediates for the synthesis of the 14α,17α-propanoestradiols,[38] and an unrelated synthetic pathway to the 14β,17β-propenoestradiols has since been developed (see Scheme 1-12).[28] It was decided to proceed with the intramolecular condensation study as a possible complementary route to the 14β,17β-propeno analogues not readily available from the forementioned study.

Thus, treament of the 17β-acetyl 14β-carbaldehyde (**123**) with toluene-*p*-sulfonic acid in benzene at 85°C gave the hydroxy enone (**163**) quantitatively, and with hydrochloric acid in tetrahydrofuran at 50°C gave the acetoxy enone (**164**) in high yield (89%) (Scheme 4.1-1). The 17-hydroxy compound (**131**) was also successfully converted to the hydroxy enone (**163**) by reaction with toluene-*p*-sulfonic acid in benzene at 85°C.

Scheme 4.1-1



123 R=Ac
131 R=H

164 R=Ac
163 R=H

Reagents: (i) TsOH, benzene, 85°C, 1.25h. (ii) HCl, THF, 50°C, 2h.

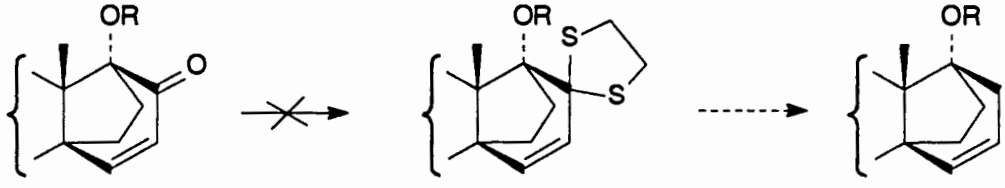
The spectroscopic features of the enones (**163**) and (**164**) were similar, with the exception of differences associated with 17-functionality. The presence of the expected functional groups was inferred by infrared absorption bands at ν_{max} 1739 cm^{-1} for (**164**) and 3480 cm^{-1} for (**163**), and a methyl singlet in the NMR spectrum of (**164**) at δ 2.17. Because

of the spectroscopic similarity between (**164**) and (**163**), the remaining spectroscopic features will be discussed for the hydroxy enone (**163**) only.

The ultraviolet spectrum of the hydroxy enone (**163**) exhibited absorption at λ_{max} 243 nm (ε 16426) which is consistent with the presence of an enone system, and the infrared absorption band at ν_{max} 1677 cm^{-1} verified the presence of the enone moiety. The structural assignment of the hydroxy enone (**163**) was supported by signals in the NMR spectrum [δ 6.07 (d, *J* 9.8 Hz, 17^2-H), 7.26 (d, *J* 9.8 Hz, 17^3-H)]. The difference in shielding effects on C(17^2) and C(17^3) was highlighted in the ^{13}C spectrum, where the signal for C(17^2) appeared as a doublet at δ 158.9 and that for C(17^3) at δ 125.0.

Deoxygenation at C(17^1) of the enones (**163**) and (**164**) was necessary to provide access to 14β,17β-propeno systems (Scheme 4.1-2), accordingly reaction of both (**163**) and (**164**) with ethanedithiol and boron trifluoride-diethyl ether in glacial acetic acid were attempted, but gave intractable product mixtures, which were not isolated. A similar reaction outcome was observed for attempted thioketal formation of the 14α,17α-propeno 17-acetate,[27] whereas the corresponding 17-alcohol reacted smoothly to give the thioketal. Several other catalyst and solvent combinations were attempted on the hydroxy enone (**163**), including zinc triflate in dichloromethane[67] and Nafion-H;[66] however none of the methods attempted gave satisfactory results, and it was concluded that both acid sensitivity and steric crowding of these systems prevents successful thioketalisation. The attempted synthesis of these estradiol analogues was thus abandoned.

Scheme 4.1-2

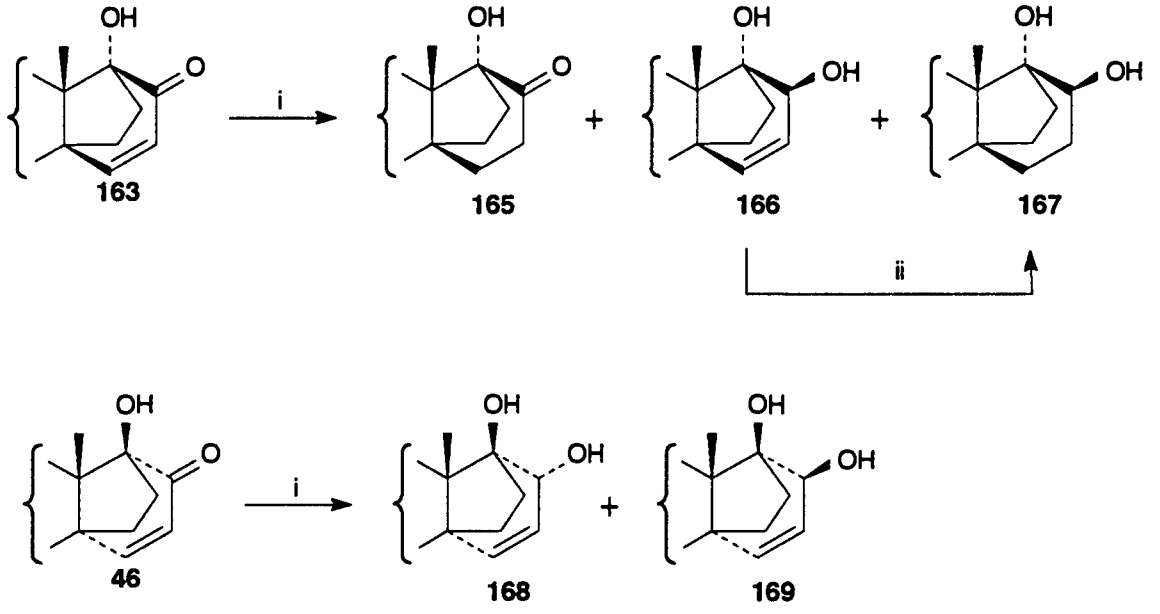


163 R=H
164 R=Ac

The bridged compound (**163**) is an obvious precursor of a new class of 'estriol' analogues, based upon chemoselective 1,2-reduction of the 17-ketone. Treatment of the hydroxy enone (**163**) with lithium aluminium hydride in tetrahydrofuran at 20°C gave a three component mixture, which, when separated on column chromatography, yielded the hydroxy ketone (**165**) (46%), (17^1S)-3-methoxy-14β,17β-prop-17^2-eno-14β-estra-1,3,5(10)-triene-17α,17^1-diol (**166**) (23%), and the saturated diol (**167**) (9%) (Scheme 4.1-

3). The two saturated products (**165**) and (**167**) were identified by spectroscopic comparison with authentic samples.[28]

Scheme 4.1-3



Reagents: (i) LAH, THF, 20°C. (ii) Pd-C, H_2, EtOH, 20°C, 5h.

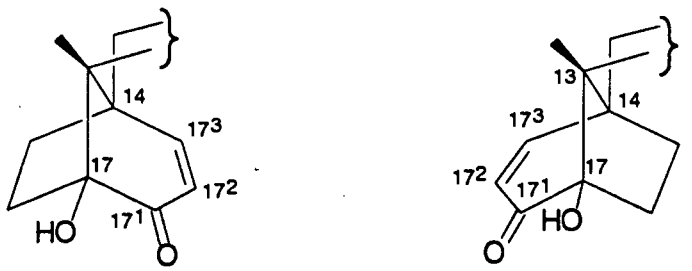
The unsaturated diol (**166**) was identified from analytical and spectroscopic data. The NMR signals for the ring D protons are tabulated (Table 4.1-1) for clarity. The stereochemistry at C(17^1) was tentatively assigned, based on the magnitude of the coupling constant between the 17^1- and 17^2-protons. These protons have a torsion angle of *ca.* 40°, whereas if the stereochemistry was reversed, the angle would be *ca.* 80°; accordingly, the coupling constant of 4.0 Hz was consistent with 17^1S-stereochemistry. The stereochemistry was verified by hydrogenation of the unsaturated diol (**166**) to the saturated diol (**167**) and correlation with an authentic sample[28] (Scheme 4.1-3).

Table 4.1-1 ^{1}H NMR Signals for the β-Bridge Protons on the Diol (**166**).

Proton	δ (ppm)	Multiplicity	*J* (Hz)
17^1	3.92	dd	4.0 and 1.0
17^2	5.77	dd	9.7 and 4.0
17^3	6.14	dd	9.7 and 1.0

The outcome of this reaction was rather surprising when compared with the analogous lithium aluminium hydride reduction in the isomeric series[27] (Scheme 4.1-3), where clean, but less stereoselective 1,2-reduction of the enone (**46**) occurred to give a *ca.* 3:2 mixture of the 17β,17^1*R*- and 17β,17^1*S*-diols (**168**) and (**169**).

The reason for the lack of 1,2-selectivity in the lithium aluminium hydride mediated reduction of the hydroxy enone (**163**) was not immediately clear, but examination of the models of (**46**) and (**163**) (Figure 4.1-1) revealed that C(17^3) of (**46**) is sterically well shielded by the elements of ring C, while C(17^3) of (**163**) is accessible to an approaching nucleophile. The face selectivity of the reaction on (**163**) and lack thereof on (**46**) led to the postulation that the *exo*-face of ring D on (**163**) is sterically hindered by the 13β-methyl group, preventing reagent approach from this face, while the carbonyl centre on (**46**) is less sterically impeded on the *exo*-face, thus allowing reagent approach from either face, but still preferring *endo*-approach.

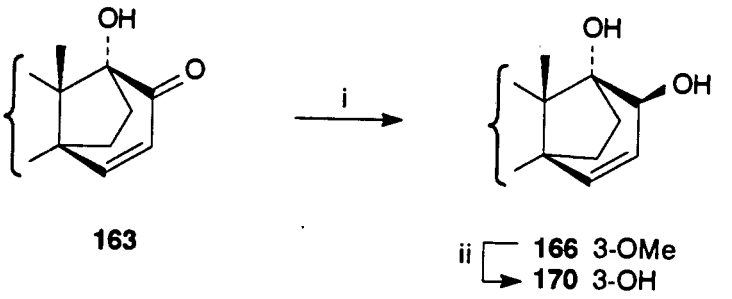


46 **163**

Figure 4.1-1 Perspective View of the Hydroxy Enones (**46**) and (**163**).

The complex outcome of the lithium aluminium hydride reduction of the hydroxy enone (**163**) was obviously not satisfactory for our purposes; accordingly, the familiar methodology for overcoming competing 1,4-addition of hydride was employed. Reaction of the hydroxy enone (**163**) with sodium borohydride and cerium trichloride heptahydrate in methanol at 0°C resulted in highly stereoselective 1,2-reduction from the *endo*-face of ring D on (**163**) to give a high yield (95%) of the unsaturated diol (**166**) (Scheme 4.1-4). The diol (**166**) was subsequently treated with diisobutylaluminium hydride in refluxing toluene to give (17^1*S*)-14β,17β-prop-17^2-eno-14β-estra-1,3,5(10)-triene-3,17α,17^1-triol (**170**) (81%), which was subjected to biological evaluation (see Chapter 6).

Scheme 4.1-4

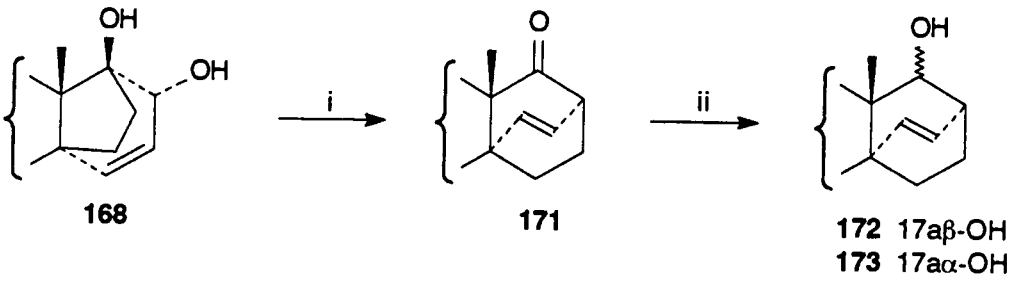


Reagents: (i) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0°C, 45min. (ii) DIBAH, toluene, 120°C, 48h.

4.2 Rearrangement Pathway to 14α,17α-Ethano-17a-homoestradiols.

One of the findings of the study on the α-bridged compounds was that the 14α,17α-propeno diol (**168**) (Scheme 4.2-1) underwent facile rearrangement to the 17a-homo compound (**171**).[27] However, aspects of this work are incomplete as uncertainty remained as to the stereochemistry at C(17a) of the products of reduction (**172**) and (**173**), and by extension, the saturated derivatives of these 17a-alcohols.

Scheme 4.2-1

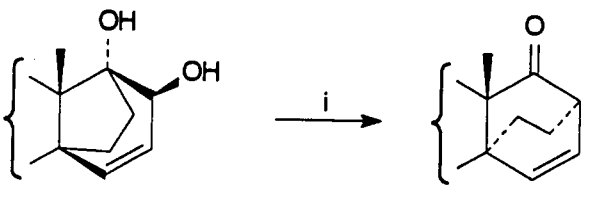


168 **171** **172** 17aβ-OH **173** 17aα-OH

Reagents: (i) $HClO_4$, THF. (ii) LAH, THF, 20°C.

The highly stereoselective formation of the 17[1]*S*-alcohol (**166**) in this work provided the opportunity to extend the rearrangement study to the synthesis of 14α,17α-ethano-Δ^{15} 17a-homoestradiols, and also to gain further insight into the configurational assignments at C(17a) of the corresponding estradiol analogues. The expectation of successful rearrangement of the diol (**166**) was realised, since treatment with perchloric acid in tetrahydrofuran gave high yields (88%) of 3-methoxy-14,17α-ethano-17a-homoestra-1,3,5(10),15-tetraen-17a-one (**174**) (Scheme 4.2-2).

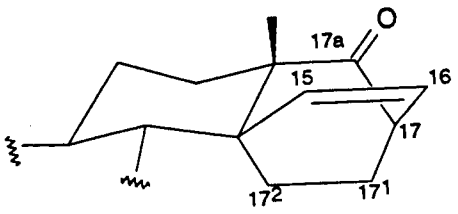
Scheme 4.2-2



166 **174**

Reagents: (i) $HClO_4$, THF, 20°C, 3h.

The spectroscopic features of (**174**) supported this structural assignment. The presence of the 17a-carbonyl group was verified by an infrared absorption band at ν_{max} 1705 cm^{-1} and a singlet at δ 219.7 in the ^{13}C NMR spectrum. The ^{1}H NMR spectrum was fairly well resolved and the signals for the ring D protons are tabulated below (Table 4.2-1). Connectivities in the HETCOR and COSY spectra allowed comprehensive and confident assignment of the ^{13}C spectrum (see Appendix for selected spectra).



174

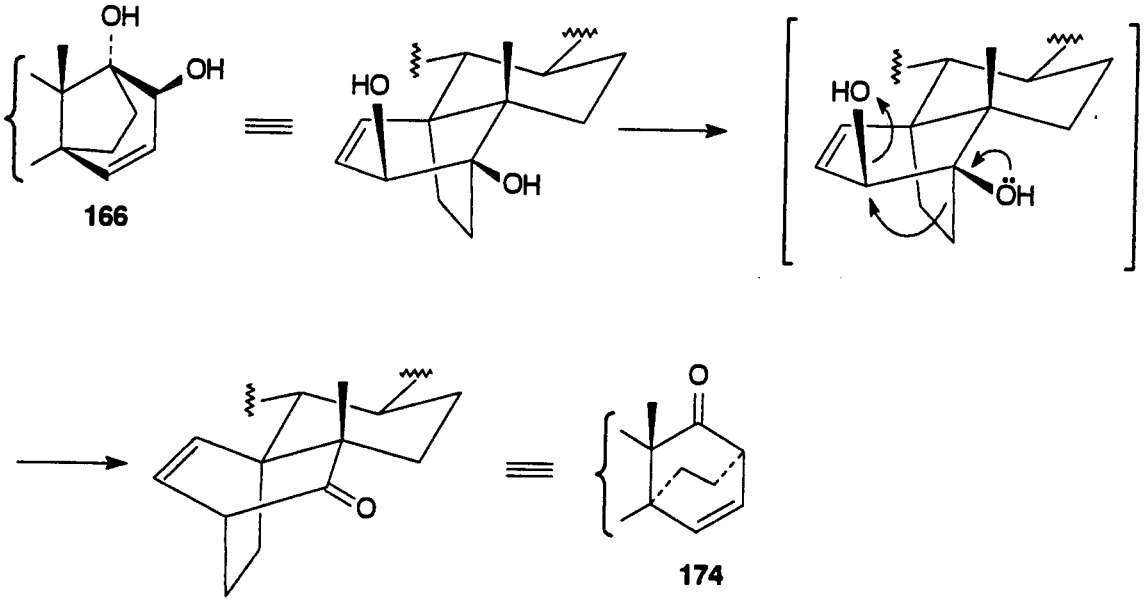
Figure 4.2-1 Perspective View of the Unsaturated Ketone (**174**).

Table 4.2-1 ^{1}H NMR Signals for Ring D Protons of Compound (**174**).

Proton	δ (ppm)	Multiplicity	*J* (Hz)
17^2	1.30	td	2x13.1 and 5.3
17^1	1.62	m	
17^1	1.79	m	
17^2	2.06	ddd	13.1, 9.8 and 4.3
17β	3.10	dddd	6.0, 3.3, 2.4 and 1.2
16	6.22	dd	8.3 and 6.0
15	6.34	d	8.3

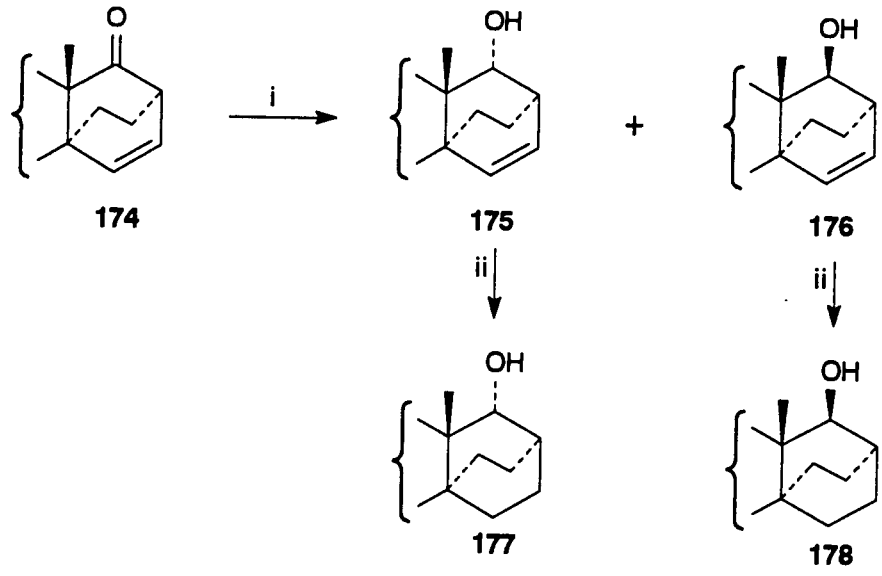
The orientation of the 17^1-hydroxy group on (**166**) clearly favoured the facile pinacol rearrangement. Thus protonation of the hydroxy group with consequent generation of an incipient carbocation at C(17^1) facilitated 16(17 → 17^1)*abeo* rearrangement with appropriate orbital alignment of the interacting centres (Scheme 4.2-3).

Scheme 4.2-3 Mechanism of 16(17 → 17[1])*abeo* Rearrangement of Diol (**166**) to Ketone (**174**).



Completion of the synthesis of estradiol analogues required reduction of the rearranged ketone (**174**). Treatment of the ketone (**174**) with lithium aluminium hydride in tetrahydrofuran was non-stereoselective and gave a separable *ca* 1:1 mixture of the unsaturated alcohols (**175**) (46%) and (**176**) (41%) (Scheme 4.2-4). This result is comparable with that obtained in the isomeric series where reduction of the ketone (**171**) gave a 1:1 mixtures of the 17a-alcohols (Scheme 4.2-1). This lack of stereoselectivity was fortunate in this instance, since it ensured adequate supplies of each of the isomeric alcohols for comparative study.

Scheme 4.2-4



Reagents: (i) LAH, THF, 20°C, 1h. (ii) Pd-C, EtOH, H_2, 20°C, 5h.

The NMR spectra of (**175**) and (**176**) were analysed in the hope of finding a solution to the problem of stereochemical assignment at C(17a). It was suspected that differences in the NMR spectra of (**175**) and (**176**) would provide clues to this problem. The effect of the proximity of the 17a-hydroxy group on the chemical shift of the 13β-methyl protons was investigated; however, no significant difference existed between this signal for the two isomers [δ 0.88 for (**175**) and δ 0.89 for (**176**)]. The signals for the ring D protons were examined and compared to those for the isomeric unsaturated diols (**172**) and (**173**), and selected signals from the spectra of all four compounds are tabulated (Table 4.2-2) for ease of interpretation. Using this analogy, the alcohol (**175**) was assigned 17aα-stereochemistry, and the alcohol (**176**) 17aβ-stereochemistry.

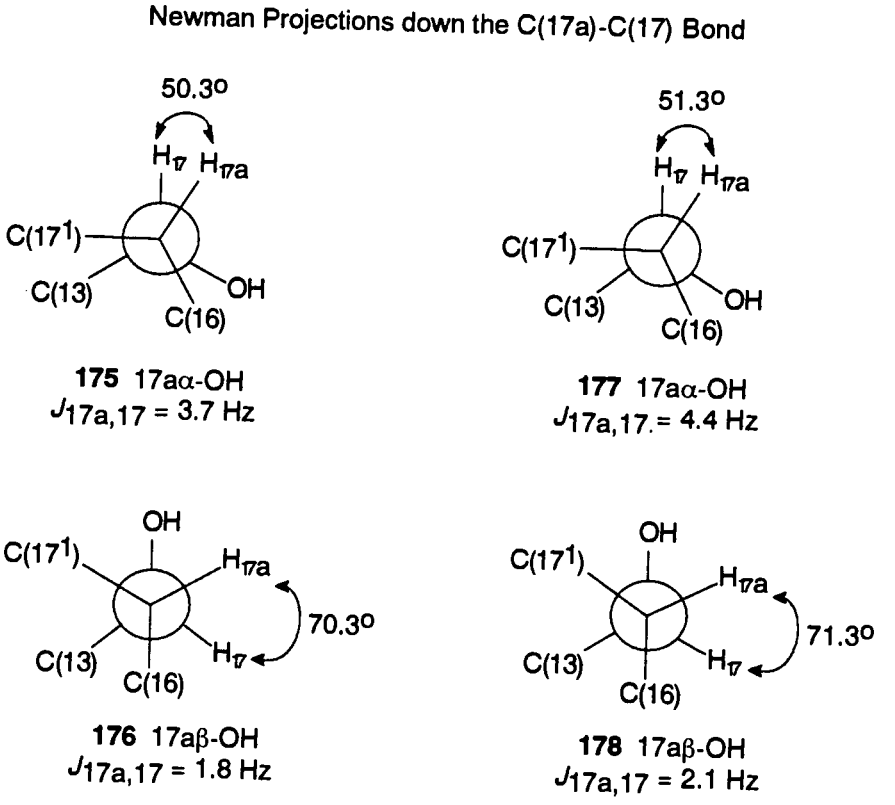


Figure 4.2-2 Diagnostic H NMR Properties of the Saturated and Unsaturated 17a-Alcohols

We now had a self-consistent set of NMR data which could not, however, be taken as conclusive as reversal of all the assignments in this series of 17a-homoestradiols would also be consistent with the data available. Conclusive proof of the structure of the 3-methoxy-14,17α-ethano-17a-homoestra-1,3,5(10),15-tetraen-17aα-ol (**175**) was obtained from the X-ray crystallographic structure determination. Final fractional atomic coordinates and equivalent isotropic parameters for (**175**) are given in Chapter 7. The perspective view of (**175**), with atomic numbering (Figure 4.2-3), confirmed all the structural features, in particular the 17aα-hydroxy configuration.

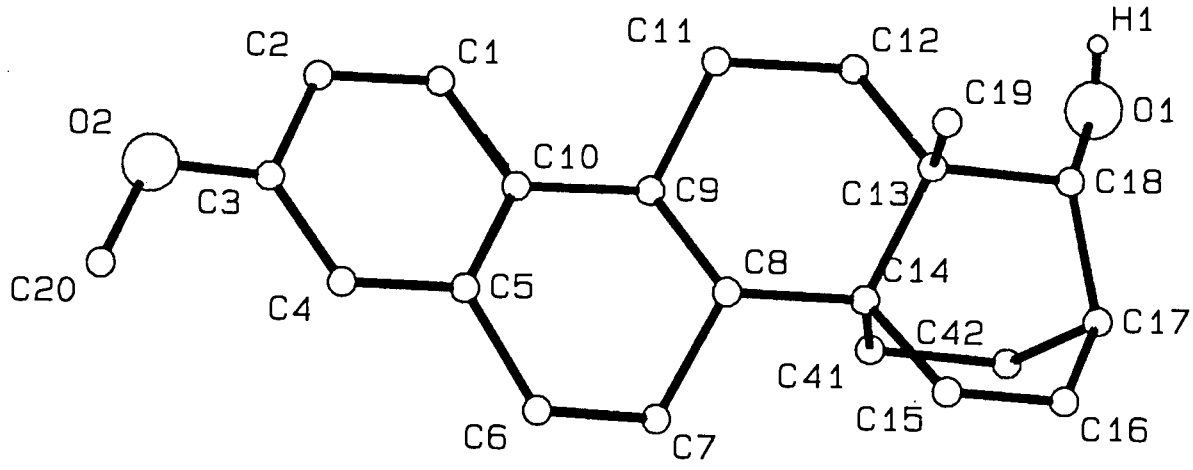


Figure 4.2-3 Perspective View of the 17aα-Alcohol (**175**) with Atomic Numbering.

The structural analysis showed that the components of rings A,B, and C correspond closely to those of estrone, with the expanded ring D having little effect on the conformation of ring C [torsion angle C(12)-C(13)-C(14)-C(8) is 54.5° while that for an unstrained cyclohexanoid is *ca.* 56°].

Table 4.2-3 Selected Ring D Torsion Angles of the 17aα-Alcohol (**175**).

	Torsion angle (°)
C(13)-C(14)-C(15)-C(16)	57.1
C(13)-C(14)-C(17^1)-C(17^2)	59.7
C(17a)-C(17)-C(16)-C(15)	57.9
C(17a)-C(17)-C(17^1)-C(17^2)	60.9
C(14)-C(13)-C(17a)-C(17)	4.8
C(14)-C(15)-C(16)-C(17)	1.4
C(14)-C(17^2)-C(17^1)-C(17)	0.8

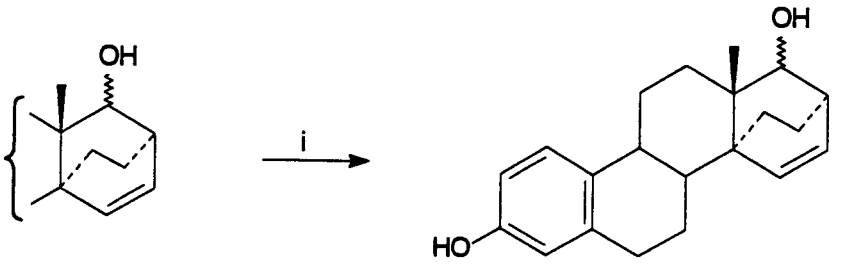
Ring D can be viewed as two fused six-membered rings in boat conformations to give a bicyclo[2.2.2]octenoid structure with high symmetry, illustrated by the torsion angles (Table 4.2-3) and internal angles for ring D (Table 4.2-4).

Table 4.2-4 Internal Angles for Ring D of the 17aα-Alcohol (**175**).

	Internal angle (°)
C(13)-C(14)-C(15)	106.6
C(13)-C(14)-C(17^2)	108.5
C(17a)-C(17)-C(16)	108.7
C(17a)-C(17)-C(17^1)	107.9
C(17^2)-C(14)-C(15)	104.7
C(17^1)-C(17)-C(16)	106.3

Both unsaturated alcohols (**175**) and (**176**) were deprotected at C(3) by treatment with diisobutyl aluminium hydride in toluene, to give 14,17α-ethano-17a-homoestra-1,3,5(10),15-tetraene-3,17aα-diol (**179**) (85%) and 14,17α-ethano-17a-homoestra-1,3,5(10),15-tetraene-3,17aβ-diol (**180**) (95%) (Scheme 4.2-5), which were subjected to biological evaluation (see Chapter 6).

Scheme 4.2-5



175 17aα-OH
176 17aβ-OH

179 17aα-OH
180 17aβ-OH

Reagents: (i) DIBAL, toluene, 120°C, 20h.

