Acid-mediated Rearrangements of 14,17-Ethenoestra-1,3,5(10)-trien-17-ols: Synthesis of 14,16-Ethano-19-norsteroids

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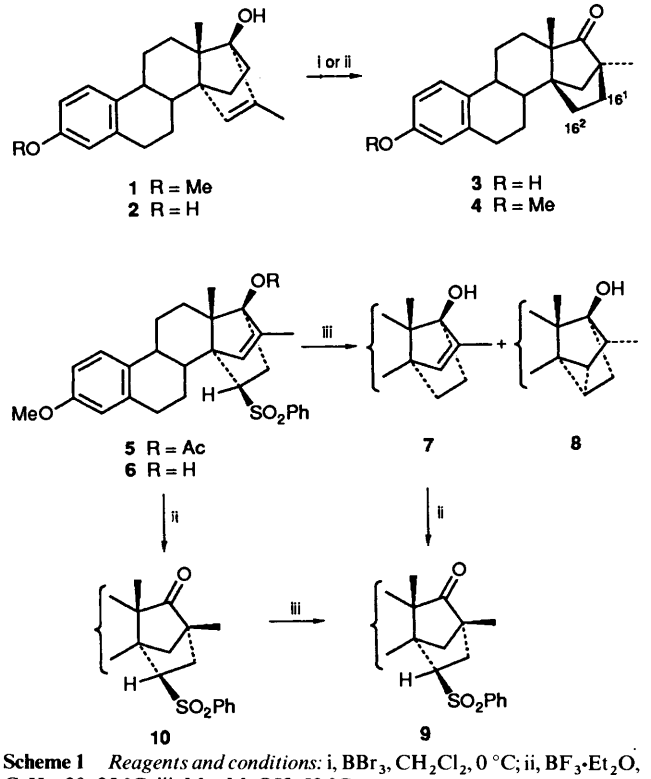
3-Methoxy-17[1]-methyl-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol **1** undergoes a 16(17→17[1])*abeo*-rearrangement in the presence of boron trihalides, to give the corresponding 16α-methyl-14β,16β-ethano 17-ketone. Similar rearrangements are described for epimeric 14,17-bridged estradiol analogues, leading to 16β-methyl-14α,16α-ethano 17-ketones. By contrast, acid-mediated reactions of 3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol **11** display reagent dependence, leading to products of competing 16(17→17[1])*abeo*-and 15(14→17[2])*abeo*-rearrangements. Conversion of certain rearrangement products into 14,16-ethano analogues of estradiol and 19-nortestosterone are described, and X-ray crystallographic structure determinations are reported for three ring-D-bridged compounds, and a novel spiro compound arising from rearrangement of the 14α,17α-etheno 17β-alcohol **11**.

We have recently developed a general synthesis of 14α,17α-etheno-19-norsteroids and hence, derived 19-norsteroids having 14,17-ethano bridges and 14-functionality.[1-3] Manifestations of biological activity in this family of compounds[4] prompted attempts to synthesize representative hormone analogues which, in the estrone-derived intermediates, entailed deprotection of 3-methyl ethers at the opportune stage of certain reaction sequences. In this work we describe acid-mediated rearrangements, which were originally recognised during attempted 3-deprotection of 3-methoxy-14,17-ethenoestra-1,3,5(10)-trien-17-ols, and which have subsequently been adapted for synthesis of 14,16-ethano-19-norsteroids.

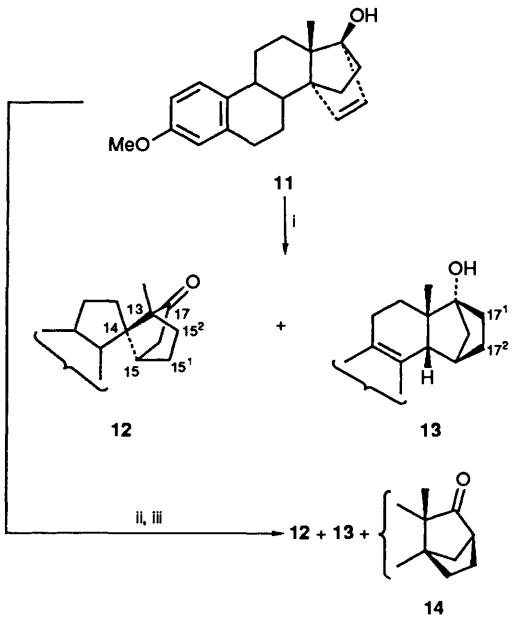
3-Methoxy-17[1]-methyl-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol **1**[2] underwent slow (7 days) but uneventful demethylation in the presence of diisobutylaluminium hydride (DIBAL) in refluxing benzene,[5] to give the corresponding estradiol analogue **2**. However, an attempt to expedite 3-deprotection by treatment of compound **1** with boron tribromide in dichloromethane at 0 °C[5] resulted in concomitant ring D rearrangement to give 3-hydroxy-16α-methyl-14,16β-ethano-14β-estra-1,3,5(10)-trien-17-one **3** (85%). The nature of the change in ring D was apparent from the absence of bridge unsaturation and the presence of ketone functionality in the product **3**. When boron trifluoride–diethyl ether was used instead of boron tribromide, compound **1** underwent ring D rearrangement without demethylation, to give the 3-methoxy-14,16-ethano compound **4** (90%), the structure of which was verified by X-ray crystallography (see below) (Scheme 1).

The foregoing results prompted an investigation of related 14,17-etheno-19-norsteroids. The bridged epimer **7** of the 17[1]-methyl-14α,17α-etheno compound **1** has not hitherto been isolated,[6] but was a suspected component of the mixture arising from reductive desulfonylation of (17[2]*R*)-3-methoxy-16-methyl-17[2]-phenylsulfonyl-14,17α-ethanoestra-1,3,5(10),15-tetraen-17β-yl acetate **5**. Thus, treatment of acetate **5** with magnesium in methanol at 50 °C[7] gave a major chromatographic fraction (~90%) comprising an inseparable mixture (~1:2) of isomers. NMR examination suggested that the minor component was indeed the desired olefin **7**, whereas the major component was the 16α-methyl-15α,17[2]-cyclo-14α,17α-ethano compound **8** arising from olefinic bond participation during reductive desulfonylation. Attempts to separate the components, or to improve the proportion of the olefin **7** in the mixture, by treatment of the substrate **5** with sodium in liquid ammonia or samarium(II) iodide–hexamethylphosphoric triamide,[8] failed.

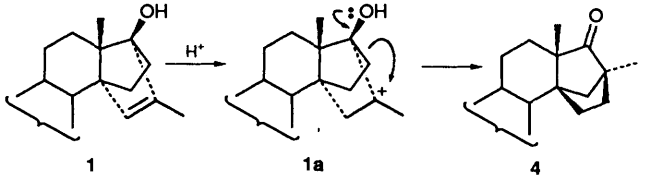


Scheme 1 *Reagents and conditions*: i, BBr_3, CH_2Cl_2, 0 °C; ii, BF_3·Et_2O, C_6H_6, 20–25 °C; iii, Mg–MeOH, 50 °C

The mixture (**7** + **8**) was treated with boron trifluoride–diethyl ether in benzene at 25 °C, to give a chromatographically separable mixture (~1:2), the major component of which was shown to be unchanged compound **8**. The structure of compound **8** was supported by 500 MHz ^{1}H NMR data and a COSY correlation, which revealed the presence of a closed spin system associated with a substituted nortricyclane skeleton, thus confirming the inference drawn from the NMR spectrum



Scheme 2 *Reagents and conditions:* i, HBr, CH_2Cl_2, 0 °C; ii, $C_5H_5N^+$-HCl^-, 205–210 °C; iii, Me_2SO_4, K_2CO_3, Me_2CO



Scheme 3 Acid-catalysed 16(17→17¹)*abeo*-rearrangement of compound **1**

of the reductive desulfonylation mixture (**7** + **8**) obtained from the acetate **5**.

It could thus be concluded that the minor component **9** of the rearrangement mixture arose exclusively from the assumed olefin **7**, and this was supported by its structural assignment as 3-methoxy-16β-methyl-14,16α-ethanoestra-1,3,5(10)-trien-17-one on the basis of spectroscopic characteristics which closely paralleled those of the isomeric bridged ketone **4**. The structure of compound **9** was confirmed through an independent synthetic pathway which circumvented the competing reactions occurring during reductive desulfonylation. Thus, alkaline hydrolysis of the cycloadduct **5** gave the sulfone **6**,[2] of crystallographically defined structure (see below), which was treated with boron trifluoride–diethyl ether under the usual conditions to give an almost quantitative yield of the rearrangement product **10**. Reductive desulfonylation of sulfonyl ketone **10** in the presence of magnesium in methanol gave the 14α,16α-ethano 17-ketone **9** (86%).

