Synthetic Routes to 11-Oxygenated 14α,17α-Ethanoestradiols

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Methods are described for the selective transformation of $\Delta^{9(11)}$ derivatives of 14α,17α-ethanoestradiol into their 11-oxygenated analogues by epoxidation–rearrangement or hydroboration–oxidation reaction sequences.

Introduction

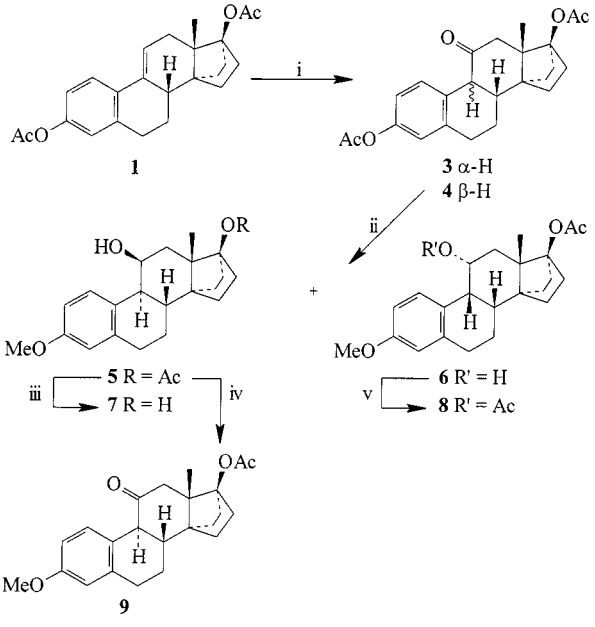
The discovery that the 14α,17α-ethano analogues of estradiol[1] and estriol[2] are potent oral estrogens with activities comparable to that of 17α-ethynylestradiol has led to an extensive investigation into the structure−activity relationships of a wide range of ring D modified estradiol analogues.[3] The recent disclosure of the structure of the receptor-bound complex of estradiol,[4] and related molecular modelling approaches,[5] has provided further impetus to the search for predictive design principles associated with estrogen agonists and antagonists.

The estradiol receptor is known to be tolerant of a wide range of 11β-substituents, with some of the most active estradiol analogues prepared to date possessing either alkyl or alkoxy groups in this position.[5] Additionally, the presence of a 17α-ethynyl group does not reduce the high receptor binding affinity of these analogues, and in some cases enhances the stability of the receptor−ligand complex.[5,6] It was therefore considered of interest to examine the effect of the 14α,17α-ethano bridge in conjunction with functionality at C-11 towards receptor binding, and a programme was initiated towards this end. In order to develop a versatile synthesis of the desired analogues, the introduction of an oxygen functionality at C-11 of 14α,17α-ethanoestradiols was identified as a primary objective. Herein we report the results of this investigation.

Results and Discussion

Our recent investigations into backbone-inverted analogues of 14,17-ethanoestradiol[7] established preparative methods for 14,17α-ethanoestra-1,3,5(10),9(11)-tetraene-3,17β-diyl diacetate **(1)**, thereby offering two alternative approaches to the target system — by epoxidation−rearrangement or hydroboration followed by oxidation.[8] Although the described preparative methods for the $\Delta^{9(11)}$ compound **1** are complicated by incomplete reaction to give chromatographically inseparable mixtures of **1** and the saturated precursor **2** (up to 35%; see ref.[7]), it was expected that 11-functionalisation of **1** would facilitate the subsequent separation of product(s) from **2**.

Epoxidation of the $\Delta^{9(11)}$ compound **1** with dimethyldioxirane[9] gave a labile intermediate, which was subjected to immediate treatment with lithium perchlorate[8] in refluxing benzene. Chromatography of the resulting product furnished a chromatographically inseparable fraction (71%, based on **1**), comprising a mixture of the 9α*H* and 9β*H* 11-ketones **3** and **4** (Scheme 1). The pure 9α*H* 11-ketone **3** could be obtained by recrystallisation of the mixture, and the configurational assignment at C-9 was confirmed with the aid of an ^{1}H NMR signal for 9α-H at δ = 3.89 (d, J = 12.8 Hz), which is diagnostic for a *trans* B,C-ring junction.[8,10,11] However, the crystallisation was preparatively wasteful, and failed to provide access to the minor 9β*H* 11-ketone **4**. Accordingly, a more practical expedient was adopted, whereby the mixture of 11-ketones was carried forward to the next step, for separation and characterisation



