Total synthesis of 3-hydroxy-6-oxaestra-1,3,5(10)-trien-17-one

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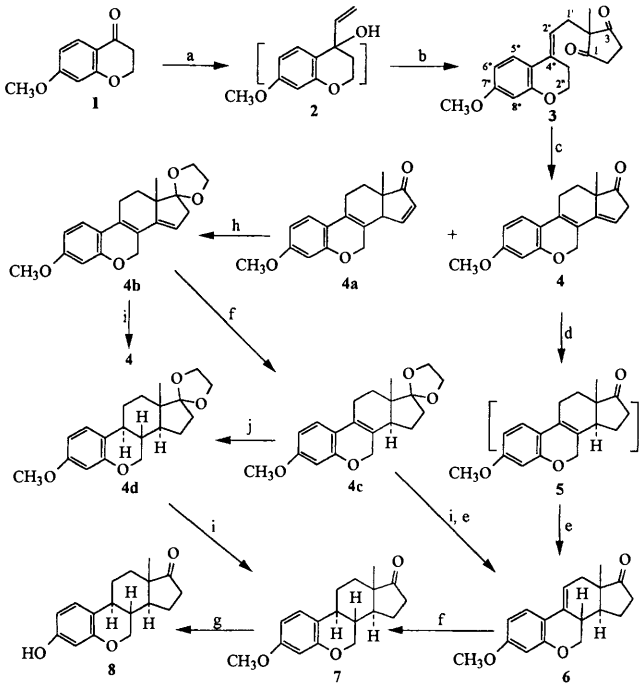
PERKIN 1

The modified steroid estrogen, 3-hydroxy-6-oxaestra-1,3,5(10)-trien-17-one, *i.e.* 6-oxaestrone 8 has been prepared from 7-methoxychromanone 1 by *de novo* synthesis of the modified steroid ring system. The ^{1}H and ^{13}C NMR data for the intermediate products 3, 4, 4a, 4b, 4c, 6, 7, and for the final product 8 support the proposed structures. A mechanism for the ring-closure reaction of 3 to intermediate products 4 and 4a is proposed.

Steroidal estrogens are converted by cytochrome P450-mediated hydroxylation mainly into catecholestrogens (2- and 4-hydroxylated estrogens) and to several minor hydroxylated metabolites such as 6α- and 16α-hydroxyestrogens.[1,2] The lower receptor binding affinities and lipophilicities of these metabolites ensure an efficient termination of hormonal action and enhanced excretion of the steroids.[1,2] In addition to increased excretion, the metabolism of steroids may result in the accumulation of estrogen metabolites with specific hormonal activities distinct from those of the parent hormones. For instance, the enhanced formation of 4-hydroxyestrogens in uterus has been postulated to play a role in embryo implantation.[3] The biological functions of estrogen metabolites independent of those of the parent hormone can be examined using modified estrogens, which retain the hormonal activity of the parent steroid yet cannot be converted into a specific estrogen metabolite.

In this study, we describe the synthesis of 6-oxaestrone as a possible tool for the exploration of biological activities of estrogen metabolites. The replacement of the 6-methylene moiety of the steroidal ring system with an oxygen atom was expected to keep intact the hormonal activity of the product as defined by the receptor binding affinity and at the same time to prevent the formation of 6-hydroxylated metabolites. Moreover, the electron-donating effect of the 6-oxa group onto the aromatic A-ring was expected to affect metabolic catecholestrogen formation.

The synthesis of 6-oxaestrone **8** involved a *de novo* synthesis of the modified steroid ring system starting with 7-methoxychromanone **1**. In the synthesis of a modified steroid ring structure, we followed Wakselman's procedure for the total synthesis of 13-trifluoromethyl estrogens.[4,5]



Scheme 1 *Reagents and conditions:* a, $CH_2{=}CH_2MgBr$, THF; b, 2-methylcyclopentane-1,3-dione, $KHCO_3$, EtOH; c, 37% aqueous HCl, EtOH, reflux; d, H_2, Pd–$CaCO_3$(Pd, 5%), C_6H_6; e, 37% aqueous HCl, EtOH, reflux; f, H_2, Pd–C, C_6H_6; g, $AlCl_3$, C_6H_6, heat; h, ethylene glycol, p-$MeC_6H_4SO_3H$, C_6H_6; i, p-$MeC_6H_4SO_3H{\cdot}H_2O$, Me_2CO; j, Na–NH_3

Results and discussion

Our synthesis contains a Torgov-type reaction[6] involving a potassium hydrogen carbonate-catalysed condensation of 7-methoxy-4-vinylchromanol **2** with 2-methylcyclopentane-1,3-dione leading to the tetracyclic intermediate products **4** and **4a** which, by further functional group manipulation, gave the final product **8** (see Scheme 1).

