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Cycloaddition-Fragmentation Route to 14β-Allylestrone and the Derived 14α,17α-Ethano Analogue of Estriol

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Abstract: 3-Methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**1**) undergoes efficient boron trifluoride catalysed cycloaddition at 20 °C with acrolein to give the corresponding 17β-acetoxy 14α,17α-etheno 16α-carbaldehyde (**2**). The derived 16α-tosyloxymethyl intermediates are converted *via* Wharton fragmentation into 14β-allyl derivatives of estrone. Oxidative cleavage of 14-allyl-3-methoxy-14β-estra-1,3,5(10)-trien-17-one (**14**) furnishes the 14β-formylmethyl derivative (**17**). Intramolecular reductive cyclisation of **17**, followed by stepwise protection-deprotection of functionality provides an efficient synthetic route to 14,17α-ethanoestra-1,3,5(10)-triene-3,16α,17β-triol (**23**), the structure of which is confirmed with the aid of X-ray crystallographic analysis of the derived triacetate.

The design and synthesis of structural and configurational variants of estradiol continues to attract attention.[1] These investigations have shed light on structure–activity relationships in estrogens,[2,3] and contribute toward the identification of structural features which alleviate side-effects associated with protracted administration of those hormonal formulations in which 17α-ethynylestradiol is the estrogenic ingredient. The requisites for an improved estrogen would be comparable or superior oral activity to 17α-ethynylestradiol, together with a lower risk of adverse effects upon liver and cardiovascular function.

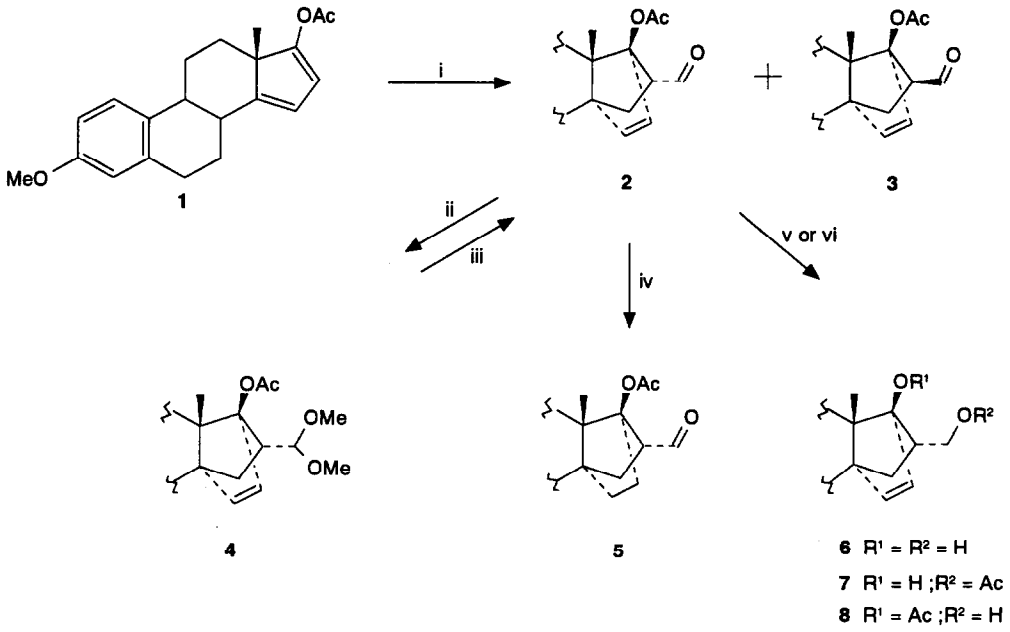
The recent finding[4] that the 14α,17α-ethano analogue of estradiol binds efficiently to the estrogen receptor, and displays oral estrogenicity comparable to 17α-ethynylestradiol, has stimulated the search for further hormone analogues incorporating this bridged ring structure. The distinctive hormonal properties of estriol [estra-1,3,5(10)-triene-3,16α,17β-triol] suggest that the 14α,17α-ethano analogue would be an interesting target for synthesis and comparative biological evaluation. Estriol is more susceptible to *in vivo* metabolic attack than estradiol, but plays an important role as a short-lived estrogen.[2] This invites speculation as to whether these properties would be retained in the bridged analogue, and perhaps confer beneficial effects upon pharmacokinetic behaviour and bioavailablity of this new class of estrogens.

A synthetic approach to this target, based upon cycloaddition of ketene equivalents to 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**1**),[5] was unsuccessful owing to the inability to achieve stereoselective reduction of the derived 16-ketones to 16α-alcohols. Accordingly, attention was turned to an alternative approach in which indirect stereoselective control could be achieved at C(16). Consideration of various formal disconnections of the target compound suggested that significant *si*-face selectivity at the 14β-formyl

group might be induced by the 13β-methyl group during intramolecular reductive coupling of a 14β–formylmethyl 17-ketone. It was further reasoned that this intermediate could readily be obtained through oxidative cleavage of a 14β-allyl 17-ketone.

The adaptation of a reported synthesis of 14β-methyl-19-norsteroids,[6,7] for 14β-allylation of 15-ketones was not considered since it was expected that difficulties similar to those previously encountered[7] during functional group transposition of the intermediates would intrude. However, an efficient synthetic route to 14β-ethyl-19-norsteroids,[8] based upon cycloaddition of phenyl vinyl sulfone to dienyl acetate (**1**), followed by base-mediated fragmentation to the corresponding 14β-phenylsulfonylmethyl Δ^{15}-17-ketone, suggested that a conceptually similar approach could be designed for the synthesis of 14β-allyl 17-ketones. Thus, it was reasoned that cycloaddition of acrolein to the dienyl acetate (**1**) would be expected to provide a precursor for conversion into a 1,3-disposed diol monosulfonate ester for Wharton fragmentation,[9] leading directly to the desired intermediate(s).

The thermal reaction of **1** with acrolein was slow, and was adversely affected by progressive decomposition of the reactants, but when the reaction was conducted at 20 °C in the presence of catalytic boron trifluoride–diethyl ether, cycloaddition proceeded cleanly during 22 h to give up to 83% of a single cycloadduct (**2**) by direct crystallisation of the total reaction product. Although spectroscopic evidence failed to furnish unambiguous proof of the assigned structure, the regio- and stereochemical analogy with similar cycloadditions is well-established,[10] and the structure of **2** was proven by subsequent transformations.



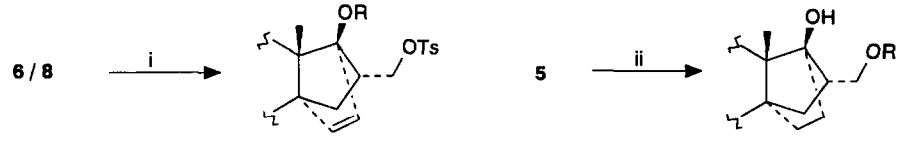
Reagents: (i) CH_2=CHCHO, $BF_3.Et_2O$, $C_6H_5CH_3$, 20 °C (ii) H^+, MeOH (iii) TMSI, CH_2=CMe_2 (iv) Pd–C, H_2 (v) LAH, THF, 20 °C (to **6**), then Ac_2O, C_5H_5N, 25 °C (to **7**) (vi) $NaBH_4$, EtOH (to **7** + **8**)

An experiment in which the mother-liquor residue, obtained after crystallisation of the total cycloaddition product from acetone–hexane, was subjected to careful chromatography yielded a small amount (*ca* 2%) of an isomer formulated as the corresponding 16β-carbaldehyde (**3**). The need for caution in the work-up of the cycloaddition reaction was demonstrated in an experiment, in which the crude product was crystallised from dichloromethane–methanol to give the expected cycloadduct (**2**). In this case however, chromatography of the mother-liquor residue also furnished the $16^1,16^1$-dimethyl acetal (**4**) (21%), presumably arising from acetalisation of **2** with solvent of crystallisation in the presence of residual acid in the work-up mixture. The acetal (**4**) was readily hydrolysed to **2** by treatment with iodotrimethylsilane–isobutene.