Scheme 1. Epoxidation-mediated synthesis of 11-ketone **9**; reagents: (i) a, dimethyldioxirane, acetone; b, $LiClO_4$, PhH, reflux (71% based on **1**); (ii) a, $NaBH_4$, THF/MeOH; b, K_2CO_3, Me_2SO_4, acetone (**5**, 56%; **6**, 11%); (iii) KOH, MeOH/THF; (iv) Dess−Martin periodinane, CH_2Cl_2 (68%); (v) Ac_2O, C_5H_5N, DMAP (71%)

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Table 1. Selected ^{1}H NMR spectroscopic data for compounds 5−8, 12, and 13.

Compound	1-H (*J*/Hz)	9-H (*J*/Hz)	11-H (*J*/Hz)	13β-Me
5	δ = 7.23 (d, *J* = 8.5)	δ = 2.77−2.96 (m)	δ = 4.75 (q, *J* = 3 × 3.2)	δ = 1.19 (s)
6	δ = 7.67 (d, *J* = 8.3)	δ = 3.11 (dd, *J* = 7.3, 5.3)	δ = 4.57 (dt, *J* = 8.8, 2 × 5.3)	δ = 1.09 (s)
7	δ = 7.22 (d, *J* = 8.6)	δ = 2.89 (dd, *J* = 12, 3.3)	δ = 4.75 (q, *J* = 3 × 3.3)	δ = 1.16 (s)
8	δ = 7.61 (d, *J* = 8.5)	δ = 3.21 (t, *J* = 2 × 6.3)	δ = 5.58 (ddd, *J* = 12.1, 5.6, 4.8)	δ = 1.13 (s)
12	δ = 7.88 (d, *J* = 8.7)	δ = 2.48 (t, *J* = 2 × 10)	δ = 4.20 (td, *J* = 2 × 10, 5.8)	δ = 0.89 (s)
13	δ = 6.95 (d, *J* = 9.4)	δ = 2.70 (m)	δ = 5.30 (td, *J* = 2 × 10.5, 5.6)	δ = 0.92 (s)

of the derived products. Reduction of the mixture of 11-ketones **3** and **4** with sodium borohydride in THF/methanol, followed by 3-*O*-methylation (necessitated by the concomitant loss of the 3-acetoxy group), gave a chromatographically separable mixture of the 9α*H* 11β-alcohol **5** (56%; from **3**) and the 9β*H* 11α-alcohol **6** (11%; from **4**). ^{1}H NMR spectroscopy of **5** (and the derived 11β,17β-diol **7**) and **6** (and the derived 11α,17β-diacetate **8**) revealed key signals for 1-H, 9-H and 11-H which unambiguously secured the structural assignments (see Table 1), and confirmed the stereoselective course of hydride reduction of the respective 11-ketones **3** and **4**.

Oxidation of the 11β-alcohol **5** with Dess−Martin periodinane[12] gave the 11-ketone **9** (68%). A ^{1}H NMR spectrum of **9** again revealed the characteristic signal at δ = 3.88 (d, *J* = 12.2 Hz) for 9α-H, and the structural assignment was further supported by NOE difference spectroscopy, in which irradiation of the signal for 9α-H (δ = 3.88) significantly enhanced those of 7α-H (δ = 1.52), 17^2_x-H (δ = 2.36) and 12α-H (δ = 2.76) (see Figure 1). Verification of the 9α-configuration of **9** thereby confirmed that no epimerisation intervened during the foregoing transformations.

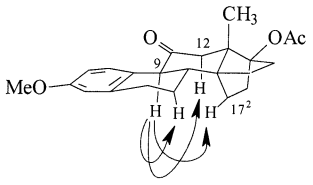
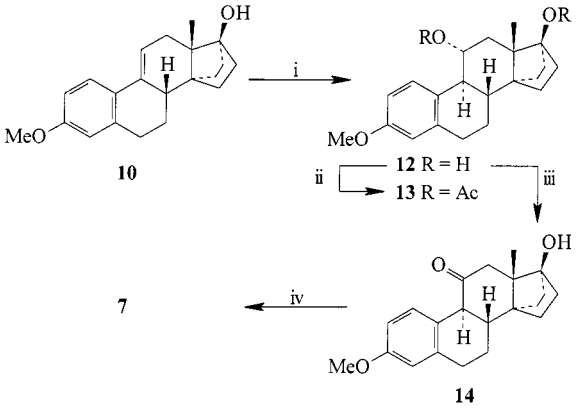