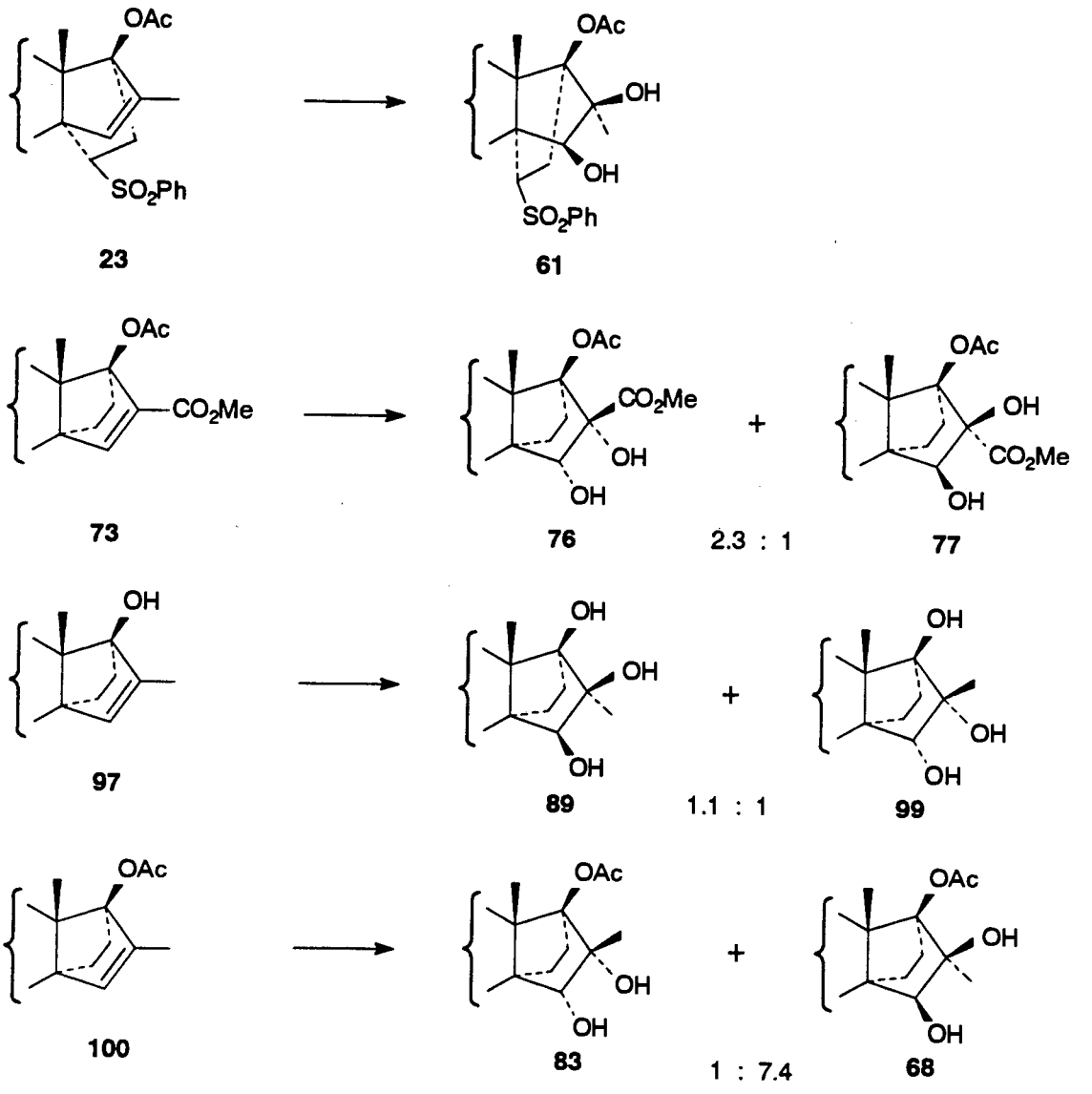
Thus, the range of 14β,17β-propenoestradiol and 17a-homoestradiol analogues was extended. Also the X-ray structure determination of (**175**) allowed conclusive assignment of the stereochemistry at C(17a) of the latter series of compounds.

CHAPTER 5

The Influence of Ring D Functionality of 14,17-Bridged 15-Olefins on the Stereochemistry of Dihydroxylation.

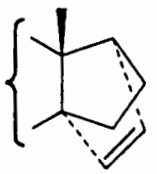
Throughout this study, dihydroxylations were performed on various 15(16)-olefins using osmium tetroxide, either stoichiometrically or catalytically (Scheme 5-1). The stereochemical outcome of these reactions was not of primary importance to the synthetic sequence as, in all cases, the diol isomers could be converted to common intermediates; however, the results were interesting as part of an ongoing study into the effect of bridgehead- and other ring D functionality on the stereochemical outcome of the dihydroxylations.

Scheme 5-1

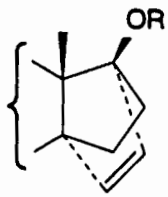


Bull *et al.*[38] have investigated the dihydroxylation of the $17^1,17^2$-olefinic bond in the ring D bridged system, represented by compounds (**A**) to (**E**) (Scheme 5-2).

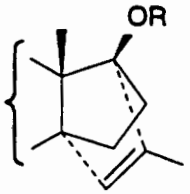
Scheme 5-2



A *endo:exo*=1.3:1



B R=H *endo:exo*=2.7:1
C R=Ac *endo:exo*=1:1.9

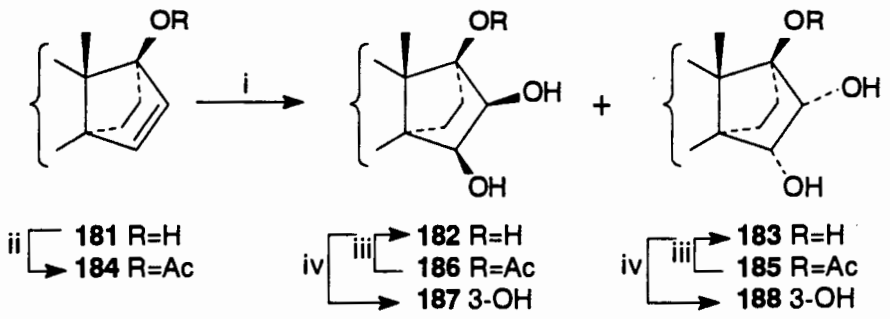


D R=H *endo:exo*=7.3:1
E R=Ac *endo:exo*=11.5:1

The authors demonstrated that where no bridgehead functionality is present (**A**), little stereodifferentiation occurred. Because this result was in conflict with the expected *endo*-preference for attack,[98] it was suggested that *exo*-attack of the reagent is stereoelectronically enhanced,[99] and bonds forming on the *exo*-face of this norbornenoid system would adopt the obligatory staggered relationship with bonds at the bridgehead.[100] Introduction of the 17-hydroxy group (**B**) partly counteracts this stereoelectronic effect, and *endo*-attack is favoured. Acetylation of the 17-hydroxy group causes stereoreversal of attack on (**C**), and this seems to support the theory presented by Kishi,[101] which suggests that dihydroxylation of allylic alcohols occurs preferentially via *anti*-approach of reagent, while this selectivity is diminished or destroyed in the corresponding acyl derivatives. Introduction of the 17^1-methyl group on (**D**) and (**E**) causes loss of distinction between the 17-hydroxy - and 17-acetoxy compounds, with *endo*-addition largely favoured in both cases.

In order to gain further insight into the stereoselectivity of dihydroxylations on ring D bridge olefins, and incidentally to synthesise further estradiol analogues, the 17-hydroxy 15-olefin (**181**) was prepared according to Bull *et al*,[22] and dihydroxylated by reaction with osmium tetroxide in pyridine for 24 h (Scheme 5-3), to give the triols (**182**) (41%) and (**183**) (37%). Treatment of the hydroxy olefin (**181**) with acetic anhydride in pyridine at 20°C gave the acetoxy olefin (**184**) (Scheme 5-3) which was dihydroxylated using osmium tetroxide in pyridine, to give the diols (**185**) (10%) and (**186**) (74%). The NMR signals (after D_2O exchange) for the 15-and 16-protons of the triols (**182**) and (**183**), and the diols (**185**) and (**186**) are tabulated (Table 5-1).

Scheme 5-3



Reagents: (i) OsO_4, pyridine, 20°C, *ca.* 24h. (ii) Ac_2O, DMAP, pyridine, 20°C, 4.3h. (iii) LAH, THF, 20°C, 2h. (iv) DIBAH, toluene, 120°C, 48h.

Table 5-1 ^1H NMR Signals for the 15- and 16-Protons on the Diols (**182**), (**183**), (**185**) and (**186**).

Compound	Proton	δ (ppm)	Multiplicity	*J* (Hz)
182	15α	3.80	d	6.6
	16α	3.99	d	6.6
183	15β	3.92	dd	9.0 and 1.8
	16β	4.01	dd	9.0 and 2.0
185	15β	4.0	dd	9.0 and 1.7
	16β	4.21	dd	9.0 and 1.7
186	15α	3.99	d	7.1
	16α	4.60	d	7.1

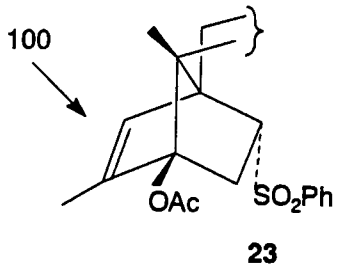
Verification of the structural assignments for these compounds was obtained by TLC scale hydride reduction of the acetate (**185**) to the alcohol (**183**), and the acetate (**186**) to the alcohol (**182**) (Scheme 5-3).

An interesting pattern of polarity emerged for the 15,16-diols arising from the dihydroxylations performed in this study. For the 17-hydroxy 15,16-diols (obtained from **181** and **97**), the 15β,16β-diols were less polar than the 15α,16α-diols. For the 17-acetoxy 15,16-diols (obtained from **184**, **73** and **100**), the 15α,16α-diols were less polar than the 15β,16β-diols. It is postulated that the 16β-hydroxy group is in close enough proximity to the 17β-hydroxy group to form a hydrogen bond, thus lowering the polarity of the 15β,16β,17β-triols relative to the 15α,16α,17β-triols. In the case of the 17-acetates, the dominant factor affecting polarity is the steric environment of the 15,16-hydroxy groups. For the 15α,16α-diols, the hydroxy groups are concealed on the *endo*-face of ring D, thus

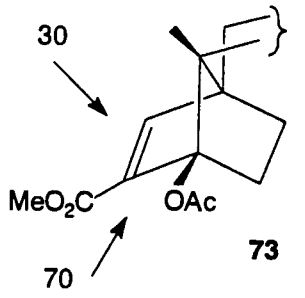
decreasing the polarity of the compound. The reverse argument is true for the 15β,16β-diols, the 15,16-hydroxy groups of which are exposed on the *exo*-face of ring D.

The triols were deprotected at C(3) in the usual manner (Scheme 5-3) to give the estradiol analogues (**187**) and (**188**), which were subjected to biological evaluation (Chapter 6).

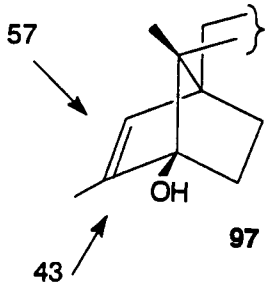
Scheme 5-4 Proportions of *endo*- vs *exo*-attack in Dihydroxylations of 14,17-Bridged 15-Olefins.



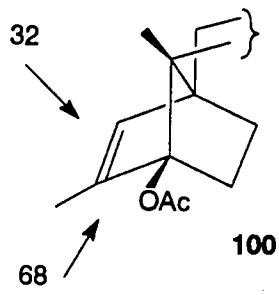
23



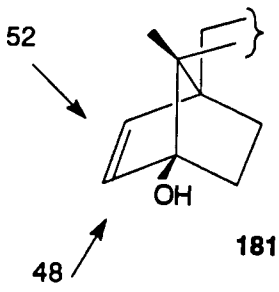
73



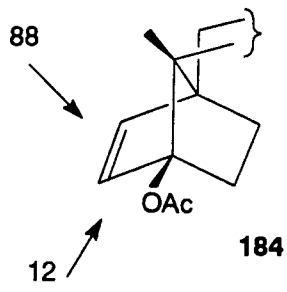
97



100



181



184

The ratios of *endo*- to *exo*-diols obtained from the six dihydroxylation reactions performed throughout this study are summarised in Scheme 5-4. Steric effects predominate in the dihydroxylation of the phenylsulfone (**23**), with *endo*-attack prevented by the presence of the bulky phenylsulfonyl group on this face, resulting in exclusive *exo*-attack of the osmium tetroxide.

Dihydroxylation of the unsaturated ester (**73**) gave predominantly the *endo*-diol, the significance of which will be discussed below.

Introduction of the 16-methyl group had an interesting effect upon reagent approach, and gave results quite different to those for the 14α,17α-bridged olefin. With the bridgehead hydroxy group in place (**97**), little stereodifferentiation occurred (1.3:1), but the presence of the 17-acetoxy group (**100**) led to favoured *endo*-approach (2.1:1). This result suggests that the nature of the substituent on C(16) is of little stereodirecting importance, as the stereochemical outcome was almost identical to that for the 16-methyl carboxylate (**73**) (*endo:exo* = 2.3:1).

In the case of the hydroxy olefin (**181**), *endo*-addition would be expected to be favoured, both in accordance with the behaviour of 7,7-disubstituted bicyclo[2.2.1]hept-2-enes[98] and Kishi's observation that for simple allylic alcohols, *anti*-approach of OsO_4 to the bridgehead hydroxy group is favoured.[101] Inspection of the result of dihydroxylation of this olefin suggests that there is no distinction between the *exo*- and *endo*-faces of the olefin on (**181**), resulting in a 1:1.1 ratio of diols. However, the effect of the 17-hydroxy group became clear when the results for reaction of the 17-acetoxy olefin (**184**) were examined For this compound, *exo*-attack is greatly favoured (7.4:1), suggesting that the 17-hydroxy group does in fact have an *endo*-directing influence.

Although no simple or obvious pattern of stereoselectivity of dihydroxylations to these systems emerged from this study, it did serve to broaden the predictive base and understanding of this reaction. Also, the order of elution of the diols resulting from dihydroxylation can confidently be used as an initial prediction of 15,16-stereochemistry, depending on the bridgehead functionality present.

CHAPTER 6

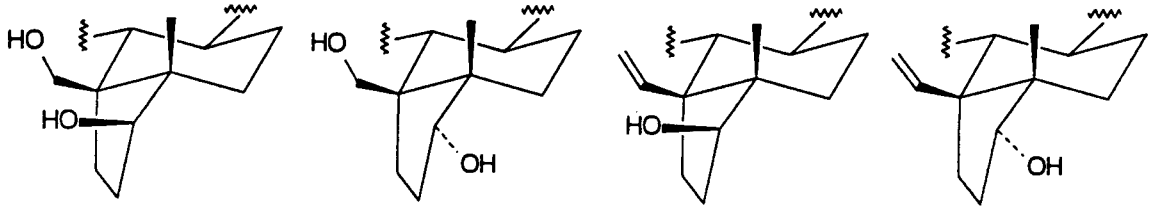
Binding Affinity of Estradiol Analogues

The estradiol and estriol analogues which were synthesised during this investigation were submitted for determination of their affinities toward the estrogen receptor.[102] The affinity which a hormone analogue has for the receptor site is measured *in vitro* and then expressed as a 'competition factor' (CF), defined as:

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

where C_{test} is the concentration of the hormone analogue, and C_{ref} is the concentration of the reference or parent hormone.[32] The parent hormone has CF = unity; hormone analogues with CF in the region of unity are regarded as competitive, and those with CF less than unity potentially more active than the parent.

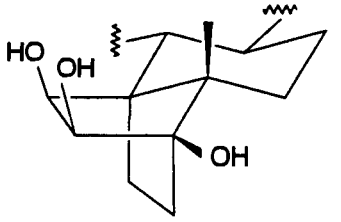
The 14β-functionalised analogues (Figure 6-1) with the 17β-hydroxy, group displayed a higher affinity for the receptor those with 17α-hydroxy group, but not a close enough affinity to be of pharmacological interest. This is a similar pattern of affinity to that displayed by the 14β-ethyl analogues synthesised elsewhere.[20]



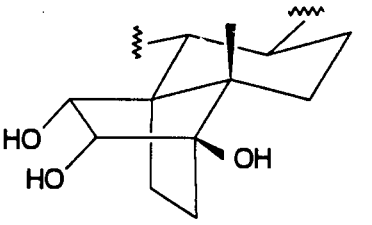
153 CF 7 **154** CF 300 **158** CF 9 **159** CF 58

Figure 6-1 Competition Factors for 14β-Substituted Estradiol Analogues.

Of the two 14α,17α-ethano 3,15,16,17-tetraols synthesised (Figure 6-2), the 15α-hydroxyestriol analogue had the higher affinity for the receptor, however neither hormone analogue displayed a biologically useful affinity for the receptor. This is in marked contrast to the 14α,17α-ethanoestriol analogue,[23] which had CF<1.



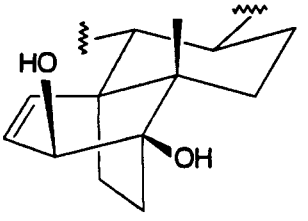
187 CF 34



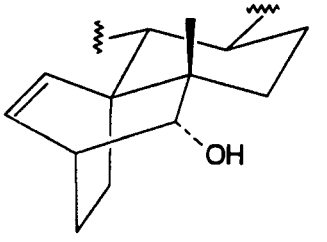
188 CF 16

Figure 6-2 Competition Factors for 14,17-Bridged 15,16-Dihydroxyestradiol Analogues.

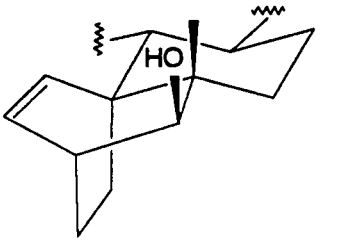
The 14β,17β-propeno analogue which was synthesised (Figure 6-3) followed the trend set by earlier syntheses of this series of analogue,[28] that is, devoid of significant receptor binding affinity. The two 14α,17α-ethano 17a-homoestradiols (Figure 6-3) also followed the trend set by the 14α,17α-etheno- and saturated 17a-homoestradiols[27] *viz.* the 17aβ-hydroxyestradiols show a high affinity for the receptor (CF close to unity), while the 17aα-hydroxyestradiols show a poor affinity for the receptor.



170 CF 180



179 CF 18



180 CF 3.1

Figure 6-3 Competition Factors for Ring D Expanded and Rearranged Estradiol Analogues.

Thus the mapping of the estrogen receptor has been extended with the synthesis and evaluation of these analogues, to allow a slightly clearer view of the demands of the binding site and enable identification of future target hormone analogues.

CHAPTER 7

Experimental

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected.

Specific rotations ($[\alpha]_D$) were determined in chloroform, unless otherwise stated, using a Perkin-Elmer 141 polarimeter and are recorded on units of 10^{-1} deg cm^2 g^{-1}.

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Varian VXR-200 (4.7 T) or Varian Unity (9.4 T), for solutions in deuteriochloroform, unless otherwise specified. Tetramethyl silane (TMS) was used as internal standard. The chemical shifts (δ) are given in ppm relative to TMS (δ 0.00).

Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian VXR-200 (4.7 T) or Varian Unity (9.4 T), for solutions in deuteriochloroform. The chemical shifts (δ) are given in ppm relative to TMS (δ 0.00).

The following abbreviations were used in the ^1H and ^{13}C NMR spectra: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quartet; m, multiplet; qd, quartet of doublets; dt, doublet of triplets; td, triplet of doublets; br, broad; exch., exchange; obsc., obscured, and *J*, coupling constant.

Elemental analyses were performed using a Heraues CHN-rapid combustion analyser.

Mass spectra were recorded on a VG micromass 16F mass spectrometer (operating at 70 eV with an accelerating voltage of 4 kV).

All reactions were monitored by thin layer chromatography (tlc) using Merck F_{254} precoated silica gel plates, with subsequent detection using an ultra-violet lamp (wavelength 254 nm) and heating the plate at 200°C after spraying with a 1% solution of cerium sulphate in 3M sulfuric acid.

Column chromatography was performed using silica gel (Kieselgel 60, Merck).

Evaporation of the solvent under reduced pressure refers to the use of a Büchi Rotary Evaporator to remove the solvent.

Commonly used solvents were purified as follows:

Tetrahydrofuran: dried over sodium wire and then distilled from sodium and benzophenone under an argon atmosphere immediately before use.

Benzene, toluene: distilled from potassium hydroxide and stored over sodium wire.

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

Ether: distilled from sodium wire immediately prior to use.

Desulfonylation of (17²R)-3-*Methoxy*-16-*methyl*-17²-(*phenylsulfonyl*)-14,17α-*ethanoestra*-1,3,5(10),15-*tetraen*-17β-*ol* (**56**).—A suspension of activated magnesium turnings (300 mg, activated with dilute hydrochloric acid) in methanol (20 ml) was heated to 50°C. On commencement of hydrogen evolution, the phenylsulfonyl compound (**56**) (272 mg, 0.58 mmol) was added to the suspension and stirred at 50°C. During the course of the reaction, additional activated magnesium turnings were added (300 mg). After 23 h, the reaction was cooled to 0°C and quenched by addition of 1M hydrochloric acid. Water was added to the mixture, which was then filtered through Celite. The filtrate was extracted into chloroform and the combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue (160 mg) was chromatographed on silica gel (16 g), using ethyl acetate-toluene (1:19) as eluent, to give unidentified material (10 mg), followed by an inseparable mixture (113 mg, 60%) of 3-methoxy-16-methyl-14,17α-ethanoestra-1,3,5(10),15-tetraen-17β-ol (**57**) and 3-methoxy-16α-methyl-15α,17²-cyclo-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol (**58**), δ_H (**57**, *ca* 35%) (200 MHz) 0.84 (3H, s, 13β-Me), 1.71 (3H, s, 16-Me), 3.77 (3H, s, 3-OMe), 5.62 (1H, s, 15-H), 6.63-7.19 (3H, m, 1-, 2-, and 4-H); δ_H (**58**, *ca* 65%) 0.90 (3H, s, 13β-Me), 0.92 (3H, d, *J* 6.8 Hz, 16α-Me), 3.76 (3H, s, 3-OMe) and 6.59-7.23 (3H, m, 1-, 2-, and 4-H).

Dihydroxylation of the Acetoxy Olefin (**23**).—Osmium tetroxide (600 mg, 2.36 mmol) was added to a solution of the olefin (**23**) (1.18 g, 2.39 mmol) in pyridine (45 ml). After reaction for 7 days at 20°C, sodium disulfite (10% aq., 90 ml) was added to the stirred reaction mixture. After 45 min, water was added and the product was extracted into chloroform. The combined organic phase was washed with hydrochloric acid (3M), saturated aqueous sodium hydrogen carbonate, and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue (1.42 g) was chromatographed on silica gel (50 g), using ethyl acetate-toluene (1:4) as eluent, to give starting material (**23**) (157 mg, 13%), followed by (17²R)-3-*methoxy*-16α-*methyl*-17²-*phenylsulfonyl*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-15β,16β,17β-*triol*-17β-*acetate* (**61**) (923 mg, 84%), double m.p. 174-176 and 232-234°C (from chloroform-hexane); $[\alpha]_D$ +115° (*c* 1.0); ν_{max} 3481br (OH) and 1708 (OAc) cm^{-1}; δ_H (400 MHz) 1.32 (3H, s, 13β-Me), 1.78 (3H, s, 16α-Me), 2.06 (3H, s, 17β-OAc), 2.14 (2H, m, 8β- and 7β-H), 2.24 (1H, dd, *J* 14.1 and 12.2 Hz, 17^1-H_{exo}), 2.42 (1H, m, 7α-H), 2.58 (1H, dd, *J* 14.1 and 5.5 Hz, 17^1-H_{endo}), 2.84 (1H, s, exch. by D_2O, 16β-OH), 2.80-3.10 (3H, m, 6-H_2 and 9α-H), 3.06 (1H, d, *J* 5.8 Hz, exch. by

D_2O, 15β-OH), 3.79 (3H, s, 3-OMe), 3.99 (1H, dd, *J* 12.2 and 5.5 Hz, 17^2-H), 4.95 (1H, d, *J* 5.8 Hz → s on D_2O exch., 15α-H), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.7 Hz, 2-H), 7.24 (1H, d, *J* 8.4 Hz, 1-H), and 7.50-7.90 (5H, m, 17^2-$SO_2C_6H_5$); δ_C (100 MHz) 170.4 (s, 17β-O*C*OCH$_3$), 157.5 (s, C-3), 140.9 (s, C-1'), 138.9 (s, C-5), 133.6 (d, C-4'), 132.5 (s, C-10), 129.5 (2xd, C-3' and C-5'), 127.8 (2xd, C-2' and C-6'), 127.1 (d, C-1), 113.6 (d, C-4), 111.9 (d, C-2), 89.2 (s, C-17), 79.5 (s, C-16), 74.7 (d, C-15), 61.6 (d, C-17^2), 58.1 (s, C-14), 55.3 (q, 3-OCH$_3$), 54.4 (s, C-13), 36.3 (d, C-9), 35.6 (d, C-8), 31.2 (t, C-6), 30.5 and 26.7 (each t, C-11 and C-12), 28.9 (t, C-17^1), 25.3 (q, 16-CH$_3$), 24.9 (t, C-7), 21.6 (q, 17β-OCO*C*H$_3$), and 18.0 (q, C-18) (Found: C, 66.4; H, 6.7%; M^+, 540. $C_{30}H_{36}O_7S$ requires C, 66.6; H, 6.7%; *M*, 540).

17α-*Acetoxy*-3-*methoxy*-15β-*phenylsulfonyl*-20-*oxo*-19-*nor*-14β-*pregna*-1,3,5(10)-*triene*-14-*carbaldehyde* (**62**).—Aqueous sodium periodate (6%, 29 ml) was added to a solution of the diol (**61**) (923 mg, 1.7 mmol) in absolute ethanol (50 ml). After 3.5 h at 20°C, water was added to the mixture and the product was isolated by extraction into chloroform. The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue (927 mg) was chromatographed on silica gel (36 g), using ethyl acetate-toluene (1:4) as eluent, to give the non-crystalline 14β-*formyl*-20-*ketone* (**62**) (778 mg, 85%), ν_{max} 1737 (OAc) and 1714 (14^1- and 20-CO) cm^{-1}; δ_H (200 MHz) 1.01 (3H, s, 13β-Me), 1.81 (1H, dd, *J* 15.9 and 9.8 Hz, 16α-H), 2.03 (3H, s, 20-Me), 2.07 (3H, s, 17α-OAc), 2.65-2.90 (3H, m, 6-H_2 and 9α-H), 3.65 (1H, dd, *J* 15.9 and 11.3 Hz, 16β-H), 3.70 (3H, s, 3-OMe), 4.28 (1H, dd, *J* 11.3 and 9.8 Hz, 15α-H), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.7 Hz, 2-H), 7.24 (1H, d, *J* 8.4 Hz, 1-H), 7.50-8.0 (5H, m, 15β-$SO_2C_6H_5$) and 10.29 (1H, s, 14β-CHO); δ_C (50 MHz) 209.4 (s, C-20), 207.5 (d, C-14^1), 170.6 (s, 17β-O*C*OCH$_3$), 157.7 (s, C-3), 140.3 (s, C-1'), 138.7 (s, C-5), 134.0 (d, C-4'), 131.2 (s, C-10), 129.5 (2xd, C-3' and C-5'), 128.3 (2xd, C-2' and C-6'), 127.4 (d, C-1), 113.6 (d, C-4), 112.4 (d, C-2), 92.8 (s, C-17), 67.9 (s, C-14), 64.8 (d, C-15), 55.2 (q, 3-OCH$_3$), 54.4 (s, C-13), 39.9 (d, C-8), 37.5, 28.2, and 26.5 (each t, C-7, C-11, and C-12), 36.2 (d, C-9), 33.1 (t, C-16), 31.6 (t, C-6), 26.6 (q, 20-CH$_3$), 20.9 (q, 17β-OCO*C*H$_3$), and 18.7 (q, C-18) (Found: M^+, 538. $C_{30}H_{34}O_7S$ requires *M*, 538).

Acid Mediated Aldol Condensation of the Formyl Ketone (**62**).—A solution of the formyl ketone (**62**) (249 mg, 0.46 mmol) in hydrochloric acid (1M in tetrahydrofuran, 11 ml) was refluxed, with further additions of acid (2 ml) during the course of the reaction. After 22 h, water was added to the cooled solution and the product was isolated by extraction into chloroform. The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue (250 mg) was chromatographed on silica gel (25 g), using ethyl acetate-toluene (3:17) as eluent, to give an inseparable non-crystalline mixture (98 mg, 41%) of 3-methoxy-15β-phenylsulfonyl-17^1-oxo-14,17β-(prop-17^2-eno)-14β-estra-1,3,5(10)-trien-17α-yl acetate (**63**), and 3-methoxy-15α-phenylsulfonyl-17^1-oxo-14,17β-(prop-17^2-eno)-14β-estra-1,3,5(10)-trien-17α-yl acetate (**64**), ν_{max} 1753br (OAc) and 1697br (CO) cm^{-1}; δ_H (**63**, *ca* 40%) (200 MHz) 0.84 (3H, s, 13β-Me), 2.09 (3H, s, 17α-OAc), 3.79 (3H, s, 3-OMe), 4.41 (1H, obsc., 15α-H), 6.35 (1H, d, *J* 9.8 Hz, 17^2-H), 6.45 (d, *J* 9.8 Hz, 17^3-H), 6.63-7.30 (3H, m, 1-, 2- and 4-H), 7.50-7.90 (5H, m, 15β-$SO_2C_6H_5$); δ_H (**64**, *ca* 60%) 0.97 (3H, s, 13β-Me), 2.16 (3H, s, 17α-OAc), 3.79 (3H, s, 3-OMe), 4.41 (1H, obsc., 15β-H), 7.35 (1H, d, *J* 9.8 Hz, 17^2-H), 7.8 (1H, d, *J* 9.8 Hz, 17^3-H), 6.63-7.30 (3H, m, 1-, 2- and 4-H), and 7.50-7.90 (5H, m, 15α-$SO_2C_6H_5$) (Found: C, 68.9; H, 6.1%; M^+, 520. $C_{30}H_{32}O_6S$ requires C, 69.2; H, 6.2%; *M*, 520), followed by an inseparable mixture (93 mg, 37%) of 17^3-hydroxy-3-methoxy-15β-phenylsulfonyl-17^1-oxo-14,17β-(propano)-14β-estra-1,3,5(10)-trien-17α-yl acetate (**65**) and 17^3-hydroxy-3-methoxy-15α-phenylsulfonyl-17^1-oxo-14,17β-(propano)-14β-estra-1,3,5(10)-trien-17α-yl acetate (**66**), ν_{max} 3527 (OH), 1745 (OAc) and 1727 (CO) cm^{-1}; δ_H (**65**, *ca* 20%) (200 MHz) 1.15 (3H, s, 13β-Me), 2.07 (3H, s, 17β-OAc), 3.79 (3H, s, 3-OMe), 6.63-7.24 (3H, m, 1-, 2- and 4-H), 7.50-8.0 (5H, m, 15β-$SO_2C_6H_5$); δ_H (**66**, *ca* 80%) 1.24 (3H, s, 13β-Me), 1.90 (1H, d, *J* 4.9 Hz, exch. by D_2O, 17^3-OH), 2.17 (3H, s, 17α-OAc), 2.25 (1H, m, 16-H), 2.70 (1H, d, *J* 17.6 Hz, 17^2-H), 3.26 (1H, dd, *J* 15.0 and 6.9 Hz, 16-H), 3.79 (3H, s, 3-OMe), 3.95 (1H, dd, *J* 17.6 and 7.8 Hz, 17^2-H), 4.18 (1H, dd, *J* 11.0 and 6.9 Hz, 15β-H), 5.17 (1H, dd, *J* 7.8 and 4.5 Hz → d on D_2O exch. *J* 7.8 Hz, 17^3-H), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.7 Hz, 2-H), 7.24 (1H, d, *J* 8.5 Hz, 1-H), and 7.50-8.0 (5H, m, 15α-$SO_2C_6H_5$) (Found: C, 66.6; H, 6.4%; M^+, 538. $C_{30}H_{34}O_7S$ requires C, 66.9; H, 6.4%; *M*, 538).

