Synthesis of 14,17-propano analogues of estradiol

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Stereocontrolled syntheses of the 14α,17α-propano and 14β,17β-propano analogues of estradiol are described, together with those of numerous derivatives in which additional functionality is incorporated into the bridged system. Intramolecular aldol condensation of 17β-acetoxy-3-methoxy-20-oxo-19-nor-17α-pregna-1,3,5(10)-triene-14-carbaldehyde 1 furnishes 3-methoxy-17^1-oxo-14,17α-prop-17^2-enoestra-1,3,5(10)-trien-17β-yl acetate 2, which is transformed into 14,17α-propanoestra-1,3,5(10)-triene-3,17β-diol 17. In the first of two synthetic approaches to the 14β,17β-propano series, cycloaddition of methyl propiolate to 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate 25 gives a 14,17-bridged intermediate 26, in which the latent propyne equivalency of the dienophile is elaborated through selective functional group transformations to give 17-acetoxy-3-methoxy-20-oxo-19-nor-14β-pregna-1,3,5(10)-triene-14-carbaldehyde 50 and the derived product 52 of intramolecular aldol condensation. The second approach entails regioselective functionalisation of 14-allyl-3-methoxy-14β-estra-1,3,5(10)-trien-17-one 54 at C-2′ or C-3′ to give intermediates for intramolecular closure between the chain terminus and C-17, leading to 14,17β-propano-14β-estra-1,3,5(10)-triene-3,17α-diol 64. The results of competitive binding assays of the hormone analogues 17 and 64 toward the estradiol receptor are reported, and compared with those of bridge-functionalised derivatives.

The quest for new predictive design principles in steroid hormone research gained impetus with the discovery that 14α,17α-ethano analogues of estradiol[1,2] and estriol[3,4] bind efficiently to the estrogen receptor and display potent oral estrogenicity. This invites speculation upon the possible role of the 14,17-ethano bridge in bestowing resistance to metabolic degradation, whilst enabling receptor binding to proceed without evident steric impediment. An attendant question is whether alteration of the bridge size might influence this property. The 14α,17α- and 14β,17β-propano analogues of estradiol appeared to be synthetic candidates of particular interest, since modelling studies reveal subtle changes in the spatial disposition of polar functionality at C-3 and C-17 and in the steric environment of the 17-hydroxy group, associated with introduction of epimerically differentiated 14,17-propano bridges. A comparison of the receptor binding affinities of these targets was therefore expected to provide further insight into structure–activity relationships in ring D bridged analogues of estradiol, and possible pointers to predictive design of new targets in which binding affinity is optimised.

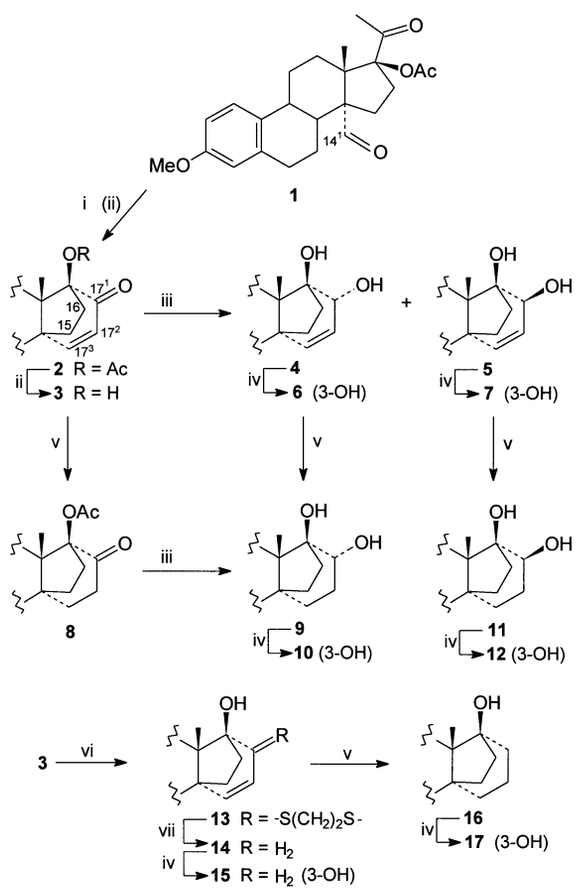
In this paper we describe stereocontrolled syntheses of 14,17α-propanoestra-1,3,5(10)-triene-3,17β-diol **17** and 14,17β-propano-14β-estra-1,3,5(10)-triene-3,17α-diol **64**,[5,6] as well as a number of bridge-functionalised derivatives of these parent systems. These products have been subjected to binding affinity and detailed structural studies.

Results and discussion

Synthesis of the 14α,17α-propano series

A simple synthetic strategy for assembly of a 14α,17α-propano bridge was suggested by the availability of 17β-acetoxy-3-methoxy-20-oxo-19-nor-17α-pregna-1,3,5(10)-triene-14-carbaldehyde **1**,[7] in which the propitious array of ring D functionality was expected to lend itself to intramolecular aldol reaction, and conversion of the resultant 14α,17α-bridged intermediate into the desired hormone analogues.

Indeed, treatment of compound **1** with hydrochloric acid in tetrahydrofuran (THF) at 50 °C resulted in near-quantitative conversion into the bridged enone **2**, the structure of which was evident from diagnostic spectroscopic data and rigorous structural elucidation of derived products. Intramolecular aldol reaction of compound **1** also proceeded in the presence of alkali, to give the product **3** arising from concomitant bridgehead hydrolysis, but accompanied by isomeric material which



Scheme 1 *Reagents and conditions:* i, HCl, THF, 50 °C (to **2**); ii, KOH, MeOH, 25 °C; iii, $LiAlH_4$, THF, 25 °C; iv, DIBAH, C_6H_5Me, reflux; v, Pd–C (10%), H_2; vi, $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, HOAc, 30 °C; vii, Na, liquid NH_3

was also detected during alkaline hydrolysis of compound **2**. Although this product proved difficult to separate chromatographically, its presence was inferred from NMR spectroscopy of the reaction products.[5] The further implications of this interfering reaction will be reported elsewhere.

Reduction of the enone **2** with lithium aluminium hydride (LAH) in THF at 25 °C gave a separable mixture (~3:2) of the isomeric diols **4** and **5** arising from exclusive 1,2-addition of hydride. The configurational assignments were deduced from NMR data, which revealed significant coupling ($J_{17^1,17^2}$ 4.1 Hz) in the 17β,17[1]*R*-diol **4**, consistent with a pseudo-axial (*exo*) orientation of 17[1]-OH, whereas the 17β,17[1]*S*-diol **5** displayed the vicinal ($J_{17^1,17^2}$ 2 Hz) and allylic ($J_{17^1,17^3}$ 1.6 Hz) couplings expected for a pseudo-equatorial (*endo*) substituent at C-17[1]. The surprisingly slight preference for *endo*-entry of hydride in **2** suggests very little steric differentiation in reagent approach. The diols **4** and **5** were deprotected [diisobutylaluminium hydride (DIBAH) in refluxing toluene[8]] at C-3, to give the respective triols **6** and **7**.

Further simplification of bridge functionality in the enone **2** was achieved through catalytic hydrogenation (Pd–C, H_2) to give the saturated 17[1]-ketone **8**, LAH reduction of which was highly stereoselective giving only the 17β,17[1]*R*-diol **9**; the NMR signal for 17[1]-H appeared at δ 4.2 (*t*, *J* 2 × 3 Hz) consistent with axial (*exo*) orientation of 17[1]-OH and hence, exclusive *endo*-directed hydride addition. Correlation of **9** with the unsaturated 17β,17[1]*R*-diol **4** was established through comparison with the product of catalytic hydrogenation of the latter, albeit in poor yield owing to unexplained rearrangements. By contrast, catalytic hydrogenation of the unsaturated 17β,17[1]*S*-diol **5** proceeded smoothly, to give the saturated product **11**. The parent hormone analogues **10** and **12** were prepared *via* conventional 3-deprotection of **9** and **11**, respectively.

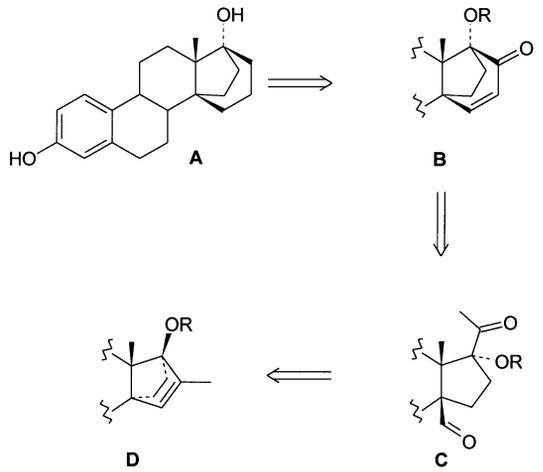
The remaining objective in this phase of the investigation was to prepare the parent 14α,17α-propano analogue of estradiol. The most direct approach appeared to be *via* 17[1]-deoxygenation of the enone **2**. Inexplicably, attempted dithioketalisation of **2** (ethanedithiol–boron trifluoride–diethyl ether complex, 30 °C) failed. Apparently this is associated with the presence of the bridgehead acetoxy group, since the saturated 17β-acetoxy 17[1]-ketone **8** behaved similarly, but the 17β-hydroxy enone **3** underwent slow but clean conversion into the corresponding 17[1],17[1]-dithioketal **13**. Desulfurisation of **13** proceeded smoothly in the presence of sodium–liquid ammonia to give the bridged olefin **14**, which underwent catalytic hydrogenation to give the 14α,17α-propano compound **16**. Deprotection of **14** and **16** at C-3 furnished the corresponding bridged estradiol analogues **15** and **17**, respectively.

The foregoing synthetic sequence commended itself as a straightforward route to the target hormone analogues for evaluation purposes, but a necessary caveat is that the synthetic route to the pivotal intermediate **1** is flawed by imperfect stereoselectivity in the cycloaddition step.[7] More direct and efficient access to 14α,17α-propano systems can be envisaged through the synthesis of 14α-alkyl 17-ketones in which a suitably functionalised three-carbon chain at C-14 can be primed for intramolecular 3′,17-closure. Our preliminary studies toward these objectives will be reported elsewhere.

Synthesis of the 14β,17β-propano series

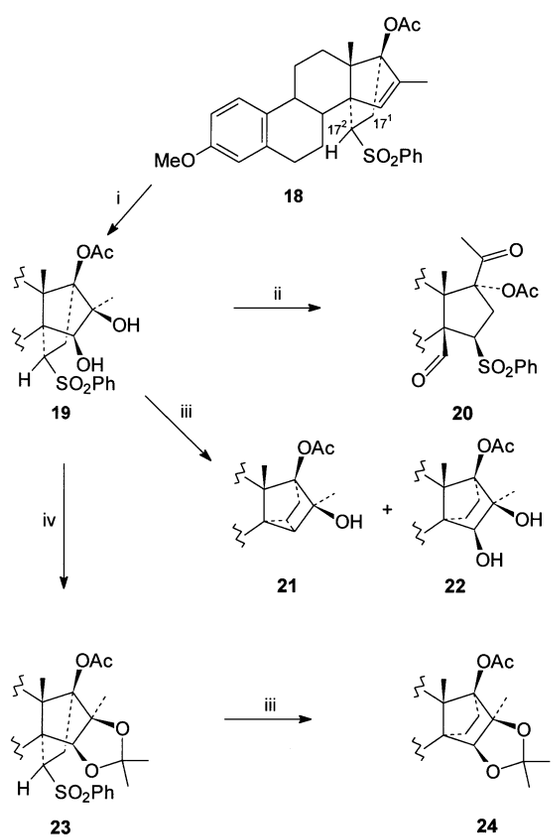
The successful completion of the foregoing synthetic route invited consideration of the scope for implementing an analogous synthetic strategy for the 14β,17β-propano series. The prerequisites would be ready access to the key intermediate **C** (a 14,17-epimer of **1**) *via* oxidative cleavage of the bridged precursor **D**, and the reasonable presumption of comparable functional group reactivity implicit in the retrosynthetic step (**A**⇒**B**, Scheme 2).

The fortuitous availability of the phenylsulfonyl compound **18**, as the 'undesired' cycloadduct in the reaction sequence leading to compound **1**,[7] offered scope for testing the feasibility of the outlined approach. Earlier experiments[9] had demonstrated the impracticality of converting **18** into a 16-methyl-Δ[15]-intermediate **D** *via* direct reductive desulfonylation, owing to unacceptably high levels of attendant olefinic bond participation. Accordingly, it was decided to postpone this step until this source of intramolecular interference had been eliminated through necessary functionalisation of the olefinic bond.



Scheme 2 Oxidative cleavage–intramolecular aldol condensation pathway to 14β,17β-propanoestradiol

cis-Hydroxylation of compound **18** (OsO_4–pyridine, 25 °C) proceeded slowly (168 h) but highly stereoselectively to give a single diol **19** (Scheme 3), confidently assigned a 15β,16β-configuration owing to the severe steric congestion on the *endo*-face of the olefinic bond. The feasibility of oxidative cleavage at this stage was demonstrated by treatment of the diol **19** with sodium periodate in aqueous ethanol to give the dioxo com-



Scheme 3 *Reagents and conditions:* i, OsO_4, C_5H_5N, 25 °C; ii, $NaIO_4$, EtOH–H_2O, 20 °C; iii, SmI_2, HMPA, THF, −20 °C; iv, Me_2CO, $HClO_4$ (70%), 20 °C

pound **20**, further elaboration of which was deemed impractical owing to the plethora of ring D functionality. Instead, reductive desulfonylation of the diol **19** was attempted; reaction with samarium(II) iodide–HMPA[10] at −20 °C proceeded slowly (4 h) to give a mixture (~1:1) of products **21** and **22**. The less polar product was formulated as the 15α,17^2-cyclo-14α,17α-ethano compound **21**, based upon NMR evidence for the presence of a cyclopropyl moiety and the absence of a secondary hydroxy group, whereas the properties of the more polar product were clearly consistent with the desulfonylated 15β,16β-diol **22**. The unexpected intrusion of an apparent participation process here, was circumvented by prior conversion of the diol **19** into the acetonide **23**, which underwent efficient reductive desulfonylation to the expected product **24**, deprotection of which to the diol **22** is described below.

Although these experiments demonstrated the feasibility of the planned approach, it was evident that a practical synthetic strategy would require a more direct method for preparation of the diol **22** or the precursor olefin **D** (Scheme 2). This, in turn, necessitated development of a plan for cycloaddition of a latent propyne equivalent to the dienyl acetate **25**, which could lead *via* selective functional group modification to such an intermediate.

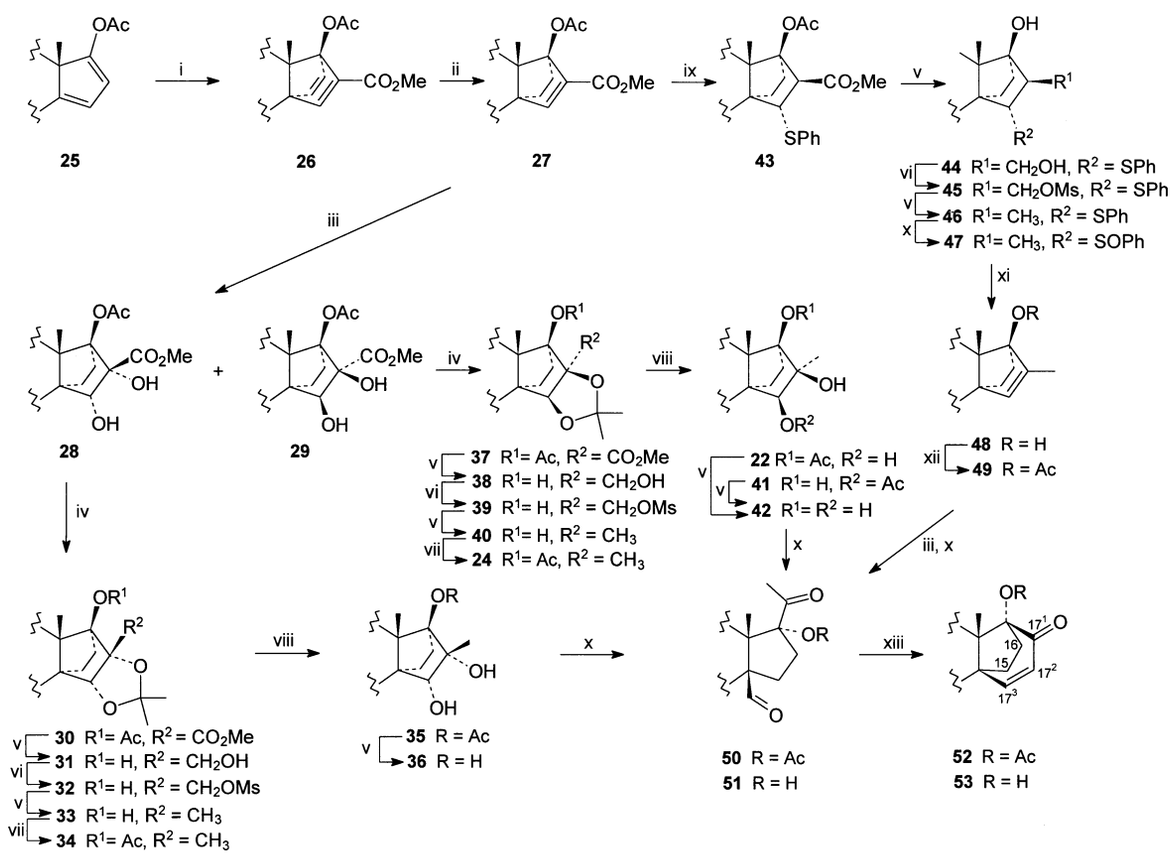
The potential of methyl propiolate to serve this purpose is implied in an earlier study upon a steroidal ring D diene,[11] in which the crucial steps demonstrated appropriate regioselectivity during cycloaddition, and chemoselective hydrogenation of the isolated olefinic bond in the primary cycloadduct.