A complementary study was undertaken of acid-mediated rearrangements of 3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol **11**.[1] In this case, attempted rearrangement in the presence of Lewis acids was slow and irreproducible. However, treatment of compound **11** with hydrogen bromide (40% in acetic acid) in dichloromethane at 0 °C proceeded to completion in 4 h, in a relatively clean reaction, to give a mixture comprising two major products, **12** (46%) and **13** (40%), accompanied by traces of minor components which could not be isolated and identified (Scheme 2). The major components were separated chromatographically, and spectroscopic examination revealed that neither was related to the foregoing rearrangement products. In particular, the NMR spectrum of ketone **12** displayed a distinctive spin system at δ 1.85 (1 H, d, *J* 18.0) and 2.37 (1 H, ddd, *J* 18.0, 4.5 and 3.7), which disappeared after prolonged treatment of the product **12** with sodium deuterioxide in refluxing 1,4-dioxane, with accompanying incorporation of two deuterium units. The inferred presence of a bridged ketone having an α-methylene group suggested an unexpected skeletal rearrangement. The structure of compound **12** was determined by X-ray crystallography (see below), from which it was possible to assign the well dispersed 500 MHz NMR spectrum fully and self-consistently, with the aid of a COSY correlation (see Experimental section). Distinctive features of this spectrum included first-order multiplets for each of the protons on the bicyclo[2.2.1]heptanoid system, giving rise to the following couplings (x *exo*; n *endo*): $^3J_{15,16x} = {}^3J_{15,15^1x} = 4.5$; $^3J_{15,16n} = {}^3J_{15,15^1n} = 0$; $^2H_{15^1x,15^1n} = 13.1$; $^3J_{15^1x,15^2x} = 12.6$; $^3J_{15^1x,15^2n} = 3.6$; $^4J_{15^1x,16x} = 3.7$; $^2J_{15^1n,15^2n} = 9.5$; $J_{15^1n,15^2x} = 5.7$; $^2J_{15^2x,15^2n} = 13.0$; $^2J_{16x,16n} = 18.0$.

The more polar rearrangement product showed evidence of a tertiary hydroxy group and a tetrasubstituted olefinic bond in conjugation with ring A, from which it was concluded that the structure was 3-methoxy-15β,17β-ethano-14β-estra-1,3,5(10),8-tetraen-17α-ol **13**. Although direct evidence for the 14β- configuration was not forthcoming from the spectroscopic data, the assignment followed from mechanistic and steric considerations.

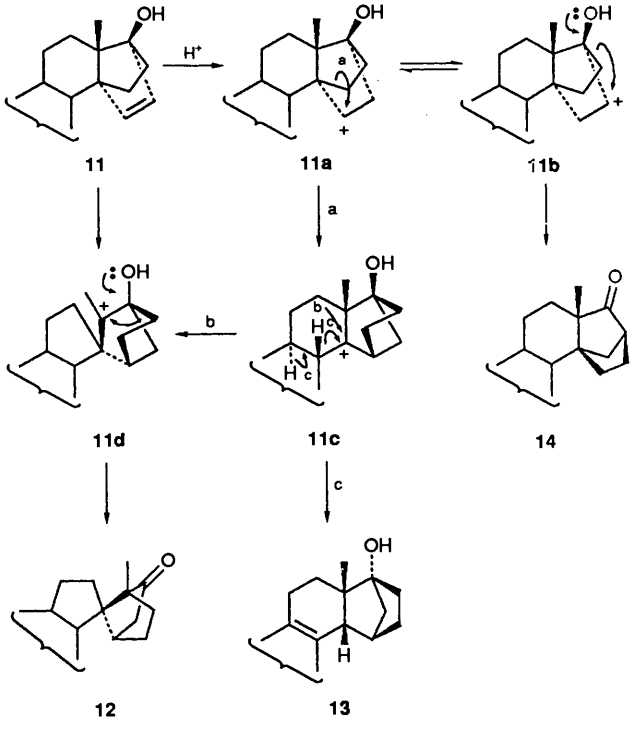
In another experiment, treatment of compound **11** with pyridinium chloride, followed by remethylation of the crude reaction product, gave a complex mixture containing a new major product (TLC). Chromatography furnished the rearrangement products **12** and **13** as minor components, accompanied by a 53% yield of the 14β,16β-ethano 17-ketone **14**. Although the structure **14** could not be assigned unequivocally from spectroscopic data, it was confirmed by X-ray crystallography (see below).

A variety of reaction conditions was used to induce the rearrangements reported in this work, but we conclude that the common mechanistic feature is initial protonation of the etheno bridge, followed by neighbouring-bond migration. Thus, formation of the 16α-methyl-14β,16β-ethano 17-ketone **4** is readily explained by a 16(17→17¹)*abeo*-rearrangement (Scheme 3). It is assumed that hydrogen halide, generated by the interaction of Lewis acid with the bridgehead hydroxy group in substrate **1**, results in protonation of the olefinic bond, and that carbocationic character centred at C(17¹) (intermediate **1a**) initiates C(16)–C(17) bond migration, leading to product **4**. Indeed, the rearrangement **1** ⟶ **4** was also observed, albeit less efficiently and cleanly, in the presence of hydrogen bromide in acetic acid.

The cognate rearrangements **6** ⟶ **10** and **7** ⟶ **9** are similarly explained, and it appears that the clean reaction course in these cases can be ascribed to strong localisation of the intermediate carbocation at the tertiary position adjacent to the bridgehead hydroxy group. By contrast, the more complex course of reaction observed in the case of the disubstituted olefin **11** reveals that migratory aptitudes of the C(16)–C(17) and C(15)–C(14) bonds are profoundly influenced by reaction conditions. Hence, in the presence of hydrogen bromide, the formation of products **12** and **13** indicates that carbocationic character is localised at C(17²) in the intermediate **11a** and, hence, predominant (perhaps exclusive) 15(14→17²)*abeo*-rearrangement results (path a), leading to a common 14-carbocationic intermediate **11c** (Scheme 4). Formation of the spiroketone **12** then requires sequential 12(13→14)*abeo*- (to intermediate **11d**) and 16(17→13)*abeo*-rearrangements (path b), whereas formation of the bridgehead alcohol **13** results from competing hydride migration from C(8) to C(14) and accompanying elimination of 9α-H (path c).

By contrast, treatment of compound **11** with pyridinium

chloride results in regioselective preference for the intermediacy of a 17[1]-carbocation **11b**, leading mainly to the product **14** of 16(17→17[1])*abeo*-rearrangement (Scheme 4).



Scheme 4 Competing 16(17→17[1])*abeo*- and 15(14→17[2])*abeo*-rearrangement pathways for compound **11**

There is no obvious reason for these differences in the localisation of carbocationic character at C(17[1]) or C(17[2]) in compound **11** under the given reaction conditions. Furthermore, the unique carbocyclic skeleton involved in these rearrangements finds little analogy in the literature. The reaction pathways *via* the 14-carbocation **11c** bear some resemblance to those induced by protonation of 5α-cholest-14-enes,[9] leading to 12(13→14)*abeo*-rearrangement products accompanied by effective isomerisation to 5α-cholest-8(14)-ene.

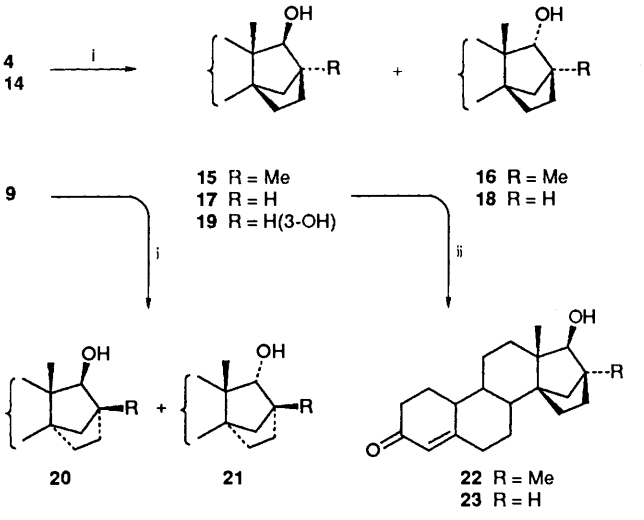
A more detailed investigation of the factors responsible for these complex reaction courses was beyond the scope of our investigation, but the findings have provided practical synthetic routes to representative 14,16-ethano 17-ketones, which could be further elaborated into 19-norsteroid hormone analogues.

In pursuance of this objective, the 14,16-ethano 17-ketones **4**, **9** and **14** were subjected to borohydride reduction in order to establish the scope for preparation of the corresponding 17β-alcohols, prior to conversion into estradiol and 19-nortestosterone analogues. Thus, treatment of the 16α-methyl-14β,16β-ethano 17-ketone **4** with sodium borohydride in ethanol at 50 °C afforded the 17β-alcohol **15** (75%) accompanied by some 17α-alcohol **16** (14%). The isomers were differentiated by the relative chemical shifts of their 13β-methyl groups, as well as by comparison with the reduction products of the structurally related 14β,16β-ethano 17-ketone **14** which gave mainly the 17β-alcohol **17** (90%).