Reduction of the Phenylsulfone (**61**).—Samarium (1.14 g, 7.6 mmol) was placed in a reaction vessel, which was then flame dried and cooled under nitrogen. Tetrahydrofuran (68 ml) and diiodoethane (1.93 g, 6.8 mmol) were added to the samarium. The mixture was stirred for 1 h and changed to a brilliant blue colour. A solution of the phenylsulfone (**61**) (360 mg, 0.6 mmol) in tetrahydrofuran (10 ml) was added and the mixture was cooled to -20°C. Hexamethylphosphoric triamide (5.5 ml) was added. After 4 h at -20°C, the mixture was poured into saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined organic phase was washed with saturated aqueous sodium thiosulfate and brine, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give a residue (303 mg). Chromatography on silica gel (25 g) using ethyl acetate-hexane (3:2) as eluent gave (17^2S)-3-*methoxy*-16α-*methyl*-15α,17^2-*cyclo*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-16β,17β-*diol* 17-*acetate* (**67**) (78 mg, 31%), double m.p. 112-114 and 146-147°C (from chloroform-methanol); $[\alpha]_D$ +41° (*c* 1.0); ν_{max} 3594 (OH) and 1738 (OAc) cm^{-1}; δ_H (400 MHz) 1.09 (1H, dd, *J* 6.2 and 1.1 and 0 Hz, 17^2-H), 1.29 (3H, s, 13β-Me), 1.33 (3H, s, 16α-Me), 1.55 (1H, d, *J* 6.2 Hz, 15-H), 1.83 (1H, d, *J* 11.4 and 0 Hz, 17^1-H_{endo}), 2.09 (3H, s, 17β-OAc), 2.34 (1H, obsc., 9α-H), 2.58 (1H, dd, *J* 11.4 and 1.1 Hz, 17^2-H_{exo}), 2.80 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 170.8 (s, 17β-O*C*OCH$_3$), 157.5 (s, C-3), 137.8 (s, C-5), 132.3 (s, C-10), 126.7 (d, C-1), 113.7 (d, C-4), 111.7 (d, C-2), 89.8 (s, C-17), 82.4 (s, C-16), 55.2 (q, 3-OCH$_3$), 47.1 (s, C-13), 42.9 (d, C-9), 35.7 (s, C-14), 34.9 (d, C-8), 32.6 (t, C-12), 31.0 (t, C-17^1), 29.8 (t, C-6), 26.8 (t, C-11), 24.9 (d, C-15), 23.4 (t, C-7), 23.2 (q, 16-CH$_3$), 21.6 (q, 17β-OCO*C*H$_3$), 17.2 (q, C-18), and 11.5 (d, C-17^2) (Found: M^+, 382.2137. $C_{24}H_{30}O_4$ requires *M*, 382.2144), followed by 3-*methoxy*-16α-*methyl*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-15β,16β,17β-*triol* 17-*acetate* (**68**) (78 mg, 30%), m.p. 182-185°C (from acetone-methanol); $[\alpha]_D$ +4° (*c* 1.0); ν_{max} 3600 and 3515 (OH), 1738 (OAc) cm^{-1}; δ_H (400 MHz) 1.24 (3H, s, 13β-Me), 1.49 (3H, s, 16α-Me), 2.11 (3H, s, 17β-OAc), 2.64 (1H, td, *J* 2x11.5 and 3.4 Hz, 9α-H), 2.78-3.0 (2H, m, 6-H_2), 3.61 (1H, d, *J* 4.7 Hz →s on D_2O exch., 15α-H), 3.76 (3H, s, 3-OMe), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, 3.1 (s, C-10), 126.3 (d, C-1), 113.7 (d, C-4), 111.5 (d, C-2), 91.6 (s, C-17), 82.3 (d, C-15), 78.7 (s, C-16), 55.2 (q, 3-OCH$_3$), 49.9 and 48.9 (each s, C-13 and C-14), 36.7 (d, C-9), 34.6 (d, C-8), 32.1 (t, C-6), 29.9 (t, C-17^1), 27.1 (q, 16-CH$_3$), 25.8, 23.7, 23.4, and 23.2 (each t, C-7, C-11, C-12, and C-17^2), 21.8 (q, 17β-OCO*C*H$_3$), and 16.3 (q, C-18) (Found:

C, 72.0; H, 8.0%; M^+, 400. $C_{24}H_{32}O_5$ requires C, 72.0; H, 8.05%; *M*, 400), followed by the phenylsulfone (**61**) (102 mg, 28%).

(17^2R)-15β,16β-*Isopropylidenedioxy*-3-*methoxy*-16α-*methyl*-17^2-*phenylsulfonyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*yl Acetate* (**69**).—Perchloric acid (70%, 0.05 ml) was added to a solution of the diol (**61**) (740 mg, 0.8 mmol) in acetone (20 ml). The mixture was stirred for 20 min and then allowed to stand for 4.5 h at 20°C. Solid sodium hydrogen carbonate (125 mg) was added, the mixture was concentrated to *ca.* 5 ml, and water (5 ml) was added. The mixture was extracted with ethyl acetate; the organic phase was washed with water and brine and dried ($MgSO_4$). The solution was concentrated under reduced pressure to yield a brown oily residue (750 mg). Chromatography of the residue on silica gel (38g), using ethyl acetate-hexane (35:65) as eluent, gave the 15β,16β-*acetonide* (**69**) (625 mg, 85%), m.p. 185-188°C (from acetone-methanol); $[\alpha]_D$ +102° (*c* 1.0); δ_H (400 MHz) 1.44 (3H, s, 13β-Me) 1.48 and 1.55 (each 3H, s, CMe_2), 1.93 (3H, s, 16α-Me), 2.07 (3H, s, 17β-OAc), 3.79 (3H, s, 3-OMe), 4.05 (1H, dd, *J* 5.5 and 12.4 Hz, 17^2-H), 5.17 (1H, s, 15α-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.21 (1H, d, *J* 8.6 Hz, 1-H), and 7.50-7.90 (5H, m, 17^2-$SO_2C_6H_5$); δ_C (50 MHz) 170.7 (s, 17β-O*C*OCH$_3$), 157.6 (s, C-3), 140.9 (s, C-1'), 138.8 (s, C-5), 133.6 (d, C-4'), 132.3 (s, C-10), 129.5 (2xd, C-3' and C-5'), 127.8 (2xd, C-2' and C-6'), 127.1 (d, C-1), 113.6 (d, C-4), 111.9 (d, C-2), 109.8 (s, 15,16-$O_2C(CH_3)_2$), 90.6 (s, C-17), 88.7 (s, C-16), 80.7 (d, C-15), 61.9 (d, C-17^2), 57.6 (s, C-13), 55.2 (q, 3-OCH_3), 52.2 (s, C-14), 36.2 (d, C-9), 35.9 (d, C-8), 31.2 (t, C-6), 29.7, 27.5, 26.9 and 24.4 (each t, C-7, C-11, C-12, and C-17^1), 26.9 and 25.6 (each q, 15,16-$O_2C(CH_3)_2$), 22.8 (q, 16-CH_3), 21.9 (q, 17β-OCO*C*H$_3$), and 18.6 (q, C-18) (Found: C, 67.9; H, 6.9%; M^+, 580. $C_{33}H_{40}O_7S$ requires C, 68.3; H, 6.9%; *M*, 580), followed by starting material (**61**) (318 mg, 15%).

15β,16β-*Isopropylidenedioxy*-3-*methoxy*-16α-*methyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*yl Acetate* (**70**).—Samarium (418 mg, 1.0 mmol) was placed in a reaction vessel, which was then flame dried and cooled under nitrogen. Tetrahydrofuran (10 ml) and diiodoethane (262 mg, 0.9 mmol) were added to the samarium. The mixture was stirred for 1 h at 25°C and changed to a brilliant blue colour. A solution of the acetonide (**69**) (200 mg, 0.34 mmol) in tetrahydrofuran (8 ml) was added and the mixture

was cooled to -20°C. Hexamethylphosphoric triamide (1.3 ml) was added to the reaction mixture. After 1.5 h at -20°C, the mixture was poured into saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined organic phase was washed with saturated aqueous sodium thiosulfate and brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a residue (240 mg). Flash chromatography on silica gel (15 g) using ethyl acetate-hexane (1:9 then 3:7) as eluent gave the 15β,16β-*acetonide* (**70**) (105 mg, 70%), m.p. 213-217°C (from chloroform-methanol); $[\alpha]_D$ -24° (*c* 1.0); ν_{max} 1732 (OAc) cm^{-1}; δ_H (400 MHz) 0.92 (1H, ddd, *J* 13.4, 9.0 and 6.2 Hz, 12α-H), 1.43 and 1.52 (each 3H, s, CMe_2), 1.33 (3H, s, 13β-Me), 1.64 (3H, s, 16α-Me), 2.11 (3H, s, 17β-OAc), 2.24 (1H, dq, *J* 13.2 and 3x3.9 Hz, 7β-H), 2.62 (1H, td, *J* 2x11.8 and 4.1 Hz, 9α-H), 2.80-3.02 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 3.89 (1H, s, 15α-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 170.8 (s, 17β-O*C*OCH$_3$), 157.5 (s, C-3), 137.7 (s, C-5), 133.1 (s, C-10), 126.3 (d, C-1), 113.7 (d, C-4), 111.4 (d, C-2), 109.9 (s, 15,16-$O_2C(CH_3)_2$), 92.4 (s, C-17), 87.9 (s, C-16), 87.1 (d, C-15), 55.2 (q, 3-OCH_3), 48.2 and 48.0 (each s, C-13 and C-14), 36.8 (d, C-9), 35.1 (d and t, C-8 and C-6), 26.7 and 25.8 (each q, 15,16-$O_2C(CH_3)_2$), 25.6, 23.3, 23.2, 23.2, and 22.5 (each t, C-7, C-11, C-12, C-17^1, C-17^2), 24.1 (q, 16-CH_3), 22.1 (q, 17β-OCO*C*H$_3$), and 16.9 (q, C-18) (Found: C, 73.4; H, 8.0%; M^+, 440. $C_{27}H_{36}O_5$ requires C, 73.6; H, 8.2%; *M*, 440).

Methyl 17β-*Acetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10),15-*tetraene*-16-*carboxylate* (**72**).—Methyl propiolate (2.5 ml, 28 mmol) was added to a solution of the dienyl acetate (**27**) (3.0 g, 9.25 mmol) in dry benzene (12 ml). After 23 h at 100°C in a sealed tube, the solution was adsorbed on silica gel (200 g). Elution with ethyl acetate-toluene (1:49) yielded starting material (**27**) (150 mg, 5%) followed by the *ester* (**72**) (3.21 g, 85%), m.p. 141-144°C (from chloroform-methanol); $[\alpha]_D$ +1° (*c* 1.0); ν_{max} 1740 (OAc) and 1710 (CO) cm^{-1}; δ_H (200 MHz) 1.19 (3H, s, 13β-Me), 2.16 (3H, s, 17β-OAc), 2.50 (1H, td, *J* 2x11.4 and 3.4 Hz, 9α-H), 2.86-2.98 (2H, m, 6-H_2), 3.69 (3H, s, 16-CO_2Me), 3.77 (3H, s, 3-OMe), 6.58 (1H, d, *J* 5.6 Hz, 17^2-H), 6.64 (1H, d, *J* 2.4 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.4 Hz, 2-H), 7.05 (1H, d, *J* 5.6 Hz, 17^1-H), 7.20 (1H, d, *J* 8.6 Hz, 1-H), and 7.44 (1H, s, 15-H); δ_C (50 MHz) 170.8 (s, 17β-O*C*OCH$_3$), 164.8 (s, 16-*C*O$_2$CH$_3$), 157.6 (s, C-3), 152.4 (d, C-15), 147.1 (s, C-16), 140.6 (d, C-17^1), 139.1 (d, C-17^2), 137.7 (s,

C-5), 131.9 (s, C-10), 126.7 (d, C-1), 113.8 (d, C-4), 111.8 (d, C-2), 98.7 (s, C-17), 88.3 (s, C-13), 65.4 (s, C-14), 55.2 (q, 3-OCH_3), 51.3 (q, 16-CO_2CH_3), 39.8 (d, C-9), 35.9 (d, C-8), 30.2 (t, C-12), 29.9 (t, C-6), 26.3 (t, C-11), 25.2 (t, C-7), 21.4 (q, 17-$OCOCH_3$), and 17.0 (q, C-18) (Found: C, 73.5; H, 7.0%; M^+, 408. $C_{25}H_{28}O_5$ requires C, 73.5; H, 6.9%; *M*, 408).

Methyl 17β-*Acetoxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10),15-*tetraene*-16-*carboxylate* (**73**).—Palladium on carbon (10%, 1.02 g) was added to a solution of the cycloadduct (**72**) (3.05 g, 7.4 mmol) in ethyl acetate (100 ml). The mixture was stirred under hydrogen for 3 h at 25°C, then filtered through Celite. The filtrate was concentrated under reduced pressure to give light orange crystals (2.98 g). The product was chromatographed on silica gel (300 g), using ethyl acetate-hexane (3:17) as eluent, to give the *dihydro compound* (**73**) (2.55 g, 83%), m.p. 104-108°C (from methanol); $[\alpha]_D$ +9° (*c* 1.0); ν_{max} 1737 (OAc) and 1713 (CO) cm^{-1}; δ_H (200 MHz) 0.95 (3H, s, 13β-Me), 2.09 (3H, s, 17β-OAc), 2.74 (1H, td, *J* 2x11.3 and 4.1 Hz, 9α-H), 2.85-2.98 (2H, m, 6-H_2), 3.71 (3H, s, 16-CO_2Me), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), 6.91 (1H, s, 15-H), and 7.18 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 170.4 (s, 17β-$OCOCH_3$), 164.6 (s, 16-CO_2CH_3), 157.6 (s, C-3), 144.4 (d, C-15), 137.9 (s, C-5), 137.5 (s, C-16), 132.6 (s, C-10), 126.2 (d, C-1), 113.8 (d, C-4), 111.6 (d, C-2), 93.8 (s, C-17), 59.6 (s, C-14), 55.2 (q, 3-OCH_3), 54.1 (s, C-13), 51.3 (q, 16-CO_2CH_3), 37.1 (d, C-9), 36.1 (d, C-8), 29.9 (t, C-6), 29.7 (t, C-12), 28.1 and 24.7 (each t, C-17^1 and C-17^2), 25.9 (t, C-7), 25.4 (t, C-11), 21.7 (q, 17-$OCOCH_3$), and 15.4 (q, C-18) (Found: C, 73.1; H, 7.5%; M^+, 410. $C_{25}H_{30}O_5$ requires C, 73.1; H, 7.4%; *M*, 410).

Attempted Selective Reduction of the Ester (**73**).—(a) Lithium aluminium hydride (85 mg) was added to a solution of the ester (**73**) (200 mg, 0.48 mmol) in tetrahydrofuran (5 ml). After 20 h at 80°C, saturated aqueous ammonium chloride was added and the product was extracted with chloroform. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the residue (167 mg) which was adsorbed on silica gel (26 g). Elution with ethyl acetate-toluene (2:3) gave starting material (**73**) (80 mg, 40%), followed by 17β-*hydroxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-16α-*carbaldehyde* (**74**) (18 mg, 11%),

m.p. 182-184°C (from chloroform-hexane); $[\alpha]_D$ +81° (*c* 1.0); δ_H (200 MHz) 1.04 (3H, s, 13β-Me), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.18 (1H, d, *J* 8.6 Hz, 1-H), and 9.72 (1H, s, 16-CHO) (Found: M^+, 340. $C_{22}H_{28}O_3$ requires *M*, 340), followed by the diol (**75**) (45 mg, 28%), m.p. 219-222°C (lit.,[23] m.p. 220-223°C); *m/z* 342 (M^+).

(b) A solution of aluminium trichloride (80 mg) in ether (2 ml) was added to a slurry of lithium aluminium hydride (68 mg) in tetrahydrofuran at 0°C. The ester (**73**) (199 mg, 0.244 mmol) was added to the reaction mixture. After 25 h at 0°C, sodium hydroxide (2N) was added, the reaction mixture was filtered through Celite and extracted with chloroform. The organic phase was washed with water and brine, dried and concentrated under reduced pressure to give the residue (75 mg), which was chromatographed on silica gel (7 g) using ethyl acetate-hexane (2:3) as eluent, to give starting material (**73**) (96 mg, 48%), followed by the carbaldehyde (**74**) (18 mg, 21%), and the diol (**75**) (26 mg, 31%).

Dihydroxylation of Methyl 17β-*Acetoxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10),15-*tetraene*-16-*carboxylate* (**73**).—(a) Osmium tetroxide (250 mg, 0.9 mmol) was added to a solution of the acetoxy olefin (**73**) (403 mg, 0.98 mmol) in dry pyridine (5 ml). After 48 h at 25°C, sodium disulfite (40 ml, 10%) was added and the mixture was stirred for 45 min. Water was added and the mixture was extracted with chloroform. The organic phase was washed with dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue (569 mg) was chromatographed on silica gel (26 g), using ethyl acetate-toluene (1:9) as eluent, to give starting material (**73**) (23 mg, 6%), followed by *methyl* 17β-*acetoxy*-15α,16α-*dihydroxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-16β-*carboxylate* (**76**) (281 mg, 65%), m.p. 169-170°C (from acetone); $[\alpha]_D$ +49° (*c* 1.0); ν_{max} 3509br (OH), 1733 (OAc), 1714 (CO) cm^{-1}; δ_H (200 MHz) 0.82 (3H, s, 13β-Me), 2.14 (3H, s, 17β-OAc), 2.70 (1H, obsc., 9α-H), 2.80-2.90 (2H, m, 6-H_2), 3.73 (3H, s, 16-CO_2Me), 3.76 (3H, s, 3-OMe), 4.42 (1H, d, *J* 1.5 Hz, 15β-H), 5.90 (1H, s, exch. by D_2O, 16α-OH), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 174.9 (s, 16-*C*O_2CH_3), 171.4 (s, 17β-O*C*OCH$_3$), 157.5 (s, C-3), 137.9 (s, C-5), 132.4 (s, C-10), 126.3 (d, C-1), 113.6 (d, C-4), 111.6 (d, C-2), 93.7 (s, C-17), 75.9 (d, C-15), 75.6 (s, C-16), 55.1 (q, 3-OCH_3), 52.5 (q, 16-CO_2CH_3), 48.3 and 46.5 (each s, C-13 and C-14), 40.0 (d, C-8), 37.1 (d, C-9), 29.9 (t, C-6), 28.4 (t, C-12), 25.3,

solvent was evaporated under reduced pressure to give the product (5.9 g). Chromatography on silica gel (150 g) using ethyl acetate-toluene (1:9) as eluent, gave the *acetonide* (**78**) (4.04 g, 85%), m.p. 130-134°C (from acetone-methanol); $[\alpha]_D$ +57° (*c* 1.0); ν_{max} 1740 (OAc and CO) cm^{-1}; δ_H (200 MHz) 0.95 (3H, s, 13β-Me), 1.35 and 1.61 (each 3H, s, CMe_2), 2.03 (3H, s, 17β-OAc), 2.68 (1H, td, *J* 2x11.4 and 4.8 Hz, 9α-H), 2.80-2.91 (2H, m, 6-H_2), 3.14 (1H, m, 17^1-H_{endo}), 3.76 (3H, s, 16β-CO_2Me), 3.78 (3H, s, 3-OMe), 5.0 (1H, d, *J* 1.1 Hz, 15β-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 69.1; H, 7.2%; M^+ 484. $C_{28}H_{36}O_7$ requires C, 69.3; H, 7.4%; *M*, 484).

16β-*Hydroxymethyl*-15α,16α-*isopropylidenedioxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*ol* (**79**).—Lithium aluminium hydride (918 mg, 80 mmol) was added slowly to a solution of the ester (**78**) (4.04 g, 8.4 mmol) in tetrahydrofuran (50 ml) at 25°C under nitrogen. After 3 h saturated aqueous ammonium chloride was added and the product was extracted with chloroform. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the residue (4.05 g) which was adsorbed on silica gel (90 g). Elution with ethyl acetate-toluene (2:3) gave the non-crystalline *diol* (**79**) (3.47 g, 100%), $[\alpha]_D$ +97° (*c* 1.0); ν_{max} 3544br (OH) cm^{-1}; δ_H (400 MHz) 0.92 (3H, s, 13β-Me), 1.48 and 1.62 (each 3H, s, CMe_2), 2.68 (1H, td, *J* 2x11.3 and 4.3 Hz, 9α-H), 2.74-2.90 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 3.79 and 4.32 (each 1H, d, *J* 11.9 Hz, 16^1-H_2), 4.22 (1H, d, *J* 1.2 Hz, 15β-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 157.5 (s, C-3), 137.8 (s, C-5), 132.9 (s, C-10), 126.4 (d, C-1), 114.7 (s, 15,16-$O_2C(CH_3)_2$), 113.8 (d, C-4), 111.6 (d, C-2), 90.1 (s, C-16), 88.6 (d, C-15), 87.4 (s, C-17), 67.2 (t, C-16^1), 55.2 (q, 3-OCH_3), 51.5 and 49.5 (each s, C-13 and C-14), 39.9 (d, C-8), 36.9 (d, C-9), 30.0 (t, C-6), 28.9 and 26.6 (each q, 15,16-$O_2C(CH_3)_2$), 28.5 (t, C-12), 26.5 and 18.6 (each t, C-17^1 and C-17^2), 25.6 (t, C-11), 24.8 (t, C-7), and 14.5 (q, C-18) (Found: C, 72.2; H, 8.2%; M^+, 414. $C_{25}H_{34}O_5$ requires C, 72.4; H, 8.3%; *M*, 414).

15α,16α-*Isopropylidenedioxy*-3-*methoxy*-16β-*methyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*ol* (**81**).—Methanesulfonyl chloride (2.1 ml, 24 mmol) was added to a solution of the diol (**79**) (3.4 g, 8.2 mmol) in dry pyridine at 0°C under nitrogen. After 1.5 h

at 0°C, water was added and the product was extracted with toluene. The combined organic layers were washed with brine and water and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the residue (4.41 g) which was adsorbed on silica gel (100 g). Elution with ethyl acetate-toluene (3:7) gave non-crystalline 15α,16α-isopropylidenedioxy-16β-(methanesulfonyloxy)methyl-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol (**80**) (4.04 g, 100%), δ_H (200 MHz) 0.99 (3H, s, 13β-Me), 1.50 and 1.60 (each 3H, s, CMe_2), 3.05 (3H, s, 16^1-OMs), 3.75 (3H, s, 3-OMe), 4.45 and 4.75 (each 1H, d, *J* 11.1 Hz, 16^1-H_2), 4.60 (1H, d, *J* 1.4 Hz, 15β-H), 6.60 (1H, d, J 2.8 Hz, 4-H), 6.70 (1H, dd, J 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, J 8.6 Hz, 1-H).

Lithium aluminium hydride (909 mg, 24 mmol) was added to a solution of the methanesulfonyloxy compound (**80**) (4.04 g, 8.2 mmol) in tetrahydrofuran (20 ml) under nitrogen. After 24 h at 25°C, saturated aqueous ammonium chloride was added and the product was extracted with toluene. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the residue (2.98 g) which was adsorbed on silica gel (200 g). Elution with ethyl acetate-toluene (3:17) gave the *hydroxy acetonide* (**81**) (2.92 g, 89%), m.p. 98-102°C (from acetone-methanol); $[\alpha]_D$ +111° (*c* 1.0); ν_{max} 3598 (OH) cm^{-1}; δ_H (400 MHz) 0.94 (3H, d, *J* 0.8 Hz, 13β-Me), 1.45 and 1.63 (each 3H, s, CMe_2), 1.54 (3H, s, 16β-Me), 2.70 (1H, td, *J* 2x11.8 and 4.8 Hz, 9α-H), 2.78-2.88 (2H, m, 6-H_2), 3.73 (3H, s, 3-OMe), 4.22 (1H, d, *J* 1.6 Hz, 15β-H), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 157.5 (s, C-3), 137.9 (s, C-5), 133.0 (s, C-10), 126.4 (d, C-1), 113.9 (s, 15,16-$O_2C(CH_3)_2$), 113.7 (d, C-4), 111.6 (d, C-2), 91.4 (d, C-15), 88.5 and 86.9 (each s, C-16 and C-17), 55.2 (q, 3-OCH_3), 51.1 and 49.6 (each s, C-13 and C-14), 39.9 (d, C-8), 37.1 (d, C-9), 30.0 (t, C-6), 28.7 and 25.9 (each q, 15,16-$O_2C(CH_3)_2$), 28.6 (t, C-7), 28.5, 26.5 and 18.6 (each t, C-12, C-17^1 and C-17^2), 26.5 (q, 16-CH_3), 25.7 (t, C-11), and 15.0 (q, C-18) (Found: C, 75.3; H, 8.6%; M^+, 398. $C_{25}H_{34}O_4$ requires C, 75.3; H, 8.6%; *M*, 398).

15α,16α-*Isopropylidenedioxy*-3-*methoxy*-16β-*methyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*yl Acetate* (**82**).—Toluene-*p*-sulfonic acid (15 mg, 0.97 mmol) was added to a solution of the alcohol (**81**) (2.59 g, 6.5 mmol) in acetic anhydride (90 ml) and tetrahydrofuran (10 ml). After 1 h at 20°C, the reaction mixture was added to saturated aqueous sodium hydrogen carbonate, extracted with chloroform, and the combined organic

phase was washed with saturated aqueous sodium hydrogen carbonate, and water. The solvent was evaporated under reduced pressure and the residue (2.5 g) was chromatographed on silica gel (200 g), using ethyl acetate-toluene (1:9) as eluent, to give the *acetate* (**82**) (2.08 g, 73%) m.p. 191-193°C (from chloroform-methanol); $[\alpha]_D$ +96° (*c* 1.0); ν_{max} 1735 (OAc) cm^{-1}; δ_H (200 MHz) 0.99 (3H, s, 13β-Me), 1.46 and 1.59 (each 3H, s, CMe_2), 1.56 (3H, s, 16β-Me), 2.05 (3H, s, 17β-OAc), 3.76 (3H, s, 3-OMe), 4.30 (1H, d, *J* 1.3 Hz, 15β-H), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 73.3; H, 8.2%; M^+, 440. $C_{27}H_{36}O_5$ requires C, 73.6; H, 8.2%; *M*, 440), followed by the alcohol (**81**) (150 mg, 6%).

3-*Methoxy*-16β-*methyl*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-15α,16α,17β-*triol* 17-*Acetate* (**83**).—The acetonide (**82**) (93 mg, 0.2 mmol) was added to a solution of iodine in methanol (1%, 13 ml). After 5.5 h at 82°C, the solution was cooled and saturated aqueous sodium thiosulfate was added until the disappearance of colour. The mixture was extracted with ethyl acetate, the combined organic phase was washed with saturated sodium thiosulfate and water, dried over magnesium sulfate and the solvent was evaporated under reduced pressure to give the residue (89 mg), which was chromatographed on silica gel (10 g) using ethyl acetate-hexane (1:9) as eluent, to give an inseparable mixture (9 mg) of the acetonide (**82**) and the product (**83**), followed by pure *diol* (**83**) (63 mg, 79%), m.p. 145-149°C (from acetone-methanol); $[\alpha]_D$ +91° (*c* 1.0); ν_{max} 3482br (OH), 1710 (OAc) cm^{-1}; δ_H (200 MHz) 0.99 (3H, s, 13β-Me), 1.35 (3H, s, 16β-Me), 2.12 (3H, s, 17β-OAc), 2.62 (1H, obsc., 9α-H), 2.76-2.90 (2H, m, 6-H_2), 3.75 (1H, d, *J* 1.1 Hz, 15β-H), 3.77 (3H, s, 3-OMe), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 173.7 (s, 17-O*C*OCH$_3$), 157.5 (s, C-3), 138.1 (s, C-5), 132.8 (s, C-10), 126.4 (d, C-1), 113.6 (d, C-4), 111.6 (d, C-2), 94.9 (s, C-17), 80.8 (d, C-15), 73.2 (s, C-16), 55.2 (q, 3-OCH_3), 48.1 and 46.4 (each s, C-13 and C-14), 39.9 (d, C-8), 37.1 (d, C-9), 30.1 (t, C-6), 28.5, 26.5, 25.7, 24.3 and 18.6 (each t, C-12, C-17^1, C-17^2, C-11 and C-7), 26.4 (q, 16-CH_3), 21.2 (q, 17-OCO*C*H$_3$), and 14.9 (q, C-18) (Found: C, 72.0; H, 8.1%; M^+, 400. $C_{24}H_{32}O_5$ requires C, 72.0; H, 8.1%; *M*, 400).

Methyl 17β-*Acetoxy*-15β,16β-*isopropylidenedioxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-16α-*carboxylate* (**84**).—Perchloric acid (70%, 1 ml) was added to a solution of the dihydroxy ester (**77**) (1.12 g, 2.52 mmol) in acetone (110 ml). After 1.5 h at 20°C, solid sodium hydrogen carbonate (1.5 g) was added and the acetone was evaporated under reduced pressure. Water was added to the mixture and the product was extracted with chloroform. The combined organic layers were washed with water and brine, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the product (1.22 g). Chromatography on silica gel (60 g) using ethyl acetate-toluene (1:9) as eluent, gave the *acetonide* (**84**) (1.22 g, 100 %), double m.p. 178-182 and 187-191°C (from chloroform-hexane); $[\alpha]_D$ +4° (*c* 1.0); ν_{max} 1732 (OAc and CO) cm^{-1}; δ_H (200 MHz) 1.22 (3H, s, 13β-Me), 1.35 and 1.55 (each 3H, s, CMe_2), 2.09 (3H, s, 17β-OAc), 2.66 (1H, td, *J* 2x11.3 and 4.0 Hz, 9α-H), 2.82-3.02 (2H, m, 6-H_2), 3.76 (3H, s, 16α-CO_2Me), 3.78 (3H, s, 3-OMe), 4.64 (1H, s, 15α-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 69.1; H, 7.2%; M^+, 484. $C_{28}H_{36}O_7$ requires C, 69.3; H, 7.4%; *M*, 484).

