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# CHEMOSELECTIVE REACTIONS OF 14,17α-BIS(HYDROXYMETHYL)-3-METHOXYESTRA-1,3,5(10)-TRIEN-17β-OL. SYNTHESIS OF NOVEL 14,17-HETERO-BRIDGED 19-NORSTEROIDS[1]

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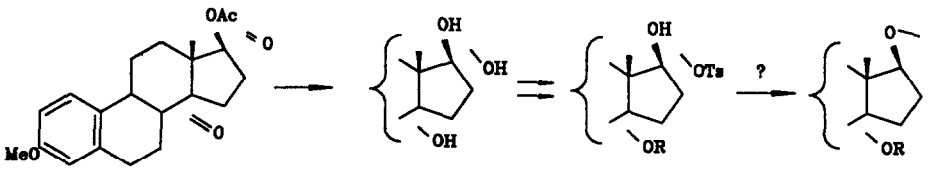
Chemoselective differentiation of the primary hydroxy groups in 14,17α-bis(hydroxymethyl)-3-methoxyestra-1,3,5(10)-trien-17β-ol (2) has been investigated in a series of reactions which lead, *inter alia*, to novel 14,17-hetero-bridged steroid hormone analogues. Thus, routes are described to 3-methoxy-14,17α-(2-oxapropano)estra-1,3,5(10)-trien-17β-ol (4) and 17α,14-epoxymethano-17β-hydroxymethyl-3-methoxyestra-1,3,5(10)-triene (8). Related experiments show that the 17[1]-hydroxy group in (2) is preferentially functionalised, and that 17[1]-tosyloxy 14[1]-ethers undergo facile intramolecular participation reactions. The utility of certain intermediates in the synthesis of hormone analogues is exemplified by conversion of (8) into 17α,14-epoxymethano-19-norpregn-4-ene-3,20-dione (36).

A cycloaddition-mediated route has recently been developed to synthesise a new group of 14,17-ethano and 14-alkyl 19-norsteroids.[3] The versatility of this approach is exemplified by modification of the cycloadducts, to give 14α-methyl, 14α-functionalised-methyl, and 14β-functionalised-ethyl compounds variously substituted at C(17).[3-5] A key intermediate in this work, 17β-acetoxy-3-methoxyestra-1,3,5(10)-triene-14,17α-dicarbaldehyde (1), has also been converted into a 14-substituted 17-spirolactone,[1,6] in order to investigate the scope for designing novel aldosterone antagonists.

An aspect of the latter investigation included attempted chemoselective differentiation of the 14- and 17-formyl groups in (1).[1] Although direct differentiation proved to be impractical, we conceived an indirect approach based upon conversion of (1) into the triol (2), for chemoselective protection or potentiation of the resultant 14[1]- and 17[1]-hydroxy groups, in particular, for possible conversion into a 17-spiro-oxirane (Scheme 1).




1 2

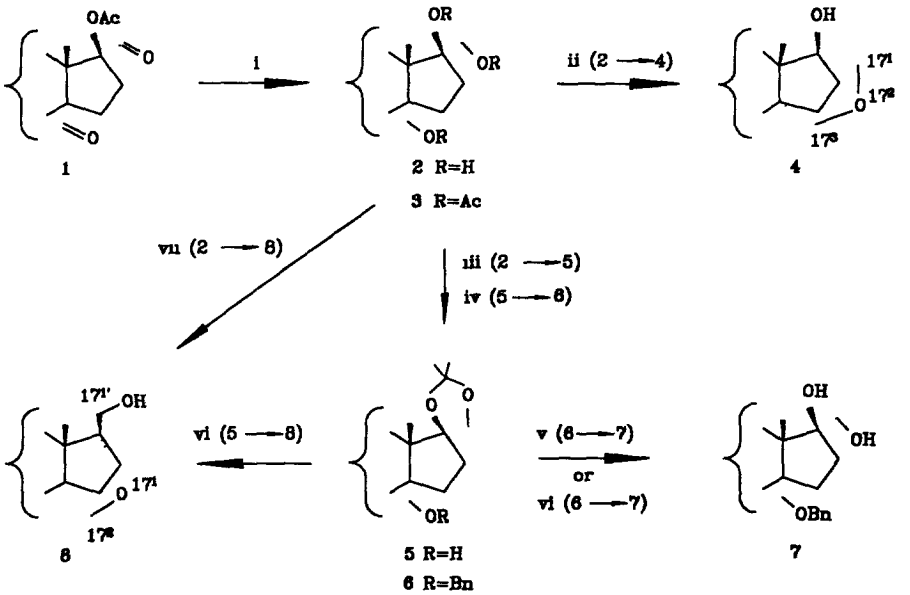
**Scheme 1 Proposed route to 14¹-functionalised 17-spiro-oxiranes**

In pursuit of this objective, the dicarbaldehyde (1) was readily converted into the corresponding triol (2), through exhaustive reduction with lithium aluminium hydride. Characterisation of the triol (2) was hampered by poor solubility in various organic media, but the derived triacetate (3) displayed the expected properties.

A first attempt to achieve chemoselective $14^1$- or $17^1$-derivatisation of (2) was through sulphonylation - it was hoped that treatment of the triol (2) with toluene-*p*-sulphonyl chloride (1 mol) in pyridine would provide an intermediate for direct base-mediated closure to the 17-spiro-oxirane. In the event, the formation or intermediacy of a tosyl derivative was not detected. However, a single less-polar product (4) (76%) was isolated, the spectroscopic characteristics of which were incompatible with a 17-spiro-oxirane. Thus, the n.m.r. spectrum of (4) displayed two AB multiplets at $\delta$ 3.29 - 4.15($J_{AB}$ 10.1 and $J_{A'B'}$ 11.1 Hz), which demonstrated the presence of a 14$\alpha$,17$\alpha$-(2-oxapropano) bridge. This result failed to distinguish which of the two possible obligatory monotosylates ($14^1$- or $17^1$-) was implicated in formation of the final product, but subsequent experiments (see below) suggest that the $17^1$-tosylate would indeed have formed preferentially. It is therefore apparent that $14^1$-OH .....C($17^1$) closure is extremely facile or, alternatively, that 17$\beta$-OH .....C($17^1$) closure to form a 17-spiro-oxirane is retarded by an unfavourable conformational alignment.

Accordingly, attention was turned to prior protection of the $14^1$-hydroxy group in (2), in order to prevent the observed mode of closure and thereby, to promote 17-spiro-oxirane formation from a $14^1$-OR,$17^1$-OTs derivative. For this purpose, the 17$\beta$,$17^1$-acetonide (5) was first prepared from the triol (2) under standard conditions, then treated with benzyl bromide in the presence of sodium hydride to give the $14^1$-benzyloxy

17β,17¹-acetonide (6). Hydrolysis of the dioxolane was slow and inefficient in the presence of aqueous 80% acetic acid, giving at best a 55% yield of the 14¹-benzyloxy 17β,17¹-diol (7). More prolonged treatment in this medium or the use of higher temperatures resulted in unacceptable levels of decomposition of the product during the course of the reaction, as did the use of a variety of other aqueous acids or ion-exchange resin.



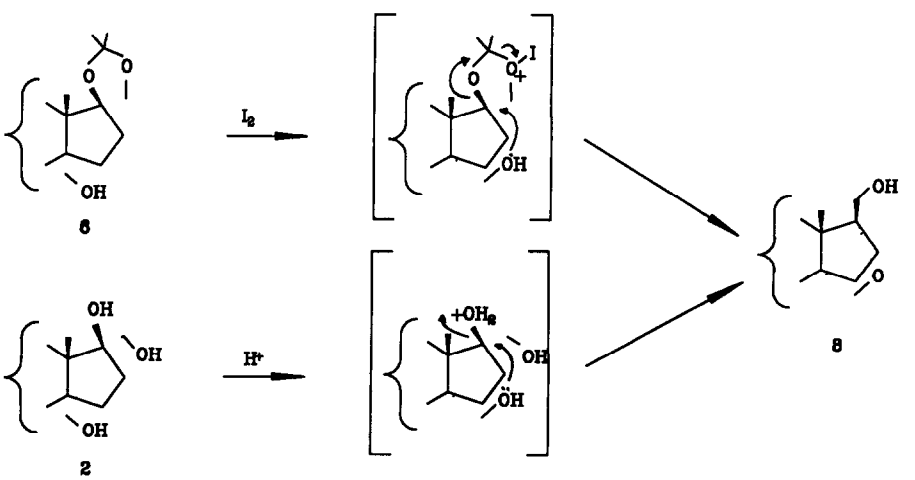

**Reagents** (i) LAH–THF, 25 °C (ii) $pTsCl–C_5H_5N$, 0 °C (iii) $Me_2CO$–anh $CuSO_4$ (iv) NaH–BnBr–DME (v) AcOH–$H_2O$, 62 °C (vi) $I_2$–MeOH, (viii) HCl–THF, 25 °C

In an attempt to overcome this problem, a mild, non-acidic method of hydrolysis was attempted.[7] However, the prescribed treatment of (6) with iodine - methanol resulted in a very poor yield (*ca* 28%) of the desired diol (7), accompanied by numerous decomposition products which were not characterised. It seemed possible that this unfavourable outcome could be ascribed to steric hindrance around C(17), and a similar experiment was therefore conducted on the 14α-hydroxymethyl 17β,17¹-acetonide (5), in order to ascertain whether the steric problem would be partially alleviated in the absence of the 14¹-benzyloxy group. However, following treatment of (5) with iodine - methanol, the triol (2) was not detected in

the reaction mixture, but the major product (62%) was formulated as 17α,14-epoxymethano-17β-hydroxymethyl-3-methoxyestra-1,3,5(10)-triene (8).

The evidence for this structure rested largely upon interpretation of a remarkably well-dispersed 500 MHz $^1$H n.m.r. spectrum, which could be fully assigned with the aid of a COSY correlation. Distinctive multiplets for the applicable C(1) - C(16) protons corresponded closely with those reported for estradiol 3-methyl ether,[8] thus establishing the skeletal integrity of (8). Diagnostic resonances for the 14,17-functionality were observed at δ 3.72 and 3.8(each 1H, dd, collapsing to d *J* 12 Hz upon $D_2O$ exchange, $17^{1'}$-$H_2$) and at δ 3.48 and 4.14(each 1H, d, *J* 7.4, and dd, *J* 7.4 and 4.1 Hz resp., $17^2$-$H_2$). The latter multiplets correspond closely with those observed for similar 17α,14α-epoxymethano-bridged systems,[3,6] in which the smaller splitting (*J* 4.1 Hz) is ascribed to four-bond coupling between $17^2$-$H_{exo}$ and 15β-H in a favourable W-conformation.

Formation of the product (8) under these reaction conditions is evidently initiated by complexation of iodine with one of the dioxolane oxygen atoms, followed by intramolecular capture of the incipient carbocation at C(17) by the $14^1$-hydroxy group (Scheme 2). A more efficient and direct synthesis was achieved through treatment of the triol (2) with conc. hydrochloric acid in tetrahydrofuran at 25 °C, to give the epoxymethano compound (8)(87%), in a mechanistically analogous intramolecular closure (Scheme 2).



