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INTRAMOLECULAR CONDENSATION OF STEROIDAL 17α-FORMYL 17β-ACETATES: MODEL STUDIES ON 19-NORSTEROIDS, AND A ROUTE TO 3-METHOXY-19-NOR-17α-PREGNA-1,3,5(10)-TRIENE-21,17-CARBOLACTONE[1]

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Methods are described for the conversion of estrone 3-methyl ether (**1**) into 17β-acetoxy-3-methoxyestra-1,3,5(10)-triene-17α-carbaldehyde (**5**), treatment of which with lithium 2,2,6,6-tetramethylpiperidide at -100°C results in efficient intramolecular condensation to 20(*R*)-hydroxy-3-methoxy-19-nor-17α-pregna-1,3,5(10)-triene-21,17-carbolactone (**14**), which is converted into the title compound (**16**). The synthesis and base-mediated treatment of 17α-(toluene-*p*-sulphonyloxymethyl)-3-methoxyestra-1,3,5(10)-trien-17β-yl-acetate (**22**) are described.

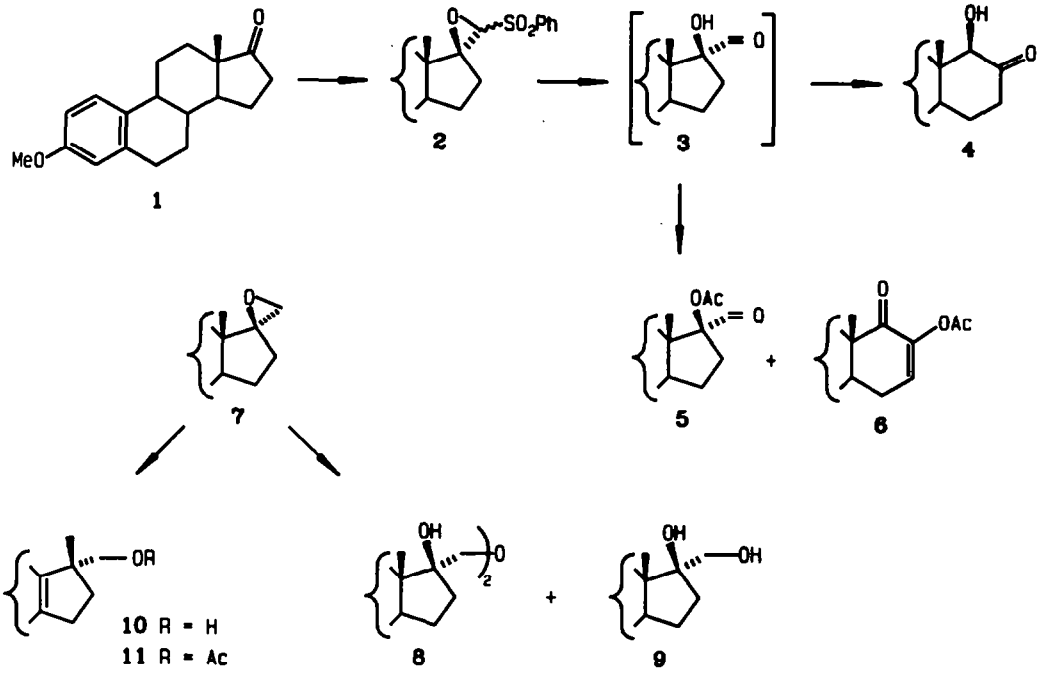
The ongoing interest in structure–activity relationships of aldosterone antagonists is reflected in numerous publications which continue to appear on new analogues of spironolactone.[2-6] Despite its central role in the clinical management of hyperaldosteronism, the endocrinological side effects associated with protracted administration of spironolactone provide scope for the design and synthesis of more specific and active analogues.[7]

Favoured approaches to synthesis of the distinctive spirolactone ring of this family of steroids include nucleophilic addition of propionic acid synthons to 17-ketones[2,3,5] or cleavage of the derived 17-spiro-oxiranes by acetic acid synthons.[6,8] In this paper, we describe the synthesis of 17β-acetoxy-3-methoxyestra-1,3,5(10)-triene-17α-carbaldehyde (**5**) and 3-methoxy-17α-(toluene-*p*-sulphonyloxymethyl)estra-1,3,5(10)-trien-17β-yl acetate (**22**), and an alternative approach to construction of the 17-spirolactone ring mediated by intramolecular ester enolate condensation. This approach was inspired by analogous condensations often encountered during reactions of 17α-acetoxy 17β-acetyl steroids in strongly basic media,[9] and by the finding[10] that α-acetoxy ketones can be induced to undergo selective ester enolisation and intramolecular condensation under exceptionally mild conditions.

For our first objective, we elected to use a recently described[11] method for homologation of estrone 3-methyl ether (**1**) to the α,β-epoxy sulphone (**2**), and to convert the derived 17β-hydroxy 17α-carbaldehyde (**3**) into the corresponding 17β-acetoxy derivative (**5**). Although compound (**3**) is susceptible to rearrangement,[12] it was reasoned that immediate acetylation would circumvent any such difficulty.

Treatment of compound (**1**) with chloromethyl phenyl sulphone in the presence of potassium t-butoxide gave the crude product (**2**), which displayed the expected spectroscopic properties but proved to be unstable during attempted purification. The prescribed treatment of this crude product (**2**) with

potassium t-butoxide in the presence of a limited amount of water was capricious in our hands. Work-up of the reaction mixture without acidification gave a product which appeared to comprise monomeric (**3**) [ν_{max} 3460 and 1710 cm^{-1}; δ 9.84(1H, s)], and underwent the expected[12] rearrangement to the D-homo product (**4**) during chromatography on silica gel. We found no evidence of a stable dimeric product using this procedure,[11] and acid work-up resulted only in isolation of the rearrangement product (**4**).



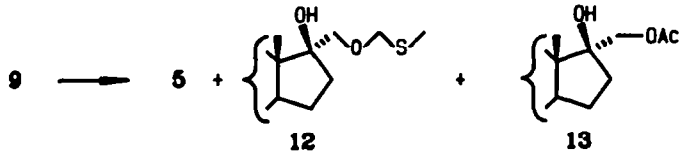
Furthermore, an attempt to acetylate the crude hydroxy aldehyde (**3**) with acetic anhydride and a catalytic amount of toluene-*p*-sulphonic acid gave only a modest yield of the desired product (**5**) (23%), accompanied by the D-homosteroid (**6**) (51%) which appears to have arisen through autoxidation of the primary rearrangement product (**4**).

