Total synthesis of 3,17β-dihydroxy-6-oxaestra-1,3,5(10),7-tetraen and related miroestrol analogues

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3,17β-Dihydroxy-6-oxaestra-1,3,5(10),7-tetraen and related steroidal compounds have been synthesized in high yield via condensation of 7-methoxy-4-vinyl coumarin and 2-methyl-1,3-pentanedione. The approximate uterotrophic activity of the synthetic compounds relative to 17β-estradiol has been determined.

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On a synthétisé avec des rendements élevés les dihydroxy-3,17β oxa-6 estra tétraène-1,3,5(10),7 ainsi que des stéroides apparentés en faisant appel à la condensation de la méthoxy-7 vinyl-4 coumarin sur la méthyl-2 pentanedione-1,3. On a déterminé l'activité utérotrophique approximative des produits synthétiques par rapport à celle de l'estradiol-17β.

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While miroestrol **1**, one of the most potent naturally occurring estrogens discovered (1), has been the subject of two synthetic studies (2) no successful synthesis has been reported to date. Since the compound possesses the 6-oxa-7-ene feature we considered it of interest to synthesize some steroidal analogues possessing this novel B ring enol ether function for pharmacological evaluation. This paper reports an efficient total synthesis of 3,17β-dihydroxy-6-oxaestra-1,3,5(10),7-tetraen, **10***c*, and related compounds.

Our synthesis contains a variant of the Torgov approach (3) involving a Michael type addition of 2-methyl-1,3-cyclopentanedione on the key intermediate 7-methoxy-4-vinyl coumarin **4** leading to the tetracyclic 3-methoxy-6-oxaestra-1,3,5(10),8(9),15-pentaen-7,17-dione, **6**, which by further functional group manipulation gave the prototype target compound **10***a* in 24% overall yield from *m*-methoxyphenol, **2**.

The vinyl coumarin **4** was prepared by condensing *m*-methoxyphenol **2** with ethyl-4-chloroacetoacetate in the presence of concentrated H_2SO_4 to give 7-methoxy-4-chloromethyl coumarin **3***a* which was readily transformed into the triphenylphosphonium salt **3***b*. The latter underwent Wittig condensation with aqueous formaldehyde in the presence of Na_2CO_3 to provide crystalline 7-methoxy-4-vinylcoumarin, **4** in 68% overall yield from **2**.

Compound **4** can also be prepared by oxidation of 7-methoxy-4-methyl coumarin with SeO_2 in refluxing diglyme/benzene to 7-methoxy-4-formyl coumarin which after reduction to the corresponding alcohol, displacement with bromide ion, and triphenylphosphonium salt formation provided **3***c* and an alternate route to **4** in a 50% overall yield. Attempted direct conversion of 7-methoxy-4-formyl coumarin to **4** via Wittig reaction under a variety of conditions was unsuccessful (4).

Condensation of **4** with 2-methyl-1,3-cyclopentanedione in acetonitrile containing KF and 18-crown-6, under N_2, gave the seco steroid **5** in 68% yield. Cyclization of the latter to the α,β-unsaturated ketone **6** was achieved in 80% yield by refluxing with *p*-toluenesulfonic acid in benzene. The ^1H nmr spectrum of **6** shows two sets of double doublets, one at δ 6.20 ($J = 5$ Hz, $J = 2$ Hz) and the other at δ 7.80 ($J = 5$ Hz, $J = 3$ Hz) assigned to C(15)H and C(16)H and constituting an AMX system with C(14)H.

Chemical corroboration of the location of the double bond between C(15) and C(16) is derived from the bromination of **11***a* to **11***b* and the dehydrobromination of **11***b* to give a single product, identical to **6**. The cyclopentanone **11***a* can be obtained by sodium borohydride reduction of **6** to the alcohol **11***c* followed by oxidation with CrO_3/H_2SO_4 or by catalytic hydrogenation of **6**.

The C/D ring junction in **6** was shown to be *cis* via the following sequence: ketalization gave **7***b* (96% yield) whose ^1H nmr spectrum features a multiplet at δ 6.92 due to the olefinic C(15)H. Deketalization