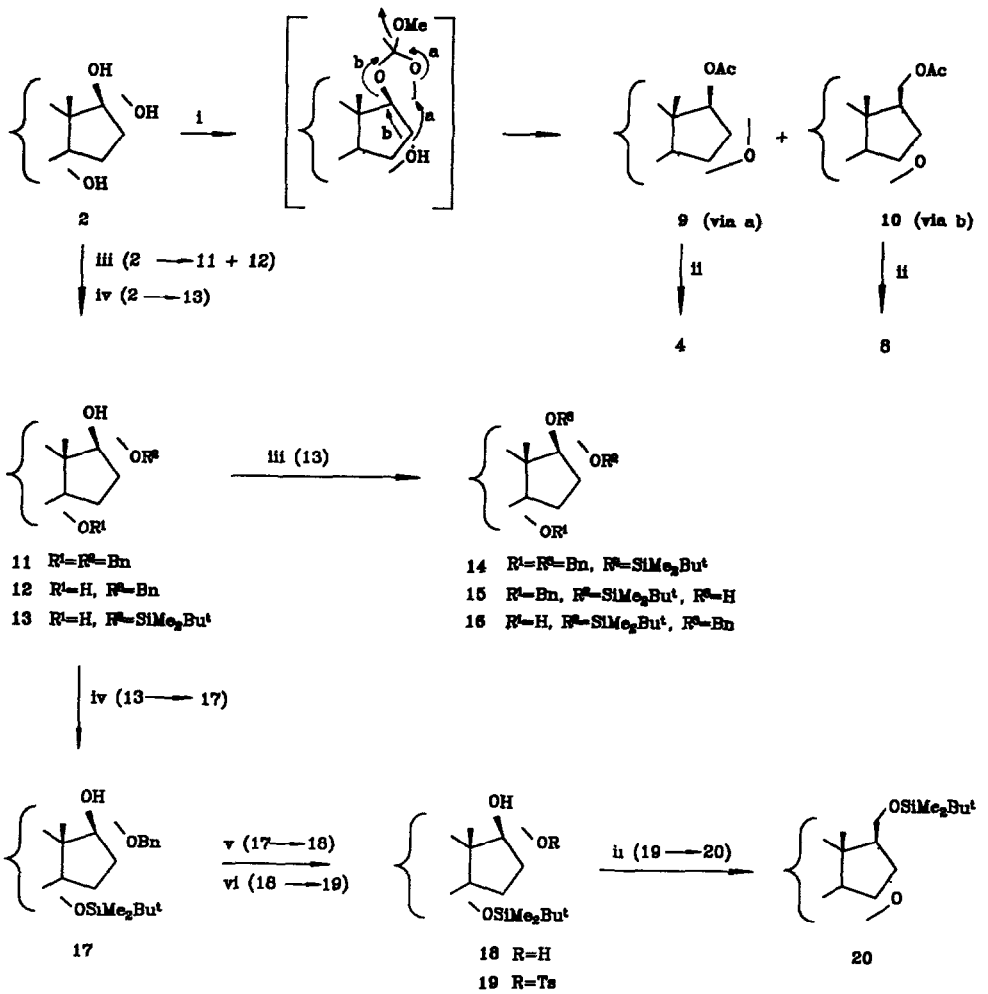

Scheme 2 Intramolecular closure of (2) and (6)

The foregoing experiments demonstrated that participation by the $14^1$-hydroxy group was likely to be a major obstacle to selective manipulation of 17-functionality for the intended purpose (Scheme 1). A possible recourse was considered to be the use of a less robust $17\beta,17^1$-protective group than the acetonide, in order to facilitate a milder 14-protection, $17\beta,17^1$-deprotection sequence. For this purpose, the preparation of a $17\beta,17^1$-orthoester was considered but, when the triol (2) was treated with trimethyl orthoacetate in the presence of catalytic 60% perchloric acid, the respective hetero-bridged 17β-acetates (9) (60%) and (10) (30%) were formed. The structures of (9) and (10) were verified spectroscopically and by hydrolysis to the corresponding 17β-alcohols (4) and (8). Here too, a facile participation reaction of the $14^1$-hydroxy group upon the presumed orthoester intermediate is evident, although the diminished regioselectivity contrasts with the previous cases.

A different reaction sequence was therefore attempted, and the triol (2) was benzylated to give, after 5 h at 0 °C (NaH - BnBr), the $17^1$-benzyloxy $14^1$,17β-diol (12)(80%), accompanied by traces of the bis-ether (11) (3%). The structure of (12) followed by comparison with the $14^1$-benzyl $17\beta,17^1$-diol (7). Similar chemoselective differentiation was observed when the triol (2) ws treated with t-butyldimethylsilyl chloride (TBDMSCl) - imidazole, to give the $17^1$-TBDMS ether (13)(81%). We then planned to introduce a base-stable protective group at C($14^1$) of (12) or (13), whereupon the $17\beta,17^1$-diol grouping could be restored for further manipulation.

The reaction of the $17^1$-TBDMS ether (13) with sodium hydride - benzyl bromide was slow and indiscriminate, leading to a mixture of the $14^1$,17β-bis(benzyl ether) (14)(32%), the $14^1$-benzyl ether (15) (28%), and the 17β-benzyl ether (16)(25%). The isomers (15) and (16) were distinguished by a diagnostic simplification of the $14^1$-$CH_2$ multiplet in the n.m.r. spectrum of the $14^1$-hydroxy compound (16) upon $D_2O$ exchange, and by desilylation of (15) to give the $14^1$-benzyloxy $17\beta,17^1$-diol (7). Clearly, the lack of chemoselectivity in the benzylation of (13) gave no advantage in the attempted optimisation of a route to the $14^1$-benzyloxy $17\beta,17^1$-diol (7).

A reversed sequence was more successful. Thus, the $17^1$-benzyloxy $14^1$,17β-diol (12) underwent smooth silylation to give a quantitative yield of the $14^1$-TBDMS ether (17). Hydrogenolysis of (17) also proceeded uneventfully, to give the corresponding $17\beta,17^1$-diol (18) (94%).

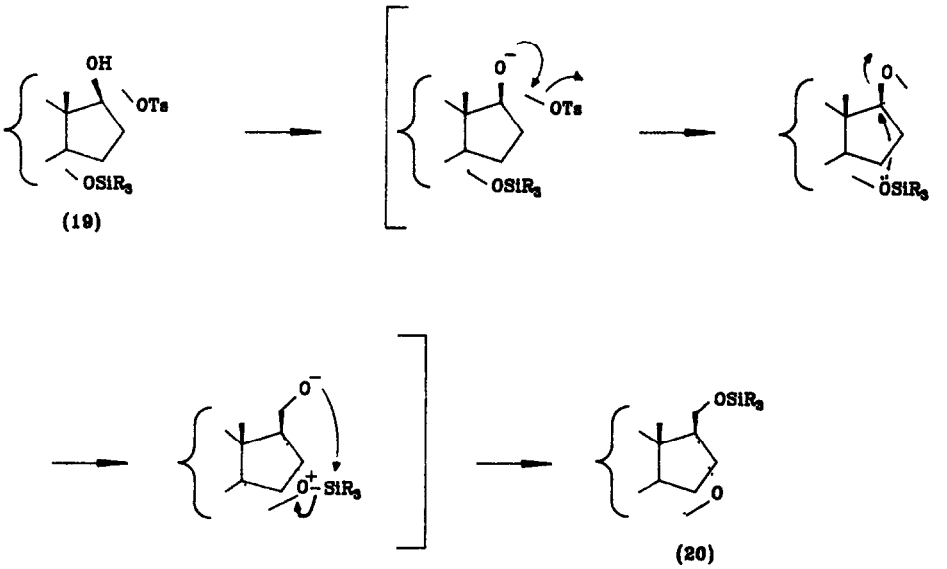



**Reagents** (i) $MeC(OMe)_3$ $-H^+$ (ii) NaOH–MeOH (iii) NaH–BnBr–DME (iv) TBDMSCl–imidazole (v) Pd–C, $H_2$ (vi) pTsCl–$C_5H_5N$, 0 °C

With the desired pattern of functionality in place, the stage was set for attempted conversion of (18) into a 17-spiro-oxirane. Treatment of (18) with toluene-*p*-sulphonyl chloride - pyridine at 0 °C gave a labile product, partial characterisation of which supported the expected structure (19). Compound (19) reacted rapidly in the presence of methanolic sodium hydroxide to give one identifiable product (20)(62%), which displayed the familiar spectroscopic characteristics associated with the 17$\alpha$,14$\alpha$-epoxymethano bridge. The structure was verified by treatment of the 17$\beta$-hydroxymethyl 17$\alpha$,14$\alpha$-epoxymethano compound (8) with TBDMSCl - imidazole to give (20).

The tosylate (19) reacted similarly in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and other bases, to give only (20).

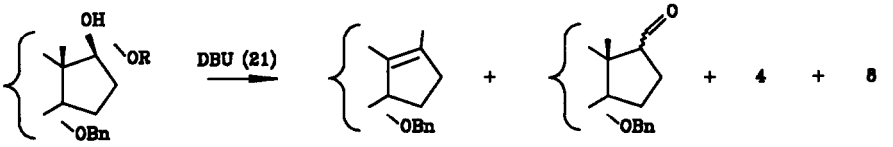
This result contrasts sharply with analogous reactions in the 14α-H series,[1,9] where 17-spiro-oxirane formation occurs with great ease. Furthermore, the course of events under these reaction conditons is not apparent. If indeed, the first step is 17-spiro-oxirane formation, it is necessary to assume that it is vulnerable to intramolecular attack at C(17) by the $14^1$-substituent, to give a silyloxonium intermediate which then undergoes intramolecular silyl transfer to give (20) (Scheme 3). Although the steric demands of the $14^1$- and $17^1$- substituents in (19) militate against ready antiperiplanar alignment of the 17β- and $17^1$-groups for 17-spiro-oxirane formation, an alternative mode of intramolecular displacement of the trialkylsilyl group from C($14^1$ ) to C($17^1$) is not clear under the basic conditions used here. Further investigations are in progress to clarify this result.




**Scheme 3 Intramolecular rearrangement of (19) ($R_3$=$Me_2Bu^t$)**

A similar reaction sequence was conducted on the $14^1$-benzyloxy 17β,$17^1$-diol (7). However, treatment of the derived $17^1$-tosylate (21) with various bases gave rise to complex mixtures of products. The cleanest reaction, conducted with DBU in toluene at 0 °C for 4 h, gave the rearrangement products (22)(30%), (23)(28%), (4)(18%), and (8)(23%). The

latter two compounds (4) and (8) were identified by comparison with authentic material.