These results demonstrate that, although the hydroxy aldehyde (**3**) was not amenable to isolation or to efficient trapping under the reaction conditions used here, it was certainly present as the major component upon base treatment of the α,β-epoxy sulphone (**2**), since it is an obligatory precursor of the rearrangement products (**4**) and (**6**). Indeed, an improved yield of the acetoxy aldehyde (**5**) (53%) was obtained when acidic conditions were avoided altogether, and the acetylation step was performed with acetic anhydride–triethylamine in the presence of a catalytic amount of 4-(dimethylamino)pyridine.

The 17β-acetoxy 17α-carbaldehyde (**5**) was stable to work-up conditions and chromatography, and was characterised by distinctive spectroscopic properties. In an attempt to develop a more efficient route to (**5**), the 17-spiro-oxirane (**7**)[13] was converted into 17α-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (**9**). Cleavage of (**7**) with alkali in aqueous dimethyl sulphoxide was efficient,[14] but the product (**9**) (81%) was accompanied by the dimeric ether (**8**) (12%). Not unexpectedly, treatment of (**7**) with aqueous perchloric acid failed to give the diol (**9**), but led rapidly and exclusively to the methyl-migration

product (**10**), the structure of which followed from analogy,[15] as well as its spectroscopic properties and those of the derived acetate (**11**).

Attempts to oxidise the diol (**9**) to the hydroxy aldehyde (**3**) proved disappointing. For example, treatment of (**9**) with buffered pyridinium chlorochromate, and similar reagents, led only to the product (**1**) of oxidative cleavage. Swern oxidation at −10°C for a brief period, followed by immediate acetylation of the crude product gave, after chromatography, the desired product (**5**) in 33% yield, accompanied by the 17[1]-methylthiomethyl ether (**12**) (19%) and the 17[1]-acetate (**13**) (26%). Variations of these reaction conditions failed to improve the yield, and attempted oxidation of (**9**) with *N*-chlorosuccinimide–dimethyl sulphide gave mainly the methylthiomethyl ether (**12**).



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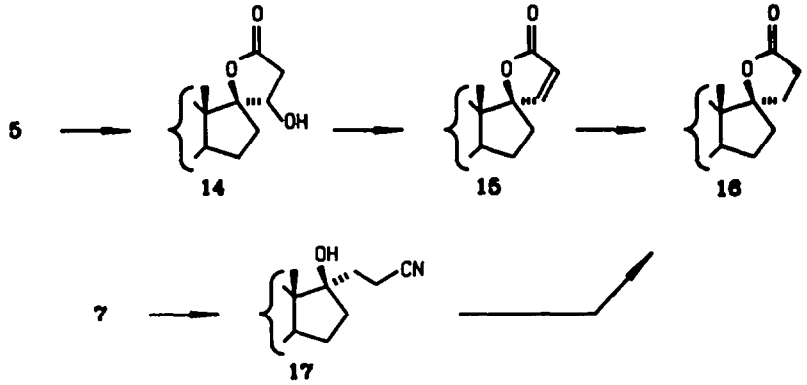
With the acetoxy aldehyde (**5**) in hand, methods for intramolecular condensation were investigated. Of a variety of bases tried under different conditions, the most successful proved to be lithium 2,2,6,6-tetramethylpiperidide in tetrahydrofuran at −100°C, which gave 20(*R*)-hydroxy-3-methoxy-19-nor-17α-pregna-1,3,5(10)-triene-21,17-carbolactone (**14**) in 89% yield. The product showed typical i.r. absorption for a γ-lactone (ν_{max} 1760 cm^{-1}), and a 500 MHz n.m.r. spectrum displayed an ABX multiplet for the spirolactone ring protons [δ 2.54(dd, *J* 18.0 and 3.4 Hz), 2.85(dd, *J* 18.0 and 6.4 Hz), and 4.44(dd after D_2O exchange, *J* 6.4 and 3.4 Hz)]. The assignment of 20*R*-configuration was based upon the chemical shift of the 16α-proton (δ 2.54), which is significantly deshielded by comparison with that of estrone 3-methyl ether (**1**) (δ 1.78),[16] denoting close spatial proximity to the 20-hydroxy group. The high stereoselectivity of the condensation may be ascribed to preferred alignment of the 17α-formyl C–O bond in (**5**), toward C(16) rather than the sterically more hindered environment of C(13) and its appended bonds.

Elimination of the 20-hydroxy group was readily achieved through treatment of (**14**) with methanesulphonyl chloride in pyridine followed by slow chromatography on silica gel, to give the unsaturated spirolactone (**15**), which was smoothly hydrogenated over palladium on calcium carbonate to the known[17] 3-methoxy-19-nor-17α-pregna-1,3,5(10)-triene-21,17-carbolactone (**16**). The overall conversion of the acetoxy aldehyde (**5**) into the saturated 17-spirolactone (**16**) proceeded in *ca* 80% yield.

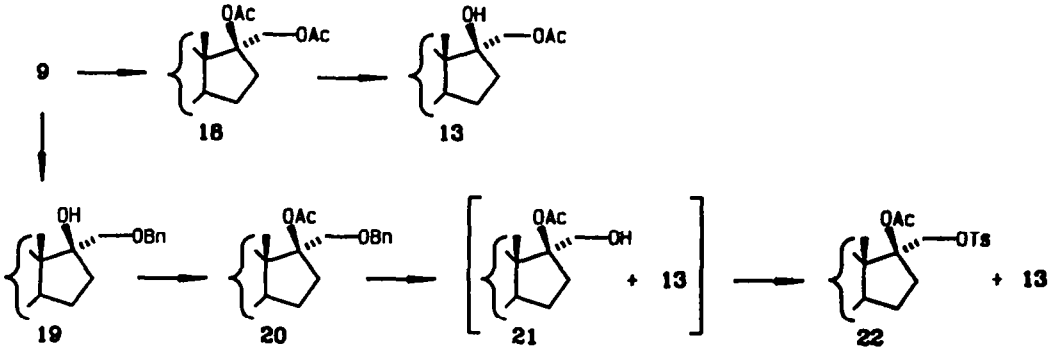
For comparative purposes, the method described by Creger[8] was applied to the 17-spiro oxirane (**7**). The described conditions for addition of lithiated acetonitrile and subsequent alkaline hydrolysis of the adduct (**17**) were modified, when it was discovered that hydrolysis of the cyano group in (**17**) proceeded efficiently when water was added to the initial reaction mixture which was then allowed to stir for 3 h. Subsequent acidification of the medium promoted lactonisation. It was thus possible to carry out the entire reaction as a one-pot procedure, to give the 17-spirolactone (**16**) in 85% yield from (**7**). Clearly, this method is simpler and more efficient than the ester enolate route in this case. Nevertheless, the latter process should have significant advantages for those substrates having labile functionality elsewhere in the molecule, since aqueous alkaline and strongly acidic conditions are avoided throughout.