Similarly, hydrogenation of the cycloadduct (**2**) in ethyl acetate at 25 °C, in the presence of palladium on carbon, proceeded uneventfully to give the dihydro compound (**5**), whereas a large-scale hydrogenation conducted in tetrahydrofuran–ethanol necessitated subsequent acid treatment of the mother-liquor residue after crystallisation of the dihydro product (**5**), in order to hydrolyse presumed $16^1,16^1$-diethyl acetal in the reaction product, and thus optimise the recovery of **5**.

The next step in the overall plan entailed reduction of the 16α-formyl group. Treatment of **2** with lithium aluminium hydride gave the corresponding 16^1,17β-diol (**6**), full characterisation of which was impaired by poor solubility in most organic solvents. Accordingly, the product was characterised as the corresponding 17β-hydroxy 16^1-acetate (**7**). NMR examination of **7** disclosed diagnostic signals for the diastereotopic 16^1-protons at δ 3.95(dd, *J* 10.7 and 6.9 Hz) and 4.04 (dd, *J* 10.7 and 8.0 Hz). In pursuance of a direct route to a more tractable intermediate, the cycloadduct (**2**) was treated with sodium borohydride in ethanol at 0 °C. The reaction proceeded efficiently to the desired 16^1-hydroxy 17β-acetate (**8**), which could be used directly for subsequent reaction steps; however, the pronounced tendency of this product to undergo transacetylation was demonstrated in an experiment in which conventional work-up followed by silica gel chromatography furnished 17β-hydroxy 16^1-acetate (**7**) (23%), mixed fractions (8%), and 16^1-hydroxy 17β-acetate (**8**) (59%). The NMR signals for the 16^1-protons in **8** resonated at δ 3.36 (dd, *J* 11.5 and 5.4 Hz) and 3.58 (dd, *J* 11.5 and 8.4 Hz). The problem of transacetylation was largely circumvented by direct precipitation of the reduction product, and rapid isolation of **8** by filtration.

Treatment of the 16^1,17β-diol (**6**) with toluene-*p*-sulfonyl chloride in pyridine at 0 °C furnished the corresponding 17β-hydroxy 16^1-tosylate (**9**), and similar treatment of **8** gave the 17β-acetoxy 16^1-tosylate (**10**). These products were isolated as stable crystalline solids which were fully characterised. The attempted two-step conversion of the 14α,17α-ethano 16α-carbaldehyde (**5**) into the corresponding 17β-hydroxy 16^1-tosylate (**12**) was less satisfactory; although the crude diol **11** was recovered in good yield, the final product **12** was obtained as non-crystalline material (54%).



9 R = H
10 R = Ac

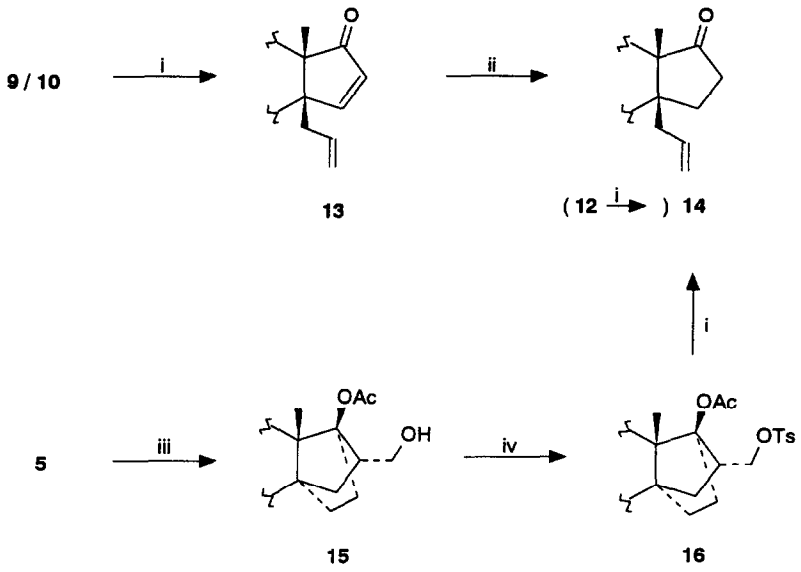
11 R = H
12 R = Ts

Reagents: (*i*) TsCl, C_5H_5N, 7 °C (*ii*) LAH, THF, 20 °C (*to* **11**), *then* TsCl, C_5H_5N, 7 °C (*to* **12**)

Wharton fragmentation of the 17β-hydroxy 16[1]-tosylate (**9**) was gratifyingly successful. Thus, treatment of **9** with methanolic potassium hydroxide at 20 °C for 1 h gave a quantitative yield of 14-allyl-3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one (**13**). The ^{1}H and ^{13}C NMR spectra of **13** displayed diagnostic signals for all the elements of the 14β-allyl group and the ring D enone moiety. The 17β-acetoxy 16[1]-tosylate (**10**) reacted more slowly under similar conditions, but rapidly at elevated temperature, to give the same product (**13**) (100%).

Reduction of the allyl enone (**13**) with methylcopper–diisobutylaluminium hydride–hexamethylphosphoric triamide[11] in tetrahydrofuran at -78 °C proceeded efficiently and chemoselectively to give the 14β-allyl 17-ketone (**14**). Again, diagnostic NMR data confirmed the structure. Wharton fragmentation of the 14α,17α-ethano 17β-hydroxy 16[1]-tosylate (**12**) in methanolic potassium hydroxide proceeded much more slowly than did that of the corresponding 14α,17α-etheno compound (**9**), but as cleanly, to furnish **14** (100%).

The foregoing experiments set the scene for a decision on a preferred large-scale reaction sequence leading to the 14β-allyl 17-ketone (**14**). It was inferred that the ease of olefinic bond hydrogenation in the primary cycloadduct (**2**) combined with the convenience of handling the less-polar 17β-acetates would compensate for the need to exercise caution in avoiding transacetylation and the slowness of fragmentation in the 14α,17α-ethano series. Accordingly, the 14α,17α-ethano 16α-carbaldehyde **5** was treated with sodium borohydride–cerium(III) chloride heptahydrate in methanol at 0 °C, then 20 °C for 16 h, to give the 16[1]-hydroxy 17β-acetate (**15**) (99%) which was directly tosylated under standard conditions to give the 17β-acetoxy 16[1]-tosylate (**16**) (99%) which, in turn, was directly treated with methanolic sodium hydroxide at 60 °C for 2.5 h, to give the 14β-allyl 17-ketone (**14**). An overall yield in excess of 85% over the three steps was thus obtained, and the structures of the intermediates (**15**) and (**16**) were verified by small-scale purification and full characterisation.