The chromanone **1**, prepared by a previously optimized procedure,[7] was used as starting material. The reaction of **1** with vinylmagnesium bromide in dry tetrahydrofuran under a nitrogen atmosphere gave the crude chromanol **2** (not obtained pure), which was further converted into the seco-oxasteroid **3** by $KHCO_3$-catalysed condensation with 2-methylcyclopentane-1,3-dione. The overall yield of **3** from **1** was 75%. An analytically pure, crystalline sample of **3** was obtained by recrystallization. The ^{1}H NMR spectrum of **3** contained a characteristic triplet at 4.12 ppm for 2″-CH_2 and the 2′-H signal was at 5.72 ppm. The 7″-OCH_3 and 2-CH_3 signals appeared as singlets at 3.76 and 1.06 ppm, respectively. All the aromatic protons resonated in the range of 6.35–7.30 ppm. The ^{13}C NMR spectrum showed a characteristic signal at 216.61 ppm for the carbonyl carbons (C-1 and C-3).

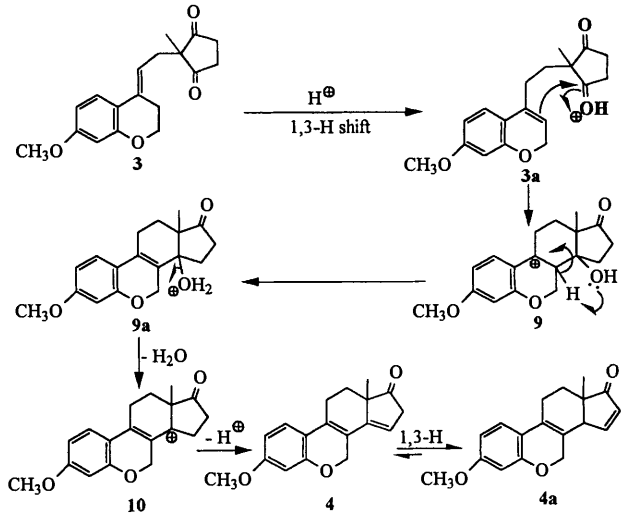
A cyclodehydration of **3** in boiling ethanol catalysed by 37% aqueous hydrochloric acid generated the tetracyclic products **4** (24%) and **4a** (71%). The ^{1}H NMR spectrum of **4** showed characteristic double doublets in the range of 4.80–4.95 ppm for 7-CH_2 as a result of coupling between the α-proton and the β-proton, whereas the double doublets in the spectrum of **4a** appeared in the range of 4.46–4.48 ppm. In the spectrum for **4**, the 15-H signal was at 5.72 ppm, whereas for **4a** it shifted downfield to 6.55 ppm owing to the α,β-unsaturated ketone feature. In the ^{13}C NMR spectra of **4** and **4a**, signals at 219.19 and 218.53 ppm indicated carbonyl carbons. Compound **4b** was formed by ketalization of **4a** with ethylene glycol in benzene catalysed by toluene-p-sulfonic acid (96% yield); its ^{1}H NMR spectrum featured a multiplet at 3.97 ppm for OCH_2CH_2O.

Deketalization of **4b** with toluene-*p*-sulfonic acid monohydrate in acetone afforded **4** (94%).

The estrapentanone **4** on selective hydrogenation in benzene over 5% palladized calcium carbonate gave the 6-oxatetraenone **5** which, without isolation, was directly transformed into the $\Delta^{9(11)}$-isomer **6** (65%) on heating under reflux in ethanolic hydrochloric acid according to Smith's procedure.[8] Monohydrogenation of **4b** in benzene over 10% palladized charcoal afforded **4c** (72%), the ^{1}H NMR spectrum of which showed a multiplet at 3.45 ppm for 14-H, and a broad singlet at 3.95 ppm for OCH_2CH_2O. Signals for 15-CH_2 and other methylenes formed complex multiplets in the range 1.20–2.70 ppm. In the ^{13}C NMR spectrum, the C-14, C-15 and C-17 signals were at 35.04, 26.54 and 140.18 ppm, respectively. Deketalization of **4c** and the subsequent heating of the product in refluxing ethanolic hydrochloric acid also gave **6** (67%). Compound **6** was characterized by the olefinic 11-H signal at 5.95 ppm in its ^{1}H NMR spectrum and the carbon signal at 114.75 ppm in its ^{13}C NMR spectrum.