In the reductions of ketones **4** and **14**, preferred α-face addition by hydride corresponds to *exo*-approach to the bicyclo[2.2.1]heptanoid system, and is sterically appropriate. The major reduction product **17** was demethylated with DIBAL to give the estradiol analogue **19**.

In the case of the inverted bridged ketone **9**, *exo*-addition of hydride corresponds to β-face reagent approach, which should be adversely influenced by the 13β-methyl group. In the event, borohydride reduction of compound **9** gave almost equal amounts of the 17β- and 17α-alcohol **20** and **21**.

Birch reduction of the 17β-alcohols **15** and **17**, followed by deprotection and isomerisation in ring A, afforded the respective 19-nortestosterone analogues **22** and **23** (Scheme 5).



Scheme 5 *Reagents and conditions:* i, $NaBH_4$, EtOH, 50 °C; ii, Li–NH_3, THF, Bu[t]OH; then HCl or $(CO_2H)_2$ followed by NaOMe

X-Ray Crystallography.—The unusual nature of the foregoing skeletal rearrangements prompted an X-ray crystallographic structure investigation of those products for which spectroscopic evidence of the proposed structures was inconclusive. These included compound **6**, which was obtained by hydrolysis of a minor and unexpected cycloadduct obtained during Diels–Alder reaction of 3-methoxy-16-methylestra-1,3,5(10),14,16-pentaen-17-yl acetate with phenyl vinyl sulfone,[2] and the 14β,16β-ethano compounds **4** and **14**. In addition, a structure determination of the spiro compound **12** was necessitated by the unprecedented nature of the rearrangement leading to its formation.

The details of these structure determinations are given in the Experimental section, and the structures are depicted in Fig.1. A selection of ring-puckering parameters[10] is given in Table 1. These data reveal that the ring D conformations of compounds **4**, **6** and **14** display the expected responses to bridging, and furthermore that no unusual conformational transmission effects are reflected in ring C conformations.

Experimental

For general directions, see ref. 1. Unless otherwise stated, NMR data refer to 90 MHz spectra in $CDCl_3$, and *J* values are given in Hz. Optical rotations $[\alpha]_D$ are given in 10^{-1} deg cm^2 g^{-1}.

17[1]-*Methyl*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-3,17β-*diol* **2**.—DIBAL (20% in toluene; 1.2 cm^3) was added to a solution of 3-methoxy-17[1]-methyl-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol **1** (130 mg, 0.4 mmol) in dry benzene (6 cm^3), and the mixture was refluxed for 4 days. Further hydride (0.3 cm^3) was added and the mixture was refluxed for 3 days. 1 Mol dm^{-3} hydrochloric was added to quench the reaction and the mixture was diluted with ethyl acetate. The organic phase was separated, washed with water, dried ($MgSO_4$), and concentrated to give a yellow syrup (135 mg). Chromatography on silica gel (15 g), with chloroform–ethyl acetate (9:1) as eluent, afforded the 3,17-*diol* **2** (105 mg, 84%) as crystals, m.p. 197–203 °C (from aq. EtOH); $[\alpha]_D$ +129 (*c* 0.9, EtOH) (Found: C, 81.0; H, 8.7%;

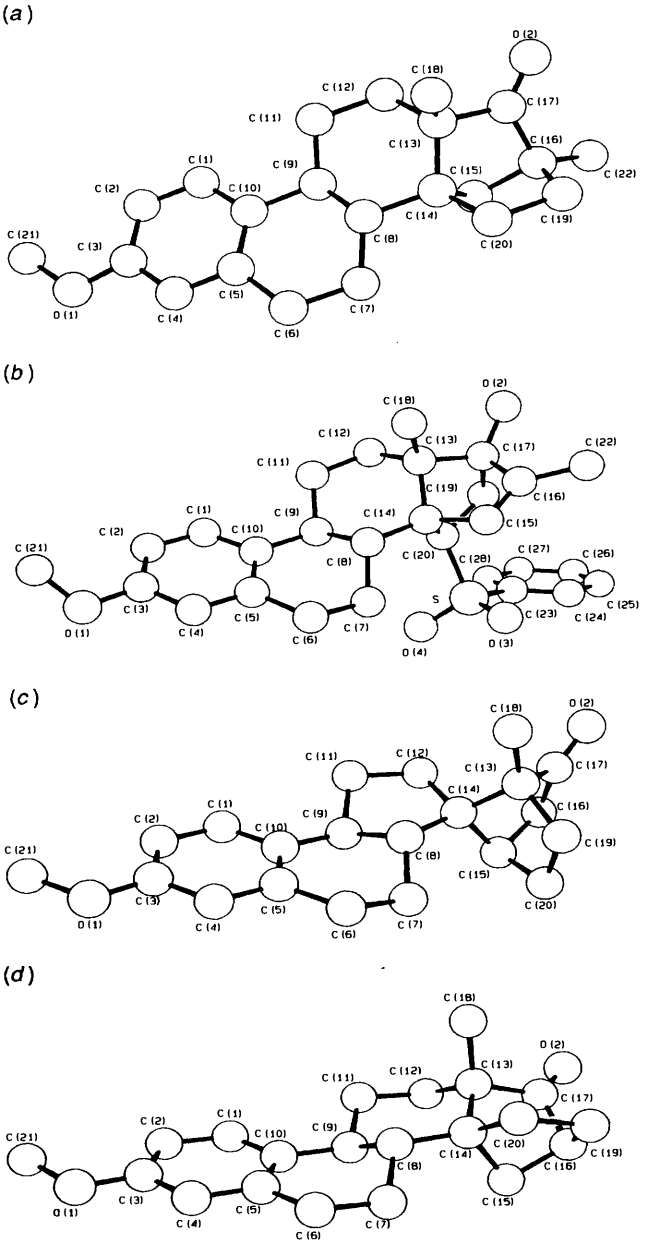


Fig. 1 X-Ray structures of (a) 3-methoxy-16α-methyl-14,16β-ethano-14β-estra-1,3,5(10)-trien-17-one **4**; (b) (17²*R*)-3-methoxy-16-methyl-17²-phenylsulfonyl-14,17α-ethanoestra-1,3,5(10),15-tetraen-17β-ol **6**; (c) (13*R*,14*S*,15*R*)-3-methoxy-13,15-ethano-12(13 → 14)*abeo*-estra-1,3,5(10)-trien-17-one **12**; (d) 3-methoxy-14,16β-ethano-14β-estra-1,3,5(10)-trien-17-one **14**. The numbering systems used in the crystallographic structure determinations are shown.

M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.25; H, 8.4; *M*, 310); ν_{max}/cm^{-1} 3590 (OH), 1610 and 1495; δ[$(CD_3)_2CO$] 0.9 (3 H, s, 13β-Me), 1.73 (3 H, d, *J* 1.6, 17¹-Me), 3.90 (1 H, s, exch. by D_2O, OH) 5.56 (1 H, d, *J* 1.6, 15-H), 6.5–6.7 (2 H, m, 2- and 4-H), 7.13 (1 H, d, *J* 8.5, 1-H) and 7.88 (1 H, s, exch. by D_2O, OH).

3-*Hydroxy*-16α-*methyl*-14,16β-*ethano*-14β-*estra*-1,3,5(10)-*trien*-17-*one* **3**.—Boron tribromide (220 mg), as a solution in dichloromethane (1 cm^3), was added to a stirred solution of compound **1** (162 mg, 0.5 mmol) in dichloromethane (5 cm^3) at −78 °C. The yellow reaction mixture was then stirred at 0 °C for 2 h, whereafter starting material **1** was no longer present (TLC). Satd. aq. sodium hydrogen carbonate was added and the mixture was stirred until colourless (*ca.* 20 min). The organic layer was separated, dried ($MgSO_4$), and concentrated to give a discoloured solid, which was adsorbed on silica gel (15 g). Elution with chloroform–ethyl acetate (25:1) afforded the 14β,16β-*ethano compound* **3** (132 mg, 85%), m.p. 228–229 °C (from ethyl acetate); $[\alpha]_D$ +178 (*c* 0.7) (Found: C, 81.6; H, 8.7%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.25; H, 8.4%; *M*, 310); ν_{max}/cm^{-1} 3580 (OH), 1725 (CO), 1610 and 1500; δ 1.07 (3 H, s, 13β-Me), 1.16 (3 H, s, 16α-Me), 4.76 (1 H, s, exch. by D_2O, 3-OH), 6.57 (1 H, d, *J* 2.8, 4-H), 6.63 (1 H, dd, *J* 8.4 and 2.8, 2-H) and 7.14 (1 H, d, *J* 8.4, 1-H).