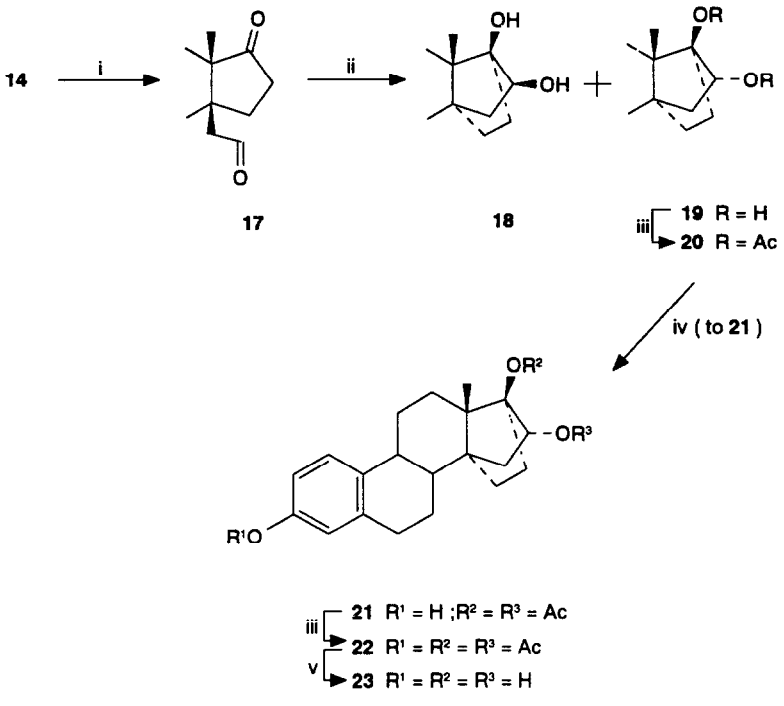


Reagents: (i) KOH, MeOH (ii) MeCu, HMPA, DIBAH, THF, -78 °C
(iii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C (iv) TsCl, C_5H_5N, 20 °C

Oxidative cleavage of the allyl ketone (**14**) was readily achieved through direct ozonolysis followed by reductive work-up with triphenylphosphine to give the 14β-formylmethyl 17-ketone (**17**) (86%). Intramolecular reductive coupling[12] of **17** proceeded smoothly with titanium(IV)chloride–zinc in dichloromethane–tetrahydrofuran at 0 °C to give a readily separable mixture of 14α,17α-ethano 16,17β-diols (**18**) and (**19**).

The structure of the minor product (**18**) (18%) was confirmed by comparison with that obtained by the previously described route,[5] and it was thus concluded that the major compound (71%) was indeed the desired 14α,17α-ethano 16α,17β-diol (**19**). The product was further characterised as the derived 16α,17β-diacetate (**20**).

The limited solubility of the target compound (**23**) in most organic solvents, and attendant handling problems, made direct 3-deprotection of **19** impractical, since it would entail an extraction step. Accordingly, the diacetate (**20**) was first deprotected at C(3) with iodotrimethylsilane, and the resultant crude 3-hydroxy 16α,17β-diacetate (**21**) was converted into the nicely crystalline 3,16α,17β-triacetate (**22**) for full characterisation. The ^{1}H NMR spectrum of **22** displayed a doublet of triplets at δ 5.48 (*J* 8 and 2 x 2 Hz) for the 16β-proton. The multiplicity of this signal clearly demonstrated the presence of long-range coupling to 17^1-H$_{exo}$ and hence the assigned 16-configuration.



Reagents: (i) O_3, CH_2Cl_2, -78 °C, then Ph_3P (ii) $TiCl_4$, Zn, THF, 0 °C
(iii) AcCl, NaI, MeCN, 20 °C (iv) TMSI, MeCN (v) NaOH, MeOH, 60 °C

In view of the importance of this assignment, an X-ray crystallographic analysis was conducted on the triacetate (**22**), which verified the structure and consequently, those of all the key precursors. The X-ray crystal structure of **22** is depicted in Figure 1, and reveals no unexpected structural or conformational properties.

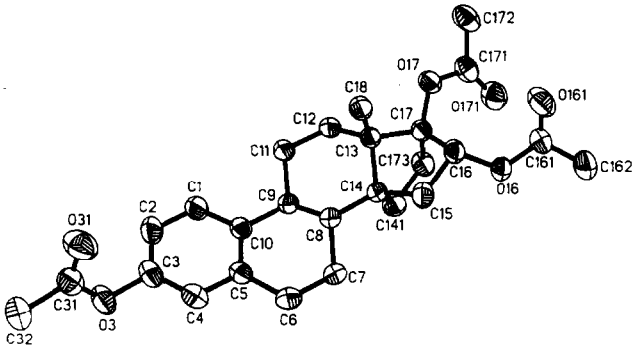


Figure 1 X-Ray crystal structure of triacetate **22**, showing crystallographic numbering

It remained only to deprotect the triacetate (**22**); this was achieved by treatment with methanolic sodium hydroxide followed by neutralisation of the medium and aqueous precipitation of the highly insoluble 14,17α-ethanoestra-1,3,5(10)-triene-3,16α,17β-triol (**23**), which was collected by filtration and characterised in the usual way. Biological evaluation of this bridged analogue of estriol has revealed that it is indeed a powerful oral estrogen.[13] These findings will be reported more fully elsewhere.

EXPERIMENTAL

For general directions, see ref.5

Cycloaddition of the Dienyl Acetate (1) with Acrolein – (a) Boron trifluoride–diethyl ether (20 μl, 0.2 mmol) in dry toluene (1 ml) was added to the dienyl acetate (**1**) (1 g, 3.1 mmol) and freshly distilled acrolein (0.52 ml, 7.7 mmol) in dry toluene (13 ml) at 0 °C under nitrogen. The reaction mixture was stirred at 20 °C for 22 h, then ice-water was added and the mixture was extracted with ethyl acetate. The extract was washed successively with aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was crystallised from acetone–hexane to give 17β-*acetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16α-*carbaldehyde* (**2**) (744 mg, 64%), m.p. 183—185 °C; $[\alpha]_D$ +100° (*c* 1.0); ν_{max} 1730 (OAc) and 1710 (16^1-CO) cm^{-1}; δ 1.0 (3H, s, 13β-Me), 2.13 (3H, s, 17β-OAc), 2.88 (2H, m, 6-H_2), 3.09 (1H, dt, *J* 8.7 and 2 x 4.4 Hz, 16β-H), 3.78 (3H, s, 3-OMe), 6.22 and 6.37 (each 1H, d, *J* 6.3 Hz, 17^1- and 17^2-H), 6.64 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.6 Hz, 2-H), 7.21 (1H, d, *J* 8.7 Hz, 1-H), and 9.49 (1H, d, *J* 4.4 Hz, 16^1-H) (Found: C, 75.5; H, 7.5%; M^+, 380. $C_{24}H_{28}O_4$ requires C, 75.8; H, 7.4%; M, 380).