Figure 1. Perspective drawing of 11-ketone **9** showing confirmatory NOE interactions for 9α-configuration

An alternative pathway to 11-oxygenated 14α,17α-ethanoestradiols entailed hydroboration−oxidation of a suitable $\Delta^{9(11)}$ precursor, and necessitated the choice of 3-methoxy-14,17α-ethanoestra-1,3,5(10),9(11)-tetraen-17β-ol **(10)**[7] as starting material in order to ensure retention of 3-*O*-protection during the alkaline hydrogen peroxide oxidation of the intermediate organoborane. Although **10** was also unavailable in a pure state, the removal of 3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol **(11)** (present as the inseparable synthetic precursor) following hydroboration was straightforward (see Experimental Section), and did not detract from evaluating the synthetic utility of this route. Hydroboration of the 3-methyl ether **10** proceeded extremely slowly (72 h in refluxing THF; Scheme 2) and gave, after oxidative workup, a single product in moderate yield (62%). The structure was assigned as the 9α*H* 11α,17β-diol **12** on



Scheme 2. Hydroboration-oxidation route to 11-ketone **14**; reagents: (i) a, BH_3·SMe_2, THF, reflux; b, H_2O_2, NaOH (62% based on **10**); (ii) Ac_2O, C_5H_5N, DMAP (74%); (iii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N (58%); (iv) $LiAlH_4$, THF (54%).

the basis of spectroscopic data, supported by those of the derived 11α,17β-diacetate **13** (Table 1). In particular, ^{1}H NMR signals for 9-H and 11-H clearly exclude the alternative structure which would be expected from β-face hydroboration.

These results suggest that the presence of the 14α,17α-ethano bridge impairs the reactivity of the $\Delta^{9(11)}$ bond in **10,** but does not have an adverse effect on α-face diastereoselectivity. This may be compared to the corresponding reaction in a functionally similar 14α-methylestratetraene, in which an approximate 19:1 preference for α-face hydroboration of the $\Delta^{9(11)}$ bond is observed.[11] Swern oxidation[13] of the 11α-alcohol **12** gave the corresponding 11-ketone **14** (58%), hydride reduction of which afforded exclusively the 11β-alcohol **7**, which was identified by comparison with material prepared by the epoxidation−rearrangement sequence.

Conclusion

This investigation has established two complementary routes to 11-oxo-14α,17α-ethanoestradiols, which should serve as versatile intermediates for the synthesis of 11β-functionalised hormone analogues.[6] While the epoxidation−rearrangement sequence is higher yielding overall, and also provides access to the 9β-series,[7] albeit as minor products, the directness and selectivity of the hydroboration−oxidation sequence offer advantages for practical synthesis of the target intermediates.

Experimental Section

General Remarks: Melting points were measured using a Reichert−Jung Thermovar hot-stage microscope and are uncorrected. Unless otherwise specified, spectra were recorded as follows: Optical rotation: Perkin−Elmer 141 polarimeter, $CHCl_3$ solution at 20 °C, $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}; infrared: Perkin−Elmer 983 or Perkin−Elmer Paragon 1000 FT−IR, $CHCl_3$ solution; mass spectra (electron impact): VG micromass 16F, accurate mass (electron impact) VG−70E; ^1H NMR: Varian VXR−200 (200 MHz) and Varian Unity (400 MHz), $CDCl_3$ solution (*J* values given in Hz); ^{13}C NMR: Varian VXR−200 (50 MHz) or Varian Unity (100 MHz), $CDCl_3$ solution. Microanalyses were determined with a Fisons EA 1108 CHNS−O instrument. Column chromatography was conducted with Merck Kieselgel 60: 70−230 mesh for gravity and 230−400 mesh for flash chromatography. 14,17α-Ethanoestra-1,3,5(10),9(11)-tetraene-3,17β-diyl diacetate **(1)** and 3-methoxy-14,17α-ethanoestra-1,3,5(10),9(11)-tetraen-17β-ol **(10)** were prepared as described previously.[7]