16α-*Hydroxymethyl*-15β,16β-*isopropylidenedioxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*ol* (**85**).—Lithium aluminium hydride (226 mg, 5.9 mmol) was added slowly to a solution of the ester (**84**) (1.22 g, 2.52 mmol) in tetrahydrofuran (16 ml) at 25°C under nitrogen. After 2.5 h saturated aqueous ammonium chloride was added and the product was extracted with chloroform. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the residue (1.21 g) which was adsorbed on silica gel (30 g). Elution with ethyl acetate-toluene (1:2) gave starting material (**84**) (117 mg, 10%) followed by the non-crystalline *diol* (**85**) (952 mg, 90%), $[\alpha]_D$ +5° (*c* 1.0); ν_{max} 3560br (OH) cm^{-1}; δ_H (200 MHz) 1.30 (3H, s, 13β-Me), 1.40 and 1.55 (each 3H, s, CMe_2), 2.64 (1H, td, *J* 2x11.2 and 4.2 Hz, 9α-H), 2.76-3.0 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 3.84 (1H, s, 15α-H), 4.02 and 4.10 (each 1H, d on D_2O exch., *J* 11.8 Hz, 16^1-H_2), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 72.6; H, 8.2%; M^+, 414. $C_{25}H_{34}O_5$ requires C, 72.4; H, 8.2%; *M*, 414).

15β,16β-*Isopropylidenedioxy*-3-*methoxy*-16α-*methyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*ol* (**87**).—Methanesulfonyl chloride (0.53 ml, 7 mmol) was added to a solution of the diol (**85**) (937 mg, 2.26 mmol) in dry pyridine (10 ml) at 0°C under nitrogen. After 1.5 h at 0°C, water was added and the product was extracted with toluene. The combined organic layers were washed with brine and water and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the residue (1.08 g) which was adsorbed on silica gel (80 g). Elution with ethyl acetate-toluene (1:2) gave the non-crystalline 15β,16β-isopropylidenedioxy-16α-(methanesulfonyloxy)-methyl-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol (**86**) (887 mg, 80%).

Lithium aluminium hydride (204 mg, 6.0 mmol) was added to a solution of (**86**) (887 mg, 1.79 mmol) in tetrahydrofuran (10 ml) under nitrogen. After 5.5 h at 25°C, saturated aqueous ammonium chloride was added and the product was extracted with chloroform. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the residue (827 mg) which was adsorbed on silica gel (60 g). Elution with ethyl acetate-toluene (1:5) gave the non-crystalline *hydroxy acetonide* (**87**) (492 mg, 69%), $[\alpha]_D$ +62° (*c* 1.0); ν_{max} 3572 (OH) cm^{-1}; δ_H (200 MHz) 1.26 (3H, s, 13β-Me), 1.43 and 1.54 (each 3H, s, CMe_2), 1.50 (3H, s, 16α-Me), 2.65 (1H, td, *J* 2x11.3 and 4.3 Hz, 9α-H), 2.80-3.0 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 3.92 (1H, s, 15α-H), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 75.4; H, 8.7%; M^+, 398. $C_{25}H_{34}O_4$ requires C, 75.3; H, 8.6%; *M*, 398).

15β,16β-*Isopropylidenedioxy*-3-*methoxy*-16α-*methyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*yl Acetate* (**70**).—Toluene-*p*-sulfonic acid (90 mg, 0.5 mmol) was added to a solution of the alcohol (**87**) (428 mg, 1.07 mmol) in acetic anhydride (12 ml) and tetrahydrofuran (5 ml). After 24 h at 25°C, the reaction mixture was added to saturated aqueous sodium hydrogen carbonate, extracted with chloroform, and the combined organic phase was washed with saturated aqueous sodium hydrogen carbonate, and water. The solvent was evaporated under reduced pressure and the residue (568 mg) was chromatographed on silica gel (40 g), using ethyl acetate-toluene (7:93) as eluent, to give the *acetoxy acetonide* (**70**) (463 mg, 88%), followed by starting material (**87**) (85 mg, 12%).

Hydrolysis of the Acetonide (**70**).—A solution of iodine in methanol (0.5%, 27 ml) was added to a solution of the acetonide (**70**) (463 mg, 1.05 mmol) in tetrahydrofuran (10 ml). After 3.5 h at 80°C, the solution was cooled and saturated aqueous sodium thiosulfate was added until the disappearance of colour. The reaction mixture was extracted with ethyl acetate, the combined organic phase was washed with saturated aqueous sodium thiosulfate and water, dried over magnesium sulfate and the solvent was evaporated under reduced pressure to give the residue (436 mg). Flash chromatography on silica gel (40 g) using ethyl acetate-hexane (35:65) as eluent gave starting material (**70**) (4 mg, 2%), followed by an inseparable mixture (379 mg, 91%) of the diol (**68**) and 3-methoxy-16α-methyl-14,17α-ethanoestra-1,3,5(10)-triene-15β,16β,17β-triol 15β-acetate (**88**).

Attempted Oxidative Cleavage of the Mixture of Diols (**68**) + (**88**).—Aqueous sodium metaperiodate (6%, 11 ml) was added to a solution of the diols (**68**) + (**88**) (794 mg, 1.99 mmol) in ethanol (80 ml). After 24 h at 20°C, water was added to the mixture and the product was isolated by extraction into chloroform. The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue (794 mg) was chromatographed on silica gel (80 g), using ethyl acetate-hexane (1:4 then 2:3) as eluent, to give the 14β-*formyl*-20-*ketone* (**123**) (464 mg, 56%) (see later), followed by 3-*methoxy*-16α-*methyl*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-15β,16β,17β-*triol* 15β-*acetate* (**88**) (258 mg, 32%), m.p. 183-186°C (from chloroform-methanol); $[\alpha]_D$ -17° (*c* 1.0); ν_{max} 3597 (OH) and 1721 (OAc) cm^{-1}; δ_H (200 MHz) 1.14 (3H, s, 13β-Me), 1.48 (3H, s, 16α-Me), 2.05 (3H, s, 15β-OAc), 2.64 (1H, td, *J* 2x11.2 and 4.8 Hz, 9α-H), 2.78-2.86 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.45 (1H, s, 15α-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 171.5 (s, 15-O*C*OCH$_3$), 157.5 (s, C-3), 137.6 (s, C-5), 133.2 (s, C-10), 126.4 (d, C-1), 113.8 (d, C-4), 111.5 (d, C-2), 84.6 (s, C-17), 83.4 (d, C-15), 78.7 (s, C-16), 55.2 (q, 3-O*C*H$_3$), 48.9 and 48.4 (each s, C-13 and C-14), 36.6 (d, C-9), 35.0 (d, C-8), 29.8 (t, C-6), 29.7, 25.6, 25.0, 23.4 and 23.1 (each t, C-12, C-17^1, C-17^2, C-11 and C-7), 26.0 (q, 16-*C*H$_3$), 20.9 (q, 15-OCO*C*H$_3$), and 15.4 (q, C-18) (Found: C, 72.1; H, 7.7; M^+, 400. $C_{24}H_{32}O_5$ requires C, 71.9; H, 8.0%; *M*, 400).

3-*Methoxy*-16α-*methyl*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-15β,16β,17β-*triol* (**89**).—Lithium aluminium hydride (18 mg, 0.48 mmol) was added to a solution of the mixture (65 mg, 0.16 mmol) of diols (**68**) + (**88**) in tetrahydrofuran (5 ml). After 1.25 h at 25°C, saturated aqueous ammonium chloride was added to the reaction mixture and the product was extracted into ethyl acetate. The combined organic phase was washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure, to give the triol (**89**) (57 mg, 98%), m.p. 190-193°C (from chloroform-hexane); $[\alpha]_D$ +22° (*c* 1.0); ν_{max} 3552 (OH) cm^{-1}; δ_H (200 MHz) 1.11 (3H, d, *J* 0.9 Hz, 13β-Me), 1.35 (3H, s, 16α-Me), 2.80-3.0 (2H, m, 6-H_2), 3.60 (1H, s, 15α-H), 3.75 (3H, s, 3-OMe), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 74.0; H, 8.3%; M^+, 358. $C_{22}H_{30}O_4$ requires C, 73.7; H, 8.4%; *M*, 358).

Chemoselective Acetylation of the Triol (**89**).—Toluene-*p*-sulfonic acid (5 mg, 0.3 mmol) was added to a solution of the triol (**89**) (50 mg, 0.16 mmol) in tetrahydrofuran (2ml) and acetic anhydride (0.015 ml, 0.16 mmol). After 20 h at 25°C, the reaction mixture was added to saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate, the combined organic phase was washed with water, dried over magnesium sulfate and the solvent was evaporated under reduced pressure to give the residue (59 mg). Chromatography on silica gel (7 g) using ethyl acetate-hexane (35:65) as eluent gave the 15β,16β,17β-*triol* 15-*acetate* (**88**) (31 mg, 46%), followed by the triol (**89**) (15.5 mg, 31%).

(14^{1}S)-14(14^1-*Acetoxy*-14^2-*oxopropyl*)-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**90**).—Lead tetraacetate (90 mg, 0.2 mmol) was added to a solution of the diol (**88**) (50 mg, 0.13 mmol) in benzene (1.5 ml). After 5 min at 20°C, ethylene glycol was added to the reaction mixture, and the product was extracted into ethyl acetate. The combined organic phase was washed with brine and water, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give the *cleavage product* (**90**) (50 mg, 100%), m.p. 204-207°C (from chloroform-methanol); $[\alpha]_D$ +104° (*c* 1.0); ν_{max} 1735 (OAc) and 1725br (CO) cm^{-1}; δ_H (200 MHz) 1.02 (3H, s, 13β-Me), 1.98 (3H, s, 14^1-OAc), 2.37 (3H, s, 14^2-Me), 3.77 (3H, s, 3-OMe), 4.77 (1H, s, 14^1-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 72.4; H, 7.4%; M^+, 398. $C_{24}H_{30}O_5$ requires C, 72.3; H, 7.6%; *M*, 398).

Methyl 17β-*Acetoxy*-3-*methoxy*-15α-*phenylthio*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-16β-*carboxylate* (**91**).—Diisopropylethylamine (1.6 ml) was added to a solution of the unsaturated ester (**73**) (3.06 g, 7.46 mmol) in thiophenol (10 ml) at 20°C. After 48h at 20°C, the reaction mixture was adsorbed directly on silica gel (200 g). Pressure elution with ethyl acetate-hexane (1:9) yielded the *product* (**91**) (3.84 g, 98%), m.p. 153-155°C (from chloroform-methanol); $[\alpha]_D$ +42° (*c* 0.8); $\nu_{max.}$ 1734 (CO), 1607, 1599, 1580 and 1571 cm^{-1}[1]; δ_H (400 MHz) 1.23 (3H, s, 13β-Me), 1.96 (1H, td, *J* 2x11.3 and 2.3 Hz, 8β-H), 2.02 (3H, s, 17β-OAc), 2.16 (1H, td, *J* 2x13.1 and 3.6 Hz), 2.72 (1H, obsc., 9α-H), 2.82-2.92 (2H, m, 6-H_2), 3.36 (1H, dd, *J* 5.6 and 2.5 Hz, 15β-H), 3.53 (3H, s, 16β-CO_2Me), 3.78 (3H, s, 3-OMe), 3.82 (1H, d, *J* 5.6 Hz, 16α-H), 6.64 (1H, d, *J* 2.4 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.4 Hz, 2-H), and 7.15-7.45 (6H, m, 1-H and SC_6H_5); δ_C (50 MHz) 173.9 (s, 16-CO_2CH_3), 170.2 (s, 17β-$OCOCH_3$), 157.5 (s, C-3), 137.9 (s, C-5), 136.2 (s, C-1'), 131.9 (s, C-10), 132.0 (2xd, C-2' and C-6'), 128.9 (2xd, C-3' and C-5'), 127.2 (d, C-4'), 126.2 (d, C-1), 113.8 (d, C-4), 111.5 (d, C-2), 90.8 (s, C-17), 58.9 (d, C-16), 58.9 (d, C-15), 55.2 (q, 3-OCH_3), 51.7 (q, 16-CO_2CH_3), 51.6 and 49.8 (each s, C-13 and C-14), 37.6 (d, C-9), 37.1 (d, C-8), 29.7 (t, C-6), 28.8, 28.6, 25.7, 24.1 and 23.7 (each t, C-7, C-11, C-12, C-17[1] and C-17[2]), 21.4 (q, 17β-$OCOCH_3$), and 15.6 (q, C-18) (Found: C, 71.35; H, 7.0%; M^+, 520. $C_{31}H_{36}O_5S$ requires C, 71.5; H, 7.0%; *M*, 520).

16β-*Hydroxymethyl*-3-*methoxy*-15α-*phenylthio*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*ol* (**92**).—Lithium aluminium hydride (1.6 g, 44.2 mmol) was added to a solution of the ester (**91**) (3.84 g, 7.38 mmol) in tetrahydrofuran. After 45 min at 20°C, saturated aqueous ammonium chloride was added to the reaction mixture and the product was extracted into ethyl acetate. The combined organic phase was washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the *diol* (**92**) (3.32 g, 100%), m.p. 207-210°C (from chloroform); $[\alpha]_D$ +41° (*c* 0.8); ν_{max} 3593br (OH) cm^{-1}; δ_H (200 MHz) 1.20 (3H, s, 13β-Me), 2.74 (1H, obsc., 15β-H), 3.77 (3H, s, 3-OMe), 3.80 (2H, m, 16[1]-H_2), 6.64 (1H, d, *J* 2.4 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.4 Hz, 2-H), and 7.15-7.45 (6H, m, 1-H and SC_6H_5) (Found: C, 74.8; H, 7.5; S, 6.6%; M^+, 450. $C_{28}H_{34}O_3S$ requires C, 74.6; H, 7.6; S, 7.1%; *M*, 450).

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[1]The infrared absorption bands for ring A appear at 1607 and 1580 cm^{-1} while those for the 15-SPh aromatic ring appear at 1599 and 1571 cm^{-1} throughout the series of compounds containing this group.

3-*Methoxy*-16β-*methyl*-15α-*phenylthio*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*ol* (**94**).—Methanesulfonyl chloride (0.7 ml, 8.8 mmol) was added to a solution of the diol (**92**) (3.32 g, 7.38 mmol) in dry pyridine at 0°C under nitrogen. After 1 h at 0°C, water was added and the product was extracted with ethyl acetate. The combined organic layers were washed with brine and water and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the residue (3.88 g) which was adsorbed on silica gel (100 g). Flash elution with ethyl acetate-toluene (2:3) gave non-crystalline 16β-(methanesulfonyloxy)methyl-3-methoxy-15α-phenylthio-14,17a-ethanoestra-1,3,5(10)-trien-17β-ol (**93**) (3.12 g, 81%).

Lithium aluminium hydride (876 mg, 29 mmol) was added to a solution of (**93**) (3.12 g, 5.9 mmol) in tetrahydrofuran (50 ml) under nitrogen. After 2.4 h at 20°C, saturated aqueous ammonium chloride was added and the product was extracted with ethyl acetate. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the residue (2.6 g) which was adsorbed on silica gel (175 g). Flash elution with ethyl acetate-toluene (1:9) gave the 16β-*methyl compound* (**94**) (2.46 g, 96%), m.p. 135-136°C (from methanol); $[\alpha]_D$ +56° (*c* 1.0); ν_{max} 3594 (OH) cm^{-1}; δ_H (400 MHz) 0.90 (3H, d, *J* 7.2 Hz, 16β-Me), 1.10 (3H, d, *J* 0.9 Hz, 13β-Me), 1.42 (1H, dq, *J* 12.4 and 3x2.6 Hz), 1.62 (1H, dq, *J* 12.4 and 3x2.5 Hz), 1.84 (1H, ddd, *J* 12.4, 9.5 and 3.1 Hz), 1.98 (1H, td, *J* 2x11.5 and 2.1 Hz), 2.05 (1H, td, *J* 2x12.7 and 3.4 Hz), 2.41 (1H, ddd, *J* 7.0, 5.7 and 2.5 Hz), 2.66 (1H, obsc., 8β-H), 2.60-2.86 (2H, m, 6-H_2), 2.84 (1H, d, *J* 5.6 Hz, 15β-H), 3.77 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.4 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.4 Hz, 2-H), and 7.15 to 7.45 (6H, m, 1-H and SC_6H_5); δ_C (50 MHz) 157.4 (s, C-3), 138.1 (s, C-1'), 137.9 (s, C-5), 133.2 (s, C-10), 132.1 (2xd, C-2' and C-6'), 128.9 (2xd, C-3' and C-5'), 127.0 (d, C-4'), 126.3 (d, C-1), 113.8 (d, C-4), 111.4 (d, C-2), 85.3 (s, C-17), 63.9 (d, C-15), 55.2 (q, 3-OCH_3), 51.6 and 48.1 (each s, C-13 and C-14), 49.6 (d, C-16), 37.9 (d, C-9), 37.5 (d, C-8), 29.7 (t, C-6), 28.6, 28.3, 25.7, 24.9 and 23.9 (each t, C-7, C-11, C-12, C-17^1 and C-17^2), 14.8 (q, C-16^1), and 13.9 (q, C-18) (Found: M^+, 434.2292. $C_{28}H_{34}O_2S$ requires *M*, 434.2278).

3-*Methoxy*-16β-*methyl*-15α-phenylthio-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*yl Acetate* (**95**).—Dimethylaminopyridine (10 mg) and acetic anhydride (0.1 ml) were added to a solution of the alcohol (**94**) (60 mg, 0.13 mmol) in pyridine. After 71 h at 20°C, the reaction mixture was added to saturated aqueous sodium hydrogen carbonate, extracted with ethyl acetate, and the combined organic phase was washed with saturated sodium hydrogen carbonate and water. The solvent was evaporated under reduced pressure and the residue (67 mg) was chromatographed on silica gel (6 g), using ethyl acetate-hexane (1:9) as eluent, to give the *acetate* (**95**) (34 mg, 52%), m.p. 130-132°C (from chloroform-methanol); $[\alpha]_D$ +33° (*c* 1.0); ν_{max} 1729 (OAc) cm^{-1}; δ_H (400 MHz) 1.16 (3H, s, 13β-Me), 1.17 (3H, d, *J* 6.8 Hz, 16β-Me), 2.01 (3H, s, 17β-OAc), 3.51 (1H, d, *J* 5.6 Hz, 15β-H), 3.76 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.4 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.4 Hz, 2-H), and 7.15-7.45 (6H, m, 1-H and SC_6H_5) (Found: C, 75.6; H, 7.6; S, 6.4%; M^+, 476. $C_{30}H_{36}O_3S$ requires C, 75.6; H, 7.6; S, 6.7%; *M*, 476), followed by the alcohol (**94**) (23 mg, 40%).

3-*Methoxy*-16-*methyl*-14,17α-*ethanoestra*-1,3,5(10),15-*tetraen*-17β-*ol* (**97**).—Sodium periodate (0.5M, 50 ml) was added to a solution of the methyl alcohol (**94**) (2.46 g, 5.66 mmol) in ethanol (60 ml) and tetrahydrofuran (20 ml). After 24 h at 20°C, the reaction mixture was concentrated under reduced pressure, water was added and the residue was extracted with chloroform. The combined organic phase was washed with saturated sodium hydrogen carbonate and water. The solvent was evaporated under reduced pressure and the residue (2.7 g) was flash chromatographed on silica gel (200 g), using ethyl acetate-toluene (2:5) as eluent, to give 3-methoxy-16β-methyl-15α-phenylsulfinyl-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol (**96**) (1.9 g, 75%), δ_H (200 MHz) 0.74 (3H, d, *J* 6.7 Hz, 16β-Me), 1.18 (3H, s, 13β-Me), 2.58 (1H, d, *J* 6.3 Hz, 15β-H), 3.79 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.4 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.4 Hz, 2-H), and 7.15-7.45 (6H, m, 1-H and SC_6H_5).

Triethylamine (0.2 ml) was added to a slurry of the phenylsulfoxide (**96**) (1.9 g, 4.2 mmol) in benzene. The mixture was heated in a sealed tube at 115°C for 16 h. The reaction mixture was cooled and concentrated under reduced pressure to give the residue (1.4 g). Flash chromatography on silica gel (60 g) using ethyl acetate-toluene (1:9) as eluent gave the *hydroxy olefin* (**97**) (1.4 g, 99%), m.p. 113-114°

J 1.6 Hz, 16-Me), 3.77 (3H, s, 3-OMe), 5.62 (1H, q, *J* 3x1.6 Hz, 15-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.18 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 157.4 (s, C-3), 144.7 (s, C-16), 137.9 (s, C-5), 133.4 (s, C-10), 127.4 (d, C-15), 126.2 (d, C-1), 113.8 (d, C-4), 111.4 (d, C-2), 91.0 (s, C-17), 56.8 (s, C-14), 55.2 (q, 3-OCH_3), 54.0 (s, C-13), 37.4 (d, C-9), 37.2 (d, C-8), 30.1 (t, C-6), 27.7, 27.5, 26.6, 25.6 and 24.6 (each t, C-7, C-11, C-12, C-17[1] and C-17[2]), 14.6 (q, C-18), and 12.0 (q, C-16[1]) (Found: C, 81.8; H, 8.7%; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; *M*, 324).

3-*Methoxy*-16β-*methyl*-14,16α-*ethanoestra*-1,3,5(10)-*trien*-17-*one* (**98**).—A slurry of the phenylsulfoxide (**96**) (120 mg, 0.26 mmol) in benzene was heated in a sealed tube at 115°C for 16 h. The reaction mixture was cooled and concentrated under reduced pressure to give the residue (130 mg). Flash chromatography on silica gel (12 g) using ethyl acetate-toluene (1:9) as eluent gave the 14α,16α-*ethano* 17-*ketone* (**98**) (86 mg, 100%), m.p. 106-109°C (from ethyl acetate-methanol) (lit.,[37] m.p. 107-109°C), identified by spectroscopic comparison with authentic material.

Dihydroxylation of the Hydroxy Olefin (**97**).—Osmium tetroxide (320 mg, 1.26 mmol) was added to a solution of the hydroxy olefin (**97**) (340 mg, 1.05 mmol) in dry pyridine (10 ml). After 72 h at 20°C, sodium disulfite (10%, 20 ml) was added and the mixture was stirred for 2 h. Water was added and the product was extracted with chloroform. The organic phase was washed with hydrochloric acid (3M), saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue (360 mg) was chromatographed on silica gel (40 g), using ethyl acetate-toluene (1:1) as eluent, to give the 15β,16β-diol (**89**) (203 mg, 50%), followed by 3-*methoxy*-16β-*methyl*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-15α,16α,17β-*triol* (**99**) (149 mg, 40%), m.p. 183-185°C (from chloroform-hexane); $[\alpha]_D$ +77° (*c* 0.61); ν_{max} 3602 (OH) cm^{-1}; δ_H (200 MHz) 0.93 (3H, s, 13β-Me), 1.44 (3H, s, 16β-Me), 2.78-2.90 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 3.72 (1H, dd, *J* 7.2 and 1.3 Hz → d on D_2O exch, *J* 1.3 Hz, 15β-H), 6.64 (1H, d, *J* 2.4 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.4 Hz, 2-H), and 7.18 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 358.2140. $C_{22}H_{30}O_4$ requires *M*, 358.2144).

3-*Methoxy*-16-*methyl*-14,17α-*ethanoestra*-1,3,5(10),15-*tetraen*-17β-*yl Acetate* (**100**).—Dimethylaminopyridine (50 mg) and acetic anhydride (1.2 ml) were added to a solution of the alcohol (**97**) (1.3 g, 4.01 mmol) in pyridine (20 ml). After 22 h at 20°C, the reaction mixture was added to saturated aqueous sodium hydrogen carbonate, extracted with ethyl acetate, and the combined organic phase was washed with saturated aqueous sodium hydrogen carbonate and water. The solvent was evaporated under reduced pressure and the residue (1.5 g) was flash chromatographed on silica gel (100 g), using ethyl acetate-toluene (2:23) as eluent, to give the *acetate* (**100**) (1.4 g, 97%), m.p. 108-110°C (from chloroform-methanol); $[\alpha]_D$ -40° (*c* 1.0); ν_{max} 1729 (OAc) cm^{-1}; δ_H (200 MHz) 0.89 (3H, s, 13β-Me), 1.74 (3H, d, *J* 1.5 Hz, 16-Me), 2.10 (3H, s, 17β-OAc), 3.78 (3H, s, 3-OMe), 5.67 (1H, q, *J* 3x1.5 Hz, 15-H), 6.64 (1H, d, *J* 2.4 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.4 Hz, 2-H), and 7.18 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 170.4 (s, 17-O*C*OCH$_3$), 157.4 (s, C-3), 144.1 (s, C-16), 137.8 (s, C-5), 133.3 (s, C-10), 128.4 (d, C-15), 126.2 (d, C-1), 113.8 (d, C-4), 111.5 (d, C-2), 96.9 (s, C-17), 58.5 (s, C-14), 55.2 (q, 3-OCH$_3$), 52.7 (s, C-13), 37.1 (d, C-9), 36.9 (d, C-8), 30.1 (t, C-6), 29.0, 26.7, 25.7, 24.7 and 24.3 (each t, C-7, C-11, C-12, C-17^1 and C-17^2), 21.6 (q, 17-OCO*C*H$_3$), 15.2 (q, C-18), and 13.7 (q, C-16^1) (Found: C, 78.4; H, 8.4%; M^+, 366. $C_{24}H_{30}O_3$ requires C, 78.65; H, 8.25%; *M*, 366).

Dihydroxylation of the Acetoxy Olefin (**100**).—Osmium tetroxide (1.2 g, 4.6 mmol) was added to a solution of the olefin (**100**) (1.4 g, 3.8 mmol) in dry pyridine (50 ml). After 96 h at 20°C, sodium disulfite (10%, 30 ml) was added and the mixture was stirred for 2 h. Water was added and the product was extracted with chloroform. The organic phase was washed with hydrochloric acid (3M), saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue (1.8 g) was chromatographed on silica gel (150 g), using ethyl acetate-toluene (3:7) as eluent, to give the 15α,16α-diol (**83**) (958 mg, 63%), followed by the 15β,16β-diol (**68**) (441 mg, 29 %).

17β-*Acetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10),15-*tetraene*-16-*carbaldehyde* (**102**).—Propynal (1.1 ml, 24.6 mmol) was added to a solution of the dienyl acetate (**27**) (4.0 g, 12.3 mmol) in benzene (60 ml). After 16 h at 80°C in a sealed tube, further propynal (0.5 ml) was added. After a total of 39 h at 80°C, the reaction mixture was

cooled and adsorbed directly on silica gel (300 g). Elution with ethyl acetate-toluene (1:9) yielded a mixture (420 mg) of less polar products, followed by the *cycloadduct* (**102**) (4.14 g, 89%), m.p. 130-135°C (from acetone-methanol); $[\alpha]_D$ -34° (*c* 1.0); λ_{max} 207 nm (ε 15649); ν_{max} 1743 (OAc), 1669 (CO) cm^{-1}; δ_H (200 MHz) 1.15 (3H, s, 13β-Me), 2.20 (3H, s, 17β-OAc), 2.56 (1H, td, *J* 2x11.4 and 4.3 Hz, 9α-H), 2.86-3.0 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.60 (1H, d, *J* 5.6 Hz, 17^2-H), 7.09 (1H, d, *J* 5.6 Hz, 17^1-H), 6.66 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), 7.21 (1H, d, *J* 8.6 Hz, 1-H), 7.61 (1H, s, 15-H), and 9.71 (1H, s, 16-CHO); δ_C (50 MHz) 186.3 (d, C-16^1), 170.8 (s, 17β-O*C*OCH_3), 161.5 (d, C-15), 157.6 (s, C-3), 156.1 (s, C-16), 141.1 and 138.5 (each d, C-17^1 and C-17^2), 137.6 (s, C-5), 133.2 (s, C-10), 126.8 (d, C-1), 113.8 (d, C-4), 111.9 (d, C-2), 97.9 (s, C-17), 88.4 (s, C-13), 66.3 (s, C-14), 55.2 (q, 3-OCH_3), 39.8 (d, C-9), 35.9 (d, C-8), 30.0 (t, C-6), 29.9, 26.3 and 25.3 (each t, C-7, C-11 and C-12), 21.3 (q, 17β-OCO*C*H_3), and 16.9 (q, C-18) (Found: C, 73.5; H, 7.1%; M^+, 378. $C_{24}H_{26}O_4$ requires C, 73.5; H, 6.9%; *M*, 378).

Methyl 17β-*Acetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10),15-*tetraen*-16-*ol* (**103**).—Cerium(III) chloride heptahydrate (3.9 g, 10.6 mmol) was added to a solution of the formyl acetate (**102**) (2 g, 5.29 mmol) in dichloromethane (13 ml) and methanol (7 ml) at -78°C, followed by sodium borohydride (600 mg, 15.8 mmol). After 30 min at this temperature, saturated aqueous ammonium chloride was added to the reaction mixture and the product was extracted into ethyl acetate. The combined organic phase was washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the residue (2.03 g). Chromatography on silica gel (190 g) using ethyl acetate-toluene (3:17) as eluent gave the *acetoxy alcohol* (**103**) (1.51 g, 75%), m.p. 107-109°C (from ethyl acetate-hexane); $[\alpha]_D$ +34° (*c* 1.0); ν_{max} 3514 (OH) and 1728 (CO) cm^{-1}; δ_H (200 MHz) 1.14 (3H, d, *J* 0.9 Hz, 13β-Me), 2.19 (3H, s, 17ß-OAc), 2.84-2.96 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.15 and 4.25 (each 2H, dd, *J* 13.6 and 1.2 Hz, 16^1-H_2), 6.47 (1H, t, *J* 2x1.2 Hz, 15-H), 6.64 (1H, d, *J* 5.8 Hz, 17^1-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 6.87 (1H, dd, *J* 5.8 and 1.2 Hz, 17^2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 75.8; H, 7.3%; M^+ 380. $C_{24}H_{28}O_4$ requires C, 75.8; H, 7.4%; *M*, 380).

Attempted Xanthate Formation on the Diene (**103**).—Carbon disulfide (1 ml) was added to a stirred solution of the diene (**103**) (100 mg, 0.26 mmol) and 1,5-diazabicyclo[4.3.0]non-5-ene (160 μl, 1.35 mmol) in dimethylformamide. After 30 min at 25°C, methyl iodide (2 ml) was added to the reaction mixture and stirring was continued for a further 40 min at 25°C. Water was added to the reaction mixture, which was subsequently extracted with ethyl acetate. The combined organic phase was washed with brine and water, and dried ($MgSO_4$). The solvent was evaporated to give the residue (150 mg). Chromatography of this residue on silica gel (18 g), using ethyl acetate-toluene (1:9) as eluent, gave an intractable mixture (61 mg) of products, followed by 16-*acetoxymethyl*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10),15-*tetraen*-17β-*ol* (**104**) (22 mg, 22%), m.p. 160-163°C (from chloroform-methanol); $[\alpha]_D$ +76° (*c* 1.0); δ_H (200 MHz) 1.08 (3H, s, 13β-Me), 2.08 (3H, s, 17β-OAc), 3.77 (3H, s, 3-OMe), 4.70 and 4.85 (each 2H, dd, *J* 12.7 and 1.1 Hz, 16^1-H_2), 6.52 and 6.59 (each 1H, d, *J* 5.6 Hz, 17^1-H and 17^2-H), 6.57 (1H, br s, 15-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 75.7; H, 7.3%; M^+, 380. $C_{24}H_{28}O_4$ requires C, 75.8; H, 7.4%; *M*, 380).