Chromatography of the mother-liquor residue (400 mg) on silica gel (40 g) with ethyl acetate–toluene (1:19) as eluent afforded 17β-*acetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5,(10)-*triene*-16β-*carbaldehyde* (**3**) (27 mg, 2%), m.p. 108—112 °C (from dichloromethane–toluene); $[\alpha]_D$ +124° (*c* 0.8); ν_{max} 1732 (OAc) and 1710 (16^1-CO) cm^{-1}; δ 0.82 (3H, s, 13β-Me), 2.19 (3H, s, 17β-OAc), 2.88 (2H, m, 6-H_2), 3.11 (1H, dd, *J* 9.4 and 4.5 Hz, 16α-H), 3.77 (3H, s, 3-OMe), 6.12 and 6.4 (each 1H, d, *J* 6.0 Hz, 17^1- and 17^2-H), 6.64 (1H, d, *J* 2.4 Hz, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.4 Hz, 2-H) 7.2 (1H, d, *J* 8.4 Hz, 1-H), and 9.89 (1H, s, 16^1-H)

(Found: M^+, 380.200. $C_{24}H_{28}O_4$ requires M, 380.199), followed by mixed fractions (220 mg) and further 16α-carbaldehyde (**2**) (50 mg).

(b) The reaction was carried out on the dienyl acetate (**1**) (7 g, 21.6 mmol), and worked up as described in the foregoing experiment. The solid residue (8.43 g) was crystallised from dichloromethane–methanol to give the 16α-carbaldehyde (5.01 g, 61%), and the mother-liquor residue (4.43 g) was adsorbed on silica gel (240 g). Elution with ethyl acetate–toluene (1:19) gave unreacted material (**1**) (192 mg, 3%), 16β-carbaldehyde (**3**) (130 mg, 2%), 16α-carbaldehyde (**2**) (685 mg, 8%), and 3-*methoxy*-16α-*dimethoxymethyl*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*yl acetate* (**4**) (1.97 g, 21%), m.p. 118—119 °C (from dichloromethane–methanol); $[\alpha]_D$ +108° (*c* 1.3); ν_{max} 1734 (OAc) cm^{-1}; δ 0.95 (3H, s, 13β-Me), 2.09 (3H, s, 17β-OAc), 2.5 (1H, m, 9α-H), 2.76 obsc (1H, td, *J* 2 x 8.6, and 3.9 Hz, 16β-H), 2.82 (2H, m, 6-H_2), 3.28 and 3.31 [each 3H, s, 16^1-$(OMe)_2$], 3.77 (3H, s, 3-OMe), 4.13 (1H, d, *J* 8.6 Hz, 16^1-H), 6.02 and 6.42 (each 1H, d, *J* 6.4 Hz, 17^1- and 17^2-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.66 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 73.2; H, 7.8%; M^+, 426. $C_{26}H_{34}O_5$ requires C, 73.2; H, 8.0%; M, 426).

(c) The reaction was conducted as before on the dienyl acetate (**1**) (228 g, 702.8 mmol). The reaction mixture was diluted with dichloromethane, to redissolve the precipitate which had formed, and was washed successively with aqueous sodium hydrogen carbonate and brine. The solid residue obtained upon evaporation of the solvent was redissolved in dichloromethane (450 ml) and toluene (580 ml), and the solution was reduced to about half volume by distillation under normal pressure, then kept at -15 °C. The resultant crystalline product (**2**) (160.5 g) was collected by filtration, and the mother-liquor residue was redissolved in dichloromethane (500 ml) and ethanol (880 ml) and then concentrated to about one-third volume to yield, after 12 h at room temperature, a second crop (61.3 g) of the product (**2**) (total yield of **2**: 221.8 g, 83%).

17β-Acetoxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-16α-carbaldehyde (**5**) – (a) The 14α,17α-etheno compound (**2**) (836 mg, 2.2 mmol) in ethyl acetate (90 ml) at 25 °C was hydrogenated at atmospheric pressure in the presence of palladium on carbon (10%; 238 mg). After 90 min the reaction was complete (TLC), and the mixture was filtered, and the filtrate evaporated under reduced pressure to give the 14α,17α-*ethano compound* (**5**) (818 mg, 97%), m.p. 151—154 °C (from acetone–hexane); $[\alpha]_D$ +7° (*c* 1.0); ν_{max} 1728 (OAc) and 1712 (16^1-CO) cm^{-1}; δ 1.01 (3H, s, 13β-Me), 2.08 (3H, s, 17β-OAc), 2.86 (2H, m, 6-H_2), 3.02 (1H, br dq, *J* 11.5 and 3 x 3.5 Hz, 16β-H), 3.77 (3H, s, 3-OMe), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.8 and 2.7 Hz, 2-H), 7.21 (1H, d, *J* 8.8 Hz, 1-H), and 9.92 (1H, d, *J* 3.5 Hz, 16-H) (Found: C, 75.9; H, 7.5%; M^+, 382. $C_{24}H_{30}O_4$ requires C, 75.8; H, 7.4%; M, 382).

(b) The foregoing hydrogenation was carried out on the 14α,17α-etheno compound (**2**) (74 g, 194.5 mmol) in tetrahydrofuran (2.2 l) and ethanol (1.8 l), in the presence of palladium on carbon (10%; 7.4 g). Work-up gave a solid residue which was suspended in diisopropyl ether (350 ml), and dichloromethane (200 ml) was added to the gently refluxing mixture, to bring about complete dissolution. The solution was concentrated to about half volume by distillation under normal pressure, then kept at room temperature for 4 h. The crystalline product (**5**) (52.4 g) was collected by filtration, and the mother-liquor residue was

dissolved in dichloromethane (60 ml). Aqueous acetic acid (70%; 200 ml) was added and the two-phase mixture was stirred vigorously at room temperature for 1 h. The organic phase was worked up and the residue was crystallised from dichloromethane–diisopropyl ether to give further product (**5**) (18.3 g) (total yield of **5**: 70.7 g, 96%).

Hydride Reductions of the Cycloadduct (2) – (a) Lithium aluminium hydride (520 mg, 13.7 mmol) was added in small portions to a stirred solution of the 16α-carbaldehyde (**2**) (1.04 g, 2.7 mmol) in dry tetrahydrofuran (65 ml) at 0 °C under nitrogen, then the mixture was stirred at 20 °C for 20 min. Aqueous sodium sulfate was added dropwise to the solution at 0 °C until a white precipitate formed. Diethyl ether (10 ml) was added and the mixture was stirred for 30 min, then filtered under pressure through layers of anhydrous magnesium sulfate and Celite in a sintered glass funnel. The filter pad was washed repeatedly with hot methanol–chloroform (1:1), and the total filtrate was evaporated under reduced pressure to give 16α-*hydroxymethyl*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*ol* (**6**) (1.38 g, 74%) as a colourless solid, m.p. 245—248 °C (from ethyl acetate); *m/z* 340 (M^+). The limited solubility of **6** in most organic solvents precluded full characterisation.

The diol (**6**) (76 mg, 0.22 mmol) was suspended in pyridine (1 ml), and acetic anhydride (0.25 ml) was added. The mixture was stirred at 25 °C for 2.5 h during which time the suspended material dissolved. The mixture was poured into water, and the product was isolated by extraction with chloroform to give oily material (110 mg) which was adsorbed on silica gel (10 g). Elution with ethyl acetate–toluene (1:9) furnished 16α-*acetoxymethyl*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*ol* (**7**) (75 mg, 88%), m.p. 123—125 °C (from acetone–hexane); $[\alpha]_D$ +131° (*c* 1.0); ν_{max} 3594 (OH) and 1728 (OAc) cm^{-1}; δ 0.95 (3H, d, *J* 0.9 Hz, 13β-Me), 1.59 (1H, s, exch. by D_2O, 17β-OH), 2.06 (3H, s, 16^1-OAc), 2.84 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 3.95 (1H, dd, *J* 10.7 and 6.9 Hz, 16^1-H), 4.04 (1H, dd, *J* 10.7 and 8.0 Hz, 16^1-H), 5.88 and 6.05 (each 1H, d, *J* 6.1 Hz, 17^1- and 17^2-H), 6.6 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 76.1; H, 7.9%; M^+, 382. $C_{24}H_{30}O_4$ requires C, 75.9; H, 7.9%; M, 382).