Further hydrogenation of **6** in benzene over 10% palladized charcoal gave 3-methoxy-6-oxaestra-1,3,5(10)-trien-17-one **7** (78%), the ^{1}H NMR spectrum of which showed singlets at 0.94 (13-CH_3) and 3.76 ppm (3-OCH_3); a complex multiplet in the range of 1.45–2.45 ppm was formed by signals for 8-H, 9-H, 11-H, 12-H, 14-H, 15-H and 16-H. The 17-C carbonyl signal appeared at 219.26 ppm in its ^{13}C NMR spectrum. Demethylation of **7** to the final product, 3-hydroxy-6-oxaestra-1,3,5(10)-trien-17-one (*i.e.* 6-oxaestrone) **8**, was accomplished in 53% yield by heating the methyl ether **7** in benzene with aluminium trichloride. A characteristic signal for 3-OH was observed at 9.11 ppm in its ^{1}H NMR spectrum. Attempted demethylation of **7** with boron tribromide or iodotrimethylsilane, gave only intractable mixtures.

A mechanism for the ring-closure of **3** to **4** and **4a** catalysed by 37% aqueous hydrochloric acid is outlined in Scheme 2. Protonation and a 1,3-H shift in **3** generates an intermediate **3a**, the cyclization of which by intramolecular nucleophilic attack followed by elimination of one molecule of water from the intermediate **9a** leads to intermediate **10**. This after deprotonation forms **4** or **4a**. The α,β-unsaturated ketone feature and one less bridgehead carbon in the structure of **4a** compared to **4** make the formation of the tetracyclic pentenone **4a** more energetically favourable than **4**. Therefore, the yield ratio of **4a** to **4** was 3 : 1.



Scheme 2

Experimental

General

Dry nitrogen was routinely used as the reaction atmosphere in all reactions. All glassware was baked at 80–100 °C for a minimum of 2 h prior to use. Melting points were obtained with an Electrothermal Melting Point apparatus and were uncorrected.

The ^{1}H and ^{13}C NMR spectra of approximately 10% (w/v) solutions in $CDCl_3$ were obtained at 270.05 MHz with a JEOL GX-270 WB NMR spectrometer. Chemical shifts are reported in parts per million (δ scale) with tetramethylsilane as an internal standard. NMR data are abbreviated as follows: coupling constants in Hz (*J*), singlet (s), broad singlet (br s), doublet (d), double doublet (dd), triplet (t) and multiplet (m). Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **3**, **4**, **4a**, **4b**, **4c**, **6**, **7** and **8** (17 pages) are available as a Supplementary publication [SUP No. 57129 (17 pages)].†

Mass spectra were recorded using a Nermag model R10–10C mass spectrometer with a resolution of 3300–5000.

Solvents routinely used such as tetrahydrofuran (Aldrich), diethyl ether and methylene dichloride were dried and distilled from CaH_2. Silica gel (230–400 mesh, Aldrich) for column chromatography was used for all product separations. Eastman chromagram (silica gel with fluorescent indicator on polyethylene) sheets were employed in thin-layer chromatography (TLC) separations.

Preparation of crude 7-methoxy-4-vinylchromanol 2

Freshly prepared 7-methoxychromanone[7] **1** (10 g, 56.2 mmol) was added to dry tetrahydrofuran (100 cm^3) in a round-bottomed flask (250 cm^3) cooled in a solid CO_2–acetone bath. The mixture was stirred for 5 min with a magnetic stirrer to give an homogeneous solution into which a solution of vinylmagnesium bromide in tetrahydrofuran (1 mol dm^3; 150 cm^3) was injected by a syringe under nitrogen. The mixture was magnetically stirred for a further 4 h, after which it was allowed to warm to room temperature and then poured, portionwise, onto stirred ice–water and extracted with diethyl ether (100 cm^3 × 4). The combined extracts were washed with distilled and deionized water (100 cm^3 × 2), dried ($MgSO_4$; 20 g) for 2 h and then evaporated to give crude compound **2** (11 g) as a yellow sticky liquid. This was stored in a refrigerator before use.

