Synthesis and structure–activity studies of 8α- and 9β-analogues of 14,17-ethanoestradiol

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Synthetic routes to the title compounds are described, commencing with readily available 19-norsteroid precursors. The reaction of 3-methoxy-8α-estra-1,3,5(10),14,16-pentaen-17-yl acetate **3** with phenyl vinyl sulfone at 150 °C proceeded in high yield, but with poor selectivity, to give a mixture of 14α,17-cycloadducts, which underwent convergent functional group modification, to furnish 14α,17α-ethano-8α-estradiol **13**. The feasibility of performing similar cycloaddition chemistry on analogous 9β-precursors was demonstrated, but the preferred synthetic route entailed configurational inversion at C-9, of 14α,17α-ethanoestradiol **25**, *via* moderately stereoselective hydrogenation of a 9,11-dehydro intermediate, leading to 14α,17α-ethano-9β-estradiol **32**. The estrogen receptor binding affinities of **13** and **32** are reported, and discussed in terms of superimpositional modelling on estradiol.

Introduction

The interpretation of structure–activity relationships in steroidal estrogens has been the subject of much attention in recent years,[1] and has been further stimulated by the first structural study of the receptor-bound complex of estradiol[2] and of molecular modelling approaches to predictive design of estradiol analogues.[3] The emerging picture of the hydrogen-bonded contacts and steric demand in the environment of ring D is of particular interest as an aid to our systematic study of the structure–activity patterns in estradiol analogues featuring ring D alkano bridges[4–6] and alkyl groups.[7] The highly competitive affinity of 14,17α-ethanoestra-1,3,5(10)-triene-3,17α-diol[8] toward the estradiol receptor invites speculation on the possible influence of 14,17-alkano bridges upon the estrogenicity of backbone-inverted analogues of estradiol. Previous studies have identified 8α-estradiol and some of its derivatives as moderately competitive estrogens[9] and, although 9β-estradiol displays negligible estrogenicity,[10a] surprisingly high levels of activity are found in a number of its functionally modified variants.[10b–d] Accordingly, the synthesis of the 14α,17α-ethano analogues of 8α- and 9β-estradiol was undertaken, in order to evaluate their affinity toward the estradiol receptor, and to explore the implications of these outcomes, in terms of comparative structural and conformational studies.

Results and discussion

8α-Series

8α-Estrone 3-methyl ether **1**[9a] was readily converted into the Δ^{15}-17-ketone **2** (100%), *via* conventional enol silylation–dehydrosilylation, and hence into the corresponding dienyl acetate **3** (78%) (Scheme 1). Treatment of **3** with phenyl vinyl sulfone (PVS) in benzene at 150 °C (sealed tube) resulted in slow formation (140 h) of a chromatographically homogeneous fraction (79%), estimated from preliminary NMR examination to comprise a ~1 : 1 : 3 mixture of the cycloadducts **4**–**6**. Fractional crystallisation of this material furnished a highly crystalline minor product **4**, which was more exhaustively characterised. Although the NMR chemical shifts and coupling constants of pertinent ring D protons did not yield unambiguous evidence for any one of eight possible isomers, a NOESY spectrum displayed cross-peaks consistent with the structure **4** (Fig. 1). The diagnostic enhancements are those between 17^2-H and 8α- and 9α-H, and between the vinylic 15- and 16-H and the 13β-methyl protons, which verified the α-face, *endo*-oriented presence of the dienophile-derived bridging elements, and the location of the $PhSO_2$ group at C-17^2.

Although no further structural information could be gleaned from the properties of the primary cycloaddition mixture, the additional components **5** and **6** were isolated during ensuing transformations of the mixture, and their structures similarly assigned with the aid of high-field NMR spectroscopy, including NOESY correlations (Fig. 1).

The foregoing cycloaddition finding poses some questions about the underlying factors leading to the observed pattern of stereo- and regio-selectivity. In contrast to the 'natural' series, in which cycloaddition of PVS to the corresponding dienyl acetate proceeds with exclusive β-face, *endo*- and head-to-head selectivity,[4] this result shows that retention of β-face selectivity is diminished (to ~80% of product), and accompanied by significant regioreversal (to 75% of β-face product), whilst the α-face addition is exclusively head-to-tail.

Alkaline treatment of the total cycloaddition product **4**–**6** furnished the expected product **7** (17%) arising from retrograde cleavage of the head-to-head component **5**, accompanied by an inseparable mixture of the 17-alcohols **8** and **9**, thus demonstrating the regiochemistry of their respective precursors. Furthermore, reacetylation of the mixture **8** + **9** gave the 17-acetates **4** and **6**, which were separated by fractional crystallisation, thereby enabling characterisation of the major cycloadduct **6**.

The primary purpose, of converting the cycloadducts **4**–**6** into the bridged estradiol analogue **13**, was not adversely influenced by the complexity of the cycloaddition reaction, since all of the products could be regarded as convergent precursors, through catalytic hydrogenation and desulfonylation. In fact, this sequence was first attempted. Catalytic hydrogenation of **4**–**6** in chloroform, in the presence of palladium on carbon, appeared to proceed readily at 60 °C/50 bar, but work-up of the reaction after 2 h, and chromatography of the product, revealed a remarkable chemodifferentiation, in that an inseparable mixture of dihydro products **10** and **11** (82%), clearly derived from the respective precursors **4** and **6**, was accompanied

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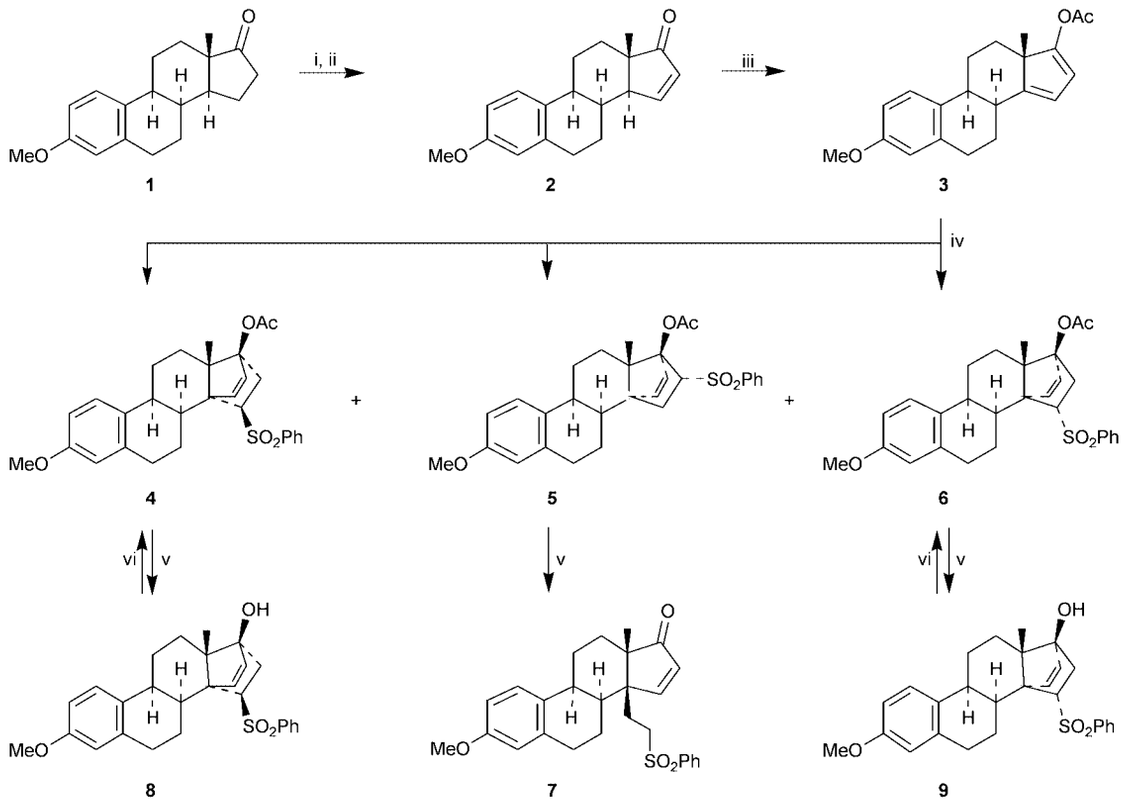


Scheme 1 *Reagents and conditions*: i, LDA , THF, −78 °C, then TMSCl; ii, $Pd(OAc)_2$, MeCN, reflux; iii, CH_2=CH(OAc)CH_3, Ac_2O, *p*-TsOH, reflux; iv, $C_6H_5SO_2CH$=CH_2, C_6H_6, 150 °C (sealed tube); v, KOH, MeOH, 25 °C; vi, Ac_2O, C_5H_5N, DMAP, 25 °C.

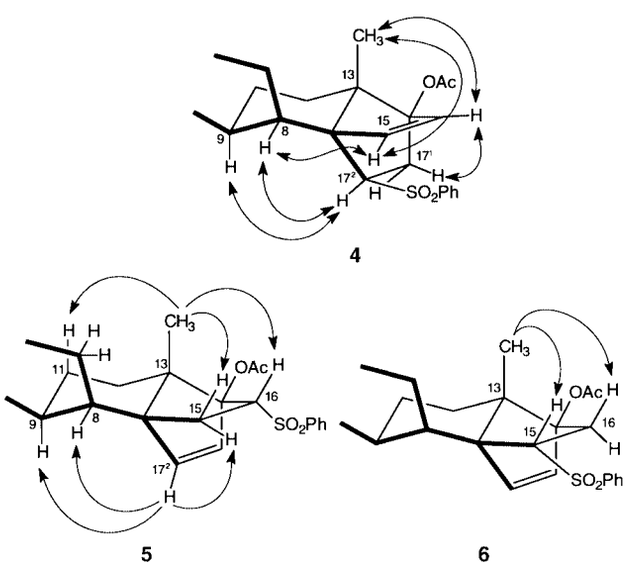


Fig. 1 Ring C/D region of the cycloadducts **4**–**6**, showing signal enhancements observed through cross-peaks in NOESY correlation spectra.

by unreacted **5** (18%) (Scheme 2). The cause of this chemoselectivity is not apparent, but it provided serendipitous access to pure **5**, thus enabling characterisation of each constituent of the chromatographically inseparable, primary cycloaddition products.