(b) Sodium borohydride (597 mg, 15.8 mmol) was added in small portions to a stirred suspension of the 16α-carbaldehyde (**2**) (2 g, 5.3 mmol) in absolute ethanol (200 ml) at 0 °C under nitrogen. After 90 min at 0 °C, the reaction was complete (TLC). Brine was added, and the mixture was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (2.09 g) which was adsorbed on silica gel (200 g). Elution with ethyl acetate–hexane (2:3) gave the 17β-hydroxy 16^1-acetate (**7**) (460 mg, 23%), followed by mixed fractions (168 mg) and 16α-*hydroxymethyl*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*yl acetate* (**8**) (1.02 g, 59%), m.p. 165—170 °C (from acetone–hexane); $[\alpha]_D$ +91° (*c* 1.0); ν_{max} 3607 (OH) and 1736 (OAc) cm^{-1}; δ 0.99 (3H, s, 13β-Me), 1.58 (1H, s, exch. by D_2O, 16^1-OH), 2.11 (3H, s, 17β-OAc), 2.84 (2H, m, 6-H_2), 3.36 (1H, dd, *J* 11.5 and 5.4 Hz, 16^1-H), 3.58 (1H, dd, *J* 11.5 and 8.4 Hz, 16^1-H), 3.76 (3H, s, 3-OMe), 6.05 and 6.37 (each 1H, d, *J* 6.4 Hz, 17^1- and 17^2-H), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H), and 7.19 (1H, d, *J* 8.7 Hz, 1-H) (Found: C, 76.0; H, 7.7%; M^+, 382. $C_{24}H_{30}O_4$ requires C, 75.9; H, 7.9%; M, 382).

Preparation of 16^1-Tosylates – (a) Toluene-*p*-sulfonyl chloride (1.55 g, 8.1 mmol) was added to a suspension of the diol (**6**) (921 mg, 2.7 mmol) in dry pyridine (30 ml) at 0 °C. After 15 min, at 0 °C the

mixture was kept at 7 °C (refrigerator) for 37 h, whereupon the reaction was complete (TLC). Water was added, the mixture was acidified with 3M-hydrochloric acid, and the product was extracted into toluene. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a solid residue (1.23 g). Flash chromatography on silica gel (60 g) with ethyl acetate–hexane (1:2) as eluent gave 3-*methoxy*-16α-*toluene*-p-*sulfonyloxymethyl*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*ol* (**9**) (1.2 g, 85%), m.p. 141—144 °C (from acetone–hexane); $[\alpha]_D$ +126° (*c* 1.0); ν_{max} 3599 (OH), 1359 and 1174 (OTs) cm^{-1}; δ 0.91(3H, s, 13β-Me), 2.38 (3H, s, 4′-Me), 2.5 obsc (1H, qd, *J* 3 x 7.9 and 4.4 Hz, 16β-H), 2.76 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 3.83 and 3.99 (each 1H, dd, *J* 9.4 and 7.9 Hz, 16¹-H_2), 5.7 and 6.01 (each 1H, d, *J* 6.2 Hz, 17¹- and 17²-H), 6.55 (1H, d, *J* 2.7 Hz, 4-H), 6.63 (1H, dd, *J* 8.7 and 2.7 Hz, 2-H), 7.19 (1H, d, *J* 8.7 Hz, 1-H), 7.35 (2H, d, *J* 8.6 Hz, 3′- and 5′-H), and 7.8 (2H, d, *J* 8.6 Hz, 2′- and 6′-H) (Found: C, 70.1; H, 6.9%; M^+, 494. $C_{29}H_{34}O_5S$ requires C, 70.4; H, 6.9%; M, 494).

(b) Treatment of the 16¹-hydroxy 17β-acetate (**8**) (300 mg, 0.8 mmol) with toluene-*p*-sulfonyl chloride (446 mg, 2.3 mmol) in dry pyridine (8 ml) at 7°C for 40 h followed by work-up, as described in the foregoing experiment, gave a solid product (413 mg). Flash chromatography on silica gel (10 g) with toluene as eluent gave 3-*methoxy*-16α-*toluene*-p-*sulfonyloxymethyl*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*yl acetate* (**10**) (388 mg, 93%), m.p. 125—126 °C (from acetone–hexane); $[\alpha]_D$ +86° (*c* 1.0); ν_{max} 1734 (OAc), and 1365 and 1173 (OTs) cm^{-1}; δ 0.92 (3H, s, 13β-Me), 2.07 (3H, s, 17β-OAc), 2.46 (3H, s, 4′-Me), 2.84 (2H, m, 6-H_2), 3.76 obsc (1H, dd, *J* 9.4 and 3.4 Hz, 16¹-H), 3.77 (3H, s, 3-OMe), 4.18 (1H, dd, *J* 9.4 and 6.1 Hz, 16¹-H), 6.01 and 6.17 (each 1H, d, *J* 6.2 Hz, 17¹- and 17²-H), 6.62 (1H, d, *J* 2.5 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.5 Hz, 2-H), 7.19 (1H, d, *J* 8.6 Hz, 1-H), 7.35 (2H, d, *J* 8.3 Hz, 3′- and 5′-H), and 7.78 (2H, d, *J* 8.3 Hz, 2′- and 6′-H) (Found: C, 69.2; H, 6.8%; M^+, 536. $C_{31}H_{36}O_6S$ requires C, 69.4; H, 6.8%; M, 536).

(c) Lithium aluminium hydride (320 mg, 8.5 mmol) was added in small portions to a stirred solution of the 14α,17α-ethano 16α-carbaldehyde (**5**) (645 mg, 1.7 mmol) in dry tetrahydrofuran (50 ml) at 0 °C under nitrogen, then the mixture was stirred at 20 °C for 20 min. Aqueous sodium sulfate was added dropwise to the solution at 0 °C until a flocculent white precipitate formed. Stirring was continued for 30 min, then the mixture was filtered and the precipitate was washed repeatedly with methanol-chloroform. The total filtrate was evaporated under reduced pressure to give the crude diol (**11**) as a crystalline residue (520 mg, 90%), m.p. 220—223 °C; *m/z* 342 (M^+). The diol (**11**) (520 mg, 1.5 mmol) was tosylated as described in the foregoing experiments, and the product (749 mg) (isolated by extraction with toluene) was chromatographed on silica gel (98 g) with ethyl acetate–hexane (2:3) as eluent, to give 3-*methoxy*-16α-*toluene*-p-*sulfonyloxymethyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*ol* (**12**) as a non-crystalline product (400 mg, 54%), ν_{max} 3596 (OH), and 1360 (OTs) cm^{-1}; δ 0.89 (3H, s, 13β-Me), 2.35 (1H, m, 16β-H), 2.44 (3H, s, 4′-Me), 2.55 (1H, m, 9α-H), 2.8 (2H, m, 6-H_2), 3.75 (3H, s, 3-OMe), 4.18 (1H, dd, *J* 9.4 and 7.8 Hz, 16¹-H), 4.24 (1H, dd, *J* 9.4 and 7.5 Hz, 16¹-H), 6.6 (1H, d, *J* 2.7 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), 7.19 (1H, d, *J* 8.6 Hz, 1-H), 7.35 (2H, d, *J* 8.1 Hz, 3′- and 5′-H), and 7.8 (2H, d, *J* 8.1 Hz, 2′- and 6′-H) (Found: C, 69.8; H, 7.2%; M^+, 496. $C_{29}H_{36}O_5S$ requires C, 70.1; H, 7.3%; M, 496).