Furthermore, the ester enolate route can readily be extended to the synthesis of substituted spirolactone rings, through the simple expedient of modifying the ester moiety, or exploiting the β-hydroxy or α,β-unsaturated γ-lactone intermediates.



An extension of the ester enolate approach may be conceived through replacement of the 17α-formyl group by other electrophiles. Indeed, if a substrate can be structured to allow an S_Ni displacement, the approach could provide a direct route to the saturated spirolactones (e.g. **16**). Accordingly, we undertook the synthesis of the 17α-(toluene-*p*-sulphonyloxymethyl) 17β-acetate (**22**) in order to examine this possibility.

An attempt to prepare this intermediate through sequential 17^1-tosylation and 17β-acetylation of the diol (**9**) failed, owing to elimination of the tosyl group during the second step, to give the 17-spiro-oxirane (**7**). An alternative approach based upon 17β,17^1-diacetylation of the diol (**9**), followed by selective hydrolysis of the primary acetoxy group was also unsuccessful. Although the diacetate (**18**) was readily formed, the attempted selective hydrolysis under a variety of conditions gave rise to mixtures comprising starting material (**18**), diol (**9**), and the 17α-acetoxymethyl 17β-alcohol (**13**). The cleanest reaction, conducted with a slight excess of potassium t-butoxide in t-butyl alcohol–tetrahydrofuran at 0°C afforded, after silica gel chromatography, the 17^1-acetate (**13**) in 65% yield. No trace of the regioisomer was detected during the course of the reaction, or in the product before and after chromatography.



The structure of (13), was evident from n.m.r. data; thus, the 17^1-CH_2 signals appeared as an AB pattern at δ 4.09 and 4.22(each d, *J* 11.3 Hz), shifted downfield by comparison with the analogous pattern in the diol (9) [δ 3.46 and 3.8(each d, *J* 11 Hz)].

It is evident from this result that the primary hydrolysis product is subject to extremely rapid transacetylation under the reaction conditions. This was also observed during reduction of the acetoxy aldehyde (5) with sodium borohydride; although the reaction was conducted at 0°C, and precautions were taken during the work-up of the product, the 17^1-acetate (13) was obtained in high yield.

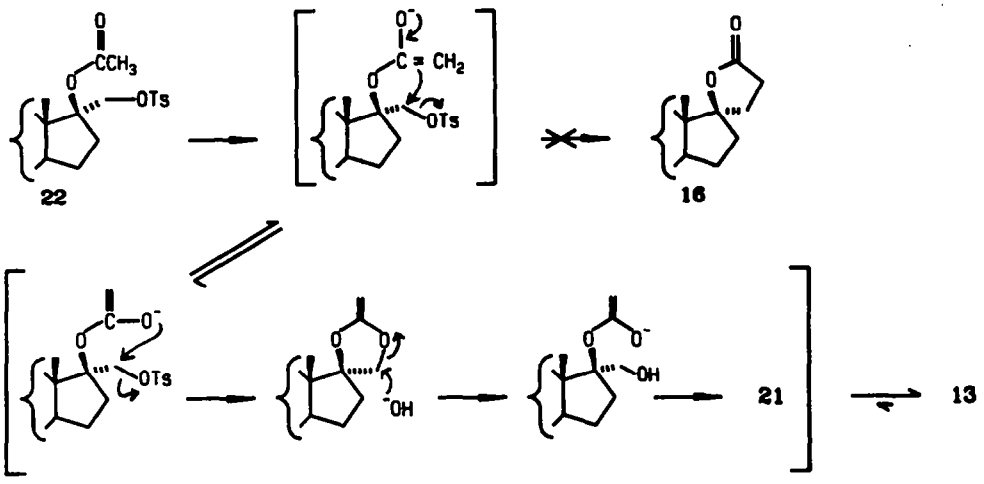
An alternative approach was adopted in order to generate the desired 17β-acetoxy 17^1-alcohol under milder and strictly neutral conditions. Accordingly, the diol (9) was converted into the 17^1-benzyl ether (19), which underwent efficient albeit slow acetylation with acetic anhydride–4-(dimethylamino)-pyridine to give the 17α-benzyloxymethyl 17β-acetate (20) (94%).

Hydrogenolysis of (20) over Pd–C proceeded rapidly and the product, isolated by filtration and evaporation of the filtrate, was examined immediately by n.m.r., which revealed that it comprised a *ca* 1:1 mixture of two isomers. In solution, this mixture underwent progressive change into the pure transacetylation product (13), thereby demonstrating that the sought isomer (21) was indeed present initially. Accordingly, the crude hydrogenolysis product was treated immediately with toluene-*p*-sulphonyl chloride–pyridine at 0°C. Flash chromatography of the product gave the 17α-(toluene-*p*-sulphonyloxymethyl) 17β-acetate (22) in 39% yield from (20), accompanied by the 17^1-acetate (13) (55%). The spectroscopic properties of (22) were consistent with the assigned structure.

Compound (22) underwent rapid reaction in the presence of lithium 2,2,6,6-tetramethyl-piperidide–tetrahydrofuran at −100°C. After 20 min, no starting material was present (t.l.c.), and an n.m.r. spectrum of the crude product revealed that the 17^1-acetate (13) was the major product. This was confirmed by chromatography, and isolation of (13) (65%). A similar result was obtained when compound (22) was treated with lithium di-isopropylamide at −100°C and, most efficiently, with sodium amide (78% yield), although no reaction took place in the presence of sodium or potassium hydride.

It is therefore evident that the desired intramolecular ester enolate displacement to the spirolactone (16) does not occur. However, the formation of the 17^1-acetate (13) invites speculation about an intramolecular mode of formation, in the absence of an intermolecular route for displacement or hydrolysis of the tosyloxy group. It is conceivable that intramolecular closure proceeds *via* the oxygen terminus of the ester enolate to yield an intermediate ketene acetal, which undergoes rapid hydrolysis and transcetylation during work-up (Scheme). Our failure to detect the ketene acetal during monitoring of the reaction and upon work-up is not surprising, in view of the known reactivity of such systems. Furthermore, the proposed *O*-terminal regioselectivity of closure is consistent with the constraints of Baldwin's rules upon 5-*endo*-trig closures.[18]

SCHEME



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. 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.