Preparation of 2-[2-(6-methoxychroman-4-ylidene)ethyl]-2-methylcyclopentane-1,3-dione 3

2-Methylcyclopentane-1,3-dione (7 g) and potassium hydrogen carbonate (0.1 g) were added to a solution of crude compound **2** (11 g) in ethanol (100 cm^3) in a round-bottomed flask (25 cm^3). The mixture was then stirred and heated under reflux for 15 h after which it was cooled to room temperature, poured onto 5% aqueous sodium hydrogen carbonate (200 cm^3) and extracted with benzene. The extract was washed with 5% aqueous sodium hydrogen carbonate, dried (Na_2SO_4; 15 g) for 3 h and evaporated. The residue was chromatographed on silica gel with diethyl ether–light petroleum ether as eluent to give pure compound **3** as a white crystalline product (75%, based on **1**) mp 110–111 °C; δ_H 1.16 (3 H, s, 2-CH_3), 2.40–2.80 (8 H, complex m, 3″-,1′-, 4- and 5-H), 3.76 (3 H, s, 7″-OCH_3), 4.12 (2 H, t, *J* 5.60, 2″-H), 5.64 (1 H, t, *J* 5.72, 2′-H), 6.35 (1 H, s, 8″-H), 6.46 (1 H, d, *J* 8.33, 6″-H) and 7.30 (1 H, d, *J* 8.29, 5″-H); δ_C 19.38 (2-CH_3), 25.69 (C-1′), 34.10 (C-3″), 35.56 (C-4, C-5), 55.28 (7″-OCH_3), 56.96 (C-2), 66.52 (C-2″), 101.51 (C-8″), 108.37 (C-6″), 112.14 (C-2′), 114.10 (C-4″), 124.76 (C-5″), 132.23 (C-4a″), 155.57 (C-8a″), 160.67 (C-7″) and 216.61 (C-1, C-3); *m*/*z* 300 (M^+, 21%) and 189 (M − 2-methylcyclopentane-1,3-dione, 100%).

† For details of the scheme see Instructions for Authors, *J. Chem. Soc., Perkin Trans 1*, 1996, Issue 1.

Cyclization of 3 to 3-methoxy-6-oxaestra-1,3,5(10),8(9),14(15)-pentaen-17-one 4 and 3-methoxy-6-oxaestra-1,3,5(10),8(9),15(16)-pentaen-17-one 4a

Freshly prepared seco dione **3** (10 g, 33.3 mmol) was added to ethanolic hydrochloric acid [ethanol (98 cm^3)–37% aqueous hydrochloric acid (2 cm^3)] in a round-bottomed flask (200 cm^3) equipped with a reflux condenser and a magnetic stirrer. The mixture was stirred and heated under reflux for 20 min and then allowed to cool to room temperature when it was transferred to a separation funnel (500 cm^3) containing water (200 cm^3). After being shaken for 10 min, the mixture was extracted with benzene (50 cm^3 × 4). The combined extracts were washed with water (150 cm^3), dried (Na_2SO_4; 10 g) for 2 h and concentrated on a rotary evaporator. The residue was chromatographed with diethyl ether–light petroleum as eluent to give pure compounds **4** and **4a** as white crystalline products after recrystallization from the eluent. Product **4** (24%), mp 145–146 °C; δ_H 1.16 (3 H, s, 13-CH_3), 1.58 (1 H, m, α- or β-12-H), 2.02 (1 H, m, β- or α-12-H), 2.60 (2 H, m, 11-H_2), 2.90 (1 H, d, *J* 22.50, α-16-H), 3.31 (1 H, d, *J* 22.35, β-16-H), 3.79 (3 H, s, 3-OCH_3), 4.80 (1 H, d, *J* 13.85, α-7-H), 4.95 (1 H, d, *J* 13.61, β-7-H), 5.72 (1 H, s, 15-H), 6.44 (1 H, s, 4-H), 6.50 (1 H, d, *J* 8.35, 2-H) and 7.13 (1 H, d, *J* 8.29, 1-H); δ_C 20.74 (13-CH_3), 21.58 (C-12), 27.07 (C-11), 41.90 (C-16), 48.84 (C-13), 55.43 (3-OCH_3), 64.87 (C-7), 101.84 (C-4), 107.48 (C-2), 114.33 (C-13), 116.70 (C-14), 118.75 (C-10), 124.32 (C-1), 127.74 (C-8), 143.60 (C-9), 155.52 (C-5), 160.89 (C-3), 218.53 (carbonyl C-17); *m/z* 282 (M^+, 100%) and 267 (M − CH_3, 65%). Product **4a** (71%), mp 153–154 °C; δ_H 1.18 (3 H, s, 13-CH_3), 1.50 (1 H, m, α-12-H), 1.90 (1 H, m, β-12-H), 2.60–3.00 (2 H, m, 11-H_2), 3.28 (1 H, d, *J* 23, 14-H), 3.88 (3 H, s, 3-OCH_3), 4.46 (1 H, d, *J* 13.56, α-7-*H*), 4.88 (1 H, d, *J* 13.19, β-7-H), 5.82 (1 H, s, 16-H), 6.55 (3 H, m, 2-H, 4-H and 15-H) and 7.08 (1 H, d, *J* 8.06, 1-H); δ_C 20.27 (13-CH_3), 25.02 (C-12), 27.74 (C-11), 41.75 (C-14), 48.45 (C-13), 55.46 (3-OCH_3), 63.26 (C-7), 104.96 (C-4), 109.36 (C-16), 114.70 (C-8), 114.77 (C-2), 114.90 (C-15), 121.58 (C-10), 129.09 (C-1), 143.78 (C-9), 156.22 (C-5), 157.66 (C-3), 219.19 (carbonyl C-17); *m/z* 282 (M^+, 100%), 267 (M − CH_3, 59%) and 213 (M − CH_3 − CH=CH–CH=O, 43%).