Epoxidation-Rearrangement of 14,17α-Ethanoestra-1,3,5(10),9(11)-tetraene-3,17β-diyl Diacetate (1): A solution of **1** [containing ≈35% 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diyl diacetate **(2)**] (450 mg, 0.8 mmol) in CH_2Cl_2 (5 mL) was stirred at 25 °C while a solution of dimethyldioxirane (ca. 0.1 M in acetone, 25 mL, 2.5 mmol) was added, and the resulting mixture was stirred for 75 min at 25 °C. The solvent was removed under reduced pressure to give a residue (500 mg) which was dissolved in benzene (15 mL) and refluxed with $LiClO_4$ (100 mg) for 1 h under N_2. The cooled solution was washed (H_2O), dried ($MgSO_4$), and the solvent evaporated under reduced pressure to give a solid residue (456 mg). Flash chromatography on silica gel (50 g) with EtOAc/hexane (1:4) as eluent gave 3,17β-diacetate **2** (149 mg) followed by a mixture of 11-ketones **3** and **4** (220 mg, 71% based on **1**). Recrystallisation of a portion of this mixture from acetone/hexane afforded 11-oxo-14α,17α-ethanoestra-1,3,5(10)-triene-3,17β-diyl diacetate **(3)** (55%), m.p. 157−160 °C. − $[\alpha]_D^{20}$ = +220 (*c* = 0.1). − IR: $\tilde{\nu}$ = 1732 cm^{-1} (C=O). − ^1H NMR (400 MHz): δ = 1.03 (d, *J* = 0.8, 3 H, 13β-Me), 1.53 (qd, *J* = 3 × 12.8, 5.8, 1 H, 7α-H), 1.84 (m, 1 H, 7β-H), 1.98 (td, *J* = 2 × 12.8, 2.2, 1 H, 8β-H), 2.02 (s, 3 H, 17β-OAc), 2.23 (d, *J* = 12.8, 1 H, 12β-H), 2.27 (s, 3 H, 3-OAc), 2.77 (dd, *J* = 12.8, 0.8, 1 H, 12α-H), 2.84 (m, 2 H, 6-H_2), 3.89 (d, *J* = 12.8, 1 H, 9α-H), 6.81 (d, *J* = 2.4, 1 H, 4-H), 6.89 (dd, *J* = 8.7, 2.4, 1 H, 2-H), 7.40 (d, *J* = 8.7, 1 H, 1-H). − ^{13}C NMR (100 MHz): δ = 14.6 (13β-Me), 21.1 (3-OC(O)*C*H_3), 21.4 (17β-OC(O)*C*H_3), 24.3 (C-7), 27.7 (C-17^2), 29.5 (C-17^1), 30.1 (C-6), 31.8 (C-15), 32.2 (C-16), 42.5 (C-8), 45.4 (C-14), 47.1 (C-12), 50.1 (C-9), 54.3 (C-13), 88.1 (C-17), 118.6 (C-2), 121.6 (C-4), 129.2 (C-10), 131.6 (C-1), 138.4 (C-5), 148.9 (C-3), 169.6 [17β-O*C*(O)CH_3], 170.9 [3-O*C*(O)CH_3], 209.2 (C-11). − MS: *m*/*z* = 396 [M^+]. − $C_{24}H_{28}O_5$ (396.49): calcd. C 72.7, H 7.1; found C 72.3, H 7.2.