Treatment of the dienyl acetate **25**[1] with methyl propiolate in benzene at 100 °C (sealed tube, 23 h) resulted in efficient formation of a single cycloadduct **26** (85%) (Scheme 4), the structure of which was assigned by well-established analogy.[11] Catalytic hydrogentation (Pd–C, H_2) proceeded chemoselectively to give the 14α,17α-ethano compound **27** (83%). Initial attempts to convert **27** into the 16-hydroxymethyl-Δ^{15}-compound for subsequent 16^1-deoxygenation were frustrated by negligible 1,2-regioselectivity during hydride reduction of the α,β-unsaturated ester grouping, under a variety of reaction conditions. Consequently, it was decided to postpone the necessary conversion of the 16-methoxycarbonyl group into a methyl group, and **27** was first osmylated to give a readily separable mixture (~7:3) of 15,16-diols **28** and **29**, distinguished by the diagnostic four-bond coupling between 15β-H and 17^2-H_{exo} (^4J 1.5 Hz) in the 15α,16α-isomer **28**. The conversion of these 16-methoxycarbonyl 15,16-diols into the corresponding 16-methyl 15,16-diols necessitated conventional multi-step reaction sequences.

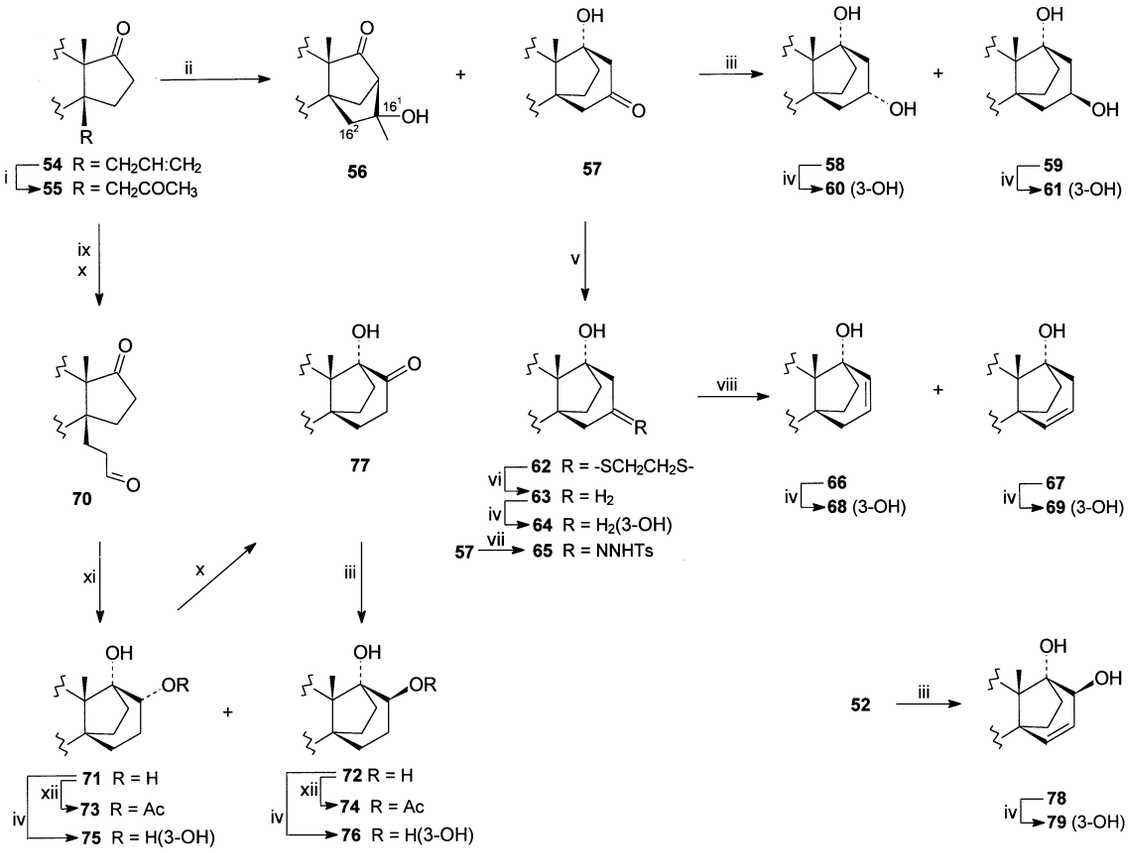
Thus, the major isomer **28** was first protected as the acetonide **30**, whereupon sequential LAH reduction (to **31**), selective 16^1-methanesulfonylation (to **32**), LAH reduction (to **33**), 17-acetylation (to **34**) and finally, acetonide deprotection gave the desired 16β-methyl 15α,16α-diol **35** in an overall yield of *ca.* 25% from **28**.

An analogous reaction sequence upon the minor isomer **29** (⟶ **37** ⟶ **38** ⟶ **39** ⟶ **40** ⟶ **24**) proceeded unexceptionally and as efficiently, to give the intermediate acetonide **24**, identical with that obtained during reductive desulfonylation of **19**. However, deprotection of **24** with iodine in methanol–THF[12] at 80 °C furnished an inseparable mixture (~1.8:1 by NMR) of the 17β-acetoxy 15β,16β-diol **22** and the 15β-acetoxy 16β,17β-diol **41**; the latter compound was isolated and characterised as the unreactive component in a subsequent reaction upon the mixture, and the structure was further inferred from treatment of the mixture **22** + **41** with LAH to give the triol **42** as a common product of hydrolysis.

It is evident that this two-fold *trans*-acetylation of **22** to give **41** requires a bridgehead–*exo* relationship of interacting functionality during the first step, since an analogous process was not observed during similarly mediated deprotection of the isomeric acetonide **34**.



Scheme 4 *Reagents and conditions:* i, HC≡CCO$_2$Me, C_6H_6, 100 °C; ii, Pd–C (10%), H_2; iii, OsO_4, C_5H_5N, 25 °C; iv, Me_2CO, $HClO_4$ (70%), 20 °C; v, $LiAlH_4$, THF, 25 °C; vi, $MeSO_2Cl$, C_5H_5N, 0 °C; vii, Ac_2O, *p*-TsOH, THF, 20 °C; viii, I_2, MeOH, reflux; ix, C_6H_5SH, Pr^i_2NEt, 20 °C; x, $NaIO_4$, THF–EtOH–H_2O, 20 °C; xi, Et_3N, C_6H_6, 115 °C; xii, Ac_2O, DMAP, C_5H_5N, 20 °C; xiii, HCl, THF, 57 °C or *p*-TsOH, C_6H_6, reflux



Scheme 5 *Reagents and conditions:* i, $PdCl_2$, CuCl, O_2, DMF–H_2O, 65 °C; ii, KOH, MeOH, 20 °C; iii, $LiAlH_4$, THF, 0 °C; iv, DIBAH, C_6H_5Me, reflux; v, $(CH_2SH)_2$, $Zn(OTf)_2$, CH_2Cl_2, 20 °C; vi, Raney-Ni, EtOH, reflux; vii, *p*-$TsNHNH_2$, TFA, THF, 20 °C; viii, BuLi, THF, 0 °C; ix, BH_3·Me_2S, THF, reflux, then H_2O_2, NaOH, 40 °C; x, $(COCl)_2$, DMSO, THF, −78 °C, then Et_3N, −78 to 20 °C; xi, $TiCl_3$·$(DME)_{1.5}$, Zn–Cu, 20 °C; xii, Ac_2O, C_5H_5N, 20 °C

Although the foregoing reaction sequences succeeded in furnishing the targeted intermediates **22** and **35** for oxidative cleavage (to **C**, Scheme 2), the need to process the isomeric diols **28** and **29** separately, and the complications attending functional group manipulation of the latter isomer **29**, detracted from the overall efficiency of the method, and an alternative approach to elaborating the propyne equivalency implicit in the key intermediate **27** was sought.

This was readily achieved *via* conjugate phenylthiolation[13] of **27**, which proceeded efficiently and stereoselectively[14] in the presence of thiophenol–diisopropylethylamine at 20 °C to give the 15α-phenylthio 16β-carboxylate **43**. The 15,16-*trans* relationship of functionality, crucial for the success of subsequent steps, was evident from NMR signals for 15β-H and 16α-H which revealed $J_{15\beta,16\alpha}$ 5.6 Hz, and the presence of a four-bond coupling, $J_{15\beta,17^2exo}$ 2.5 Hz confirmed the configuration at C-15. A three-step reduction–mesylation–reductive deoxygenation sequence (*via* **44** and **45**) proceeded smoothly to give the corresponding 16β-methyl compound **46** in high yield (78% from **43**). The derived sulfoxide **47** underwent smooth *syn*-elimination at 115 °C in the presence of triethylamine to give the olefin **48**, thus fulfilling the objective of conferring effective propyne equivalency on methyl propiolate cycloaddition to the dienyl acetate **25**.

cis-Hydroxylation of **48** (to **36** + **42**) and of the derived 17-acetate **49** (to **22** + **35**) completed the preferred synthetic routes to the key intermediates for oxidative cleavage. Treatment of **22** (or mixtures of **22** + **35**) with sodium periodate in aqueous ethanol gave 17-acetoxy-3-methoxy-20-oxo-19-nor-14β-pregna-1,3,5(10)-triene-14-carbaldehyde **50**[15] in high yield, whereas similar oxidative cleavage of the 15,16,17-triols **36** and **42** proceeded with high 15,16-regioselectivity to give the corresponding 17-hydroxy 14β-carbaldehyde **51**.

Intramolecular aldol reaction of **50** was readily achieved in the presence of hydrochloric acid in THF at 57 °C to give the expected bridged enone **52**, whereas treatment with *p*-TsOH in refluxing benzene resulted in concomitant bridgehead hydrolysis to give **53**.

The foregoing reaction sequence thus succeeded in demonstrating preparative and structural analogy with the corresponding 14,17-isomeric series, but preliminary experiments revealed poor regioselectivity during attempted functional group modification of **52**. The need to explore this problem in more depth was overtaken by the development of an alternative and more amenable strategy for the synthesis of the 14β,17β-propano analogues of estradiol, based upon regioselective modification of the readily available 14β-allyl 17-ketone **54**.[3]

Thus, Wacker oxidation[16] of **54** led readily to the 14β-acetonyl 17-ketone **55** (70%), which underwent an intramolecular aldol reaction in the presence of alkali, to give the 14β,17β-(17^2-oxopropano) compound **57** (70%) accompanied by minor amounts (6%) of the alternative aldol closure product **56** as a mixture (~2:1 by NMR) of 16^1-epimers. LAH reduction of **57** proceeded in accordance with expectations for a bicyclo[3.2.1]octan-2-one system, to give a separable mixture (~2:3) of axial and equatorial 17^2-alcohols **58** and **59**, which were converted into the respective hormone analogues **60** and **61**.

The primary purpose of this phase of the investigation was served through 17^2-deoxygenation of the bridged intermediate **57**. The method of choice entailed dithioketalisation of **57** in the presence of zinc trifluoromethanesulfonate as catalyst,[17] which ensured conditions sufficiently mild for preparation of the ethylenedithio derivative **62** without interference from retro aldol cleavage of the bridge. Desulfurisation of **62** in the presence of Raney nickel furnished the 14β,17β-propano compound **63**, which was deprotected to give the estradiol analogue **64**.

A complementary 17²-deoxygenation routine provided access to 14β,17β-propeno analogues. Thus, the ketone **57** was converted into a separable *syn/anti* mixture (~2:1) of the 17²-tosylhydrazones **65**, treatment of which with butyllithium gave the separable unsaturated products **66** and **67**. Deprotection of these products at C-3 furnished the respective estradiol analogues **68** and **69**. The spectroscopic properties of **66** and **67** were remarkably similar, and failed to furnish irrefutable evidence of their respective structures. However, an unambiguous synthesis of the 17¹-olefin **66**[6] was decisive for this purpose.

The scope for regioselective 3′-functionalisation of the 14β-allyl 17-ketone **54** was also explored in order to gain access, *via* intramolecular 3′,17-closure, to 14β,17β-propano 17,17¹-diols. This was readily achieved through hydroboration–oxidation of compound **54**, followed by Swern oxidation of the resultant 3′,17ξ-diol mixture, to give the 14β-formylethyl 17-ketone **70** (70%). The dioxo compound **70** underwent intramolecular reductive cyclisation in the presence of McMurry reagent[18] [prepared by Zn–Cu couple reduction of $TiCl_3$·$(DME)_{1.5}$] in DME at 20 °C, to give a separable mixture of 14β,17β-propano 17,17¹-diols **71** (53%) and **72** (4%). The configurational assignments followed from distinctive NMR data for the diols **71** and **72**, and their derived 17¹-acetates **73** and **74**, and the product distribution is consistent with the expectation of stereoselectivity mediated by favoured co-linear alignment of the 17- and 3′-oxo groups of **70** in a chair-like transition state. The consequent presentation of the *si*-face of the 3′-oxo group to C-17 thus leads to preferential formation of the 17¹*R*-isomer **71**.

An attempt to prepare sufficient of the minor 17¹*S*-isomer **72** for further study, *via* Mitsunobu inversion of compound **71**, was unsuccessful. However, Swern oxidation of **71** gave the 17¹-ketone **77**, which underwent highly stereoselective LAH reduction to give **72**. Deprotection of the diols **71** and **72** furnished the corresponding bridged analogues **75** and **76** of estriol.

In further experiments conducted for comparison, LAH reduction, or preferably for high-yield recovery, $NaBH_4$–$CeCl_3$ reduction of the bridged enone **52** gave only the corresponding 17,17¹*S*-diol **78**, the structure of which was confirmed by catalytic hydrogenation to give compound **72**. The stereoselectivity of hydride reduction in this case contrasts with that of the epimeric bridged enone **2**, suggesting that the 13β-methyl group in **52** is a more decisive sterically inhibiting factor to *exo*-approach of hydride, than are the ring C elements in **2**. The 17,17¹*S*-diol **78** was also converted into the corresponding 3,17,17¹-triol **79** for comparative biological evaluation.

Receptor affinity studies

Competitive binding affinities for the estradiol receptor have been determined for the hormone analogues described here,[19] using the competition factor[20] (CF) as determinant. 14,17α-Propanoestra-1,3,5(10)-triene-3,17β-diol **17** displays highly competitive binding (CF 1.5), which is amplified in 14,17α-prop-17²-enoestra-1,3,5(10)-triene-3,17β-diol **15** (CF 0.4), but strongly attenuated by introduction of a 17¹-hydroxy group both in the 14α,17α-propano and the 14α,17α-prop-17²-eno series, as exemplified by **6** (CF 60), **7** (CF 44), **10** (CF 98) and **12** (CF >500). In the 14β,17β-propano series, the weak competitive binding of the parent estradiol analogue, 14,17β-propano-14β-estra-1,3,5(10)-triene-3,17α-diol **64** (CF 69), is even more pronounced in all of the derived variants bearing β-bridge functionality or unsaturation: **60** (CF ∞), **61** (CF ∞), **68** (CF 318), **69** (CF 470), **75** (CF 360), **76** (CF >500) and **79** (CF 180). It is therefore evident that the binding affinity associated with the presence of a 14α,17α-ethano bridge in estradiol[2] is retained in the presence of a 14α,17α-propano bridge, which suggests that the corresponding binding domain in the estradiol receptor is indifferent to the steric demand of these structural features on the α-face of ring D. By contrast, the poor binding affinity of the epimeric 14β,17β-propano analogue reveals a receptor domain associated with the β-surface near ring D which is exceptionally sensitive to skeletal change. This influence may be largely steric, since superimpositional modelling studies display very small differences in the spatial disposition of polar binding regions in these analogues. A further conclusion is that polar functionality on the bridges, exemplified by the analogues in this study, is inimical to receptor binding, even in the example (*viz*. **75**) manifesting structural resemblance to estriol and its 14α,17α-ethano analogue.

An interpretation of these findings will be presented in the context of more detailed structural and molecular modelling studies, to be published elsewhere, but the trends described here suffice to reveal a pattern of structure–activity relationships which has been instrumental in identifying additional synthetic targets based upon ring D bridged analogues of estradiol.