7 R=H
21 R=Ts

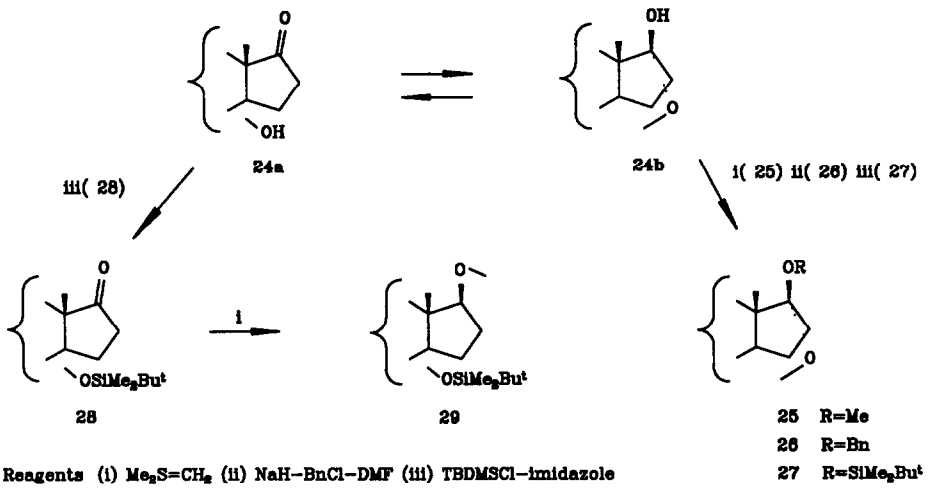
22

23

The structures assigned to (22) and (23) are tentative, but are supported by analytical and spectroscopic data. Thus, n.m.r. of (22) demonstrated the presence of a tetrasubstituted olefinic bond, vinyl attachment of the methyl group, and retention of the 14$\alpha$-benzyloxymethyl group. Similarly, the $^1$H n.m.r. spectrum of (23) showed diagnostic resonances for the 14- and 17- substitution; doubling of those for $14^1$-, $17^1$-, and 18-protons indicated that (23) comprised an inseparable mixture (*ca* 1:1) of 17-epimers.

Formation of (22) and (23) [and perhaps (8) (*cf* Scheme 3)] supports prior 17-spiro-oxirane formation, with the intervention of an 18(13→17)*abeo* rearrangement and decarbonylation to (22) (for which a thermally-induced analogy exists[10]), or a hydride shift to (23), whereas formation of (4) can be explained through intramolecular displacement of the $17^1$-tosyloxy group by $14^1$-O, and base-mediated decomposition of the resultant benzyloxonium ion.[11,12]

Although the results of the base-mediated reactions of (19) and (21) have interesting and unexpected mechanistic implications, they demonstrate the impracticability of adopting this approach to $14^1$-protected 17-spiro-oxiranes. An alternative possibility would be the direct methylenation of 14-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17-one (**24a**);[3] however, the solution-state equilibrium of this form with the corresponding hemiketal (**24b**) was expected to influence the reaction outcome. Indeed, treatment of (24) with dimethylsulphonium methylide in dimethyl sulphoxide - tetrahydrofuran gave only the 17$\beta$-methoxy 17$\alpha$,14$\alpha$-epoxymethano product (**25**), identified by distinctive n.m.r. signals for the $17^2$-protons.



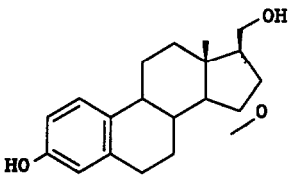

An attempt to circumvent this problem by first preparing a $14^1$-benzyl ether was also frustrated, since treatment of (24) with sodium hydride - benzyl chloride in dimethylformamide resulted in exclusive formation of the 17$\beta$-benzyloxy 17$\alpha$,14$\alpha$-epoxymethano compound (26). By contrast, silylation of (24) with TBDMSCl - imidazole in dimethylformamide gave the ketal (27)(66%) accompanied by the 17-oxo-$14^1$-TBDMS ether (28)(33%).

Notwithstanding the unfavourable regiochemical outcome of this reaction, it was possible to ascertain whether (28) could be converted into a 17-spiro-oxirane. In the event, methylenation of (28) was slow and inefficient; treatment with dimethylsulphonium methylide in dimethyl sulphoxide - tetrahydrofuran at 20 °C for 10 h resulted in partial conversion into a labile product (29%) which was isolated by flash chromatography and formulated as the 17($S$)-spiro-oxirane (29). The n.m.r. spectrum of (29) displayed the expected signals at $\delta$ 2.61 and 2.72(each 1H, d, $J$ 4.5 Hz) for the oxiranyl methylene group, and the 17-configuration was tentatively assigned by correlation of the chemical shift of the 13$\beta$-methyl signal with those reported[13] for epimeric 17-spiro-oxiranes. The small amount of (29) obtained by this route precluded further exploitation.

In summary, the investigations reported here have demonstrated that, whereas efficient chemoselective differentiation of the $14^1$ - and $17^1$-hydroxy groups in the triol (2) is possible, the attempted conversion of intermediates into 14-functionalised 17-spiro-oxiranes has been frustrated by facile participation reactions. Nevertheless, efficient routes to

precursors of new 14,17-hetero-bridged hormone analogues, exemplified by compounds (4) and (8), have been uncovered.

To this end, the 17$\beta$-hydroxymethyl 17$\alpha$,14$\alpha$-epoxymethano compound (8) was readily converted into the respective estradiol and 19-nortestosterone analogues (30) and (31) by standard methods.

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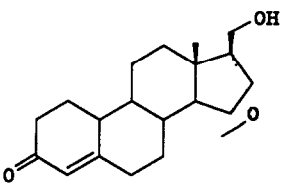


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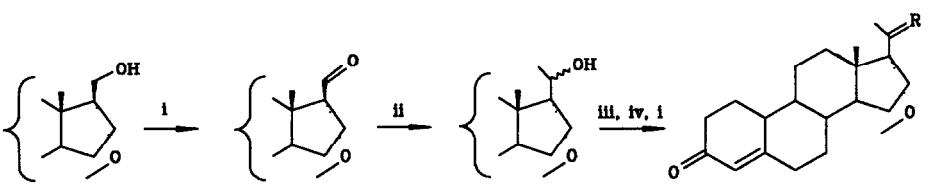
In addition, an efficient synthesis of the 17$\alpha$,14$\alpha$-epoxymethano analogue (36) of 19-norprogesterone was carried out as follows: oxidation of (8) with pyridinium chlorochromate gave the 17$\beta$-carbaldehyde (32), treatment of which with methylmagnesium iodide gave a separable mixture (95%; *ca* 3:2) of (20*S*)- and (20*R*)-17$\alpha$,14-epoxymethano-3-methoxy-19-norpregna-1,3,5(10)-trien-20-ols (33) and (34). The configurational assignments are based upon relative chemical shifts of the 13$\beta$-methyl signal and analogy,[14] but were incidental to our objective.




8 32 33 20S 34 20R 35 R=H,OH 36 R=O

Reagents: (i) PCC–$CH_2Cl_2$ (ii) MeMgI (iii) Li–$NH_3$ (iv) HCl–THF

Birch reduction of the mixture (33 + 34) followed by acid treatment gave a mixture of 20-isomers (35) which was oxidised with pyridinium chlorochromate to give 17$\alpha$,14-epoxymethano-19-norpregn-4-ene-3,20-dione (36), in an overall yield of *ca* 60% from the 17$\beta$-hydroxymethyl compound (8). The spectroscopic properties of (36) provided unequivocal evidence of the assigned structure, and the synthetic pathway exemplifies the

accessibility of new classes of 14,17-hetero-bridged hormone analogues from the rearrangement products obtained in this investigation.

## EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. Unless otherwise specified, spectra were recorded as follows: i.r., Perkin-Elmer 257, chloroform solutions; u.v., Unicam SP 800, ethanol solutions: $^1$H n.m.r., Bruker WM-500 (tetramethylsilane as an internal standard) (500 MHz), deuteriochloroform solutions; mass (electron impact), Varian MAT 212; c.d., Jasco J-20, methanol solutions. Optical rotations were measured for chloroform solutions at 20 °C with a Perkin-Elmer 241 polarimeter. Silica gel for column chromatography refers to Merck Kieselgel 60: 70-230 mesh for gravity, and 230-400 mesh for flash chromatography.

*Reduction of* 17*β*-*Acetoxy*-3-*methoxyestra*-1,3,5(10)-*triene*-14,17*α*-*dicarbaldehyde* (1)

Lithium aluminium hydride (100 mg; 2.6 mmol) was added to the dialdehyde (1) (100 mg; 0.26 mmol) in dry tetrahydrofuran (20 ml), and the mixture was stirred at 25 °C for 3 h. Ethyl acetate was added dropwise to destroy excess reagent, and the mixture was concentrated to a small volume under reduced pressure. Extraction of the residue with ethyl acetate gave crude triol (2) (104 mg), *m/z* 346 ($M^+$). Treatment of this material with 4-(dimethylamino)pyridine (5 mg), acetic anhydride (1.5 ml), and triethylamine (5 ml) at 25 °C for 10 h, and chromatography [ethyl acetate-toluene (1:4)] of the product on silica gel (10 g) afforded 14,17*α*-*bis(acetoxymethyl)*-3-*methoxyestra*-1,3,5(10)-*trien-17β-yl acetate* (3) (76 mg; 62%), m.p.173-179 °C decomp.* (from acetone-methanol); $[\alpha]_D$ + 52° (*c* 0.8); $\upsilon_{max}$ 1730 $cm^{-1}$; $\delta$ 1.09(3H, s, 13*β*-Me), 1,99, 2.04, and 2.05(each 3H, s, 3 x OAc), 2.79-2.86(2H, m, 6-$H_2$), 3.75(3H, s, 3-OMe), 4.26 and 4.32(each 1H, d, *J* 12.8 Hz, 14$^1$- or 17$^1$-$H_2$), 4.52 and 4.84(each 1H, d, *J* 12.5 Hz, 14$^1$- or 17$^1$-$H_2$), 6.59(1H, d, *J* 2.8 Hz, 4-H), 6.69(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.16(1H, d, *J* 8.6 Hz, 1-H) (Found: C, 68.9; H, 7.9%; $M^+$, 472. $C_{27}H_{36}O_7$ requires C, 68.6; H, 7.6%; *M*, 472). (*The triacetate decomposed on heating to form two less polar compounds. Sintering occurred when drying the triacetate *in vacuo* at 65 °C.)

*3-Methoxy-14,17α-(2-oxapropano)estra-1,3,5(10)-trien-17β-ol* (4)
Toluene-*p*-sulphonyl chloride (125 mg; 0.65 mmol) was added to a solution of the triol (2) (100 mg; 0.3 mmol) in pyridine (0.5 ml) at 0 °C. After 2 h, the mixture was poured into water. Extraction with toluene gave material (118 mg), which was chromatographed [methanol-chloroform (1:49)] on silica gel (10 g) to give the *compound* (4) (72 mg; 76%), m.p. 186-188 °C (from acetone-hexane); $[\alpha]_D$ +78° (*c* 1.1); $\upsilon_{max}$ 3585 and 3200-3540 $cm^{-1}$; $\delta$ 1.07(3H, s, 13β-Me), 2.63(1H, dt, *J* 2 x 12.2, and 5.4 Hz, 9α-H), 2.76-2.89(2H, m, 6-$H_2$), 3.29 and 3.88(each 1H, d, *J* 10.1 Hz, $17^1$-$H_2$), 3.36 and 4.15(each 1H, d, *J* 11.1 Hz, $17^3$-$H_2$), 3.75(3H, s, 3-OMe), 6.58(1H, d, *J* 2.6 Hz, 4-H), 6.69(1H, dd, *J* 8.6 and 2.6 Hz, 2-H), and 7.18(1H, d, *J* 8.6 Hz, 1-H) (Found: C, 76.6; H, 8.65%; $M^+$, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.5%; *M*, 328).