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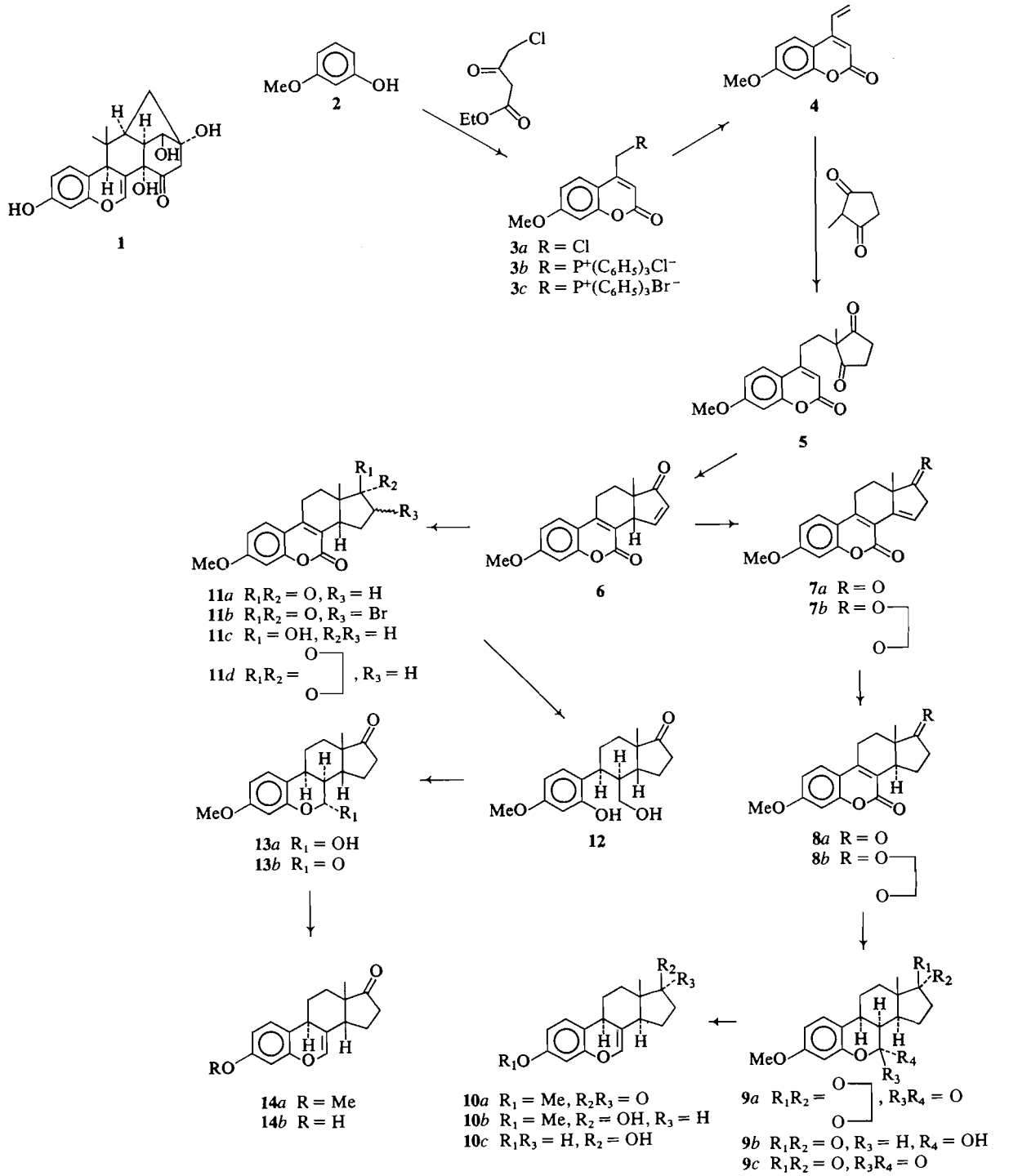

afforded the β,γ-unsaturated ketone **7***a* (96% yield) which on hydrogenation using 10% Pd/C in benzene gave the single tetraenone **8***a* in 93% yield, different from the isomer **11***a* obtainable by direct catalytic reduction of **6**. The *trans* C/D ring junction stereochemistry of **8***a* was confirmed by X-ray studies (5) on the reduction product **9***a* of its ketal **8***b* (*vide infra*). Development of the trans C/D ring junction via the H_2/Pd/C/benzene reducing medium has been successfully employed in similar steroidal systems (6).

Direct confirmation of the *cis* C/D ring junction in

TABLE 1. Uterotropic activity of miroestrol analogues

Compound (racemic)	No.	Uterotrophic activity relative to 17β-estradiol
8α-3-Methoxy-7-hydroxy-6-oxaestra-1,3,5(10)trien-17-one	**9***b*	Inactive
8α-3-Methoxy-6-oxaestra-1,3,5(10)-trien-7,17-dione	**9***c*	Slightly active
3-Methoxy-6-oxaestra-1,3,5(10),7-tetraen-17-one	**10***a*	Slightly active
3-Methoxy-6-oxaestra-1,3,5(10),7-tetraen-17β-ol	**10***b*	Slightly active
3-Hydroxy-6-oxaestra-1,3,5(10),7-tetraen-17β-ol	**10***c*	Quite active, but less than 17β-estradiol
14β-3-Methoxy-6-oxaestra-1,3,5(10),7-tetraen-17-one	**14***a*	Inactive

6 and **11***a* comes from X-ray diffraction studies (7) on the hemi-acetal ketone **13***a*, obtained by $Na_2Cr_2O_7$/DMSO oxidation of the major Li/NH_3 reduction product **12** of **11***d*, which revealed the existence of the *cis–anti–cis* ring junction stereochemistry for **13***a*. The ethylene ketal of dione **13***b* was also obtained (17%) in the reduction of **11***d* by Li/NH_3.

Compound **14***a* was obtained in quantitative yield from **13***a* by dehydration with *p*-toluenesulfonic acid in refluxing benzene while **14***b* was available directly from **13***a* in 85% yield by treatment with boron tribromide in dichloromethane at 0°C.

With the stereochemistry of the C/D ring junction now under rigorous control, the α,β-unsaturated lactone ketal **8***b* was transformed into the saturated lactone ketal **9***a* in 93% yield by means of Li/NH_3. Further reduction with one equivalent of diisobutylaluminum hydride at −70°C followed by acidic work up gave the crystalline hemi-acetal ketone **9***b* (85% yield). The ^1H nmr spectrum of the latter shows a doublet at δ 5.60 (J = 9 Hz) indicative of a *trans* diaxial relationship of C(7)H/C(8)H.