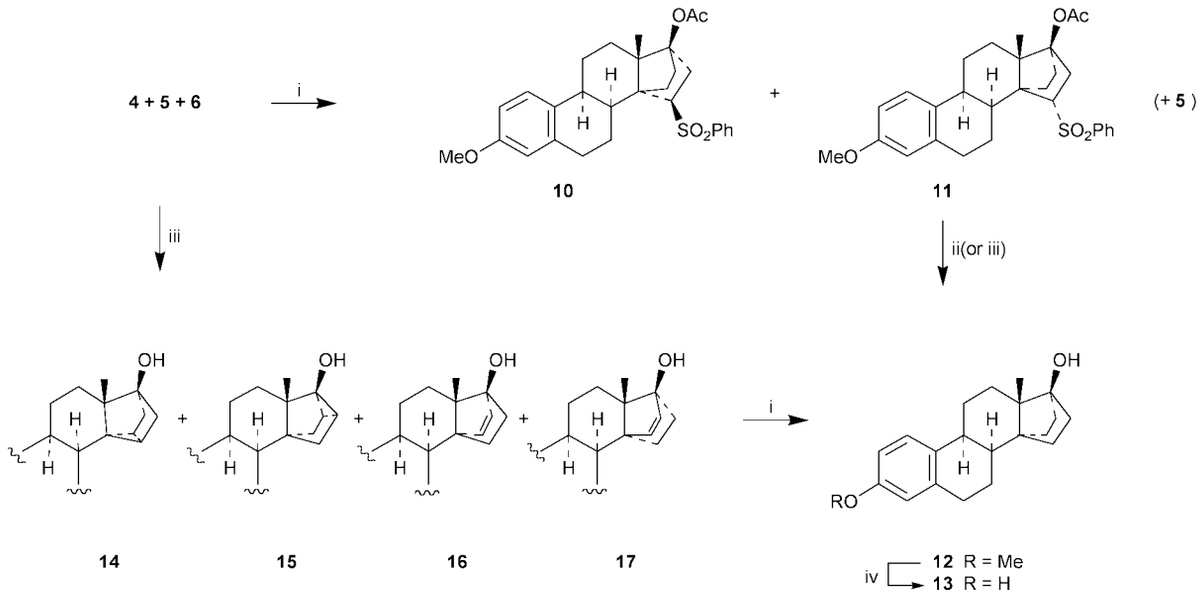
The dihydro mixture **10** + **11** was smoothly desulfonylated with samarium(II) iodide–HMPA,[11] and subsequent alkaline hydrolysis gave **12** (78%), which was deprotected at C-3 to give 14,17α-ethano-8α-estra-1,3,5(10)-triene-3,17β-diol **13**. The overall conversion efficiency for **3**→**13** is ~41%, but there is scope for optimisation of certain steps.

Among the preliminary experiments directed toward this goal, attempted desulfonylation of the dihydro mixture **10** + **11** with sodium–liquid ammonia had the virtue of achieving concomitant bridgehead hydrolysis, but gave a significantly reduced yield (53%) of the product **12**. In another experiment, reversal of the reduction sequence for the cycloaddition mixture proved to be unrewarding. In the first instance, desulfonylation of **4**–**6** gave a poor yield (36%) of an inseparable mixture comprising the expected 14,17-etheno compounds **16** and **17** (~50%), and the secondary products **14** and **15** (~50%) arising from olefinic bond participation during desulfonylation. This reaction outcome was inferred from catalytic hydrogenation of the mixture, to give the 14,17-ethano compound **12** (47%) and a mixture of **14** and **15** (52%), from which pure **14** was recovered by crystallisation, and characterised by comparison of spectroscopic properties with those of structurally related analogues.[4,5]

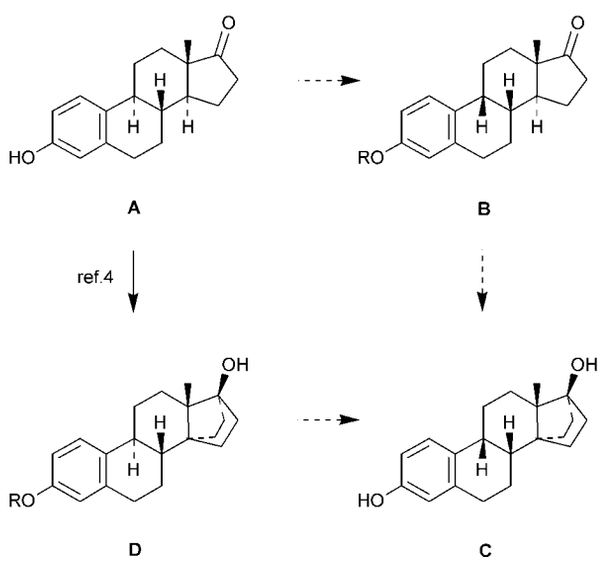
9β-Series

Two possible approaches to the synthesis of the 9β-analogue of 14α,17α-ethanoestradiol were considered (Scheme 3). In the first, the intention was to convert an estrone derivative **A** into an 11-oxo-9β-intermediate, using adaptations and variations of reported methods,[10c,12,13] and hence, to deoxygenate at C-11 to give the 9β-estrone analogue **B**. Subsequent elaboration of ring D functionality for cycloaddition mediated introduction of the 14,17-ethano bridge (leading to **C**) was expected to follow the precedent of the natural series (**A**→**D**). This approach has the additional advantage of affording scope for investigating cycloaddition mediated approaches to other, possibly bioactive ring D modified 9β-estradiols. Alternatively, formal configurational inversion of a 14α,17α-ethanoestradiol derivative **D** at C-9 would lead directly to the target system **C**.

Estrone 3-methyl ether was first converted into the 9β-11-ketone **18** (overall yield, 15%), following a described procedure.[12] Although attempted 11-deoxygenation of **18** failed, the derived 11α-alcohol was converted into the *S*-methyl 11α-dithiocarbonate **19**, which underwent Barton–McCombie deoxygenation[14] in modest yield to give, after 17-deprotection, the target compound **21** (28%). In an alternative approach,



Scheme 2 *Reagents and conditions*: i, Pd-C, H_2, $CHCl_3$; ii, SmI_2, HMPA, THF, −20 °C, then KOH, MeOH, 20 °C; iii, Na, NH_3, THF; iv, BBr_3, CH_2Cl_2, 0 °C.



Scheme 3 Inversion–cycloaddition (**A**→**B**→**C**) *vs.* cycloaddition–inversion (**A**→**D**→**C**) reaction pathways leading to 14α,17α-ethano-9β-estradiol.

estrone was dehydrogenated with DDQ, and the derived 17,17-ethylenedioxy compound was hydrogenated, to give 9β-estrone as the minor product (15%), and hence, the 3-methyl ether **21**.

Numerous variations in the foregoing reaction sequences were explored in attempts to improve the overall conversion to this key intermediate **21**, but to no avail. However, the remaining steps toward constructing the 14,17-bridged system proceeded satisfactorily. Thus, **21** was dehydrogenated *via* silyl enol ether formation and dehydrosilylation, to give the Δ^{15}-17-ketone **22** (52%). The derived dienyl acetate **23** was treated with phenyl vinyl sulfone in benzene at 140 °C (sealed tube) for 48 h, to give a product (73%) comprising of a mixture of cycloadducts (~7:1, by NMR), from which the major component was partially separated by careful chromatography. NMR data were consistent with the structure **24**.

Although these experiments demonstrated the feasibility of accessing the target compound *via* this reaction pathway, its practical implementation will necessitate a greatly improved synthetic route to the 9β-estrone derivative **21**. Accordingly, the alternative approach, *via* 9-inversion of 14,17-ethanoestradiol derivatives, was examined. It was expected that the critical step would entail efficient introduction of central ring unsaturation, since the presence of a 14α,17α-ethano bridge was likely to facilitate β-face stereoselectivity during hydrogenation of a $\Delta^{9(11)}$- or Δ^{8}-bond.

Treatment of 14α,17α-ethanoestradiol **25** with DDQ in methanol at 25 °C followed by acetylation (Ac_2O–DMAP, 25 °C) of the reaction product gave an inseparable mixture (65%) comprising a ~2:1 mixture of the $\Delta^{9(11)}$ compound **28** and the diacetate **26** of starting material. Similar treatment of the 3-methyl ether **27** gave a less favourable ~1:1 mixture of the desired product **29** and starting material, and an attempt to apply more forcing conditions (DDQ–*p*-TsOH, reflux) resulted in exhaustive dehydrogenation to give the hexaene **30**.

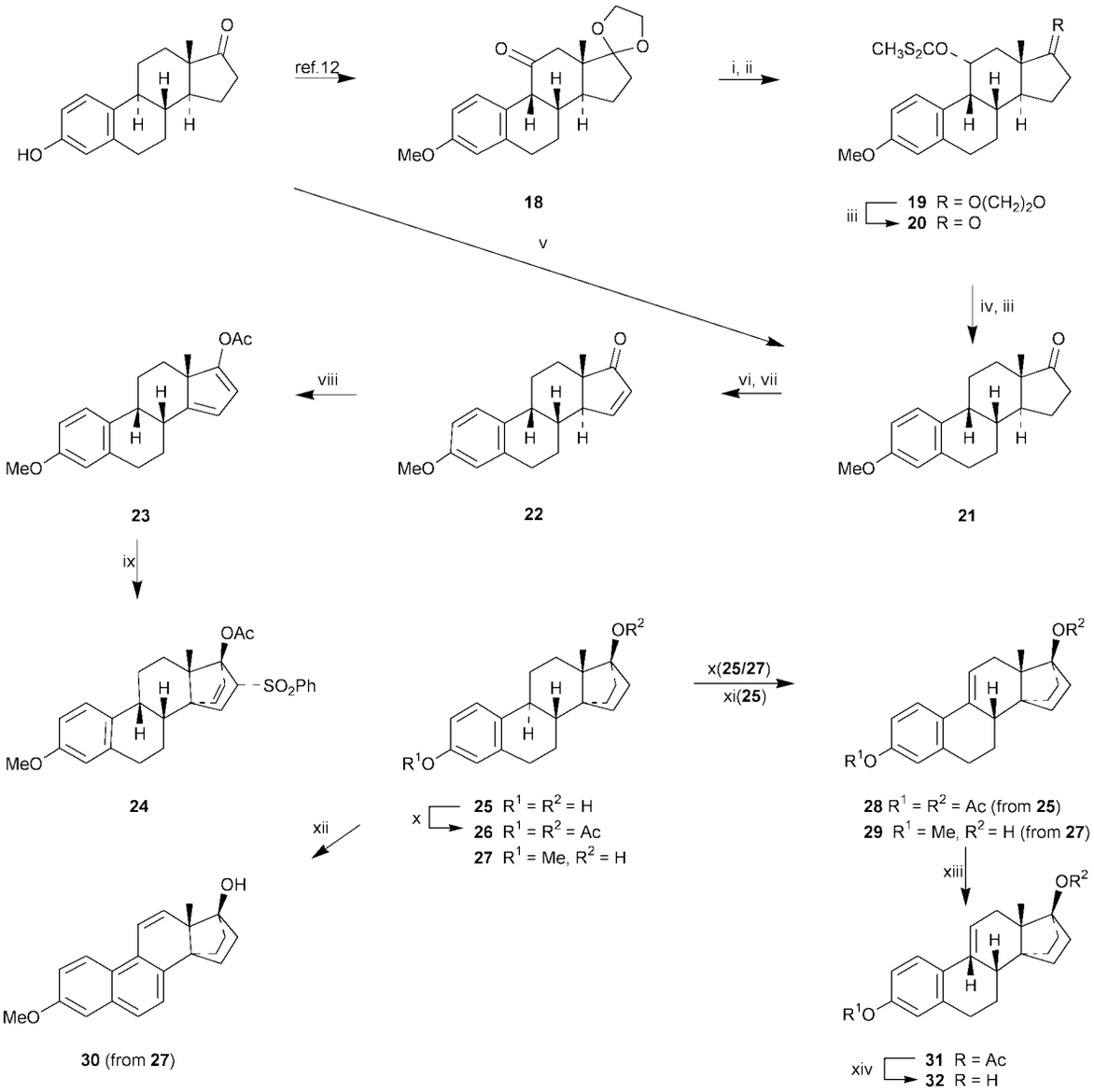
Catalytic hydrogenation of the mixture of **26** + **28** gave a separable mixture (~5:2) of **26** and **31**, implying that the reduction of the $\Delta^{9(11)}$ component **28** proceeded with slight β-face selectivity. Alkaline hydrolysis of the diacetate **31** furnished 14,17α-ethano-9β-estra-1,3,5(10)-triene-3,17β-diol **32**.