(17S)-2',2'-*Dimethylspiro*[14-*hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*triene*-17,4'[1,3]*dioxolane*] (5)
The triol (2) (993 mg) was dissolved in dry acetone (20 ml) and anhydrous copper sulphate (500 mg) was added. After 5 h the mixture was filtered, and the filtrate was concentrated under reduced pressure, to give material (1.06 g) which was chromatographed [ethyl acetate-toluene (1:4)] on silica gel (15 g) to furnish the *acetonide* (5) (888 mg; 88%), m.p. 179-181 °C (from chloroform-methanol); $[\alpha]_D$ +68° (*c* 0.9); $\upsilon_{max}$ 3200-3640 $cm^{-1}$; $\delta$ 1.08(3H, s, 13β-Me), 1.17(1H, br. s, exch. by $D_2O$, $14^1$-OH), 1.33 and 1.37[each 3H, s, $OC(CH_3)_2O$], 3.51(1H, dd, *J* 11.8 and 3.7 Hz → d, *J* 11.8 Hz on $D_2O$ exch., $14^1$-H), 3.75 obsc.(1H, m, $14^1$-H), 3.75(3H, s, 3-OMe), 3.75 and 4.32(each 1H, d, *J* 8.6 Hz, $17^1$-$H_2$), 6.59(1H, d, *J* 2.6 Hz, 4-H), 6.69(1H, dd, *J* 8.6 and 2.6 Hz, 2-H), and 7.19(1H, d, *J* 8.6 Hz, 1-H) (Found: C, 74.6; H, 9.0%; $M^+$. 386. $C_{24}H_{34}O_4$ requires C, 74.6; H, 8.8%; *M*, 386).

(17S)-2',2'-*Dimethylspiro*-[14-*benzyloxymethyl*-3-*methoxyestra*-1,3,5(10)-*triene*-17,4'[1,3]*dioxolane*] (6)
Sodium hydride (50% suspension in oil; 212 mg; 4,4 mmol) was added to a solution of the acetonide (5) (278 mg; 0.74 mmol) in dry dimethoxyethane (20 ml) at 0 °C. The resulting suspension was stirred at 25 °C for 45 min. Benzyl bromide (0.83 ml; 7 mmol) was added in five aliquots over a period of 3 days, whereupon t.l.c. showed complete reaction. Water was added, and extraction of the mixture with toluene gave the crude product (600 mg), which was chromatographed [ethyl acetate-toluene (1:19)] on

silica gel (30 g), to give the 14$^1$-*benzyl ether* (6) (317 mg; 92%), m.p. 80-85 °C (from benzene-hexane); $[\alpha]_D$ +76° (*c* 1.0); $\delta$ 1.06(3H, s, 13$\beta$-Me), 1.3 and 1.37[each 3H, s, OC$(CH_3)_2$O], 2.77-2.88(2H, m, 6-$H_2$), 2.97(1H, ddd, *J* 12.2, 11.8, and 6 Hz, 9$\alpha$-H), 3.26 and 3.34(each 1H, d, *J* 10.8 Hz, 14$^1$-$H_2$), 3.75(3H, s, 3-OMe), 3.58 and 4.25(each 1H, d, *J* 8.7 Hz, 17$^1$-$H_2$), 4.35 and 4.41(each 1H, d, *J* 12.0 Hz, OC$H_2C_6H_5$), 6.59(1H, d, *J* 2.8 Hz, 4-H), 6.69(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.19(1H, d, *J* 8.6 Hz, 1-H), and 7.23-7.33(5H, m, OC$H_2C_6H_5$) (Found: C, 78.2; H, 8.35%; $M^+$, 476. $C_{31}H_{40}O_4$ requires C, 78.15; H, 8.4%; *M*, 476).

14-*Benzyloxymethyl*-17$\alpha$-*hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17$\beta$-*ol* (7)

(a) The acetonide (6) (110 mg) was stirred in aqueous 80% acetic acid (10 ml) at 62 °C for 4 h. Aqueous sodium hydrogen carbonate was added and the acetic acid was removed under reduced pressure. Extraction of the residue with chloroform gave material (120 mg) which was chromatographed [ethyl acetate-toluene (3:7)] on silica gel (10 g), to give starting material (6) (30 mg; 27%) and the 17$\beta$,17$^1$-*diol* (7) (55 mg; 55%), m.p. 113-115 °C (from toluene-hexane); $[\alpha]_D$ +82° (*c* 0.8); $\nu_{max}$ 3200-3600 cm$^{-1}$; $\delta$ 1.1(3H, s, 13$\beta$-Me), 1.86(1H, dd, *J* 7.4 and 4,2 Hz, exch. by $D_2O$, 17$^1$-OH), 2.77-2.89(2H, m, 6-$H_2$), 3.0(1H, dt, 2 x 11.8 and 5.7 Hz, 9$\alpha$-H), 3.44 and 3.56(each 1H, d, *J* 11.0 Hz, 14$^1$-$H_2$), 3.58(1H, dd, *J* 11.2 and 7.4 Hz -▸ d, *J* 11.2 Hz on $D_2O$ exch., 17$^1$-H), 3.75(3H, s, 3-OMe), 3.81(1H, dd, *J* 11.2 and 4.2 Hz -▸ d, *J* 11.2 Hz on $D_2O$ exch., 17$^1$-H), 4.37 and 4.41 (each 1H, d, *J*, 12.0 Hz, OC$H_2C_6H_5$), 6.59(1H, d, *J* 2.7 Hz, 4-H), 6.69(1H, dd, *J* 8.6 and 2.7 Hz, 2-H), 7.17(1H, d, *J* 8.6 Hz, 1-H), and 7.22-7.32(5H, m, OC$H_2C_6H_5$) (Found: C, 76.7; H, 8.3%; $M^+$, 436. $C_{28}H_{36}O_4$ requires C, 77.0; H, 8.3%; *M*, 436).

(b) The acetonide (6) (30 mg) was dissolved in methanol (16 ml) and resin [1.8 g; Ag 50W-X2($H^+$), 200-400 mesh] was added. The suspension was stirred at 45 °C for 5 h, whereupon decomposition started to occur (t.l.c.). The resin was removed by filtration through a Celite pad and the filtrate was concentrated under reduced pressure. Chromatography [ethyl acetate-toluene (1:2)] of the residue (39 mg) on silica gel (5 g) afforded a mixture of non-polar compounds (15 mg), followed by the diol (7) (10 mg; 36%), m.p. and mixed m.p. 113-115 °C (from toluene-hexane).

*17α,14-Epoxymethano-17β-hydroxymethyl-3-methoxyestra-1,3,5(10)-triene* (**8**)
(a) The acetonide (**5**) (70 mg) was dissolved in methanol (10 ml) and iodine (100 mg) was added. The reaction was stirred at under reflux for 4 h, then cooled, and solid sodium thiosulphate was added. The mixture was concentrated under reduced pressure, and the product (81 mg) was isolated by extraction with chloroform. Chromatography [ethyl acetate-toluene (1:2)] afforded five minor products (30 mg), followed by *17α,14-epoxymethano-17β-hydroxymethyl-3-methoxyestra-1,3,5(10)-triene* (**8**) (37 mg; 62%), m.p. 149-151 °C (from chloroform-methanol); $[\alpha]_D$ + 50° (*c* 1.0); δ 0.9(3H, s, 13β- Me), 2.0(1H, dd, *J* 6.5 and 5.5 Hz, exch. by $D_2O$, $17^{1'}$-OH), 2.63(1H, dt, *J* 2 x 11.7, and 4.2 Hz, 9α-H), 2.83(1H, ddd, *J* 16.9, 6.8, and 2.5 Hz, 6α-H), 2.88(1H, ddd, *J* 16.9, 11.5, and 6.4 Hz, 6β-H), 3.48(1H, d, *J* 7.4 Hz, $17^2$-$H_{endo}$), 3.72(1H, dd, *J* 12.0 and 5.5 Hz → d, *J* 12.0 Hz on $D_2O$ exch., $17^{1'}$-H), 3.75(3H, s, 3-OMe), 3.8(1H, dd, *J* 12.0 and 6.5 Hz → d, *J* 12.0 Hz on $D_2O$ exch., $17^{1'}$-H), 4.14(1H, dd, *J* 7.4 and 4.1 Hz, $17^2$-$H_{exo}$), 6.61(1H, d, *J* 2.8 Hz, 4-H), 6.7(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.2(1H, d, *J* 8.6 Hz, 1-H) (Found: C, 76.5; H, 8.7%; $M^+$, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.5%; *M*, 328).
(b) The triol (**2**) (420 mg) was stirred in tetrahydrofuran (30 ml) and conc. hydrochloric acid (1 ml) at 25 °C for 18 h. Aqueous sodium hydrogen carbonate was added and the tetrahydrofuran was removed under reduced pressure. Extraction of the residue with chloroform gave material (550 mg) which was chromatographed [ethyl acetate-toluene (1:1)] on silica gel (40 g) to furnish the 17α,14α-epoxymethano compound (**8**) (370 mg; 87%), m.p. and mixed 149-151 °C (from chloroform-methanol).

*Treatment of the Triol* (**2**) *with Trimethyl Orthoacetate*
60% Perchloric acid (5 μl) was added to the triol (**2**) (50 mg) in trimethyl orthoacetate (0.5 ml). After 3 h, aqueous sodium hydrogen carbonate was added. Extraction with toluene gave material (64 mg) which was chromatographed [ethyl acetate-toluene (1:4)] on silica gel (10 g), to give *3-methoxy-14,17α-(2-oxapropano)estra-1,3,5(10)-trien-17β-yl acetate* (**9**) (32 mg; 60%), m.p. 135-136.5 °C (from chloroform-methanol); $[\alpha]_D$ +67° (*c* 0.9); $\upsilon_{max}$ 1735 $cm^{-1}$; δ 1.06(3H, s, 13β-Me), 1.99(3H, s, 17β-OAc), 2.76-2.89(2H, m, 6-$H_2$), 3.36 and 4.15(each 1H, d, *J* 11.1 Hz, $17^3$-$H_2$), 3.75(3H, s, 3-OMe), 3.91 and 3.94(each 1H, d, *J* 10.1 Hz, $17^1$-$H_2$), 6.59(1H, d, *J* 2.8 Hz, 4-H), 6.7(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.18(1H, d, *J* 8.6 Hz, 1-H) (Found: C, 74.6; H, 8.4%; $M^+$, 370. $C_{23}H_{30}O_4$ requires C, 74.6; H, 8.1%; *M*, 370), followed by *17β-acetoxymethyl-17α,14-epoxymethano-3-*

*methoxyestra*-1,3,5(10)-*triene* (**10**) (16 mg; 30%), m.p. 68-70 °C (from ether-methanol); $[\alpha]_D$ +43° (*c* 0.7); $\nu_{max}$ 1735 $cm^{-1}$; $\delta$ 0.92(3H, s, 13$\beta$-Me), 2.08(3H, s, 17$\beta$-OAc), 2.64(1H, dt, *J* 2 x 11.9, and 4.2 Hz, 9$\alpha$-H), 2.82(1H, ddd, *J* 17.0, 6.7, and 2.5 Hz, 6$\alpha$-H), 2.88(1H, ddd, *J* 17.0, 11.4, and 6.4 Hz, 6$\beta$-H), 3.49(1H, d, *J* 7.5 Hz, $17^2$-$H_{endo}$), 3.75(3H, s, 3-OMe), 4.14(1H, dd, *J* 7.5 and 4.0 Hz, $17^2$-$H_{exo}$), 4.2 and 4.31(each 1H, d, *J* 11.8 Hz, $17^{1'}$-$H_2$), 6.6(1H, d, *J* 2.8 Hz, 4-H) 6.7(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.19(1H, d, *J* 8.6 Hz, 1-H) (Found: C, 74.3; H, 7.9%; $M^+$, 370. $C_{23}H_{30}O_4$ requires C, 74.6; H, 8.1%; *M* , 370).