The keto lactone **9***c* was prepared in quantitative yield by deketalization of **9***a* using *p*-toluenesulfonic acid in acetone.

Dehydration of **9***b* using *p*-toluenesulfonic acid–benzene gave a quantitative yield of the 6-oxa-7-ene steroid **10***a* whose ^1H nmr spectrum displays a signal at δ 6.23 for the vinylic C(7)H. Infrared absorptions at 1730 and 1685 cm^{-1} attest to the presence of five-membered ketone and vinyl ether functionalities. 17β-Hydroxy-3-methoxy-6-oxaestra-1,3,5(10)7-tetraen, **10***b*, was obtained from **10***a* in quantitative yield by reduction with sodium borohydride in benzene/methanol. The ^1H nmr spectrum displays a signal at δ 3.80 (t, J = 8 Hz) characteristic (8) of the α configuration for C(17)H. Demethylation of **10***b* to 3,17β-dihydroxy-6-oxaestra-1,3,5(10),7-tetraen, **10***c*, was accomplished in 68% yield by heating it at 180–190°C with CH_3MgI. Attempted demethylation of **10***b* using boron tribromide led to intractable mixtures.

The racemic compounds **9***b*, **9***c*, **10***a*, **10***b*, **10***c*, and **14***a* prepared by this route have been tested for uterotrophic activity using the procedure of Rubin *et al.* (9) with minor modification and the results are contained in Table 1. Compound **10***c* was the most potent of the series but less active than 17β-estradiol. Herr *et al.* (10) have shown that the Δ^7-estrogens are more active than those which are saturated in ring B. The results indicate that formation of 6-cyclo-ether analogues of Δ^7-estrogens results in a decrease of uterotrophic activity.

Experimental

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Mass spectra were obtained with an Hitachi-Perkin-Elmer RMU-6D spectrometer. The ^1H nmr spectra were recorded in $CDCl_3$ with a Varian T-60 instrument employing tetramethylsilane as internal standard. Line positions are reported in ppm from this standard. The ir spectra were recorded with a Perkin-Elmer 457 grating infrared spectrophotometer.

7-Methoxy-4-chloromethylcoumarin, 3a from 2

Concentrated H_2SO_4 (200 mL) in a two necked 1-L round bottom flask fitted with dropping funnel and thermometer was cooled below 10°C and a mixture of *m*-methoxyphenol (10 g, 81 mmol) and ethyl 4-chloroacetoacetate (13.15 g, 85 mmol) was slowly added to the stirred solution maintaining the temperature below 15°C. The mixture was then stirred at room temperature for 15 h and the reaction mixture poured into ice/water (800 mL) with vigorous stirring. The precipitated product was filtered off and washed with water to neutrality and then treated with aqueous 5% NaOH (80 mL) to remove phenolic impurities. The residue was washed with water (3 × 50 mL) affording white crystalline 7-methoxy-4-chloromethylcoumarin **3***a* (17.02 g, 94%). Recrystallization from ethanol gave analytically pure material mp 195°C. *Anal.* calcd. for $C_{11}H_9O_3Cl$: C 58.79, H 4.01; found: C 58.48, H 4.30. The mass spectrum *m/e* 226 (32, $M+2$), 224 (100, M^+), 196 (43, $M-CO$), 189 (26, $M-Cl$), 161 (36). The ^1H nmr spectrum δ_{TMS} ($CDCl_3$): 3.90 (s, 3H, CH_3O), 4.63 (s, 2H, $ClCH_2$—), 6.40 (s, 1H, C(3)H), 6.80–7.67 (m, 3H, aromatic). The ir spectrum ν_{max} (KBr): 1725 (carbonyl), 1610 (aromatic), 1400, 1357, 1294, 1269, 1219, 1144, 1061, 1030, 1000, 880, 859, 831 cm^{-1}.

((7-Methoxy-2-oxo-2H-1-benzopyran-4-yl)methyl)triphenylphosphonium Bromide 3c

A mixture of 7-methoxy-4-bromomethylcoumarin (**4**) (0.25 g, 0.93 mmol) and triphenylphosphine (0.24 g, 0.95 mmol) was suspended in dry acetonitrile (15 mL). The mixture was stirred and refluxed under N_2 and the suspended mixture dissolved after 30 min. Refluxing was continued for 18 h, during which

time the white phosphonium salt precipitated. The mixture was cooled, filtered, and the salt **3***c* was washed several times with boiling benzene, then dried *in vacuo*, affording pure product (0.44 g, 90%) mp 272–274°C. The product was also obtained (79%) when benzene was used instead of acetonitrile as reaction solvent.

*((7-Methoxy-2-oxo-2*H*-1-benzopyran-4-yl)methyl)triphenylphosphonium Chloride* **3**b

The phosphonium chloride salt **3***b* was prepared in 82% yield from chloromethylcoumarin **3***a* and excess triphenylphosphine in acetonitrile as previously described for the phosphonium bromide salt **3***c*. The salt, a white powder, was dried *in vacuo* and melted at 266–268°C.