Although the latter pathway to this target compound is clearly superior to the former, the overall efficiency is still compromised by the modest success of the dehydrogenation step and the marginally favourable stereoselectivity of reduction. Nevertheless, it provided ready access to material for biological evaluation and conformational analysis.

Structure–activity investigation

Competitive binding affinities of the bridged estradiol analogues **13** and **32**, toward the estradiol receptor [expressed as 'competition factor' (CF), the ratio of concentration of the test sample (c_{test}) to that of estradiol (c_{ref}) at 50% competition [15]] were determined in accordance with conventional protocols for uterine cytosol fractions, and revealed that the 8α-isomer **13** (CF 2.2) is a competitive estradiol mimic (by comparison with a CF value of unity for estradiol), where the 9β-isomer **32** (CF 7.9) displays relatively diminished competition. Studies on selectivity of the response toward the recently described estrogen receptor subtypes-α and -β [1c] are incomplete, but preliminary findings reveal little evidence of differentiation.

A first consideration, in search of a structure based rationalisation of these results, is the comparison of the degree of estradiol mimicry, expressed in the preferred conformations and steric demand of the analogue structures. The recent progress in understanding the nature of the ligand bound



Scheme 4 *Reagents and conditions*: i, $NaBH_4$, THF, H_2O, 20 °C; ii, NaH, Imidazole, THF, then CS_2 followed by MeI; iii, *p*-TsOH, Me_2CO, H_2O; iv, Bu_3SnH, AIBN, C_6H_5Me, reflux; v, (a) DDQ, MeOH, (b) $(CH_2OH)_2$, $(COOH)_2$, C_6H_6, reflux, (c) Pd-C, H_2, THF, (d) HCl, MeOH, H_2O, (e) Me_2SO_4, K_2CO_3, Me_2CO, H_2O; vi, LDA, THF, −78 °C, then TMSCl; vii, $Pd(OAc)_2$, MeCN, reflux; viii, CH_2=CH(OAc)CH_3, Ac_2O, *p*-TsOH, reflux; ix, $C_6H_5SO_2CH$=CH_2, C_6H_6, 140 °C (sealed tube); x, DDQ, MeOH; xi, Ac_2O, DMAP, C_5H_5N; xii, DDQ, *p*-TsOH, MeOH, reflux; xiii, R-Ni, H_2, THF–MeOH, 50 °C, 50 bar; xiv, KOH, MeOH.

receptor [1–3] provides scope for using this approach as a basis for determining the compatibility of the 14,17-ethano bridge with the binding domain, and hence, determining the influence of this feature, combined with backbone inversion, on bioactivity. A first approach entails determination of feasible conformations of **13** and **32**, and their superimposability on that of estradiol.

In the absence of X-ray crystallographic data on the compounds, the first resort was to examine the spectroscopic properties of appropriate derivatives for evidence of any preferred ground state conformations. In the 8α-series, the NMR data confirmed the inference drawn from molecular models that the ring system is conformationally quite rigid, and that a ring B half-chair, ring C chair conformation is fully reconcilable with observed couplings and NOE correlations. Similarly, these data in the 9β-series, furnished no evidence of significant deviation from a ring C chair conformation, despite the attendant α-face steric congestion imposed by the *cis* ring-junction. The latter observation is reminiscent of earlier findings on a 14α-methyl 9β-analogue of estradiol,[16] in which similar steric factors are present.

A conformational search was conducted on the respective hormone analogues to determine their respective, global minimum energy structures (Table 1), and confirmed that both the 8α- and 9β-isomers **13** and **32** adopt preferred ring B half-chair, ring C chair ($^7H_8$,$^8C_{12}$) conformations **13a** and **32a** respectively. In the case of the 9β-isomer **32**, three additional, higher energy conformations **32b**, **32c** and **32d** were also identified. The first of these, **32b**, entails the minimal energy-demand modification of ring B to a boat-like ($^{6,9}B$) conformation, whereas **32c** and **32d** reveal the more radical deformation of ring C to a twist ($^9T_{14}$) conformation.

The energy minimisation confirms that **13** is indeed conformationally rigid, despite the presence of a *cis* B,C-ring junction and, although a molecular dynamics simulation revealed that a transient $^{6,9}B$ conformation can be attained, it has no influence on the overall ground-state conformation. No ring C inversion could be detected during this simulation. By contrast, the relative steric energies of the two lower energy forms of the 9β-isomer **32a** and **32b** are very similar, and a molecular dynamics simulation demonstrated that the $^7H_8$ and $^{6,9}B$ states of ring B are readily interconvertible, and that the latter is

Table 1 Steric energies of discrete conformers of 14,17α-ethano-8α-estradiol **13** and 14,17α-ethano-9β-estradiol **32**, showing respective puckering parameters of rings B and C[a]

		Ring B				Ring C			
Compound	E (kcal mol^{-1})	Q/Å	φ	θ	Conf.	Q/Å	φ	θ	Conf.
8α-isomer **13a**	99.9	0.458	207.7	44.7	$^{7}H_{8}$	0.522	205.7	4.0	$^{8}C_{12}$
9β-isomer **32a**	93.0	0.439	200.8	44.8	$^{7}H_{8}$	0.542	259.4	6.9	$^{8}C_{12}$
32b	93.9	0.601	116.1	90.4	$^{6,9}B$	0.528	246.2	8.1	$^{8}C_{12}$
32c	98.2	0.434	57.2	130.0	E_{7}	0.680	267.6	88.4	$^{9}T_{14}$
32d	99.8	0.504	275.7	73.4	$^{7}S_{6}$	0.640	274.4	88.7	$^{9}T_{14}$

[a] Steric energies are represented by E, and puckering parameters by Q, φ and θ, and conformational descriptors are defined in accordance with described practice.[17]

relatively persistent. Although ring C retains its $^{8}C_{12}$ state more tenaciously in this simulation, conformational inversion to a $^{9}T_{14}$ state is nevertheless observed, implying that the higher energy flexible structures represented by **32c** and **32d** are attainable.

An initial approach to comparing these analogues with estradiol entailed superimpositions of the feasible conformers upon the energy minimised structure of the parent hormone. For this purpose, the ring A carbon atoms and the oxygen atoms at C-3 and C-17 were chosen as the elements for superimposition, using a root mean-square fitting protocol.

The 'fit' achieved by superimposing the minimum energy structure of the 8α-analogue **13a** upon estradiol (Fig. 2) revealed reasonably good overlap of the polar termini, with ring D and the ethano bridge occupying the space in the α-face region of estradiol. This region has been shown to be capable of accommodating sterically demanding hydrophobic structures without adversely influencing the ligand affinity for the estradiol receptor,[5,8] and provides a working hypothesis to explain the moderately high competition factor exhibited by **13**. The poor alignment of the central-ring elements in this superimposition suggests why the affinity is not more competitive with that of estradiol, and is probably responsible for inherently lower binding affinities in the 8α-series.[9] It is concluded therefore, that the 14,17-ethano bridge is not inimical to receptor binding in this series, although more comparative studies based upon definitive comparison of X-ray crystal structures would be required to substantiate this conclusion.

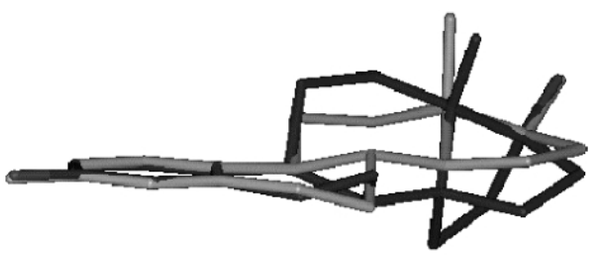


Fig. 2 Superimposition on estradiol (light), of the minimum-energy $^{7}H_{8}$,$^{8}C_{12}$-conformation **13a** of 14α,17α-ethano-8α-estradiol (dark).

In the case of the 9β-analogue **32**, the superimposition of the lower energy forms **32a** and **32b** on estradiol is extremely poor (Fig. 3). This result is unsurprising, given the profound influence of 9-inversion upon the overall conformation. However, consideration of the higher energy states, represented by the flexible conformers **32c** and **32d**, reveals that reasonable alignment of the polar termini with those of estradiol is possible, particularly in **32c**, despite the consequent intrusion of ring D and 14,17-ethano bridge elements into the ring D β-space of estradiol and some deviance in the central-ring superimposition (Fig. 3). The partial occupancy of α-space by the 14,17-ethano bridge in the conformer **32c** is compatible with the proven tolerance of the receptor toward steric demand in this region, but the very weak receptor binding affinity of the parent

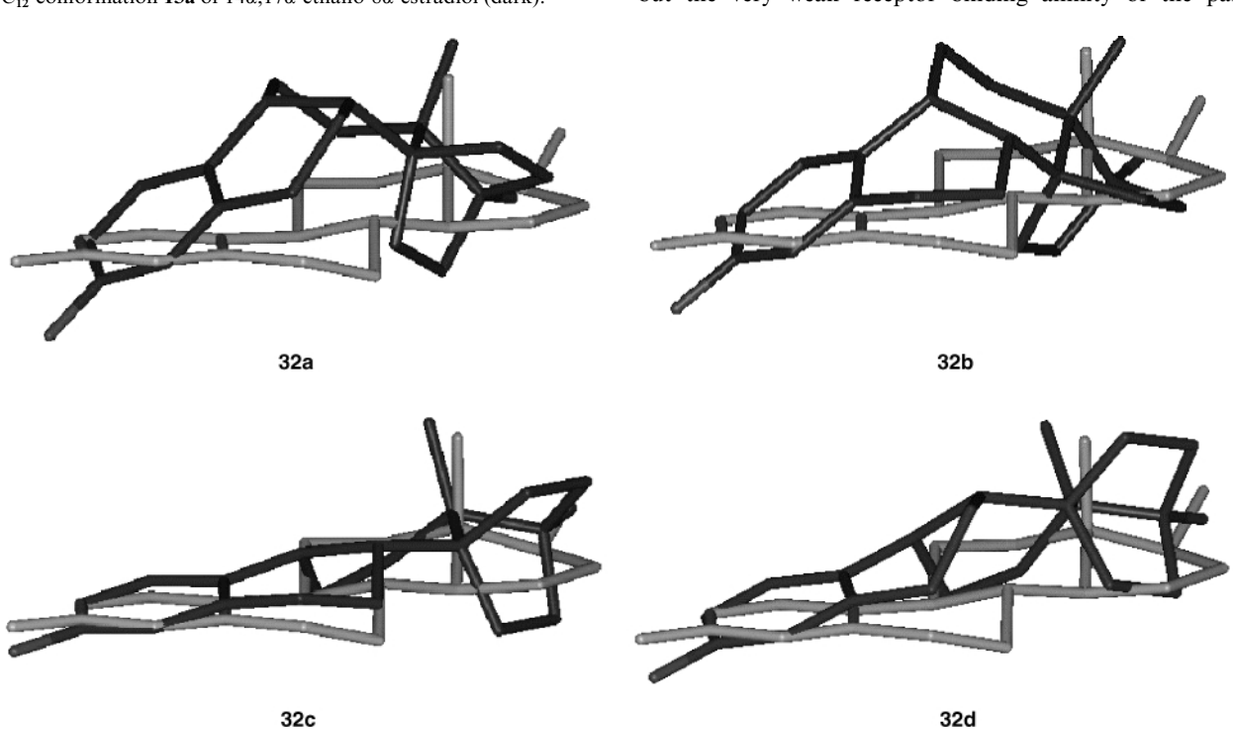


Fig. 3 Superimposition on estradiol (light), of 14α,17α-ethano-9β-estradiol (dark): (i) $^{7}H_{8}$,$^{8}C_{12}$-conformation **32a**; (ii) $^{6,9}B$,$^{8}C_{12}$-conformation **32b**; (iii) E_{7},$^{9}T_{14}$-conformation **32c**; (iv) $^{7}S_{6}$,$^{9}T_{14}$-conformation **32d**.