3-*Methoxy*-16α-*methyl*-14,16β-*ethano*-14β-*estra*-1,3,5(10)-*trien*-17-*one* **4**.—A solution of the hydroxy olefin **1** (400 mg, 1.23 mmol) and boron trifluoride–diethyl ether (0.6 cm^3) in dry benzene (10 cm^3) was stirred at 25 °C. After 18 h, starting material **1** was no longer present (TLC), and the mixture was treated with satd. aq. sodium hydrogen carbonate. The organic phase was washed with water, dried ($MgSO_4$), and concentrated, to give a solid residue (432 mg), which was chromatographed on silica gel (50 g), with ethyl acetate–benzene (1:9) as eluent, to furnish the 14β,16β-*ethano* 17-*ketone* **4** (362 mg, 90.5%), m.p. 145–146 °C (from ethyl acetate–hexane); $[\alpha]_D$ +173 (*c* 0.85) (Found: C, 81.6; H, 8.9; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; *M*, 324); ν_{max}/cm^{-1} 1725 (CO), 1605 and 1500; δ(500 MHz; C_6D_6) 0.99 (3 H, s, 13β-Me), 1.2 (3 H, s, 16α-Me), 1.73 (1 H, m, 7α-H), 1.98 (1 H, dq, *J* 13.1 and 3 × 3.5, 11α-H), 2.19 (1 H, dt, *J* 2 × 11.3 and 3.4, 9α-H), 2.7 (2 H, m, 6-H_2), 3.43 (3 H, s, 3-OMe), 6.71 (1 H, d, *J* 2.8, 4-H), 6.79 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.08 (1 H, d, *J* 8.6, 1-H).

Reductive Desulfonylation of the Cycloadduct **5**.—A suspension of activated magnesium turnings (150 mg) in dry methanol (10 cm^3) was heated to 50 °C. When hydrogen evolution commenced, the sulfone **5** (134 mg, 0.29 mmol) was added and the mixture was stirred at 50 °C for 1.5 h. Further magnesium (150 mg) was added and the mixture was stirred until starting material had disappeared (TLC) (*ca.* 1.5 h). The mixture was cooled to 0 °C, acidified with 1 mol dm^{-3} hydrochloric acid, and extracted with chloroform. Work-up of the extract gave a crystalline residue (130 mg), which was chromatographed on silica gel (15 g) with ethyl acetate–benzene (1:9) to give unidentified material (8 mg) [*m/z* 322.193 (M^+)] followed by an inseparable mixture of 3-methoxy-16-methyl-14,17α-ethanoestra-1,3,5(10), 15-tetraen-17β-ol **7** and 3-methoxy-16α-methyl-15α,17²-cyclo-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol **8** as crystalline material (84 mg, 90%), m.p. 135–148 °C (from aq. MeOH); ν_{max}/cm^{-1} 3600; δ(**7**; ~35%) 0.83 (3 H, d, *J* 0.6, 13β-Me), 1.71 (3 H, d, *J* 1.7, 16-Me), 3.76 (3 H, s, 3-OMe), 5.62 (1 H, d, *J* 1.7, 15-H) and 6.63–7.19 (3 H, m, 1-, 2- and 4-H); δ(**8**; ~65%) 0.9 (3 H, s, 13β-Me), 0.92 (3 H, d, *J* 6.8, 16α-Me), 1.28 (1 H, s, exch. by D_2O, 17β-OH), 3.76 (3 H, s, 3-OMe) and 6.59–7.23 (3 H, m, 1-, 2- and 4-H); *m/z* 324 [M^+ for **7** and **8**].

Acid-catalysed Rearrangement of the Hydroxy Olefin **7**.—A mixture (60 mg) of the hydroxy olefin **7** (~35%) and the 15,17²-cyclosteroid **8** (~65%) in dry benzene (2 cm^3) was treated with boron trifluoride–diethyl ether (0.1 cm^3) for 2 h at 25 °C, and worked up as described previously. Chromatography of the crystalline residue (60 mg) on silica gel (6 g), with ethyl acetate–benzene (1:9) as eluent, gave 3-*methoxy*-16β-*methyl*-14,16α-*ethanoestra*-1,3,5(10)-*trien*-17-*one* **9** (21 mg), m.p. 107–109 °C (from hexane); $[\alpha]_D$ +91 (*c* 0.35) (Found: C, 80.9; H, 8.9%; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; *M*, 324); ν_{max}/cm^{-1} 1725 (CO), 1610 and 1495; δ(500 MHz) 0.99 (3 H, s, 13β-Me), 1.2 (3 H, s, 16β-Me), 1.6 (1 H, d, *J* 10.1), 2.35 (1 H, ddt, *J* 13.7, 2 × 4.5, and 2.2, 11α-H), 2.57 (1 H, dt, *J* 2 × 11.9, and 4.4, 9α-H), 2.87 (2 H, m, 6-H_2), 3.76 (3 H, s, 3-OMe), 6.62 (1 H, d, *J* 2.6, 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), followed by 3-*methoxy*-16α-*methyl*-

Table 1 Selected ring-puckering parameters for compounds **4**, **6**, **12** and **14**

Ring atoms[a]	Puckering parameters θ	φ	Q	Conformation[b]
Compound **4**				
8–9–11–12–13–14 (ring C)	6.3	99.9	0.58	$^{8}C_{12}$
13–17–16–15–14 (ring D)		110.4	0.57	$^{13}T_{17}$
13–17–16–19–20–14	91.9	303.8	0.99	$B_{16,14}$
14–15–16–19–20		29.1	0.58	$^{19}T_{20}$
Compound **6**				
8–9–11–12–13–14 (ring C)	5.9	272.5	0.57	$^{8}C_{12}$
13–17–16–15–14 (ring D)		0.3	0.56	$^{15}T_{16}$
13–17–19–20–14		174.4	0.63	$^{19}T_{20}$
14–15–16–17–19–20	88.7	182.2	0.99	$B_{17,14}$
Compound **12**				
8–9–11–12–14 (ring C)		32.5	0.43	$^{12}T_{14}$
13–17–16–15–14		322.5	0.60	$^{17}T_{16}$
13–19–20–15–14		144.0	0.57	$^{20}T_{19}$
13–17–16–15–20–19	89.8	180.4	0.99	$B_{15,13}$
Compound **14**				
8–9–11–12–13–14 (ring C)	9.7	144.8	0.57	$^{8}C_{12}$
13–17–16–15–14 (ring D)		109.5	0.57	$^{13}T_{17}$
13–17–16–19–20–14	90.0	301.5	0.97	$B_{16,14}$
14–20–19–16–15		146.5	0.60	$^{19}T_{20}$
3-Methoxyestra-1,3,5(10)-trien-17-one[c]				
8–9–11–12–13–14 (ring C)	8.1	220.0	0.65	$^{8}C_{12}$
13–17–16–15–14 (ring D)		328.5	0.42	$^{17}T_{16}$

[a] Crystallographic numbering is used to indicate sequence of carbon atoms defining selected rings. [b] Conformational descriptions as defined in ref. 11. [c] Data taken from ref. 12.

15α,17²-*cyclo*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*ol* **8** (35 mg, 58%), m.p. 157–159 °C (from aq. MeOH); $[\alpha]_D$ +78 (*c* 0.5) (Found: C, 81.1; H, 8.6%; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; *M*, 324); ν_{max}/cm^{-1} 3600 (OH), 3050, 1610 and 1495; δ(500 MHz), 0.9 (3 H, s, 13β-Me), 0.92 (3 H, d, *J* 6.8, 16α-Me), 0.97 (1 H, d, *J* 6.0, 17²-H), 1.08 (1 H, dq, *J* 3 × 12.2, and 5.9, 7α-H), 1.22 (1 H, d, *J* 6.0, 15β-H), 1.28 (1 H, s, exch. by D_2O, OH), 1.35–1.42 (2 H, m, 7β- and 12α-H), 1.47 (1 H, ddd, *J* 12.5, 11.9, and 3.6, 11β-H), 1.56 (1 H, dd, *J* 12.5 and 4.0, 12β-H), 1.61 (1 H, d, *J* 10.7, 17^1-H_{endo}) 1.68 (1 H, dd, *J* 10.7 and 1.1, 17^1-H_{exo}), 1.78 br (1 H, dt, *J* 2 × 10.5 and ~2, 8β-H), 1.98 (1 H, dq, *J* 3 × 6.8, and 1.0, 16β-H), 2.27 (1 H, dt, *J* 2 × 11.1, and 3.4, 9α-H), 2.37 (1 H, dq, *J* 12.5 and 3 × 3.4, 11α-H), 2.74–2.85 (2 H, m, 6-H_2), 3.76 (3 H, s, 3-OMe), 6.59 (1 H, d, *J* 2.7, 4-H), 6.71 (1 H, dd, *J* 8.6 and 2.7, 2-H) and 7.23 (1 H, d, *J* 8.6, 1-H).