7-Methoxy-4-vinylcoumarin **4** *from* **3**c

(*a*) The triphenylphosphonium bromide **3***c* (0.61 g, 1.14 mmol) was suspended in 37% formaldehyde (2.2 mL). A solution of 15% Na_2CO_3 (1.5 mL) was added intermittently by a dropping funnel. Each subsequent addition was made after the orange-yellow color of the phosphorane formed had disappeared. When the addition of the base was complete, the mixture was stirred at room temperature for 2 h. The suspended white crystalline product containing triphenylphosphine oxide by-product was extracted three times with ether (100, 50, and 30 mL). The ethereal layer was dried (anhydrous Na_2SO_4) and evaporated. The white residue obtained was chromatographically purified on a short column of silica gel. Elution with ethyl acetate – cyclohexane (2:5) gave pure white crystalline vinylcoumarin **4** (0.20 g, 98%), mp 98°C. Attempts to recrystallize this compound in several solvents were unsuccessful.

Anal. calcd. for $C_{12}H_{10}O_3$: C 71.30, H 4.95; found: C 70.80, H 5.07. The mass spectrum *m/e*: 202 (100, M^+), 174 (78, $M - CO$), 159 (62, $M - CO - CH_3$). The ^1H nmr spectrum δ_{TMS} ($CDCl_3$): 3.90 (s, 3H, CH_3O—), 5.63–6.12 (m, 2H, vinylic), 6.30 (s, 1H, C(3)H), 6.43–7.71 (complex m, 4H, aromatic and vinylic). The ir spectrum ν_{max} (KBr): 1720 (C=O), 1610, 1500, 1155, 861, 814 cm^{-1}.

(*b*) Vinylcoumarin **4** was synthesized as described above in 91% yield from phosphonium chloride salt **3***b* instead of phosphonium bromide salt **3***c*.

3-Methoxy-8,14-seco-6-oxaestra-1,3,5(10),8-tetraen-7,14,17-trione **5** *from* **4**

To a stirred solution of 18-crown-6 (80 mg) in acetonitrile (15 mL) was added KF (310 mg) and the mixture was dried by heating *in vacuo* at 135°C for 1.5 h. Vinylcoumarin **4** (1.73 g, 8.56 mmol) and 2-methylcyclopentane-1,3-dione (1.10 g, 9.81 mmol) were then added to the stirred mixture. The mixture was refluxed under N_2 and the suspended material dissolved. The mixture was refluxed overnight and the resulting white precipitate containing excess diketone reagent was removed by filtration while the reaction mixture was hot. The precipitate was washed with acetonitrile (2 × 10 mL). The filtrate and the washings were combined and acetonitrile was evaporated under reduced pressure. The residue was dissolved in chloroform (100 mL) and washed with 5% $NaHCO_3$ (2 × 20 mL) to remove excess cyclopentanedione. The organic layer was worked up in the usual manner. The pale orange residue was purified by chromatography on silica gel (100 g). Elution with ethyl acetate – cyclohexane (1:2) furnished the pale orange crystalline seco-steroid **5** (1.83 g, 68%). An analytical sample recrystallized from ethyl acetate had mp 128°C.

Anal. calcd. for $C_{18}H_{18}O_5$: C 68.80, H 5.73; found: C 68.14, H 5.66. The mass spectrum *m/e*: 314 (100, M^+), 277 (17), 203 (64, M – H – methylcyclopentanedione), 202 (67, M – methylcyclopentanedione), 190 (29), 174 (36). The ^1H nmr spectrum δ_{TMS} ($CDCl_3$): 1.23 (s, 3H, CH_3—), 1.85–2.30 (m, 2H, C(12)H), 2.40–2.73 (m, 2H, C(13)H), 2.90 (s, 2H, C(15)H and C(16)H), 3.90 (s, 3H, CH_3O—), 6.07 (s, 1H, C(8)H), 6.79–7.98 (m, 2H, aromatic C(2)H and C(4)H), 7.53 (d, J = 8 Hz, 1H, aromatic C(1)H). The ir spectrum ν_{max} (KBr): 1718 (broad, lactone, ketone, C=O), 1612, 1429 cm^{-1}.

*14*β*-3-Methoxy-6-oxaestra-1,3,5(10),8,15-pentaen-7,17-dione* **6** *from* **5**

The secosteroid **5** (2.24 g, 7.13 mmol) was suspended in dry benzene (20 mL) and *p*-toluenesulfonic acid monohydrate (430 mg) was added to the mixture. The mixture was stirred and refluxed under N_2 for 15 h. Water was removed azeotropically employing a Dean–Stark trap filled with Linde molecular sieves, type 5A. The resulting reddish brown mixture was cooled and diluted with benzene (20 mL). The mixture was then washed with 5% $NaHCO_3$ (2 × 20 mL) to remove *p*-toluenesulfonic acid. The organic layer after drying (anhydrous Na_2SO_4) and evaporation gave a reddish brown residue which was chromatographed on a silica gel (100 g) column and elution with ethyl acetate – cyclohexane (2:5) afforded **6** (1.69 g, 80%), mp 143–145°C (recrystallized from ethyl acetate). An analytical sample was homogeneous on tlc and proved to be sensitive to light and moist air resulting in a bright purple color.