Reduction of 11-Ketones 3 and 4: Sodium borohydride (200 mg, 5 mmol) was added to a solution of the 11-ketones **3** and **4** (200 mg, 0.5 mmol) in a mixture of THF (2 mL) and MeOH (2 mL) and the mixture was stirred for 18 h at 25 °C. Water was then added and the resulting mixture was extracted with EtOAc followed by $CHCl_3$. The combined organic phase was washed (H_2O, satd. aq. NaCl), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a residue (188 mg) which was dissolved in dry acetone (5 mL) and stirred with K_2CO_3 (1 g) and Me_2SO_4 (1 mL) for 18 h at 25 °C under N_2. Aqueous NH_3 (25%, 3 mL) was added and the mixture was stirred for 30 min. Water was added again and the mixture was extracted into EtOAc. The combined organic phase was washed (water, satd. aq. NaCl), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a residue (170 mg) which was chromatographed on silica gel (20 g) with EtOAc/toluene (1:9) as eluent to give 17β-acetoxy-3-methoxy-14α,17α-ethanoestra-1,3,5(10)-trien-11β-ol (**5**; 106 mg, 56%), m.p. 193−194 °C (from MeOH). − $[\alpha]_D^{20}$ = +92 (*c* = 0.5). − IR: $\tilde{\nu}$ = 3573 cm^{-1} (OH), 1728 (C=O). − ^1H NMR (400 MHz): δ = 1.19 (s, 3 H, 13β-Me), 1.56 (s, 1 H, D_2O exch., 11β-OH), 2.02 (s, 3 H, 17β-OAc), 2.77−2.96 (m, 3 H, 6-H_2, 9α-H), 4.75 (q, *J* = 3 × 3.2, 1 H, 11α-H), 6.67 (d, *J* = 2.6, 1 H, 4-H), 6.77 (dd, *J* = 8.5, 2.6, 1 H, 2-H), 7.23 (d, *J* = 8.5, 1 H, 1-H). − MS: *m*/*z* = 370 [M^+]. − $C_{23}H_{30}O_4$ (370.49): calcd. C 74.6, H 8.2; found C 74.5, H 8.3. Further elution with the same solvent afforded 17β-acetoxy-3-methoxy-14α,17α-ethano-9β-estra-1,3,5(10)-trien-11α-ol (**6**; 21 mg, 11%), as an oil. − IR: $\tilde{\nu}$ = 3691, 3600 cm^{-1} (OH), 1727 (C=O). − ^1H NMR (400 MHz): δ = 0.94 (m, 1 H, 17^2_n-H), 1.09 (s, 3 H, 13β-Me), 2.54 (td, *J* = 2 × 13.2, 5.1, 1 H, 6α-H), 2.65 (ddd, *J* = 13.2, 4.7, 2.9, 1 H, 6β-H), 3.11 (dd, *J* = 7.3, 5.3, 1 H, 9β-H), 3.78 (s, 3 H, 3-OMe), 4.57 (dt, *J* = 8.8, 2 × 5.3, 1 H, 11β-H), 6.68 (d, *J* = 2.6, 1 H, 4-H), 6.72 (dd, *J* = 8.3, 2.6, 1 H, 2-H), 7.67 (d, *J* = 8.3, 1 H, 1-H).

3-Methoxy-14,17α-ethanoestra-1,3,5(10)-triene-11β,17β-diol (7): (a) A solution of the 17β-acetate **5** (11 mg, 0.03 mmol) in a mixture of methanolic KOH (1%, 1 mL) and THF (0.5 mL) was stirred at 25 °C for 22 h. Water was added and the mixture was extracted with EtOAc. The combined organic phase was washed (water, satd. aq. NaCl), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the product **7** (10 mg). The analytical sample was recrystallised from methanol, m.p. 193−194 °C. − $[\alpha]_D^{20}$ = +105 (*c* = 1.2). − IR: $\tilde{\nu}$ = 3685, 3598 cm^{-1} (OH). − ^1H NMR (400 MHz): δ = 1.16 (s, 3 H, 13β-Me), 1.33 (qd, *J* = 3 × 12.0, 5.6, 1 H, 7α-H), 1.51 and 1.54 (both s, 1 H, D_2O exch, 11β-, 17β-OH), 1.88 (td, *J* = 2 × 12.0, 2.3, 1 H, 8β-H), 2.82 (m, 2H, 6-H_2), 2.89 (dd, *J* = 12.0, 3.3, 1 H, 9α-H), 3.78 (s, 3 H, 3-OMe), 4.75 (q, *J* = 3 × 3.3, 1 H, 11α-H), 6.66 (d, *J* = 2.7, 1 H, 4-H), 6.76 (dd, *J* = 8.6, 2.7, 1 H, 2-H), 7.22 (d, *J* = 8.6, 1 H, 1-H). − ^{13}C NMR (100 MHz): δ = 16.3 (13β-Me), 23.4 (C-7), 26.3 (C-17^2), 30.4 (C-6), 32.2 (C-15), 33.3 (C-17^1), 35.5 (C-16), 33.0 (C-12), 35.2 (C-8), 43.4 (C-9), 46.4 (C-13), 47.7 (C-14), 55.2 (3-OMe), 67.3 (C-11), 84.3 (C-17), 112.4 (C-2), 114.7 (C-4), 126.3 (C-1), 128.2 (C-10), 139.9 (C-5), 157.7 (C-3). − MS: *m*/*z* = 328 [M^+]. − $C_{21}H_{28}O_3$ (328.45): calcd. C 76.8, H 8.6; found C 77.0, H 8.5.
(b) $LiAlH_4$ (1 g, 26 mmol) was added to a solution of 17β-hydroxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-11-one (**14**; 513 mg, 1.6 mmol) in THF (20 mL) and the mixture was stirred for 1 h at 25 °C. EtOAc (20 mL) was added, and once effervescence ceased (10 min) the mixture was extracted with EtOAc. The combined organic phase was washed (H_2O, satd. aq. NaCl), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a residue (424 mg) which was flash chromatographed on silica gel (50 g) with EtOAc/toluene (1:4) affording the 11β,17β-diol **7** (280 mg, 54%), identical in all respects with that synthesised previously.