14-Allyl-3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one (**13**) – (a) Methanolic M-potassium hydroxide (11 ml, 11 mmol) was added to a stirred solution of the 17β-hydroxy 16¹-tosylate (**9**) (1.812 g, 3.7 mmol) in

methanol (65 ml) at 20 °C under nitrogen. After 1 h at 20 °C the reaction was complete (TLC). Water was added and the mixture was acidified with 3M-hydrochloric acid, and extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (1.3 g) which was flash chromatographed on silica gel (65 g). Elution with ethyl acetate–toluene (1:24) gave the 14β-*allyl enone* (**13**) (1.18 g, 100%), m.p. 61—63 °C (from diisopropyl ether); $[\alpha]_D$ + 216° (*c* 1.0); ν_{max} 1701 (CO) and 1640 (C:C) cm^{-1}; λ_{max} 325 (ε 233) and 245 (10395) nm; δ 1.13 (3H, s, 13β-Me), 2.44 (1H, ddt, *J* 15.3, 8.6, and 2 x 1.5 Hz, 14^1-H) 2.58 (1H, dd, *J* 15.3 and 8.6 Hz, 14^1-H), 2.76 (2H, m, 6-H_2), 3.75 (3H, s, 3-OMe), 5.12—5.2 (2H, m, 14^3-H_2), 5.83 (1H, m, *W* 41.4 Hz, 14^2-H), 6.22 (1H, d, *J* 5.9 Hz, 16-H), 6.56 (1H, d, *J* 2.7 Hz, 4-H), 6.69 (1H, dd, *J* 8.7 and 2.7 Hz, 2-H), 7.06 (1H, d, *J* 8.7 Hz, 1-H), and 7.31 (1H, d, *J* 5.9 Hz, 15-H); δ_C 214.1 (s, C-17), 165.1 (d, C-15), 157.5 (s, C-3), 137.1 (s, C-5), 134.0 (d, $C\text{-}14^2$), 133.1 (s, C-10), 131.3 (s, C-16), 128.1 (d, C-1), 118.6 (t, $C\text{-}14^3$), 113.1 (d, C-4), 112.3 (d, C-2), 55.2 (q, 3-OMe), 54.2 and 52.2 (each s, C-13 and C-14), 41.7 (d, C-9), 38.3 (t, $C\text{-}14^1$), 34.3 (d, C-8), 30.7 (t, C-6), 30.3, (t, C-12), 27.8 (t, C-7), 24.2 (t, C-11), and 21.5 (q, C-18) (Found: C, 82.1; H, 8.4%; M^+, 322. $C_{22}H_{26}O_2$ requires C, 82.0; H, 8.1%; M, 322).

(b) Similar alkaline treatment of the 17β-acetoxy 16^1-tosylate (**10**) (600 mg, 1.1 mmol) was incomplete after 1 h at 20 °C, but a further reaction time of 1 h at 55 °C and isolation and chromatography gave the product (**13**) (361 mg, 100%).

14-Allyl-3-methoxy-14β-estra-1,3,5(10)-trien-17-one (14) – (a) Ethereal 5% methyllithium (0.54 ml, 1.2 mmol) was added to a stirred suspension of copper(I) iodide (237 mg, 1.2 mmol) in dry tetrahydrofuran (15 ml) at 0 °C under nitrogen. The resultant suspension of methylcopper was cooled to -78 °C, and hexamethylphosphoric triamide (2.7 ml, 15.5 mmol) and 20% diisobutylaluminium hydride in hexane (11 ml, 15.5 mmol) were added successively. The mixture was stirred at -78 °C for 30 min, then the enone (**13**) (1 g, 3.1 mmol) in dry tetrahydrofuran (3.5 ml) was added, and the mixture was stirred at -78 °C for 1 h. 0.5M-Hydrochloric acid (10 ml) was added and the mixture was extracted with toluene. The extract was washed successively with M-hydrochloric acid, aqueous sodium hydrogen carbonate, and brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a solid residue (1.04 g). Flash chromatography on silica gel (50 g) with ethyl acetate–toluene (1:19) as eluent yielded the 14β-*allyl ketone* (**14**) (919 mg, 91%), m.p. 75—78 °C (from acetone–methanol); $[\alpha]_D$ +81° (*c* 1.0); ν_{max} 1725 (CO) cm^{-1}; δ 1.1 (3H, s, 13β-Me), 2.63 (1H, m, 9α-H), 2.84 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.97—5.14 (2H, m, 14^3-H_2), 5.78 (1H, m, *W* 41.5 Hz, 14^2-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.19 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 81.5; H, 8.5%; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; M, 324).

(b) The 17β-hydroxy 16^1-tosylate (**12**) (362 mg, 0.73 mmol) in methanol (9 ml) under nitrogen was treated with methanolic M-potassium hydroxide (2.2 ml, 2.2 mmol) at 20 °C for 16 h and, after addition of further base (2 ml), at 50 °C for 3 h. Water was added and the mixture was acidified with 3M-hydrochloric acid. The product (296 mg) was isolated by extraction with toluene and purified by filtration through silica gel (24 g) with ethyl acetate–toluene (1:99) to give the 14β-allyl ketone (**14**) (237 mg, 100%).

(c) A solution of the 16α-carbaldehyde (**5**) (87.1 g, 227.7 mmol) in tetrahydrofuran (1.218 l) and methanol (957 ml) was added to a solution of cerium(III) chloride heptahydrate (63 g) in methanol (1.069 l)

at 0 °C. Sodium borohydride (8.45 g) was added in small portions, and the mixture was stirred at room temperature for 16 h, then poured into water (5 l). The mixture was extracted with dichloromethane to give crude 16¹-hydroxy 17β-acetate (**15**) (86.5 g, 98.8%), sufficiently pure for further processing. An analytical sample was obtained by chromatography on silica gel with ethyl acetate–hexane (1:4) as eluent to give 16α-*hydroxymethyl*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*yl acetate* (**15**), m.p. 148–149 °C (from ethyl acetate–diisopropyl ether); $[\alpha]_D$ + 19° (*c* 0.52); ν_{max} (KBr) 3440 (OH) and 1735 (OAc) cm^{-1}; δ_H 1.03 (3H, s, 13β-Me), 2.08 (3H, s, 17β-OAc), 2.83 (2H, m, 6-H_2), 3.08 (1H, dd, *J* 11 and 3 Hz, 16¹-OH), 3.59 (1H, ddd, *J* 13, 11, and 5 Hz, 16¹-H), 3.78 (3H, s, 3-OMe), 3.89 (1H, dd, *J* 13, 10, and 3 Hz, 16¹-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8 and 2.7 Hz, 2-H), and 7.21 (1H, d, *J* 8 Hz, 1-H) (Found: C, 74.7; H, 8.2. $C_{24}H_{32}O_4$ requires C, 75.0; H, 8.4%).