9β-estradiol precludes a meaningful interpretation of any binding contribution of this factor. Nevertheless, it is perhaps remarkable that the ethano analogue **32** reveals any affinity for the estradiol receptor, and suggests that the binding which is observed may be attributable to the adoption of a higher energy conformation during the interaction with the receptor. The attendant energy demand is feasible, given the energy release associated with receptor binding.[18] The alternative option, of a receptor–substrate interaction, in which **32** retains the ground state conformation, can conceivably be accommodated by the steric latitude of the binding domain above and below rings B and C, but at the cost of a proximal relationship, for hydrogen bonding contact, between the 17-hydroxy group and the histidine-524 residue of the receptor.[2]

Although the findings presented here, provide a basis for a working hypothesis of structure–activity in backbone-inverted analogues of 14α,17α-ethanoestradiol, it is evident that more refined modelling, based upon X-ray crystal structure data, are necessary to substantiate some of the provisional conclusions presented in this study.

Experimental

Mps were determined on a Reichert-Jung hot-stage microscope and are uncorrected. Unless otherwise stated, spectra were recorded as follows: IR, Perkin-Elmer 983 or Perkin-Elmer Paragon 1000, chloroform solutions; ^{1}H NMR, Varian VXR (200 MHz) or Varian Unity (400 MHz), deuteriochloroform solutions (*J* values in Hz; J_x refers to *exo*; J_n refers to *endo*); mass spectra, VG Micromass 16F (low resolution, electron impact) and VG-70E (accurate masses). 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 cm^2 g^{-1}. Microanalyses were determined using a Fisons EA 1108 instrument. Silica gel for chromatography refers to Merck Kieselgel 60, 63–200 μm (gravity) and 40–63 μm (flash).

Computational results were obtained using software programmes from Molecular Simulations Inc (San Diego, USA). Energy minimisations were performed using the CVFF force-field in the Discover® programme (version 2.9.8), applying a combination of steepest descents, conjugate gradient and Newton–Raphson minimisation techniques incorporated in the software, and superimpositions were similarly carried out with the aid of the 'superimpose' command in the software. Molecular dynamics simulations were performed using a constant volume, constant temperature (NVT) ensemble at 298 K with a Verlet leapfrog integrator and a 1 fs timestep. An initial 10 ps equilibration period was followed by a 100 ps data collection period in which structures were sampled every 50 fs.

3-Methoxy-8α-estra-1,3,5(10),15-tetraen-17-one 2

A solution of the 17-ketone **1** (800 mg, 2.8 mmol) in THF (20 cm^3) was added to a solution of lithium diisopropylamide [prepared from *n*-butyllithium (2.5 mol dm^{-3} in hexanes, 6 cm^3, 15 mmol) and diisopropylamine (2 cm^3, 15.3 mmol) in THF (10 cm^3)] at −78 °C and the mixture was stirred for 30 min. Chlorotrimethylsilane (1.9 cm^3, 15 mmol) was added and the mixture was stirred for 10 min and then allowed to warm up to 25 °C. Saturated aqueous ammonium chloride was added and the resultant mixture was extracted into ethyl acetate. The combined organic phase was washed (water), dried ($MgSO_4$) and concentrated under reduced pressure to give a residue (1.2 g) which was refluxed with palladium acetate (670 mg, 3 mmol) in acetonitrile (70 cm^3) for 1 h. The solids were filtered off, and the filtrate was evaporated under reduced pressure to give a solid residue (1.01 g) which was flash chromatographed on silica gel (75 g) with toluene as eluent to afford the *Δ^{15}-17-ketone* **2** (795 mg, 100%), mp 115–116 °C (from diisopropyl ether); $[\alpha]_D$ −39 (*c* 0.2) (Found: C, 81.0; H, 8.0%; M$^+$, 282. $C_{19}H_{22}O_2$ requires C, 80.8; H, 7.9%; *M*, 282); ν_{max}/cm^{-1} 1707 (C=O); δ_H (400 MHz) 1.24 (3H, s, 13β-Me), 2.41 (H, m, 8α-H), 2.66–2.85 (3H, m, 6-H$_2$ and 9α-H), 2.97 (1H, m, $W_{\frac{1}{2}}$ 8, 14α-H), 3.77 (3H, s, 3-OMe), 6.09 (1H, dd, *J* 6.0 and 3.4, 16-H), 6.61 (1H, d, *J* 2.7, 4-H), 6.73 (1H, dd, *J* 8.4 and 2.7, 2-H), 7.08 (1H, d, *J* 8.4, 1-H) and 7.59 (1H, ddd, *J* 6.0, 2.0 and 0.6, 15-H); δ_C (100 MHz) 22.8 (C-7), 23.3 (C-18), 28.5 (C-11), 30.3 (C-12), 31.6 (C-6), 37.8 (C-8), 40.8 (C-9), 52.0 (C-13), 54.0 (C-14), 55.2 (3-OMe), 112.3 (C-2), 113.5 (C-4), 130.1 (C-1), 131.9 (C-16), 132.9 (C-10), 137.4 (C-5), 157.5 (C-3), 160.4 (C-15) and 212.8 (C-17).

3-Methoxy-8α-estra-1,3,5(10),14,16-pentaen-17β-yl acetate 3

A solution of the Δ^{15}-17-ketone **2** (1.4 g, 4.9 mmol) and toluene-*p*-sulfonic acid (200 mg) in a mixture of isopropenyl acetate (15 cm^3) and acetic anhydride (15 cm^3) was heated under reflux for 2 h. The mixture was then poured into ice-water and stirred for 1.5 h, with the regular addition of solid sodium hydrogen carbonate until effervescence ceased. The resulting mixture was extracted into diethyl ether, and the extract was washed (satd. aq. $NaHCO_3$, water), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (1.5 g) which was flash chromatographed on silica gel (50 g), eluting with toluene–hexane (1 : 1), to give the *dienyl acetate* **3** (1.25 g, 78%), mp 107–110 °C (from methanol); $[\alpha]_D$ +108 (*c* 0.3) (Found: C, 77.9; H, 7.7%; M$^+$, 324. $C_{21}H_{24}O_3$ requires C, 77.7; H, 7.5%; *M*, 324); ν_{max}/cm^{-1} 1748 (C=O); δ_H (400 MHz) 1.21 (3H, s, 13β-Me), 1.94 (1H, dt, *J* 12.8 and 2 × 3.1, 12β-H), 2.21 (3H, s, 17-OAc), 2.61 (1H, dt, *J* 11.6 and 2 × 5.5, 9α-H), 2.79 (2H, m, 6-H$_2$), 2.94 (1H, ddd, *J* 13.3, 5.4 and 2.6, 8α-H), 3.77 (3H, s, 3-OMe), 5.98 (1H, d, *J* 3.0, 15-H), 6.08 (1H, d, *J* 3.0, 16-H), 6.62 (1H, d, *J* 2.6, 4-H), 6.71 (1H, dd, *J* 8.4 and 2.6, 2-H) and 7.02 (1H, d, *J* 8.4, 1-H).

Cycloaddition of dienyl acetate 3 with phenyl vinyl sulfone (PVS)

A mixture of the dienyl acetate **3** (400 mg, 1.23 mmol) and PVS (1 g, 5.95 mmol) in anhydrous benzene (10 cm^3) was heated at 150 °C for 140 h in a sealed tube. The cooled solution was adsorbed on silica gel (50 g) and eluted with ethyl acetate–toluene (1 : 9) to give unidentified products (144 mg), followed by an inseparable mixture of cycloadducts **4**, **5** and **6** (476 mg, 79%). Recrystallisation from chloroform–methanol afforded *(17^{2}R)-3-methoxy-17^2-phenylsulfonyl-14,17α-ethano-8α-estra-1,3,5(10),15-tetraen-17β-yl acetate* **4**, mp 286–287 °C; $[\alpha]_D$ +92 (*c* 0.4) (Found: C, 70.4; H, 6.6; S, 6.4%; M$^+$, 492. $C_{29}H_{32}O_5S$ requires C, 70.7; H, 6.5; S, 6.5%; *M*, 492); ν_{max}/cm^{-1} 1739 (C=O), 1318, 1147 (SO_2Ph); δ_H (400 MHz) 1.03 (3H, s, 13β-Me), 2.05 (3H, s, 17β-OAc), 2.14 (1H, dd, *J* 12.2 and 9.4, 17^1_x-H), 2.57 (1H, dd, *J* 12.2 and 4.3, 17^1_n-H), 2.79 (2H, m, 6-H$_2$), 3.09 (2H, m, 8α-H and 9α-H), 3.78 (3H, s, 3-OMe), 4.25 (1H, dd, *J* 9.4 and 4.3, 17^2_x-H), 6.33 (1H, d, *J* 6.0, 15-H), 6.40 (1H, d, *J* 6.0, 16-H), 6.62 (1H, d, *J* 2.8, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.8, 2-H), 7.04 (1H, d, *J* 8.4, 1-H), 7.50 (2H, m, *m*-H of $PhSO_2$), 7.58 (1H, m, *p*-H of $PhSO_2$) and 7.80 (2H, m, *o*-H of $PhSO_2$); δ_C (100 MHz) 16.9 (C-18), 21.3 (17-OCOCH$_3$), 22.6 (C-11), 27.2 (C-7), 28.1 (C-12), 31.1 (C-17^1), 31.3 (C-6), 34.6 (C-8), 35.4 (C-9), 55.2 (3-OMe), 60.3 (C-13), 61.1 (C-14), 66.3 (C-17^2), 92.4 (C-17), 112.4 (C-2), 113.2 (C-4), 128.1 (C-2′ and C-6′), 129.2 (C-3′ and C-5′), 130.4 (C-1), 132.5 (C-15), 132.7 (C-10), 133.3 (C-4′), 135.5 (C-16), 137.6 (C-5), 141.3 (C-1′), 157.6 (C-3) and 170.4 (17-O*C*OCH$_3$).