3-Methoxy-14,17α-ethano-9β-estra-1,3,5(10)-triene-11α,17β-diyl Diacetate (8): A solution of the 11α-alcohol **6** (20 mg, 0.05 mmol) in a mixture of pyridine (1 mL) and Ac_2O (1 mL) was stirred with a catalytic amount of 4-dimethylaminopyridine for 30 min at 25 °C. Satd. aq. $NaHCO_3$ was added and once the effervescence ceased the mixture was extracted into EtOAc. The combined organic phase was washed (satd. aq. $NaHCO_3$, 1M HCl, H_2O, satd. aq. NaCl), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a residue (28 mg) which was chromatographed on silica gel (5 g) with EtOAc/toluene (1:9) as eluent to give the 11α,17β-diacetate (**8**; 15 mg, 74%), as an oil, − $[\alpha]_D^{20}$ = +57 (*c* =

1.5). − IR: $\tilde{\nu}$ = 1724 cm^{-1} (C=O). − ^1H NMR (400 MHz): δ = 0.86 (m, 1 H, 17^2_n-H), 1.13 (s, 3 H, 13β-Me), 1.70 (dd, *J* = 12.3, 4.2, 1 H, 12β-H), 1.92 (s, 3 H, 11α-OAc), 2.02 (s, 3 H, 17β-OAc), 2.49 (td, *J* = 2 × 13.3, 5.2, 1 H, 6α-H), 2.58 (ddd, *J* = 13.3, 4.8, 2.8, 1 H, 6β-H), 3.21 (t, *J* = 2 × 6.3, 1 H, 9β-H), 3.78 (s, 3 H, 3-OMe), 5.58 (ddd, *J* = 12.1, 5.6, 4.8, 1 H, 11β-H), 6.69 (d, *J* = 2.8, 1 H, 4-H), 6.71 (dd, *J* = 8.5, 2.8, 1 H, 2-H), 7.61 (d, *J* = 8.5, 1 H, 1-H). − MS: *m*/*z* = 412 [M^+]. − HRMS ($C_{25}H_{32}O_5$, M^+): calcd. 412.255; found 412.256.

3-Methoxy-11-oxo-14,17α-ethanoestra-1,3,5(10)-trien-17β-yl acetate (9): To a solution of 17β-acetoxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-11β-ol **5** (94 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) was added Dess−Martin periodinane (120 mg, 0.33 mmol) and the solution was stirred for 1 h. Et_2O (20 mL) was then added and the resulting suspension was poured into a mixture of aq. $NaHCO_3$ (30 mL) and $Na_2S_2O_3$ (2 g). The resulting mixture was extracted into Et_2O. The combined organic phase was washed (aq. $NaHCO_3$, H_2O, satd. aq. NaCl), dried ($MgSO_4$), and the solvent evaporated under reduced pressure to give a residue (95 mg) which was chromatographed on silica gel (1 g) with Et_2O/hexane (3:7) as eluent to give the 11-ketone **9** (59 mg, 68%), m.p. 135−138 °C (from iPr_2O). − $[\alpha]_D^{20}$ = +239 (*c* = 0.4). − IR: $\tilde{\nu}$ = 1729, 1711 cm^{-1} (C=O). − ^1H NMR (400 MHz): δ = 0.90 (d, *J* = 0.8, 3 H, 13β-Me), 1.52 (qd, *J* = 3 × 12.2, 5.6, 1 H, 7α-H), 1.98 (td, *J* = 2 × 12.2, 2.0, 1 H, 8β-H), 2.01 (s, 3 H, 17β-OAc), 2.22 (d, *J* = 12.0, 1 H, 12β-H), 2.36 (tt, *J* = 2 × 12.7, 2 × 3.7, 1 H, 17^2_x-H), 2.76 (dd, *J* = 12.0, 0.8, 1 H, 12α-H), 2.80 (m, 2 H, 6-H_2), 3.88 (d, *J* = 12.2, 1 H, 9α-H), 3.76 (s, 3 H, 3-OMe), 6.61 (d, *J* = 2.9, 1 H, 4-H), 6.75 (dd, *J* = 8.8, 2.9, 1 H, 2-H), 7.30 (d, *J* = 8.8, 1 H, 1-H). − ^{13}C NMR (100 MHz): δ =14.7 (13β-Me), 21.4 [17β-OC(O)*C*H_3], 24.7 (C-7), 27.8 (C-17^2), 29.6 (C-17^1), 30.4 (C-6), 31.8 (C-15), 32.2 (C-16), 42.8 (C-8), 45.4 (C-14), 47.0 (C-12), 50.0 (C-9), 54.4 (C-13), 55.2 (3-O*Me*), 88.1 (C-17), 111.6 (C-2), 113.8 (C-4), 123.8 (C-10), 131.5 (C-1), 138.2 (C-5), 157.9 (C-3), 170.7 [17β-O*C*(O)CH_3], 209.7 (C-11). − MS: *m*/*z* = 368 [M^+]. − $C_{23}H_{28}O_4$ (368.47): calcd. C 75.0, H 7.7; found C 75.0, H 7.8.