16-*Hydroxymethyl*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10),15-*tetraen*-17β-*ol* (**105**).—(a) Potassium hydroxide (M in methanol, 11 ml) was added to a solution of the diene (**104**) (506 mg, 1.4 mmol) in tetrahydrofuran. After 5 min at 25°C water was added to the reaction mixture, which was then extracted into chloroform. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated to give the *diol* (**105**) (475 mg, 100%), m.p. 175-177°C (from chloroform- methanol); $[\alpha]_D$ +1.1° (*c* 1.0); ν_{max} 3593 (OH) cm^{-1}; δ_H (200 MHz) 1.16 (3H, d, *J* 0.9 Hz, 13β-Me), 3.77 (3H, s, 3-OMe), 4.42 (2H, br.s, 16^1-H_2), 6.31 (1H, t, *J* 2x1.5 Hz, 15-H), 6.57 and 6.61 (each 1H, d, *J* 5.6 Hz, 17^2-H and 17^1-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 78.2; H, 7.6%; M^+, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; *M*, 338).

(b) In a similar experiment, the 17β-acetate (**103**) (506 mg, 1.4 mmol) was converted to the diol (**105**) (475 mg, 100 %).

Acetylation of the Dienediol (**105**).—Acetic anhydride (0.08 ml) was added to a solution of the dienol (**105**) (180 mg, 0.59 mmol) in pyridine (10 ml). After 4 h at 20°C, the reaction mixture was added to ice-water and extracted into chloroform. The combined organic phase was washed with brine and water, dried ($MgSO_4$) and the solvent was evaporated to give the residue (90 mg). Chromatography on silica gel (10 g) using ethyl acetate-toluene (3:7) as eluent gave the 16^1-acetate (**104**) (187 mg, 84%).

S-*Methyl* 17β-*Hydroxy*-16-*methylene*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-15-*dithiocarbonate* (**106**).—1,5-Diazabicyclo[4.3.0]non-5-ene (0.4 ml), then carbon disulfide (2.5 ml), was added to a solution of the dienediol (**105**) (508 mg, 1.5 mmol) in dimethylformamide (3 ml) at 0°C. After 30 min methyl iodide was added at 0°C. After 15 min at 0°C, water was added to the reaction mixture, which was then extracted into ethyl acetate. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated to give the residue (459 mg). Chromatography on silica gel (45 g) using ethyl acetate-toluene (1:9) as eluent gave the non-crystalline *thiocarbonate* (**106**) (469 mg, 73%), $[\alpha]_D$ +180° (*c* 0.87); ν_{max} 3591 (OH) and 1731 (CO) cm^{-1}; δ_H (400 MHz) 0.96 (3H, s, 13β-Me), 2.46 (3H, s, 15-SCOSMe), 2.78-2.90 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.69 (1H, t, *J* 2x1.8 Hz, 15β-H), 5.19 and 5.29 (each 1H, dd, *J* 1.8 and 0.4 Hz, 16^1-H_2), 5.95 and 6.09 (each 1H, d, *J* 5.9 Hz, 17^2-H and 17^1-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17(1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 190.6 (s, 15-S*C*OSCH$_3$), 157.5 (s, C-3), 156.2 (s, C-16), 137.8 (s, C-5), 135.9 and 133.0 (each d, C-17^2 and C-17^1), 131.8 (s, C-10), 127.0 (d, C-1), 113.5 (d, C-4), 111.7 (d, C-2), 106.7 (t, C-16^1), 92.1 (s, C-17), 61.2 and 58.5 (s, C-14 and C-13), 55.2 (q, 3-OCH$_3$), 51.8 (d, C-15), 40.4 (d, C-9), 39.4 (d, C-8), 29.7 (t, C-6), 27.4 (t, C-12), 26.8 (t, C-11), 24.2 (t, C-7), 14.7 (q, 15-SCOS*C*H$_3$), and 13.2 (q, C-18) (Found: M^+, 428.1462. $C_{24}H_{28}O_3S_2$ requires *M*, 428.1478).

Epoxidation of the Diene (**103**).—*tert*-Butyl hydroperoxide (80%, 0.25 ml) was diluted in dry toluene and added to a solution of the diene (**103**) (156 mg, 0.41 mmol) and vanadyl acetylacetonate (13.7 mg, 0.005 mmol) in dry toluene (10 ml) at 0°C. After 19 h at 20°C, saturated aqueous sodium sulfite (10 ml) was added to the reaction mixture, which was subsequently extracted into toluene. The combined organic phase was washed with

brine and water and dried ($MgSO_4$). The solvent was evaporated to give the residue (170 mg). Chromatography of this residue on silica gel (18 g), using ethyl acetate-toluene (1:5) as eluent, gave the 17-hydroxy-16[1]-acetate (**104**) (60 mg, 38%), followed by 15α,16α-*epoxy*-16β-*hydroxymethyl*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*yl acetate* (**109**) (50 mg, 30%), m.p. 145-149°C (from chloroform-hexane); $[\alpha]_D$ +1.2° (*c* 1.0); ν_{max} 3577 (OH) and 1741 (OAc) cm^{-1}; δ_H (200 MHz) 1.19 (3H, s, 13β-Me), 2.14 (3H, s, 17β-OAc), 3.52 (1H, s, 15-H), 3.77 (3H, s, 3-OMe), 3.90 and 4.09 (2H, each d, *J* 13.0 Hz, 16^1-H_2), 5.90 (1H, d, *J* 5.6 Hz, 17^2-H), 6.14 (1H, d, *J* 5.6 Hz, 17^1-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17(1H, d, *J* 8.6 Hz, 1-H) (Found: C, 72.6; H, 7.3%; M^+, 396. $C_{24}H_{28}O_5$ requires C, 72.7; H, 7.1%; *M*, 396), followed by more polar products (40 mg).

Epoxidation of the Dienediol (**105**).—*tert*-Butyl hydroperoxide (80%, 0.1 ml) was diluted in dry toluene and added dropwise to a solution of the diene (**105**) (100 mg, 0.29 mmol) and vanadyl acetylacetonate (9.6 mg, 0.04 mmol) in dry toluene (8 ml) at 0°C. After 4.5 h at 25°C, saturated aqueous sodium sulfite (10 ml) was added to the reaction mixture, which was subsequently extracted into ethyl acetate. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated to give the residue (110 mg). Chromatography of this residue on silica gel (12 g), using ethyl acetate-toluene (1:2) as eluent, gave a non-crystalline compound (81 mg, *ca.* 75%). Due to difficulties experienced with the purification of this product, a derivative was synthesised.

Acetic anhydride (0.03 ml) was added to a solution of the foregoing compound (56 mg, 0.15 mmol) in pyridine. After 3h at 25°C, the reaction mixture was added to ice water and extracted into chloroform.The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated to give an unidentified product (60 mg, *ca.* 92%), m.p. 196-198°C (from chloroform-methanol); $[\alpha]_D$ -17° (*c* 1.0); ν_{max} 3501 (OH) and 1746 (OAc) cm^{-1}; δ_H (200 MHz) 1.08 (3H, s, 13β-Me), 2.05 (3H, s, OAc), 3.39 (1H, dd, *J* 3.4 and 1.8 Hz), 3.79 (3H, s, 3-OMe), 3.89 (1H, d, *J* 12.0 Hz, disp. on D_2O exch.), 4.12 (1H, dt → t on D_2O exch., *J* 2x1.9 Hz), 4.18 (1H, dd, *J* 3.4 and 1.9 Hz), 4.52 and 4.64 (each 2H, d, *J* 11.8 Hz), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17(1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 412. $C_{24}H_{28}O_6$ requires *M*, 412).

Attempted Selective Epoxidation of the Dienediol (**105**).—*tert*-Butyl hydroperoxide (80%, 0.2 ml) was diluted in dry chloroform and added to a solution of the diene (**105**) (200 mg, 0.51 mmol) and vanadyl acetylacetonate (20 mg, 0.06 mmol) in dry chloroform (10 ml) at 0°C. After 50 min at 0°C, saturated aqueous sodium sulfite (10 ml) was added to the reaction mixture, which was subsequently extracted into chloroform. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated to give the residue (200 mg). Chromatography of this residue on silica gel (20 g), using ethyl acetate-toluene (1:2) as eluent, gave a mixture of products (50 mg), followed by an unidentified crystalline product (70 mg, *ca.* 33%), m.p. 160-162°C (from chloroform-methanol); $[\alpha]_D$ +30° (*c* 1.0); δ_H (200 MHz) 1.12 (3H, s, 13β-Me), 3.78 (3H, s, 3-OMe), 3.98 and 4.10 (each 2H, d, *J* 12.0 Hz), 4.62 (1H, t, *J* 2x1.1 Hz); 5.94 (1H, dt, *J* 5.7 and 2x1.1 Hz), 6.67 (1H, d, *J* 5.7 Hz), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17(1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 354.1813. $C_{22}H_{26}O_4$ requires *M*, 354.1831).

Conjugate Addition to the Diene (**72**).—Diisopropylethylamine (0.5 ml) was added to a solution of the diene (**72**) (1.0 g, 2.45 mmol) in thiophenol (4 ml) at 0°C. After 22h at 20°C, the reaction mixture was adsorbed directly on silica gel (100 g). Elution with ethyl acetate-hexane (1:49) yielded non-crystalline *methyl* 17β-*acetoxy*-3-*methoxy*-15α-*phenylthio*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16β-*carboxylate* (**112**) (748 mg, 60%), $[\alpha]_D$ +64° (*c* 0.5); ν_{max} 1725 (OAc and CO) cm^{-1}; δ_H (200 MHz) 0.95 (3H, s, 13β-Me), 2.12 (3H, s, 17β-OAc), 3.44 (1H, d, *J* 4.5 Hz, 15β-H), 3.51 (3H, s, 16-CO_2Me), 3.76 (3H, s, 3-OMe), 4.25 (1H, d, *J* 4.5 Hz, 16α-H), 6.34 (1H, d, *J* 6.1 Hz, 17^2-H), 6.61 (1H, d, *J* 6.1 Hz, 17^1-H), 6.64 (1H, d, *J* 2.4 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.4 Hz, 2-H), and 7.15 to 7.45 (6H, m, 1-H and SC_6H_5) (Found: M^+, 518.2133. $C_{31}H_{34}O_5S$ requires *M*, 518.2126), followed by an inseparable mixture (457 mg, 36%) of methyl 17β-acetoxy-3-methoxy-15α-phenylthio-14,17α-ethenoestra-1,3,5(10)-triene-16α-carboxylate (**113**) and methyl 17β-acetoxy-3-methoxy-15β-phenylthio-14,17α-ethenoestra-1,3,5(10)-triene-16α-carboxylate (**114**), δ_H (**113**, *ca.* 71%) (200 MHz) 0.79 (3H, s, 13β-Me), 1.69 (3H, s, 17β-OAc), 3.35 (3H, s, 16-CO_2Me), 3.39 (3H, s, 3-OMe), 3.88 and 4.24 (each 1H, d, *J* 9.2 Hz, 15β- and 16β-H), 6.09 (1H, d, *J* 6.2 Hz, 17^2-H), 6.5 to 7.6 (m, 17^1-H, 4-H, 2-H, and SC_6H_5); δ_H (**114**, *ca.* 29%) (200 MHz) 1.30 (3H, s, 13β-Me), 1.71 (3H, s, 17β-OAc), 3.40 (3H, s, 16-CO_2Me), 3.42 (3H, s, 3-OMe), 3.76 and 3.84 (each 1H, d, *J* 4.8 Hz, 15α- and

16β-H), 5.91 (1H, d, *J* 5.8 Hz, 17^2-H), and 6.5 to 7.6 (m, for 17^1-H, 4-H, 2-H, and SC_6H_5).

Reduction of Methyl 17β-*Acetoxy*-3-*methoxy*-15α-*phenylthio*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16β-*carboxylate* (**112**).—Lithium aluminium hydride (286 mg, 7.7 mmol) was added to a solution of the ester (**112**) (500 mg, 0.96 mmol) in tetrahydrofuran. After 1 h at 20°C, saturated ammonium chloride was added to the reaction mixture and the product was extracted into ethyl acetate. The combined organic phase was washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Chromatography of the residue (300 mg) on silica gel (50 g) using ethyl acetate-toluene (3:7) as eluent gave non-crystalline 16β-hydroxymethyl-3-methoxy-15α-phenylthio-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol (**115**) (206 mg, 48%), δ_H (200 MHz) 1.02 (3H, s, 13β-Me), 3.38 (1H, d, *J* 5.1 Hz, 15β-H), 3.46 (1H, m → dd on D_2O exch., *J* 10.7 and 4.6 Hz, 16^1-H), 3.77 (3H, s, 3-OMe), 4.15 (1H, m → t on D_2O exch., *J* 2x10.7 Hz, 16^1-H), 6.08 (1H, d, *J* 6.1 Hz, 17^2-H), 6.24 (1H, d, *J* 6.1 Hz, 17^1-H), 6.64 (1H, d, *J* 2.4 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.4 Hz, 2-H), and 7.15 to 7.45 (6H, m, 1-H and SC_6H_5) (Found: M^+, 448. $C_{28}H_{32}O_3S$ requires *M*, 448), followed by mixtures of more polar products (80 mg).

3-*Methoxy*-16β-*methyl*-15α-*phenylthio*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*ol* (**117**).—Methanesulfonyl chloride (0.04 ml, 0.5 mmol) was added to a solution of the diol (**115**) (180 mg, 0.4 mmol) in dry pyridine at 0°C under nitrogen. After 1 h, water was added and the product was extracted with ethyl acetate. The combined organic layers were washed with brine and water and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the residue (190 mg).

Lithium aluminium hydride (50 mg, 1.3 mmol) was added to a solution of the crude residue (190 mg) in tetrahydrofuran under nitrogen. After 12 h, saturated ammonium chloride was added and the product was extracted with ethyl acetate. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the residue (140 mg) which was adsorbed on silica gel (14 g). Elution with ethyl acetate-toluene (2:23) gave the non-crystalline *hydroxy sulfide* (**117**) (114 mg, 73%), δ_H (200 MHz) 1.03 (3H, s, 13β-Me), 1.06 (3H, d, *J* 7.5 Hz, 16β-Me), 3.46 (1H, d, *J* 4.7 Hz, 15β-H), 3.76 (3H, s, 3-OMe), 6.06 (1H, d, *J* 6.1 Hz, 17^2-H), 6.16 (1H, d,

J 6.1 Hz, 17^1-H), 6.64 (1H, d, *J* 2.4 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.4 Hz, 2-H), and 7.15 to 7.45 (6H, m, 1-H and SC_6H_5) (Found: M^+, 432. $C_{28}H_{32}O_2S$ requires *M*, 432), followed by the diol (**115**) (19 mg, 15%).

Oxidative Elimination of the Sulfide (**117**).—Sodium periodate (0.5M aq., 1.6 ml) was added to a solution of the sulfide (**117**) (114 mg, 0.26 mmol) in ethanol. After 16 h at 20°C, the reaction mixture was concentrated under reduced pressure, water was added and the residue was extracted with chloroform. The combined organic phase was washed with saturated sodium hydrogen carbonate and water. The solvent was evaporated under reduced pressure to give the residue (130 mg).

Triethylamine (0.1 ml) was added to a solution of the crude residue (130 mg) in benzene. The mixture was heated in a sealed tube at 120°C for 16 h. The reaction mixture was cooled and concentrated under reduced pressure to give the residue (117 mg). Chromatography on silica gel (10 g) using ethyl acetate-toluene (2:23) as eluent gave 3-*methoxy*-16-*methyl*-14,17α-*ethenoestra*-1,3,5(10),15-*tetraen*-17β-*ol* (**120**) (35 mg, 42%), m.p. 111-114°C (from methanol); $[\alpha]_D$ +95° (*c* 0.4); ν_{max} 3598 (OH) cm^{-1}; δ_H (400 MHz) 1.08 (3H, d, *J* 0.9 Hz, 13β-Me), 1.83 (3H, d, *J* 1.9 Hz, 16-Me), 2.50 (1H, td, *J* 2x11.2 and 2.3 Hz, 9α-H), 2.84-2.96 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.06 (1H, q, *J* 1.9 Hz, 15-H), 6.50 (1H, dd, *J* 5.6 and 0.9 Hz, 17^2-H), 6.60 (1H, d, *J* 5.6 Hz, 17^1-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.18 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 157.4 (s, C-3), 155.1 (s, C-16), 138.1 (s, C-5), 142.2 and 141.7 (each d, C-17^2 and C-17^1), 132.7 (s, C-10), 132.2 (d, C-15), 126.8 (d, C-1), 113.8 (d, C-4), 111.7 (d, C-2), 97.9 (s, C-17), 84.9 (s, C-13), 58.5 (s, C-14), 55.2 (q, 3-OCH_3), 40.2 (d, C-9), 36.7 (d, C-8), 30.2 (t, C-6), 29.6 (t, C-12), 26.5 and 25.2 (each t, C-11 and C-7), 16.5 (q, C-18) and 13.7 (q, C-16^1) (Found: C, 81.6; H, 8.1%; M^+, 322. $C_{22}H_{26}O_2$ requires C, 81.95; H, 8.1%; *M*, 322), followed by 3-*methoxy*-16-*methyl*-15α-*phenylsulfonyl*-14,17α-*ethenoestra*-1,3,5(10),15-*tetraen*-17β-*ol* (**118**) (26 mg, 22%), m.p. 225-228°C (from chloroform-methanol); $[\alpha]_D$ +6° (*c* 0.76); ν_{max} 3596 (OH) cm^{-1}; δ_H (400 MHz) 0.44 (3H, d, *J* 7.2 Hz, 16β-Me), 0.97 (3H, d, *J* 1.2 Hz, 13β-Me), 1.22 (1H, dq, *J* 12.8 and 3x2.3 Hz), 2.08 (1H, td, *J* 2x13.0 and 3.5 Hz, 8β-H), 2.24 (1H, dq, *J* 13.0 and 3x2.3 Hz), 2.56 (1H, td, *J* 2x13.0 and 3.5 Hz, 9α-H), 2.84-3.0 (2H, m, 6-H_2), 3.09 (1H, d, *J* 5.4 Hz, 15β-H), 3.77 (3H, s, 3-OMe), 6.08 (1H, d, *J* 6.1 Hz, 17^2-H), 6.20 (1H, d, *J* 6.1 Hz, 17^1-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), 7.18 (1H, d, *J* 8.6 Hz, 1-H), and 7.42-7.70

(5H, m, $SO_2C_6H_5$) (Found: C, 72.5; H, 7.1; S, 7.1%; M^+, 323 (464 - SO_2Ph). $C_{28}H_{32}O_4S$ requires C, 72.4; H, 6.9; S, 6.9%; *M*, 464).

17α-*Acetoxy*-3-*methoxy*-20-*oxo*-19-*nor*-14β-*pregna*-1,3,5(10)-*triene*-14-*carbaldehyde* (**123**).—(a) Sodium periodate (0.5M, 23 ml) was added to a solution of the diol (**83**) (1.38 g, 3.5 mmol) in ethanol (100 ml). After 4 h at 20°C, water was added to the reaction mixture, and the residue was extracted with chloroform. The combined organic phase was washed with brine and water, dried over magnesium sulfate and the solvent was evaporated under reduced pressure to give the residue (1.4 g). Flash chromatography on silica gel (90 g) using ethyl acetate-hexane (1:4) as eluent gave 17α-*acetoxy*-3-*methoxy*-20-*oxo*-19-*nor*-14β-*pregna*-1,3,5(10)-*triene*-14-*carbaldehyde* (**123**) (1.24 g, 90%), m.p. 174-177°C (from chloroform-methanol); $[\alpha]_D$ +74° (*c* 1.0); ν_{max} 1731 (OAc and 20-CO) and 1711 (14^1-CO) cm^{-1}; δ_H (400 MHz) 1.18 (3H, s, 13β-Me), 1.34 (1H, qd, *J* 3x11.4 and 7.0 Hz, 7α-H), 1.52 (1H, obsc., 7β-H), 1.74 (1H, td, *J* 12.0 and 3.3 Hz, 8β-H), 2.04 (3H, s, 17α-OAc), 2.10 (1H, m, 16-H), 2.15 (3H, s, 20-Me), 2.60 (1H, td, *J* 2x12.0 and 3.2 Hz, 9α-H), 2.70-2.80 (2H, m, 6-H_2), 2.92 (1H, ddd, *J* 16.9, 10.0 and 6.9 Hz, 15β-H), 3.77 (3H, s, 3-OMe), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.21 (1H, d, *J* 8.6 Hz, 1-H) and 9.67 (1H, s, 14^1-CHO); δ_C (50 MHz) 209.2 (s, C-20), 207.2 (s, C-14^1), 170.9 (s, 17α-$OCOCH_3$), 157.7 (s, C-3), 137.5 (s, C-5), 131.4 (s, C-10), 126.4 (d, C-1), 113.4 (d, C-4), 111.9 (d, C-2), 96.4 (s, C-17), 61.0 (s, C-14), 55.2 (q, 3-OCH_3), 51.4 (s, C-13), 40.1 (d, C-8), 36.9 (d, C-9), 33.6 (t, C-12), 32.3 (t, C-15), 30.2 (t, C-6), 26.9 (q, 20-CH_3), 25.9 (t, C-16), 25.1 (t, C-11), 24.1 (t, C-7), 21.1 (q, 17α-$OCOCH_3$), and 16.5 (q, C-18) (Found: C, 72.3; H, 7.6%; M^+, 398. $C_{24}H_{30}O_5$ requires C, 72.3; H, 7.6%; *M*, 398).

(b) Similarly, the diol (**68**) (500 mg, 1.27 mmol) gave the cleavage product (**123**) (479 mg, 95%).

Attempted Deacetoxylation of 17α-*Acetoxy*-3-*methoxy*-20-*oxo*-19-*nor*-14β-*pregna*-1,3,5(10)-*triene*-14-*carbaldehyde* (**123**).—(a) Samarium (83 mg, 0.55 mmol) was placed in a reaction vessel, which was then flame dried and cooled under nitrogen. Tetrahydrofuran (0.2 ml), then diiodoethane (142 mg, 0.5 mmol) in tetrahydrofuran (0.5 ml) were added to the samarium. The mixture was stirred for 1 h at 25°C and changed to a brilliant blue colour. A solution of the steroid (**123**) (100 mg, 0.25 mmol) in tetrahydrofuran (0.6 ml) was

added to the reagent mixture at 0°C. After 15 h at 0°C, the mixture was poured into saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined organic phase was washed with saturated aqueous sodium thiosulfate and brine, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give a residue (90 mg). Chromatography on silica gel (9 g) using ethyl acetate-toluene (1:19) as eluent gave non-crystalline 3-*methoxy*-20-*oxo*-19-*nor*-14β,17α-*pregna*-1,3,5(10)-*triene*-14-*carbaldehyde* (**124**) (15 mg, 18%), $[\alpha]_D$ +35° (*c* 1.0); ν_{max} 1705 br (CO) cm^{-1}; δ_H (400 MHz) 1.33 (3H, s, 13β-Me), 2.12 (3H, s, 20-Me), 2.58 (1H, td, *J* 2x11.4 and 3.2 Hz, 9α-H), 2.71 (1H, t, *J* 2x9.6 Hz, 17β-H), 2.76-2.92 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.21 (1H, d, *J* 8.6 Hz, 1-H) and 9.62 (1H, d, *J* 1.3 Hz, 14β-CHO); δ_C (100 MHz) 209.0 (s and d, C-20 and C-14^1), 157.7 (s, C-3), 137.4 (s, C-5), 131.5 (s, C-10), 126.8 (d, C-1), 113.7 (d, C-4), 111.9 (d, C-2), 63.7 (s, C-14), 61.7 (s, C-17), 55.2 (q, 3-OCH_3), 47.2 (s, C-13), 37.7 (d, C-9), 36.4 (d, C-8), 31.9 (q and t, 20-CH_3 and C-12), 30.2 (t, C-6), 26.3 (t, C-11), 26.1 (t, C-7), 23.1 (t, C-16), 22.5 (t, C-15), and 20.3 (q, C-18) (Found: M^+, 340.2042. $C_{22}H_{28}O_3$ requires *M*, 340.2038), followed by an inseparable mixture (20 mg) of (**124**) and (**125**), followed by pure 3-*methoxy*-14^1,20ξ-*epoxy*-14,20-*dimethyl*-19-*nor*-14β-*pregna*-1,3,5(10)-*triene*-17α,20-*diol* 17-*acetate* (**125**) (48 mg, 48%), m.p. 146-148°C (from chloroform-methanol); $[\alpha]_D$ +90° (*c* 1.0); ν_{max} 3481br (OH), 1709 (OAc) cm^{-1}; δ_H (400 MHz) 0.98 (3H, d, *J* 0.8 Hz, 13β-Me), 1.34 (3H, s, 20-Me), 2.12 (3H, s, 17-OAc), 3.50 (1H, d, *J* 7.3 Hz, 14^1-H_{endo}), 3.74 (1H, dd, *J* 7.3 and 2.1 Hz, 14^1-H_{exo}), 3.76 (3H, s, 3-OMe), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 173.7 (s, 17-O*C*OCH_3), 157.5 (s, C-3), 138.1 (s, C-5), 132.8 (s, C-10), 126.4 (d, C-1), 113.6 (d, C-4), 111.6 (d, C-2), 94.9 (s, C-17), 80.8 (t, C-14^1), 73.2 (s, C-17^1), 55.2 (q, 3-OCH_3), 48.1 (s, C-13), 46.4 (s, C-14), 39.9 (d, C-8), 37.1 (d, C-9), 30.1 (t, C-6), 26.4 (q, 20-CH_3), 26.4 and 25.7 (each t, C-11 and C-12), 24.3 (t, C-7), 24.2 (t, C-15), 21.2 (q, 17-OCO*C*H_3), 17.8 (t, C-16), and 14.9 (q, C-18) (Found: C, 71.8; H, 8.0%; M^+, 400. $C_{24}H_{32}O_5$ requires C, 71.9; H, 8.05%; *M*, 400).

(b) The compound (**123**) (200 mg, 0.5 mmol) in dry tetrahydrofuran (10 ml) was added during 15 min to a stirring solution of calcium (150 mg, 3.75 mmol) in liquid ammonia (50 ml, distilled from sodium) at -78°C. The reaction mixture was stirred for a further 20 min at -78°C, then solid ammonium chloride (10 g) was added slowly. The ammonia was allowed to evaporate, and the residue was partitioned between water and chloroform. The organic phase was washed with water and brine, and dried ($MgSO_4$). The

solvent was evaporated under reduced pressure to give a residue (200 mg). Chromatography of this residue on silica gel (25 g) using ethyl acetate-toluene (2:3) as eluent gave an unidentifiable product (27 mg, *ca.* 16%), m.p. 192-194°C (from chloroform-methanol); $[\alpha]_D$ +17° (*c* 1.0); δ_H (200 MHz) 1.40 (3H, s, 13β-Me), 2.20 (3H, s,), 3.05 (1H, t, *J* 2x9.9 Hz), 3.77 (3H, s, 3-OMe), 4.14 (1H, d, *J* 6.1 Hz → s on D_2O exch.), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 340.2020. $C_{22}H_{28}O_3$ requires 340.2020), followed by non-crystalline 14-*hydroxymethyl*-3-*methoxy*-19-*nor*-14β,17α-*pregna*-1,3,5(10)-*trien*-20-*one* (**127**) (80 mg, 47%), $[\alpha]_D$ +82° (*c* 1.0); δ_H (200 MHz) 1.34 (3H, s, 13β-Me), 2.17 (3H, s, 20-Me), 3.22 (1H, t, *J* 2x8.8 Hz, 17β-H), 3.62 and 3.82 (each 1H, d, *J* 11.7 Hz, 14^1-H_2), 3.77 (3H, s, 3-OMe), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 342. $C_{22}H_{30}O_3$ requires *M*, 342), followed by 14-*hydroxymethyl*-3-*methoxy*-19-*nor*-14β,17α-*pregna*-1,3,5(10)-*trien*-20ξ-*ol* (**128**) (20 mg, 12%), $[\alpha]_D$ +33° (*c* 1.0); ν_{max} 3419 (OH) cm^{-1}; δ_H (400 MHz) 1.16 (3H, d, *J* 6.3 Hz, 20-Me), 1.24 (3H, s, 13β-Me), 1.76 (1H, td, *J* 2x11.3 and 2.3 Hz), 2.26 (1H, dq, *J* 13.0 and 3x3.8 Hz, 11α-H), 2.54 (1H, td, *J* 2x11.2 and 3.3 Hz, 9α-H), 2.76-2.92 (2H, m, 6-H_2), 3.58 and 3.82 (each 1H, dd→d on D_2O exch., *J* 12.0 Hz, 14^1-H_2), 3.77 (3H, s, 3-OMe), 3.83 (1H, obsc., *J* obsc and 6.3 Hz, 20-H), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 344.2338. $C_{22}H_{32}O_3$ requires *M*, 344.2351).

Oxidation of the Alcohol (**127**) *to the Aldehyde* (**124**).—1,1,1-Triacetoxy-2,1-benzoxoiodol-3(3H)-one (10 mg) was added to a solution of the alcohol (**127**) (11 mg, 0.03 mmol) in dichloromethane. After 10 min, the reaction mixture was added to saturated aqueous sodium hydrogen carbonate and thiosulfate and was extracted with diethyl ether. The combined organic phase was washed with brine and water, dried over magnesium sulfate and the solvent was evaporated under reduced pressure to give the residue (11 mg). Flash chromatography on silica gel (3 g) using ethyl acetate-toluene (1:19) as eluent gave the aldehyde (**124**) (7 mg, 70%).