Treatment of the 17$\beta$-acetate (**9**) (10 mg) with methanolic 0.1M -sodium hydroxide at 25 °C for 4 h, followed by addition of solid carbon dioxide, evaporation of methanol, and extraction of the residue with chloroform, gave the 17$\beta$-alcohol (**4**) (7 mg), m.p. and mixed m.p. 187-189 °C (from acetone-hexane).

Similar treatment of the 17$\beta$-acetoxymethyl compound (**10**) (19 mg) for 1 h, and work-up gave the corresponding 17$\beta$-hydroxymethyl compound (**8**) (16 mg), m.p. and mixed m.p. 150-152 °C (from chloroform-methanol).

*Benzylation of the Triol* (**2**)

Sodium hydride (50% suspension in oil; 100 mg; 2.1 mmol) was added to a solution of the triol (**2**) (500 mg; 1.4 mmol) in dry dimethoxyethane (50 ml), and the suspension was stirred at 0 °C under nitrogen for 45 min. Benzyl bromide (86 $\mu$l; 7 mmol) was added. After 5 h at 0 °C, water was added and the dimethoxyethane was evaporated under reduced pressure. The residue was extracted with chloroform to give material (861 mg) which was chromatographed [ethyl acetate-toluene (3:17)] on silica gel (45 g), to give 14,17$\alpha$-*bis*(*benzyloxymethyl*)-3-*methoxyestra*-1,3,5(10)-*trien*-17$\beta$-*ol* (**11**) as an oil (26 mg; 3%), *m/z* 526 ($M^+$); $\delta$ (90MHz) 1.1(3H, s, 13$\beta$-Me), 3.75(3H, s, 3-OMe), 4.19(2H, s, $CH_2C_6H_5$), 4.39 and 4.56(each 1H, d, *J* 12.0 Hz, $CH_2C_6H_5$), and 6.6-7.47(13H, m, arom. H's), followed by 17$\alpha$-*benzyloxymethyl*-14-*hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17$\beta$-*ol* (**12**) (505 mg; 80%), m.p. 139-141 °C (from benzene-hexane); $[\alpha]_D$ +46.5° (*c* 1.0); $\nu_{max}$ 3250-3690 $cm^{-1}$; $\delta$ 1.09(3H, s, 13$\beta$-Me), 2.78-2.90(3H, m, 9$\alpha$-H and 6-$H_2$), 3.04(1H, s, exch. by $D_2O$, 17$\beta$-OH), 3.61 and 3.75(each 1H, d, *J* 9.0 Hz, $17^1$-$H_2$), 3.74 and 3.76 obsc.(each 1H, br → d, *J* 12.2 Hz on $D_2O$ exch., $14^1$-$H_2$), 3.75(3H, s, 3-OMe), 4.53 and 4.59(each 1H, d, *J* 11.9 Hz $CH_2C_6H_5$), 6.59(1H, d, *J* 2.6 Hz, 4-H), 6.68(1H, dd, *J* 8.6 and 2.6 Hz, 2-H), 7.16(1H, d, *J* 8.6 Hz, 1-H), and 7.24-7.37(5H, m, $CH_2C_6H_5$) (Found: C, 77.1; H, 8.5%; $M^+$, 436. $C_{28}H_{36}O_4$ requires C, 77.1; H, 8.3%; *M*, 436), followed by the triol (**2**) (75 mg; 15%).

*Silylation of the Triol* (2)

The triol (2) (75 mg; 0.22 mmol) was dissolved in dimethylformamide (1.5 ml) and stirred under nitrogen at 0 °C. Imidazole (118 mg; 1.8 mmol) was added followed by t-butyldimethylsilyl chloride (130 mg; 0.9 mmol). After 0.5 h, water was added, and the mixture was extracted with ether. Chromatography [methanol-chloroform (1:49)] of the product (108 mg) on silica gel (10 g) afforded 17$\alpha$-t-*butyldimethylsilyloxymethyl*-14-*hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17$\beta$-*ol* (13) (81 mg; 81%), m.p. 212-217 °C (from chloroform-methanol); $[\alpha]_D$ +49° (*c* 1.0); $\nu_{max}$ 3520 $cm^{-1}$; $\delta$ 0.09(6H, s, $SiMe_2$), 0.9(9H, s, $SiBu^t$), 1.1(3H, s, 13$\beta$-Me), 2.8-2.9(2H, m, 6-$H_2$), 3.28(1H, s, exch. by $D_2O$, 17$\beta$-OH), 3.64 and 3.94(each 1H, d, *J* 9.5 Hz, $17^1$-$H_2$), 3.75(3H, s, 3-OMe) 3.78 and 3.84(each 1H, dd, *J* 12.0 and 2.5 Hz → d, *J* 12.0 Hz on $D_2O$ exch., $14^1$-$H_2$), 6.59(1H, d, *J* 2.7 Hz, 4-H), 6.68(1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.17(1H, d, *J* 8.6 Hz, 1-H) (Found: C, 70.4; H, 9.5%; $M^+$, 460. $C_{27}H_{44}O_4Si$ requires C, 70.4; H, 9.6%; *M*, 460).

*Benzylation of the* $17^1$-*Silyl Ether* (13)

The silyl ether (13) (142 mg; 0.31 mmol) was dissolved in dimethoxyethane (10 ml) and sodium hydride (50% suspension in oil; 22 mg; 0.46 mmol) was added to the stirred solution at 0 °C. After 45 min at 0 °C, the mixture was warmed to 20 °C and benzyl bromide (220 $\mu$l; 1.8 mmol) was added in four aliquots (55 $\mu$l each) over 3 days. Water was added and the dimethoxyethane was evaporated under reduced pressure. Extraction of the residue with chloroform gave material (250 mg) which was chromatographed [ethyl acetate-hexane (1:19)] on silica gel (20 g), to give 17$\beta$-*benzyloxy*-14-*benzyloxymethyl*-17$\alpha$-*t-butyldimethylsilyloxymethyl*-3-*methoxyestra*-1,3,5(10)-*triene* (14) (64 mg; 32%), m.p. 112-114 °C (from benzene-hexane); $[\alpha]_D$ +45° (*c* 1.0); $\delta$ 0.06 and 0.09(each 3H, s, $SiMe_2$), 0.87(9H, s, $SiBu^t$), 1.08(3H, s, 13$\beta$-Me), 2.76-2.89(2H, m, 6-$H_2$), 3.11(1H, dt, *J* 2 x 11.8, and 5.2 Hz, 9$\alpha$-H), 3.24 and 3.45(each 1H, d, *J* 11.0 Hz, $14^1$-$H_2$), 3.43 and 3.7(each 1H, d, *J* 10.1 Hz, $17^1$-$H_2$), 3.75(3H, s, 3-OMe), 3.95 and 4.03(each 1H, d, *J* 12.1 Hz, $CH_2C_6H_5$), 4.23 and 4.59(each 1H, d, *J* 12.2 Hz, $CH_2C_6H_5$), 6.59(1H, d, *J* 2.7 Hz, 4-H), 6.68(1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.14 -7.39(11H, m, 1-H and 2 x $CH_2C_6H_5$) (Found: C, 77.0; H, 8.8%; $M^+$, 640. $C_{41}H_{56}O_4Si$ requires C, 76.9; H, 8.75%; *M*, 640), followed by 14-*benzyloxymethyl*-17$\alpha$-*t-butyldimethylsilyloxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17$\beta$-*ol* (15) (48 mg; 28%), m.p. 113-115 °C (from benzene-hexane); $[\alpha]_D$ +64°(*c* 1.0); $\nu_{max}$ 3400-3560 $cm^{-1}$; $\delta$ 0.02 and 0.03(each 3H, s, $SiMe_2$), 0.88(9H, s, $SiBu^t$), 1.09(3H, s, 13$\beta$-Me), 2.76-2.89(2H, m, 6-$H_2$),

2.98(1H, ddd, *J* 12.1, 11.5, and 5.2 Hz, 9α-H), 3.28(1H, s, exch. by $D_2O$, 17β-OH), 3.41 and 3.55(each 1H, d, *J* 10.9 Hz, $14^1$-$H_2$), 3.53 and 3.85(each 1H, d, *J* 9.3 Hz, $17^1$-$H_2$), 3.75(3H, s, 3-OMe), 4.35 and 4.43(each 1H, d, *J* 12.0 Hz $CH_2C_6H_5$), 6.59(1H, d, *J* 2.6 Hz, 4-H), 6.69(1H, dd, *J* 8.6 and 2.6 Hz, 2-H), 7.18(1H, d, *J* 8.6 Hz, 1-H), and 7.22-7.35(5H, m, $CH_2C_6H_5$) (Found: C, 74.2; H, 9.4%; M$^+$, 550. $C_{34}H_{50}O_4Si$ requires C, 74.2; H, 9.1%; M, 550), then 17β-*benzyloxymethyl*-17α-*t-butyldimethylsilyloxymethyl*-14-*hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*triene* (16) (42 mg; 25%), m.p. 125-128 °C (from benzene-hexane); $[\alpha]_D$ +31° (*c* 1.0); δ 0.05 and 0.07 (each 3H, s, $SiMe_2$) 0.84(9H, s, $SiBu^t$), 1.04(3H, s, 13β-Me), 2.77-2.84(2H, m, 6-$H_2$), 2.92(1H, dt, *J* 2 x 11.9, and 5.5 Hz, 9α-H), 3.38 and 3.73(each 1H, d, *J* 10.1 Hz, $17^1$-$H_2$), and 3.42 and 3.63(each 1H, dd, *J* 12.4 and 3.7 Hz → d, *J*, 12.4 Hz on $D_2O$ exch., $14^1$-$H_2$), 4.33 and 4.65(each 1H, d, *J* 12.0 Hz, $CH_2C_6H_5$), 6.57(1H, d, *J* 2.6 Hz, 4-H), 6.67(1H, dd, *J* 8.6 and 2.6 Hz, 2-H), 7.15(1H, d, *J* 8.6 Hz, 1-H), and 7.24-7.40(5H, m, $CH_2C_6H_5$) (Found: C, 74.3; H, 9.3%; M$^+$, 550. $C_{34}H_{50}O_4Si$ requires C, 74.2; H, 9.1%; *M*, 550), and starting material (13) (15 mg; 10%), m.p. 212-217 °C (from chloroform-methanol). Tetra-n-butylammonium fluoride (1 M-solution in tetrahydrofuran; 0.23 ml) was added to a solution of the $17^1$-silyl ether (15) (27 mg; 0.05 mmol) in dry tetrahydrofuran (1 ml). The solution was stirred at 25 °C for 3 h. Extraction with ethyl acetate and chromatography [ethyl acetate-toluene (3:7)] of the product (42 mg) on silica gel (5 g) afforded the $14^1$-benzyloxy-$17^1$,17β-diol (7) (19 mg; 89%), m.p. and mixed m.p. 113-115 °C (from toluene-hexane).