3-Methoxy-14,17α-ethanoestra-1,3,5(10)-triene-11α,17β-diol (12): BH_3·SMe_2 (10 M, 10 mL, 100 mmol) was added slowly to a stirred solution of 3-methoxy-14,17α-ethanoestra-1,3,5(10),9(11)-tetraen-17β-ol [**10**; 2.7 g, ca. 8.7 mmol; containing ≈50% 3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol **(11)**] in dry THF (150 mL) at 25 °C under N_2. The mixture was refluxed for 72 h under N_2, with a further aliquot of reagent being added after 24 h. After cooling to 0 °C, H_2O_2 (100 vol., 20 mL) and aq. NaOH (4 M, 20 mL) were added simultaneously (***CAUTION: vigorous effervescence***) and the mixture was stirred for 18 h at 25 °C. H_2O (80 mL) was then added and the mixture was extracted into EtOAc. The combined organic phase was washed (satd. aq. NaCl), dried ($MgSO_4$) and the solvent evaporated to give a residue (ca. 3 g) which was adsorbed onto silica gel (150 g) and eluted with EtOAc-toluene (1:9) to give **11** (958 mg). Further elution with EtOAc/toluene (3:2) afforded the 11α,17β-diol **12** (888 mg, 62% based on **10**) as an oil, − IR: $\tilde{\nu}$ = 3597, 3457 cm^{-1} (OH). − ^1H NMR (200 MHz): δ = 0.89 (s, 3 H, 13β-Me), 2.48 (t, *J* = 2 × 10.0, 1 H, 9α-H), 2.76 (m, 2 H, 6-H_2), 3.77 (s, 3 H, 3-OMe), 4.20 (td, *J* = 2 × 10.0, 5.8, 1 H, 11β-H), 6.64 (d, *J* = 2.8, 1 H, 4-H), 6.74 (dd, *J* = 8.7, 2.8, 1 H, 2-H), 7.88 (d, *J* = 8.7, 1 H, 1-H). − ^{13}C NMR (50 MHz): δ = 14.4 (13β-Me), 23.0 (C-7), 27.0 (C-17^2), 29.1 (C-6), 32.1 (C-15), 32.9 (C-17^1), 35.3 (C-16), 38.0 (C-8), 39.5 (C-12), 45.4 (C-9), 46.8 (C-13), 48.1 (C-14), 55.2 (3-OMe), 71.2 (C-11), 83.8 (C-17), 111.1 (C-2), 113.7 (C-4), 127.5 (C-1), 132.9 (C-10), 139.1 (C-5), 157.7 (C-3). − MS: *m*/*z* = 328 [M^+].