17-Homologation of Estrone 3-Methyl Ether (1)

(a) M-Potassium t-butoxide in t-butyl alcohol (5.6 ml) was added to 3-methoxyestra-1,3,5(10)-trien-17-one (1) (1.25 g; 4.4 mmol) and chloromethyl phenyl sulphone (825 mg; 4.4 mmol) in dry tetrahydrofuran (10 ml) at 18°C under nitrogen. After 3 h, t.l.c. [ethyl acetate–hexane (1:2)] showed that all the reagent had been consumed and only a trace of starting material remained. Water was added, and extraction of the mixture with ether gave the α,β-epoxy sulphone (2) (1.8 g), δ 0.87(3H, s, 13β-Me), 3.75 (3H, s, 3-OMe), 4,00(1H, s, 17^1-H), and 6,65–8,07(8H, m, arom.H). The crude product (1.8 g) was dried under vacuum and stored as a froth under nitrogen at 0°C. The compound was not crystallised as a result of its lability.

Potassium t-butoxide (2.35 g; 21.0 mmol) and water (114 μl; 6.3 mmol) were added to the crude α,β-epoxy sulphone (2) (1 g; 2.3 mmol) in dry tetrahydrofuran (30 ml) under nitrogen, and the mixture was stirred for 2 h at 20°C. Extraction with dichloromethane–ether (1:9) afforded the crude hydroxy aldehyde (3) (680 mg), ν_{max} 3460 and 1710 cm^{-1}; *m/z* 314 (M^+); δ 0.87(3H, s, 13β-Me), 3.75(3H, s, 3-OMe), 6.63–7.40(3H, m, arom.H), and 9.84(1H, s, 17α-CHO). Attempted purification of the crude product by chromatography on silica gel gave the D-homosteroid (4), δ 0.68(3H, s, 13β-Me), 3.52(1H, d, *J* 4 Hz, exch. by D_2O, 17aβ-OH), 3.76(3H, s, 3-OMe), 3.87 (1H, d, *J* 4 Hz, →s on exch. by D_2O, 17aα-H), and 6.56–7.33(3H, m, arom.H).

(b) Acetic anhydride (5 ml) and toluene-*p*-sulphonic acid (150 mg) were added to the crude hydroxy aldehyde (3) (400 mg) (prepared according to the foregoing procedure) in benzene (15 ml). The reaction mixture was stirred for 2 days under nitrogen, then neutralised with aqueous sodium hydrogen carbonate. Extraction with benzene afforded crude material (505 mg), which was chromatographed on silica gel (40 g), with benzene as eluent, to give *17β-acetoxy-3-methoxyestra-1,3,5(10)-triene-17β-carbaldehyde* (**5**) (106 mg; 23%), m.p. 127–129°C (from acetone–methanol); $[\alpha]_D$ +20° (*c* 1.0); ν_{max} 1725 cm^{-1}; δ 1.0(3H, s, 13β-Me), 2.12(3H, s, 17β-OAc), 3.75(3H, s, 3-OMe), 6.56–7.33(3H, m, arom.H), and 9.57(1H, s, 17^1-H)(Found: C, 74.3; H, 8.05%; M^+, 356. $C_{22}H_{28}O_4$ requires C, 74.2; H, 7.9%; *M*, 356), followed by *17-acetoxy-3-methoxy-17a-homoestra-1,3,5(10),16-tetraen-17a-one* (**6**) (230 mg; 51%), m.p. 176–179°C (from ethyl acetate–hexane); $[\alpha]_D$ +5° (*c* 0.9); λ_{max} 226 nm (log ε 4.05); ν_{max} 1740 and 1680 cm^{-1}; Δε −0.08(351 nm) and +0.34(314 nm); δ (500MHz) 1.12(3H, s, 13β-Me), 1.43(1H, dddd, *J* 13.4, 13.1, 11.3, and 3.4 Hz, 11β-H), 1.51(1H, ddt, *J* 2 x 11.3, 11.0, and 2.5 Hz, 8β-H), 1.61(1H, ddd, *J* 13.9, 13.4, and 4.0 Hz, 12α-H), 1.87(1H, dt, *J* 2 x 11.0, and 4.6 Hz, 14α-H), 2.04(1H, dddd, *J* 12.3, 5.3, 3.3, and 2.5 Hz, 7β-H), 2.12(1H, ddd, *J* 13.9, 4.0, and 3.4 Hz, 12β-H), 2.20(1H, ddd, *J* 18.9, 11.0, and 2.3 Hz, 15β-H), 2.21(3H, s, 17-OAc), 2.26(1H, dt, *J* 2 x 11.3, and 3.7 Hz, 9α-H), 2.38 (1H, ddt, *J* 13.1, 2 x 4.0, and 3.7 Hz, 11α-H), 2.66(1H, ddd, *J* 18.9, 6.3, and 4.6 Hz, 15α-H), 2.80–2.90(2H, m, 6-H_2), 3.75(3H, s, 3-OMe), 6.47(1H, dd, *J* 6.3 and 2.3 Hz, 16-H), 6.61(1H, d, *J* 2.8 Hz, 4-H), 6.71(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.20(1H, d, *J* 8.6 Hz, 1-H)(Found: C, 74.5; H, 7.1%; M^+, 354. $C_{22}H_{26}O_4$ requires C, 74.6; H, 7.3%; *M*, 354).

(c) The crude hydroxy aldehyde (3) (100 mg), acetic anhydride (86 μl), and 4-(dimethylamino)-pyridine (5 mg) were dissolved in triethylamine (40 ml). The resulting solution was stirred for 2 days at 25°C. Methanol (10 ml) was added, and the mixture was stirred for 30 min, then concentrated under reduced pressure. Extraction of the residue with benzene, and chromatography of the product (111 mg) on silica gel (10 g), with benzene as eluent, afforded the acetoxy aldehyde (**5**) (60 mg; 53%), m.p. 127–129°C (from acetone–methanol).

Cleavage of the Spiro-oxirane (**7**)