Base hydrolysis of cycloaddition mixture 4, 5 and 6

A solution of the mixture of cycloadducts **4** + **5** + **6** (55 mg, 0.11 mmol) in methanolic potassium hydroxide (1%; 5 cm^3) was stirred for 18 h at 25 °C. The mixture was poured into saturated aqueous sodium hydrogen carbonate (10 cm^3) and extracted into ethyl acetate. The combined organic phase was washed (water), dried ($MgSO_4$) and evaporated under reduced pressure

to give a crude residue (39 mg) which was chromatographed on silica gel (4.5 g), with ethyl acetate–toluene (1:9) as eluent, to give *3-methoxy-14-phenylsulfonylethyl-8α,14β-estra-1,3,5(10),15-tetraen-17-one* **7** (9 mg, 17%), as an oil, $[\alpha]_D$ +14 (*c* 0.8) (Found: M^+, 450.185. $C_{27}H_{30}O_4S$ requires *M*, 450.186); ν_{max}/cm^{-1} 1708 (C=O), 1307, 1152 (SO_2Ph); δ_H (200 MHz) 1.08 (3H, s, 13β-Me), 3.76 (3H, s, 3-OMe), 6.20 (1H, d, *J* 5.9, 16-H), 6.60 (1H, d, *J* 2.8, 4-H), 6.70 (1H, dd, *J* 8.4 and 2.8, 2-H), 6.92 (1H, d, *J* 8.4, 1-H) and 7.14–7.90 (6H, m, $PhSO_2$ and 15-H) followed by an inseparable mixture of *(17²R)-3-methoxy-17²-phenylsulfonyl-14,17α-ethanoestra-1,3,5(10),15-tetraen-17β-ol* **8** and *3-methoxy-15α-phenylsulfonyl-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol* **9** (33 mg, 66%) as an oil, *m/z* 450; ν_{max}/cm^{-1} 3599, 3412 (OH), 1307, 1148 (SO_2Ph); δ_H (400 MHz) for **9** (~70%) 0.95 (3H, s, 13β-Me), 3.76 (3H, s, 3-OMe), 4.00 (1H, dd, *J* 8.7 and 4.7, 15β-H), 5.96 (1H, d, *J* 5.9, 17²-H), 6.06 (1H, d, *J* 5.9, 17¹-H), 6.57 (1H, d, *J* 2.6, 4-H), 6.66–6.74 (1H, m, 2-H), 6.98 (1H, d, *J* 8.4, 1-H) and 7.48–7.88 (5H, m, 15α-SO_2Ph); δ_H (400 MHz) for **8** (~30%) 1.00 (1H, s, 13β-Me), 3.77 (3H, s, 3-OMe), 4.17 (1H, dd, *J* 7.8 and 5.4, 17²$_x$-H), 6.06 (1H, d, *J* 5.9, 15-H), 6.31 (1H, d, *J* 5.9, 16-H), 6.61 (1H, d, *J* 2.8, 4-H), 6.66–6.74 (1H, m, 2-H), 7.02 (1H, d, *J* 8.4, 1-H), 7.48–7.99 (5H, m, 17²$_n$-SO_2Ph).

(17²*R*)-3-Methoxy-17²-phenylsulfonyl-14,17α-ethano-8α-estra-1,3,5(10),15-tetraen-17β-ol 8

A solution of the 17β-acetate **4** (20 mg, 0.05 mmol) in methanolic potassium hydroxide (1%, 2 cm³) was stirred for 18 h at 25 °C. Work-up, as in the previous experiment, gave a crude residue (17 mg) which was chromatographed on silica gel (1.5 g) with ethyl acetate–hexane (1:1) as eluent to give the *17β-alcohol* **8** (13 mg, 73%) as an oil (Found: M^+, 450.185. $C_{27}H_{30}O_4S$ requires *M*, 450.186); ν_{max}/cm^{-1} 3599, 3412 (OH), 1306, 1148 (SO_2Ph); δ_H (400 MHz) 1.00 (3H, s, 13β-Me), 1.90 (1H, br s, 17β-OH), 3.77 (3H, s, 3-OMe), 4.17 (1H, dd, *J* 7.8 and 5.4, 17²$_x$-H), 6.06 (1H, d, *J* 5.9, 15-H), 6.31 (1H, d, *J* 5.9, 16-H), 6.61 (1H, d, *J* 2.8, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.8, 2-H), 7.02 (1H, d, *J* 8.6, 1-H) and 7.48–7.80 (5H, m, 17²$_n$-SO_2Ph).

Acetylation of the mixture of alcohols 8 and 9

The mixture of alcohols **8** + **9** (26 mg, 0.05 mmol) and 4-(dimethylamino)pyridine (DMAP) (5 mg) in pyridine (2 cm³) was stirred for 4 h at 25 °C. Saturated aqueous ammonium chloride was added and the resultant mixture was extracted into ethyl acetate. The combined organic phase was washed [aq. HCl (1 mol dm³), satd. aq. $NaHCO_3$, water, brine], dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (30 mg) which was chromatographed on silica gel (2 g), with ethyl acetate–toluene (1:19) as eluent, to give a mixture of the 17β-acetates **4** and **6** (25 mg; 88%). Recrystallisation from chloroform–methanol afforded 17β-acetate **4**, mp 285–287 °C. Evaporation of the mother liquor afforded *3-methoxy-15α-phenylsulfonyl-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate* **6** as an oil, $[\alpha]_D$ −1 (*c* 1.4) (Found: M^+, 492. $C_{29}H_{32}O_5S$ requires *M*, 492); ν_{max}/cm^{-1} 1739 (C=O), 1319, 1149 (SO_2Ph); δ_H (400 MHz) 1.00 (3H, s, 13β-Me), 2.05 (3H, s, 17β-OAc), 2.09 (1H, dd, *J* 12.3 and 9.0, 16β-H), 2.63 (1H, dd, *J* 12.3 and 4.8, 16α-H), 3.77 (3H, s, 3-OMe), 4.03 (1H, dd, *J* 9.0 and 4.8, 15β-H), 6.00 (1H, d, *J* 6.0, 17²-H), 6.37 (1H, d, *J* 6.0, 17¹-H), 6.59 (1H, d, *J* 2.7, 4-H), 6.70 (1H, dd, *J* 8.4 and 2.7, 2-H), 7.00 (1H, d, *J* 8.4, 1-H), 7.55 (2H, m, *m*-H of $PhSO_2$), 7.63 (1H, m, *p*-H of $PhSO_2$) and 7.88 (2H, m, *o*-H of $PhSO_2$).

Hydrogenation of the mixture of cycloadducts 4, 5 and 6

The mixture of cycloadducts **4** + **5** + **6** (460 mg, 0.9 mmol) was stirred with palladium on carbon (10%, 100 mg) in chloroform (10 cm³) under hydrogen (50 bar) at 60 °C for 5 h. The solution was filtered through Celite and the filtrate was evaporated under reduced pressure to give a solid residue (483 mg) which was adsorbed on silica gel (50 g). Elution with ethyl acetate–toluene (1:19) gave an inseparable mixture of (17²*R*)-3-methoxy-17²-phenylsulfonyl-14,17α-ethano-8α-estra-1,3,5(10)-trien-17β-yl acetate **10** and 3-methoxy-15α-phenylsulfonyl-14,17α-ethano-8α-estra-1,3,5(10)-trien-17β-yl acetate **11** (375 mg, 82%).

Recrystallisation from chloroform–methanol afforded **11**, mp 312–313 °C; $[\alpha]_D$ +7 (*c* 0.3) (Found: C, 70.0; H, 6.9; S, 6.3%; M^+, 494. $C_{29}H_{34}O_5S$ requires C, 70.4; H, 6.9; S, 6.5%; *M*, 494); ν_{max}/cm^{-1} 1734 (C=O), 1306, 1147 (SO_2Ph); δ_H (200 MHz) 1.01 (3H, s, 13β-Me), 2.00 (3H, s, 17β-OAc), 3.79 (3H, s, 3-OMe), 3.99 (1H, ddd, *J* 11.7, 4.3 and 2.4, 15β-H or 17²$_x$-H), 6.62 (1H, d, *J* 2.7, 4-H), 6.74 (1H, dd, *J* 8.5 and 2.7, 2-H), 7.06 (1H, d, *J* 8.5, 1-H), 7.58 (3H, m, *m*- and *p*-H of $PhSO_2$) and 7.88 (2H, m, *o*-H of $PhSO_2$). Further elution with ethyl acetate–toluene (1:19) gave *3-methoxy-16α-phenylsulfonyl-14,17α-etheno-8α-estra-1,3,5(10)-trien-17β-yl acetate* **5** (82 mg, 18%), mp 218–220 °C (from chloroform–methanol); $[\alpha]_D$ +22 (*c* 0.2) (Found: C, 70.8; H, 6.7; S, 6.3%; M^+, 492. $C_{29}H_{32}O_5S$ requires C, 70.7; H, 6.5; S, 6.5%; *M*, 492); ν_{max}/cm^{-1} 1746 (C=O), 1320, 1152 (SO_2Ph); δ_H (400 MHz) 0.91 (1H, dt, *J* 13.8 and 2 × 3.2, 12β-H), 0.95 (3H, s, 13β-Me), 1.44 (1H, qd, *J* 3 × 13.8 and 3.8, 11β-H), 1.63 (3H, s, 17β-OAc), 1.72 (1H, dd, *J* 12.6 and 4.6, 15α-H), 2.18 (1H, ddd, *J* 13.5, 4.6 and 2.4, 8α-H), 2.31 (1H, tdd, *J* 13.8, 2 × 4.2 and 0.8, 12α-H), 2.52 (1H, dd, *J* 12.6 and 9.0, 15β-H), 2.74 (2H, m, 6-H_2), 2.85 (1H, dt, *J* 12.6 and 2 × 4.2, 9α-H), 3.76 (3H, s, 3-OMe), 4.05 (1H, dd, *J* 9.0 and 4.6, 16β-H), 5.96 (1H, d, *J* 6, 17²-H), 6.43 (1H, d, *J* 6, 17¹-H), 6.60 (1H, d, *J* 2.6, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.6, 2-H), 7.00 (1H, d, *J* 8.6, 1-H), 7.62 (3H, m, *m*- and *p*-H of $PhSO_2$) and 7.91 (2H, m, *o*-H of $PhSO_2$); δ_C (100 MHz) 16.5 (13β-Me), 20.1 (C-7), 20.9 (17-OCO*C*H_3), 28.2 (C-11), 28.9 (C-15), 29.2 (C-12), 30.5 (C-6), 37.8 (C-8), 38.2 (C-9), 55.2 (3-OMe), 54.4 (C-13), 61.2 (C-14), 67.2 (C-16), 95.1 (C-17), 112.3 (C-2), 113.2 (C-4), 128.5 (C-2′ and C-6′), 129.1 (C-3′ and C-5′), 129.2 (C-17¹), 130.4 (C-1), 133.3 (C-4′), 133.4 (C-10), 136.3 (C-17²), 136.9 (C-5), 140.9 (C-1′), 157.6 (C-3) and 168.9 (17-O*C*OCH$_3$).