3-Methoxy-14,17α-ethanoestra-1,3,5(10)-triene-11α,17β-diyl Diacetate (13): To a solution of the 11α,17β-diol **12** (160 mg, 0.5 mmol) in pyridine (5 mL) at 25 °C was added Ac_2O (0.2 mL, 2.2 mmol) and 4-dimethylaminopyridine (10 mg). The mixture was stirred for 16 h at 25 °C, H_2O was then added and the solution was extracted with EtOAc. The combined organic phase was washed (3 M HCl, satd. aq. $NaHCO_3$, satd. aq. NaCl), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a residue (196 mg) which was adsorbed onto silica gel (20 g) and eluted with EtOAc/toluene (1:9) to give the 11α,17β-*diacetate* **13** (150 mg, 74%), m.p. 156−157 °C (from MeOH). − $[\alpha]_D^{20}$ = +101 (*c* = 0.9). − IR: $\tilde{\nu}$ = 1724 cm^{-1} (C=O). − ^1H NMR (200 MHz): δ = 0.92 (s, 3 H, 13β-Me), 1.93 (s, 3 H, 11α-OAc), 2.03 (s, 3 H, 17β-OAc), 2.70 (m, 3 H, 9α-H, 6-H_2), 3.70 (s, 3 H, 3-OMe), 5.30 (td, *J* = 2 × 10.5, 5.6, 1 H, 11β-H), 6.62 (m, 2 H, 2-H, 4-H), 6.95 (d, *J* = 9.4, 1 H, 1-H). − ^{13}C NMR (50 MHz): δ = 14.5 (13β-Me), 21.4 and 21.7 [11α- and 17β-OC(O)*C*H_3], 22.8 (C-7), 27.8 (C-17^2), 28.7 (C-17^1), 29.2 (C-6), 32.0 (C-15), 32.4 (C-16), 33.5 (C-12), 39.0 (C-8), 41.2 (C-9), 44.7 (C-13), 49.2 (C-14), 55.1 (3-OMe), 74.1 (C-11), 89.1 (C-17), 111.1 (C-2), 113.8 (C-4), 125.3 (C-1), 132.2 (C-10), 139.3 (C-5), 157.8 (C-3), 170.7 and 170.8 [11α- and 17β-O*C*(O)CH_3]. − MS: *m*/*z* = 352 [M^+ − HOAc]. − $C_{25}H_{32}O_5$ (412.53): calcd. C 72.8, H 7.8; found C 72.8, H 7.7.

17β-Hydroxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-11-one (14): A solution of Me_2SO (0.7 mL, 9 mmol) in dry CH_2Cl_2 (5 mL) was added to a solution of oxalyl chloride (2 M in CH_2Cl_2, 1.5 mL, 3 mmol) at −78 °C. After stirring for 5 min at −78 °C, 11α,17β-diol **12** (780 mg, 2.4 mmol) in dry CH_2Cl_2 (10 mL) was added and the mixture stirred for 20 min at −78 °C. Et_3N (1.7 mL, 12 mmol) was then added and the mixture allowed to warm to 25 °C. H_2O (20 mL) was added and the mixture extracted with CH_2Cl_2. The combined organic phase was washed (3 M HCl, H_2O, aq. Na_2CO_3, H_2O), dried ($MgSO_4$) and the solvent evaporated to give a residue (600 mg) which was flash chromatographed on silica gel (80 g), eluting with EtOAc/toluene (1:4) to give the 11-*ketone* **14** (450 mg, 58%) as an oil, − IR: $\tilde{\nu}$ = 1709 cm^{-1} (C=O). − ^1H NMR (200 MHz): δ = 0.79 (3 H, s, 13β-Me), 3.70 (3 H, s, 3-OMe), 3.80 (d, *J* = 12.0, 1 H, 9α-H), 6.55 (d, *J* = 2.6, 1 H, 4-H), 6.69 (dd, *J* = 8.5, 2.6, 1 H, 2-H) and 7.22 (d, *J* = 8.5, 1 H, 1-H). − ^{13}C NMR (50 MHz): δ = 14.2 (13β-Me), 24.2 (C-7), 27.1 (C-17^2), 30.3 (C-6), 31.4 (C-15), 33.1 (C-17^1), 35.5 (C-16), 43.4 (C-8), 46.5 (C-12), 47.3 (C-13), 50.0 (C-9), 53.4 (C-14), 55.2 (3-OMe), 82.9 (C-17), 111.5 (C-2), 113.8 (C-4), 123.9 (C-1), 131.5 (C-10), 138.2 (C-5), 157.9 (C-3), 210.3 (C-11). − MS: *m*/*z* = 326 [M^+].

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