(a) The spiro-oxirane (**7**) (416 mg) was added to a solution of potassium hydroxide (287 mg) in dimethyl sulphoxide (12.8 ml) and water (2.2 ml), and the mixture was stirred for 3 h at 120°C. Water was added to the cooled solution, and the resultant precipitate was collected by filtration and dried under vacuum to give the product (455 mg). Chromatography on silica gel (30 g), with methanol–chloroform (1:19) as eluent, afforded starting material (**7**) (4 mg), followed by *bis[17β-hydroxy-3-methoxy-17α-methylestra-1,3,5(10)-trien-17^1-yl]*-ether (**8**) (53 mg; 12%), m.p. 227–229°C (from chloroform–methanol); $[\alpha]_D$ +28° (*c* 0.5); ν_{max} 3260–3550 cm^{-1}; δ (300MHz) 0,93(2 x 13β-Me), 3.41 and 3.70(each 1H, d, *J* 9.2 Hz, 2 x 17^1-H_2), 3.77(2 x 3-OMe), 6.63(2H, d, *J* 2.7 Hz, 2 x 4-H), 6.71(2H, dd, *J* 8.6 and 2.7 Hz, 2 x 2-H), and 7.18(2H, d, *J* 8.6 Hz, 2 x 1-H)(Found: C, 78.3; H, 8.9%; M^+, 614. $C_{40}H_{54}O_5$ requires C, 78.2; H, 8.8%; *M*, 614), and the 17β,17^1-diol (**9**) (359 mg; 81%), m.p. 169–171°C (from methanol)(lit.,[14] m.p. 168–171°C); δ (500MHz) 0.92(3H, s, 13β-Me), 1.32(1H, ddt, *J* 12.3, 2 x 11.8, and 7.4 Hz, 7α-H), 1.88(1H, ddt, *J* 12.3, 6.0, and 2 x 2.9 Hz, 7β-H), 1.93(1H, dd, *J* 6.8 and 4.4 Hz, exch. by D_2O, 17^1-OH), 2.16(1H, dt, *J* 2 x 10.8, and 4.2 Hz, 9α-H), 2.79–2.90(2H, m, 6-H_2), 3.46(1H, dd, *J* 11.0 and 6.8 Hz, →d, *J* 11.0 Hz on D_2O exch., 17^1-H), 3.76(3H, s, 3-OMe), 3.80(1H, dd, *J* 11.0 and 4.4 Hz, →d, *J* 11.0 Hz on D_2O exch., 17^1-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 7.17(1H, d, *J* 8.6 Hz, 1-H).

(b) Compound (**7**) (203 mg) was dissolved in methyl ethyl ketone (8 ml; distilled from potassium permanganate). Perchloric acid (60%; 0.1 ml) was added to the solution at 0°C. The reaction was practically instantaneous, and was quenched with aqueous sodium hydrogen carbonate. The methyl ethyl ketone was evaporated under reduced pressure, and the product (225 mg) was isolated by extraction with chloroform, and adsorbed on silica gel (35 g). Elution with ethyl acetate–toluene (1:19) afforded three minor products followed by *17α-hydroxymethyl-3-methoxy-17β-methylgona-1,3,5(10),13-tetraene* (**10**) (158

mg; 73%), m.p. 75–77°C (from hexane–ethyl acetate); $[\alpha]_D$ -28° (*c* 0.9); ν_{max} 3300–3600 cm^{-1}; δ 1.02(3H, s, 17β-Me), 3.41 and 3.55 (each 1H, d, *J* 11 Hz, 17^1-H_2), 3.76(3H, s, 3-OMe), and 6.58–7.35(3H, m, arom.H)(Found: C, 80.2; H, 9.1%; M^+, 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.8%; *M*, 298).

The derived 17^1-*acetate* (**11**) had m.p. 98–100°C (from methanol–chloroform); $[\alpha]_D$ -10° (*c* 0.8); ν_{max} 1720 cm^{-1}; δ 1.06(3H, s, 17β-Me), 2.03(3H, s, 17^1-OAc), 3.76(3H, s, 3-OMe), 3.85 and 4.07(each 1H, d, *J* 12 Hz, 17^1-H_2),and 6.63–7.39(3H, m, arom.H)(Found: C, 77.3; H, 8.4%; M^+, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; *M*, 340).

Oxidation of 17α-*Hydroxymethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17β-*ol* (**9**)

(a) Pyridinium chlorochromate (52 mg; 0.24 mmol) and sodium acetate (4 mg; 0.048 mmol) were suspended in dry dichloromethane (2 ml). The diol (**9**) (50 mg; 0.16 mmol) in dichloromethane (1 ml) was added. After 30 min, the reaction was quenched by adding dry ether (4 ml), and the supernatant solution was decanted from the black gum, which was washed with ether (x3). The combined organic phase was filtered through Celite and concentrated. Chromatography of the residue (51 mg) on silica gel (5 g), with ethyl acetate–toluene (1:9) as eluent, afforded the 17-ketone (**1**) (40 mg; 86%), m.p. and mixed m.p. 169–171°C (from chloroform–ethyl acetate).

(b) Dimethyl sulphoxide (0.12 ml; 1.7 mmol) in dry dichloromethane (1 ml) was added dropwise to oxalyl chloride (0.06 ml; 0.70 mmol) in dry dichloromethane (1 ml) at -60°C. After 2 min, the temperature was raised to -10°C, and the diol (**9**) (100 mg; 0.32 mmol) was added. The reaction was stirred for 15 min at -10°C, then triethylamine (0.2 ml; 1.43 mmol) was added. After a further 5 min at -10°C, the reaction mixture was warmed up to 20°C and water was added. Extraction with chloroform gave the reaction product (96 mg), which was treated with 4-(dimethylamino)pyridine (5 mg) and acetic anhydride (0.1 ml) in triethylamine (10 ml) at 20°C for 4 h. The product (111 mg) was isolated in the usual way, and chromatographed on silica gel (10 g), with ethyl acetate–toluene (1:9) as eluent, to give the 17β-acetoxy 17α-carbaldehyde (**5**) (37 mg; 33%), m.p. 125–128°C (from acetone–methanol), followed by the 17^1-methylthiomethyl ether (**12**) (23 mg; 19%), *m/z* 376 (M^+); δ 0.93(3H, s, 13β-Me), 2.19(3H, s, SMe), 3.45 and 3.72(each 1H, *J* 9 Hz, 17^1-H_2), 3.77(3H, s, 3-OMe), 4.72(2H, s, OCH_2S), and 6.60–7.33(3H, m, arom.H), and the monoacetate (**13**) (30 mg; 26%), m.p. 89–91°C (from benzene–hexane) (see below for full characterisation).

20(R)-*Hydroxy*-3-*methoxy*-19-*nor*-17α-*pregna*-1,3,5(10)-*triene*-21,17-*carbolactone* (**14**)