Ketalization of 4a to 3-methoxy-6-oxaestra-1,3,5(10),8(9),14(15)-pentaen-17-one ethylene acetal 4b

Ethylene glycol (20 cm^3) and toluene-*p*-sulfonic acid (0.2 g) were added to a solution of the tetracyclic pentaene **4a** (6 g, 21.3 mmol) in benzene (300 cm^3) and the solution was refluxed for 5 h while water was removed azeotropically. Removal of benzene afforded **4b** as a homogeneous fraction by TLC with diethyl ether–light-petroleum (1 : 4) as developer, mp 130–131 °C; yield 96%; δ_H 1.07 (3 H, s, 13-CH_3), 1.58–2.90 (6 H, complex m, 11-, 12- and 16-H), 3.78 (3 H, s, 3-OCH_3), 3.97 (4 H, m, 17-OCH_2CH_2O), 4.83 (2 H, dd, *J* 12.40, 13.20, α-7-H and β-7-H), 5.42 (1 H, s, 15-H), 6.41 (1 H, s, 4-H), 6.48 (1 H, d, *J* 8.46, 2-H) and 7.13 (1 H, d, *J* 8.45, 1-H); δ_C 19.02 (3-CH_3), 21.85 (C-16), 26.30 (C-12), 41.70 (C-11), 47.92 (C-13), 55.39 (3-OCH_3), 64.53 (C-7), 65.20, 65.35 (17-OCH_2CH_2O), 101.80, 107.30, 115.90, 117.19, 118.83, 119.28, 124.12, 127.05 (C-1, C-2, C-4, C-8, C-9, C-10, C-14 and C-15), 143.67 (C-17), 155.52 (C-5) and 160.67 (C-3); *m/z* 326 (M^+, 100%), 311 (M − CH_3, 2%), 298 (M − C=O, 5%), 281 (M − CH_2 − CH_2 − OH, 2%), 254 (M − C=O − C_2H_4O, 85%) and 239 (M − CH_3 − C=O − C_2H_4O, 70%).

Deketalization of 4b

A catalytic amount of toluene-*p*-sulfonic acid monohydrate was added to a solution of **4b** (6 g, 18.4 mmol) in acetone (200 cm^3) and the mixture was stirred at room temperature for 15 h. It was then transferred to a separatory funnel (1 dm^3) containing water (500 cm^3), shaken for 5 min and then extracted with benzene (100 cm^3 × 3). The combined extracts were washed with water (100 cm^3 × 2), dried (Na_2SO_4, 10 g), filtered and evaporated to give **4** (94%). This provided an homogeneous spot on a TLC plate (solvent system: diethyl ether–light petroleum ether, 1 : 4). The mp and ^1H NMR spectrum of this compound were identical with those of the earlier described preparation.