3-Methoxy-14,17α-ethano-8α-estra-1,3,5(10)-trien-17β-ol 12

(a) A solution of 1,2-diiodoethane (1.9 g, 6.8 mmol) in THF (68 cm³) was added slowly to samarium (1.1 g, 7.6 mmol) and the mixture was allowed to stir at 25 °C until a deep-blue solution was formed (~90 min). Hexamethylphosphoramide (HMPA) (5.5 cm³) was added and the mixture was stirred for 1 h at 25 °C to give a dark-purple solution which was cooled to −20 °C. A solution of the mixture of sulfones **10** +**11** (366 mg, 0.7 mmol) in THF (35 cm³) was added and the mixture was stirred at −20 °C for 4 h. Saturated aqueous ammonium chloride was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (water, saturated aq. $Na_2S_2O_3$, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (382 mg) which was chromatographed on silica gel (40 g), with ethyl acetate–toluene (1:19) as eluent, to give starting material (5 mg), preceded by a fraction (206 mg) which was stirred in a methanolic potassium hydroxide solution (1%, 10 cm³) for 18 h. The mixture was poured into water and extracted with ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a solid residue (181 mg) which was chromatographed on silica gel (20 g), with ethyl acetate–toluene (1:19) as eluent, to give *3-methoxy-14,17α-ethano-8α-estra-1,3,5(10)-trien-17β-ol* **12** (180 mg, 78%), mp 146–148 °C (from methanol); $[\alpha]_D$ −34 (*c* 0.3) (Found: C, 80.5; H, 9.1%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; *M*, 312); ν_{max}/cm^{-1} 3601, 3438br (OH); δ_H (200 MHz) 1.00 (3H, s, 13β-Me), 2.6–3.2 (3H, m, 6-H_2 and 9α-H), 3.78 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.8, 4-H), 6.74 (1H, dd, *J* 8.4 and 2.8, 2-H) and 7.08 (1H, d, *J* 8.4, 1-H).

(b) A solution of the sulfones **10** + **11** (320 mg, 0.65 mmol) in THF (10 cm^3) was added to a solution of sodium (700 mg, 30 mmol) in a mixture of ammonia (40 cm^3, freshly distilled from sodium) and THF (5 cm^3) at −33 °C. The resulting solution was stirred for 2 h at −33 °C. Solid ammonium chloride was added and the ammonia was allowed to evaporate. Water was added and the resulting mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a solid residue (133 mg) which was chromatographed on silica gel (13 g), eluting with ethyl acetate–toluene (1:19), to give compound **12** (108 mg, 53%), identical in all respects (mp and $[\alpha]_D$) to that synthesised previously.

14,17α-Ethano-8α-estra-1,3,5(10)-triene-3,17β-diol 13

A solution of boron tribromide (1.0 mol dm^{-3} in dichloromethane, 3 cm^3, 3 mmol) was added to a solution of the 3-methyl ether **12** (206 mg, 0.7 mmol) in dichloromethane (20 cm^3) at 0 °C and the mixture was stirred at 0 °C for 90 min. The mixture was poured into water and extracted with ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and concentrated under reduced pressure to give a residue (186 mg) which was adsorbed onto silica gel (18 g) and eluted with methanol–chloroform (1:9) to give the *3,17β-diol* **13** (160 mg, 81%), mp 248–249 °C (from methanol); $[\alpha]_D$ −34 (*c* 0.8 in THF) (Found: C, 80.5; H, 8.9%; M^+, 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.8%; *M*, 298); ν_{max}/cm^{-1} (in THF) 3442, 3320br (OH).

Desulfonylation of the mixture of phenyl vinyl sulfone cycloadducts 4, 5 and 6

A solution of the phenyl vinyl sulfone cycloadducts **4** + **5** + **6** (700 mg, 1.4 mmol) in THF (20 cm^3) was added to a solution of sodium (700 mg, 30 mmol) in a mixture of ammonia (40 cm^3; freshly distilled from sodium) and THF (5 cm^3) at −33 °C. The resulting mixture was stirred for 2 h at −33 °C. Solid ammonium chloride was added, and the ammonia was allowed to evaporate. Water was added and the resulting mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (616 mg). Chromatography on silica gel (60 g) with ethyl acetate–toluene (1:19) as eluent gave two unidentified fractions (50 and 12 mg), followed by an inseparable mixture of products **14**, **15**, **16** and **17** (157 mg, 36%), mp 83–85 °C (from methanol) (Found: C, 81.1; H, 8.7%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; *M*, 310); ν_{max}/cm^{-1} 3598 (OH); δ_H (200 MHz) 0.97 and 0.98 (each 3H, s, 13β-Me), 3.77 (3H, s, 3-OMe), 5.75 (0.5H, d, *J* 5.9), 5.90 (0.5H, d, *J* 5.9), 6.60 (1H, m, 4-H), 6.70 (1H, m, 2-H) and 7.01–7.05 (1H, m, 1-H).

Hydrogenation of the desulfonylation mixture 14, 15, 16 and 17

A solution of the mixture of products **14** + **15** + **16** + **17** (33 mg, 0.1 mmol) in ethyl acetate (2 cm^3) at 25 °C was stirred with palladium on carbon (10%, 3 mg) under hydrogen for 3 h. After filtration of the catalyst (Celite), evaporation of the filtrate gave a residue (34 mg) which was chromatographed on silica gel (5 g) with ethyl acetate–toluene (1:19) as eluent to give a mixture of compounds **14** and **15** (17 mg, 52%). Recrystallisation from methanol afforded *3-methoxy-15,17²-cyclo-14,17α-ethano-8α-estra-1,3,5(10)-trien-17β-yl acetate* **14**, mp 77–80 °C; $[\alpha]_D$ +2 (*c* 0.5) (Found: C, 81.1; H, 8.6%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; *M*, 310); ν_{max}/cm^{-1} 3596 (OH); δ_H (400 MHz) 0.76 (1H, dt, *J* 5.8 and 2 × 1.5, 17^2-H), 0.98 (3H, s, 13β-Me), 1.44 and 1.48 (each 1H, dd, *J* 9.7 and 1.5, 16α-H and 17^1_n-H), 1.81 and 1.90 (each 1H, dt, *J* 9.7 and 2 × 1.6, 16β-H and 17^1_x-H), 3.77 (3H, s, 3-OMe), 6.60 (1H, d, *J* 2.7, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.7, 2-H) and 7.06 (1H, d, *J* 8.4, 1-H). Further elution with the same solvent afforded 3-methoxy-14α,17α-ethano-8α-estra-1,3,5(10)-trien-17β-ol **12** (16 mg, 47%), mp 145–147 °C (from methanol).

S-Methyl *O*-(3-methoxy-11-oxo-9β-estra-1,3,5(10)-trien-11α-yl)dithiocarbonate 20

Sodium borohydride (500 mg, 12.5 mmol) was added to a solution of 17,17-ethylenedioxy-3-methoxy-9β-estra-1,3,5(10)-trien-11-one **18**[12] (465 mg, 1.4 mmol) in a mixture of THF (10 cm^3) and water (1 cm^3) and the mixture was stirred for 2 h. Water was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure. The crude 11α-alcohol (430 mg, 1.3 mmol), sodium hydride (0.5 g of a 60% suspension in mineral oil, 12.5 mmol) and imidazole (10 mg) were refluxed in THF (20 ml) for 90 min. Carbon disulfide (0.2 cm^3, 3 mmol) was added and the mixture was refluxed for 30 min, then methyl iodide (0.2 cm^3, 3 mmol) was added. The resulting mixture was refluxed for 30 min. Acetic acid (2 cm^3) was added to the cooled solution and the mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (826 mg) which was chromatographed on silica gel (50 g) with ethyl acetate–hexane (1:9) as eluent to give the *11α-dithiocarbonate* **19** (402 mg, 74%), as an oil, $[\alpha]_D$ +50 (*c* 0.3) (Found: M^+, 434. $C_{23}H_{30}O_4S_2$ requires *M*, 434); ν_{max}/cm^{-1} 1235, 1120, 1052 (C=S); δ_H (200 MHz) 1.09 (3H, s, 13β-Me), 2.56 (3H, s, 11α-OCS_2Me), 3.50 (1H, t, *J* 2 × 4.3, 9β-H), 3.75–3.9 (4H, m, 17,17-OCH_2CH_2O), 3.78 (3H, s, 3-OMe), (1H, dt, *J* 10.9 and 2 × 4.3, 11β-H), 6.63 (1H, d, *J* 2.7, 4-H), 6.73 (1H, dd, *J* 8.8 and 2.7, 2-H) and 7.61 (1H, d, *J* 8.8, 1-H). Treatment of a portion of this product with toluene-*p*-sulfonic acid in a mixture of acetone and water (7:1) at 25 °C for 22 h, followed by standard work-up, and chromatography of the residue on silica gel with ethyl acetate–toluene (1:19) as eluent gave the *17-ketone* **20** (85%), mp 152–154 °C (from acetone–hexane); $[\alpha]_D$ +161 (*c* 0.4) (Found: C, 64.9; H, 6.9; S, 16.4%; M^+, 390. $C_{21}H_{26}O_3S_2$ requires C, 64.6; H, 6.7; S, 16.4%; *M*, 390); ν_{max}/cm^{-1} 1734 (C=O), 1239, 1150, 1055 (C=S); δ_H (200 MHz) 1.11 (3H, s, 13β-Me), 2.53 (3H, s, 11α-OCS_2Me), 3.50 (1H, t, *J* 2 × 4.7, 9β-H), 3.77 (3H, s, 3-OMe), 6.31 (1H, dt, *J* 8.3 and 2 × 4.6, 11β-H), 6.64 (1H, d, *J* 2.6, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.6, 2-H) and 7.51 (1H, d, *J* 8.5, 1-H).