*Silylation of the* $17^1$-*Benzyl Ether* (12)

The $17^1$-benzyl ether (12) (400 mg; 0.9 mmol) was dissolved in dry dimethylformamide (3.5 ml), and imidazole (500 mg; 7.2 mmol) and t-butyldimethylsilyl chloride (542 mg; 3.6 mmol) were added. The reaction was stirred at 65 °C for 3 h, then further imidazole (250 mg) and t-butyldimethylsilyl chloride (270 mg) were added. After another 1 h at 65 °C, the mixture was extracted with ether. Chromatography [ethyl acetate-toluene (1:9)] of the residue (585 mg) on silica gel (45 g) afforded 17α-*benzyloxyymethyl*-14-*t-butyldimethylsilyloxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17β-*ol* (17) as an oil (535 mg; 100%), $\upsilon_{max}$ 3540 $cm^{-1}$; δ -0.01 and 0.0(3H, s, $SiMe_2$), 0.87(9H, s, $SiBu^t$), 1.1(3H, s, 13β-Me), 2.79-2.87(2H, m, 6-$H_2$), 2.91(1H, dt, *J* 2 x 11.8, and 5.2 Hz, 9α-H), 3.12(1H, s, exch. by $D_2O$, 17β-OH), 3.61 and 3.72(each 1H, d, *J* 11.6 Hz, $14^1$-$H_2$), 3.62 and 3.81(each 1H, d, *J* 9.0 Hz, $17^1$-$H_2$), 3.75(3H, s, 3-OMe), 4.53 and 4.58(each 1H, d, *J* 11.8 Hz, $CH_2C_6H_5$), 6.6(1H, d, *J* 2.6 Hz,

4-H), 6.7(1H, dd, *J* 8.6 and 2.6 Hz, 2-H), 7.17(1H, d, *J* 8.6 Hz, 1-H), and 7.27-7.38(5H, m, $CH_2C_6H_5$) (Found: $M^+$, 550.348. $C_{34}H_{50}O_4Si$ requires *M*, 550.348).

*14-t-Butyldimethylsilyloxymethyl-17α-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol* (**18**)
The $17^1$-benzyl ether (**17**) (500 mg) in ethyl acetate (30 ml) was hydrogenated over 5% palladium on carbon (100 mg) at 25 °C and 760 mm Hg. After 1 h, hydrogen uptake ceased, and the catalyst was removed by filtration, and the filtrate was concentrated to afford crystalline material (430 mg). Recrystallisation afforded the $17\beta,17^1$-*diol* (**18**) (391 mg; 94%), m.p. 185-187 °C (from chloroform-methanol); $[\alpha]_D$ +76° (*c* 1.0); $\upsilon_{max}$ 3200-3600 $cm^{-1}$; $\delta$ 0.02 and 0.04(each 3H, s, $SiMe_3$), 0.88(9H, s, $SiBu^t$), 1.1(3H, s, 13β-Me), 1.9(1H, dd, *J* 7.3 and 4.4 Hz, exch. by $D_2O$ $17^1$-OH), 2.34(1H, s, exch. by $D_2O$, 17β-OH), 2.80-2.86(2H, m, 6-$H_2$), 2.94(1H, ddd, *J* 11.7, 11.4, and 5.4 Hz, 9α-H), 3.62 and 3.75(each 1H, d, *J* 11.7 Hz, $14^1$-$H_2$), 3.70(1H, dd, *J* 11.1 and 7.3 Hz -► d, *J* 11.1 Hz on $D_2O$ exch., $17^1$-H), 3.75(3H, s, 3-OMe), 3.91(1H, dd, *J* 11.1 and 4.4 Hz -► d, 11.1 Hz on $D_2O$ exch., $17^1$-H), 6.59(1H, d, *J* 2.8 Hz, 4-H), 6.68(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.16(1H, d, *J* 8.6 Hz, 1-H) (Found: C, 70.3; H, 9.9%; $M^+$, 460. $C_{27}H_{44}O_4Si$ requires C, 70.4; H, 9.6%; *M*, 460).

*Treatment of the $14^1$-Silyl Ether* (**18**) *with Toluene-p-sulphonyl Chloride*
The $14^1$-silyloxy-$17^1$,17β-diol (**18**) (140 mg; 0.3 mmol) in pyridine (2 ml) at 0°C was treated with toluene-*p*-sulphonyl chloride (87 mg; 0.45 mmol). The mixture was stirred at 0 °C for 7 h, then poured into ice-water and extracted with toluene. Flash chromatography [ethyl acetate-toluene (1:9)] of the product (202 mg) on silica gel (15 g) gave the $17^1$ tosylate (**19**) (140 mg; 75%), $\upsilon_{max}$ 1360 and 1165 $OSO_2$ $cm^{-1}$; $\delta$ (90MHz) 0.05 and 0.07 (each 3H, s, $SiMe_2$), 0.85(9H, s, $SiBu^t$ ), 1.1(3H, s, 13β-Me), 2.42(3H, s, Ts-Me), 3.56 and 3.80(each 1H, d, *J* 10 Hz, $14^1$-$H_2$), 4.23 and 4.38(each 1H, d, *J* 10 Hz, $17^1$-$H_2$), and 7.3 and 7.8(each 2H, d, *J* 9.0 Hz, Ts-$C_6H_4$), followed by starting material (**18**) (5 mg; 4%). The lability of the tosylate (**19**) precluded full characterisation, and it was used directly in the following reactions.

*17β-t-Butyldimethylsilyloxymethyl-17α,14-epoxymethano-3-methoxyestra-1,3,5(10)-triene* (**20**)
(a) The tosylate (**19**) (81 mg; 0.13 mmol) was dissolved in methanol (10 ml) at 25 °C, and sodium hydroxide (6 mg; 0.13 mmol) was added with stirring.

After 20 min, solid $CO_2$ was added, and the reaction mixture was concentrated under reduced pressure, extracted with toluene, and the isolated product (58 mg) was chromatographed [ethyl acetate-hexane (1:19)] on silica gel (10 g) to furnish the 17α,14-*epoxymethano compound* (**20**) (37 mg; 63%), m.p. 99-101 °C (from chloroform-methanol); $[\alpha]_D$ +44° (*c* 1.0); δ 0.06(6H, s, $SiMe_2$), 0.89(9H, s, $SiBu^t$), 0.91(3H, s, 13β-Me), 2.63(1H, dt, *J* 2 x 11.4, and 4.1 Hz, 9α-H ), 2.77-2.92(2H, m, 6-$H_2$), 3.45(1H, *J* 7.3 Hz, $17^2$-$H_{endo}$), 3.73 and 3.77(each 1H, d, *J* 10.9 Hz, $17^{1'}$-$H_2$), 3.75(3H, s, 3-OMe), 4.09(1H, dd, *J* 7.3 and 4.0 Hz, $17^2$-$H_{endo}$), 6.6(1H, d, *J* 2.5 Hz, 4-H), 6.7(1H, dd, *J* 8.6 and 2.5 Hz, 2-H), and 7.2(1H, d, *J* 8.6 Hz, 1-H) (Found: C, 73.4; H, 9.8%; $M^+$, 442. $C_{27}H_{42}O_3Si$ requires C, 73.3; H, 9.5%; *M*, 442).

(b) 1,8-Diazabicyclo[5.4.0]undec-7-ene (7μl) was added to the tosylate (**19**) (30 mg; 0.05 mmol) in dry toluene (3 ml) at 0 °C. The reaction was instantaneous (t.l.c.). Water was added and the product (38 mg) was isolated by extraction with toluene. Chromatography [ethyl acetate-hexane (1:19)] on silica gel (5 g) gave the 17α,14-epoxymethano compound (**20**) (16 mg; 74%), m.p. 99-101 °C (from chloroform-methanol).

(c) Treatment of the 17β-hydroxymethyl compound (**8**) (26 mg; 0.08 mmol) with imidazole (43 mg; 0.4 mmol) and t-butyldimethysilyl chloride (4.8 mg; 0.32 mmol) in dry dimethylformamide (0.5 ml) at 25 °C for 2 h, extraction of the product with toluene, and chromatography [ethyl acetate-hexane (1:19)] on silica gel (5 g) afforded the 17α,14-epoxymethano compound (**20**) (28 mg; 80%), m.p. and mixed m.p. 99-101 °C (from chloroform-methanol).

*Treatment of the* $14^1$*-Benzyl Ether* (**7**) *with Toluene-p-sulphonyl Chloride*

The $14^1$-benzyl ether (**7**) (180 mg; 0.4 mmol) was treated with toluene-*p*-sulphonyl chloride (163 mg; 0.8 mmol) in pyridine (2 ml) at 0 °C for 2 h. The product (320 mg) was isolated by extraction with toluene and chromatographed rapidly [ethyl acetate-toluene (1:19)] on silica gel (20 g) to give the $17^1$-tosylate (**21**) (180 mg; 74%), $\upsilon_{max}$ 1365 and 1170 $cm^{-1}$ ($OSO_2$); δ (90 MHz) 1.13(3H, s, 13β-Me), 2.43(3H, s, Ts-Me), 3.43 and 3.7(each 1H, d, *J* 12.0 Hz, $14^1$-$H_2$), 3.75(3H, s, 3-OMe), 4.23 and 4.36(each 1H, d, *J* 10.0 Hz, $17^1$-$H_2$), 4.4(2H, s, $CH_2C_6H_5$), and 7.3 and 7.82(each 2H, d, *J* 9.0 Hz, Ts-$C_6H_4$) and starting material (**7**) (22 mg; 12%). The lability of the tosylate (**21**) precluded full characterisation, and it was used directly in the following reactions.