Monohydrogenation of 4b to 3-methoxy-6-oxaestra-1,3,5(10),8(9)-tetraen-17-one ethylene acetal 4c

A suspension of 10% palladium-on-charcoal (50 mg) in benzene (10 cm^3) was added to a purplish solution of **4b** (130 mg, 0.4 mmol) in benzene (10 cm^3) and the mixture was vigorously stirred at room temperature under a hydrogen atmosphere for 4 h. The catalyst was filtered off and washed with chloroform (20 cm^3) and the combined filtrate and washings were evaporated and the residue column chromatographed with diethyl ether–light petroleum (1 : 4) as eluent to give **4c** (72%). A pure sample was obtained as white crystals after recrystallization from diethyl ether, mp 167–168 °C; δ_H 1.11 (3 H, s, 13-CH_3), 1.20–2.70 (8 H, complex m, 11-, 12-, 15- and 16-H), 3.45 (1 H, m, 14-H), 3.75 (3 H, s, 3-OCH_3), 3.95 (4 H, br s, 17-OCH_2CH_2O), 4.55 (2 H, dd, *J* 11.73, 11.36, α- and β-H), 6.38 (1 H, s, 4-H), 6.53 (1 H, d, *J* 8.38, 2-H) and 7.12 (1 H, d, *J* 8.42, 1-H); δ_C 22.53 (13-CH_3), 22.60 (C-16), 25.78 (C-12), 26.54 (C-15), 32.05 (C-11), 35.09 (C-14), 46.53 (C-13), 55.13 (3-OCH_3), 64.70 (C-7), 65.43, 66.11 (17-OCH_2CH_2O), 101.38 (C-4), 107.34 (C-2), 118.27 (C-8), 119.72 (C-9), 122.75 (C-10), 127.27 (C-1), 140.18 (C-17), 155.00 (C-5) and 158.72 (C-3); *m/z* 328 (M^+, 100%), 313 (M − CH_3, 2%), 284 (M − CH_2CH_2O, 5%), 256 (M − C=O − C_2H_4O, 85%) and 239 (M − CH_3 − C=O − C_2H_4O, 71%).

Preparation of 3-methoxy-6-oxaestra-1,3,5(10),9(11)-tetraen-17-one 6 from 4

The pentaenone **4** (4 g, 14.2 mmol) dissolved in benzene (120 cm^3) was hydrogenated over a slurry of 5% palladium–calcium carbonate (3 g), which had been pre-equilibrated for at least 4 h with hydrogen at room temperature and atmospheric pressure. After 4 h, the catalyst was removed by filtration through Celite and thoroughly washed with chloroform. The combined filtrate and washings were evaporated and the residue was dissolved in ethanolic hydrochloric acid [ethanol (95 cm^3) + 37% aqueous hydrochloric acid (5 cm^3)]. After this solution had been refluxed for 15 h it was allowed to cool to room temperature whereupon it was poured onto water (400 cm^3) in a separatory funnel (1 dm^3) and extracted with benzene, (60 cm^3 × 3). The combined extracts were washed with water (50 cm^3 × 2), dried (Na_2SO_4, 15 g) for 3 h, filtered and evaporated under reduced pressure. The residue was column chromatographed with diethyl ether–light petroleum as eluent to give pure **6** as a white crystalline product after crystallization from the eluent, mp 179–180 °C; it afforded one spot on a TLC plate with diethyl ether–light petroleum as developer; δ_H 0.90 (3 H, s, 13-CH_3), 1.48–2.51 (8 H, complex m, 8-, 12-, 14-, 15- and 16-H), 3.63 (1 H, m, α-7-H), 3.69 (3 H, s, 3-OCH_3), 4.35 (1 H, m, β-7-H), 5.95 (1 H, s, 11-*H*), 6.30 (1 H, s, 4-H), 6.42 (1 H, d, *J* 8.79, 2-H) and 7.31 (1 H, d, *J* 8.42, 1-H); δ_C 14.92 (13-CH_3), 22.25 (C-16), 33.71 (C-15), 35.97 (C-12), 36.19 (C-14), 43.09 (C-8), 46.35 (C-13), 55.43 (3-OCH_3), 69.54 (C-7), 101.62 (C-4), 108.42 (C-2), 114.13 (C-10), 114.75 (C-11), 125.13 (C-1), 130.29 (C-9), 154.92 (C-5), 160.31 (C-3) and 220.06 (C-17); *m/z* 284 (M^+, 100%), 269 (M − CH_3, 36%) and 256 (M − C=O, 45%). Deketalization of **4c** followed by heating under reflux in ethanolic hydrochloric acid also afforded **6** whose melting point and ^1H NMR spectrum were identical with those described earlier.