2,2,6,6-Tetramethylpiperidine (1.66 ml; 9.8 mmol) was added to ethereal n-butyl-lithium (1.4*M*; 3.5 ml; 4.9 mmol) in dry tetrahydrofuran (3 ml) at 0°C. After 10 min, the solution was cooled to -100°C and the acetoxy aldehyde (**5**) (350 mg; 0.98 mmol) in dry tetrahydrofuran (5 ml) was added slowly with stirring. After 30 min at -100°C, dilute acetic acid was added, and the product (404 mg) was isolated by extraction with benzene. Chromatography on silica gel (30 g), with ethyl acetate–benzene (1:4) as eluent, afforded 20(R)-*hydroxy*-3-*methoxy*-19-*nor*-17α-*pregna*-1,3,5(10)-*triene*-21,17-*carbolactone* (**14**) (310 mg; 89%), m.p. 181–184°C (from ethyl acetate–hexane); $[\alpha]_D$ +19° (*c* 0.9); ν_{max} 3200–3600 and 1760 cm^{-1}; δ (500MHz) 0.97(3H, s, 13β-Me), 1.33(1H, ddt, *J* 12.9, 2 x 11.9, and 7.0 Hz, 7α-H), 1.64(1H, ddd, *J* 11.2, 3.1, and 2.9 Hz, 12β-H), 1.90(1H, ddt, *J* 12.9, 6.0, and 2 x 2.7 Hz, 7β-H), 1.94(1H, ddd, *J* 14.7, 10.9, and 3.1 Hz, 16β-H), 2.05 (1H, d, *J* 5.8 Hz, exch. by D_2O, 20-OH), 2.15(1H, dt, *J* 2 x 10.6, and 4.2 Hz, 9α-H), 2.32(1H, ddt, *J* 13.4, 2 x 4.2, and 3.1 Hz, 11α-H), 2.54(1H, dd, *J* 18.0 and 3.4 Hz, 21-H), 2.54(1H, ddd, *J* 14.7, 9.5, and 5.7 Hz, 16α-H), 2.79–2.91(2H, m, 6-H_2), 2.85(1H, dd, *J* 18.0 and 6.4 Hz, 21-H), 3.76 (3H, s, 3-OMe), 4.44(1H, ddd, *J* 6.4, 5.8, and 3.4 Hz, →dd, *J* 6.4 and 3.4 Hz on D_2O exch., 20-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 7.15(1H, d, *J* 8.6 Hz, 1-H)(Found: C, 73.9; H, 8.0%; M^+, 356. $C_{22}H_{28}O_4$ requires C, 74.2; H, 7.9%; *M*, 356).

3-Methoxy-19-nor-17α-pregna-1,3,5(10),20-tetraene-21,17-carbolactone (**15**)

Methanesulphonyl chloride (0.14 ml) was added to the spirolactone (**14**) (100 mg; 0.28 mmol) in pyridine (1.5 ml). The reaction was stirred for 5 h at 20°C, and further methanesulphonyl chloride (0.22 ml) was added. After a further 16 h, the reaction mixture was poured into ice–water, and the product (120 mg) was isolated by extraction with toluene. Slow chromatography on silica gel (10 g), with ethyl acetate–toluene (1:9) as eluent, afforded *3-methoxy-19-nor-17α-pregna-1,3,5(10),20-tetraene-21,17-carbolactone* (**15**) (88 mg; 93%), m.p. 176–178°C (from ethyl acetate–hexane); $[\alpha]_D$ +85° (*c* 0.4); ν_{max} 1735 cm^{-1}; δ (500MHz) 1.06(3H, s, 13β-Me), 1.38(1H, ddt, *J* 2 x 12.4, 11.0, and 6.8 Hz, 7α-H), 2.27(1H, ddt, *J* 13.6, 2 x 4.2, and 2.9 Hz, 11α-H), 2.32(1H, ddd, *J* 14.2, 11.3, and 2.8 Hz, 16β-H), 2.84 (1H, ddd, *J* 17.2, 6.8, and 3.0 Hz, 6α-H), 2.89(1H, ddd, *J* 17.2, 11.0, and 5.8 Hz, 6β-H), 3.75(3H, s, 3-OMe), 5.96(1H, d, *J* 5.6 Hz, 20-H), 6.62(1H, d, *J* 2.8 Hz, 4-H), 6.69(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.15(1H, d, *J* 8.6 Hz, 1-H), and 7.49(1H, d, *J* 5.6 Hz, 21-H)(Found: C,78.1; H, 7.6%; M^+, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; *M*, 338).

3-Methoxy-19-nor-17α-pregna-1,3,5(10)-triene-21,17-carbaldehyde (**16**)

(a) The Δ^{20}-21,17-carbolactone (**15**) (27 mg) was dissolved in ethyl acetate (3 ml) and hydrogenated over palladium on calcium carbonate (10%; 10 mg) at atmospheric pressure and room temperature. After 2 h, the catalyst was removed by filtration and the reaction mixture was concentrated under reduced pressure. Crystallisation of the residue from ethyl acetate–hexane afforded 3-methoxy-19-nor-17α-pregna-1,3,5(10)-triene-21,17-carbolactone (**16**) (26 mg; 96%), m.p. 153–155°C (lit.,[17] m.p. 150–152°C); δ (500MHz) 0.96 (3H, s, 13β-Me), 1.33(1H, dddd, *J* 12.5, 12.0, 11.0, and 6.8 Hz, 7α-H), 1.46(1H, dq, *J* 3 x 12.1, and 5.5 Hz, 15β-H), 1.84(1H, ddd, *J* 14.0, 9.6, and 5.5 Hz, 16α-H), 1.89(1H, ddt, *J* 12.5, 5.6, and 2 x 2.8 Hz, 7β-H), 1.93(1H, ddd, *J* 12.6, 9.1, and 7.6 Hz, 20-H), 2.17(1H, dt, *J* 2 x 10.4 and 4.8 Hz, 9α-H), 2.27(1H, ddd, *J* 14.0, 12.1, and 3.5 Hz, 16β-H), 2.44(1H, ddd, *J* 12.6, 8.6, and 6.4 Hz, 20-H), 2.51(1H, ddd, J 17.5, 8.6, and 7.6 Hz, 21-H), 2.57(1H, ddd, *J* 17.5, 9.1, and 6.4 Hz, 21-H), 2.83(1H, ddd, *J* 17.2, 6.8, and 2.8 Hz, 6α-H), 2.87(1H, ddd, J 17.2, 11.0, and 5.6 Hz, 6β-H), 3.76(3H, s, 3-OMe), 6.62(1H, d, *J* 2.7 Hz, 4-H), 6.70(1H, dd *J* 8.6 and 2.7 Hz, 2-H), and 7.17(1H, d, *J* 8.6 Hz, 1-H).

(b) n-Butyl-lithium (1.4M; 7.12 ml; 9.9 mmol) was added with stirring to di-isopropylamine (1.36 ml; 9.6 mmol) in dry tetrahydrofuran (5 ml) at 0°C. After 10 min, acetonitrile (0.53 ml; 9.2 mmol) in dry tetrahydrofuran (1.0 ml) was added. After a further 15 min of stirring, a precipitate formed, and the spiro-oxirane (**7**) (300 mg; 1.0 mmol) in tetrahydrofuran (10 ml) was added. The reaction mixture was stirred at 30°C for 3 h, then water (5 ml) was added and the tetrahydrofuran was removed under reduced pressure. The resulting basic solution was stirred for 3 h, at which stage, t.l.c. showed the presence of a very polar compound. Conc. hydrochloric acid (2 ml) was added. After 6 h, no further change was detected (t.l.c.) and the reaction mixture was neutralised with aqueous sodium hydrogen carbonate. Extraction with chloroform, and chromatography of the product (401 mg) on silica gel (30 g), with ethyl acetate–toluene (1:9) as eluent afforded the 21,17-carbolactone (**16**) (291 mg; 85%), m.p. 153–155°C (from methanol–chloroform), followed by *17α-(2-cyanoethyl)-3-methoxyestra-1,3,5(10)-trien-17β-ol* (**17**) (30 mg; 9%), m.p. 177–179°C (from chloroform–methanol); $[\alpha]_D$ +46° (*c* 1.0); ν_{max} 2235 (CN) cm^{-1}; δ 0.90(3H, s, 13β-Me), 3.77(3H, s, 3-OMe), and 6.56–7.30(3H, m, arom.H)(Found: C, 78.0; H, 8.8; N, 4.2%; M^+, 339. $C_{22}H_{29}NO_2$ requires C, 77.9; H, 8.55; N, 4.1%; *M*, 339).