Acid-catalysed Rearrangement of the Sulfone **6**.—A mixture of sulfone **6** (340 mg, 0.73 mmol) and boron trifluoride–diethyl ether (0.5 cm^3) was stirred at 25 °C for 4 h, then the reaction mixture was worked up as described in similar experiments. Flash chromatography of the residue on silica gel (35 g), with ethyl acetate–benzene (1:4) as eluent, gave (16²R)-3-*methoxy*-16β-*methyl*-16²-*phenylsulfonyl*-14,16α-*ethanoestra*-1,3,5(10)-*trien*-17-*one* **10** as a foam (330 mg, 97%), $[\alpha]_D$ +104 (*c* 0.9); ν_{max}/cm^{-1} 1730 (CO), 1605, 1495, 1310 and 1140; δ(500 MHz) 1.08 (3 H, s, 13β-Me), 1.18 (3 H, s, 16β-Me), 1.6 (1 H, dq, *J* 3 × 12.6, and 4.8, 11β-H), 1.73 (1 H, dd, *J* 12.8 and 7.2, 16^1-H_{endo}), 1.78–1.88 (2 H, m, 12α- and 12β-H), 1.96 (1 H, m, 7β-H), 2.15 (1 H, dt, *J* 2 × 11.8, and 2.5, 8β-H), 2.41 (1 H, d, *J* 11.0), 2.46 (1 H, br m, 11α-H), 2.64 (1 H, dq, *J* 3 × 12.8, and 5.2), 2.83–2.92 (2 H, m, 6-H_2), 3.55 (1 H, dt, *J* 2 × 11.3, and 5.0, 9α-H), 3.76 (3 H, s, 3-OMe), 3.78 obsc (1 H, t?, *J* 2 × 7.2, 16²-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 7.12–7.84 (6 H, m, 1-H and SO_2Ph) (Found: M^+, 464.202. $C_{28}H_{32}O_4S$ requires *M*, 464.202).

Reductive Desulfonylation of the 14,16-*Ethano* 16²-*Sulfone* **10**.—Activated magnesium turnings (450 mg, 18.5 mmol) were added to a solution of the sulfone **10** (320 mg, 0.69 mmol) in absolute methanol (30 cm^3). The mixture was stirred at 50 °C for 1.5 h. Further magnesium (450 mg, 18.5 mmol) was added, and the mixture was stirred for 1.5 h at 50 °C. The mixture was cooled with ice–water, and conc. hydrochloric acid (8 cm^3) was added. The mixture was concentrated under reduced pressure and the residue was partitioned between water and chloroform. The organic phase was separated, dried ($MgSO_4$), and concentrated to give a crystalline residue (224 mg). Chromatography on silica gel (25 g), with ethyl acetate–toluene (1:19) as eluent, afforded the pure 17-ketone **9** (192 mg, 86%).

Acid-catalysed Rearrangement of the Hydroxy Olefin **11**.—(*a*) Hydrogen bromide (40% in acetic acid; 0.25 cm^3) was added to a stirred solution of the hydroxy olefin **11** (109 mg, 0.35 mmol) in dry dichloromethane (5 cm^3) at 0 °C under argon. After 4 h, starting material was no longer present (TLC), and aq. sodium hydrogen carbonate was added and the product (112 mg) was isolated by extraction with chloroform. Chromatography on silica gel (10 g), with ethyl acetate–toluene (1:49→1:19) as gradient eluent, gave (13R,14S,15R)-3-*methoxy*-13,15-*ethano*-12(13→14)abeo-*estra*-1,3,5(10)-*trien*-17-*one* **12** (50 mg, 46%), m.p. 106–107 °C (from MeOH); $[\alpha]_D$ +83 (*c* 0.96) (Found: C, 81.2; H, 8.4%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.25; H, 8.4%; *M*, 310); ν_{max}/cm^{-1} 1730; Δε +4.1 (295 nm); δ(500 MHz) 0.96 (3 H, s, 13-Me), 1.24 (1 H, dddd, *J* 12.8, 12.0, 11.8 and 8.0, 11β-H), 1.33 (1 H, ddd, *J* 13.1, 9.5, and 5.7, 15^1-H_{endo}), 1.45 (1 H, ddd, *J* 13.0, 9.5 and 3.6, 15²-H_{endo}), 1.48 (1 H, ddd, *J* 13.4, 8.0 and 1.9, 12β-H), 1.57 (1 H, ddd, *J* 12.3, 12.1 and 3.3, 8β-H), 1.69

(1 H, ddd, *J* 13.0, 12.6 and 5.7, 15^2-H_{exo}), 1.75 (1 H, ddd, *J* 13.4, 11.8 and 6.5, 12α-H), 1.85 (1 H, d, *J* 18.0, 16-H_{endo}), 1.94 (1 H, dddd, *J* 12.4, 12.3, 10.1 and 7.5, 7α-H), 2.14 (1 H, m, 7β-H), 2.14 (1 H, ddddd, *J* 13.1, 12.6, 4.5, 3.7 and 3.6, 15^1-H_{exo}), 2.21 (1 H, dddd, *J* 12.8, 6.5, 5.6 and 1.9, 11α-H), 2.37 (1 H, ddd, *J* 18.0, 4.5 and 3.7, 16-H_{exo}), 2.46 (1 H, t, *J* 4.5, 15-H), 2.67 (1 H, ddd, *J* 12.1, 12.0 and 5.6, 9α-H), 2.96 (2 H, m, 6-H_2), 3.76 (3 H, s, 3-OMe), 6.66 (1 H, d, *J* 2.7, 4-H), 6.68 (1 H, dd, *J* 8.2 and 2.7, 2-H) and 7.03 (1 H, d, *J* 8.2, 1-H); δ_C(125 MHz) 219.1 (2, C-17), 157.9 (s, C-3), 137.3 (s, C-5), 133.4 (s, C-10), 126.6 (d, C-1), 113.2 (d, C-4), 111.3 (d, C-2), 59.0 and 58.4 (each s, C-13 and -14), 55.2 (q, 3-OMe), 46.3, 45.8 and 42.0 (each d, C-8, -9 and -15), 45.8, 32.3, 30.8, 30.6, 29.4, 28.0 and 27.8 (each t, C-6, -7, -11, -12, -16, -15^1 and -15^2) and 10.2 (q, C-18).

This was followed by 3-*methoxy*-15β,17β-*ethano*-14β-*estra*-1,3,5(10),8-*tetraen*-17α-*ol* **13** (43 mg, 40%), m.p. 118.5–120 °C (from diethyl ether–hexane); $[\alpha]_D$ −11 (*c* 0.9) (Found: C, 81.1; H, 8.5%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.25; H, 8.4%; *M*, 310); λ_{max}/nm 274 (ε 18 410); ν_{max}/cm^{-1} 3600 and 3460 br; δ(500 MHz) 1.07 (3 H, s, 13β-Me), 1.29 (1 H, td, *J* 9.5 and 2 × 1.6), 1.52 (1 H, s, exch. by D_2O, 17α-OH), 1.69 (1 H, dt, *J* 2 × 12.5, and 4.5), 2.3 (1 H, br dt, *J* ~2 × 14, and 7), 2.52 (1 H, br d, *J* ~16), 2.7 (2 H, m, 6-H_2), 3.78 (3 H, s, 3-OMe), 6.67 (1 H, d, *J* 2.8, 4-H), 6.72 (1 H, dd, *J* 8.5 and 2.8, 2-H) and 7.18 (1 H, d, *J* 8.5, 1-H); δ_C(125 MHz) 157.9 (s, C-3), 137.2 (s, C-5), 132.7 (s, C-10), 129.4 and 128.2 (each s, C-8 and -9), 122.9 (d, C-1), 113.4 (d, C-4), 110.9 (d, C-2), 85.9 (s, C-17), 55.9 (d, C-14), 55.3 (q, 3-OMe), 40.6 (s, C-13), 39.7, 30.4, 30.1, 30.0, 29.0, 26.9 and 21.2 (each t, C-6, -7, -11, -12, -16, -15^1 and -15^2), 37.3 (d, C-15) and 21.1 (q, C-18).