Hydrogenation of 6 to 3-methoxy-6-oxaestra-1,3,5(10)-trien-17-one 7

Compound **7** was prepared by catalytic hydrogenation of **6** over 10% palladium–charcoal with the procedure described for the hydrogenation of **4b** to **4c**. Thus **6** (3 g, 10.6 mmol) after hydrogenation afforded pure **7** (2.36 g, 78%) as a white

crystalline product after crystallization from diethyl ether, mp 154–155 °C; it was homogeneous by TLC analysis with diethyl ether–light petroleum (1 : 3) as developer; δ_H 0.94 (3 H, s, 13-CH_3), 1.45–2.55 (11 H, complex m, 8-, 9-, 11-, 12-, 14-, 15- and 16-H), 3.76 (3 H, s, 3-OCH_3), 4.08–4.20 (2 H, m, α- and β-7-H), 6.39 (1 H, s, 4-H), 6.50 (1 H, d, *J* 8.42, 2-H) and 7.02 (1 H, d, *J* 8.39, 1-H); δ_C 16.58 (13-CH_3), 21.44 (C-16), 28.06 (C-12), 31.74 (C-15), 35.62 (C-11), 37.05 (C-14), 37.28 (C-8), 46.73 (C-13), 46.79 (C-9), 55.24 (3-OCH_3), 64.43 (C-7), 101.72 (C-4), 107.70 (C-2), 119.16 (C-10), 130.21 (C-1), 155.21 (C-5), 159.16 (C-3) and 219.26 (C-17); *m/z* 286 (M^+, 100%), 271 (M − CH_3, 34%), 258 (M − C=O, 45%) and 230 (M − C=O − C_2H_4, 43%).

Preparation of 7 from 4c

Sodium (10 mg), cut into small pieces, was added to dry liquid ammonia (30 cm^3) and ketalized **4c** (100 mg, 0.3 mmol) was quickly added to the blue solution that had been stirred vigorously for 10 min. The mixture was vigorously stirred for a further 30 min after which it was quenched carefully with dry ammonium chloride (50 mg). After evaporation of the ammonia, the residue was washed with water several times, dried and recrystallized from diethyl ether to give white crystalline **4d** (60 mg, 61%), mp 168–169 °C; *m/z* 330 (M^+, 100%). The product **4d** was then deketalized to give product **7**, the mp and ^1H NMR spectrum of which were identical with those obtained in an earlier preparation.

Demethylation of 7 to 3-hydroxy-6-oxaestra-1,3,5(10)-trien-17-one (6-oxaestrone) 8

Aluminium trichloride (1 g) was added to a solution of **7** (2 g, 7.0 mmol) in dry benzene (50 cm^3) and the mixture was stirred at 55 ± 5° for 30 min. It was then diluted with dry benzene (100 cm^3), thoroughly washed with water (100 cm^3 × 4), dried (Na_2SO_4) and evaporated. Chromatography of the residue with tetrahydofuran–light petroleum as eluent gave, after crystallization of the product from eluent, a white crystalline product **8** (1 g, 53%), mp 169–170 °C, which was homogeneous on a TLC plate with tetrahydrofuran–light petroleum (1 : 5) as developer; δ_H 0.82 (3 H, s, 13-CH_3), 1.20–2.60 (11 H, complex m, 8-, 9-, 11-, 12-, 14-, 15- and 16-H), 3.80–4.20 (2 H, m, α- and β-7-H), 6.12 (1 H, s, 4-H), 6.26 (1 H, d, *J* 6.0, 2-H), 6.85 (1 H, d, *J* 8.4, 1-H) and 9.11 (1 H, s, 3-OH); δ_C 16.55 (13-CH_3), 20.77 (C-16), 27.52 (C-12), 31.28 (C-15), 36.12 (C-14), 36.75 (C-8), 45.74 (C-9), 45.96 (C-13), 63.57 (C-7), 103.45 (C-4), 108.05 (C-2), 117.66 (C-10), 129.95 (C-1), 154.71 (C-5), 156.27 (C-3) and 218.72 (C-17); *m/z* 272 (M^+, 12%), 257 (M − CH_3, 20%), 243 (M − H − C=O, 20%), 229 (M − CH_3 − C=O, 11%) and 149 (100%).

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