14-*Acetoxymethyl*-3-*methoxy*-19-*nor*-14β,17α-*pregna*-1,3,5(10)-*trien*-20-*one* (**129**).—Acetic anhydride (0.04 ml, 0.37 mmol) was added to a solution of the hydroxy methyl compound (**127**) (64 mg, 0.19 mmol) in pyridine. After 6 h at 20°C, the reaction mixture was added to saturated aqueous sodium hydrogen carbonate and the residue was extracted with chloroform. The combined organic phase was washed with brine and water, dried over magnesium sulfate and the solvent was evaporated under reduced pressure to give the residue (73 mg). Flash chromatography on silica gel (7 g) using ethyl acetate-toluene (3:7) as eluent gave the *acetate* (**129**) (55 mg, 75%), m.p. 124-126°C (from chloroform-methanol); $[\alpha]_D$ -17° (*c* 1.0); ν_{max} 1718 (OAc) and 1696 (CO) cm^{-1}; δ_H (400 MHz) 1.14 (1H, dt, *J* 13.7 and 2x3.3 Hz, 12β-H), 1.25 (3H, s, 13β-Me), 1.74 (1H, td, *J* 2x11.5 and 2.2 Hz, 8β-H), 1.91 (1H, m, 7β-H), 2.04 (3H, s, 14^1-OAc), 2.16 (3H, s, 20-Me), 2.55 (1H, td, *J* 2x11.5 and 3.1 Hz, 9α-H), 2.78-2.84 (2H, m, 6-H_2), 3.14 (1H, dd, *J* 8.8 and 8.6 Hz, 17β-H), 3.76 (3H, s, 3-OMe), 4.08 and 4.20 (each 1H, d, *J* 12.3 Hz, 14^1-H_2), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 209.8 (s, C-20), 170.9 (s, 14^1-O*C*OCH$_3$), 157.6 (s, C-3), 137.7 (s, C-5), 132.6 (s, C-10), 126.7 (d, C-1), 113.4 (d, C-4), 111.8 (d, C-2), 67.5 (t, C-14^1), 62.0 (s, C-17), 55.2 (q, 3-OCH_3), 52.1 (s, C-14), 46.6 (s, C-13), 39.0 (d, C-8), 37.0 (d, C-9), 32.5 (t, C-12), 32.1 (q, 20-CH_3), 30.6 (t, C-6), 26.8 (t, C-15), 26.5 (t, C-11), 24.6 (t, C-7), 22.1 (t, C-16), 21.4 (q, C-18), and 21.1 (q, 14^1-OCO*C*H$_3$) (Found: C, 74.6; H, 8.4%; M^+, 384. $C_{24}H_{32}O_4$ requires C, 74.9; H, 8.4%; *M*, 384), followed by starting material (**127**) (7 mg, 10%).

17α-*Hydroxy*-3-*methoxy*-20-*oxo*-19-*nor*-14β-*pregna*-1,3,5(10)-*triene*-14-*carbaldehyde* (**131**).—(a) Sodium periodate (0.5M, 2 ml) was added to a solution of the triol (**89**) (42 mg, 0.11 mmol) in ethanol (100 ml). After 2 h at 20°C, water was added to the reaction mixture, and the residue was extracted with chloroform. The combined organic phase was washed with brine and water, dried over magnesium sulfate and the solvent was evaporated under reduced pressure to give the residue (40 mg). Flash chromatography on silica gel (4 g) using ethyl acetate-toluene (0→3:7) as eluent gave the *cleavage product* (**131**) (39 mg, 100%), m.p. 161-163°C (from chloroform-hexane); $[\alpha]_D$ +134° (*c* 1.0); ν_{max} 3605 (OH), 1708 (CO) cm^{-1}; δ_H (400 MHz) 1.11 (3H, s, 13β-Me), 2.21 (3H, s, 20-Me), 2.58 (1H, td, *J* 2x11.4 and 3.2 Hz, 9α-H), 2.72-2.77 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.21 (1H, d, *J* 8.6 Hz,

1-H) and 9.62 (1H, s, 14β-CHO); δ_C (100 MHz) 214.8 (s, C-20), 205.6 (d, C-14^1), 157.7 (s, C-3), 137.6 (s, C-5), 131.5 (s, C-10), 126.6 (d, C-1), 113.5 (d, C-4), 111.9 (d, C-2), 90.8 (s, C-17), 62.0 (s, C-14), 55.2 (q, 3-OCH_3), 50.4 (s, C-13), 39.0 (d, C-8), 37.2 (d, C-9), 30.3 (t, C-6), 27.9 (q, 20-CH_3), 35.7, 33.1, 26.3, 22.9 (each t, C-16, C-15, C-12, and C-11), 24.8 (t, C-7) and 16.5 (q, C-18) (Found: C, 73.9; H, 7.9%; M^+, 356. $C_{22}H_{28}O_4$ requires C, 74.1; H, 7.9%; *M*, 356).

(b) Similarly, the triol (**99**) (158 mg, 0.44 mmol) gave the *cleavage product* (**131**) (156 mg, 100%)

Methyl 17-*Acetoxy*-14-*formyl*-3-*methoxy*-20-*oxo*-19-*nor*-14β-*pregna*-1,3,5(10)-*trien*-20-*oate* (**132**).—(a) Sodium periodate (6%, 2.4 ml) was added to a solution of the diol (**76**) (150 mg, 0.34 mmol) in ethanol. After 30 min at 20°C, water was added and the reaction mixture was extracted into ethyl acetate. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated to give the residue (150 mg). Chromatography of this residue on silica gel (15 g), using ethyl acetate-toluene (1:9) as eluent, gave the *cleavage product* (**132**) (143 mg, 95%), m.p. 184-187°C (from chloroform-methanol); $[\alpha]_D$ +91° (*c* 1.0); ν_{max} 1740 (OAc), 1725 (20-CO), 1715 (14^1-CO) cm^{-1}; δ_H (200 MHz) 1.30 (3H, s, 13β-Me), 2.10 (3H, s, 17α-OAc), 2.62 (1H, td, *J* 2x11.9 and 3.4 Hz, 9α-H), 2.70-2.80 (2H, m, 6-H_2), 3.76 (6H, s, 3-OMe and 20-CO_2Me), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.17 (1H, d, *J* 8.6 Hz, 1-H), and 9.65 (1H, s, 14β-CHO); δ_C (50 MHz) 205.2 (d, C-14^1), 192.4 (s, C-20), 172.4 (s, 17-O*C*OCH_3), 160.5 (s, 20-*C*O_2CH_3), 157.8 (s, C-3), 137.5 (s, C-5), 131.4 (s, C-10), 126.5 (d, C-1), 113.5 (d, C-4), 112.0 (d, C-2), 94.3 (s, C-17), 62.4 (s, C-14), 55.2 (q, 3-OCH_3), 52.9 (q, 20-CO_2CH_3), 52.3 (s, C-13), 38.5 (d, C-8), 36.8 (d, C-9), 34.0 (t, C-12), 33.7 (t, C-15), 30.2 (t, C-6), 26.1 (t, C-16), 25.1 (t, C-11), 23.1 (t, C-7), 20.8 (q, 17-OCO*C*H_3), and 16.0 (q, C-18) (Found: C, 67.5; H, 6.9 %; M^+, 442. $C_{25}H_{30}O_7$ requires C, 67.8; H, 6.8%; *M* 442).

(b) Similarly, the diol (**77**) (300 mg, 0.68 mmol) gave the cleavage product (**132**) (247 mg, 82%).

17α-*Hydroxy*-3-*methoxy*-14-*methyl*-14β-*estra*-1,3,5(10)-*triene*-17β,14^1-*carbolactone* (**134**).—Lithium aluminium hydride (131 mg, 3.4 mmol) was added to a solution of the steroid (**132**) (191 mg, 0.43 mmol) in tetrahydrofuran. After refluxing for 4h and subsequent cooling, ethyl acetate (5 ml) and sodium periodate (6%, 4.5 ml) were added. After a further 10 h at 20°C, water was added to the reaction mixture, which was then extracted into ethyl acetate. The combined organic phase was washed with brine and water, dried ($MgSO_4$) and the solvent was evaporated to give the residue (146 mg). Chromatography on silica gel (15g) using ethyl acetate-toluene (1:9) as eluent gave the *carbolactone* (**134**) (82 mg, 56%), m.p. 173-175°C (from chloroform-methanol); $[\alpha]_D$ +7° (*c* 1.0); ν_{max} 3521 (OH), 1726 (CO) cm^{-1}; δ_H (200 MHz) 1.0 (3H, s, 13β-Me), 2.64 (1H, td, *J* 2x11.3 and 3.0 Hz, 9α-H), 2.76-2.86 (2H, m, 6-H_2), 3.70 (3H, s, 3-OMe), 4.15 (1H, dd, *J* 10.7 and 1.9 Hz, 14^1-H_{exo}), 4.37 (1H, d, *J* 10.7 Hz, 14^1-H_{endo}), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 177.0 (s, C-20), 157.7 (s, C-3), 137.0 (s, C-5), 131.6 (s, C-10), 126.5 (d, C-1), 113.6 (d, C-4), 111.9 (d, C-2), 83.1 (s, C-17), 80.5 (t, C-14^1), 55.2 (q, 3-OCH_3), 46.3 (s, C-14), 43.6 (s, C-13), 39.1 (d, C-8), 36.7 (d, C-9), 29.8 (t, C-6), 32.9, 27.6, 25.6, 25.6, and 23.1 (each t, C-16, C-15, C-12, C-11, and C-7), and 14.6 (q, C-18) (Found: C, 73.5; H, 7.6%; M^+, 342. $C_{21}H_{26}O_4$ requires C, 73.6; H, 7.7%; *M*, 342).

14β-*Formyloxymethyl*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**136**).—Lithium aluminium hydride (27 mg, 0.7 mmol) was added to a solution of the lactone (**134**) (80 mg, 0.23 mmol) in tetrahydrofuran (8 ml). After 2.5 h at 20°C, saturated aqueous ammonuim chloride was added. The product was extracted into chloroform, the combined organic phase was washed with brine and water, dried ($MgSO_4$) and the solvent was evaporated to give the residue (75 mg).

Lead tetraacetate (300 mg, 0.8 mmol) was added to a solution of the residue (75 mg) in tetrahydrofuran. After 20 min at 25°C, ethane-1,2-diol was added to the reaction mixture, which was then extracted into chloroform. The combined organic phase was washed with brine and water, dried ($MgSO_4$) and the solvent was evaporated to give the residue (67 mg). Chromatography on silica gel (7 g) using ethyl acetate-toluene (1:9) as eluent gave the *ketone* (**136**) (47 mg, 70%), m.p. 158-160°C (from chloroform-methanol); $[\alpha]_D$ +81° (*c* 1.0); ν_{max} 1724 (CO) cm^{-1}; δ_H (200 MHz) 1.04 (3H, s, 13β-Me), 2.65 (1H, td, *J* 2x11.1 and 3.5 Hz, 9α-H), 2.80-2.90 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.03 and

4.36 (each 1H, d, *J* 11.4 Hz, 14^1-H_2), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.17 (1H, d, *J* 8.6 Hz, 1-H), and 8.01 (1H, s, 14^1-OCHO) (Found: C, 73.6; H, 7.9%; M^+, 342. $C_{21}H_{26}O_4$ requires C, 73.6; H, 7.7%; *M*, 342).

14-*Hydroxymethyl*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**137**).—Potassium hydroxide (M in methanol, 0.13 ml) was added to a solution of the ketone (**136**) (22 mg, 0.06 mmol) in tetrahydrofuran. After 5 min at 25°C, the reaction mixture was added to water and extracted with chloroform. The combined organic layer was washed with brine and water, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give the 14β-*hydroxymethyl* 17-*ketone* (**137**) (18 mg, 95%), m.p. 188-191°C (from ethyl acetate); $[\alpha]_D$ +82° (*c* 0.5); ν_{max} 3434 (OH), and 1724 (CO) cm^{-1}; δ_H (200 MHz) 1.11 (3H, s, 13β-Me), 2.70 (1H, td, *J* 2x11.3 and 3.2 Hz, 9α-H), 2.80-2.90 (2H, m, 6-H_2), 3.57 (1H, dd, *J* 10.4 and 3.1 Hz → dd on D_2O exch., *J* 10.4 and 0.9 Hz, 14^1-H), 3.88 (1H, dd, *J* 10.4 and 3.8 Hz → d on D_2O exch., *J* 10.4 Hz, 14^1-H), 3.77 (3H, s, 3-OMe), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 76.3; H, 8.3%; M^+, 314. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%; *M*, 314).

14-*Acetoxymethyl*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**138**).—Acetic anhydride (0.05 ml) and N,N-dimethylaminopyridine (10 mg) were added to a solution of the hydroxy ketone (**137**) (81 mg, 0.25 mmol) in pyridine (3 ml). After 2 h at 20°C, the reaction mixture was added to ice water and extracted with ethyl acetate. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated to give the residue (89 mg). Chromatography of this residue on silica gel (8 g), using ethyl acetate-toluene (1:9) as eluent, gave the 14^1-*acetate* (**138**) (73 mg, 82%), m.p. 102-104°C (from chloroform-methanol); $[\alpha]_D$ +66° (*c* 1.0); ν_{max} 1732 (OAc and CO) cm^{-1}; δ_H (200 MHz) 1.03 (3H, s, 13β-Me), 2.0 (3H, s, 14^1-OAc), 2.65 (1H, td, *J* 2x11.9 and 3.4 Hz, 9α-H), 2.80-2.90 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 3.95 (1H, dd, *J* 11.1 and 0.9 Hz, 14^1-H), 4.30 (1H, d, *J* 11.1 Hz, 14^1-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 220.2 (s, C-17), 170.6 (s, 14^1-O*C*OCH$_3$), 157.8 (s, C-3), 137.5 (s, C-5), 131.7 (s, C-10), 126.5 (d, C-1), 113.5 (d, C-4), 111.9 (d, C-2), 71.1 (t, C-14^1), 55.2 (q, 3-OCH_3), 50.6 (s, C-13), 46.9 (s, C-14), 39.9 (d, C-8), 37.5 (d, C-9), 33.6 (t, C-16), 32.5 (t, C-12), 30.1 (t, C-6), 25.5 (t,

C-11), 23.6 (t, C-15), 23.6 (t, C-7), 20.8 (q, 14[1]-OCO*C*H$_3$) and 14.5 (q, C-18) (Found: C, 74.2; H, 8.1%; M^+, 356. $C_{22}H_{28}O_4$ requires C, 74.1; H, 7.9%; *M*, 356).

21-*Acetoxy*-17α-*hydroxy*-3-*methoxy*-20-*oxo*-19-*nor*-14β-*pregna*-1,3,5(10)-*triene*-14-*carbaldehyde* (**141**).—(a) Lithium aluminium hydride (280 mg, 7.3 mmol) was added to a solution of the 15β,16β-diol (**77**) (400 mg, 0.8 mmol) in tetrahydrofuran (50 ml). After refluxing for 2.5 h, the reaction mixture was cooled and saturated aqueous ammonium chloride was added. The product was extracted into chloroform, the combined organic layer was washed with brine and water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the tetraol (**139**) (330 mg).

Acetic anhydride (1 ml) was added to a solution of the crude diol (**139**) (330 mg) in pyridine. Water was added to the reaction mixture after 1.5 h at 20°C, and the crude product was extracted into ethyl acetate. The combined organic layer was washed with brine and water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the 16[1]-acetate (**140**) (367 mg).

The two foregoing compounds were not isolated and characterised due to their extreme polarity and insolubility.

Sodium periodate (6%, 12.4 ml) was added to a solution of the crude acetate (**140**) (367 mg) in ethanol and tetrahydrofuran (50 ml). After 15 h at 20°C, water was added, the tetrahydrofuran and ethanol were evaporated under reduced pressure and the reaction mixture was extracted into chloroform. The combined organic layer was washed with brine and water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the residue (355 mg). Chromatography on silica gel (20 g) using ethyl acetate-toluene (1:4) as eluent gave the *cleavage product* (**141**) (300 mg, 80%), m.p. 170-173°C (from acetone-hexane); $[\alpha]_D$ +105° (*c* 1.0); ν_{max} 3519 (OH), 1745 (OAc), 1728 (20-CO), 1715 (14[1]-CO) cm^{-1}; δ_H (200 MHz) 1.17 (3H, s, 13β-Me), 2.14 (3H, s, 21-OAc), 3.76 (3H, s, 3-OMe), 4.86 and 5.41 (each 1H, d, *J* 17.9 Hz, 21-H_2), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.17 (1H, d, *J* 8.6 Hz, 1-H), and 9.60 (1H, s, 14β–CHO) (Found: C, 69.6; H, 7.3%; M^+, 414. $C_{24}H_{30}O_6$ requires C, 69.5; H, 7.3%; *M*, 414).

(b) The 15α,16α-diol (**76**) (300 mg, 0.6 mmol) was reacted as before to give the formyl ketone (**141**) (212 mg, 83%).

$14^1\xi$,20ξ-*Epoxy*-14-*hydroxymethyl*-3-*methoxy*-19-*nor*-14β-*pregna*-1,3,5(10)-*triene*-17α,21-*diol* 21 *Acetate* (**142**).—A solution of the starting material (**141**) (134 mg, 0.32 mmol) in tetrahydrofuran was added to a solution of sodium borohydride (61 mg, 1.9 mmol) in tetrahydrofuran and water (*ca.* 1μl) at 0°C over 15 min. After 30 min at 0°C, water was added, and the reaction mixture was extracted into chloroform. The combined organic layer was washed with brine and water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the residue (135 mg). Chromatography on silica gel (13 g) using ethyl acetate-toluene (1:1) as eluent gave the *product* (**142**) (93 mg, 70%), m.p. 160-164°C (from chloroform-ethanol); $[\alpha]_D$ +17° (*c* 0.5); ν_{max} 3586 (OH), 1731 (OAc) cm^{-1}; δ_H (400 MHz) 1.25 (3H, s, 13β-Me), 1.70 (1H, s, disp. on D_2O exch., 17α-OH), 2.05 (3H, s, 21-OAc), 2.56 (1H, d, *J* 3.5 Hz, disp. on D_2O exch., 14^1-OH), 2.58 (1H, td, *J* 2x12.7 and 3.3 Hz, 9α-H), 2.74-2.82 (2H, m, 6-H_2), 3.71 (3H, s, 3-OMe), 4.09 (1H, dd, *J* 11.6 and 7.0 Hz, 21-H), 4.50 (1H, dd, *J* 11.6 and 2.6 Hz, 21-H), 4.29 (1H, dd, *J* 7.0 and 2.6 Hz, 20-H), 5.01 (1H, d, *J* 3.5 Hz, → s on D_2O exch, 14^1-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 171.5 (s, 21-O*C*OCH$_3$), 157.4 (s, C-3), 137.5 (s, C-5), 132.8 (s, C-10), 126.3 (d, C-1), 113.5 (d, C-4), 111.6 (d, C-2), 98.8 (d, C-14^1), 80.6 (s, C-17), 72.6 (d, C-20), 65.4 (t, C-21), 55.2 (q, 3-O*C*H$_3$), 50.0 (s, C-14), 44.6 (s, C-13), 36.7 (2xd, C-8 and C-9), 30.1 (t, C-6), 30.0, 27.7, 25.3 and 22.9 (each t, C-7, C-12, C-15 and C-16), 25.8 (t, C-11), 21.1 (q, 21-OCO*C*H$_3$) and 14.7 (q, C-18) (Found: C, 69.3; H, 7.7%; M^+, 416. $C_{24}H_{32}O_6$ requires C, 69.2; H, 7.7%; *M*, 416).

3-*Methoxy*-17-*oxoestra*-1,3,5(10)-*triene*-14β-*carbaldehyde* (**144**).—(a) Lithium aluminium hydride (350 mg, 9.2 mmol) was added to a solution of the 15β,16β-diol (**77**) (500 mg, 1.13 mmol) in tetrahydrofuran (50 ml). After refluxing for 2.5 h, the reaction mixture was cooled and saturated aqueous ammonium chloride was added. The product was extracted into chloroform, the combined organic layer was washed with brine and water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the tetraol intremediate (**139**) (403 mg).

Sodium periodate (6%, 20 ml) was added to a solution of the crude tetraol (**139**) (403 mg) in ethanol and tetrahydrofuran (50 ml). After 16 h at 20°C, water was added, the tetrahydrofuran and ethanol were evaporated under reduced pressure and the reaction mixture was extracted into chloroform. The combined organic layer was washed with brine

and water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the residue (428 mg).

Lead tetraacetate (2.5 g, 5.6 mmol) was added to a solution of the latter residue (428 mg) in tetrahydrofuran (40 ml). After 15 min at 20°C, ethane-1,2-diol and water were added to the reaction mixture, which was then extracted into ethyl acetate. The combined organic layer was washed with brine and water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the residue (340 mg). Chromatography on silica gel (20 g) using ethyl acetate-toluene (1:3) as eluent gave the *formyl ketone* (**144**) (278 mg, 79%), m.p. 143-146°C (from chloroform-methanol); $[\alpha]_D$ +148° (*c* 0.8); ν_{max} 1735 (17-CO), 1715 (14^1-CO) cm^{-1}; δ_H (400 MHz) 1.12 (3H, s, 13β-Me), 1.65 (1H, td, *J* 2x14.2 and 3.3 Hz, 12α-H), 2.0 (1H, dtd, *J* 13.5, 2x10.0 and 1.3 Hz, 15α-H), 2.12 (1H, td, *J* 2x11.2 and 2.8 Hz, 8β-H), 2.16 (1H, obsc., 15β-H), 2.41 (1H, dq, *J* 12.9 and 3x3.5 Hz, 11α-H), 2.54 (2H, m, 16-H_2), 2.66 (1H, td, *J* 2x11.2 and 3.5 Hz, 9α-H), 2.85 (1H, ddd, *J* 16.9, 5.9 and 2.5 Hz, 6-H), 2.90-3.0 (1H, m, 6-H), 3.76 (3H, s, 3-OMe), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.17(1H, d, *J* 8.6 Hz, 1-H), and 9.62 (1H, d, *J* 1.3 Hz, 14β-CHO); δ_C (50 MHz) 218.9 (s, C-17), 207.2 (d, C-14^1), 157.8 (s, C-3), 137.3 (s, C-5), 130.9 (s, C-10), 126.5 (d, C-1), 113.7 (d, C-4), 112.0 (d, C-2), 59.4 (s, C-14), 55.2 (q, 3-OCH_3), 51.4 (s, C-13), 37.4 (d, C-8), 36.8 (d, C-9), 34.2 (t, C-16), 32.6 (t, C-12), 30.1 (t, C-6), 25.6 (t, C-11), 24.8 (t, C-7), 20.1 (t, C-15), and 14.7 (q, C-18) (Found: C, 76.6; H, 7.6%; M^+, 312. $C_{20}H_{24}O_3$ requires C, 76.9; H, 7.7%; *M*, 312).

(b) In a similar series of experiments, the 15α,16α-diol (**76**) (500 mg, 1.13 mmol) was reacted to give the formyl ketone (**144**) (266 mg, 76%).

Chemoselective Reduction of the Formyl Ketone (**144**).—Lithium tri(s-butyl)borohydride (M in tetrahydrofuran, 0.96 ml) was added to a solution of the formyl ketone (**144**) (200 mg, 0.64 mmol) in tetrahydrofuran at 0°C. After 15 min at 0°C, water was added and the reaction mixture was extracted into ethyl acetate. The combined organic layer was washed with brine and water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the residue (200 mg). Chromatography on silica gel (20 g) using ethyl acetate-toluene (2:5) as eluent gave the hydroxymethyl ketone (**137**) (189 mg, 94%).

Hydride Reduction of the Formyl Ketone (**144**).—Lithium aluminium hydride (146 mg, 3.8 mmol) was added to a solution of the formyl ketone (**144**) (300 mg, 0.96 mmol) in tetrahydrofuran (20 ml). After 30 min at 20°C, saturated aqueous ammonium chloride was added to the reaction mixture. The product was extracted into chloroform, the combined organic layer was washed with brine and water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the residue (330 mg). Chromatography on silica gel (33 g) using ethyl acetate-toluene (1:1) as eluent gave 14-*hydroxymethyl*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-17β-*ol* (**145**) (136 mg, 45%), m.p. 188-190°C (from chloroform-ethyl acetate); $[\alpha]_D$ +38° (*c* 1.0); ν_{max} 3494 br (OH) cm^{-1}; δ_H (200 MHz) 0.99 (3H, s, 13β–Me), 1.10 (1H, td, *J* 2x10.9 and 2.9 Hz, 12α-H), 2.68-2.80 (2H, m, 6-H_2), 3.42 and 3.74 (each 1H, d, *J* 11.1 Hz, 14^1-H_2), 3.70 (1H, dd obsc., *J* 8.2 and 1.6 Hz, 17α-H), 3.7 (3H, s, 3-OMe), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 75.8; H, 8.9%; M^+, 316. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%; *M*, 316), followed by 14-*hydroxymethyl*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-17α-*ol* (**146**) (134 mg, 44%), m.p. 160-162°C (from toluene); $[\alpha]_D$ +33° (*c* 1.0 in tetrahydrofuran); ν_{max} 3489 br (OH) cm^{-1}; δ_H (200 MHz) 1.05 (3H, s, 13β-Me), 2.48 (1H, td, *J* 2x11.5 and 3.2 Hz, 9α-H), 2.71-2.82 (2H, m, 6-H_2), 3.49 and 3.67 (each 1H, d, *J* 11.6 Hz, 14^1-H_2), 3.7 (3H, s, 3-OMe), 4.2 (1H, obsc. t, *J* 2x8.5 Hz, 17β-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 75.9; H, 9.1%; M^+, 316. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%; *M*, 316).

14-*Acetoxymethyl*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-17β-*acetate* (**147**).—Acetic anhydride (0.04 ml) and dimethylaminopyridine (20 mg) were added to a solution of the diol (**145**) (27 mg, 0.085 mmol) in pyridine. After 1.25 h at 20°C, the reaction mixture was added to ice water and neutralised with sodium hydrogen carbonate. The product was extracted into chloroform, the combined organic layer was washed with brine and water, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give the residue (33 mg). Chromatography on silica gel (3 g) using ethyl acetate-toluene (1:3) as eluent gave the non-crystalline *diacetate* (**147**) (33 mg, 97%), $[\alpha]_D$ +25° (*c* 0.7); ν_{max} 1718 (OAc) cm^{-1}; δ_H (200 MHz) 0.92 (3H, s, 13β-Me), 1.97 and 2.0 (each 3H, s, 14^1- and 17β-OAc), 2.70-2.80 (2H, m, 6-H_2), 3.71 (3H, s, 3-OMe), 4.16 and 4.36 (each 1H, d, *J* 11.9 Hz, 14^1-H_2), 4.78 (1H, dd, *J* 8.0 and 2.3 Hz, 17α-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6

and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 400.2242. $C_{24}H_{32}O_5$ requires *M*, 400.2250).

14-*Acetoxymethyl*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-17α-*acetate* (**148**).—Acetic anhydride (0.06 ml) and dimethylaminopyridine (20 mg) were added to a solution of the diol (**146**) (36 mg, 0.11 mmol) in pyridine. After 40 min at 20°C, the reaction mixture was added to ice water and neutralised with sodium hydrogen carbonate. The product was extracted into ethyl acetate, the combined organic layer was washed with brine and water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the residue (44 mg). Chromatography on silica gel (2.5 g) using ethyl acetate-toluene (1:3) as eluent gave the non-crystalline *diacetate* (**148**) (42 mg, 91%), $[\alpha]_D$ +16° (*c* 1.1); ν_{max} 1725 (OAc) cm^{-1}; δ_H (200 MHz) 0.95 (3H, s, 13β-Me), 1.99 and 2.0 (each 3H, s, 14^1- and 17α-OAc), 2.50 (1H, td, *J* 2x11.3 and 2.7 Hz, 9α-H), 2.70-2.80 (2H, m, 6-H_2), 3.71 (3H, s, 3-OMe), 3.94 and 4.14 (each 1H, d, *J* 11.9 Hz, 14^1-H_2), 5.14 (1H, dd, *J* 9.3 and 7.9 Hz, 17β-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 400.2239. $C_{24}H_{32}O_5$ requires *M*, 400.2250).

14-*Hydroxymethyl*-14β-*estra*-1,3,5(10)-*triene*-3,17β-*diol* (**153**).—Diisobutylaluminium hydride (M in toluene, 1 ml) was added to a solution of the diol (**145**) (70 mg, 0.22 mmol) in toluene. After refluxing for 24 h, further diisobutylaluminium hydride (1 ml) was added. After 48h at 120°C, the reaction mixture was cooled to 0°C and quenched with saturated aqueous ammonium chloride and acid. The product was extracted into ethyl acetate, the combined organic layer was washed with brine and water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the residue (69 mg). Chromatography on silica gel (7 g) using ethyl acetate-toluene (1:1) as eluent gave the *triol* (**153**) (61 mg, 92%), m.p. 247-248°C (from ethanol); $[\alpha]_D$ +41° (*c* 0.64 in pyridine) (Found: C, 75.7; H, 8.6%; M^+, 302. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.7%; *M*, 302).

14-*Hydroxymethyl*-14β-*estra*-1,3,5(10)-*triene*-3,17α-*diol* (**154**).—Diisobutylaluminium hydride (M in toluene, 1 ml) was added to a solution of the diol (**146**) (72 mg, 0.23 mmol) in toluene. After refluxing for 24 h, further diisobutylaluminium hydride (1 ml) was added. After 31 h at 120°C, the reaction mixture was cooled to 0°C and quenched with saturated aqueous ammonium chloride and acid. The product was extracted into ethyl acetate, the combined organic layer was washed with brine and water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the residue (69 mg). Chromatography on silica gel (7 g) using ethyl acetate-toluene (1:1) as eluent gave the *triol* (**154**) (60 mg, 88%), m.p. 230-233°C (from ethanol); $[\alpha]_D$ +33° (*c* 0.48 in pyridine) (Found: C, 75.7; H, 8.6%; M^+, 302. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.7%; *M*, 302).

3-*Methoxy*-14-*vinyl*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**155**).—*n*-Butyllithium (1.6M in hexane, 3 ml) was added dropwise under nitrogen to a suspension of methyltriphenylphosphonium bromide (1.7 g, 1.6 mmol) in dry tetrahydrofuran (2 ml). After 30 min at 20°C, during which time the suspension became deep yellow in colour, the steroid (**144**) (500 mg, 1.6 mmol) was added in a solution of tetrahydrofuran, to the suspension at 0°C. The temperature was allowed to increase gradually to room temperature, and after 17h, saturated aqueous ammonium chloride was added to the reaction, which was then extracted with chloroform. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated to give the residue (600 mg). Chromatography of this residue on silica gel (60 g), using ethyl acetate-toluene (1:19) as eluent, gave the *product* (**155**) (247 mg, 50%), m.p. 106-109°C (from chloroform-methanol); $[\alpha]_D$ +161° (*c* 0.7); ν_{max} 1726 (CO) cm^{-1}; δ_H (400 MHz) 1.03 (3H, s, 13β-Me), 1.44 (1H, dt obsc., *J* obsc. and 2x3.2 Hz, 12β-H), 1.52 (1H, td, *J* 2x11.7 and 2.0 Hz, 8β-H), 1.68 (1H, td, *J* 2x11.7 and 3.8 Hz, 12α-H), 1.88 (1H, dtd, *J* 12.9, 2x4.1 and 2.0 Hz, 7β-H), 1.91-2.19 (2H, m, 15-H_2), 2.26 (1H, q, *J* 3x9.7 Hz, 16-H), 2.36 (1H, dq, *J* 11.1 and 3x3.6 Hz, 11α-H), 2.52 (1H, m, 16-H), 2.66 (1H, td, *J* 2x11.7 and 3.6 Hz, 9α-H), 2.80-2.90 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 4.99 (1H, dd, *J* 17.6 and 0.8 Hz, 14^2-H_{trans}), 5.16 (1H, dd, *J* 11.0 and 0.8 Hz, 14^2-H_{cis}), 5.60 (1H, ddd, *J* 17.6, 11.0, and 1.1 Hz, 14^1-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H); δ_c (100 MHz) 220.9 (s, C-17), 157.7 (s, C-3), 142.4 (d, C-14^1) 137.9 (s, C-5), 132.1 (s, C-10), 126.6 (d, C-1), 114.1 (t, C-14^2) 113.7 (d, C-4), 111.8 (d, C-2), 55.2 (q, 3-OCH_3), 52.9 and 51.0 (each s, C-13 and C-14), 41.3 (d, C-8), 37.3 (d, C-9), 33.9 (t,

C-16), 32.1 (t, C-12), 30.6 (t, C-6), 25.8 (t, C-11), 23.8 (t, C-7), 21.3 (t, C-15), and 15.2 (q, C-18) (Found: C, 81.2; H, 8.4 %; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; *M*, 310), followed by starting material (**144**) (185 mg, 37%).