(*b*) The hydroxy olefin **11** (200 mg, 0.65 mmol) and anhydrous pyridinium chloride (1 g) were placed in a combustion tube which was evacuated, sealed, and heated at 205–210 °C for 18 h. The tube was cooled, and the contents were partitioned between ethyl acetate and water. The organic phase was washed, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (195 mg), which was dissolved in dry acetone (20 cm^3) and the solution was stirred with potassium carbonate (1.6 g) and dimethyl sulfate (0.63 cm^3). After 3 h at 25 °C, further potassium carbonate (0.55 g) was added, and the mixture was stirred for a further 16 h. Ammonium hydroxide (1 cm^3) was added, and the mixture was poured into water, and extracted with ethyl acetate. The extract was worked up to give a residue (220 mg), which was adsorbed on silica gel (30 g). Gradient elution with ethyl acetate–toluene (1:49→1:19) gave the spiroketone **12** (12 mg, 6%) followed by 3-*methoxy*-14,16β-*ethano*-14β-*estra*-1,3,5(10)-*trien*-17-*one* **14** (106 mg, 53%), m.p. 168–170 °C (from Et_2O–MeOH); $[\alpha]_D$ +174 (*c* 1.0) (Found: C, 81.2; H, 8.7%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.25; H, 8.4%; *M*, 310); ν_{max}/cm^{-1} 1732; $\Delta\varepsilon_{max}$(MeOH) +3.93 (291 nm); δ(500 MHz) 1.05 (3 H, s, 13β-Me), 1.37 (1 H, dddd, *J* 14.0, 13.7, 12.8 and 3.5, 11β-H), 1.39 (1 H, d, *J* 10.5), 1.58 (1 H, ddd, *J* 11.4, 11.3 and 2.8, 8β-H), 1.69 (1 H, ddd, *J* 14.0, 13.8 and 3.6, 12α-H), 1.82 (2 H, m), 1.96 (1 H, dq, *J* 10.5 and 3 × 2.1), 2.07 (1 H, ddt, *J* 12.4, 2 × 3.8 and 2.8, 7β-H), 2.31 (1 H, ddt, *J* 13.7, 2 × 3.6 and 3.5, 11α-H), 2.52 (1 H, ddd, *J* 12.8, 11.4 and 3.5, 9α-H), 2.64 (1 H, d, *J* 4.8, 16α-H), 2.87 (2 H, m, 6-H_2), 3.76 (3 H, s, 3-OMe), 6.63 (1 H, d, *J* 2.6, 4-H), 6.71 (1 H, dd, *J* 8.6 and 2.6, 2-H) and 7.19 (1 H, d, *J* 8.6, 1-H); δ_C(125 MHz) 222.2 (s, C-17), 157.6 (s, C-3), 137.7 (s, C-5), 132.4 (s, C-10), 126.5 (d, C-1), 113.6 (d, C-4), 111.7 (d, C-2), 55.2 (q, 3-OMe), 52.7 and 48.7 (each s, C-13 and -14), 50.3 (d, C-16), 40.2 and 38.7 (each d, C-8 and -9), 33.8, 30.5 (× 2), 26.1, 25.7, 25.1 and 23.75 (each t, C-6, -7, -11, -12, -15, -16^1 and -16^2) and 16.7 (q, C-18).

Further elution gave mixed fractions (62 mg) containing the 15β,17β-ethano-17α-alcohol **13**.

Hydride Reduction of the 14,16-*Ethano*-17-*ketones*.—(*a*) A solution of the ketone **4** (50 mg, 0.154 mmol) and sodium borohydride (80 mg, 2.1 mmol) in absolute ethanol (5 cm^3) was stirred for 18 h at 50 °C. The excess of reagent was destroyed with aq. acetic acid (50%), and the mixture was concentrated under reduced pressure. The oily residue was partitioned between aq. sodium hydrogen carbonate and chloroform. The organic phase was washed with water, dried ($MgSO_4$), and concentrated to give a syrup (55 mg). Flash chromatography on silica gel (10 g), with ethyl acetate–benzene (1:99) as eluent, gave 3-*methoxy*-16α-*methyl*-14,16β-*ethano*-14β-*estra*-1,3,5(10)-*trien*-17β-*ol* **15** (38 mg, 75%), m.p. 101–102 °C (from aq. MeOH); $[\alpha]_D$ +43 (*c* 0.94) (Found: C, 80.9; H, 9.3%; M^+, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; *M*, 326); ν_{max}/cm^{-1} 3600 (OH), 1610 and 1500; δ(500 MHz) 0.91 (3 H, s, 13β-Me), 1.1 (3 H, s, 16α-Me), 1.6 (1 H, dt, *J* 2 × 13.5, and 3.5, 8β-H), 2.01 (1 H, ddt, *J* 12.0, 2 × 4.5, and 2.2), 2.2 (1 H, dq, *J* 13.1, and 3 × 3.5, 11α-H), 2.42 (1 H, dt, *J* 2 × 11.5, and 3.3, 9α-H), 2.82 (2 H, m, 6-H_2), 3.32 (1 H, d, *J* 4.1, 17α-H), 3.75 (3 H, s, 3-OMe), 6.61 (1 H, d, *J* 2.8, 4-H), 6.69 (1 H, dd, *J* 8.6 and 2.7, 2-H) and 7.19 (1 H, d, *J* 8.6, 1-H).

Elution with ethyl acetate–benzene (1:49) gave 3-*methoxy*-16α-*methyl*-14,16β-*ethano*-14β-*estra*-1,3,5(10)-*trien*-17α-*ol* **16** (7 mg, 14%) as a glass, δ(500 MHz) 0.95 (1 H, dd, *J* 10.1 and 1.7), 1.04 (3 H, s, 13β-Me), 1.05 (3 H, s, 16α-Me), 1.68 (1 H, td, *J* 10.1 and 2 × 2.3), 1.94 (1 H, dt, *J* 2 × 13.7 and 3.7), 2.03 (1 H, td, *J* 10.1 and 2 × 4.4), 2.27 (1 H, dq, *J* 13.0, and 3 × 3.6, 11α-H), 2.39 (1 H, br dt, *J* ~2 × 11.0, and 3.0, 9α-H), 2.8 (2 H, m, 6-H_2) 3.21 (1 H, br s, 17β-H), 3.76 (3 H, s, 3-OMe), 6.6 (1 H, d, *J* 2.7, 4-H), 6.69 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.22 (1 H, d, *J* 8.6, 1-H) (Found: M^+, 326.225. $C_{22}H_{30}O_2$ requires *M*, 326.225).

(*b*) A solution of the ketone **14** (200 mg, 0.645 mmol) and sodium borohydride (320 mg, 8.5 mmol) in absolute ethanol (25 cm^3) was stirred at 50 °C under argon for 2 h, then the reaction mixture was worked up as described in the foregoing experiment. The resultant residue (220 mg), was adsorbed on silica gel (40 g). Elution with ethyl acetate–toluene (1:19) gave 3-*methoxy*-14,16β-*ethano*-14β-*estra*-1,3,5(10)-*trien*-17β-*ol* **17** (181 mg, 90%), m.p. 120–121 °C (from benzene–hexane); $[\alpha]_D$ +60 (*c* 0.98) (Found: C, 80.75; H, 9.0%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; *M*, 312); ν_{max}/cm^{-1} 3622 and 3467 br; δ(500 MHz) 0.91 (3 H, s, 13β-Me), 1.14 (1 H, dd, *J* 10.2 and 1.2), 1.47 (1 H, ddd, *J* 11.5, 11.4, and 2.5, 8β-H), 1.55 (1 H, m, exch. by D_2O, 17β-OH), 2.45 (1 H, ddd, *J* 11.6, 11.5, and 3.4, 9α-H), 2.83 (2 H, m, 6-H_2), 3.69 (1 H, d, *J* 4.2, 17α-H), 3.76 (3 H, s, 3-OMe), 6.61 (1 H, d, *J* 2.6, 4-H), 6.69 (1 H, dd, *J* 8.6 and 2.6, 2-H) and 7.19 (1 H, d, *J* 8.6, 1-H), followed by 3-*methoxy*-14,16β-*ethano*-14β-*estra*-1,3,5(10)-*trien*-17α-*ol* **18** (14 mg, 7%), m.p. 132–134 °C (from aq. MeOH); $[\alpha]_D$ +45 (*c* 0.3) (Found: C, 80.5, H, 8.9%; M^+, 312); ν_{max}/cm^{-1} 3619 and 3480 br; δ(500 MHz) 1.03 (3 H, s, 13β-Me), 1.06 (1 H, d, *J* 10.2) 1.59 (1 H, m, exch. by D_2O, 17α-OH), 1.86 (1 H, dd, *J* 10.2 and 1.2), 2.44 (1 H, dt, *J* 2 × 11.4, and 3.6, 9α-H), 2.83 (2 H, m, 6-H_2), 3.46 (1 H, br s, $W_{\frac{1}{2}}$ 3.7, 17β-H), 3.76 (3 H, s, 3-OMe), 6.61 (1 H, d, *J* 2.6, 4-H), 6.7 (1 H, dd, *J* 8.6 and 2.6, 2-H) and 7.22 (1 H, d, *J* 8.6, 1-H).

A solution of the 3-methyl ether **17** (86 mg, 0.28 mmol) in dry toluene (4 cm^3) was treated with DIBAL (1.2 mol dm^{-3} in toluene; 2.3 cm^3), and the mixture was refluxed under argon for 24 h. The cooled solution was acidified with hydrochloric acid, and the product was isolated by extraction with ethyl acetate. Evaporation of the extract under reduced pressure gave a residue (90 mg), which was filtered through silica gel (6 g) with ethyl acetate–toluene (1:4) to give the 3,17β-*diol* **19** (75 mg, 92%), m.p. 166–167 °C (from benzene); $[\alpha]_D$ +59 [*c* 0.96, tetrahydrofuran (THF)] (Found: C, 80.5; H, 8.7%; M^+, 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.8%; *M*, 298); ν_{max}/cm^{-1} 3319 br.