Experimental

Mps were determined on a Reichert-Jung Thermovar apparatus and are uncorrected. Unless otherwise stated, spectra were recorded as follows: IR, Perkin-Elmer 983, chloroform solutions, ^{1}H NMR, Varian VXR (200 MHz) and Varian Unity (400 MHz), deuteriochloroform solutions (*J* values are given in Hz); ^{13}C NMR, Varian VXR (50 MHz) or Varian Unity (100 MHz), deuteriochloroform solutions; mass spectra (electron-impact), VG Micromass 16F. Optical rotations were measured on a Perkin-Elmer 141 polarimeter for chloroform solutions at 20 °C, and $[\alpha]_D$-values are given in 10^{-1} deg cm² g^{-1}. Microanalyses were performed on a Carlo Erba EA 1108 instrument. Silica gel for chromatography refers to Merck Kieselgel 60, 63–200 μm (gravity) or 40–63 μm (flash).

3-Methoxy-17¹-oxo-14,17α-prop-17²-enoestra-1,3,5(10)-trien-17β-yl acetate 2

17β-Acetoxy-3-methoxy-20-oxo-19-nor-17α-pregna-1,3,5(10)-triene-14-carbaldehyde **1** (250 mg, 0.63 mmol) was treated with hydrochloric acid (12 mol dm^{-3}; 1 cm³) in tetrahydrofuran (THF; 10 cm³) at 50 °C for 3 h. The cooled reaction mixture was neutralised with saturated aq. $NaHCO_3$, and the product was isolated by extraction with toluene. Filtration of the residue (260 mg) through silica gel (20 g) with EtOAc–toluene (1:19) gave the *product* **2** (234 mg, 98%), mp 200–204 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +174 (*c* 1.0 in $CHCl_3$) (Found: C, 75.5; H, 7.1%; M^+, 380. $C_{24}H_{28}O_4$ requires C, 75.8; H, 7.4%; *M*, 380); ν_{max}/cm^{-1} 1739 and 1693; δ_H(400 MHz) 1.13 (3 H, d, *J* 0.8, 13β-Me), 1.45 (1 H, td, *J* 2 × 13.1 and 4.5, 12α-H), 1.68 (1 H, ddd, *J* 12.5, 9.0 and 2.8), 1.92 (1 H, ddd, *J* 12.5, 9.8 and 5.8), 2.15 (3 H, s, 17β-OAc), 2.22–2.29 (1 H, m, 12β-H), 2.34 (1 H, ddd, *J* 14.9, 9.8 and 2.8, 16β-H), 2.47 (1 H, td, *J* 2 × 11.7 and 4.3, 9α-H), 2.53 (1 H, br ddd, *J* 14.9, 9.0 and 5.1, 16α-H), 2.86–2.93 (2 H, m, 6-H_2), 3.77 (3 H, s, 3-OMe), 6.11 (1 H, d, *J* 10.0, 17²-H), 6.62 (1 H, d, *J* 2.7, 4-H), 6.71 (1 H, dd, *J* 8.6 and 2.7, 2-H), 7.0 (1 H, d, *J* 10.0, 17³-H) and 7.17 (1 H, d, *J* 8.6, 1-H); δ_C(100 MHz) 196.1 (s, C-17¹), 169.9 (s, O*C*OMe), 157.7 (s, C-3), 153.5 (d, C-17³), 137.6 (s, C-5), 131.7 (s, C-10), 127.0 (d, C-17²), 127.3 (d, C-1), 113.8 (d, C-4), 112.0 (d, C-2), 93.8 (s, C-17), 55.2 (q, 3-OMe), 54.3 (s, C-14*), 53.5 (s, C-13*), 41.1 (d, C-8), 39.3 (d, C-9), 31.0 (t, C-16), 30.4 (t, C-6), 29.5 (t, C-15), 27.9 (t, C-11), 26.9 (t, C-12), 23.5 (t, C-7), 21.2 (q, OCO*Me*) and 15.9 (q, C-18). Assignments marked * may be the other way round.

17β-Hydroxy-3-methoxy-14,17α-prop-17²-enoestra-1,3,5(10)-trien-17¹-one 3

(a) Compound **1** (430 mg, 1.08 mmol) was dissolved in methanolic potassium hydroxide (1 mol dm^{-3}; 20 cm³). After 3 h at 25 °C, the mixture was diluted with water and the product was isolated by extraction with toluene. Crystallisation of the residue (402 mg) from $CHCl_3$–MeOH gave the *product* **3** (114 mg), mp 177–180 °C; $[\alpha]_D$ +195 (*c* 0.8 in $CHCl_3$) (Found: C,

78.1; H, 7.8%; M^+, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7; *M*, 338); ν_{max}/cm^{-1} 3460 and 1670; δ_H(200 MHz) 1.17 (3 H, s, 13β-Me), 2.46 (1 H, td, *J* 2 × 10.3 and 3.9, 9α-H), 2.86–2.96 (2 H, m, 6-H_2), 3.78 (3 H, s, 3-OMe), 6.21 (1 H, d, *J* 9.8, 17^2-H), 6.64 (1 H, d, *J* 2.7, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.7, 2-H), 7.17 (2 H, superimposed d, *J* 9.8, 17^3-H and d, *J* 8.6, 1-H). Chromatography of the mother-liquor residue (280 mg) on silica gel (30 g) with EtOAc–toluene (1:9) as eluent gave further product **3** (197 mg) followed by mixed fractions (17 mg).

(b) Similar alkaline treatment of the 17β-acetate **2** (50 mg, 0.13 mmol) for 5 h, followed by crystallisation of the product (42 mg) from $CHCl_3$–MeOH gave the 17β-alcohol **3** (25 mg). The mother-liquor residue comprised an inseparable mixture (TLC) of **3** and an isomeric product (~25% by NMR).

Hydride reduction of the enone 2

Lithium aluminium hydride (LAH) (319 mg, 8.4 mmol) was added to a stirred solution of the enone **2** (958 mg, 2.8 mmol) in dry THF (100 cm^3) at 25 °C. After 2 h at 25 °C, the mixture was treated with ethyl acetate, added slowly to destroy excess reagent, and then acidified with aq. acetic acid. The resultant mixture was extracted with EtOAc–toluene (3:7), and the extract, on work-up, gave a residue (1.05 g) which was adsorbed on silica gel (35 g). Elution with MeOH–$CHCl_3$ (3:97) gave (17^{1}R)-3-*methoxy*-14,17α-*prop*-17^2-*enoestra*-1,3,5(10)-*triene*-17β,17^1-*diol* **4** (483 mg, 56%), mp 139–143 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +63 (*c* 0.9 in THF) (Found: C, 77.2; H, 8.2%; M^+, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; *M*, 340); δ_H[200 MHz, MeOD–$CDCl_3$ (7:93)] 0.97 (3 H, s, 13β-Me), 2.39 (1 H, m, 9α-H), 2.70–2.82 (2 H, m, 6-H_2), 3.68 (3 H, s, 3-OMe), 3.8 (1 H, d, *J* 4.1, 17^1-H), 5.68 (1 H, dd, *J* 9.8 and 4.1, 17^2-H), 5.87 (1 H, d, *J* 9.8, 17^3-H), 6.52 (1 H, d, *J* 2.8, 4-H), 6.61 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.09 (1 H, d, *J* 8.6, 1-H), followed by (17^{1}S)-3-*methoxy*-14,17α-*prop*-17^2-*enoestra*-1,3,5(10)-*triene*-17β,17^1-*diol* **5** (320 mg, 37%), mp 170–173 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +180 (*c* 0.9 in THF) (Found: C, 77.4; H, 8.2; M^+, 340); δ_H[200 MHz, MeOD–$CDCl_3$ (7:93)] 1.0 (3 H, s, 13β-Me), 2.66–2.82 (2 H, m, 6-H_2), 3.69 (3 H, s, 3-OMe), 4.3 (1 H, br s, $W_{1/2}$ 3, 17^1-H), 5.43 (1 H, dd, *J* 9.8 and 2.0, 17^2-H), 5.55 (1 H, dd, *J* 9.8 and 1.6, 17^3-H), 6.52 (1 H, d, *J* 2.8, 4-H), 6.63 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.1 (1 H, d, *J* 8.6, 1-H).

3-Demethylation of **4** (120 mg, 0.35 mmol) [diisobutylaluminium hydride (DIBAH; 10 equiv.) in dry toluene (5 cm^3); reflux, 72 h] gave (17^{1}R)-14,17α-*prop*-17^2-*enoestra*-1,3,5(10)-*triene*-3,17β,17^1-*triol* **6** (70 mg, 61%), mp 215–218 °C (from MeOH); $[\alpha]_D$ +67 (*c* 0.5 in THF) (Found: C, 76.9; H, 7.8%; M^+, 326. $C_{21}H_{26}O_3$ requires C, 77.3; H, 8.0%; *M*, 326).

Similar treatment of **5** (100 mg, 0.29 mmol) gave (17^{1}S)-14,17α-*prop*-17^2-*enoestra*-1,3,5(10)-*triene*-3,17β,17^1-*triol* **7** (64 mg, 67%), mp 177–181 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +170 (*c* 0.9 in THF) (Found: C, 76.8; H, 7.8%; M^+, 326).

3-Methoxy-17^1-oxo-14,17α-propanoestra-1,3,5(10)-trien-17β-yl acetate 8

A solution of the enone **2** (230 mg, 0.61 mmol) in ethanol (40 cm^3) at 25 °C was hydrogenated for 8 h at 200 kPa in the presence of palladium–carbon (10%; 60 mg). The mixture was filtered, and the filtrate was evaporated under reduced pressure. Chromatography of the residue (225 mg) on silica gel (20 g) with EtOAc–toluene (1:9) as eluent gave the 17^1-*ketone* **8** (192 mg, 83%), mp 205–208 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +44 (*c* 1.0 in $CHCl_3$) (Found: C, 75.4; H, 7.9%; M^+, 382. $C_{24}H_{30}O_4$ requires C, 75.4; H, 7.9%; *M*, 382); ν_{max}/cm^{-1} 1743 and 1722; δ_H(400 MHz) 1.1 (3 H, s, 13β-Me), 1.69 (1 H, dd, *J* 13.5 and 9.6), 2.05 (1 H, obsc. td), 2.11 (3 H, s, 17β-OAc), 2.37 (1 H, dd, *J* 14.8 and 7.3), 2.74 (2 H, m), 2.81 (1 H, ddd, *J* 14.6, 9.4 and 5.2), 2.86–2.93 (2 H, m, 6-H_2), 3.77 (3 H, s, 3-OMe), 6.62 (1 H, d, *J* 2.7, 4-H), 6.7 (1 H, dd, *J* 8.6 and 2.7, 2-H) and 7.14 (1 H, d, *J* 8.6, 1-H); δ_C(100 MHz) 206.4 (s, C-17^1), 170.1 (s, O*C*OMe), 157.5 (s, C-3), 137.4 (s, C-5), 133.2 (s, C-10), 126.6 (d, C-1), 113.8 (d, C-4), 111.7 (d, C-2), 92.6 (s, C-17), 55.1 (q, 3-OMe), 55.1 (s, C-14), 46.2 (s, C-13), 42.4 (d, C-8), 36.9 (d, C-9), 34.7, 33.6, 32.1, 27.9 and 26.1 (each t, C-11, C-15, C-16, C-17^2 and C-17^3), 30.7 (t, C-6), 27.2 (t, C-12), 24.1 (t, C-7), 21.0 (q, OCO*Me*) and 15.9 (q, C-18).

(17^1*R*)-3-Methoxy-14,17α-propanoestra-1,3,5(10)-triene-17β,17^1-diol 9

The 17^1-ketone **8** (110 mg, 0.29 mmol) was reduced with LAH, as described for compound **2**. Crystallisation of the product (105 mg) from Me_2CO furnished the (17^{1}R)-17β,17^1-*diol* **9** (76 mg, 77%), mp 180–183 °C; $[\alpha]_D$ +61 (*c* 0.9 in THF) (Found: C, 77.0; H, 8.6%; M^+, 342. $C_{22}H_{30}O_3$ requires C, 77.2; H, 8.8%; *M*, 342); ν_{max}/cm^{-1} 3553 and 3391; δ_H(200 MHz, C_5D_5N) 1.26 (3 H, s, 13β-Me), 2.75–2.88 (2 H, m, 6-H_2), 3.15 (1 H, td, *J* 2 × 13.3 and 4.7, 9α-H), 3.71 (3 H, s, 3-OMe), 4.2 (1 H, t, *J* 2 × 3.0, 17^1-H), 6.79 (1 H, d, *J* 2.7, 4-H), 6.91 (1 H, dd, *J* 8.6 and 2.7, 2-H) and 7.31 (1 H, d, *J* 8.6, 1-H).

The derived (17^{1}R)-3,17β,17^1-*triol* **10** had mp 262–265 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +81 (*c* 1.0 in THF) (Found: C, 76.5; H, 8.5%; M^+, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%; *M*, 328).

(17^1*S*)-3-Methoxy-14,17α-propanoestra-1,3,5(10)-triene-17β,17^1-diol 11

A solution of the olefinic diol **5** (50 mg, 0.15 mmol) in ethanol (5 cm^3) at 25 °C was hydrogenated for 6 h at 100 kPa in the presence of palladium–carbon (10%; 10 mg). The mixture was filtered, and the residue (53 mg) obtained from concentration of the filtrate was chromatographed on silica gel (6 g) with MeOH–$CHCl_3$ (3:97) as eluent to give the (17^{1}S)-17β,17^1-*diol* **11** (37 mg, 74%), mp 185–187 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +76 (*c* 0.8 in THF) (Found: C, 76.8; H, 8.5%; M^+, 342. $C_{22}H_{30}O_3$ requires C, 77.2; H, 8.8%; *M*, 342); δ_H[200 MHz, MeOD–$CDCl_3$ (7:93)] 0.98 (3 H, s, 13β-Me), 2.25 (1 H, m, 11α-H), 2.62 (1 H, td, *J* 2 × 12.0 and 5.4, 9α-H), 2.71–2.83 (2 H, m, 6-H_2), 3.7 (3 H, s, 3-OMe), 3.86 (1 H, dd, *J* 9.9 and 6.1, 17^1-H), 6.53 (1 H, d, *J* 2.7, 4-H), 6.62 (1 H, dd, *J* 8.5 and 2.7, 2-H) and 7.1 (1 H, d, *J* 8.5, 1-H).

The derived (17^{1}S)-3,17β,17^1-*triol* **12** had mp 286–290 °C (from Me_2CO); $[\alpha]_D$ +70 (*c* 1.0 in THF) (Found: C, 76.3; H, 8.3%; M^+, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6; *M*, 328).

3-Methoxy-14,17α-prop-17^2-enoestra-1,3,5(10)-trien-17β-ol 14

Boron trifluoride–diethyl ether (0.12 cm^3) was added in three equal aliquots during 30 h to a solution of compound **3** (466 mg, 1.4 mmol) in ethanedithiol (1 cm^3) and glacial acetic acid (3 cm^3) at 30 °C. The reaction mixture was then poured into saturated aq. $NaHCO_3$, and the product (618 mg) was isolated by extraction with toluene and adsorbed on silica gel (50 g). Elution with EtOAc–toluene (1:9) gave the crude dithioketal **13** (560 mg, 98%), ν_{max}/cm^{-1} 3481; δ_H(200 MHz) 1.09 (3 H, s, 13β-Me), 3.10–3.45 (4 H, m, SCH_2CH_2S), 3.77 (3 H, s, 3-OMe), 5.69 and 5.8 (each 1 H, d, *J* 9.6, 17^2- and 17^3-H), 6.62 (1 H, d, *J* 2.7, 4-H), 6.71 (1 H, dd, *J* 8.6 and 2.7, 2-H) and 7.19 (1 H, d, *J* 8.6, 1-H); *m/z* 414 (M^+), which was used directly in the next step.

Compound **13** (700 mg, 1.7 mmol) in dry THF (20 cm^3) was added dropwise to a stirred solution of sodium (390 mg) in liquid ammonia (120 cm^3). After 2 h, solid NH_4Cl was added to the mixture to disperse the blue colour, and the ammonia was allowed to evaporate. Extraction of the residue with toluene gave material (560 mg) which was chromatographed on silica gel (30 g) with EtOAc–toluene (1:19) as eluent, to give the *product* **14** (459 mg, 84%), mp 141–142 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +137 (*c* 1.0 in $CHCl_3$) (Found: C, 81.3; H, 8.5%; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%;

M, 324); δ_H(200 MHz) 1.06 (3 H, s, 13β-Me), 2.8–2.9 (2 H, m, 6-H_2), 3.78 (3 H, s, 3-OMe), 5.57 (1 H, ddd, *J* 9.7, 4.4 and 2.2, 17^2-H), 5.75 (1 H, br d, *J* 9.7, 17^3-H), 6.63 (1 H, d, *J* 2.7, 4-H), 6.72 (1 H, dd, *J* 8.6 and 2.7, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H).