3-Methoxy-9β-estra-1,3,5(10)-trien-17-one 21

(a) A solution of the 17,17-ethylenedioxy-11α-dithiocarbonate **19** (100 mg, 0.2 mmol), tributylstannane (1 g, 3.4 mmol) and α,α′-azobis(isobutyronitrile) (AIBN) (30 mg) in toluene (5 cm^3) was refluxed for 3 h. The cooled mixture was adsorbed onto silica gel (20 g) and eluted with toluene (to remove the tin residues) followed by ethyl acetate–toluene (1:19) to give an oily residue (36 mg, 0.1 mmol) which was dissolved in a mixture of acetone and water (7:1; 10 cm^3) and stirred with toluene–*p*-sulfonic acid (10 mg) for 18 h. The acetone was removed under reduced pressure and the resulting solution was extracted with ethyl acetate. The combined organic phase was washed (saturated aq. $NaHCO_3$, water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (25 mg) which was filtered through silica gel (0.5 g) with ethyl acetate–toluene (1:19) to give *3-methoxy-9β-estra-1,3,5(10)-trien-17-one* **21** (18 mg, 28%) as an oil, $[\alpha]_D$ +40 (*c* 0.2) (lit.,[12] $[\alpha]_D$ +43) (Found: M^+, 284. $C_{19}H_{24}O_2$ requires *M*, 284); ν_{max}/cm^{-1} 1728 (C=O); δ_H (400 MHz) 0.97 (3H, s, 13β-Me), 1.24 (1H, td, *J* 2 × 12.8 and 3.8, 12α-H), 2.20 (1H, m, 8β-H), 2.70 (1H, dt, *J* 16.8 and 2 × 4.6, 6β-H), 2.80 (1H, td, *J* 2 × 16.8 and 8.8, 6α-H), 3.01 (1H, br s, $W_{\frac{1}{2}}$ 10, 9β-H), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.7, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.22 (1H, d, *J* 8.6, 1-H); δ_C (100 MHz) 13.4 (13β-Me), 21.8 (C-15), 24.2 (C-11), 24.8 (C-7), 26.0 (C-6), 27.4 (C-12), 33.8 (C-8), 35.4 (C-16), 37.3

(C-9), 42.3 (C-14), 47.9 (C-13), 55.2 (3-OMe), 112.0 (C-2), 113.9 (C-4), 127.4 (C-1), 129.6 (C-10), 138.4 (C-5), 157.5 (C-3) and 220.8 (C-17).

(b) A solution of DDQ (1.8 g, 7.9 mmol) in dry methanol (10 cm^3) was added to a suspension of estrone **21** (2 g, 7.4 mmol) in dry methanol (320 cm^3) and the resulting dark-red solution was stirred for 5 h at 45 °C, during which time the solution faded to a dark orange. The methanol was removed under reduced pressure and the residue was triturated with chloroform (200 cm^3) and allowed to stand for 18 h. Activated charcoal was added and the mixture was stirred for 5 min then filtered through Celite and concentrated under reduced pressure. The resultant residue (1.9 g) was dissolved in a mixture of benzene (100 cm^3) and ethanediol (10 cm^3) and was refluxed with oxalic acid (200 mg) for 18 h with azeotropic removal of water. The cooled reaction mixture was poured into saturated aqueous sodium hydrogen carbonate (100 cm^3) and the mixture was extracted with chloroform. The combined organic phase was washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a dark-blue solid (1.8 g), which was dissolved in THF (40 cm^3) and stirred with palladium on carbon catalyst (10%, 200 mg) under hydrogen (30 bar) for 72 h at 40 °C. The catalyst was removed by filtration through Celite and the residue after removal of the solvent (1.9 g) was dissolved in a mixture of methanol (40 ml), water (4 ml) and hydrochloric acid (10 mol dm^{-3}, 2 cm^3) and the mixture was stirred for 30 min. Water was added and the resulting precipitate was collected by filtration (1.5 g). Recrystallation from a mixture of ethanol (40 cm^3) and water (5 cm^3) afforded estrone (390 mg). Chromatography of the mother liquor material (900 mg) on silica gel with ethyl acetate–chloroform (1:9) as eluent afforded further estrone (447 mg) followed by 3-hydroxy-9β-estra-1,3,5(10)-trien-17-one (300 mg, 15%), mp 182–184 °C (from methanol–water) (lit.,[12] 186–189 °C), methylation of which gave the product **21** (264 mg, 84%).

3-Methoxy-9β-estra-1,3,5(10),15-tetraen-17-one 22

A solution of the 17-ketone **21** (264 mg, 0.93 mmol) in THF (10 cm^3) was added to a freshly prepared solution of LDA [from diisopropylamine (0.6 cm^3, 4.6 mmol) and *n*-BuLi (2.5 mol dm^{-3} in hexanes, 1.8 cm^3, 4.5 mmol) in THF (15 cm^3)] at −78 °C and the resulting mixture was stirred for 1 h at −78 °C. Chlorotrimethylsilane (0.6 cm^3, 4.6 mmol) was added and the mixture was allowed to warm up to 25 °C. Saturated aqueous ammonium chloride was added and the reaction mixture was extracted into diethyl ether (3×). The combined organic phase was washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford an oily residue (450 mg) which was dissolved in acetonitrile (50 cm^3) and refluxed with palladium(II) acetate (225 mg, 1 mmol) and potassium carbonate (500 mg) for 30 min. The solids were removed by filtration and the residue after concentration was chromatographed on silica gel (25 g) with ethyl acetate–toluene (1:19) as eluent to give starting material **21** (89 mg, 33%) followed by the *product* **22** (132 mg, 52%) as an oil, $[\alpha]_D$ +24 (*c* 0.3) (Found: C, 80.2; H, 8.0%; M^+, 282.162. $C_{19}H_{22}O_2$ requires C, 80.8; H, 7.9%; *M*, 282.162); ν_{max}/cm^{-1} 1703 (C=O); δ_H (400 MHz) 1.21 (3H, s, 13β-Me), 1.55 (1H, m, obscured, 12α-H), 1.66 (1H, dt, *J* 13.0 and 2 × 4.0, 12β-H), 1.74–2.16 (3H, m, 7-H_2 and 11-H), 2.36–2.48 (2H, m, 8β-H and 11-H), 2.61 (1H, ddd, *J* 12.2, 3.2 and 2.1, 14α-H), 2.76 (2H, m, 6-H_2), 3.11 (1H, m, 9β-H), 3.77 (3H, s, 3-OMe), 6.00 (1H, dd, *J* 6.0 and 3.2, 16-H), 6.63 (1H, d, *J* 2.8, 4-H), 6.75 (1H, dd, *J* 8.5 and 2.8, 2-H), 7.28 (1H, d, *J* 8.5, 1-H) and 7.56 (1H, ddd, *J* 6.0, 2.1 and 0.8, 15-H); δ_C (100 MHz) 20.8 (C-18), 24.3 (C-11), 24.9 (C-7), 25.7 (C-12), 26.3 (C-6), 31.1 (C-8), 37.5 (C-9), 48.9 (C-14), 51.6 (C-13), 55.2 (3-OMe), 112.3 (C-2), 113.8 (C-4), 127.8 (C-1), 129.5 (C-10), 131.6 (C-16), 138.2 (C-5), 157.5 (C-3), 159.1 (C-15) and 213.2 (C-17).

3-Methoxy-9β-estra-1,3,5(10),14,16-pentaen-17-yl acetate 23

A solution of the Δ^{15}-17-ketone **22** (114 mg, 0.4 mmol) and toluene-*p*-sulfonic acid (20 mg) in a mixture of acetic anhydride (2 cm^3) and isopropenyl acetate (2 cm^3) was refluxed for 3 h. The cooled reaction mixture was poured into a mixture of ice and solid sodium hydrogen carbonate and was stirred for 1 h, with the addition of further sodium hydrogen carbonate to quench the acid generated. The resulting mixture was extracted into ethyl acetate (3×), the combined organic phase was washed with water and brine, dried and evaporated under reduced pressure to give a residue (178 mg) which was chromatographed on silica gel (10 g) with toluene–hexane (7:3) as eluent to give the *product* **23** (114 mg, 88%) as an oil, $[\alpha]_D$ +36 (*c* 0.2) (Found: M^+, 324.172. $C_{21}H_{24}O_3$ requires *M*, 324.1725); ν_{max}/cm^{-1} 1744 (C=O); δ_H (400 MHz) 1.10 (1H, td, *J* 2 × 13.2 and 3.4, 12α-H), 1.16 (3H, s, 13β-Me), 1.68 (1H, dt, *J* 13.2 and 2 × 3.4, 12β-H), 1.95–2.12 (2H, m, 7-H and 11β-H), 2.16 (3H, s, 17β-OAc), 2.24 (1H, m, 7-H), 2.37 (1H, dq, *J* 13.2 and 3 × 3.4, 11α-H), 2.73 (1H, ddd, *J* 17.4, 7.3 and 3.4, 6β-H), 2.86 (1H, m, 8β-H), 3.10–3.20 (2H, m, 6α-H and 9β-H), 3.75 (3H, s, 3-OMe), 5.96 (1H, t, *J* 2.2, 15-H), 6.03 (1H, d, *J* 2.2, 16-H), 6.59 (1H, d, *J* 2.8, 4-H), 6.63 (1H, dd, *J* 8.7 and 2.8, 2-H) and 7.06 (1H, d, *J* 8.7, 1-H).

Cycloaddition of phenyl vinyl sulfone to dienyl acetate 23

A solution of the dienyl acetate **23** (80 mg, 0.25 mmol) and phenyl vinyl sulfone (400 mg, 2.4 mmol) in dry, deoxygenated benzene (2 cm^3) was heated in a sealed tube for 48 h at 140 °C. The cooled reaction mixture was chromatographed on silica gel (10 g) with ethyl acetate–hexane (1:9) as eluent to give a mixture of cycloadducts (80 mg, 73%) (estimated at 7:1 by ^1H NMR). Careful rechromatography using diethyl ether–pentane (1:1) as eluent resulted in partial separation to give *3-methoxy-16α-phenylsulfonyl-14,17α-etheno-9β-estra-1,3,5(10)-trien-17β-yl acetate* **24** as a glassy solid, $[\alpha]_D$ +135 (*c* 4.2) (Found: C, 70.0; H, 6.7; S, 6.2%; M^+, 492.195. $C_{29}H_{32}O_5S$ requires C, 70.7; H, 6.55; S, 6.5%; *M*, 492.196); ν_{max}/cm^{-1} 1745 (C=O); δ_H (400 MHz) 0.88 (1H, dt, *J* 13.6 and 2 × 4.0, 12β-H), 0.96 (3H, d, *J* 0.4, 13β-Me), 1.50 (1H, m, 7α-H), 1.62 (3H, s, 17β-OAc), 1.77 (1H, m, 11β-H), 1.83 (1H, dd, *J* 12.7 and 4.7, 15α-H), 1.96 (1H, dd, *J* 12.7 and 9.1, 15β-H), 2.10–2.16 (2H, m, 7β-H and 8β-H), 2.21 (1H, m, 11α-H), 2.35 (1H, td, *J* 2 × 13.6 and 4.2, 12α-H), 2.60–2.76 (2H, m, 6-H_2), 2.80 (1H, m, 9β-H), 3.80 (3H, s, 3-OMe), 4.13 (1H, dd, *J* 9.1 and 4.7, 16β-H), 5.10 (1H, d, *J* 6.2, 17^2-H), 5.98 (1H, d, *J* 6.2, 17^1-H), 6.70–6.75 (2H, m, 2-H and 4-H), 7.10 (1H, d, *J* 8.2, 1-H), 7.54 (2H, m, *m*-H′s), 7.61 (1H, m, *p*-H) and 7.82 (2H, m, *o*-H′s); δ_C (100 MHz) 14.9 (C-18), 21.0 (17β-OAc), 22.6 (C-11), 23.7 (C-7), 25.4 (C-12), 28.2 (C-6), 31.8 (C-15), 33.9 (C-8), 34.3 (C-9), 52.3 (C-13), 55.2 (3-OMe), 62.5 (C-14), 66.3 (C-16), 95.1 (C-17), 111.4 (C-2), 112.9 (C-4), 125.9 (C-1), 127.6 (C-17^1), 128.4 (*o*-C′s), 129.0 (*m*-C′s), 131.7 (C-10), 132.8 (C-17^2), 133.2 (*p*-C), 140.2 (C-5), 140.9 (*ipso*-C), 157.6 (C-3) and 169.0 (17β-OAc).