(*c*) The 17-ketone **9** (115 mg, 0.35 mmol) was treated with

Table 2 Crystallographic data acquisition and refinement details of compounds **4**, **6**, **12** and **14**

Compound	**3**	**6**	**12**	**14**
Empirical formula	$C_{22}H_{28}O_2$	$C_{28}H_{32}O_4S$	$C_{21}H_{26}O_2$	$C_{21}H_{26}O_2$
Relative molecular mass	324.5	464.6	310.4	310.4
Crystal dimensions, mm	0.22 × 0.27 × 0.32	0.13 × 0.22 × 0.40	0.14 × 0.24 × 0.24	0.27 × 0.32 × 0.50
Space group (no.)	$P2_12_12_1$ (19)	$P2_12_12_1$ (19)	$P2_1$ (14)	$P2_1$ (14)
Cell dimensions:				
a/Å	7.167(1)	7.913(2)	6.981(2)	7.953(1)
b/Å	10.189(1)	12.276(2)	11.274(2)	7.726(2)
c/Å	24.708(2)	24.689(3)	11.081(2)	13.844(1)
β/°	90	90	101.78(2)	98.41(1)
Z	4	4	2	2
Volume (Å^3)	1804(1)	2399(1)	854(1)	841(1)
D_{calc}/g cm^{-3}	1.19	1.29	1.21	1.23
μ/cm^{-1}	5.0	1.3	0.41	0.42
Radiation (λ, Å)	Cu-Kα, 1.5418	Mo-Kα, 0.7107	Mo-Kα, 0.7107	Mo-Kα, 0.7107
T/°C	23	23	23	23
F(000)	704	992	336	336
Scan type (ω:2θ)	1:1	3:1	1:0	1:1
Scan range, θ°	$5 < \theta < 78$	$3 < \theta < 27$	$3 < \theta < 30$	$3 < \theta < 30$
Zone collected:				
h	0, 9	0, 10	0, 9	0, 11
k	0, 13	0, 15	0, 15	0, 10
l	0, 31	0, 31	−15, 15	−19, 19
Maximum scan speed (variable deg min^{-1})	5.49	5.49	5.49	5.49
Maximum scan time (s)	50	50	50	50
Scan angle (ω + (DOMB tanθ)°	0.55, 0.14	0.55, 0.34	0.52, 0.34	0.44, 0.34
Aperture size (mm)	1.4 × 4.0	1.3 × 4.0	1.3 × 4.0	1.4 × 4.0
Reflections collected	2230	3001	2606	2623
Decay (%)	<1	<1	<1	<1
Unique reflections used ($F >$)	2113, $F > 0$	2573, $F > 0$	2284, $F > 0$	2043, $F > 0$
R_{int}	0.00	0.00	0.00	0.00
Parameters refined	302	371	286	214
Max. positional shift/esd	0.14	0.20	0.14	0.06
Residual electron density (e Å^3):				
Maximum	0.15	0.40	0.20	0.29
Minimum	−0.21	−0.40	−0.20	−0.32
U_{iso}(H)/Å^2	0.073(2)	0.051(3)	0.075(2)	0.083(3)
R	0.049	0.081	0.070	0.103
R_w	0.037	0.032	0.028	0.036

Table 3 Fractional atomic co-ordinates (× 10^4) for compound **4**

	x	y	z
C(1)	6862(5)	427(3)	4498(1)
C(2)	7202(5)	1170(3)	4964(1)
C(3)	5944(5)	1065(3)	5384(1)
C(4)	4402(5)	259(3)	5338(1)
C(5)	4070(4)	9538(3)	4870(1)
C(6)	2354(5)	8687(4)	4840(1)
C(7)	1794(4)	8374(3)	4253(1)
C(8)	3498(4)	7835(3)	3951(1)
C(9)	4961(4)	8926(3)	3899(1)
C(10)	5324(4)	9618(3)	4439(1)
C(11)	6750(4)	8388(3)	3637(1)
C(12)	6288(4)	7867(3)	3074(1)
C(13)	4831(4)	6768(3)	3088(1)
C(14)	3031(4)	7217(3)	3394(1)
C(15)	2056(4)	8071(3)	2961(1)
C(16)	2050(5)	7016(3)	2514(1)
C(17)	4079(4)	6626(3)	2509(1)
C(18)	5691(6)	5485(4)	3283(2)
C(19)	1137(5)	5836(3)	2811(2)
C(20)	1665(5)	6053(3)	3413(1)
O(1)	6085(4)	1750(2)	5863(1)
O(2)	4991(3)	6247(2)	2125(1)
C(21)	7674(9)	2573(4)	5931(2)
C(22)	1201(7)	7350(4)	1965(1)

sodium borohydride (180 mg, 4.74 mmol) in absolute ethanol (12 cm^3) for 20 h at 50 °C. Work-up of the reaction mixture gave a crystalline residue (120 mg), which was adsorbed on silica gel (12 g). Elution with ethyl acetate–toluene (1:99) gave starting material **9** (5 mg, 4% recovery) followed by 3-*methoxy*-16β-*methyl*-14,16α-*ethanoestra*-1,3,5(10)-*trien*-17β-*ol* **20** (54 mg, 47%), m.p. 124–125 °C (from aq. MeOH) (Found: C, 80.1; H, 9.1%; M$^+$, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; *M*, 326); ν_{max}/cm^{-1} 3600 (OH), 1605 and 1495; δ(500 MHz) 0.99 (3 H, s, 13β-Me), 1.15 (3 H, s, 16β-Me), 1.45 (1 H, td, *J* 10.0, and 2 × 2.6), 1.72 (1 H, ddt, *J* 12.5, 5.7, and 2 × 2.8, 7β-H), 2.09 (1 H, dt, *J* 2 × 13.0, and 4.6, 8β-H), 2.33 (1 H, dtt, *J* 13.5, 2 × 5.1, and 2 × 2.0, 11α-H), 2.51 (1 H, dt, *J* 2 × 11.7, and 5.0, 9α-H), 2.77–2.9 (2 H, m, 6-H$_2$), 3.47 (1 H, d, *J* 4.4, 17α-H), 3.75 (3 H, s, 3-OMe), 6.6 (1 H, d, *J* 2.7, 4-H), 6.69 (1 H, dd, *J* 8.6 and 2.7, 2-H) and 7.18 (1 H, d, *J* 8.6, 1-H), followed by 3-*methoxy*-16β-*methyl*-14,16α-*ethanoestra*-1,3,5(10)-*trien*-17α-*ol* **21** (52 mg, 45%), m.p. 157–158 °C (from aq. MeOH) (Found: C, 80.5; H, 9.2%; M$^+$, 326); ν_{max}/cm^{-1} 3600 (OH), 1605 and 1495; δ(500 MHz) 0.98 (3 H, s, 13β-Me), 1.07 (3 H, s, 16β-Me), 1.1 (1 H, d, *J* 10.2), 1.15 (1 H, tt, *J* 2 × 11.9, and 2 × 3.0), 1.47 (1 H, td, *J* 9.8, and 2 × 2.5), 1.88 (1 H, dt, *J* 2 × 11.3, and 2.8), 1.92 (1 H, dt, *J* 2 × 13.3, and 4.7), 2.27 (1 H, dtt, *J* 13.6, 2 × 4.9, and 2 × 2.0, 11α-H), 2.51 (1 H, dt, *J* 2 × 11.7, and 5.0, 9α-H), 2.8–2.9 (2 H, m, 6-H$_2$), 3.2 (1 H, d, *J* 4.7, 17β-H), 3.76 (3 H, s, 3-OMe), 6.6 (1 H, d, *J* 2.7, 4-H), 6.69 (1 H, dd, *J* 8.6 and 2.7, 2-H) and 7.17 (1 H, d, *J* 8.6, 1-H).

Birch Reduction of the 17β-*Alcohols*.—(*a*) A solution of compound **15** (123 mg, 0.38 mmol) in dry THF (10 cm^3) was added to liquid ammonia (100 cm^3, freshly distilled from sodium) containing dry *tert*-butyl alcohol (8 cm^3). Lithium metal (210 mg, 30 g atom) was added in portions and the mixture was stirred for 4 h at −35 °C. Methanol (8 cm^3) was

Table 4 Fractional atomic co-ordinates (× 10^4) for compound **6**

	x	*y*	*z*
C(1)	1959(6)	2090(4)	515(2)
C(2)	1371(6)	2542(4)	990(2)
C(3)	−190(7)	2195(4)	1194(2)
C(4)	−1114(6)	1424(4)	922(2)
C(5)	−522(6)	956(4)	442(2)
C(6)	−1549(7)	71(5)	175(2)
C(7)	−943(6)	−233(5)	−384(2)
C(8)	979(6)	−377(4)	−374(2)
C(9)	1811(6)	749(4)	−273(2)
C(10)	1081(6)	1274(4)	238(2)
C(11)	3745(6)	654(4)	−233(2)
C(12)	4557(6)	34(4)	−706(2)
C(13)	3718(6)	−1081(4)	−777(2)
C(14)	1770(6)	−946(4)	−859(2)
C(15)	1280(6)	−2124(4)	−1005(2)
C(16)	2546(6)	−2551(4)	−1273(2)
C(17)	3927(6)	−1679(4)	−1322(2)
C(18)	4230(7)	−1817(5)	−301(3)
C(19)	3218(6)	−873(4)	−1746(2)
C(20)	1802(5)	−296(4)	−1422(2)
O(1)	−884(5)	2625(3)	1664(1)
C(21)	163(9)	2769(6)	2092(2)
O(2)	5534(4)	−2124(3)	−1448(2)
C(22)	2720(8)	−3626(5)	−1560(3)
S	−191(2)	−164(1)	−1776(1)
O(3)	−1261(4)	−1106(3)	−1706(2)
O(4)	−869(5)	900(3)	−1630(1)
C(23)	421(6)	−114(4)	−2466(2)
C(24)	98(7)	−977(4)	−2794(2)
C(25)	685(7)	−963(5)	−3319(2)
C(26)	1580(7)	−99(6)	−3502(2)
C(27)	1885(7)	798(5)	−3171(2)
C(28)	1279(7)	793(4)	−2646(2)