Anal. calcd. for $C_{18}H_{16}O_4$: C 72.97, H 5.40; found: C 72.61, H 5.40. The mass spectrum *m/e*: 296 (100, M^+), 281 (13, $M - CH_3$), 269 (12), 268 (76, M – CO), 253 (21). The ^1H nmr spectrum δ_{TMS} ($CDCl_3$): 12.7 (s, 3H, CH_3—), 1.40–3.33 (complex m, 6H), 3.90 (s, 3H, CH_3O—) 6.20 (q, 1H, J = 5 Hz, J = 2 Hz, C(15)H), 6.90 (m, 2H, aromatic C(2)H and C(4)H), 7.48 (d, J = 8 Hz, 1H, aromatic C(1)H), 7.80 (q, 1H, J = 5 Hz, J = 3 Hz, C(16)H). The ir spectrum ν_{max} (KBr): 1730 (shoulder, ketone C=O), 1710 (broad, lactone C=O), 1615, 1520, 1460 cm^{-1}.

3-Methoxy-6-oxaestra-1,3,5(10),8,14-pentaen-7-oxo-17-ethylene acetal **7**b *from* **6**

To a solution of tetracyclic pentaene **6** (1 g, 3.38 mmol) in benzene (50 mL) was added ethylene glycol (3 mL) and *p*-toluenesulfonic acid (30 mg). The solution was refluxed (while water was removed azeotropically) for 4 h and then cooled to room temperature. The solution was diluted with benzene (50 mL) and the organic layer was evaporated to give the ketal **7***b* in 96% yield, homogeneous on tlc. An analytical sample was recrystallized from ethyl acetate (mp 168°C).

Anal. calcd. for $C_{20}H_{20}O_5$: C 70.59, H 5.88; found: C 70.70, H 5.92. The ^1H nmr spectrum δ_{TMS} ($CDCl_3$): 1.06 (s, 3H, CH_3—), 1.50–3.26 (complex m, 6H), 3.86 (s, 3H, CH_3O—), 4.00 (s, 4H, —OCH_2CH_2O—), 6.92 (m, 1H, C(15)H), 6.84 (m, 2H, aromatic C(2)H and C(4)H), 7.43 (d, J = 8 Hz, 1H, aromatic C(1)H). The ir spectrum ν_{max} (KBr): 1725 (lactone C=O), 1620, 1600 (aromatic), 1300, 1160, 1030, 885, 850, 810 cm^{-1}. The uv spectrum (95% EtOH) λ_{max} nm (ε_{max}): 221 (22 422), 250 (13 918), 350 (25 773).

3-Methoxy-6-oxaestra-1,3,5(10),8,14-pentaen-7,17-dione **7**a

A solution of the tetracyclic ketal **7***b* (1 g, 2.94 mmol) in acetone (30 mL) was treated with a catalytic amount of *p*-toluenesulfonic acid monohydrate. The solution was stirred overnight at room temperature. Most of the product precipitated out of the solution and this fraction was filtered out and washed with 5% $NaHCO_3$ and water to give a pure product **7***a*. The filtrate was concentrated and diluted with benzene (50 mL). The organic layer was washed with 5% $NaHCO_3$ (20 mL) and water. The dried organic layer was evaporated to give a crude residue which was purified on silica gel column and eluted with *n*-hexane – ethyl acetate (1:1). The two fractions were combined to give a total yield of the pentaendione **7***a* (0.835 g, 96%). An analytical sample was recrystallized in acetone – petroleum ether (2:1) to give light orange crystals (mp 212°C dec.).

The mass spectrum *m/e*: 296 (65, M^+), 269 (19, $M^+ - CH_2{=}CH$), 268 (100, $M^+ - CO$), 267 (12), 253 (26), 240 (13), 239 (13). The ^1H nmr spectrum δ_{TMS} ($CDCl_3$): 1.17 (s, 3H, CH_3—), 1.44–3.33 (complex m, 6H), 3.90 (s, 3H, CH_3O—), 6.90 (multiplet, 2H, aromatic C(2)H and C(4)H), 7.03 (t, J = 2 Hz, 1H, C(15)H), 7.60 (d, J = 8 Hz, 1H, aromatic C(1)H). The ir spectrum ν_{max} (KBr): 1746 (ketone C=O), 1710 (α,β-unsaturated lactone C=O), 1625, 1610, 1595 (aromatic), 1460, 1450, 1400, 1290, 1260, 1210, 1170, 1140, 1030, 830, 820 cm^{-1}. The uv spectrum (95% EtOH) λ_{max} nm (ε_{max}): 216 (18 179), 247 (8 848), 350 (18 179).

3-Methoxy-6-oxaestra-1,3,5(10),8-tetraen-7,17-dione **8***a from* **7**a

A suspension of 10% palladium on charcoal (50 mg) in sulfur-free benzene (10 mL) was degassed and saturated with H_2. To this catalyst mixture was added a purplish solution of the tetracyclic pentaen **7***a* (100 mg, 0.34 mmol) in benzene (15 mL). The mixture was vigorously stirred and hydrogenation was stopped after about 7 mL of H_2 (required to saturate one double bond) was absorbed. The catalyst was filtered and the clear solution evaporated to dryness to give pure tetraen dione **8***a* (0.094 g, 93%). An analytical sample was recrystallized from benzene to afford white crystals, mp 223–225°C.