Hydride Reduction of the Vinyl Ketone (**155**).—Lithium aluminium hydride (171 mg, 4.5 mmol) was added to a solution of the ketone (**155**) (275 mg, 0.88 mmol) in tetrahydrofuran. After 25 min at 20°C, saturated aqueous sodium hydrogen carbonate was added to the reaction mixture, which was then filtered through a sintered glass funnel, and extracted with ethyl acetate. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated to give the residue (270 mg). Chromatography of this residue on silica gel (27 g), using toluene as eluent, gave 3-*methoxy*-14-*vinyl*-14β-*estra*-1,3,5(10)-*trien*-17β-*ol* (**156**) (79 mg, 29%), m.p. 50-53°C (from chloroform-methanol); $[\alpha]_D$ +117° (*c* 0.97); ν_{max} 3555 (OH) cm^{-1}; δ_H (400 MHz) 1.08 (3H, s, 13β-Me), 2.58 (1H, obsc., 9α-H), 2.74-2.80 (2H, m, 6-H_2), 3.57 (1H, ddd, *J* 10.9, 7.4 and 1.3 Hz → dd on D_2O exch., *J* 7.4 and 1.3 Hz, 17α-H), 3.77 (3H, s, 3-OMe), 5.22 (1H, dd, *J* 17.7 and 1.4 Hz, 14^2-H_{trans}), 5.24 (1H, dd, *J* 11.1 and 1.4 Hz, 14^2-H_{cis}), 5.90 (1H, ddd, *J* 17.7, 11.1 and 0.8 Hz, 14^1-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 312.2071. $C_{21}H_{28}O_2$ requires *M*, 312.2089), followed by 3-*methoxy*-14-*vinyl*-14β-*estra*-1,3,5(10)-*trien*-17α-*ol* (**157**) (185 mg, 67%), m.p. 58-60°C (from chloroform-methanol); $[\alpha]_D$ +96° (*c* 1.0); ν_{max} 3593 (OH) cm^{-1}; δ_H (200 MHz) 0.97 (3H, s, 13β-Me), 2.58 (1H, td, *J* 2x11.3 and 3.3 Hz, 9α-H), 2.72-2.82 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 3.93 (1H, m → t on D_2O exch., *J* 2x8.6 Hz, 17β-H), 4.99 (1H, dd, *J* 17.5 and 1.3 Hz, 14^2-H_{trans}), 5.14 (1H, dd, *J* 10.9 and 1.3 Hz, 14^2-H_{cis}), 5.66 (1H, ddd, *J* 17.5, 10.9 and 1.1 Hz, 14^1-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 312.2086. $C_{21}H_{28}O_2$ requires *M*, 312.2089).

14-*Vinyl*-14β-*estra*-1,3,5(10)-*triene*-3,17β-*diol* (**158**).—Diisobutylaluminium hydride (1.5M in toluene, 0.7 ml) was added to a suspension of the steroid (**156**) (66 mg, 0.21 mmol) in toluene (7 ml). After 18 h at 120°C, further diisobutylaluminium hydride (0.7 ml) was added to the reaction mixture. After a further 8 h at 120°C, saturated aqueous ammonium chloride was added to the cooled solution, which was then extracted into ethyl

acetate, with a dilute solution of HCl to facilitate separation of organic and aqueous layers. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated to give the residue (66 mg). Chromatography of this residue on silica gel (6 g), using ethyl acetate-toluene (1:4) as eluent, gave the *diol* (**158**) (69 mg, 99%), m.p. 147-149°C (from ethyl-acetate); $[\alpha]_D$ +52° (*c* 0.4 in tetrahydrofuran) (Found: M^+, 298.1947. $C_{20}H_{26}O_2$ requires *M*, 298.1933).

14-*Vinyl*-14β-*estra*-1,3,5(10)-*triene*-3,17α-*diol* (**159**).—Diisobutylaluminium hydride (1.5M in toluene, 1.4 ml) was added to a suspension of the steroid (**157**) (128mg, 0.41 mmol) in toluene (10 ml). After 20 h at 120°C, further diisobutylaluminium hydride (1.4ml) was added to the reaction mixture. After a further 6 h at 120°C, saturated aqueous ammonium chloride was added to the cooled solution, which was then extracted into ethyl acetate, with hydrochloric acid (3M) to facilitate separation of organic and aqueous layers. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated to give the residue (130 mg). Chromatography of this residue on silica gel (13 g), using ethyl-acetate-toluene (1:4) as eluent, gave the *diol* (**159**) (119 mg, 97%), m.p. 183-186°C (from ethyl-acetate); $[\alpha]_D$ +77° (*c* 0.48 in tetrahydrofuran) (Found: M^+, 298.1948. $C_{20}H_{26}O_2$ requires *M*, 298.1933).

(14[1]R)-1-(3-*methoxy*-17-*oxo*-14β-*estra*-1,3,5(10)-*trien*-14-*yl*)*ethanol* (**160**).—Magnesium (39 mg, 1.6 mmol) was flame dried in a reaction vessel and allowed to cool under nitrogen. A crystal of iodine was added to the reaction vessel. Methyl iodide (0.13 ml in 1 ml ether) was added slowly to the magnesium. After 30 min a solution of the steroid (**144**) (100 mg, 0.32 mmol) in tetrahydrofuran was added to the reaction mixture at 0°C. After 5 min at 0°C, saturated aqueous ammonium chloride was added to the reaction, which was then extracted with chloroform. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated to give the residue 1:6) as eluent, gave the *product* (**160**) (100 mg, 95%), m.p. 211-214°C (from chloroform); $[\alpha]_D$ +78° (*c* 1.0); ν_{max} 3525 (OH) and 1725 (CO) cm^{-1}; δ_H (200 MHz) 1.23 (3H, s, 13'β-Me), 1.29 (3H, d, *J* 6.9 Hz, 1-Me), 2.66 (1H, td, *J* 2x12.7 and 3.3 Hz, 9'α-H), 2.80-2.90 (2H, m, 6'-H_2), 3.78 (3H, s, 3'-OMe), 4.22 (1H, m → q on D_2O exch., *J* 3x6.9 Hz, 1-H), 6.67 (1H, d, *J* 2.8 Hz, 4'-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2'-H), and 7.17 (1H, d,

J 8.6 Hz, 1'-H); δ_c (50 MHz) 221.2 (s, C-17'), 157.7 (s, C-3'), 137.4 (s, C-5'), 132.3 (s, C-10'), 126.7 (d, C-1'), 113.6 (d, C-4'), 111.8 (d, C-2'), 76.9 (d, C-1), 55.2 (q, 3'-OCH_3), 51.3 and 50.7 (each s, C-13' and C-14'), 40.0 and 37.9 (each d, C-9' and C-8'), 30.2 (t, C-6'), 34.2, 33.6, 27.6, 25.9, and 23.2 (each t, C-16', C-15', C-12', C-11', and C-7'), 21.2 (q, C-2), and 17.4 (q, C-18') (Found: C, 77.0; H, 8.8%; M^+, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%; *M*, 328).

(1R)-1-(3-*methoxy*-17-oxo-14β-*estra*-1,3,5(10)-*trien*-14-yl)prop-2-enol (**161**).—Magnesium (78 mg, 3.2 mmol) was flame dried in a reaction vessel and allowed to cool under nitrogen. A crystal of iodine was added to the reaction vessel. Vinyl bromide (0.4 ml in 1 ml ether) was added slowly to the magnesium. After 20 min, a solution of the steroid (**144**) (200 mg, 0.64 mmol) in tetrahydrofuran was added to the reaction mixture at 0°C. After 20 min at 0°C, saturated aqueous ammonium chloride was added to the reaction, which was then extracted with chloroform. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated to give the residue (150 mg). Chromatography of this residue on SiO_2 (15 g), using ethyl acetate-toluene (3:17) as eluent, gave the *product* (**161**) (154 mg, 71%), m.p. 187-190°C (from ethyl acetate); $[\alpha]_D$ +57° (*c* 1.0); ν_{max} 3603 (OH) and 1725 (CO) cm^{-1}; δ_H (400 MHz) 1.22 (3H, s, 13'β-Me), 2.74-2.80 (2H, m, 6'-H_2), 3.77 (3H, s, 3'-OMe), 4.47 (1H, br dd, *J* 8.3 and 2.9 Hz → br d on D_2O exch., *J* 8.3 Hz, 1-H), 5.16 (1H, ddd, *J* 10.2, 1.5 and 1.0 Hz, 3-H_{cis}), 5.22 (1H, dt, *J* 18.5 and 2x1.5 Hz, 3-H_{trans}), 6.15 (1H, ddd, *J* 18.5, 10.2, and 8.3 Hz, 2-H), 6.67 (1H, d, *J* 2.8 Hz, 4'-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2'-H), and 7.17 (1H, d, *J* 8.6 Hz, 1'-H) (Found: C, 77.5; H, 8.4%; M^+, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; *M*, 340).

14β-*(Methanesulfonyloxy)methyl*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**162**).—Methane sulfonyl chloride (0.1 ml, 1.38 mmol) was added to a solution of the steroid (**137**) (143 mg, 0.46 mmol) in pyridine (10 ml) at 0°C. After 1.5 h at 20°C, water was added to the reaction mixture, which was then extracted with ethyl acetate. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated to give the residue (187 mg). Chromatography of this residue on silica gel (18 g), using ethyl acetate-toluene (2:3) as eluent, gave the non-crystalline *product* (**162**)

(148 mg, 82%); $[\alpha]_D$ +59° (*c* 1.0); ν_{max} 1729 (CO) and 1340 (OMs) cm^{-1}; δ_H (200 MHz) 1.11 (3H, s, 13β-Me), 2.98 (3H, s, 14^1-OMs), 3.78 (3H, s, 3-OMe), 4.10 (1H, dd, *J* 9.6 and 0.7 Hz, 14^1-H), 4.4 (1H, d, *J* 9.6, 14^1-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 392.1667. $C_{21}H_{28}O_5S$ requires *M*, 392.1657).

Attempted Cyclisations of the Aldehyde (**144**) *and Mesylate* (**162**).—(a) A solution of the aldehyde (**144**) (50 mg, 0.16 mmol) in tetrahydrofuran (3 ml) was added to samarium(II) iodide (0.1 M in tetrahydrofuran, 5 ml) at 20°C. After 15 min, tert-butyl alcohol (0.05 ml) was added to the reaction mixture. After 4 h at 80°C, the reaction mixture was cooled and saturated aqueous ammonium chloride was added. The reaction mixture was then extracted with ethyl acetate; the combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was evaporated to give the residue (50 mg). Chromatography of this residue on silica gel (5 g), using ethyl acetate-toluene (2:3) as eluent, gave the hydroxymethyl compound (**137**) (19 mg, 38%), followed by an inseparable mixture of more polar compounds (26 mg).

(b) Reaction of the mesylate (**162**) as above, with samarium (II) iodide and tert-butyl alcohol at 80°C for 1 h, gave inseparable mixtures of three less - and two more polar compounds.

(c) Diisopropylethylamine (0.05 ml) was added to a solution of sodium iodide (311 mg, 2.08 mmol) in acetone (5 ml). A solution of the mesylate (**162**) (139 mg, 0.35 mmol) in acetone was added to the reagent mixture at 0°C. After 18 h at 20°C, no reaction had occurred.

17α-*Hydroxy*-3-*methoxy*-14,17β-*prop*-17^2-*eno*-14β-*estra*-1,3,5(10)-*trien*-17^1-*one* (**163**).—(a) Toluene-*p*-sulfonic acid (623 mg, 3.1 mmol) was added to benzene (20 ml) and boiled for 15 min. A solution of the formyl ketone (**123**) (436 mg, 1.09 mmol) in benzene (10 ml) was added to the cooled mixture. After 1.75 h at 85°C, the reaction mixture was added to saturated aqueous sodium hydrogen carbonate and extracted into ethyl acetate. The combined organic phase was washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the residue (380 mg). Chromatography on silica gel (30 g) using ethyl acetate-hexane (1:4) as eluent gave the *hydroxy enone* (**163**) (370 mg,

100%), m.p. 158-161°C (from chloroform-methanol); $[\alpha]_D$ +117° (*c* 1.0); λ_{max} 243 nm (ε 16426); ν_{max} 3480 (OH), 1677 (CO) cm^{-1}; δ_H (200 MHz) 0.73 (3H, s, 13β-Me), 2.72 (1H, td, *J* 2x11.3 and 4.3 Hz, 9α-H), 2.81-2.90 (2H, m, 6-H_2), 3.71 (3H, s, 3-OMe), 6.07 (1H, d, *J* 9.8 Hz, 17^2-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.17 (1H, d, *J* 8.6 Hz, 1-H), and 7.26 (1H, d, *J* 9.8 Hz, 17^3-H); δ_C (50 MHz) 203.0 (s, C-17^1), 158.9 (d, C-17^3), 157.6 (s, C-3), 137.4 (s, C-5), 132.3 (s, C-10), 126.2 (d, C-1), 125.0 (d, C-17^2), 113.3 (d, C-4), 111.6 (d, C-2), 88.7 (s, C-17), 55.2 (q, 3-OCH_3), 52.5 (2xs, C-13 and C-14), 38.7 (d, C-9), 37.4 (d, C-8), 30.2 (t, C-6), 28.5, (t, C-15), 28.5, 28.5, 25.6, 25.0 and 24.0 (each t, C-12, C-7, C-11, C-15 and C-16), and 13.8 (q, C-18) (Found: C, 78.3; H, 7.6%; M^+ 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; *M*, 338).

(b) The 17α-hydroxy 14β-formyl 17-ketone (**131**) (170 mg, 0.47 mmol) was reacted in a similar manner to give the hydroxy enone (**163**) (138 mg, 87%).

17α-*Acetoxy*-3-*methoxy*-14,17β-*prop*-17^2-*eno*-14β-*estra*-1,3,5(10)-*trien*-17^1-*one* (**164**).—A solution of hydrochloric acid in tetrahydrofuran (1N, 10 ml) was added to the acetyl carbaldehyde (**123**) (100 mg, 0.25 mmol). After 2 h at 50°C, the reaction mixture was added to saturated aqueous sodium hydrogen carbonate and extracted into chloroform. The combined organic phase was washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the residue (90 mg). Chromatography on silica gel (9 g) using ethyl acetate-hexane (3:7) as eluent gave the *acetoxy enone* (**164**) (85 mg, 89%), m.p. 170-172°C (from chloroform-methanol); $[\alpha]_D$ -1° (*c* 1.0); ν_{max} 1739 (OAc), 1694 (CO) cm^{-1}; δ_H (200 MHz) 0.95 (3H, s, 13β-Me), 2.17 (3H, s, 17α-OAc), 2.80 (1H, td, *J* 2x10.9 and 3.9 Hz, 9α-H), 2.90-3.0 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 6.07 (1H, d, *J* 9.9 Hz, 17^2-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.17 (1H, d, *J* 9.9 Hz, 17^3-H) and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 75.9; H, 7.3%; M^+ 380. $C_{24}H_{28}O_4$ requires C, 75.8; H, 7.4%; *M*, 380).

Hydride Reduction of 17α-*Hydroxy*-3-*methoxy*-14,17β-*prop*-17^2-*eno*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**163**).—Lithium aluminium hydride (30 mg, 0.8 mmol) was added to a solution of the enone (**163**) (87 mg, 0.25 mmol) in tetrahydrofuran. After 5 h at 20°C, saturated aqueous ammonium chloride was added to the reaction mixture, which was then extracted with chloroform. The combined organic phase was washed with brine, dried

($MgSO_4$) and the solvent evaporated under reduced pressure to give the residue (87 mg). Chromatography on silica gel (8 g), using ethyl acetate-hexane (1:10) as eluent, gave 17α-hydroxy-3-methoxy-14,17β-propano-14β-estra-1,3,5(10)-trien-17^1-one (**165**) (40 mg, 46%), m.p. 152-155°C (lit.,[28] m.p. 153-156°C), followed by (17^1S)-3-*methoxy*-14β,17β-*prop*-17^2-*eno*-14β-*estra*-1,3,5(10)-*triene*-17α,17^1-*diol* (**166**) (20 mg, 23%), m.p. 170-172°C (from chloroform-hexane); $[\alpha]_D$ +19° (*c* 1.0); ν_{max} 3607 and 3542 (OH) cm^{-1}; δ_H (200 MHz) 0.94 (3H, s, 13β-Me), 2.82-2.94 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 3.92 (1H, dd, *J* 4.0 and 1.0 Hz, 17^1-H), 5.77 (1H, dd, *J* 9.7 and 4.0 Hz, 17^2-H), 6.14 (1H, dd, *J* 9.7 and 1.0 Hz, 17^3-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 77.6; H, 8.4%; M^+,340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; *M*, 340), followed by (17^1S)-3-methoxy-14β,17β-propano-14β-estra-1,3,5(10)-triene-17α,17^1-diol (**167**) (8 mg, 9%), m.p. 186-189°C (lit.,[28] m.p. 184-187°C); δ_H (200 MHz) 1.13 (3H, s, 13β-Me), 3.77 (3H, s, 3-OMe), 3.81 (1H, dd, *J* 5.8 and 0.9 Hz, 17^1-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 342. $C_{22}H_{28}O_3$ requires *M*, 342).

(17^1S)-3-*Methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*triene*-17α,17^1-*diol* (**167**).—Palladium on activated charcoal (10%, 10 mg) was added to a solution of the 17^1(*S*)-alcohol (**166**) (12 mg, 0.04 mmol) in ethanol. After stirring the slurry for 5 h at 20°C under hydrogen, the catalyst was removed by filtration through Celite. The solvent was evaporated under reduced pressure to give the *saturated product* (**167**) (10 mg, 84%).

Selective 1,2-Reduction of 17α-*Hydroxy*-3-*methoxy*-14,17β-*prop*-17^2-*eno*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**163**).—Sodium borohydride (144 mg, 3.8 mmol) was added to a solution of the hydroxy enone (**163**) (326 mg, 0.96 mmol) and cerium trichloride heptahydrate (716 mg, 1.9 mmol) in methanol (20 ml) at 0°C. After 45 min at this temperature, saturated aqueous sodium hydrogen carbonate was added to the reaction mixture and the products were extracted into ethyl acetate. The combined organic phase was washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the residue (340 mg). Chromatography on silica gel (35 g), using ethyl acetate-hexane (35:65) as eluent, gave the *unsaturated diol* (**166**) (310 mg, 95%).

(17^1S)-14β,17β-*Prop*-17^2-*enoestra*-1,3,5(10)-*triene*-3,17α,17^1-*triol* (**170**).—Diisobutylaluminium hydride (1.5M in toluene, 460 mg) was added to a solution of the diol (**166**) (110 mg, 0.32 mmol) in toluene (5 ml). After 48 h at 120°C, saturated aqueous ammonium chloride was added to the reaction mixture at 0°C. The product was extracted into ethyl acetate. The combined organic phase was washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the residue (100 mg). Chromatography on silica gel (5 g) using ethyl acetate-hexane (1:1) as eluent gave the *triol* (**170**) (84 mg, 81%), m.p. 249-253°C (from acetone-hexane); $[\alpha]_D$ -28° (*c* 1.0 in pyridine); (Found: M^+ 326. $C_{21}H_{26}O_3$ requires *M*, 326).

3-*Methoxy*-14,17α-*ethano*-17a-*homoestra*-1,3,5(10),15-*tetraen*-17a-*one* (**174**).—Perchloric acid (70%, 0.1 ml) was added to a solution of the unsaturated diol (**166**) (332 mg, 0.97 mmol) in tetrahydrofuran. After 3 h at 20°C, the reaction mixture was added to saturated aqueous sodium hydrogen carbonate, and the product was extracted into chloroform. The combined organic phase was washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the residue (330 mg). Chromatography on silica gel (26 g), using ethyl acetate-toluene (1:9) as eluent, gave the *rearrangement product* (**174**) (275 mg, 88%), m.p. 156-158°C (from chloroform-methanol); $[\alpha]_D$ +180° (*c* 1.0); ν_{max} 1705 (CO) cm^{-1}; δ_H (400 MHz) 0.99 (3H, s, 13β-Me), 1.30 (1H, td, *J* 2x13.1 and 5.3 Hz, 17^2-H), 1.50 (1H, m, 11β-H), 1.54 (1H, m, 7-H), 1.62 (1H, m, 17^1-H), 1.68 (1H, td, 2x13.2 and 4.2 Hz, 12α-H), 1.79 (1H, m, 17^1-H), 1.84 (1H, ddd, *J* 13.2, 4.2 and 2.5 Hz, 12β-H), 1.9 (2H, m, 7-H and 8β-H), 2.06 (1H, ddd, *J* 13.1, 9.8 and 4.3 Hz, 17^2-H), 2.36 (1H, dq, *J* 13.1 and 3x4.2 Hz, 11α-H), 2.76 (1H, td, *J* 2x11.6 and 4.2 Hz, 9α-H), 2.84-3.0 (2H, m, 6-H_2), 3.10 (1H, dddd, *J* 6.0, 3.3, 2.4 and 1.2 Hz, 17β-H), 3.78 (3H, s, 3-OMe), 6.22 (1H, dd, *J* 8.3 and 6.0 Hz, 16-H), 6.34 (1H, d, *J* 8.3 Hz, 15-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 219.7 (s, C-17a), 157.6 (s, C-3), 139.9 (s, C-5), 139.9 (d, C-15), 132.8 (s, C-10), 127.4 (d, C-16), 126.8 (d, C-1), 113.7 (d, C-4), 111.8 (d, C-2), 55.2 (q, 3-OCH_3), 48.3 (d, C-17), 46.9 and 46.7 (each s, C-13 and C-14), 39.4 (d, C-8), 37.1 (d, C-9), 31.1 (t, C-6), 29.5 (t, C-12), 25.8 (t, C-11), 24.9, (t, C-7), 23.9 (t, C-17^1), 20.9 (q, C-18) and 20.1 (t, C-17^2) (Found: C, 81.7; H, 8.1%; M^+, 322. $C_{22}H_{26}O_2$ requires C, 81.95; H, 8.1%; *M*, 322).

Hydride Reduction of 3-*Methoxy*-14,17α-*ethano*-17a-*homoestra*-1,3,5(10),15-*tetraen*-17a-*one* (**174**).—Lithium aluminium hydride (100 mg, 3.0 mmol) was added to a solution of the ketone (**174**) (259 mg, 0.8 mmol) in tetrahydrofuran. After 1 h at 20°C, saturated aqueous ammonium chloride was added to the reaction mixture, which was then extracted with chloroform. The combined organic phase was washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the residue (260 mg). Chromatography on silica gel (26 g), using ethyl acetate-toluene (1:11) as eluent, gave 3-*methoxy*-14,17α-*ethano*-17a-*homoestra*-1,3,5(10),15-*tetraen*-17aα-*ol* (**175**) (120 mg, 46%), m.p. 122-124°C (from chloroform-methanol); $[\alpha]_D$ -19° (*c* 1.0); ν_{max} 3613 (OH) cm^{-1}; δ_H (400 MHz) 0.88 (3H, s, 13β-Me), 1.02 (1H, td, *J* obsc. and 3.1 Hz, 17^2-H), 1.12 (1H, dtd , *J* 12.3, 2x3.1 and 1.2 Hz, 17^1-H), 1.42 (1H, ddd, *J* 13.5, 4.2 and 2.7 Hz, 12β-H), 2.34 (1H, dtd, *J* 13.4 and 2x4.6 and 2.7 Hz, 11α-H), 2.56 (1H, dddd, *J* 7.9, 6.4, 3.7 and 1.2 Hz, 17β-H), 2.70 (1H, td, *J* 2x11.8 and 4.6 Hz, 9α-H), 2.80-2.94 (2H, m, 6-H_2), 3.44 (1H, d, *J* 3.7 Hz, 17aβ-H), 3.78 (3H, s, 3-OMe), 6.14 (1H, dd, *J* 8.0 and 0.5 Hz, 15-H), 6.15 (1H, dd, *J* 8.0 and 6.4 Hz, 16-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 157.4 (s, C-3), 138.1 (s, C-5), 139.3 (d, C-15), 133.5 (s, C-10), 130.2 (d, C-16), 126.8 (d, C-1), 113.6 (d, C-4), 111.7 (d, C-2), 78.5 (d, C-17a), 55.2 (q, 3-OCH_3), 43.4 and 39.4 (each s, C-13 and C-14), 40.2 (d, C-8), 37.9 (d, C-17), 36.9 (d, C-9), 31.3 (t, C-6), 28.2 (t, C-12), 26.3 (t, C-11), 26.0 (q, C-18), 25.3 (t, C-7), 19.5 (t, $C\text{-}17^2$) and 18.1 (t, $C\text{-}17^1$) (Found: C, 81.1; H, 8.8%; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; *M*, 324), followed by 3-*methoxy*-14,17α-*ethano*-17a-*homoestra*-1,3,5(10),15-*tetraen*-17aβ-*ol* (**176**) (107 mg, 41%), m.p. 113-114°C (from chloroform-methanol); $[\alpha]_D$ +26° (*c* 1.0); ν_{max} 3601 (OH) cm^{-1}; δ_H (400 MHz) 0.89 (3H, s, 13β-Me), 1.02 (1H, td, *J* 2x12.7 and 4.4 Hz, 17^2-H), 1.28 (1H, tt, *J* 2x12.2 and 2x3.8 Hz, 17^1-H), 1.94 (1H, m, 11β-H), 2.26 (1H, dtd, *J* 12.8, 2x4.3 and 1.7 Hz, 11α-H), 2.54 (1H, tt, *J* 2x5.7 and 2x1.8 Hz, 17β-H), 2.72 (1H, td, *J* 2x10.5 and 4.0 Hz, 9α-H), 2.80-2.96 (2H, m, 6-H_2), 3.44 (1H, d, *J* 1.8 Hz, 17aα-H), 3.78 (3H, s, 3-OMe), 6.18 (1H, dd, *J* 8.6 and 5.7 Hz, 16-H), 6.22 (1H, dd, *J* 8.6 and 1.2 Hz, 15-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 157.4 (s, C-3), 138.0 (s, C-5), 139.9 (d, C-15), 133.5 (s, C-10), 129.3 (d, C-16), 126.8 (d, C-1), 113.7 (d, C-4), 111.7 (d, C-2), 82.4 (d, C-17a), 55.2 (q, 3-OCH_3), 44.3 (2xs, C-13 and C-14), 40.4 (d, C-8), 39.7 (d, C-17), 36.9 (d, C-9), 35.4 (t, C-12), 31.4 (t, C-6), 26.6 (t, C-11), 25.7 (t, C-7), 24.4 (t, $C\text{-}17^1$), 19.1 (t, $C\text{-}17^2$) and 15.9 (q, C-18) (Found: C, 81.2; H, 8.9%; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; *M*, 324).

3-*Methoxy*-14,17α-*ethano*-17a-*homoestra*-1,3,5(10)-*trien*-17aα-*ol* (**177**).— Palladium on activated charcoal (10%, 10 mg) was added to a solution of the 17aα-alcohol (**175**) (12 mg, 0.04 mmol) in ethanol. After stirring the slurry for 5 h at 20°C under hydrogen, the catalyst was removed by filtration through Celite. The solvent was evaporated under reduced pressure to give the *saturated product* (**177**) (12 mg, 95%), m.p. 137-139°C (lit.,[27] m.p. 138-139°C); δ_H (400 MHz) 1.04 (3H, s, 13β-Me), 2.18 (1H, td, *J* 2x13.9 and 4.1, 12α-H), 2.28 (1H, dq, *J* 13.1 and 3x3.0, 11α-H), 2.5 (1H, td, *J* 2x11.5 and 3.9, 9α-H), 2.74-2.80 (2H, m, 6-H_2), 3.58 (1H, dd, *J* 4.4 and 0.7 Hz, 17aβ-H), 3.77 (3H, s, 3-OMe), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 157.3 (s, C-3), 138.1 (s, C-5), 133.5 (s, C-10), 127.2 (d, C-1), 113.4 (d, C-4), 111.7 (d, C-2), 79.2 (d, C-17a), 55.2 (q, 3-OCH_3), 38.6 and 36.2 (each s, C-13 and C-14), 43.6 (d, C-8), 37.2 (d, C-9), 32.5 (d, C-17), 31.3 (t, C-6), 28.8 (t, C-12), 27.0 (t, C-11), 27.0 and 26.6 (each t, C-15 and C-16), 24.8 (q, C-18), 23.4 (t, C-7), 21.0 (t, C-17^1), and 19.0 (t, C-17^2).

3-*Methoxy*-14,17α-*ethano*-17a-*homoestra*-1,3,5(10)-*trien*-17aβ-*ol* (**178**).— Palladium on activated charcoal (10%, 20 mg) was added to a solution of the 17aβ-alcohol (**176**) (24 mg, 0.08 mmol) in ethanol. After stirring the slurry for 5 h at 20°C under hydrogen, the catalyst was removed by filtration through Celite. The solvent was evaporated under reduced pressure to give the *saturated product* (**178**) (25 mg, 98%), m.p. 157-159°C (from acetone-hexane) (lit.,[27] m.p. 157-159°C); δ_H (400 MHz) 1.07 (3H, s, 13β-Me), 2.19 (1H, dq, *J* 13.3 and 3x3.6 Hz, 11α-H), 2.53 (1H, td, *J* 2x11.7 and 4.1 Hz, 9α-H), 2.74-2.80 (2H, m, 6-H_2), 3.42 (1H, t on D_2O exch., *J* 2x2.1 Hz, 17aα-H), 3.76 (3H, s, 3-OMe), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 157.3 (s, C-3), 138.1 (s, C-5), 133.4 (s, C-10), 127.2 (d, C-1), 113.4 (d, C-4), 111.8 (d, C-2), 80.0 (d, C-17a), 55.2 (q, 3-OCH_3), 39.5 and 36.6 (each s, C-13 and C-14), 43.6 (d, C-8), 37.6 (t, C-12), 37.4 (d, C-9), 34.2 (d, C-17), 31.4 (t, C-6), 27.4 (t, C-11), 27.1 and 24.4 (each t, C-15 and C-16), 23.5 (t, C-7), 21.3 (t, C-17^1), 19.7 (t, C-17^2), and 15.5 (q, C-18).