Toluene-*p*-sulfonyl chloride (171.4 g) was added in small portions to a solution of the crude 16¹-hydroxy 17β-acetate (**15**) (172.8 g, 449.4 mmol) in pyridine (1.8 l). After 2.5 h at room temperature, the reaction mixture was diluted with water (5 l), and solid sodium hydrogen carbonate (75 g) was added in portions of 5 g. The mixture was then stirred for 30 min and extracted with ethyl acetate. The combined organic phase was washed successively with 2M-hydrochloric acid and water, dried (Na_2SO_4), and concentrated under reduced pressure to give an oily residue comprising the crude 17β-acetoxy 16¹-tosylate (**16**) (240 g, 99%), which was used in the following step without further purification. An analytical sample was obtained by chromatography on silica gel with ethyl acetate–hexane (1:4) as eluent to give 3-*methoxy*-16α-*toluene*-p-*sulfonyloxymethyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*yl acetate* (**16**), m.p. 120—122 °C (from ethyl acetate–diisopropyl ether); $[\alpha]_D$ + 5° (*c* 0.52); ν_{max} (KBr) 1740(sh), 1735 (OAc), 1350 and 1170 (OTs) cm^{-1}; δ_H 0.95 (3H, s, 13β-Me), 1.99 (3H, s, 17β-OAc), 2.46 (3H, s, 4′-Me), 2.83 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 4.16 (1H, t, *J* 9.8 Hz, 16¹-H), 4.55 (1H, dd, *J* 9.8 and 4.9 Hz, 16¹-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8 and 2.7 Hz, 2-H), 7.70 (1H, d, *J* 8 Hz, 1-H), 7.37 (2H, d, *J* 8.5 Hz, 3′- and 5′-H), and 7.82 (2H, d, *J* 8.5 Hz, 2′- and 6′-H) (Found: C, 69.0; H, 7.05; S, 5.9. $C_{31}H_{38}O_6$ requires C, 69.1; H, 7.1; S, 5.95%).

2M-Sodium hydroxide (964 ml) was added to the crude tosylate (**16**) (240 g, 446.1 mmol) in methanol (2.4 l), and the mixture was stirred at 60 °C for 2.5 h then diluted with water. Extraction with dichloromethane afforded a crude product which was redissolved in dichloromethane (600 ml) and filtered through Celite to remove insoluble impurities. The filtrate was concentrated and the residue was redissolved by heating in methanol (200 ml) and ethyl acetate (50 ml). After 12 h at room temperature, the crystalline product (**14**) (107.8 g) was collected by filtration and the mother-liquor residue was chromatographed on silica gel with a hexane → ethyl acetate-hexane (2:3) gradient eluent to give further **14** (19 g) (total yield of **14**, m.p. 77—78 °C: 126.8 g, 85.6%).

14-Formylmethyl-3-methoxy-14β-estra-1,3,5(10)-trien-17-one (17) – A stream of ozone–oxygen (generated via passage of 80 l min^{-1} oxygen through a Fischer Type 302-000 ozone generator) was passed through a vigorously stirred solution of the 14β-allyl 17-ketone (**14**) (25 g, 77.1 mmol) in dichloromethane (750 ml) and methanol (375 ml) at -78 °C for 50 min. The reaction mixture was then purged with nitrogen and triphenylphosphine (17.33 g) was added portionwise. The mixture was stirred for 15 min at -78 °C and 30 min at room temperature, then poured into aqueous sodium hydrogen carbonate (3 l). The organic phase was separated, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography of the residue on

silica gel (1.1 kg) with ethyl acetate–hexane (13:87 → 65:35) as eluent gave the *aldehyde* (**17**) (21.65 g, 86.1%), m.p. 126—128 °C (from ethyl acetate–diisopropyl ether); $[\alpha]_D$ + 88° (*c* 0.5); δ 1.13 (3H, s, 13β-Me), 3.78 (3H, s, 3-OMe), 6.66 (1H, d, *J* 3 Hz, 4-H), 6.74 (1H, dd, *J* 8 and 3 Hz, 2-H), 7.21 (1H, d, *J* 8 Hz, 1-H), and 9.88 (1H, t, *J* 2 x 3 Hz, 14^2-H).

Intramolecular Reductive Coupling of the 14β-Formylmethyl 17-Ketone (17) – M-Titanium(IV) chloride in dichloromethane (160 ml) was added dropwise during 30 min to a stirred solution of the aldehyde (**17**) (32 g, 98 mmol) in dry tetrahydrofuran (570 ml) at -10 °C. The temperature was raised to 0 °C and zinc powder (15.5 g) was added in small portions during 40 min. The mixture was stirred for a further 60 min at 0 °C, then poured into aqueous 15% potassium carbonate, precooled to 5 °C. The resultant suspension was filtered through Celite and the filtrate was diluted with dichloromethane. The organic phase was separated, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography of the residue on silica gel (1 kg) with acetone–hexane (9:91 → 80:20) as eluent gave 3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-16β,17β-diol (**18**)[5] (5.9 g, 18.3%), m.p. 170—172 °C (from ethyl acetate–diisopropyl ether); $[\alpha]_D$ +49° (*c* 0.5), followed by 3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-16α,17β-*diol* (**19**) (22.8 g, 70.8%), m.p. 201—203 °C (from ethyl acetate); $[\alpha]_D$ +39° (*c* 0.52); δ(C_5D_5N) 1.15 (3H, s, 13β-Me), 3.74 (3H, s, 3-OMe), 4.8 (1H, br d, *J* 9 Hz, 16β-H), 6.8 (1H, d, *J* 3 Hz, 4-H), 6.93(1H, dd, *J* 8 and 3 Hz, 2-H), and 7.35 (1H, d, *J* 8 Hz, 1-H) (Found: C, 76.1; H, 8.8. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%).

14,17α-Ethanoestra-1,3,5(10)-triene-3,16α,17β-triol (23) – Acetyl chloride (44 ml) was added dropwise to a stirred suspension of the 16α,17β-diol (**19**) (20 g, 60.9 mmol) and sodium iodide (91.65 g) in acetonitrile (1 l) at 0 °C. The mixture was then stirred at room temperature for 20 min, and poured into aqueous sodium hydrogen sulfite. Extraction with ethyl acetate gave 3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-16α,17β-*diyl diacetate* (**20**) (24 g, 95.5%), sufficiently pure for use in the following step. An analytical sample of the diacetate (**20**) had m.p. 169—170 °C (from ethyl acetate–diisopropyl ether); $[\alpha]_D$ + 27° (*c* 0.54); δ_H (300 MHz) 1.01 (3H, s, 13β-Me), 1.99 (3H, s, 16α-OAc), 2.09 (3H, s, 17β-OAc), 3.77 (3H, s, 3-OMe), 5.48 (3H, m, 16β-H), 6.62 (1H, d, *J* 3 Hz, 4-H), 6.72 (1H, dd, *J* 8 and 3 Hz, 2-H), and 7.21 (1H, d, *J* 8 Hz, 1-H) (Found: C, 72.8; H, 7.7. $C_{25}H_{32}O_5$ requires C, 72.8; H, 7.8%)