Anal. calcd. for $C_{18}H_{18}O_4$: C 72.48, H 6.04; found: C 72.70, H 6.09. The mass spectrum *m/e*: 299 (15, M + 1), 298 (100, M^+), 270 (19, $M^+ - CO$), 255 (50), 243 (39), 242 (55), 241 (44), 229 (28), 227 (20). The ^1H nmr spectrum δ_{TMS} ($CDCl_3$): 0.90 (s, 3H, CH_3O—), 6.90 (m, 2H, aromatic C(2)H and C(4)H), 7.50 (d, J = 8 Hz, 1H, aromatic C(1)H). The ir spectrum ν_{max} (KBr): 1735 (ketone C=O), 1720 (lactone C=O), 1620, 1610 (aromatic), 1510, 1450, 1395, 1295, 1275, 1260, 1230, 1215, 1185 cm^{-1}. The uv spectrum (95% EtOH) λ_{max} nm (ε_{max}): 225 (11 569), 328 (14 204).

3-Methoxy-6-oxaestra-1,3,5(10),8-tetraen-7-oxo-17-ethylene Acetal **8**b *from* **8**a

The tetracyclic ketone **8***a* was ketalized as described in the procedure for compound **7***b* to give the ketal **8***b* in 88% yield. Analytical sample was recrystallized in acetone to give white crystals, mp 184°C. The ^1H nmr spectrum δ_{TMS} ($CDCl_3$): 0.87 (s, 3H, CH_3—), 1.50–3.23 (complex m, 9H), 3.87 (s, 3H, CH_3O—), 3.95 (s, 4H, —OCH_2CH_2O—), 6.42 (m, 2H, aromatic C(2)H and C(4)H), 7.47 (d, J = 8 Hz, 1H, aromatic C(1)H). The ir spectrum ν_{max} (KBr): 1710 (broad lactone C=O), 1610, 1385, 1320, 1300, 1285, 1200, 1160 (broad), 1070 (broad), 970, 855, 810, 790, 780 cm^{-1}. The mass spectrum *m/e*: 342 (17, M^+), 298 (98, $M^+ - CH_2CH_2O$—), 283 (18, $M^+ - CH_2CH_2O + CH_3$), 270 (21, $M^+ - CH_2CH_2O - CO$), 256 (42), 255 (20), 243 (88), 242 (100), 241 (93), 227 (47), 226 (25).

8α-3-Methoxy-6-oxaestra-1,3,5(10)-trien-7-oxo-17-ethylene Acetal **9**a *from* **8**b

Into dry liquid ammonia (300 mL) was added lithium (45 mg), cut into small pieces. The deep blue solution thus formed was stirred vigorously with a magnetic stirrer for 10 min and a suspension of ketalized tetraen **8***b* (1 g, 2.92 mmol) in anhydrous ether (75 mL) was quickly added. The mixture was vigorously stirred for an additional 30 min and quenched with dry NH_4Cl (500 mg) carefully. The ammonia condenser was removed and ammonia allowed to evaporate in a stream of nitrogen. The residual ammonia and ether were evaporated under reduced pressure. The white residue was treated with 5% NaOH solution (25 mL) to remove over-reduced phenolic material. The mixture was stirred, filtered, and washed with water several times and dried. The white crystalline triene **9***a* (0.94 g, 93%) was recrystallized from benzene to give white needles, mp 164°C.

Anal. calcd. for $C_{20}H_{24}O_5$: C 69.76, H 6.97; found: C 69.36, H 6.82. The mass spectrum *m/e*: 344 (88, M^+), 259 (18), 258 (100), 256 (21), 190 (18), 177 (27), 139 (54). The ^1H nmr spectrum δ_{TMS} ($CDCl_3$): 1.00 (s, 3H, CH_3—), 1.33–3.00 (complex m, 11H), 3.80 (s, 3H, CH_3O—), 3.90 (s, 4H, OCH_2CH_2O), 6.63 (m, 2H, aromatic C(2)H and C(4)H), 7.70 (d, J = 8 Hz, 1H, aromatic C(1)H). The ir spectrum ν_{max} (KBr): 1770 (lactone C=O), 1630, 1600 (aromatic), 1515, 1460, 1285, 1240, 1170, 1150 (broad), 1040, 985, 850 cm^{-1}.

8α-3-Methoxy-6-oxaestra-1,3,5(10)-trien-7,17-dione **9**c

The tetracyclic ketal **9***a* was deketalized by stirring in acetone with a catalytic amount of *p*-toluenesulfonic acid monohydrate overnight to give a quantitative yield of the tetracyclic dione **9***c*. An analytical sample was recrystallized from benzene to give white crystals, mp 171°C.

The mass spectrum *m/e*: 301 (20, M + 1), 300 (100, M^+), 229 (18), 216 (14), 215 (12), 177 (27), 176 (20), 163 (24), 150 (38), 148 (20), 137 (31), 124 (20). The ^1H nmr spectrum δ_{TMS} ($CDCl_3$): 1.00 (s, 3H, CH_3—), 1.33–3.23 (complex m, 11H), 3.80 (s, 3H, CH_3O—), 6.60–6.80 (m, 2H, aromatic C(2)H and C(4)H), 7.10 (d, J = 8 Hz, 1H, aromatic C(1)H). The ir spectrum ν_{max} (KBr): 1770 (lactone C=O), 1730 (ketone C=O), 1620, 1590 (aromatic), 1510 (broad), 1450, 1430, 1360, 1330, 1278, 1240, 1201, 1170, 1130 (broad), 1055, 1035, 975, 876, 835 cm^{-1}. The uv spectrum (95% EtOH) λ_{max} nm (ε_{max}): 220 (11 491), 280 (2 771), 285 (2 608).