14,17α-*Ethano*-17a-*homoestra*-1,3,5(10),15-*tetraene*-3,17aα-*diol* (**179**). — Diisobutylaluminium hydride (1.5M in toluene, 2.5 ml) was added to a solution of the diol (**175**) (120 mg, 0.37 mmol) in toluene (5 ml). After 20 h at 120°C, saturated aqueous ammonium chloride was added to the reaction mixture at 0°C. The product was extracted into chloroform. The combined organic phase was washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the residue (134 mg). Chromatography on silica gel (10 g) using ethyl acetate-toluene (1:9) as eluent gave the *diol* (**179**) (98 mg, 85%), m.p. 217-220°C (from methanol); $[\alpha]_D$ +11° (*c* 1.0 in tetrahydrofuran); (Found: C, 80.9; H, 8.5%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.2; H, 8.4%; *M*, 310).

14,17α-*Ethano*-17a-*homoestra*-1,3,5(10),15-*tetraene*-3,17aβ-*diol* (**180**).— Diisobutylaluminium hydride (1.5M in toluene, 2.2 ml) was added to a solution of the diol (**176**) (107 mg, 0.33 mmol) in toluene (5 ml). After 20 h at 120°C, saturated aqueous ammonium chloride was added to the reaction mixture at 0°C. The product was extracted into chloroform. The combined organic phase was washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the residue (107 mg). Chromatography on silica gel (9 g) using ethyl acetate-toluene (3:17) as eluent gave the *diol* (**180**) (94 mg, 92%), m.p. 205-208°C (from methanol); $[\alpha]_D$ +22° (*c* 1.0 in tetrahydrofuran); (Found: M^+, 310.1926. $C_{21}H_{26}O_2$ requires *M*, 310.1933).

Dihydroxylation of the Hydroxy Olefin (**181**).—Osmium tetroxide (200 mg, 0.78 mmol) was added to a solution of the olefin (**181**) (200 mg, 0.65 mmol) in pyridine. After 24 h at 20°C, aqueous sodium disulfite (10%, 30 ml) was added to the reaction mixture, which was then stirred for 2 h. Water was added, and the organic mixture was extracted into ethyl acetate. The combined organic phase was washed with brine and water, dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography of the residue (230 mg) on silica gel (23 g), using ethyl acetate-toluene (1:1) as eluent, gave 3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-15β,16β,17β-*triol* (**182**) (90 mg, 41%), m.p. 216-218°C (from chloroform); $[\alpha]_D$ +17° (*c* 1.0); ν_{max} 3537 (OH) cm^{-1}; δ_H (200 MHz) 1.08 (3H, s, 13β-Me), 3.77 (3H, s, 3-OMe), 3.80 obsc. and 3.99 (each 1H, dd, *J* 6.6 and

4.8 Hz → d on D_2O exch, *J* 6.6 Hz, 15α- and 16α-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 72.9; H, 8.25%; M^+, 344. $C_{21}H_{28}O_4$ requires C, 72.9; H, 8.2%; *M*, 344), followed by 3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-15α,16α,17β-*triol* (**183**) (82 mg, 37%), m.p. 223-225°C (from chloroform); $[\alpha]_D$ +4° (*c* 0.3); δ_H (400 MHz) 0.91 (3H, s, 13β-Me), 3.77 (3H, s, 3-OMe), 3.92 (1H, m → dd on D_2O exch., *J* 9.0 and 1.8 Hz, 15β-H), 4.01 (1H, m → dd on D_2O exch, *J* 9.0 and 2.0 Hz, 16β-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.17 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 157.5 (s, C-3), 137.7 (s, C-5), 133.2 (s, C-10), 126.4 (d, C-1), 113.8 (d, C-4), 111.5 (d, C-2), 82.7 (s, C-17), 77.4 (d, C-16), 74.4 (d, C-15), 55.2 (q, 3-OCH_3), 49.9 and 45.8 (each s, C-13 and C-14), 37.3 (d, C-9), 34.9 (d, C-8), 30.2 (t, C-12), 29.9 (t, C-6), 28.4 (t, C-17^1), 25.4 (t, C-11), 23.6 (t, C-7), 22.9 (t, C-17^2), and 15.4 (q, C-18) (Found: C, 72.7; H, 8.2 %; M^+, 344. $C_{21}H_{28}O_4$ requires C, 72.9; H, 8.2%; *M* 344).

3-*Methoxy*-14α,17α-*ethanoestra*-1,3,5(10),15-*tetraen*-17β-*yl Acetate* (**184**).—Acetic anhydride (0.1 ml) and N,N-dimethylaminopyridine (10 mg) were added to a solution of the enol (**181**) (90 mg, 0.3 mmol) in pyridine. After 4.3 h at 20°C, a saturated aqueous solution of sodium hydrogen carbonate, and water were added to the reaction mixture. The mixture was extracted with ethyl acetate, and the combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was removed to give the residue (89 mg), which was flash chromatographed on silica gel (9 g), using ethyl acetate-toluene (1:20) as eluent, to give the *acetate* (**184**) (75 mg, 71%), m.p. 93-94°C (from ethyl acetate-methanol); $[\alpha]_D$ -9° (*c* 1.0); ν_{max} 1728 (OAc) cm^{-1}; δ_H (200 MHz) 0.92 (3H, s, 13β-Me), 2.09 (3H, s, 17β-OAc), 3.78 (3H, s, 3-OMe), 6.15 and 6.25 (each 1H, d, *J* 6.1 Hz, 15-H and 16-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 78.4; H, 8.0%; M^+, 352. $C_{23}H_{28}O_3$ requires C, 78.4; H, 8.1%; *M*, 352), followed by the enol (**181**) (11 mg, 15%).

Dihydroxylation of the Acetoxy Olefin (**184**).—Osmium tetroxide (100 mg, 0.39 mmol) was added to a solution of the olefin (**184**) (100 mg, 0.28 mmol) in pyridine. After 25 h at 20°C, aqueous sodium disulfite (10%, 30 ml) was added to the reaction mixture, which was then stirred for 2 h. Water was added, and the organic mixture was extracted

into ethyl acetate. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was removed to give the residue (94 mg). Chromatography of this residue on silica gel (9 g), with ethyl acetate-toluene (1:1) as eluent, gave 3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-15α,16α,17β-*triol*-17-*acetate* (**185**) (10 mg, 10%), m.p. 163-166°C (from ethyl-acetate); δ_H (200 MHz) 0.94 (3H, s, 13β-Me), 2.11 (3H, s, 17β-OAc), 3.77 (3H, s, 3-OMe), 4.0 and 4.21 (each 1H, m → dd on D_2O exch., *J* 9.04 and 1.7 Hz, 15β-H and 16β-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 71.5; H, 7.9%; M^+, 386. $C_{23}H_{30}O_5$ requires C, 71.5; H, 7.8%; *M*, 386), followed by 3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-15β,16β,17β-*triol*-17-*acetate* (**186**) (80 mg, 74%), m.p. 181-185°C (from chloroform-methanol); $[\alpha]_D$ +26° (*c* 1.0); ν_{max} 3521 (OH) and 1723 (OAc) cm^{-1}; δ_H (200 MHz) 1.16 (3H, s, 13β-Me), 2.11 (3H, s, 17β-OAc), 2.85 (1H, d, *J* 4.0 Hz, disp. on D_2O exch., 15β-OH), 3.21 (1H, d, *J* 7.1 Hz, disp. on D_2O exch., 16β-OH), 3.77 (3H, s, 3-OMe), 3.99 (1H, dd, *J* 7.1 and 4.0 Hz → d on D_2O exch., *J* 7.1 Hz, 16α-H), 4.60 (1H, t, *J* 2x7.1 Hz → d on D_2O exch., *J* 7.1 Hz, 15α-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 171.7 (s, 17β-O*C*OCH$_3$), 157.4 (s, C-3), 137.9 (s, C-5), 133.1 (s, C-10), 126.3 (d, C-1), 113.7 (d, C-4), 111.5 (d, C-2), 89.3 (s, C-17), 74.9 (d, C-15), 74.3 (d, C-16), 55.2 (q, 3-OCH$_3$), 48.2 and 47.1 (each s, C-13 and C-14), 37.1 (d, C-9), 34.4 (d, C-8), 30.7 (t, C-6), 29.9 (t, C-17^1), 26.9 (t, C-12), 25.3 (t, C-11), 23.8 (t, C-7), 23.6 (t, C-17^2), 21.4 (q, 17β-OCO*C*H$_3$), and 15.5 (q, C-18) (Found: C, 71.5; H, 7.95 %; M^+, 386. $C_{23}H_{30}O_5$ requires C, 71.5; H, 7.8%; *M*, 386).

14α,17α-*Ethanoestra*-1,3,5(10)-*triene*-3,15β,16β,17β-*tetraol* (**187**).—Diisobutylaluminium hydride (1.5M in toluene,1 ml) was added to a suspension of the steroid (**182**) (71 mg, 0.21 mmol) in toluene. After 24 h at 120°C, further diisobutylaluminium hydride (1ml) was added to the reaction mixture. After a further 24 h at 120°C, saturated aqueous ammonium chloride was added to the cooled solution, which was then extracted into ethyl acetate, using hydrochloric acid (3M) to facilitate separation of organic and aqueous layers. The combined organic phase was washed with brine and water, and dried ($MgSO_4$). The solvent was removed to give the residue (80 mg). Chromatography of this residue on silica gel (8 g), using methanol-chloroform (1:20) as eluent, gave the *tetraol* (**187**) (69 mg, 99%), m.p. 234-236°C (from methanol); $[\alpha]_D$ +50° (*c* 0.93 in pyridine) (Found: M^+, 330.1818. $C_{21}H_{28}O_4$ requires *M*, 330.1831).

14α,17α-*Ethanoestra*-1,3,5(10)-*triene*-3,15α,16α,17β-*tetraol* (**188**).—
Diisobutylaluminium hydride (1.5M in toluene, 0.6 ml) was added to a suspension of the steroid (**183**) (40 mg, 0.12 mmol) in toluene. After 24 h at 120°C, further diisobutylaluminium hydride (1ml) was added to the reaction mixture. After a further 24 h at 120°C, saturated aqueous ammonium chloride was added to the cooled solution, which was then extracted into chloroform, using hydrochloric acid (3M) to facilitate separation of organic and aqueous layers. The combined organic phase was washed with brine and water and dried ($MgSO_4$). The solvent was removed to give the residue (40 mg). Chromatography of this residue on silica gel (3 g), using methanol-chloroform (1:20) as eluent, gave the *tetraol* (**188**) (30 mg, 76%), decomposed at 287°C (from ethanol); $[\alpha]_D$ +39° (*c* 0.5 in pyridine) (Found: M^+, 330.1818. $C_{21}H_{28}O_4$ requires *M*, 330.1831).

Crystal Structure Determination of 3-*Methoxy*-14,17α-*ethano*-17a-*homoestra*-1,3,5(10),15-*tetraen*-17aα-*ol* (**175**).—The structure of the compound (**175**) was solved by direct methods (SHELXS-86)[104] and refined using SHELXL93. Table 7.1 gives refined atom coordinates (x 10^4) and thermal parameters (x 10^3 Å^2), with U(eq) defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 7.1

	x/a	*y/b*	*z/c*	*U*(eq)
C(1)	-353(5)	11169(5)	1149(2)	40(1)
C(2)	-1121(6)	12498(5)	500(2)	46(1)
C(3)	-768(5)	11630(5)	-96(2)	43(1)
O(2)	-1622(4)	13028(4)	-718(2)	59(1)
C(20)	-1319(7)	12173(7)	-1330(2)	60(1)
C(4)	405(5)	9482(6)	-44(2)	44(1)
C(5)	1198(5)	8139(5)	612(2)	38(1)
C(6)	2496(6)	5787(5)	619(2)	49(1)
C(7)	3662(5)	4561(5)	1327(2)	43(1)
C(8)	2187(5)	5246(5)	1908(2)	32(1)
C(9)	1626(4)	7544(5)	1939(2)	32(1)
C(10)	791(5)	8981(5)	1220(2)	34(1)
C(11)	147(5)	8342(5)	2517(2)	41(1)
C(12)	972(5)	6840(5)	3220(2)	38(1)
C(13)	1467(4)	4557(5)	3202(2)	32(1)
C(19)	-595(5)	4503(6)	3038(2)	48(1)
C(14)	3034(4)	3745(5)	2622(2)	31(1)
C(41)	5191(5)	3523(5)	2863(2)	37(1)
C(42)	6083(5)	1954(5)	3559(2)	40(1)
C(15)	3437(5)	1496(5)	2623(2)	41(1)
C(16)	4169(6)	176(5)	3223(2)	47(1)
C(17)	4538(5)	1099(5)	3810(2)	40(1)
C(18)	2470(5)	2990(5)	3919(2)	36(1)
O(1)	2905(4)	3928(4)	4444(1)	43(1)

Table 7.2 gives selected data obtained from the crystal structure determination.

Table 7.2

Molecular formula	$(C_{22}H_{29}O_2)_2.H_2O$
Formula weight	333.45
Temperature	293(2) K
Wavelength	0.71070 A
Crystal system	triclinic
Space group	*P*1
Unit cell dimensions	*a* = 7.206(2) Å α = 79.76(4)°
	b = 7.218(2) Å β = 89.00(3)°
	c = 19.451(9) Å γ = 62.70(2)°
Volume	882.3(5) Å^3
Z	2
Density (calculated)	1.255 Mg.m^{-3}
Absorption coefficient	0.080 mm^{-1}
F(000)	362
Crystal size	0.30 x 0.30 x 0.35 mm
Theta range for data collection	1.07 to 24.97°
Index ranges	-8≤h≤8, -8≤k≤8, 0≤l≤23
Reflections collected	3205
Independent reflections	3205 [*R*(int) = 0.0000]
Refinement method	Full matrix least squares on F^2
Data / restraints / parameters	3204 / 3 / 462
Goodness-of-fit on F^2	1.042
Final *R* indices [I>2sigma(I)]	*R*1 = 0.0416, *wR*2 = 0.1070
R indices (all data)	*R*1 = 0.0591, *wR*2 = 0.1174
Absolute structure parameter	0.1(15)
Largest diff. peak and hole	0.140 and -0.256 eÅ^{-3}

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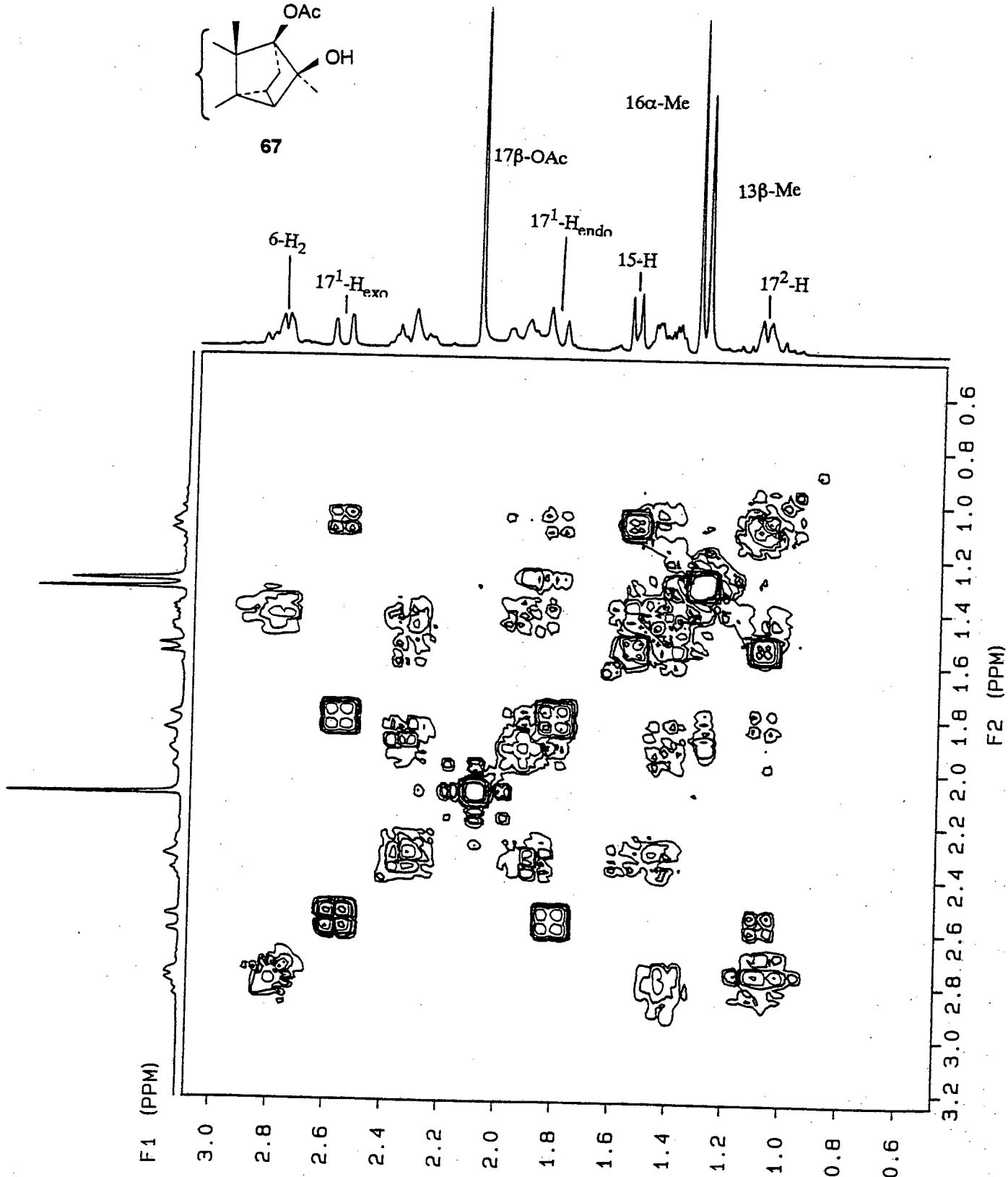
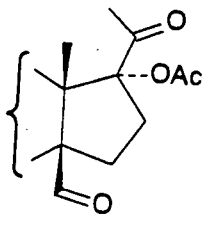
APPENDIX

This appendix contains expanded sections (from *ca.* δ 0.0 to δ 3.0) of selected ^{1}H- and COSY NMR spectra.

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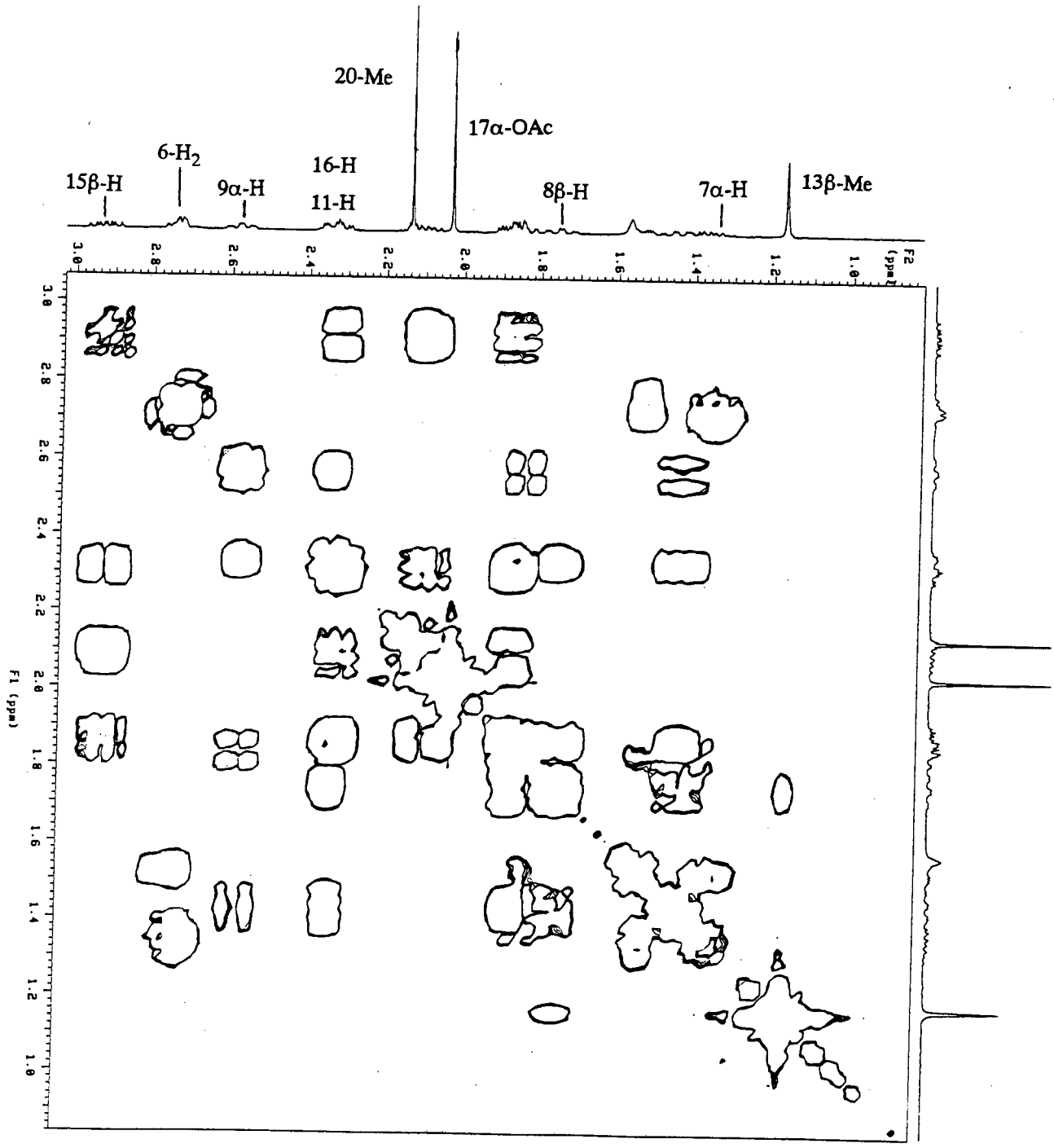
O

123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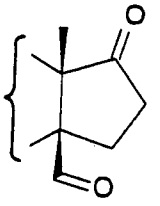
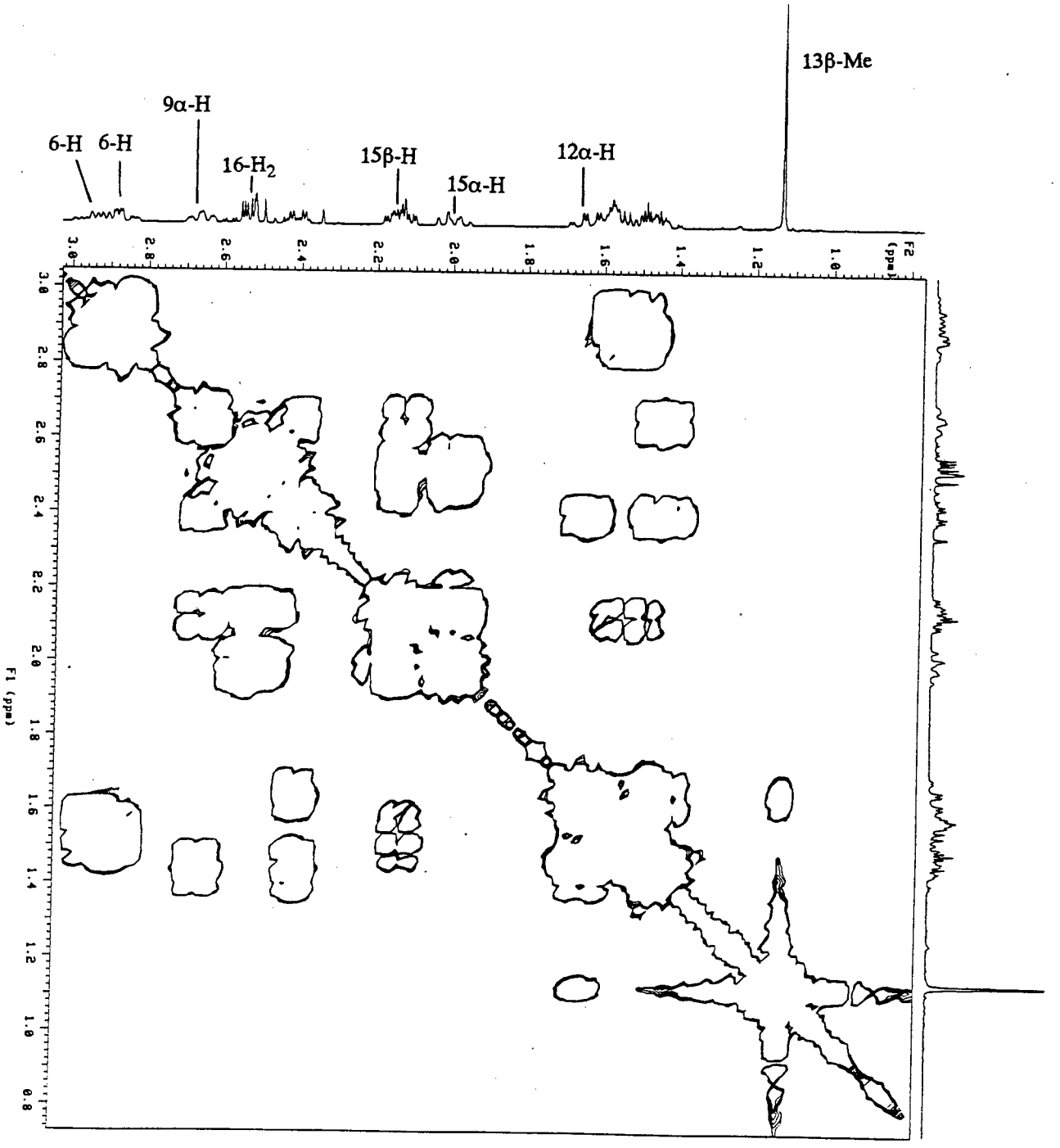
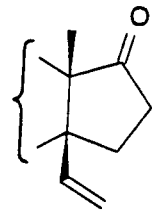


144





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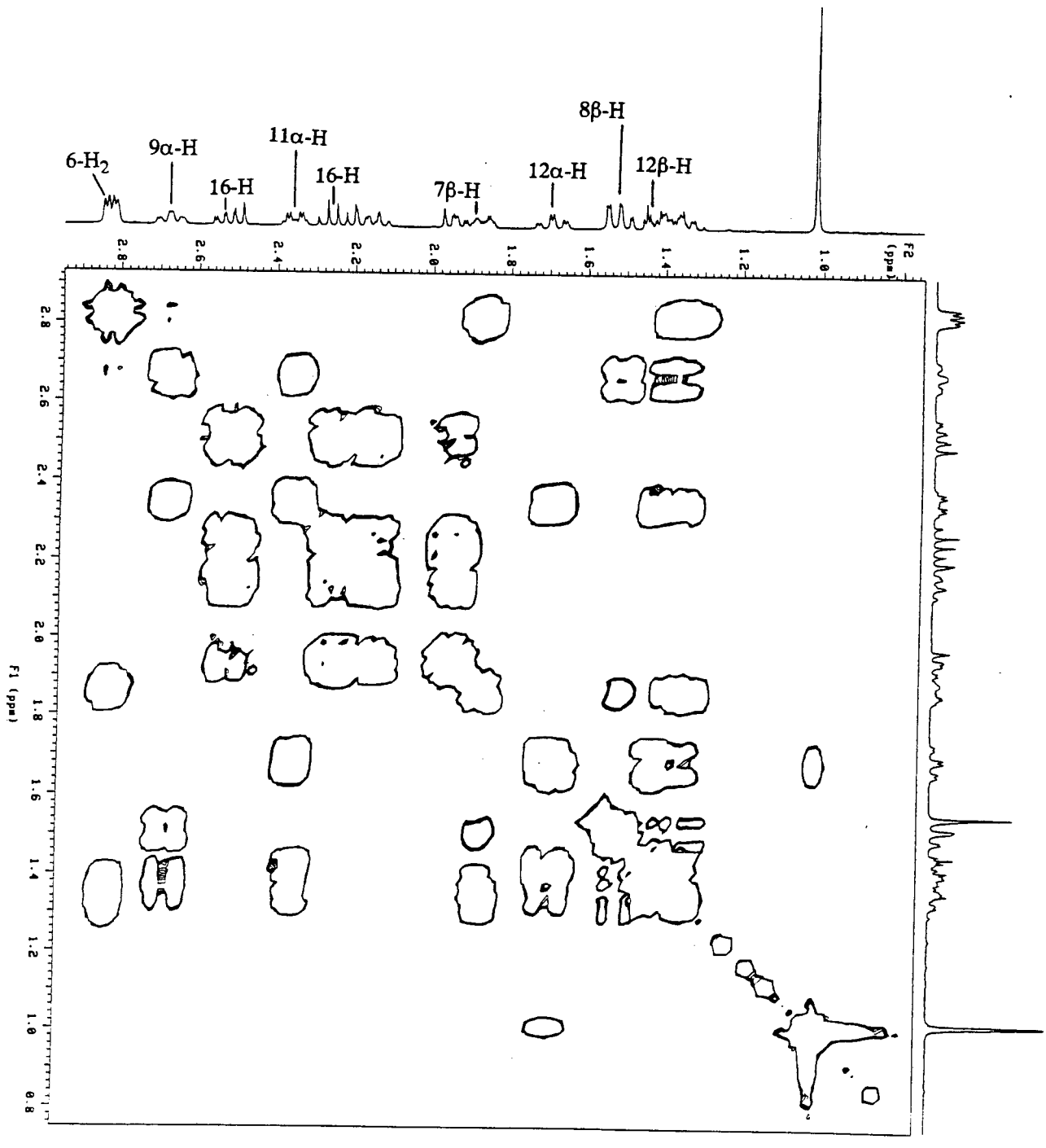

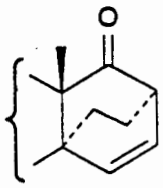

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