*Base Treatment of the 14$^1$-Benzyloxy 17$^1$-Tosylate* (21)

(a) The tosylate (21) (100 mg; 0.17 mmol) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (50 μl; 0.35 mmol) in dry toluene (10 ml) at 0 °C under nitrogen. After 4 h, water was added, and the reaction mixture was extracted with toluene to give crude material (110 mg). Chromatography [toluene] on silica gel (15 g) afforded 14-*benzyloxymethyl*-3-*methoxy*-17-*methylgona*-1,3,5(10),13(17)-*tetraene* (22) (20 mg; 30%) as an oil, δ 1.13(1H, ddt, *J* 2 x 13.0, 12.2, and 4.4 Hz, 11β-H), 1.34(1H, ddd, *J* 12.0, 11.6, and 2.3 Hz, 8β-H), 1.52-1.16 obsc.(2H, m, 7α- and 15β-H), 1.66(3H, br. s, 17-Me), 1.86(1H, ddt, *J* 11.9, 2 x 4.2, and 2.3 Hz, 7β-H), 2.09(1H, ddd, *J* 12.7, 8.6, and 2.0 Hz, 15α-H), 2.1-2.18(2H, m, 12α- and 16-H), 2.4-2.49(2H, m, 11α- and 16-H), 2.55(1H, ddd, *J* 14.1, 4.4, and 2.5 Hz, 12β-H), 2.75-2.79(2H, m, 6-$H_2$), 2.9(1H, ddd, *J* 12.2, 12.0, and 4.2 Hz, 9α-H), 3.5 and 3.58(each 1H, d, *J* 9.1 Hz, 14$^1$-$H_2$), 3.76(3H, s, 3-OMe), 4.45 and 4.48(each 1H, d, *J* 12.4 Hz, $CH_2C_6H_5$), 6.58(1H, d, *J* 2.8 Hz, 4-H), 6.7(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.22(1H, d, *J* 8.6 Hz, 1-H), and 7.23-7.33(5H, m, $CH_2C_6H_5$) (Found: $M^+$, 388.240. $C_{27}H_{32}O_2$ requires *M*, 388.240), followed by 1:1 mixture of 14-*benzyloxymethyl*-3-*methoxyestra*-1,3,5(10)-*triene*-17$^1$ξ-*carbaldehydes* (23) (20 mg; 28%), $\nu_{max}$ 1711 cm$^{-1}$; *m/z* 417 ($M^+$) and 327 ($M^+$ - $C_7H_7$); δ 0.91('1.5H', s, 13β-Me), 1.09('1.5H', s, 13β-Me), 3.09, 3.48, 3.51, and 3.69(each '0.5H', d, *J* 10.3 Hz, 14$^1$-$H_2$), 3.76(3H, s, 3-OMe), 4.31 and 4.36(each '0.5H', d, *J* 12.0 Hz $CH_2C_6H_5$), 4.42 and 4.49(each '0.5H', d, *J* 12.2 Hz, $CH_2C_6H_5$), 6.6(1H, m, $W_{\frac{1}{2}}$ 6 Hz, 4-H), 6.7(1H, dd, *J* 8.6 and 2.9 Hz, 2-H), 7.16 and 7.17(each '0.5H', d, *J* 8.6 Hz, 1-H), 7.23-7.34(5H, m, $CH_2C_6H_5$), and 9.62 and 9.78(each 0.5H, s, 17$^1$-H). Further elution gave the 14α,17α-(2-oxapropano) compound (4) (10 mg; 18%) m.p. and mixed m.p. 186-188 °C (from acetone-hexane), and the 17α,14α-epoxymethano compound (8) (13 mg; 23%), m.p. and mixed m.p. 149-151 °C (from chloroform-methanol).

(b) Sodium hydroxide (4 mg) was added to the tosylate (21) (52 mg; 0.09 mmol) in methanol (5 ml) at 0 °C. After 1 h, solid $CO_2$ was added and the methanol was removed under reduced pressure. Extraction of the residue with chloroform afforded material (46 mg), which was chromatographed (toluene) on silica gel (10 g) to give compounds (22)(5 mg; 15%), (23)(2 mg; 5%),(4)(9 mg; 31%), and (8)(10 mg; 35%).

*Attempted Selective Derivatisation of the 14α-Hydroxymethyl 17-Ketone* (24)

(a) Trimethylsulphonium iodide (400 mg; 2 mmol) in dry dimethyl sulphoxide (4.9 ml) was added to sodium hydride (50% suspension in oil; 96 mg; 2 mmol) in dry dimethyl sulphoxide (1.7 ml) and dry tetrahydrofuran

(5 ml) at 20 °C, with stirring under nitrogen. The ketone (**24**) (160 mg; 0.05 mmol), in dry tetrahydrofuran (7 ml) and dimethyl sulphoxide (1 ml), was added and the mixture was kept at 60 °C for 16 h, then poured into water. The reaction product (182 mg) was isolated by extraction with ether and filtered, [ethyl acetate-toluene (3:2)] through silica gel (15 g) to give 17α,14-*epoxymethano*-3,17β-*dimethoxyestra*-1,3,5(10)-*triene* (**25**) (165 mg; 99%), m.p. 146-148 °C (from ethyl acetate); $[\alpha]_D$ +40° (*c* 1.0); δ 0.94(3H, s, 13β-Me), 2.64(1H, dt, *J* 2 x 11.7, and 4.1 Hz, 9α-H), 2.78-2.9(2H, m, 6-$H_2$), 3.46(3H, s, 17β-OMe), 3,53(1H, d, *J* 7.5 Hz, $17^2$-$H_{endo}$), 3.75(3H, s, 3-OMe), 4.21(1H, dd, *J* 7.5 and 4.1 Hz, $17^2$-$H_{exo}$), 6.6(1H, d, *J* 2.8 Hz, 4-H), 6.7(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21(1H, d, *J* 8.6 Hz, 1-H) (Found: C, 76.8; H, 8.5%; $M^+$, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.5%; *M*, 328).

(b) Sodium hydride (50% suspension in oil; 15 mg; 0.3 mmol) was added to the 17-ketone (**24**) (48 mg; 0.15 mmol) in dry dimethylformamide (1 ml) at 0 °C, with stirring under nitrogen, and the resulting suspension was stirred for 45 min at 0 °C. Benzyl chloride (34 μl; 0.3 mmol) was added dropwise to the suspension and the reaction was stirred for 5 h at 25 °C A further aliquot of benzyl chloride (34 μl) was added and, after stirring for a further 48 h, water was added. Extraction with chloroform gave material (87 mg), which was chromatographed [ethyl acetate-toluene (1:49)] on silica gel (5 g) to give 17β-*benzyloxy*-17α,14-*epoxymethano*-3-*methoxyestra*-1,3,5(10)-*triene* (**26**) (50 mg; 81%), m.p. 123-125 °C (from benzene-hexane); $[\alpha]_D$ +31° (*c* 0.7); $\upsilon_{max}$ 3240-3600 $cm^{-1}$; δ 0.99(3H, s, 13β-Me), 2.66(1H, ddd, *J* 12.4, 11.6, and 4.2 Hz, 9α-H), 2.79-2.91(1H, m, 6-$H_2$), 3.58(1H, d, *J* 7.4 Hz, $17^2$-$H_{endo}$), 3.76(3H, s, 3-OMe), 4.26(1H, dd, *J* 7.4 and 4.1 Hz, $17^2$-$H_{exo}$), 4.72 and 4.79(each 1H, d, *J* 11.9 Hz, $CH_2C_6H_5$), 6.61(1H, d, *J* 2.8 Hz, 4-H), 6.71(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.22(1H, d, *J* 8.6 Hz, 1-H), and 7.25-7.37(5H, m, $CH_2C_6H_5$) (Found: C, 80.2; H, 8.0%; $M^+$, 404. $C_{27}H_{32}O_3$ requires C, 80.2; H, 7.9%; *M*, 404), followed by starting material (**24**) (5 mg; 10%).

(c) The 17-ketone (**24**) (400 mg; 1.2 mmol) in dry dimethylformamide (10 ml) was treated with t-butyldimethylsilyl chloride (1.09 g; 7.2 mmol) in the presence of imidazole (995 mg; 14 mmol) at 0 °C under nitrogen for 4 h. Water was added, and the product (550 mg) was isolated by extraction with ether. Chromatography (toluene) on silica gel (40 g) gave 17β-*t-butyldimethylsilyloxy*-17α,14-*epoxymethano*-3-*methoxyestra*-1,3,5(10)-*triene* (**27**) (360 mg; 66%), m.p. 100-102 °C (*from chloroform-methanol*); $[\alpha]_D$ +31° (*c* 1.1); δ 0.11 and 0.13(each 3H, s, $SiMe_2$), 0.88(12H, s, $SiBu^t$ and 13β-Me), 2.78-2.9(2H, m, 6-$H_2$), 3.47(1H, d, *J* 7.4 Hz, $17^2$-$H_{endo}$), 3.76(3H, s,

3-OMe), 4.14(1H, dd, *J* 7.4 and 4.1 Hz, $17^2$-$H_{exo}$), 6.6(1H, d, *J* 2.8 Hz, 4-H), 6.7(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21(1H, d, *J* 8.6 Hz, 1-H) (Found: C, 72.8; H, 9.5%; $M^+$, 428. $C_{26}H_{40}O_3Si$ requires C, 72.9; H, 9.35%; *M*, 428), and 14-*t-butyldimethylsilyloxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**28**) (180 mg; 33%), m.p. 100-102 °C (from chloroform-methanol); $[\alpha]_D$ +73° (*c* 1.1); $\nu_{max}$ 1735 $cm^{-1}$; $\Delta\epsilon$ +1.52 (292 nm); $\delta$ 0.0, and 0.01(each 3H, s, $SiMe_2$), 0.87(9H, s, $SiBu^t$), 1.01(3H, s, 13$\beta$-Me), 2.81(1H, ddd, *J* 12.2, 11.9, and 5.3 Hz, 9$\alpha$-H), 2.8-2.9(2H, m, 6-$H_2$), 3.45 and 3.86(each 1H, d, *J* 10.7 Hz, $14^1$-$H_2$), 3.76(3H, s, 3-OMe), 6.61(1H, d, *J* 2.8 Hz, 4-H), 6.7(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.18(1H, d, *J* 8.6 Hz, 1-H) (Found: C, 73.0; H, 9.5%; $M^+$, 428. $C_{26}H_{40}O_3Si$ requires C, 72.9; H, 9.35%; *M*, 428).

(17R)-*Spiro*[14-t-*butyldimethylsilyloxymethyl*-3-*methoxyestra*-1,3,5(10)-*triene*-17,$2^1$-*oxirane*] (**29**)

Trimethylsulphonium iodide (171 mg; 0.84 mmol) in dimethyl sulphoxide (1.5 ml) was added to a stirred suspension of sodium hydride (50% suspension in oil; 90 mg; 2 mmol) in dry dimethyl sulphoxide (0.5 ml) and dry tetrahydrofuran (1.5 ml) at 0 °C under nitrogen, followed by the 17-ketone (**28**) (90 mg; 0.21 mmol). After 10 min at 0 °C, the temperature was raised to 20 °C and the mixture was stirred for 10 h then poured into water. Flash chromatography of the product (103 mg), isolated by extraction with toluene, on silica gel (6 g) with toluene as eluent, afforded the *spiro-oxirane* (**29**) (27 mg; 29%), m.p. 123-128 °C (from acetone); $[\alpha]_D$ +70° (*c* 1.0); $\delta$ 0.02 and 0.04(each 3H, s, $SiMe_2$), 0.88(9H, s, $SiBu^t$), 0.96(3H, s, 13$\beta$-Me), 2.61 and 2.72(each 1H, d, *J* 4.5 Hz, $17^1$-$H_2$), 2.77-2.86(2H, m, 6-$H_2$), 2.9(1H, m, 9$\alpha$-H), 3.73(1H, dd, *J* 10.9 and 1.0 Hz, $14^1$-H), 3.76(3H, s, 3-OMe), 4.02(1H, dd, *J* 10.9 and 1.6 Hz, $14^1$-H), 6.61(1H, d, *J* 2.8 Hz, 4-H), 6.69(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.19(1H, d, *J* 8.6 Hz, 1-H) (Found: C, 73.1; H, 9.7%; $M^+$, 442. $C_{27}H_{42}O_3Si$ requires C, 73.3; H, 9.5%; *M*, 442), and starting material (**28**) (59 mg; 66%).