The derived 3,17β-*diol* **15** had mp 156–159 °C (from EtOAc); $[\alpha]_D$ +150 (*c* 0.9 in THF) (Found: C, 81.0; H, 8.1%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.25; H, 8.4%; *M*, 310).

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

A solution of the olefin **14** (175 mg, 0.54 mmol) in ethyl acetate (10 cm^3) at 25 °C was hydrogentated in the presence of palladium–carbon (10%, 50 mg) for 30 h at 200 kPa. The mixture was filtered, and the filtrate was evaporated to give the 17β-alcohol **16** (170 mg, 97%), mp 155–157 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +86 (*c* 0.9 in $CHCl_3$) (Found: C, 80.7; H, 9.0%; M^+, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; *M*, 326); ν_{max}/cm^{-1} 3602; δ_H(200 MHz) 1.03 (3 H, s, 13β-Me), 2.07 (1 H, td, *J* 2 × 12.5 and 4.9, 12α-H), 2.38 (1 H, dddd, *J* 13.1, 5.9, 4.9 and 2.0, 11α-H), 2.74 (1 H, td, *J* 2 × 11.9 and 5.9, 9α-H), 2.8–2.9 (2 H, m, 6-H_2), 3.77 (3 H, s, 3-OMe), 6.61 (1 H, d, *J* 2.8, 4-H), 6.71 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H).

The derived 3,17β-*diol* **17** had mp 228–231 °C (from EtOAc); $[\alpha]_D$ +87 (*c* 0.6 in THF) (Found: C, 80.4; H, 8.8%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; *M*, 312).

(17^2*R*)-3-Methoxy-16α-methyl-17^2-phenylsulfonyl-14,17α-ethanoestra-1,3,5(10)-triene-15β,16β,17β-triol 17-acetate 19

Compound **18** (1.18 g, 2.33 mmol) was treated with osmium tetraoxide (600 mg, 2.36 mmol) in pyridine (45 cm^3) at 25 °C for 168 h. Aq. sodium dithionite (10%, 90 cm^3) was added to the mixture which was then stirred at 25 °C for 45 min; after this it was diluted with water and extracted with $CHCl_3$. The extract was washed successively with dilute hydrochloric acid, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1.42 g) on silica gel (50 g) with EtOAc–toluene (1:4) as eluent gave starting material **18** (157 mg) followed by the 15β,16β-*diol* **19** (923 mg, 73%), double mp 174–176 and 232–234 °C (from $CHCl_3$–hexane), $[\alpha]_D$ +115 (*c* 1.0 in $CHCl_3$) (Found: C, 66.4; H, 6.7%; M^+, 540. $C_{30}H_{36}O_7S$ requires C, 66.6; H, 6.7%; *M*, 540); ν_{max}/cm^{-1} 3481 and 1708; δ_H(400 MHz) 1.32 (3 H, s, 13β-Me), 1.78 (3 H, s, 16α-Me), 2.06 (3 H, s, 17β-OAc), 2.14 (2 H, m, 7β- and 8β-H), 2.24 (1 H, dd, *J* 14.1 and 12.2, 17^1-H_{exo}), 2.42 (1 H, m, 7α-H), 2.58 (1 H, dd, *J* 14.1 and 5.5, 17^1-H_{endo}), 2.84 (1 H, s, exch. by D_2O, 16β-OH), 2.8–3.1 (3 H, m, 6-H_2 and 9α-H), 3.06 (1 H, d, *J* 5.8, exch. by D_2O, 15β-OH), 3.79 (3 H, s, 3-OMe), 3.99 (1 H, dd, *J* 12.2 and 5.5, 17^2-H), 4.95 (1 H, d, *J* 5.8→s on D_2O exch., 15α-H), 6.63 (1 H, d, *J* 2.7, 4-H), 6.72 (1 H, dd, *J* 8.4 and 2.7, 2-H), 7.24 (1 H, d, *J* 8.4, 1-H) and 7.5–7.9 (5 H, m, SO_2Ph); δ_C(100 MHz) 170.4 (s, 17β-O*C*OMe), 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 (2 C, d, C-3′ and C-5′), 127.8 (2 C, d, 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-OMe), 54.4 (s, C-13), 36.3 (d, C-9), 35.6 (d, C-8), 31.2 (t, C-6), 30.5 (t, C-12), 28.9 (t, C-17^1), 26.7 (t, C-11), 25.3 (q, 16-Me), 24.9 (t, C-7), 21.6 (q, 17β-OCO*Me*) and 18.0 (q, C-18).

17-Acetoxy-3-methoxy-20-oxo-15β-phenylsulfonyl-19-nor-14β-pregna-1,3,5(10)-triene-14-carbaldehyde 20

Aq. sodium periodate (6%; 29 cm^3) was added to a solution of the diol **19** (923 mg, 1.7 mmol) in ethanol (50 cm^3). After 3.5 h at 20 °C, the mixture was diluted with water and the product (927 mg) was isolated by extraction with $CHCl_3$ and adsorbed on silica gel (36 g). Elution with EtOAc–toluene (1:4) gave the 14-*carbaldehyde* **20** (778 mg, 85%) as an oil, ν_{max}/cm^{-1} 1737 and 1714; δ_H(200 MHz) 1.01 (3 H, s, 13β-Me), 1.81 (1 H, dd, *J* 15.9 and 9.8, 16α-H), 2.03 (3 H, s, 20-Me), 2.07 (3 H, s, 17α-OAc), 2.65–2.9 (3 H, m, 6-H_2 and 9α-H), 3.65 (1 H, dd, *J* 15.9 and 11.3, 16β-H), 3.7 (3 H, s, 3-OMe), 4.28 (1 H, dd, *J* 11.3 and 9.8, 15α-H), 6.63 (1 H, d, *J* 2.7, 4-H), 6.72 (1 H, dd, *J* 8.4 and 2.7, 2-H), 7.24 (1 H, d, *J* 8.4, 1-H), 7.5–8.0 (5 H, m, SO_2Ph) and 10.29 (1 H, s, 14β-CHO); *m/z* 538 (M^+).

Reductive desulfonylation of compound 19

A solution of the phenylsulfonyl compound **19** (360 mg, 0.6 mmol) in THF (12 cm^3) was added to samarium(II) iodide [generated by reaction of samarium (1.14 g) with diiodoethane (1.93 g, 6.8 mmol)] in THF (68 cm^3) at −20 °C with stirring, followed by hexamethylphosphoric triamide (HMPA) (5.5 cm^3). After 4 h at −20 °C, the mixture was poured into saturated aq. NH_4Cl. The mixture was extracted with EtOAc, and the extract was washed successively with aq. sodium dithionite and brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue (303 mg) was chromatographed on silica gel (25 g) with EtOAc–hexane (3:2) as eluent to give (17^{2}S)-3-*methoxy*-16α-*methyl*-15α,17^2-*cyclo*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-16β,17β-*diol* 17-*acetate* **21** (78 mg, 31%), double mp 112–114 and 146–147 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +41 (*c* 1.0 in $CHCl_3$) (Found: M^+, 382.214. $C_{24}H_{30}O_4$ requires *M*, 382.214); ν_{max}/cm^{-1} 3594 and 1738; δ_H(400 MHz) 1.09 (1 H, dd, *J* 5.2 and 1.1, 17^2-H), 1.29 (3 H, s, 13β-Me), 1.33 (3 H, s, 16α-Me), 1.55 (1 H, d, *J* 5.2, 15-H), 1.83 (1 H, d, *J* 11.4, 17^1-H_{endo}), 2.09 (3 H, s, 17β-OAc), 2.34 (1 H, obsc. m, 9α-H), 2.58 (1 H, dd, *J* 11.4 and 1.1, 17^1-H_{exo}), 2.8 (2 H, m, 6-H_2), 3.76 (3 H, s, 3-OMe), 6.67 (1 H, d, *J* 2.8, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H); δ_C(50 MHz) 171.5 (s, 17β-O*C*OMe), 158.1 (s, C-3), 138.5 (s, C-5), 133.0 (s, C-10), 127.4 (d, C-1), 114.4 (d, C-4), 112.4 (d, C-2), 90.5 (s, C-17), 83.1 (s, C-16), 55.9 (q, 3-OMe), 47.8 (s, C-13), 43.6 (d, C-9), 36.4 (s, C-14), 35.6 (d, C-8), 33.3 (t, C-12), 31.7 (d, C-17^1), 30.5 (t, C-6), 27.5 (t, C-11), 25.7 (t, C-15), 24.1 (t, C-7), 23.9 (q, 16α-Me), 22.3 (q, 17β-OCO*Me*), 17.9 (q, C-18) and 12.2 (d, C-17^2); followed by 3-*methoxy*-16α-*methyl*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-15β,16β,17β-*triol* 17-*acetate* **22** (78 mg, 29%), mp 182–185 °C (from Me_2CO–MeOH); $[\alpha]_D$ +4 (*c* 1.0 in $CHCl_3$) (Found: C, 72.0; H, 8.0%; M^+, 400. $C_{24}H_{32}O_5$ requires C, 72.0; H, 8.05%; *M*, 400); ν_{max}/cm^{-1} 3600, 3575 and 1738; δ_H(400 MHz) 1.24 (3 H, s, 13β-Me), 1.49 (3 H, s, 16α-Me), 2.11 (3 H, s, 17β-OAc), 2.64 (1 H, td, *J* 2 × 11.5 and 3.4, 9α-H), 2.78–3.0 (2 H, m, 6-H_2), 3.61 (1 H, d, *J* 4.7→s on D_2O exch., 15α-H), 3.76 (3 H, s, 3-OMe), 6.67 (1 H, d, *J* 2.8, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H); δ_C(50 MHz) 170.2 (s, 17β-O*C*OMe), 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), 91.6 (s, C-17), 82.3 (d, C-16), 78.7 (s, C-15), 55.2 (q, 3-OMe), 49.9 and 48.9 (each s, C-13 and C-14), 36.6 (d, C-9), 34.6 (d, C-8), 32.1 (t, C-6), 29.9 (t, C-17^1), 27.1 (q, 16α-Me), 25.8 (t, C-11), 23.7 (t, C-12), 23.4 (t, C-17^2), 23.2 (t, C-7), 21.8 (q, 17β-OCO*Me*) and 16.3 (q, C-18). Further elution gave starting material **19** (102 mg, 28%).

Acetonide formation–reductive desulfonylation of compound 19

The diol **19** (740 mg, 1.37 mmol) was treated with aq. perchloric acid (70%; 0.05 cm^3) in acetone (20 cm^3) at 20 °C for 5 h. $NaHCO_3$ was added to the mixture which was then concentrated under reduced pressure, treated with water and extracted with EtOAc. Work-up of the extract gave a brown oily residue (750 mg) which was adsorbed on silica gel (38 g). Elution with EtOAc–hexane (7:13) gave (17^{2}R)-15β,16β-*isopropylidenedioxy*-3-*methoxy*-16α-*methyl*-17^2-*phenylsulfonyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*yl acetate* **23** (625 mg, 79%), mp 185–188 °C (from Me_2CO–MeOH); $[\alpha]_D$ +102 (*c* 1.0 in $CHCl_3$) (Found: C, 67.9; H, 6.9%; M^+, 580. $C_{33}H_{40}O_7S$ requires C, 68.25; H, 6.9%; *M*, 580); ν_{max}/cm^{-1} 1735; δ_H(400 MHz) 1.43, 1.48 and 1.55 (each 3 H, s, 13β-Me and CMe_2), 1.93 (3 H, s, 16α-Me), 2.07 (3 H, s, 17β-OAc), 3.79 (3 H, s, 3-OMe), 4.05 (1 H, dd, *J*

12.4 and 5.5, 17²-H), 5.17 (1 H, s, 15α-H), 6.67 (1 H, d, *J* 2.8, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.8, 2-H), 7.21 (1 H, d, *J* 8.6, 1-H) and 7.5–7.9 (5 H, m, SO_2Ph).

The acetonide **23** (200 mg, 0.34 mmol) was treated with samarium(II) iodide and HMPA in THF (18 cm^3) at −20 °C for 1.5 h, as described for compound **19**. Chromatography of the product (240 mg) on silica gel (15 g) with EtOAc–hexane (1:9→3.7) as eluent gave 15β,16β-*isopropylidenedioxy*-3-*methoxy*-16α-*methyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*yl acetate* **24** (105 mg, 70%), mp 213–217 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ −24 (*c* 1.0 in $CHCl_3$) (Found: C, 73.4; H, 8.0%; M^+, 440. $C_{27}H_{36}O_5$ requires C, 73.6; H, 8.2%; *M*, 440); δ_H(400 MHz) 0.92 (1 H, ddd, *J* 13.4, 9.0 and 6.2, 12α-H), 1.33 (3 H, s, 13β-Me), 1.43 and 1.52 (each 3 H, s, CMe_2), 1.64 (3 H, s, 16α-Me), 2.11 (3 H, s, 17β-OAc), 2.24 (1 H, dq, *J* 13.2 and 3 × 3.9, 7β-H), 2.62 (1 H, td, *J* 2 × 11.8 and 4.1, 9α-H), 2.8–3.02 (2 H, m, 6-H_2), 3.76 (3 H, s, 3-OMe), 3.89 (1 H, s, 15α-H), 6.67 (1 H, d, *J* 2.8, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H).

Methyl 17β-acetoxy-3-methoxy-14,17α-ethenoestra-1,3,5(10),15-tetraene-16-carboxylate 26

3-Methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate **25** (162 mg, 0.5 mmol) and methyl propiolate (0.09 cm^3, 1 mmol) in dry benzene (2 cm^3) was kept at 100 °C (sealed tube) for 23 h. The reaction mixture was then adsorbed directly on silica gel (16 g) and eluted with EtOAc–toluene (1:49) to give starting material (8 mg) followed by the *cycloadduct* **26** (174 mg, 85%), mp 141–144 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +1 (*c* 1.0 in $CHCl_3$) (Found: C, 73.5; H, 7.0%; M^+, 408. $C_{25}H_{28}O_5$ requires C, 73.5; H, 6.9%; *M*, 408); δ_H(200 MHz) 1.19 (3 H, s, 13β-Me), 2.16 (3 H, s, 17β-OAc), 2.5 (1 H, td, *J* 2 × 11.4 and 3.4, 9α-H), 2.86–2.98 (2 H, m, 6-H_2), 3.69 (3 H, s, 16-CO_2Me), 3.77 (3 H, s, 3-OMe), 6.58 (1 H, d, *J* 5.6, 17²-H), 6.64 (1 H, d, *J* 2.4, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.4, 2-H), 7.05 (1 H, d, *J* 5.6, 17¹-H), 7.2 (1 H, d, *J* 8.6, 1-H) and 7.44 (1 H, s, 15-H); δ_C(50 MHz) 170.8 (s, 17β-O*C*OMe), 164.8 (s, 16-*C*O_2Me), 157.6 (s, C-3), 152.4 (d, C-15), 147.1 (d, C-16), 140.6 and 139.1 (each d, C-17¹ and C-17²), 137.8 (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-OMe), 51.3 (q, 16-CO_2*Me*), 39.8 (d, C-9), 35.9 (d, C-8), 30.2 (t, C-6), 29.9 (t, C-12), 26.3 (t, C-7), 25.2 (t, C-11), 21.4 (q, 17β-OCO*Me*) and 17.0 (q, C-18).

Methyl 17β-acetoxy-3-methoxy-14,17α-ethanoestra-1,3,5(10),15-tetraene-16-carboxylate 27

A solution of the cycloadduct **26** (3.05 g, 7.5 mmol) in ethyl acetate (100 cm^3) at 25 °C was hydrogenated for 3 h in the presence of palladium–carbon (10%; 1.02 g) and then filtered through Celite. The filtrate was evaporated and the residue (2.98 g) was chromatographed on silica gel (300 g) with EtOAc–hexane (3:17) as eluent, to give the *dihydro compound* **27** (2.55 g, 83%), mp 104–108 °C (from MeOH); $[\alpha]_D$ +9 (*c* 1.0 in $CHCl_3$) (Found: C, 73.1; H, 7.5%; M^+, 410. $C_{25}H_{30}O_5$ requires C, 73.1; H, 7.4%; *M*, 410); ν_{max}/cm^{-1} 1737 and 1713; δ_H(200 MHz) 0.95 (3 H, s, 13β-Me), 2.09 (3 H, s, 17β-OAc), 2.74 (1 H, td, *J* 2 × 11.3 and 4, 9α-H), 2.85–2.98 (2 H, m, 6-H_2), 3.71 (3 H, s, 16-CO_2Me), 3.77 (3 H, s, 3-OMe), 6.62 (1 H, d, *J* 2.7, 4-H), 6.7 (1 H, dd, *J* 8.6 and 2.7, 2-H), 6.91 (1 H, s, 15-H) and 7.18 (1 H, d, *J* 8.6, 1-H); δ_C(50 MHz) 170.4 (s, 17β-O*C*OMe), 164.6 (s, 16-*C*O_2Me), 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), 113.9 (d, C-4), 111.6 (d, C-2), 93.8 (s, C-17), 59.6 (s, C-14), 55.2 (q, 3-OMe), 54.1 (s, C-13), 51.3 (q, 16-CO_2*Me*), 37.1 (d, C-9), 36.0 (d, C-8), 29.9 (t, C-6), 29.7 (t, C-12), 28.1 (t, C-17¹), 25.9 (t, C-7), 25.4 (t, C-11), 24.7 (t, C-17²), 21.7 (q, 17β-OCO*Me*) and 15.4 (q, C-18).