8α-3-Methoxy-7-hydroxy-6-oxaestra-1,3,5(10)-trien-17-one **9**b *from* **9**a

Into an oven dried pear-shaped flask was added the ethylene ketal lactone **9***a* (0.1 g, 0.29 mmol) and dry toluene (5 mL). The solution was cooled to −70°C and a 1 *M* diisobutylaluminium hydride solution (0.3 mL) was added from a syringe through a septum. The reaction mixture was stirred for 20 min at −70°C and then quenched with methanol (0.5 mL). The mixture was allowed to warm to 0°C and cold 5% HCl (20 mL) was added. The product was extracted twice with chloroform (30 ml, 25 ml) and the organic layer was washed with water twice and dried with $MgSO_4$. Evaporation of the solvent left white crystals which were subsequently deketalized as before affording pure white tetracyclic hemiacetal **9***b* in 85% yield. Recrystallization in ethyl acetate – *n*-hexane (2:1) afforded white needles melting at 175°C.

Anal. calcd. for $C_{18}H_{22}O_4$: C 71.52, H 7.28; found: C 71.56, H 7.30. The mass spectrum *m/e*: 302 (45, M^+), 164 (15), 163 (93), 161 (19), 150 (100), 137 (33). The ^1H nmr spectrum δ_{TMS} ($CDCl_3$): 1.07 (s, 3H, CH_3—), 1.40–3.00 (complex m, 11H), 3.87 (s, 3H, CH_3O—), 5.60 (t, J = 6 Hz, 1H, C(7)H; D_2O added, d, J = 9 Hz), 6.43 (m, 2H, aromatic C(2)H and C(4)H), 6.60 (d, J = 7 Hz, 1H, C(7)OH), 7.00 (d, J = 8 Hz, 1H, aromatic C(1)H). The ir spectrum ν_{max} (KBr): 3420 (OH), 1730 (ketone C=O), 1620, 1590, 1510, 1460, 1450, 1340, 1275, 1200, 1180, 1160, 1124, 1040, 1000, 935, 830 cm^{-1}.

3-Methoxy-6-oxaestra-1,3,5(10),7-tetraen-17-one **10**a *from* **9**b

To a solution of the tetracyclic hemiacetal **9***b* (0.1 g, 0.33 mmol) in benzene (15 mL) was added *p*-toluenesulfonic acid monohydride (30 mg). The mixture was refluxed azeotropically under nitrogen for 1 h. The mixture was cooled to room temperature and diluted with benzene (30 mL). It was washed with 5% $NaHCO_3$ (20 mL), with water, and then dried. Evaporation of the solvent gave a pure white crystalline tetracyclic vinyl ether **10***a* in quantitative yield. A sample was recrystallized from ethyl acetate – *n*-hexane (1:1) giving white crystals, mp 175°C.

Anal. calcd. for $C_{18}H_{20}O_3$: C 76.05, H 7.04; found: C 75.93, H 7.14. The mass spectrum *m/e*: 284 (100, M^+), 269 (9, $M^+ - CH_3$), 256 (35, $M^+ - CO$), 255 (39), 241 (67), 228 (34), 227 (26), 213 (22), 188 (23), 187 (40), 160 (27). The ^1H nmr spectrum δ_{TMS} ($CDCl_3$):

0.87 (s, 3H, CH_3—), 1.23–2.70 (complex m, 9H), 3.23 (broad m, 1H, benzylic), 3.80 (s, 3H, CH_3O—), 6.23 (t, J = 2 Hz, 1H, C(7)H), 6.60 (m, 2H, aromatic C(2)H and C(4)H), 7.05 (d, J = 8 Hz, 1H, aromatic C(1)H). The ir spectrum ν_{max} (KBr): 1730 (ketone C=O), 1685 (medium, vinyl ether O—CH=C), 1615, 1575, 1500, 1440, 1250, 1240, 1210, 1205, 1175, 1150, 1125, 1040, 935, 860, 830 cm^{-1}. The uv spectrum (95% EtOH) λ_{max} nm (ε_{max}): 225 (11 410), 250 (5 167), 290 (4 629).

3-Methoxy-6-oxaestra-1,3,5(10),7-tetraen-17β-ol ***10b*** *from* ***10a***

To a solution of the tetracyclic ketone **10*a*** (0.412 g, 1.45 mmol) in benzene (15 mL) was added methanol (15 mL). The solution was cooled in an ice-water bath and sodium borohydride (100 mg) was added at once. The mixture was stirred for 5 min and gradually allowed to warm to room temperature. After 45 min the mixture was poured into ice-cold 5% HCl solution (20 mL) and the product was extracted with benzene and the organic layer washed twice with water and dried with $MgSO_4$. Evaporation of the solvent left a white crystalline alcohol **10*b*** (96% yield), pure by ^1H nmr spectrum. A sample was recrystallized from ethyl acetate – *n*-hexane (2:1) to give white crystals melting at 124°C.