Table 5 Fractional atomic co-ordinates (× 10^4) for compound **12**

	x	*y*	*z*
C(1)	2314(5)	845	5082(3)
C(2)	1015(6)	1239(4)	5809(3)
C(3)	596(5)	2435(4)	5829(3)
C(4)	1458(5)	3229(4)	5143(3)
C(5)	2750(5)	2832(4)	4425(2)
C(6)	3582(5)	3728(4)	3648(3)
C(7)	5320(5)	3271(4)	3128(3)
C(8)	4832(4)	2027(4)	2607(3)
C(9)	4653(4)	1204(4)	3669(3)
C(10)	3185(4)	1635(4)	4400(2)
C(11)	4269(5)	5(5)	3036(3)
C(12)	5684(6)	8(5)	2148(3)
C(13)	5834(4)	1609(5)	474(2)
C(14)	6130(4)	1331(4)	1875(2)
C(15)	8357(5)	1574(5)	2116(3)
C(16)	9021(6)	705(5)	1214(4)
C(17)	7329(5)	755(5)	118(3)
C(18)	3820(5)	1485(6)	−332(3)
C(19)	6801(6)	2832(5)	477(4)
C(20)	8510(6)	2818(5)	1580(4)
C(21)	−1597(8)	2152(6)	7211(4)
O(1)	−661(4)	2936(4)	6499(2)
O(2)	7181(3)	220(4)	−842(2)

added to disperse the blue colour, and the ammonia was allowed to evaporate. The residue was diluted with methanol (20 cm^3) and acidified with conc. hydrochloric acid (3 cm^3). The clear solution was stirred for 18 h at 25 °C, then concentrated under reduced pressure, and the residue was partitioned between water and ethyl acetate. The organic phase was washed with water, dried ($MgSO_4$), and concentrated to give a yellow solid (140 mg), which was adsorbed on silica gel (15 g). Elution with ethyl acetate–benzene (1:4) gave 17β-*hydroxy*-16α-*methyl*-14,16β-*ethano*-14β-*estr*-4-*en*-3-*one* **22** (84 mg, 70.9%), m.p. 144–145 °C (from benzene–hexane); $[\alpha]_D$ −2.5 (*c* 0.5) (Found: C, 80.1; H, 10.0%; M^+, 314, $M^+ - H_2O$, 296. $C_{21}H_{30}O_2$ requires C, 80.2; H, 9.6%; *M*, 314); ν_{max}/cm^{-1} 3600 (OH), 1660 (CO) and 1615 (C=C); δ 0.93 (3 H, s, 13β-Me), 1.06 (3 H, s, 16α-Me), 3.25 (1 H, d, *J* 4.8, 17α-H) and 5.8 (1 H, s, 4-H).

(*b*) A solution of the 3-methyl ether **17** (78 mg, 0.25 mmol) in dry THF (7.5 cm^3) was added to liquid ammonia (freshly distilled from sodium, 16 cm^3) at −78 °C under argon. Lithium (52 mg, 7.5 g atom) was added in small portions to the stirred solution. After 10 min, dry ethanol (0.45 cm^3) was added during 3 min, and the mixture was stirred at −78 °C for 2 h. Ammonium chloride (500 mg) was added in portions and the mixture was stirred until the blue colour was dispersed. The ammonia was evaporated off, and water (40 cm^3) was added. The product (77 mg) was isolated by extraction with ethyl acetate; the residue obtained on evaporation of the extract was dissolved in methanol (25 cm^3) and the solution was treated with oxalic acid (62 mg) in water (3 cm^3) at 20 °C under argon for 18 h. Aq. sodium hydrogen carbonate was added and the product (75 mg) was isolated by extraction with ethyl acetate; the extract was evaporated and the residue was dissolved in ethanol (8 cm^3) and treated with ethanolic 0.1 mol dm^{-3} sodium ethoxide (1 cm^3) at 20 °C for 6 h. Water (20 cm^3) was added, and the product (80 mg) was isolated by extraction with ethyl acetate, and adsorbed on silica gel (10 g). Elution with ethyl acetate–toluene (1:4) gave 17β-*hydroxy*-14,16β-*ethano*-14β-*estr*-4-*en*-3-*one* **23** (51 mg, 68%), m.p. 173–175 °C (from CH_2Cl_2–EtOAc); $[\alpha]_D$ +18 (*c* 0.35) (Found: C, 79.8; H, 9.7%; M^+, 300. $C_{20}H_{28}O_2$ requires C, 80.0; H, 9.4; *M*, 300); λ_{max}/nm 240 (ε 17 110); ν_{max}/cm^{-1} 3617, 3463br and 1663; $\Delta\varepsilon_{max}$(MeOH) −2.1 (316 nm); δ(500 MHz) 0.93 (3 H, s, 13β-Me), 1.07 (1 H, d, *J* 10.3 and 1.8), 1.53 (1 H, m, exch. by D_2O, 17β-OH), 3.62 (1 H, d, *J* 4.0, 17α-H) and 5.8 (1 H, br s, $w_{\frac{1}{2}}$ 4.2, 4-H); δ_C(125 MHz) 199.9 (s, C-3), 166.6 (s, C-5), 124.2 (d, C-4), 81.3 (d, C-17), 53.3 (s, C-14), 46.6, 43.6, 43.3 and 41.5 (each d, C-8, -9, -10 and -16), 40.4 (s, C-13), 39.7, 36.5, 36.0, 33.5, 27.7, 27.2, 26.6, 26.4 and 19.5 (each t, C-1, -2, -6, -7, -11, 12, -15, -16[1] and -16[2]) and 15.5 (q, C-18).

Table 6 Fractional atomic co-ordinates (× 10^4) for compound **14**

	x	*y*	*z*
C(1)	1 354(5)	8 386	877(3)
C(2)	451(5)	8 367(10)	−663(3)
C(3)	1 173(6)	9 180(9)	−797(3)
C(4)	2 740(6)	9 942(9)	−590(3)
C(5)	3 628(5)	9 910(9)	350(3)
C(6)	5 416(6)	10 620(9)	504(3)
C(7)	6 251(6)	10 702(10)	1 525(3)
C(8)	5 804(5)	9 134(9)	2 108(3)
C(9)	3 897(5)	9 142(9)	2 140(2)
C(10)	2 939(5)	9 147(9)	1 105(3)
C(11)	3 398(5)	7 645(10)	2 764(3)
C(12)	4 346(4)	7 783(9)	3 808(2)
C(13)	6 293(5)	7 641(9)	3 805(3)
C(14)	6 894(5)	9 059(9)	3 122(3)
C(15)	6 976(6)	10 675(9)	3 795(3)
C(16)	8 128(5)	9 834(9)	4 666(3)
C(17)	7 162(5)	8 212(10)	4 823(3)
C(18)	6 769(6)	5 749(9)	3 606(3)
C(19)	9 643(5)	9 247(10)	4 163(3)
C(20)	8 819(4)	8 762(9)	3 093(3)
O(1)	412(4)	9 268(8)	−1 760(2)
C(21)	−1 139(6)	8 339(10)	−2 022(3)
O(2)	7 087(4)	7 475(8)	5 583(2)

Crystal Structure Determinations.—All measurements were carried out on an Enraf–Nonius CAD4 single-crystal diffractometer equipped with a graphite monochromator. Unit-cell parameters were refined by least squares on the basis of

optimised setting angles of 25 reflections for each compound. Crystal stability was checked at regular intervals during all data collections. Data reduction consisted of correction for background and Lp factors only. The structures were solved by direct methods and refined by full-matrix least squares using the SHELX programs [13,14] for all computations. The details related to the data collection, structure analyses and refinement, using $\sigma^{-2}(F_0)$ weights, are summarised in Table 2. The hydrogen atoms for compound **14** were included in the refinement in calculated positions and with a common isotropic thermal factor that was also refined. The hydrogen atoms for compounds **4**, **6** [except those attached to C(20) and C(21)] and **12** were located experimentally and refined without any restriction, using common isotropic thermal factors for the different molecules. The refined atomic co-ordinates are given in Tables 3–6. Full lists of bond lengths, bond angles, calculated atomic co-ordinates, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDB).*

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* See 'Instructions for Authors,' section 5.6.3, in the January issue.

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