Hydroxylation of the unsaturated ester 27

Compound **27** (403 mg, 0.98 mmol) was treated with osmium tetraoxide (250 mg, 0.9 mmol) in pyridine (5 cm^3) at 25 °C for 48 h. Aq. sodium dithionite (10%, 40 cm^3) was added to the mixture which was then stirred at 25 °C for 45 min. The product was isolated by extraction with $CHCl_3$ and chromatographed on silica gel (26 g) with EtOAc–toluene (1:9) as eluent to give starting material **27** (23 mg) followed by *methyl* 17β-*acetoxy*-15α,16α-*dihydroxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-16β-*carboxylate* **28** (281 mg, 65%), mp 169–170 °C (from Me_2CO); $[\alpha]_D$ +49 (*c* 1.0 in $CHCl_3$) (Found: C, 67.9; H, 7.2%; M^+, 444. $C_{25}H_{32}O_7$ requires C, 67.5; H, 7.25%; *M*, 444); ν_{max}/cm^{-1} 3509br, 1733 and 1714; δ_H(200 MHz) 0.82 (3 H, s, 13β-Me), 2.14 (3 H, s, 17β-OAc), 2.7 (1 H, obsc. m, 9α-H), 2.8–2.9 (2 H, m, 6-H_2), 3.73 (3 H, s, 16β-CO_2Me), 3.76 (3 H, s, 3-OMe), 4.42 (1 H, d, *J* 1.5, 15β-H), 5.9 (1 H, s, exch. by D_2O, 16α-OH), 6.67 (1 H, d, *J* 2.8, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H); δ_C(50 MHz), 174.9 (s, 16-*C*O_2Me), 171.4 (s, 17β-O*C*OMe), 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-OMe), 52.5 (q, 16-CO_2*Me*), 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), 25.4 (t, C-7), 24.4 (t, C-11), 24.0 (t, C-17²), 21.2 (q, 17β-OCO*Me*), 17.8 (t, C-17¹) and 13.4 (q, C-18) and *methyl* 17β-*acetoxy*-15β,16β-*dihydroxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-16α-*carboxylate* **29** (121 mg, 27%), mp 182–185 °C (from Me_2CO); $[\alpha]_D$ +45 (*c* 1.0 in $CHCl_3$) (Found: C, 67.7; H, 7.1%; M^+, 444); ν_{max}/cm^{-1} 3410, 1730 and 1710; δ_H(200 MHz) 1.23 (3 H, s, 13β-Me), 2.07 (3 H, s, 17β-OAc), 2.7 (1 H, obsc. m, 9α-H), 2.82–3.0 (2 H, m, 6-H_2), 3.76 (3 H, s, 3-OMe), 3.91 (3 H, s, 16α-CO_2Me), 4.11 (1 H, s, 15α-H), 4.45 (1 H, s, exch. by D_2O, 16β-OH), 6.67 (1 H, d, *J* 2.8, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H); δ_C(50 MHz) 175.2 (s, 16α-*C*O_2Me), 170.7 (s, 17β-O*C*OMe), 157.4 (s, C-3), 137.8 (s, C-5), 132.9 (s, C-10), 126.2 (d, C-1), 113.7 (d, C-4), 111.4 (d, C-2), 90.3 (s, C-17), 80.8 (s, C-16), 79.9 (d, C-15), 55.1 (q, 3-OMe), 53.6 (q, 16α-CO_2*Me*), 50.8 and 48.8 (each s, C-13 and C-14), 36.8 (d, C-9), 34.5 (d, C-8), 30.7 (t, C-6), 25.6 (t, C-7), 23.8 (t, C-11), 23.6 (t, C-17¹), 22.9 (t, C-17²), 21.0 (q, 17β-OCO*Me*) and 15.8 (q, C-18).

Methyl 17β-acetoxy-15α,16α-isopropylidenedioxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-16β-carboxylate 30

The diol **28** (4.37 g, 9.84 mmol) was treated with aq. perchloric acid (70%; 5.5 ml) in acetone (440 cm^3) at 20 °C for 2 h. $NaHCO_3$ (5 g) was added to the mixture which was then concentrated under reduced pressure and diluted with water; the product was isolated by extraction with $CHCl_3$. Work-up followed by chromatography of the residue (5.9 g) on silica gel (150 g) with EtOAc–toluene (1:9) as eluent gave the *acetonide* **30** (4.04 g, 85%), mp 130–134 °C (from Me_2CO–MeOH); $[\alpha]_D$ +57 (*c* 1.0 in $CHCl_3$) (Found: C, 69.1; H, 7.2%; M^+, 484. $C_{28}H_{36}O_7$ requires C, 69.4; H, 7.5%; *M*, 484); ν_{max}/cm^{-1} 1740; δ_H(200 MHz) 0.95 (3 H, s, 13β-Me), 1.35 and 1.61 (each 3 H, s, CMe_2), 2.03 (3 H, s, 17β-OAc), 2.68 (1 H, td, *J* 2 × 11.4 and 4.8, 9α-H), 2.8–2.91 (2 H, m, 6-H_2), 3.14 (1 H, m), 3.76 (3 H, s, 16β-CO_2Me), 3.78 (3 H, s, 3-OMe), 5.0 (1 H, d, *J* 1.1, 15β-H), 6.67 (1 H, d, *J* 2.8, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H).

16β-Hydroxymethyl-15α,16α-isopropylidenedioxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol 31

LAH (918 mg, 80 mmol) was added in small portions to a stirred solution of the ester **30** (4.04 g, 8.4 mmol) in THF (50 cm^3) at 25 °C under nitrogen. After 3 h at 25 °C, saturated aq. NH_4Cl was added to the mixture and the product was isolated by extraction with $CHCl_3$. Filtration of the product (4.05 g) through silica gel (90 g) with EtOAc–toluene (2:3) gave the *diol* **31** (3.47 g, 100%) as an oil, $[\alpha]_D$ +97 (*c* 1.0 in $CHCl_3$) (Found: C, 72.2; H, 8.2%; M^+, 414. $C_{25}H_{34}O_5$ requires C, 72.4; H, 8.3%; *M*, 414); ν_{max}/cm^{-1} 3544br; δ_H(400 MHz) 0.92 (3 H, s, 13β-Me), 1.48 and 1.62 (each 3 H, s, CMe_2), 2.68 (1 H, td, *J* 2 × 11.3 and 4.3, 9α-H), 2.74–2.9 (2 H, m, 6-H_2), 3.76 (3 H, s, 3-OMe), 3.79

and 4.32 (each 1 H, d, *J* 11.9, 16β-C*H*$_2$OH), 4.22 (1 H, d, *J* 1.2, 15β-H), 6.67 (1 H, d, *J* 2.8, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H).

15α,16α-Isopropylidenedioxy-3-methoxy-16β-methyl-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol 33

Methanesulfonyl chloride (2.1 cm^3, 24 mmol) was added to a solution of the diol **31** (3.4 g, 8.2 mmol) in dry pyridine (20 cm^3) at 0 °C under nitrogen. After 1.5 h at 0 °C, the mixture was diluted with water and the product was isolated by extraction with toluene. Work-up followed by chromatography of the residue (4.4 g) on silica gel (100 g) with EtOAc–toluene (3:7) as eluent gave the non-crystalline 16^1-methanesulfonate **32** (4.04 g, 100%), δ_H(200 MHz) 0.99 (3 H, s, 13β-Me), 1.5 and 1.6 (each 3 H, s, CMe$_2$), 3.05 (3 H, s, 16^1-OMs), 3.75 (3 H, s, 3-OMe), 4.45 and 4.75 (each 1 H, d, *J* 11.1, 16-C*H*$_2$OMs), 4.6 (1 H, d, *J* 1.4, 15β-H), 6.6 (1 H, d, *J* 2.8, 4-H), 6.7 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H).

The methanesulfonate **32** (4.04 g, 8.2 mmol) was treated with LAH (909 mg, 24 mmol) in dry THF (20 cm^3) at 25 °C under nitrogen for 24 h. Saturated aq. NH_4Cl was added to the reaction mixture and the product (2.98 g) was isolated by extraction with toluene. Work-up followed by absorption of the residue on silica gel (200 g) and elution with EtOAc–toluene (3:17) gave the 16β-*methyl compound* **33** (2.92 g, 89%), mp 98–102 °C (from Me$_2$CO–MeOH); $[\alpha]_D$ +111 (*c* 1.0 in $CHCl_3$) (Found: C, 75.3; H, 8.6%; M$^+$, 398. $C_{25}H_{34}O_4$ requires C, 75.3; H, 8.6%; *M*, 398); ν_{max}/cm^{-1} 3598; δ_H(400 MHz) 0.94 (3 H, s, 13β-OMe), 1.45 and 1.63 (each 3 H, s, CMe$_2$), 1.54 (3 H, s, 16β-Me), 2.7 (1 H, td, *J* 2 × 11.8 and 4.8, 9α-H), 2.78–2.88 (2 H, m, 6-H$_2$), 3.73 (3 H, s, 3-OMe), 4.22 (1 H, d, *J* 1.6, 15β-H), 6.6 (1 H, d, *J* 2.8, 4-H), 6.7 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H).

The derived (Ac$_2$O–*p*-TsOH–THF, 20 °C, 1 h) 17β-*acetate* **34** had mp 191–193 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +96 (*c* 1.0 in $CHCl_3$) (Found: C, 73.3; H, 8.2%; M$^+$, 440. $C_{27}H_{36}O_5$ requires C, 73.6; H, 8.2%; *M*, 440); δ_H(200 MHz) 0.99 (3 H, s, 13β-Me), 1.46 and 1.59 (each 3 H, s, CMe$_2$), 1.56 (3 H, s, 16β-Me), 2.05 (3 H, s, 17β-OAc), 3.76 (3 H, s, 3-OMe), 4.3 (1 H, d, *J* 1.3, 15β-H), 6.6 (1 H, d, *J* 2.8, 4-H), 6.7 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H).

3-Methoxy-16β-methyl-14,17α-ethanoestra-1,3,5(10)-triene-15α,16α,17β-triol 17-acetate 35

A solution of the acetonide **34** (93 mg, 0.21 mmol) in methanolic iodine (1%; 13 cm^3) was refluxed for 5.5 h, cooled and treated with aq. sodium thiosulfate. Extraction of the reaction mixture with EtOAc and work-up gave a product (80 mg) which was adsorbed on silica gel (10 g). Elution with EtOAc–hexane (1:9) gave mixed fractions (9 mg) followed by the 15α,16α-*diol* **35** (63 mg, 79%), mp 145–149 °C (from Me$_2$CO–MeOH); $[\alpha]_D$ +91 (1.0 in $CHCl_3$) (Found: C, 72.0; H, 8.1%; M$^+$, 400. $C_{24}H_{32}O_5$ requires C, 72.0; H, 8.05%; *M*, 400); ν_{max}/cm^{-1} 3482br and 1710; δ_H(200 MHz) 0.99 (3 H, s, 13β-Me), 1.35 (3 H, s, 16β-Me), 2.12 (3 H, s, 17β-OAc), 2.62 (1 H, obsc. m, 9α-H), 2.76–2.9 (2 H, m, 6-H$_2$), 3.75 (1 H, d, *J* 1.1, 15β-H), 3.77 (3 H, s, 3-OMe), 6.6 (1 H, d, *J* 2.8, 4-H), 6.7 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H).

The derived (LAH–THF, 20 °C) 15α,16α,17β-*triol* **36** had mp 183–185 °C (from $CHCl_3$–hexane); $[\alpha]_D$ +77 (*c* 0.6 in $CHCl_3$) (Found: M$^+$, 358.214. $C_{22}H_{30}O_4$ requires *M*, 358.214); δ_H(200 MHz) 0.93 (3 H, s, 13β-Me), 1.44 (3 H, s, 16β-Me), 2.78–2.9 (2 H, m, 6-H$_2$), 3.72 (1 H, dd, *J* 7.2 and 1.3→d, *J* 1.3 on D_2O exch., 15β-H), 3.77 (3 H, s, 3-OMe), 6.64 (1 H, d, *J* 2.4, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.4, 2-H) and 7.18 (1 H, d, *J* 8.6, 1-H).

15β,16β-Isopropylidenedioxy-3-methoxy-16α-methyl-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol 40

A reaction sequence similar to that described in the foregoing experiments was used to convert the 16α-carboxylate **29** into the 16α-methyl compound **40**. The intermediates and product were characterised as follows.

Methyl 17β-*acetoxy*-15β,16β-*isopropylidenedioxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-16α-*carboxylate* **37**, double mp 178–182 and 187–191 °C (from $CHCl_3$–hexane); $[\alpha]_D$ +4 (*c* 1.0 in $CHCl_3$) (Found: C, 69.1; H, 7.2%; M$^+$, 484. $C_{28}H_{36}O_7$ requires C, 69.4; H, 7.5%; *M*, 484); ν_{max}/cm^{-1} 1732; δ_H 1.22 (3 H, s, 13β-Me), 1.35 and 1.55 (each 3 H, s, CMe$_2$), 2.09 (3 H, s, 17β-OAc), 2.66 (1 H, td, *J* 2 × 11.3 and 4.0, 9α-H), 2.8–3.02 (2 H, m, 6-H$_2$), 3.76 (3 H, s, 16α-CO$_2$Me), 3.78 (3 H, s, 3-OMe), 4.64 (1 H, s, 15α-H), 6.67 (1 H, d, *J* 2.8, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H).

16α-*Hydroxymethyl*-15β,16β-*isopropylidenedioxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*ol* **38**, gum; $[\alpha]_D$ +5 (*c* 1.0 in $CHCl_3$) (Found: C, 72.6; H, 8.2%; M$^+$, 414. $C_{25}H_{34}O_5$ requires C, 72.4; H, 8.3%; *M*, 414); ν_{max}/cm^{-1} 3544br; δ_H(200 MHz) 1.31 (3 H, s, 13β-Me), 1.41 and 1.56 (each 3 H, s, CMe$_2$), 2.64 (1 H, td, *J* 2 × 11.2 and 4.2, 9α-H), 2.76–3.0 (2 H, m, 6-H$_2$), 3.77 (3 H, s, 3-OMe), 3.84 (1 H, s, 15α-H), 4.02 and 4.1 (each 1 H, d, after D_2O exch., *J* 11.8, 16-H$_2$), 6.67 (1 H, d, *J* 2.8, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H).

15β,16β-*Isopropylidenedioxy*-3-*methoxy*-16α-*methyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*ol* **40**, gum; $[\alpha]_D$ +62 (*c* 1.0 in $CHCl_3$) (Found: C, 75.4; H, 8.7%; M$^+$, 398. $C_{25}H_{34}O_4$ requires C, 75.3; H, 8.6%; *M*, 398); ν_{max}/cm^{-1} 3572; δ_H(200 MHz) 1.26 (3 H, s, 13β-Me), 1.43 and 1.54 (each 3 H, s, CMe$_2$), 1.5 (3 H, s, 16α-Me), 2.65 (1 H, td, *J* 2 × 11.3 and 4.3, 9α-H), 2.8–3.0 (2 H, m, 6-H$_2$), 3.78 (3 H, s, 3-OMe), 3.92 (1 H, s, 15α-H), 6.6 (1 H, d, *J* 2.8, 4-H), 6.7 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H).

Acetylation (Ac$_2$O–*p*-TsOH–THF, 25 °C, 24 h) of **40** gave compound **24**, identical with that prepared in a previous experiment.

Deprotection of the acetonide 24

Treatment of compound **24** (970 mg, 2.2 mmol) with methanolic iodine in THF as described in a previous experiment, followed by flash chromatography of the product (914 mg) on silica gel (70 g) with EtOAc–hexane (7:13), gave starting material (17 mg) followed by an inseparable mixture (794 mg, 91%) of the isomers **22** and **41**. A subsequent experiment (see later) resulted in isolation of pure 3-*methoxy*-16α-*methyl*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-15β,16β,17β-*triol* 15-*acetate* **41** (258 mg, 32%), mp 183–186 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ −17 (*c* 1.0 in $CHCl_3$) (Found: C, 72.1; H, 7.7%; M$^+$, 400. $C_{24}H_{32}O_5$ requires C, 72.0; H, 8.05%; *M*, 400); ν_{max}/cm^{-1} 3597 and 1721; δ_H(200 MHz) 1.14 (3 H, s, 13α-Me), 1.48 (3 H, s, 16α-Me), 2.05 (3 H, s, 15β-OAc), 2.64 (1 H, td, *J* 2 × 11.2 and 4.8, 9α-H), 2.78–2.86 (2 H, m, 6-H$_2$), 3.77 (3 H, s, 3-OMe), 4.45 (1 H, s, 15α-H), 6.67 (1 H, d, *J* 2.8, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H).