Attempted Tosylation–Acetylation of the Diol (**9**)

The diol (**9**) (100 mg; 0.32 mmol) was dissolved in pyridine (0.5 ml) and toluene-*p*-sulphonyl chloride (72 mg; 0.38 mmol) was added at 0°C. After 30 min, the reaction mixture was poured into ice–water, and

the precipitate was collected by filtration and dried under vacuum to afford the crude 17[1]-tosylate (140 mg), ν_{max} 1360 and 1165 (OSO_2) cm^{-1}; δ 0.88(3H, s, 13β-Me), 2.42(3H, s, TsMe), 3.76(3H, s, 3-OMe), 4.15 and 3.99(each 1H, d, *J* 10 Hz, 17[1]-H_2), 6.60–7.33(3H, m, arom.H), 7.82(2H, d, *J* 9 Hz, tosyl-H_2), and 7.36(2H, d, *J* 9 Hz, tosyl-H_2). The product was dissolved in triethylamine (10 ml), and acetic anhydride (0.5 ml) and 4-(dimethylamino)pyridine (5 mg) were added. After 1 h, methanol (5 ml) was added, and the mixture was stirred for 30 min, then concentrated under reduced pressure. Extraction of the product with toluene and chromatography of the residue (98 mg) on silica gel (5 g), with toluene–ethyl acetate (19:1) as eluent, afforded the 17-spiro-oxirane (**7**) (78 mg; 83%), m.p. and mixed m.p. 103–105°C (from ethyl acetate).

17α-Acetoxymethyl-3-methoxyestra-1,3,5(10)-trien-17β-yl Acetate (**18**)

The diol (**9**) (1 g) in dry triethylamine (80 ml), was treated with acetic anhydride (5 ml) and 4-(dimethylamino)pyridine (10 mg) for 2 days at 25°C. Methanol (5 ml) was added, and the mixture was stirred for 30 min, then concentrated under reduced pressure to a third of its volume. Extraction with toluene gave the product (1.2 g) which was chromatographed on silica gel (100 g), with ethyl acetate–toluene (1:9) as eluent, to give *17α-acetoxymethyl-3-methoxyestra-1,3,5(10)-trien-17β-yl acetate (18)* (994 mg; 79%), m.p. 121–124°C (from benzene–hexane); $[\alpha]_D$ +21° (*c* 0.9); ν_{max} 1730 cm^{-1}; δ (500MHz) 0.90(3H, s, 13β-Me), 1.36(1H, ddt, *J* 12.5, 2 x 11.6, and 7.2 Hz, 7α-H), 1.87(1H, ddt, *J* 12.5, 5.5, and 2 x 2.7 Hz, 7β-H), 2.01 and 2.06(each 3H, s, 17[1]- and 17β-OAc), 2.79–2.90(2H, m, 6-H_2), 3.75(3H, s, 3-OMe), 4.47 and 4.61(each 1H, d, *J* 12.0 Hz, 17[1]-H_2), 6.61(1H, d, *J* 2.8 Hz, 4-H), 6.69(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.17(1H, d, *J* 8.6 Hz, 1-H) (Found: C, 71.8; H, 8.3%; M^+, 400. $C_{24}H_{32}O_5$ requires C, 72.0; H, 8.0%; M^+, 400), followed by 17α-acetoxymethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (**13**) (219 mg; 19%), m.p. 89–91°C (from benzene–hexane) (lit.,[14] m.p. 90–92°C); $[\alpha]_D$ +29° (*c* 1.0); ν_{max} 1730 cm^{-1}; δ (500MHz) 0.94(3H, s, 13β-Me), 1.32(1H, dddd, *J* 12.3, 12.0, 11.3, and 7.2 Hz, 7α-H), 1.43(1H, ddt, *J* 2 x 13.0, 11.1, and 4.2 Hz, 11β-H), 1.76(1H, ddd, *J* 12.1, 4.2, and 3.6 Hz, 12β-H), 1.87(1H, ddt, *J* 12.3, 5.5, and 2 x 2.7 Hz, 7β-H), 2.12(3H, s, 17[1]-OAc), 2.16(1H, dt, *J* 2 x 11.1, and 4.2 Hz, 9α-H), 2.29(1H, ddt, *J* 13.0, 2 x 4.2, and 3.6 Hz, 11α-H), 2.79–2.90(2H, m, 6-H_2), 3.76(3H, s, 3-OMe), 4.09 (1H, d, *J* 11.3 Hz, 17[1]-H), 4.22(1H, dd, *J* 11.3 and 0.8 Hz, 17[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 7.17(1H, d, *J* 8.6 Hz, 1-H)(Found: C, 73.7; H, 8.55%; M^+, 358. $C_{22}H_{30}O_4$ requires C, 73.7; H, 8.4%; *M*, 358).

Attempted Selective Hydrolysis of the 17β,17[1]*-Diacetate* (**18**)

M-Potassium t-butoxide in t-butyl alcohol (0.2 ml; 0.2 mmol) was added to a stirred solution of the diacetate (**18**) (50 mg; 0.13 mmol) in dry tetrahydrofuran (3 ml) at 0°C. After 40 min, the reaction mixture was poured into ice–water, and the product (49 mg) was isolated by extraction with chloroform. Chromatography on silica gel (5 g), with ethyl acetate–toluene (2:3) as eluent afforded, in elution order, starting material (**18**) (4 mg; 8%), the monoacetate (**13**) (29 mg; 65%), m.p. 89–91°C (from benzene–hexane), and the diol (**9**) (8 mg; 20%), m.p. 169–171°C (from methanol).

Borohydride Reduction of the 17β*-Acetoxy* 17α*-Carbaldehyde* (**5**)

The acetoxy aldehyde (**5**) (17 mg; 0.05 mmol) was dissolved in absolute ethanol (4 ml), and sodium borohydride (10 mg; 0.25 mmol) was added at 0°C. After 20 min, the reaction mixture was poured into ice–water, and the precipitate was washed, dried under vacuum, and recrystallised from benzene–hexane, to give the 17[1]-acetate (**13**) (15 mg; 88%), m.p. and mixed m.p. 88–90°C.