Trimethylsilyl chloride (73.5 ml) was added dropwise to a suspension of the diacetate (**20**) (24 g) and sodium iodide (87.03 g) in acetonitrile (1 l), and the mixture was heated under reflux for 1.5 h, cooled, and poured into aqueous sodium hydrogen sulfite. Extraction with ethyl acetate furnished the crude 3-hydroxy 16α,17β-diacetate (**21**) which was acetylated as described for **19**. Similar work-up, followed by chromatography on silica gel with ethyl acetate–hexane (1:5) gave material (22.4 g) which was crystallised from ethyl acetate–diisopropyl ether (1:10) to give 14,17α-*ethanoestra*-1,3,5(10)-*triene*-3,16α,17β-*triyl triacetate* (**22**) (19.6 g, 73%), m.p. 159—161 °C; $[\alpha]_D$ + 25° (*c* 0.53); δ (300 MHz), 1.02 (3H, s, 13β-Me), 2.0 (3H, s, 16α-OAc), 2.1 (3H, s, 17β-OAc), 2.28 (3H, s, 3-OAc), 5.48 (1H, dt, *J* 8 and 2 x 2 Hz, 16β-H), 6.79 (1H, d, *J* 3 Hz, 4-H), 6.85 (1H, dd, *J* 8 and 3 Hz, 2-H), and 7.29 (1H, d, *J* 8 Hz, 1-H) (Found: C 70.6; H, 7.4. $C_{26}H_{32}O_6$ requires C, 70.9; H, 7.3%). 2M-Sodium hydroxide (155 ml) was added to a solution of the triacetate (**22**) (40 g, 90.9 mmol) in methanol (400 ml), and the mixture was stirred at 60 °C for 2.5 h. The resultant suspension was cooled to room temperature and neutralised by dropwise addition of M-hydrochloric acid. The neutral suspension was diluted with water (1.2 l) and stirred at 25 °C for 30 min.

The precipitate was collected by filtration, washed with distilled water and dried (50 °C/100 mm Hg for 18 h) to give the triol (**23**) (28.6 g, 100%), m.p. 324—326 °C; $[\alpha]_D$ +22.9° (*c* 0.52, DMSO); ν_{max} 3440, 3260, 3160 sh (OH), and 1608 and 1585 (C=C) cm^{-1}; δ (C_5D_5N) 1.18 (3H, s, 13β-Me), 4.8 (1H, d, *J* 9 Hz, 16β-H), 7.0 (1H, d, *J* 3 Hz, 4-H), 7.12 (1H, dd, *J* 8 and 3 Hz, 2-H), and 7.37 (1H, d, *J* 8 Hz, 1-H) (Found:C, 75.8; H, 8.35. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%).

Crystal Data for the Triacetate (22) – $C_{26}H_{32}O_6$, M, 440.5; monoclinic, space group $P2_1$, a = 11.739(3), b = 7.083(2), c = 14.375(4) Å, β = 102.82(2)°, V = 1165.5(6)Å^3, Z = 2, D_c = 1.255 mg m^{-3}, μ = 0.088 mm^{-1}, $F(000)$ = 472. A colourless crystal of dimensions 0.6 x 0.6 x 0.6 mm was used for data collection.

Data Collection and Processing – Data collection was performed at 293K on a Siemens P4 diffractometer using graphite monochromated Mo-*K*α radiation (λ = 0.71073Å); 2θ–θ scan mode with ω scan width = 1.20° + Kα separation, ω scan speed = 4.99 — 29.30° min^{-1}, ; 6301 reflections measured ($2.0 \leq 2\theta \leq 55.0°$; $-15 \leq h \leq 15$, $-9 \leq k \leq 9$, $-18 \leq l \leq 18$); 5362 independent reflections (R_{int} = 2.49%), giving 5360 observed reflections with $F > 4.0\sigma(F)$; no absorption correction. Background measurement comprised stationary crystal and stationary counter at beginning and end of scan, each for 25% of total scan time. Three standard reflections were measured for every 247 reflections.

Structure Analysis and Refinement – The structure was solved by direct methods using the Siemens SHELXTL PLUS(VMS) program and refined by full-matrix least-squares method with weighting scheme, $\omega^{-1} = \sigma^2(F) + 0.0015F^2$. Analysis and refinement details are: quantity minimised, $\Sigma w(F_o-F_c)^2$; hydrogen atoms, riding model with fixed isotropic U; number of parameters refined, 291; R 5.30% and wR 5.90% (all data); final R 5.30% and final wR 5.87% (observed data); goodness-of-fit 0.93; largest Δ/σ 0.312; mean Δ/σ 0.055; data-to-parameter ratio 18.4:1; largest difference peak 0.42eÅ^{-3}; largest difference hole -0.29eÅ^{-3}.

The refined atom coordinates are given in Table 1 and full lists of bond lengths, bond angles, torsion angles, calculated hydrogen atomic coordinates, and anisotropic thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

Table 1: Fractional Atomic Coordinates (× 10^4) and Equivalent Isotropic Displacement Coefficients (Å^2 x 10^3)

	x/a	*y/b*	*z/c*	*U*equiv.
C(1)	8506(2)	-839	4375(1)	50(1)
C(2)	9257(2)	-1535(5)	5185(2)	55(1)
C(3)	9323(2)	-612(5)	6034(2)	49(1)
C(4)	8683(2)	975(5)	6090(1)	50(1)
C(5)	7922(2)	1688(4)	5276(1)	43(1)
C(6)	7212(2)	3412(5)	5383(2)	60(1)
C(7)	6516(2)	4218(4)	4455(2)	51(1)
C(8)	5992(2)	2631(4)	3773(1)	37(1)
C(9)	6990(2)	1508(4)	3507(1)	37(1)
C(10)	7818(1)	751(4)	4401(1)	39(1)
C(11)	6539(2)	-51(4)	2771(1)	44(1)
C(12)	5666(2)	680(4)	1890(1)	43(1)
C(13)	4648(2)	1685(4)	2188(1)	35(1)
C(14)	5116(2)	3308(4)	2888(1)	36(1)
C(15)	3963(2)	4162(4)	3042(1)	49(1)
C(16)	3116(2)	3956(4)	2055(1)	42(1)

C(17)	3900(2)	3034(4)	1445(1)	38(1)
C(18)	3918(2)	195(4)	2550(2)	48(1)
O(3)	10129(1)	-1242(4)	6864(1)	57(1)
C(31)	9831(2)	-2792(5)	7291(2)	49(1)
O(31)	8934(2)	-3608(4)	7023(1)	73(1)
C(32)	10764(2)	-3313(5)	8129(2)	62(1)
C(141)	5594(2)	4722(4)	2242(2)	49(1)
O(16)	2683(1)	5800(4)	1713(1)	49(1)
C(161)	1574(2)	5928(5)	1227(1)	48(1)
O(161)	921(1)	4624(4)	1064(1)	74(1)
C(162)	1275(2)	7920(5)	943(2)	68(1)
O(17)	3271(1)	1966(4)	638(1)	47(1)
C(171)	2718(2)	2830(5)	-168(2)	49(1)
O(171)	2713(2)	4516(4)	-292(1)	69(1)
C(172)	2137(2)	1403(5)	-879(2)	65(1)
C(173)	4774(2)	4499(5)	1248(2)	49(1)

*Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor

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