Hydrolysis (LAH–THF, 25 °C) of the mixture (65 mg, 0.16 mmol) of **22** and **41** gave the corresponding 15β,16β,17β-*triol* **42** (57 mg, 98%), mp 190–193 °C (from $CHCl_3$–hexane); $[\alpha]$ +22 (*c* 1.0 in $CHCl_3$) (Found: C, 74.0; H, 8.3%; M$^+$, 358. $C_{22}H_{30}O_4$ requires C, 73.7; H, 8.4%; *M*, 358); ν_{max}/cm^{-1} 3552; δ_H(200 MHz) 1.11 (3 H, d, *J* 0.9, 13β-Me), 1.35 (3 H, s, 16α-Me), 2.8–3.0 (2 H, m, 6-H$_2$), 3.6 (1 H, s, 15α-Me), 3.75 (3 H, s, 3-OMe), 6.67 (1 H, d, *J* 2.8, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H).

Methyl 17β-acetoxy-3-methoxy-15α-phenylthio-14,17α-ethanoestra-1,3,5(10)-triene-16β-carboxylate 43

Diisopropylethylamine (1.6 cm^3) was added to a solution of the unsaturated ester **27** (3.06 g, 7.46 mmol) in thiophenol (10 cm^3) at 20 °C. After 48 h at 20 °C, flash chromatography of the reaction mixture on silica gel (200 g) with EtOAc–hexane (1:9) as eluent gave the 15α-*phenylthio compound* **43** (3.84 g, 98%), mp 153–155 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +42 (*c* 0.8 in $CHCl_3$) (Found: C, 71.35; H, 7.0%; M$^+$, 520. $C_{31}H_{36}O_5S$ requires C, 71.5; H, 7.0%; *M*, 520); ν_{max}/cm^{-1} 1734, 1607, 1599, 1580 and

1571; δ_H(400 MHz) 1.23 (3 H, s, 13β-Me), 1.96 (1 H, td, *J* 2 × 11.3 and 2.3, 8β-H), 2.02 (3 H, s, 17β-OAc), 2.16 (1 H, td, *J* 2 × 13.1 and 3.6), 2.72 (1 H, obsc. m, 9α-H), 2.82–2.92 (2 H, m, 6-H_2), 3.36 (1 H, dd, *J* 5.6 and 2.5, 15β-H), 3.53 (3 H, s, 16β-CO_2Me), 3.78 (3 H, s, 3-OMe), 3.82 (1 H, d, *J* 5.6, 16α-H), 6.64 (1 H, d, *J* 2.4, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.4, 2-H) and 7.15–7.45 (6 H, m, 1-H and 15α-SPh); δ_C(50 MHz) 173.9 (s, 16β-*C*O_2Me), 170.2 (s, 17β-O*C*OMe), 157.5 (s, C-3), 137.9 (s, C-5), 136.2 (s, C-1′), 131.9 (s, C-10), 132.0 (2 × d, C-2′ and C-6′), 128.9 (2 × d, 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 (2 × d, C-15 and C-16), 55.2 (q, 3-OMe), 51.7 (q, 16-CO_2*Me*), 51.6 and 49.8 (each s, C-13 and C-14), 37.6 (d, C-8), 29.7 (t, C-6), 28.8 (t, C-12), 28.6 (t, C-17[1]), 25.7 (t, C-7), 24.1 (t, C-11), 23.8 (t, C-17[2]), 2.14 (q, 17β-OCO*Me*) and 15.6 (q, C-18).

3-Methoxy-16β-methyl-15α-phenylthio-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol 46

The ester **43** (3.84 g, 7.38 mmol) was treated with LAH (1.6 g, 44.2 mmol) in THF (50 cm[3]) at 20 °C for 45 min. The mixture was treated with aq. NH_4Cl, added slowly to destroy excess reagent, and then extracted with EtOAc. Work-up gave 16β-*hydroxymethyl*-3-*methoxy*-15α-*phenylthio*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*ol* **44** (3.32 g, 100%), mp 207–210 °C (from $CHCl_3$); $[\alpha]_D$ +41 (*c* 0.8 in $CHCl_3$) (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); ν_{max}/cm^{-1} 3593; δ_H(200 MHz) 1.2 (3 H, s, 13β-Me), 2.74 (1 H, br d, *J* 6.1, 15β-H), 3.77 (3 H, s, 3-OMe), 3.8 (2 H, obsc. m, 16β-C*H_2*OH), 6.64 (1 H, d, *J* 2.4, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.4, 2-H) and 7.15–7.45 (6 H, m, 1-H and 15α-SPh).

Methanesulfonation (MsCl–pyridine, 0 °C, 1 h) of the diol **44** (3.32 g, 7.38 mmol), followed by dilution of the mixture with water and isolation of the product by extraction with EtOAc gave material (3.88 g) which was flash chromatographed on silica gel (100 g) with EtOAc–toluene (2:3) as eluent to give the non-crystalline 16β-(methanesulfonyloxy)methyl derivative **45** (3.12 g, 81%).

The methanesulfonate **45** (3.12 g, 5.9 mmol) was treated with LAH (876 mg, 29 mmol) in THF (50 cm[3]) at 20 °C under nitrogen for 2.4 h. Excess reagent was destroyed by cautious addition of aq. NH_4Cl to the mixture, and the product (2.6 g) was isolated by extraction with EtOAc. Flash chromatography on silica gel (100 g) with EtOAc–toluene (1:9) as eluent gave the 16β-*methyl compound* **46** (2.46 g, 96%), mp 135–136 °C (from MeOH); $[\alpha]_D$ +56 (*c* 1.0 in $CHCl_3$) (Found: M^+, 434.229. $C_{28}H_{34}O_2S$ requires *M*, 434.228); ν_{max}/cm^{-1} 3594; δ_H(400 MHz) 0.9 (3 H, d, *J* 7.2, 16β-Me), 1.1 (3 H, d, *J* 0.9, 13β-Me), 1.42 (1 H, dq, *J* 12.4 and 3 × 2.6), 1.62 (1 H, dq, *J* 12.4 and 3 × 2.5), 1.85 (1 H, ddd, *J* 12.4, 9.5 and 3.1), 1.98 (1 H, td, *J* 2 × 11.5 and 2.1), 2.05 (1 H, td, *J* 2 × 12.7 and 3.4), 2.41 (1 H, ddd, *J* 7.0, 5.7 and 2.5), 2.66 (1 H, obsc., 8β-H), 2.6–2.86 (2 H, m, 6-H_2), 2.84 (1 H, d, *J* 5.6, 15β-H), 3.77 (3 H, s, 3-OMe), 6.64 (1 H, d, *J* 2.4, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.4, 2-H) and 7.15–7.45 (6 H, m, 1-H and 15α-SPh).

Oxidation–elimination of the phenylthio compound 46

Aq. sodium periodate (0.5 mol dm[3], 50 cm[3]) was added to a stirred solution of the phenylthio compound **46** (2.46 g, 5.66 mmol) in ethanol–THF (3:1, 80 cm[3]) at 20 °C. After 24 h at 20 °C, the reaction mixture was concentrated under reduced pressure and diluted with water. The product was isolated by extraction with chloroform. Flash chromatography of the residue (2.7 g) on silica gel (200 g) with EtOAc–toluene (2:5) as eluent gave the 15α-phenylsulfinyl compound **47** (1.9 g, 75%), which was dissolved in triethylamine (0.2 cm[3]) and benzene (30 cm[3]), and heated at 115 °C (sealed tube) for 16 h. The reaction mixture was concentrated under reduced pressure and the residue (1.4 g) was flash chromatographed on silica gel (60 g) with EtOAc–toluene (1:9) as eluent, to give 3-*methoxy*-16-*methyl*-14,17α-*ethanoestra*-1,3,5(10),15-*tetraen*-17β-*ol* **48** (1.4 g, 99%), mp 113–114 °C (from EtOAc–MeOH); $[\alpha]_D$ −22 (*c* 1.0 in $CHCl_3$) (Found: C, 81.8; H, 8.7%; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; *M*, 324); ν_{max}/cm^{-1} 3598; δ_H(200 MHz) 0.84 (3 H, s, 13β-Me), 1.73 (3 H, d, *J* 1.6, 16-Me), 3.77 (3 H, s, 3-OMe), 5.62 (1 H, q, *J* 3 × 1.6, 15-H), 6.62 (1 H, d, *J* 2.7, 4-H), 6.7 (1 H, dd, *J* 8.6 and 2.7, 2-H) and 7.18 (1 H, d, *J* 8.6, 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), 127.5 (d, C-15), 126.2 (d, C-1), 113.9 (d, C-4), 111.4 (d, C-2), 91.0 (s, C-17), 56.8 (s, C-14), 55.2 (q, 3-OMe), 54.1 (s, C-13), 37.4 (d, C-9), 37.2 (d, C-8), 30.1 (t, C-6), 27.8 (t, C-12), 27.5 (t, C-17[1]), 26.6 (t, C-17[2]), 25.6 (t, C-7), 24.6 (t, C-11), 14.7 (q, C-18) and 12.0 (q, 16-Me).

The derived (Ac_2O–DMAP–pyridine, 20 °C, 72 h) 17β-*acetate* **49** had mp 108–110 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ −40 (*c* 1.0 in $CHCl_3$) (Found: C, 78.4; H, 8.4%; M^+, 366. $C_{24}H_{30}O_3$ requires C, 78.65; H, 8.25%; *M*, 366); ν_{max}/cm^{-1} 1729; δ_H(200 MHz) 0.89 (3 H, s, 13β-Me), 1.74 (3 H, d, *J* 1.5, 16-Me), 2.1 (3 H, s, 17β-OAc), 3.78 (3 H, s, 3-OMe), 5.67 (1 H, q, *J* 3 × 1.5, 15-H), 6.64 (1 H, d, *J* 2.4, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.4, 2-H) and 7.18 (1 H, d, *J* 8.6, 1-H).

Hydroxylation of the 16-methyl Δ[15]-compounds 48 and 49

(a) Treatment of the 17β-alcohol **48** (340 mg, 1.05 mmol) with osmium tetraoxide (320 mg, 1.26 mmol) in pyridine (10 cm[3]) at 20 °C for 72 h, followed by standard work-up and chromatography of the product (360 mg) on silica gel (40 g) with EtOAc–toluene (1:1) as eluent, gave the 15β,16β,17β-triol **42** (203 mg, 50%) followed by the 15α,16α,17β-triol **36** (149 mg, 40%).

(b) Similar treatment of the 17β-acetate **49** (1.4 g, 3.8 mmol), and chromatography of the product (1.8 g) on silica gel (150 g) with EtOAc–toluene (3:7) as eluent, gave the 17β-acetoxy 15α,16α-diol **35** (958 mg, 63%), followed by the 17β-acetoxy 15β,16β-diol **22** (441 mg, 29%).

Oxidative cleavage of the 15,16-diols

(a) The following procedure is representative. Aq. sodium periodate (0.5 mol dm[3]; 23 cm[3]) was added to a solution of the diols **22** + **35** (1.38 g, 3.5 mmol) in ethanol (100 cm[3]) at 20 °C. After 4 h at 20 °C, the mixture was diluted with water and the product (1.4 g) was isolated by extraction with chloroform. Flash chromatography of the residue on silica gel (90 g) with EtOAc–hexane (1:4) as eluent gave 17-*acetoxy*-3-*methoxy*-20-*oxo*-19-*nor*-14β-*pregna*-1,3,5(10)-*triene*-14-*carbaldehyde* **50** (1.24 g, 90%), mp 174–177 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +74 (*c* 1.0 in $CHCl_3$) (Found: C, 72.3; H, 7.6%; M^+, 398. $C_{24}H_{30}O_5$ requires C, 72.3; H, 7.6; *M*, 398); ν_{max}/cm^{-1} 1731 and 1711; δ_H(400 MHz) 1.18 (3 H, s, 13β-Me), 1.34 (1 H, qd, *J* 3 × 11.4 and 7, 7α-H), 1.52 (1 H, obsc. m, 7β-H), 1.74 (1 H, td, *J* 2 × 12 and 3.3, 8β-H), 2.04 (3 H, s, 17α-OAc), 2.1 (1 H, m), 2.15 (3 H, s, 20-Me), 2.6 (1 H, td, *J* 2 × 12 and 3.3, 9α-H), 2.7–2.8 (2 H, m, 6-H_2), 2.92 (1 H, ddd, *J* 16.9, 10.0 and 6.9, 15β-H), 3.77 (3 H, s, 3-OMe), 6.6 (1 H, d, *J* 2.8, 4-H), 6.7 (1 H, dd, *J* 8.6 and 2.8, 2-H), 7.21 (1 H, d, *J* 8.6, 1-H) and 9.67 (1 H, s, 14β-CHO); δ_C(50 MHz) 209.2 (s, C-20), 207.2 (d, 14β-CHO), 170.9 (s, 17α-O*C*OMe), 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-OMe), 51.4 (s, C-13), 40.1 (d, C-81), 36.9 (d, C-9), 33.6 (t, C-12), 32.3 (t, C-15), 30.2 (t, C-6), 26.9 (q, 20-Me), 25.9 (t, C-16), 25.1 (t, C-11), 24.1 (t, C-7), 21.1 (q, 17α-OCO*Me*) and 16.5 (q, C-18).

(b) Similar treatment of the 15,16,17-*triols* **36** or **42** for 2 h at 20 °C gave the 17α-*alcohol* **51** (100%), mp 161–163 °C (from $CHCl_3$–hexane); $[\alpha]_D$ +134 (*c* 1.0 in $CHCl_3$) (Found: C, 73.9; H, 7.9%; M^+, 356. $C_{22}H_{28}O_4$ requires C, 74.1; H, 7.9%; *M*, 356); ν_{max}/cm^{-1} 3605 and 1708.

Intramolecular aldol condensation of the 14-carbaldehyde 50

(a) Compound **50** (100 mg, 0.25 mmol) was treated with hydrochloric acid (12 mol dm^{-3}; 1 cm[3]) in THF (9 cm[3]) at 57 °C for

2 h. The cooled reaction mixture was neutralised with saturated aq. $NaHCO_3$, and the product was isolated by extraction with $CHCl_3$. Work-up and chromatography of the residue (90 mg) on silica gel (9 g) with EtOAc–hexane (3:7) as eluent gave 3-*methoxy*-17^1-*oxo*-14,17β-*prop*-17^2-*eno*-14β-*estra*-1,3,5(10)-*trien*-17α-*yl acetate* **52** (72 mg, 76%), mp 170–172 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ −1 (*c* 1.0 in $CHCl_3$) (Found: C, 75.9; H, 7.3%; M^+, 380. $C_{24}H_{28}O_4$ requires C, 75.8; H, 7.4%; *M*, 380); ν_{max}/cm^{-1} 1739 and 1694; δ_H(200 MHz) 0.95 (3 H, s, 13β-Me), 2.17 (3 H, s, 17α-OAc), 2.8 (1 H, td, *J* 2 × 10.9 and 3.9, 9α-H), 2.9–3.0 (2 H, m, 6-H$_2$), 3.79 (3 H, s, 3-OMe), 6.07 (1 H, d, *J* 9.9, 17^2-H), 6.67 (1 H, d, *J* 2.8, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.8, 2-H), 7.17 (1 H, d, *J* 9.9, 17^3-H) and 7.21 (1 H, d, *J* 8.6, 1-H).

(b) Treatment of compound **50** (436 mg, 1.1 mmol) with toluene-*p*-sulfonic acid (623 mg, 3.1 mmol) in benzene (10 cm^3) under reflux for 1.75 h, followed by work-up as described above gave 17α-*hydroxy*-3-*methoxy*-14,17β-*prop*-17^2-*eno*-14β-*estra*-1,3,5(10)-*trien*-17^1-*one* **53** (370 mg, 100%), mp 158–161 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +117 (*c* 1.0 in $CHCl_3$) (Found: C, 78.3; H, 7.6%; M^+, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; *M*, 338); ν_{max}/cm^{-1} 3480 and 1677; λ_{max}(EtOH)/nm 243 (ε/dm^3 mol^{-1} cm^{-1} 16 426); δ_H(200 MHz) 0.73 (3 H, s, 13β-Me), 2.72 (1 H, td, *J* 2 × 11.3 and 4.3, 9α-H), 2.81–2.9 (2 H, m, 6-H$_2$), 3.71 (3 H, s, 3-OMe), 6.07 (1 H, d, *J* 9.8, 17^2-H), 6.67 (1 H, d, *J* 2.8, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.8, 2-H), 7.17 (1 H, d, *J* 8.6, 1-H) and 7.26 (1 H, d, *J* 9.8, 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-OMe), 52.5 (2 C, s, C-13 and C-14), 38.7 (d, C-8), 37.4 (d, C-9), 30.2 (t, C-6), 28.5 (2 t, C-11 and C-12), 25.6 (t, C-15), 25.0 (t, C-16), 24.0 (t, C-7) and 13.8 (q, C-18).