17$\alpha$,14-*Epoxymethano*-17$\beta$-*hydroxymethylestra*-1,3,5(10)-*trien*-3-*ol* (**30**)

Diisobutylaluminium hydride (1.2M in toluene; 1.5 ml; 1.8 mmol) was added to a stirred solution of the 3-methyl ether (**8**) (60 mg; 0.18 mmol) in dry toluene (2 ml). The mixture was refluxed for 8 h, then cooled, and hydrochloric acid (10%; 10 ml) was added. Extraction with chloroform gave material (64 mg), which was chromatographed [chloroform-methanol (19:1)] on silica gel (3 g) to give the 3,$17^1$-*diol* (**30**) (52 mg; 91%), m.p. 245-248 °C (from chloroform-ethanol); $[\alpha]_D$ +60° (*c* 0.5; tetrahydrofuran);

$\delta$ 0.9(3H, s, 13$\beta$-Me), 3.48(1H, d, $J$ 7.3 Hz, $17^2$-$H_{endo}$), 4.14(1H, dd, $J$ 7.3 and 4.1 Hz, $17^2$-$H_{exo}$), 6.54-7.15(3H, m, 1-, 2-, and 4-H) (Found: C, 76.55; H, 8.4%; $M^+$, 314. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%; $M$, 314).

17$\alpha$,14-*Epoxymethano*-17$\beta$-*hydroxymethylestr*-4-*en*-3-*one* (31)
Liquid ammonia (100 ml; distilled from sodium) was added to a solution of the compound (8) (100 mg; 0.3 mmol) in dry tetrahydrofuran (10 ml) and t-butyl alcohol (10 ml). Lithium (210 mg; 30 mmol) was added in portions, and the solution was stirred for 3 h at -35 to -40 °C. Solid ammonium chloride was added to disperse the blue colour of the mixture, and the ammonia was evaporated. The residue was dissolved in tetrahydrofuran (30 ml), and conc. hydrochloric acid (3 ml) in water (6 ml) was added. After stirring overnight, aqueous sodium hydrogen carbonate was added and the tetrahydrofuran was removed *in vacuo*. Extraction of the residue with ethyl acetate gave material (130 mg) which was chromatographed [chloroform-methanol (49:1)] on silica gel (10 g) to afford 17$\alpha$,14-*epoxymethano*-17$\beta$-*hydroxymethylestr*-4-*en*-3-*one* (31) (74 mg; 77%), m.p. 144-146 °C (from chloroform-ethyl acetate); $[\alpha]_D$ +42 ° ($c$ 1.1); $\lambda_{max}$ 238 nm (log$\epsilon$ 4.24); $\upsilon_{max}$ 1665 and 1620 $cm^{-1}$; $\Delta\epsilon$ -1.85 (316 nm); $\delta$ 0.93(3H, s, 13$\beta$-Me), 1.64(1H, dd, $J$ 6.7 and 5.4 Hz, exch. by $D_2O$, $17^1$-OH), 2.48(1H, ddd, $J$ 14.7, 4.0, and 2.4 Hz, 2$\alpha$-H), 3.4(1H, d, $J$ 7.4 Hz, $17^2$-$H_{endo}$), 3.69(1H, dd, $J$ 12.0 and 5.4 Hz -► d, $J$ 12.0 Hz on $D_2O$ exch., $17^1$-H), 3.75(1H, dd, $J$ 12.0 and 6.7 Hz -► d, $J$ 12.0 Hz on $D_2O$ exch., $17^1$-H), 3.97(1H, dd, $J$ 7.4 and 4.1 Hz, $17^2$-$H_{exo}$), and 5.8(1H, t, $J$ 2 x 2.0 Hz, 4-H) (Found: C, 76.0; H, 8.7%; $M^+$, 316. $C_{20}H_{28}O_3$ requires C, 75.95; H, 8.9%; $M$, 316).

17$\alpha$,14-*Epoxymethano*-3-*methoxyestra*-1,3,5(10)-*triene*-17$\beta$-*carbaldehyde* (32)
Pyridinium chlorochromate (644 mg; 3 mmol) was added to the 17$\beta$-hydroxymethyl compound (8) (280 mg; 0.85 mmol) in dry dichloromethane (30 ml). The reaction mixture was stirred for 4 h at 25 °C, then isopropyl alcohol (3 ml) was added. The black residue was filtered off and the filtrate was concentrated under reduced pressure. Chromatography [ethyl acetate-toluene (1:9)] of the residue (470 mg) on silica gel (20 g) gave the 17$\beta$-*carbaldehyde* (32) (225 mg; 81%), m.p. 151-153 °C (from ethyl acetate); $[\alpha]_D$ +167° ($c$ 0.9); $\upsilon_{max}$ 1725 $cm^{-1}$; $\Delta\epsilon$ +0.44 (309 nm); $\delta$ 1.0(3H, s, 13$\beta$-Me), 2.83(1H, ddd, $J$ 17.2, 6.8, and 2.7 Hz, 6$\alpha$-H), 2.88(1H, ddd, $J$ 17.2, 11.3, and 6.4 Hz, 6$\beta$-H), 3.61(1H, d, $J$ 7.6 Hz, $17^2$-$H_{endo}$), 3.76(3H, s, 3-OMe), 4.31(1H, dd, $J$ 7.6 and 4.1 Hz, $17^2$-$H_{exo}$), 6.61(1H, d, $J$ 2.8 Hz, 4-H), 6.7(1H, dd, $J$ 8.6 and 2.8 Hz, 2-H), 7.18(1H, d, $J$ 8.6 Hz, 1-H), and

9.86(1H, s, $17^1$-H) (Found: C, 77.4; H, 8.2%; $M^+$, 326. $C_{21}H_{26}O_3$ requires C, 77.3; H, 8.0%; *M*, 326).

*Reaction of the* 17β-*Carbaldehyde* (32) *with Methylmagnesium Iodide*
The 17β-carbaldehyde (32) (150 mg; 0.46 mmol) in benzene (8 ml) was added to a stirred solution of methylmagnesium iodide [generated from the reaction of methyl iodide (88 μl) with magnesium (50 mg) in diethyl ether (45 ml)] at 25 °C. After 1 h, aqueous ammonium chloride was added, and the resulting solution was stirred for 5 min and then extracted with toluene to give the crude product (183 mg). Chromatography [ethyl acetate-toluene (1:4)] on silica gel (30 g) afforded (20S)-17α,14-*epoxymethano*-3-*methoxy*-19-*norpregna*-1,3,5(10)-*trien*-20-*ol* (33) (91 mg; 58%), m.p. 139-140 °C (from chloroform-methanol); $[\alpha]_D$ + 42° (*c* 1.0); $\upsilon_{max}$ 3590 $cm^{-1}$; δ 0.92(3H, s, 13β-Me), 1.2(3H, d, *J* 6.6 Hz, 20-Me), 2.11(1H, d, *J* 7.7 Hz, exch. by $D_2O$, 20-OH), 2.82(1H, ddd, *J* 17.1, 6.8, and 2.8 Hz, 6α-H), 2.87(1H, ddd, *J* 17.1, 11.3, and 6.2 Hz, 6β-H), 3.47(1H, d, *J* 7.4 Hz, $17^2$-$H_{endo}$), 3.76(3H, s, 3-OMe), 3.93(1H, dq, *J* 7.7 and 3 x 6.6 Hz → q, *J* 3 x 6.6 Hz on $D_2O$ exch., 20-H), 4.13(1H dd, *J* 7.4 and 4.0 Hz, $17^2$-$H_{exo}$), 6.61(1H, d, *J* 2.8 Hz, 4-H), 6.7(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.2(1H, d, *J* 8.6 Hz, 1-H) (Found: C, 77.2; H, 9.1%; $M^+$, 342. $C_{22}H_{30}O_3$ requires C, 77.2; H, 8.8%; *M*, 342), and (20R)-17α,14-*epoxymethano*-3-*methoxy*-19-*norpregna*-1,3,5(10)-*trien*-20-*ol* (34) (58 mg; 37%), m.p. 160-161 °C (from chloroform-methanol); $[\alpha]_D$ +54° (*c* 1.0); $\upsilon_{max}$ 3600 $cm^{-1}$; δ 0.99(3H, s, 13β-Me), 1.27(3H, d, *J* 6.7 Hz, 20-Me), 1.91(1H, d, *J* 5 1 Hz, exch. by $D_2O$, 20-OH), 2.82(1H, ddd, *J* 17.5, 6.8, and 2,7 Hz, 6α-H), 2.88(1H, ddd, *J* 17.5, 11.6, and 6.3 Hz, 6β-H), 3.45(1H, d, *J* 7.4 Hz, $17^2$-$H_{endo}$), 3.76(3H, s, 3-OMe), 3.98(1H, dq, *J* 3 x 6.7, and 5.1 Hz → q, *J* 3 x 6.7 Hz on $D_2O$ exch., 20-H), 4.1(1H, dd, *J* 7.4 and 4.1 Hz, $17^2$-$H_{exo}$), 6.61(1H, d, *J* 2.8 Hz, 4-H), 6.7(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.2(1H, d, *J* 8.6 Hz, 1-H) (Found: C, 77.2; H, 9.1%; $M^+$, 342. $C_{22}H_{30}O_3$ requires C, 77.2; H, 8.8%; *M*, 342).

17α,14-*Epoxymethano*-19-*norpregn*-4-*ene*-3,20-*dione* (36)
A mixture of the 20-hydroxy compounds (33 + 34) (96 mg; 0.28 mmol) was subjected to Birch reduction and acid treatment, as described for compound (8), to give a mixture of 17α,14-*epoxymethano*-20ξ-hydroxy-19-*norpregn*-4-*en*-3-*ones* (35) (114 mg), $\upsilon_{max}$ 3600, 1670 and 1620 $cm^{-1}$; *m/z* 330 ($M^+$); δ (90MHz) 0.96('1.8H', s, 13β-Me), 1.04('1.2H', s, 13β-Me), 1.16('1.8H', s, 20-Me), 1.23('1.2H', s, 20-Me), 3.4(1H, m, $W_{\frac{1}{2}}$ 12 Hz, $17^2$-$H_{endo}$), 3.92(2H, m, $W_{\frac{1}{2}}$ 18 Hz, 20-H and $17^2$-$H_{exo}$), and 5.82(1H, s, 4-H). The total product was

treated with pyridinium chlorochromate (130 mg; 0.6 mmol) in dry dichloromethane (20 ml). After 4 h, isopropyl alcohol (3 ml) was added and the black residue was removed by filtration. The filtrate was concentrated under reduced pressure and the residue (105 g) was chromatographed [ethyl acetate-toluene (1:4)] on silica gel (5 g) to afford 17$\alpha$,14-*epoxymethano*-19-*norpregn*-4-*ene*-3,20-*dione* (**36**) (70 mg; 76% from 33 + 34), m.p. 161-163 °C (from benzene-hexane); $[\alpha]_D$ +170° (*c* 1.0); $\lambda_{max}$ 238 nm (log$\epsilon$ 4.25); $\upsilon_{max}$ 1705, 1670, and 1620 $cm^{-1}$; $\Delta\epsilon$ -1.5(326 nm) and +2.7 (286 nm); $\delta$ 0.98(3H, s, 13$\beta$-Me), 2.19(3H, s, 20-Me), 2.48(1H, ddd, *J* 14.7, 4.1, and 2.4 Hz, 2$\alpha$-H), 3.47(1H, d, *J* 7.4 Hz, $17^2$-$H_{endo}$), 4.09(1H, dd, *J* 7.4 and 4.0 Hz, $17^2$-$H_{exo}$), and 5.8(1H, t, *J* 2 x 2.1 Hz, 4-H) (Found: C, 77.0; H, 8.6%; $M^+$, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.5%; *M*, 328).

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