Dehydrogenation of 14α,17α-ethano compounds

(a) A solution of 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol **25**[4] (390 mg, 1.3 mmol) in dry methanol (60 cm^3) was stirred at 25 °C while a solution of DDQ (320 mg, 1.4 mmol) in dry methanol was added over 2 min. The dark-red solution was stirred at 40 °C for 3 h, during which time the colour faded to a light orange. The methanol was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (50 cm^3). This solution was washed [aq. K_2CO_3 (1 mol dm^{-3}), aq. Na_2SO_3 (2 mol dm^{-3}), aq. K_2CO_3 (1 mol dm^{-3}), water, brine]. The combined washings were extracted with ethyl acetate, and these extracts were combined with the original solution, and the resulting mixture was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (428 mg). This was dissolved in a mixture of pyridine (5 cm^3) and acetic

anhydride (5 cm^3) and stirred with DMAP (20 mg) at 25 °C for 24 h. Water and solid sodium hydrogen carbonate were added, and once effervescence ceased the mixture was extracted with ethyl acetate. The combined organic phase was washed [saturated aq. $NaHCO_3$, aq. HCl (1 mol dm^{-3}), water, brine], dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (515 mg) which was adsorbed onto silica gel (50 g) and eluted with ethyl acetate–hexane (1:9) to give an inseparable mixture of the *diacetate* **26** and *14,17α-ethanoestra-1,3,5(10),9(11)-tetraene-3,17β-diyl diacetate* **28** (324 mg, 65%), *m/z* 382 and 380; ν_{max}/cm^{-1} 1729 (C=O); δ_H (400 MHz) (**28**, ~65%) 0.93 (3H, s, 13β-Me), 2.03 (3H, s, 17β-OAc), 2.28 (3H, s, 3-OAc), 6.29 (1H, dt, *J* 5.4 and 2 × 2.7, 11-H), 6.80 (1H, d, *J* 2.5, 4-H), 6.85 (1H, dd, *J* 8.7 and 2.5, 2-H) and 7.66 (1H, d, *J* 8.7, 1-H); (**26**, ~35%) 0.93 (3H, s, 13β-Me), 2.03 (3H, s, 17β-OAc), 2.28 (3H, s, 3-OAc), 6.78 (1H, d, *J* 2.5, 4-H), 6.84 (1-H, dd, *J* 8.5 and 2.5, 2-H) and 7.30 (1H, d, *J* 8.5, 1-H).

(b) To a stirred solution of 3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol **27**[4] (2.7 g, 8.7 mmol) in dry methanol (430 cm^3) at 25 °C was added DDQ (2 g, 8.8 mmol) in methanol (25 cm^3) over a period of 2 min. After stirring for 1 h, during which time the solution faded from a deep red to a pale orange, the methanol was evaporated under reduced pressure and the residue was triturated with hot chloroform (50 cm^3) and then allowed to stand at 4 °C for 16 h. After stirring with activated charcoal for 5 min the solution was filtered through Celite to give a pale-yellow solution which was concentrated under reduced pressure to give a residue (3.74 g) which was absorbed onto alumina (activity III, 100 g) and eluted with ethyl acetate–toluene (3:17) to give an inseparable mixture of starting material **27** and *3-methoxy-14,17α-ethanoestra-1,3,5(10),9(11)-tetraen-17β-ol* **29** (2.7 g), *m/z* 312 and 310; δ_H (200 MHz) (**27**, ~50%) 0.89 (3H, s, 13β-Me), 3.76 (3H, s, 3-OMe), 6.6–6.9 (2H, m, 2- and 4-H) and 7.20 (1H, d, *J* 8.5, 1-H); δ_H (200 MHz) (**29**, ~50%) 0.89 (3H, s, 13β-Me), 3.76 (3H, s, 3-OMe), 6.20 (1H, m, 11-H), 6.6–6.8 (2H, m, 2- and 4-H) and 7.60 (1H, d, *J* 8.8, 1-H).

(c) A solution of 3-methoxy-14α,17α-ethanoestra-1,3,5(10)-trien-17β-ol **27** (270 mg, 0.9 mmol) and toluene-*p*-sulfonic acid (300 mg, 1.74 mmol) in dry methanol (50 cm^3) was stirred at 25 °C while a solution of DDQ (400 mg, 1.76 mmol) in dry methanol (5 cm^3) was added dropwise. The reaction was stirred for 18 h at 25 °C followed by 2 h at reflux. The solvent was removed under reduced pressure and the residue was dissolved in chloroform (20 cm^3). This solution was washed (saturated aq. $NaHCO_3$), dried ($MgSO_4$) and evaporated to give a residue (220 mg). Chromatography on silica gel (25 g) with ethyl acetate–toluene (1:9) as eluent gave the *hexaene* **30** (154 mg, 58%), mp 198–200 °C (from methanol); $[\alpha]_D$ −31 (*c* 0.2) (Found: C, 82.4; H, 7.5; M^+, 306. $C_{21}H_{22}O_2$ requires C, 82.3; H, 7.2; *M*, 306); ν_{max}/cm^{-1} 3609, 3464 (OH); δ_H (200 MHz) 0.85 (3H, s, 13β-Me), 1.70 (1H, s, D_2O exch., 17β-OH), 3.92 (3H, s, 3-OMe), 6.65 (1H, d, *J* 9.8, 12-H), 7.12 (1H, d, *J* 2.7, 4-H), 7.15 (1H, d, *J* 9.8, 11-H), 7.18 (1H, dd, *J* 9.3 and 2.7, 2-H), 7.21 (1H, d, *J* 8.3, 7-H), 7.64 (1H, d, *J* 8.3, 6-H) and 8.60 (1H, d, *J* 9.3, 1-H).

14,17α-Ethano-9β-estra-1,3,5(10)-triene-3,17β-diyl diacetate 31

A solution of the tetraene **28** (contaminated with **26**) (324 mg, 0.9 mmol) in THF (10 cm^3) and ethanol (10 cm^3) was stirred with Raney nickel (Aldrich W-2, 10 cm^3) at 50 °C under a hydrogen atmosphere (50 bar) for 48 h. The cooled solution was filtered through Celite, the catalyst was washed thoroughly with ethyl acetate and chloroform. The residue (272 mg) after evaporation of the solvent was adsorbed onto silica gel (35 g) and eluted with ethyl acetate–toluene (1:99) to give 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diyl diacetate **26** (121 mg, 37%), mp 138–140 °C (from acetone–hexane), mixed fractions (109 mg), and *14,17α-ethano-9β-estra-1,3,5(10)-triene-3,17β-diyl diacetate* **31** (27 mg, 9%), mp 106–109 °C (from propan-2-ol); $[\alpha]_D$ +46 (*c* 0.4) (Found: C, 75.2; H, 8.0; M^+, 382. $C_{24}H_{30}O_4$ requires C, 75.4; H, 7.9; *M*, 382); ν_{max}/cm^{-1} 1750, 1727 (C=O); δ_H (400 MHz) 0.94 (1H, ddd, *J* 13, 9.8 and 5.2, 17^2_n-H), 1.03 (3H, s, 13β-Me), 1.16 (1H, dt, *J* 13 and 2 × 3.5, 17^2_x-H), 1.99 (3H, s, 17β-OAc), 2.27 (3H, s, 3-OAc), 2.44 (1H, br d, *J* 15, 11α-H), 2.55 (1H, ddd, *J* 15, 11 and 5.6, 6α-H), 2.66 (1H, dt, *J* 15 and 2 × 5.2, 6β-H), 2.84 (1H, br t, *J* 2 × 6.2, 9β-H), 6.82 (1H, d, *J* 2.5, 4-H), 6.89 (1H, dd, *J* 8.5 and 2.5, 2-H) and 7.31 (1H, d, *J* 8.5, 1-H); δ_C (100 MHz) 14.2 (13β-Me), 21.2 (3-OCO*C*H_3), 21.6 (17β-OCO*C*H_3), 21.8 (C-11), 23.2 (C-7), 24.5 (C-12), 28.4 (C-6), 28.8 (C-17^2), 29.1 (C-17^1), 31.8 (C-16), 33.8 (C-15), 34.3 (C-9), 35.3 (C-8), 45.2 (C-14), 48.7 (C-13), 89.8 (C-17), 118.8 (C-2), 120.3 (C-4), 124.5 (C-1), 139.3 (C-10), 141.2 (C-5), 148.1 (C-3), 169.7 (17β-O*C*OCH$_3$) and 170.9 (3-O*C*OCH$_3$); δ_H (400 MHz, C_6D_6) 0.68 (1H, ddd, *J* 12.6, 9.9 and 5.1, 17^2_n-H), 0.92 (3H, s, 13β-Me), 1.00 (1H, m, 7β-H), 1.28 (1H, dt, *J* 12.6 and 2 × 4.1, 12β-H), 1.46 (1H, m, 17^1_n-H), 1.65 (3H, s, 17β-OAc), 1.76 (3H, s, 3-OAc), 2.44 (1H, br t, *J* 2 × 6.7, 9β-H), 6.88 (1H, d, *J* 2.3, 4-H), 6.93 (1H, dd, *J* 8.3 and 2.3, 2-H) and 7.07 (1H, d, *J* 8.3, 1-H); δ_C (100 MHz, C_6D_6) 14.4 (13β-Me), 20.6 (3-OCO*C*H_3), 21.1 (17β-OCO*C*H_3), 22.0 (C-11), 23.4 (C-7), 25.0 (C-12), 28.6 (C-6), 28.9 (C-17^2), 29.4 (C-17^1), 32.3 (C-16), 33.9 (C-15), 34.4 (C-9), 35.4 (C-8), 45.4 (C-14), 48.9 (C-13), 89.7 (C-17), 119.4 (C-2), 120.8 (C-4), 124.5 (C-1), 139.2 (C-10), 141.2 (C-5), 149.1 (C-3), 168.6 (17β-O*C*OCH$_3$) and 169.8 (3-O*C*OCH$_3$). The mixed fractions were rechromatographed on silica gel (15 g) eluting with ethyl acetate–toluene (1:99) to give further **26** (150 mg, 15%) and **31** (33 mg, 10%).

14α,17α-Ethano-9β-estra-1,3,5(10)-triene-3,17β-diol 32

A solution of the 3,17β-diacetate **31** (46 mg, 0.1 mmol) in methanolic potassium hydroxide (1%, 10 cm^3) was stirred for 24 h at 25 °C. Water was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (40 mg) which was chromatographed on silica gel (5 g) with ethyl acetate–toluene (1:4) as eluent to give the *3,17β-diol* **32** (33 mg, 91%), mp 208–209 °C (from chloroform); $[\alpha]_D$ +48 (*c* 0.5) (Found: M^+, 298.192. $C_{20}H_{26}O_2$ requires *M*, 298.193).

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