14-Acetonyl-3-methoxy-14β-estra-1,3,5(10)-trien-17-one 55

Palladium(II) chloride (142 mg, 0.8 mmol) and copper(I) chloride (395 mg, 3.99 mmol) were added to water–dimethylformamide (1:10; 41 cm^3), and the mixture was stirred vigorously at 20 °C for 2.5 h under an oxygen atmosphere. 14-Allyl-3-methoxy-14β-estra-1,3,5(10)-trien-17-one **54** (500 mg, 1.54 mmol) was added to the mixture which was then kept at 65 °C for 5 h, before being poured into water. The product (627 mg) was isolated by extraction with toluene and adsorbed on silica gel (55 g). Elution with EtOAc–toluene (1:9) gave starting material (22 mg) and uncharacterised material (191 mg), followed by the *diketone* **55** as an oil (363 mg, 69%), $[\alpha]_D$ +8 (*c* 0.8 in $CHCl_3$) (Found: M^+, 340.203. $C_{22}H_{28}O_3$ requires *M*, 340.204); ν_{max}/cm^{-1} 1726br; δ_H(200 MHz) 1.01 (3 H, s, 13β-Me), 2.15 (3 H, s, COMe), 2.39 and 2.62 (each 1 H, d, *J* 17.2, 14^1-H$_2$), 2.83–2.91 (2 H, m, 6-H$_2$), 3.78 (3 H, s, 3-OMe), 6.63 (1 H, d, *J* 2.7, 4-H), 6.74 (1 H, dd, *J* 8.7 and 2.7, 2-H) and 7.21 (1 H, d, *J* 8.7, 1-H).

Intramolecular aldol condensation of the diketone 55

Methanolic potassium hydroxide (1 mol dm^{-3}; 5.5 cm^3) was added to a stirred solution of the diketone **55** (470 mg, 1.38 mmol) in THF (17 cm^3) at 20 °C under nitrogen. After 30 min at 20 °C, the reaction was complete (TLC), and water was added followed by aqueous hydrochloric acid (2 mol dm^{-3}; 3 cm^3). Extraction with toluene and work-up gave material (420 mg) which was adsorbed on silica gel (21 g). Elution with EtOAc–toluene (2:3) gave an isomeric mixture (~2:1 by NMR, 27 mg) formulated as (16^1*R/S*)-16^1-hydroxy-3-methoxy-16^1-methyl-14,16β-ethano-14β-estra-1,3,5(10)-trien-17-ones **56**, ν_{max}/cm^{-1} 3584 and 1733; δ_H(200 MHz) 1.04 (3 H, s, 13β-Me) and 1.35 (3 H, s, 16^{1}ξ-Me) (minor component); 1.16 (3 H, s, 13β-Me) and 1.45 (3 H, s, 16^{1}ξ-Me) (major component); and 2.84–2.93 (2 H, m, 6-H$_2$), 3.78 (3 H, s, 3-OMe), 6.64 (1 H, d, *J* 2.9, 4-H), 6.73 (1 H, dd, 8.6 and 2.9, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H); *m/z* 340.203 (M^+), followed by mixed fractions (49 mg) and 17α-*hydroxy*-3-*methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*trien*-17^2-*one* **57** (327 mg, 70%), mp 215–217 °C (from CH_2Cl_2–MeOH); $[\alpha]_D$ +11 (*c* 1.0 in $CHCl_3$) (Found: C, 77.4; H, 8.4%; M^+, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; *M*, 340); δ_H(400 MHz) 1.06 (3 H, s, 13β-Me), 1.5 (1 H, qd, *J* 3 × 12.3 and 4.7), 2.04 (1 H, qt, *J* 3 × 13.1 and 2 × 3.6), 2.2 (1 H, dd, *J* 17.4 and 2.6, 17^3-H), 2.4 (1 H, dq, *J* 13.4 and 3 × 3.8, 11α-H), 2.49 (1 H, dd, *J* 17.4 and 2, 17^1-H), 2.51 (1 H, dd, *J* 17.4 and 2, 17^3-H), 2.63 (1 H, td, *J* 2 × 14.6 and 3.8, 9α-H), 2.8 (1 H, obsc. dd, *J* 17.4 and 2.8, 17^1-H), 2.8–2.84 (2 H, m, 6-H$_2$), 3.77 (3 H, s, 3-OMe), 6.64 (1 H, d, *J* 2.7, 4-H), 6.74 (1 H, dd, *J* 8.6 and 2.7, 2-H) and 7.24 (1 H, d, *J* 8.6, 1-H); δ_C(50 MHz) 209.7 (s, C-17^2), 157.6 (s, C-3), 137.6 (s, C-5), 132.4 (s, C-10), 126.5 (d, C-1), 113.5 (d, C-4), 111.8 (d, C-2), 81.2 (s, C-17), 55.2 (q, 3-OMe), 53.4 (t, C-17^1), 50.6 (t, C-17^3), 45.9 and 45.2 (each s, C-13 and C-14), 42.0 (d, C-8), 37.5 (d, C-9), 34.9 (t, C-16), 30.3 (t, C-6), 28.9 (t, C-12), 26.0 (t, C-15), 25.8 (t, C-11), 23.3 (t, C-7) and 13.5 (q, C-18).

Hydride reduction of the 17^2-ketone 57

The ketone **57** (200 mg, 0.59 mmol) was treated with LAH (111 mg, 2.9 mmol) in THF (14 cm^3) at 0 °C for 1 h. Excess of reagent was destroyed by addition of saturated aq. NH_4Cl to the mixture which was then concentrated under reduced pressure. Extraction with EtOAc and work-up gave the product as a colourless oil (200 mg), which was adsorbed on silica gel (20 g). Elution with EtOAc–toluene (7:13) gave (17^{2}R)-3-*methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*triene*-17α,17^2-*diol* **58** (70 mg, 35%), mp 179–182 °C (from $CHCl_3$–hexane); $[\alpha]_D$ +9 (*c* 1.0 in $CHCl_3$) (Found: C, 77.3; H, 9.0%; M^+, 342. $C_{22}H_{30}O_3$ requires C, 77.2; H, 8.8%; *M*, 342); ν_{max}/cm^{-1} 3602; δ_H(200 MHz) 0.82 (3 H, s, 13β-Me), 2.55–2.69 (1 H, m, 9α-H), 2.76–2.85 (2 H, m, 6-H$_2$), 3.77 (3 H, s, 3-OMe), 4.27 (1 H, t, *J* 2 × 6.2, 17^2-H), 6.62 (1 H, d, *J* 2.8, 4-H), 6.72 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.23 (1 H, d, *J* 8.6, 1-H); δ_C(50 MHz) 157.5 (s, C-3), 137.9 (s, C-5), 133.4 (s, C-10), 126.4 (d, C-1), 113.5 (d, C-4), 111.6 (d, C-2), 80.8 (s, C-17), 66.3 (d, C-17^2), 55.2 (q, 3-OMe), 48.4 and 46.2 (each s, C-13 and C-14), 44.4 (t, C-17^1), 42.2 (d, C-8), 41.0 (t, C-17^3), 36.9 (d, C-9), 34.0 (t, C-16), 30.5 (t, C-6), 28.6 (t, C-12), 25.9 (t, C-15), 24.6 (t, C-11), 23.5 (t, C-7) and 13.5 (q, C-18); followed by (17^{2}S)-3-*methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*triene*-17α,17^2-*diol* **59** (113 mg, 56%), mp 185–188 °C (from EtOAc); $[\alpha]_D$ +5 (*c* 1.0 in $CHCl_3$) (Found: C, 77.0; H, 8.95%; M^+, 342); ν_{max}/cm^{-1} 3601; δ_H(200 MHz) 0.97 (3 H, s, 13β-Me), 2.32 (1 H, dq, *J* 13.2 and 3 × 4.0, 11α-H), 2.53–2.66 (1 H, m, 9α-H), 2.77–2.85 (2 H, m, 6-H$_2$), 3.77 (3 H, s, 3-OMe), 4.04 (1 H, tt, *J* 2 × 10.5 and 2 × 7.4, 17^2-H), 6.62 (1 H, d, *J* 2.8, 4-H), 6.72 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.22 (1 H, d, *J* 8.6, 1-H); δ_C(50 MHz) 157.5 (s, C-3), 137.9 (s, C-5), 133.3 (s, C-10), 126.3 (d, C-1), 113.5 (d, C-4), 111.6 (d, C-2), 81.0 (s, C-17), 66.0 (d, C-17^2), 55.2 (q, 3-OMe), 45.9 and 45.1 (each s, C-13 and C-14), 44.1 (t, C-17^1), 41.6 (d, C-8), 40.0 (t, C-17^3), 37.3 (d, C-9), 34.3 (t, C-16), 30.5 (t, C-6), 28.8 (t, C-12), 25.8 (t, C-15), 25.2 (t, C-11), 23.8 (t, C-7) and 13.7 (q, C-18).

3-Demethylation (DIBAH–toluene, heat, 41 h) of compound **58** gave the corresponding (17^{2}R)-3,17α,17^2-*triol* **60**, mp 277–280 °C (from EtOAc); $[\alpha]_D$ −21 (*c* 1.0 in pyridine) (Found: C, 76.6; H, 8.6%; M^+, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%, *M*, 328).

Similarly, compound **59** was converted into the (17^{2}S)-3,17α,17^2-*triol* **61**, mp 251–253 °C (from Me_2CO–hexane); $[\alpha]_D$ −2 (*c* 0.5 in pyridine) (Found: C, 77.1; H, 8.5%; M^+, 328).

3-Methoxy-14,17β-propano-14β-estra-1,3,5(10)-trien-17α-ol 63

The 17^2-ketone **57** (100 mg, 0.29 mmol) in dichloromethane (4 cm^3) was added to vigorously stirred ethane-1,2-dithiol (0.1 cm^3, 1.2 mmol) and zinc trifluoromethanesulfonate (210 mg, 0.58 mmol) in dichloromethane (4 cm^3) at 20 °C under nitrogen. After 3.5 h at 20 °C, the mixture was treated with saturated aq. $NaHCO_3$ and the product was isolated by extraction with $CHCl_3$. Work-up gave a foam (132 mg) which was

adsorbed on silica gel (13 g). Elution with EtOAc–toluene (1:9) gave the 17²,17²-*ethylenedithio compound* **62** (102 mg, 85%), mp 86–90 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +8 (*c* 1.0 in $CHCl_3$) (Found: M^+, 416.184. $C_{24}H_{32}O_2S_2$ requires *M*, 416.184); ν_{max}/cm^{-1} 3598; δ_H(200 MHz) 0.94 (3 H, s, 13β-Me), 2.16 and 2.46 (each 1 H, d, *J* 14.9, 17³-H_2), 2.34 and 2.7 (each 1 H, d, *J* 13.9, 17¹-H_2), 2.78–2.83 (2 H, m, 6-H_2), 3.24–3.46 (4 H, m, SCH_2-CH_2S), 3.77 (3 H, s, 3-OMe), 6.62 (1 H, d, *J* 2.8, 4-H), 6.74 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.24 (1 H, d, *J* 8.6, 1-H).

A mixture of the thioketal **62** (268 mg, 0.64 mmol) and Raney nickel (~1 g) in ethanol (10 cm^3) was refluxed with vigorous stirring under nitrogen. After 3 h, the mixture was filtered, and the filtrate was evaporated under reduced pressure to give the 14β,17β-*propano compound* **63** (199 mg, 95%), mp 155–156 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +8 (*c* 1.0 in $CHCl_3$) (Found: C, 81.1; H, 9.4%; M^+, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; *M*, 326); ν_{max}/cm^{-1} 3596; δ_H(200 MHz) 0.91 (3 H, s, 13β-Me), 2.31 (1 H, dq, *J* 12.6 and 3 × 3.6, 11α-H), 2.6 (1 H, br td, *J* 2 × 11.3 and 3.6, 9α-H), 2.76–2.83 (2 H, m, 6-H_2), 3.77 (3 H, s, 3-OMe), 6.62 (1 H, d, *J* 2.7, 4-H), 6.72 (1 H, dd, *J* 8.6 and 2.7, 2-H) and 7.24 (1 H, d, *J* 8.6, 1-H); δ_C(50 MHz) 157.4 (s, C-3), 138.0 (s, C-5), 133.6 (s, C-10), 126.3 (d, C-1), 113.4 (d, C-4), 111.4 (d, C-2), 82.0 (s, C-17), 55.2 (q, 3-OMe), 46.9 and 45.2 (each s, C-13 and C-14), 41.9 (d, C-8), 37.5 (d, C-9), 34.5 (t, C-16), 34.2 (t, C-17¹), 30.6 (t, C-12), 30.2 (t, C-6), 29.2 (t, C-17³), 25.9 (t, C-15), 25.2 (t, C-11), 23.7 (t, C-7), 18.8 (t, C-17²) and 13.4 (q, C-18).

3-Demethylation (DIBAH–toluene, heat, 24 h) of compound **63** gave the corresponding 3,17α-*diol* **64**, mp 270–271 °C (from EtOAc); $[\alpha]_D$ +9 (*c* 1.0 in THF) (Found: C, 80.5; H, 9.0%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; *M*, 312).

Preparation of the 14β,17β-propeno compounds 66 and 67

A stirred solution of the 17²-ketone **57** (50 mg, 0.15 mmol) in THF (5 cm^3) at 20 °C under nitrogen was treated with toluene-*p*-sulfonohydrazide (81 mg, 0.45 mmol) and trifluoroacetic acid (0.016 cm^3). After 16 h at 20 °C, saturated aq. $NaHCO_3$ was added to the mixture and the product (149 mg) was isolated by extraction with chloroform. Work-up and chromatography of the residue on silica gel (15 g) with EtOAc–toluene (3:7) as eluent gave the 17²-*toluene*-p-*sulfonylhydrazone* **65** as separable *syn*- and *anti*-isomers: isomer *a* (49 mg, 64%), mp 154–158 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ −3 (*c* 1.0 in $CHCl_3$) (Found: M^+, 508.238. $C_{29}H_{36}N_2O_4S$ requires *M*, 508.239); ν_{max}/cm^{-1} 3599, 3290, 3216, 1336 and 1162; δ_H(200 MHz) 0.85 (3 H, s, 13β-Me), 2.41 (3 H, s, 4′-Me), 2.72–2.82 (2 H, m, 6-H_2), 3.75 (3 H, s, 3-OMe), 6.59 (1 H, d, *J* 2.0, 4-H), 6.69 (1 H, dd, *J* 8.6 and 2.0, 2-H), 7.18 (1 H, d, *J* 8.6, 1-H), 7.3 (2 H, d, *J* 8.2, 3′- and 5′-H) and 7.79 (2 H, d, *J* 8.2, 2′- and 6′-H); isomer *b* (27 mg, 36%), mp 177–180 °C (from Me_2CO–hexane); $[\alpha]_D$ −24 (*c* 1.0 in $CHCl_3$) (Found: M^+, 508.239); ν_{max}/cm^{-1} 3599, 3292, 3201, 1336 and 1163; δ_H(200 MHz) 0.89 (3 H, s, 13β-Me), 2.42 (3 H, s, 4′-Me), 2.75–2.85 (2 H, m, 6-H_2), 3.76 (3 H, s, 3-OMe), 6.61 (1 H, d, *J* 2.9, 4-H), 6.71 (1 H, dd, *J* 8.6 and 2.9, 2-H), 7.21 (1 H, d, *J* 8.6, 1-H), 7.32 (2 H, d, *J* 8.2, 3′- and 5′-H) and 7.84 (2 H, d, *J* 8.2, 2′- and 6′-H).

The *syn/anti* mixture of compound **65** (76 mg, 0.15 mmol) was treated with butyllithium (1.5 mol dm^{-3} in hexane; 0.5 cm^3) in THF (5 cm^3) at 0 °C under nitrogen. After 1.5 h at 0 °C, the mixture was treated with further reagent (0.5 cm^3) and then kept at 0 °C for a further 1.5 h, whereupon the reaction was complete (TLC). After dilution with water to destroy excess reagent, the mixture was acidified and extracted with toluene. Work-up of the extract gave an oil (90 mg) which was chromatographed on silica gel (13.5 g) with EtOAc–toluene (1:9) to give 3-*methoxy*-14,17β-*prop*-17¹-*eno*-14β-*estra*-1,3,5(10)-*trien*-17α-*ol* **66** (15 mg, 31%), mp 112–114 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +2 (*c* 1.1 in $CHCl_3$) (Found: M^+, 324.209. $C_{22}H_{28}O_2$ requires *M*, 324.209); ν_{max}/cm^{-1} 3600; δ_H(200 MHz) 0.94 (3 H, d, *J* 0.6, 13β-Me), 2.18 (1 H, ddd, *J* 17.8, 3.9 and 1.5, 17³-H), 2.34 (1 H, dq, *J* 12.9 and 3 × 3.5, 11α-H), 2.46–2.61 (1 H, br td, 9α-H), 2.76–2.85 (1 H, m, 6-H_2), 3.77 (3 H, s, 3-OMe), 5.5 (1 H, ddd, *J* 9.8, 3.9 and 2.6, 17²-H), 5.75 (1 H, ddd, *J* 9.8, 2.3 and 1.5, 17¹-H), 6.62 (1 H, d, *J* 2.8, 4-H), 6.72 (1 H, dd, *J* 8.5 and 2.8, 2-H) and 7.24 (1 H, d, *J* 8.5, 1-H); δ_C(50 MHz) 157.5 (s, C-3), 137.9 (s, C-5), 136.9 (d, C-17¹), 133.0 (s, C-10), 126.6 (d, C-1), 123.8 (d, C-17²), 113.5 (d, C-4), 111.7 (d, C-2), 82.3 (s, C-17), 55.2 (q, 3-OMe), 46.0 and 44.5 (each s, C-13 and C-14), 42.8 (d, C-8), 40.0 (t, C-16), 38.6 (t, C-17³), 37.8 (d, C-9), 30.6 (t, C-6), 29.2 (t, C-12), 27.1 (t, C-15), 26.4 (t, C-11), 22.8 (t, C-7) and 14.0 (q, C-18).