17α-Benzyloxymethyl-3-methoxyestra-1,3,5(10)-*trien*-17*β*-*ol* (**19**)

Sodium hydride (50% dispersion in oil; 169 mg; 3.5 mmol) was washed twice by decantation with dry benzene under nitrogen, and the diol (**9**) (1 g; 3,2 mmol) in dry dimethyl sulphoxide (14 ml) and dry dimethoxyethane (7 ml) was added at 0°C. The reaction mixture was stirred for 45 min, then benzyl chloride (0.4 ml; 3.5 mmol) was added dropwise at 25°C. After 1.5 h, water was added carefully, and the product was isolated by extraction with chloroform. Chromatography on silica gel (100 g), with ethyl acetate–benzene (1:9) as eluent, afforded *17α-benzyloxymethyl-3-methoxyestra*-1,3,5(10)-*trien*-17*β*-*ol* (**19**) as an oil (1.28 g; 99%); $[\alpha]_D$ +25° (*c* 0.9); ν_{max} 3550 cm^{-1}; δ 0.90(3H, s, 13*β*-Me), 3.37 and 3.69(each 1H, d, J 9 Hz, 17^1-H_2), 3.77(3H, s, 3-OMe), 4.57(2H, s, $CH_2C_6H_5$), 6.60–7.30(3H, m, arom. H), and 7.17–7.36(5H, m, $CH_2C_6H_5$)(Found: M^+, 406.251. $C_{27}H_{34}O_3$ requires *M*, 406.251).

17α-Benzyloxymethyl-3-methoxyestra-1,3,5(10)-*trien*-17*β*-*yl Acetate* (**20**)

The benzyl ether (**19**) (1.28 g) was treated with acetic anhydride (4 ml) and 4-(dimethylamino)pyridine (5 mg) in triethylamine (12 ml) at 25°C for 5.5 days. Methanol (5 ml) was added and, after 30 min, the mixture was concentrated under reduced pressure. The residue was extracted with toluene, and the product (1.8 g) was chromatographed on silica gel (50 g), with ethyl acetate–benzene (1:19) as eluent, to give *17^1-benzyloxymethyl-3-methoxyestra*-1,3,5(10)-*trien*-17*β*-*yl acetate* (**20**) (1.33 g; 94%), m.p. 100–103°C (from benzene–hexane); $[\alpha]_D$ +16° (*c* 1.0); ν_{max} 1730 cm^{-1}; δ 0.89(3H, s, 13*β*-Me), 2.01(3H, s, 17*β*-OAc), 3.77(3H, s, 3-OMe), 3.82 and 4.0 (each 1H, d, *J* 10 Hz, 17^1-H_2), 4.46(2H, s, $CH_2C_6H_5$), and 6.59–7.43(8H, m, arom. H)(Found: C, 77.7; H, 8.2%; M^+, 448. $C_{29}H_{36}O_4$ requires C, 77.7; H, 8.0%; *M*, 448).

17α-(*Toluene*-p-*sulphonyloxymethyl*)-3-*methoxyestra*-1,3,5(10)-*trien*-17*β*-*yl Acetate* (**22**)

The benzyl ether (**20**) (450 mg; 1.0 mmol) was dissolved in dry ethyl acetate (12 ml) and hydrogenolysed over palladium on carbon (5%; 110 mg) at atmospheric pressure and room temperature for 20 min. The catalyst was removed by filtration, and the filtrate was concentrated to afford a *ca* 1:1 mixture of monoacetates (**13**) and (**21**) (380 mg), δ (500 MHz) 0.93(3H, s, 13*β*-Me of **21**), 0.94(3H, s, 13*β*-Me of **13**), 2.06(3H, s, OAc of **21**), 2.11(3H, s, OAc of **13**), 3.75 and 3.92(each 1H, d, *J* 12.4 Hz, 17^1-H_2 of **21**), and 4.09 and 4.22 (each 1H, d, *J* 11.3 Hz, 17^1-H_2 of **13**) (the remaining signals at 500 MHz were either indistinguishable or unassigned; *cf* n.m.r. data for pure **13**).

The mixture was promptly treated with toluene-*p*-sulphonyl chloride (241 mg) in pyridine at 0°C. After 4 h, the reaction mixture was poured into ice–water, and standard work-up by extraction with toluene gave crude material (460 mg). Flash chromatography on silica gel (50 g), with ethyl acetate–toluene (2:23) as eluent, afforded *17α-(toluene*-p-*sulphonyloxymethyl)estra*-1,3,5(10)-*trien*-17*β*-*yl acetate* (**22**) (202 mg; 39% from **20**), m.p. 122–124°C (from chloroform–methanol); $[\alpha]_D$ +17° (*c* 0.8); ν_{max} 1730(OAc), and 1370 and 1180 (OSO_2) cm^{-1}; δ 0.85(3H, s, 13*β*-Me), 1.89(3H, s, 17*β*-OAc), 2.42(3H, s, TsMe), 3.75(3H, s, 3-OMe), 4.42 and 4.62(each 1H, d, *J* 10Hz, 17^1-H_2), and 6.60–7.92(7H, m, arom.H)(Found: C, 67.6; H, 6.9%; M^+, 512. $C_{29}H_{36}O_6S$ requires C, 67.9; H, 7.0%; *M*, 512), followed by the 17^1-acetate (**13**) (198 mg; 55%), m.p. and mixed m.p. 88–90°C (from benzene–hexane).

Base Treatment of the 17*β*-*Acetoxy* 17^1-*Tosylate* (**22**)

2,2,6,6-Tetramethylpiperidine (0.17 ml; 1.0 mmol) was added to ethereal n-butyl-lithium (1.4 M; 0.36 ml; 0.50 mmol) in dry tetrahydrofuran (2 ml) at 0°C. After 10 min, the solution was cooled to −100°C and the acetoxy tosylate (**22**) (50 mg; 0.1 mmol) in dry tetrahydrofuran (2 ml) was added slowly with stirring. T.l.c. showed the absence of starting material after 20 min. The reaction was quenched with water at 0°C, and extraction of the mixture with toluene afforded crude material (45 mg). The n.m.r. spectrum

(90MHz) of this material showed signals corresponding to those of the 17^1-acetate (**13**). Chromatography on silica gel (5 g), with ethyl acetate–toluene (1:4) as eluent, afforded a minor product (4 mg) followed by the 17^1-acetate (**13**) (24 mg; 69%), m.p. and mixed m.p. 88–90°C (from benzene–hexane).

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