Further elution gave 3-*methoxy*-14,17β-*prop*-17²-*eno*-14β-*estra*-1,3,5(10)-*trien*-17α-*ol* **67** (12 mg, 25%), mp 127–130 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ −46 (*c* 0.8 in $CHCl_3$) (Found: M^+, 324.209); ν_{max}/cm^{-1} 3600; δ_H(200 MHz) 0.91 (3 H, s, 13β-Me), 2.59–2.72 (1 H, m, 9α-H), 2.82–2.88 (2 H, m, 6-H_2), 3.77 (3 H, s, 3-OMe), 5.51 (1 H, ddd, *J* 9.6, 3.8 and 2.7, 17²-H), 5.88 (1 H, ddd, *J* 9.6, 2.2 and 2.0, 17³-H), 6.63 (1 H, d, *J* 2.7, 4-H), 6.72 (1 H, dd, *J* 8.6 and 2.7, 2-H) and 7.24 (1 H, d, *J* 8.6, 1-H); δ_C(50 MHz) 157.5 (s, C-3), 137.9 (s, C-5), 135.6 (d, C-17³), 133.3 (s, C-10), 126.2 (d, C-1), 123.6 (d, C-17²), 113.6 (d, C-4), 111.5 (d, C-2), 81.7 (s, C-17), 55.2 (q, 3-OMe), 49.6 (s, C-14), 44.7 (s, C-13), 42.5 (t, C-17¹), 38.9 (d, C-8), 37.4 (d, C-9), 36.3 (t, C-16), 30.5 (t, C-6), 30.3 (t, C-15), 27.8 (t, C-12), 25.6 (t, C-11), 23.8 (t, C-7) and 13.2 (q, C-18).

3-Demethylation (DIBAH–toluene, heat, 25 h) of compound **66** gave the corresponding 3,17α-*diol* **68**, mp 263–264 °C (from EtOAc); $[\alpha]_D$ +5 (*c* 0.4 in pyridine) (Found: C, 81.0; H, 8.5%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.25; H, 8.4%; *M*, 310).

Similarly, compound **67** was converted into the 3,17α-*diol* **69**, mp 273–274 °C (from EtOAc); $[\alpha]_D$ −57 (*c* 0.5 in pyridine) (Found: C, 81.0; H, 8.5%, M^+, 310).

14-Formylethyl-3-methoxy-14β-estra-1,3,5(10)-trien-17-one 70

Borane–dimethyl sulfide (2.5 cm^3, 26 mmol) was added to a stirred solution of the 14β-allyl 17-ketone **54** (1.2 g, 3.7 mmol) in THF (90 cm^3) at 20 °C under nitrogen. The solution was refluxed for 2 h, cooled to 0 °C and treated successively with aq. sodium hydroxide (6 mol dm^{-3}, 8 cm^3) and hydrogen peroxide (30%; 6 cm^3) and then kept at 40 °C for 12 h. The mixture was concentrated under reduced pressure, diluted with water and the product was isolated as a crystalline solid (1.217 g) by extraction with ethyl acetate.

Dimethyl sulfoxide (1.5 cm^3, 18 mmol) in THF (5 cm^3) was added to a stirred solution of oxalyl chloride (0.9 cm^3, 9 mmol) in THF (21 cm^3) at −78 °C under nitrogen. After 2 min, the hydroboration product (317 mg, 0.9 mmol) in THF (21 cm^3) was added over 5 min to the mixture which was then stirred at −78 °C for 45 min. Triethylamine (5.1 cm^3, 36 mmol) was added to the mixture which was then stirred at −78 °C for 5 min before being allowed to warm to 20 °C. The mixture was concentrated under reduced pressure, diluted with water, and the product (310 mg) was isolated by extraction with CH_2Cl_2. Work-up followed by flash chromatography on silica gel (31 g) with EtOAc–toluene (3:17) as eluent gave the 14β-formylethyl compound **70** as a colourless oil (220 mg, 70%) (Found: M^+, 340.203. $C_{22}H_{28}O_3$ requires *M*, 340.204); ν_{max}/cm^{-1} 1726br; δ_H(200 MHz) 1.04 (3 H, s, 13β-Me), 2.82–2.9 (2 H, m, 6-H_2), 3.78 (3 H, s, 3-OMe), 6.64 (H, d, *J* 2.7, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.7, 2-H), 7.2 (1 H, d, *J* 8.6, 1-H) and 9.74 (1 H, t, *J* 2 × 1.2, CHO).

Intramolecular reductive coupling of the 14β-formylethyl 17-ketone 70

A mixture of $TiCl_3$·$(DME)_{1.5}$ (4.57 g, 13.7 mmol) and zinc–copper couple (2.66 g, 41 mmol) in freshly distilled dimethoxyethane (DME) (100 cm^3) was refluxed with vigorous stirring for 1.5 h. The resultant black suspension was cooled to 0 °C and compound **70** (310 mg, 0.91 mmol) in DME (150 cm^3) was added to it over 10 min with stirring. The mixture was then allowed to warm to 20 °C. After 4 h at 20 °C, the reaction was

complete (TLC), and aq. K_2CO_3 (20%, 100 cm^3) was added to the mixture which was then stirred for 12 h. After concentration under reduced pressure, the mixture was diluted with water and the product was isolated by extraction with EtOAc. Work-up and crystallisation of the solid residue (295 mg) from EtOAc gave (17¹R)-3-*methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*triene*-17α,17¹-*diol* **71** (146 mg, 50%), mp 177–181 °C; $[\alpha]_D$ +18 (*c* 1.0 in THF) (Found: M^+, 342.217. $C_{22}H_{30}O_3$ requires *M*, 342.219); ν_{max}/cm^{-1} 3600 and 3450br; δ_H(200 MHz) 0.88 (3 H, s, 13β-Me), 2.31 (1 H, br dq, *J* 12.6 and 3 × 3.3, 11α-H), 2.6 (1 H, br td, *J* 2 × 10.8 and 3.1, 9α-H), 2.75–2.85 (2 H, m, 6-H_2), 3.77 (3 H, s, 3-OMe), 3.99 (1 H, t, *J* 2 × 8.0, 17¹-H), 6.61 (1 H, d, *J* 2.6, 4-H), 6.71 (1 H, dd, *J* 8.6 and 2.6, 2-H) and 7.23 (1 H, d, *J* 8.6, 1-H).

Chromatography of the mother-liquor residue on silica gel (16 g) with EtOAc–toluene (3:7) gave starting material **70** (23 mg) followed by (17¹S)-3-*methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*triene*-17α,17¹-*diol* **72** (14 mg, 4%), mp 184–187 °C (from EtOAc); $[\alpha]_D$ +21 (*c* 1.0 in THF) (Found: M^+, 342.217); δ_H(200 MHz) 1.13 (3 H, s, 13β-Me), 2.53–2.67 (1 H, m, 9α-H), 2.77–2.85 (2 H, m, 6-H_2), 3.77 (3 H, s, 3-OMe), 3.84 (1 H, obsc. d, *J* 6.2, 17¹-H), 6.62 (1 H, d, *J* 2.8, 4-H), 6.71 (1 H, dd, *J* 8.5 and 2.8, 2-H) and 7.23 (1 H, d, *J* 8.5, 1-H); and the (17¹*R*)-17α,17¹-diol **71** (10 mg, 3%).

3-Methoxy-14,17β-propano-14β-estra-1,3,5(10)-triene-17α,17¹-diol 17¹-acetates 73 and 74

(a) Treatment of the (17¹*R*)-17α,17¹-diol **71** with acetic anhydride in pyridine at 20 °C gave the corresponding 17¹-*acetate* **73**, mp 175–178 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +27 (*c* 1.0 in $CHCl_3$) (Found: C, 74.8; H, 8.3%; M^+, 384. $C_{24}H_{32}O_4$ requires C, 75.0; H, 8.4%; *M*, 384); ν_{max}/cm^{-1} 3591 and 1709; δ_H(200 MHz) 0.94 (3 H, s, 13β-Me), 2.09 (3 H, s, 17¹-OAc), 2.3 (1 H, dq, *J* 12.9 and 3 × 3.6, 11α-H), 2.59 (1 H, td, *J* 2 × 11.2 and 4.5, 9α-H), 2.76–2.84 (2 H, m, 6-H_2), 3.77 (3 H, s, 3-OMe), 5.32 (1 H, ddd, *J* 9.8, 6.8 and 1.8, 17¹-H), 6.61 (1 H, d, *J* 2.8, 4-H), 6.71 (1 H, dd, *J* 8.7 and 2.8, 2-H) and 7.23 (1 H, d, *J* 8.7, 1-H); δ_C(50 MHz) 172.0 (s, O*C*OMe), 157.5 (s, C-3), 137.8 (s, C-5), 133.3 (s, C-10), 126.4 (d, C-1), 113.5 (d, C-4), 111.5 (d, C-2), 83.2 (s, C-17), 75.4 (d, C-17¹), 55.2 (q, 3-OMe), 46.2 and 46.1 (each s, C-13 and C-14), 41.6 (d, C-8), 37.4 (d, C-9), 30.5 (t, C-6), 30.5 (t, C-16), 29.4 (t, C-12), 28.0 (t, C-17²), 25.7 (t, C-17³), 25.6 (t, C-15), 25.2 (t, C-11), 23.7 (t, C-7), 21.4 (q, 17¹-OCO*Me*) and 13.0 (q, C-18).

(b) Similarly prepared was the 17¹-*acetate* **74**, mp 181–184 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +36 (*c* 1.0 in $CHCl_3$) (Found: C, 75.2; H, 8.2%; M^+, 384); ν_{max}/cm^{-1} 3585 and 1727; δ_H(200 MHz) 1.08 (3 H, s, 13β-Me), 2.09 (3 H, s, 17¹-OAc), 2.28 (1 H, br dq, *J* 13.3 and 3 × 3.4, 11α-H), 2.62 (1 H, br td, *J* 2 × 10.7 and 3.8, 9α-H), 2.78–2.86 (2 H, m, 6-H_2), 3.78 (3 H, s, 3-OMe), 4.9 (1 H, d, *J* 5.5, 17¹-H), 6.62 (1 H, d, *J* 2.7, 4-H), 6.72 (1 H, dd, *J* 8.6 and 2.7, 2-H) and 7.24 (1 H, d, *J* 8.6, 1-H); δ_C(50 MHz) 171.7 (s, 17¹-O*C*OMe), 157.4 (s, C-3), 137.8 (s, C-5), 133.4 (s, C-10), 126.3 (d, C-1), 113.5 (d, C-4), 111.5 (d, C-2), 82.7 (s, C-17), 78.2 (d, C-17¹), 55.2 (q, 3-OMe), 46.7 (s, C-14), 45.2 (s, C-13), 41.2 (d, C-8), 37.3 (d, C-9), 33.4 (t, C-16), 30.5 (t, C-6), 29.5 (t, C-12), 27.8 (t, C-17³), 25.1 (t, C-15), 24.8 (t, C-11), 24.0 (t, C-17²), 23.7 (t, C-7), 21.5 (q, 17¹-OCO*Me*) and 14.5 (q, C-18).

14,17β-Propano-14β-estra-1,3,5(10)-triene-3,17β,17¹-triols 75 and 76

(a) 3-Demethylation (DIBAH–toluene, heat, 24 h) of the (17¹*R*)-17α,17¹-diol **71** gave the corresponding (17¹R)-3,17α,17¹-*triol* **75**, mp 269–270 °C (from EtOAc) (Found: C, 76.6; H, 8.8%; M^+, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%; *M*, 328).

(b) Similarly prepared was the (17¹S)-3,17α,17¹-*triol* **76**, mp 251–254 °C (from EtOAc) (Found: C, 77.0; H, 8.5%; M^+, 328).

17α-Hydroxy-3-methoxy-14,17β-propano-14β-estra-1,3,5(10)-trien-17¹-one 77

Dimethyl sulfoxide (0.5 cm^3, 6 mmol) in THF (1.4 cm^3) was added to a stirred solution of oxalyl chloride (0.3 cm^3, 3 mmol) in THF (7 cm^3) at −78 °C under nitrogen. After 2 min, the 17α,17¹-diol **71** (100 mg, 0.3 mmol) was added over 5 min to the mixture which was then stirred at −78 °C for 30 min. After this triethylamine (1.7 cm^3, 12 mmol) was added to the mixture which was then stirred at −78 °C for 5 min before being allowed to warm to 20 °C. The mixture was then diluted with water and extracted with EtOAc. Work-up of the extract gave a residue (360 mg) which was chromatographed on silica gel (15 g) with EtOAc–toluene (3:17) as eluent, to give the 17¹-*ketone* **77** (62 mg, 63%), mp 153–156 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +6 (*c* 1.0 in $CHCl_3$) (Found: C, 77.4; H, 8.4%; M^+, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; *M*, 340); ν_{max}/cm^{-1} 3480 and 1706; δ_H(400 MHz) 0.74 (3 H, s, 13β-Me), 1.8 (1 H, qd, *J* 3 × 10.3 and 4.1), 2.26 (1 H, tdd, *J* 2 × 13.3, 4.5 and 2.5), 2.36 (1 H, dq, *J* 13.4 and 3 × 3.8, 11α-H), 2.48 (1 H, ddd, *J* 17.1, 7.7 and 1.4, 17²-H_{exo}), 2.56 (1 H, m, *W* 38, 17²-H_{endo}), 2.65 (1 H, td, *J* 2 × 11 and 4.1, 9α-H), 2.82–2.88 (2 H, m, 6-H_2), 3.69 (1 H, s, exch. by D_2O, 17α-OH), 3.77 (3 H, s, 3-OMe), 6.62 (1 H, d, *J* 2.7, 4-H), 6.73 (1 H, dd, *J* 8.5 and 2.7, 2-H) and 7.23 (1 H, d, *J* 8.5, 1-H).

Hydride reduction of the 17¹-ketone 77

Treatment of compound **77** (113 mg, 0.33 mmol) in THF (8 cm^3) at 20 °C with LAH (63 mg, 1.66 mmol) for 45 min, followed by destruction of the excess of reagent with saturated aq. NH_4Cl, and extraction with EtOAc gave material (100 mg, 88%) which was crystallised from EtOAc to give the (17¹*S*)-17α,17¹-diol **72**.

(17¹*S*)-3-Methoxy-14,17β-prop-17²-eno-14β-estra-1,3,5(10)-triene-17α,17¹-diol 78

Sodium borohydride (74 mg, 1.95 mmol) was added to a stirred mixture of the enone **53** (219 mg, 0.65 mmol) and cerium(III) chloride heptahydrate (480 mg, 1.3 mmol) in methanol (10 cm^3) at 0 °C. After 45 min at 0 °C, the mixture was treated with saturated aq. $NaHCO_3$, and the product (208 mg) was isolated by extraction with EtOAc. Work-up of the extract and chromatography of the residue on silica gel (35 g) with EtOAc–hexane (7:13) as eluent gave the *diol* **78** (209 mg, 95%), mp 170–172 °C (from $CHCl_3$–hexane); $[\alpha]_D$ +19 (*c* 1.0 in $CHCl_3$) (Found: C, 77.6; H, 8.4%; M^+, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; *M*, 340); ν_{max}/cm^{-1} 3607 and 3542; δ_H(200 MHz) 0.94 (3 H, s, 13β-Me), 2.82–2.94 (2 H, m, 6-H_2), 3.76 (3 H, s, 3-OMe), 3.92 (1 H, dd, *J* 4.0 and 1.0, 17¹-H), 5.77 (1 H, dd, *J* 9.7 and 4.0, 17²-H), 6.14 (1 H, dd, *J* 9.7 and 1.0, 17³-H), 6.67 (1 H, d, *J* 2.8, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.17 (1 H, d, *J* 8.6, 1-H).

The derived (17¹S)-3,17α,17¹-*triol* **79** had mp 249–253 °C (from Me_2CO–hexane); $[\alpha]_D$ −28 (*c* 1.0 in pyridine) (Found: C, 76.9; H, 7.8%; M^+, 326. $C_{21}H_{26}O_3$ requires C, 77.3; H, 8.0%; *M*, 326).

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