Anal. calcd. for $C_{18}H_{22}O_3$: C 75.52, H 7.69; found: C 75.96, H 7.56. The mass spectrum *m/e*: 286 (100, M^+), 257 (50), 241 (49), 187 (82), 161 (48), 137 (25). The ^1H nmr spectrum δ_{TMS} ($CDCl_3$): 0.73 (s, 3H, CH_3—), 1.20–2.50 (complex m, 10H), 3.17 (broad m, 1H, benzylic), 3.80 (s, 3H, CH_3O—), 3.80 (t, 1H, C(17)H), 6.10 (t, J = 2 Hz, 1H, C(7)H), 6.33–6.60 (m, 2H, aromatic C(2)H and C(4)H), 7.00 (d, J = 8 Hz, 1H, aromatic C(1)H). The ir spectrum ν_{max} (KBr): 3420 (broad, OH), 1700 (weak, vinyl ether O—CH=C), 1620, 1585 (aromatic), 1510, 1450, 1210, 1200, 1180, 1135, 1040, 940, 865, 840 cm^{-1}.

3-8Hydroxy-6-oxaestra-1,3,5(10),7-tetraen-17β-ol ***10c*** *from* ***10b***

To methylmagnesium iodide (1.59 mmol) in anhydrous ether (20 mL) was added methyl ether **10*b*** (0.228 g, 0.80 mmol) under nitrogen. The mixture was stirred and ether was removed with a stream of nitrogen. The solid mixture was heated at 180–190°C for 3 h. The mixture was cooled to room temperature and hydrolysed with ice-cold 5% HCl (25 mL). The product was extracted with chloroform (20 mL × 4) and the organic layer was washed several times and dried with $MgSO_4$. Evaporation of the solvent left a crude brown residue which was purified by silica gel preparative tlc (using ethyl acetate – *n*-hexane (1:1)) to give yellowish crystals of the diol **10*c*** (0.148 g, 68%). An analytical sample was recrystallized from 95% ethanol to give white needles, mp 196–201°C (dec.).

The mass spectrum *m/e*: 272 (95, M^+), 243 (48, M^+ – CHO), 227 (35), 173 (100), 147 (52), 123 (24). The ^1H nmr spectrum δ_{TMS} ($CDCl_3$–DMSO-d_6, two drops): 0.73 (s, 3H, CH_3—), 1.00–3.33 (complex m, 9H), 3.33 (broad m, 1H, benzylic C(9)H), 3.80 (broad m, 1H, C(17)OH), 6.10 (broad s, 1H, C(7)H), 6.33–6.60 (m, 2H, aromatic C(2)H and C(4)H), 7.00 (d, J = 8 Hz, 1H, aromatic C(1)H), 8.70 (s, 1H, phenolic OH). The ir spectrum ν_{max} (KBr): 3410 (OH), 3240 (broad, phenolic OH), 1700 (weak, vinyl ether O—CH=C), 1620 (aromatic), 1510, 1460, 1350, 1260, 1180 (sharp), 1135, 1050 cm^{-1}.

14β-3-Methoxy-6-oxaestra-1,3,5(10),8-tetraen-7,17-dione ***11a*** *from* ***6***

Into a 100 mL round-bottomed flask was added 10% Pd/C (100 mg) and dry benzene (15 mL). The mixture was degassed by pumping at reduced pressure and prehydrogenated. A solution of the tetracyclic pentaene **6** (200 mg, 0.68 mmol) in dry benzene (915 mL) was added at once to the catalyst–benzene mixture in a hydrogen atmosphere. The mixture was stirred until one equivalent of hydrogen was absorbed (~15 min). The catalyst was filtered and removal of benzene under reduced pressure gave white crystalline tetracyclic tetraen **11*a*** (200 mg, 98%). An analytical sample, crystallized from benzene–cyclohexane (1:1), had mp 156–159°C.

Anal. calcd. for $C_{18}H_{18}O_4$: C 72.48, H 6.04; found: C 72.11, H 6.06. The mass spectrum *m/e*: 298 (100, M^+), 283 (15, M – CH_3), 270 (16, M – CO), 255 (17), 244 (50), 243 (50), 242 (38), 227 (38). The ^1H nmr spectrum δ_{TMS} ($CDCl_3$): 1.10 (s, 3H, CH_3—), 1.39–3.32 (complex m, 9H), 3.90 (s, 3H, CH_3O—), 6.83–7.00 (m, 2H, aromatic C(2)H and C(4)H), 7.50 (d, J = 8 Hz, 1H, aromatic C(1)H). The ir spectrum ν_{max} (KBr): 1730 (shoulder ketone C=O), 1701 (lactone C=O) cm^{-1}.

14β-3-Methoxy-6-oxaestra-1,3,5(10),8-tetraen-7,17-dione ***11a***

The chromic acid solution (prepared by dissolving CrO_3 (5.298 g) in 10 mL water and then adding H_2SO_4 (5 mL)) was added to a cooled (20°C) solution of the tetracyclic alcohol **11*c*** (0.5 g, 1.67 mmol) in acetone (15 mL). The oxidizing solution (1 mL) was added dropwise, so that the temperature of the reaction mixture did not exceed 35°C. The addition was stopped when the orange color of the oxidizing solution persisted. The mixture was stirred for 30 min and excess oxidant was destroyed with isopropyl alcohol (1/2 mL). The liquid was decanted and the green salts washed with acetone (30 mL) twice. To the combined washings was added $NaHCO_3$ until the solution was neutral. The mixture was filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (50 mL) and washed with water, saturated sodium chloride solution, and dried with $MgSO_4$. Evaporation of the solution left a residue which was recrystallized to give white crystals of the ketone **11*a*** (0.408 g) in 82% yield, identical with material obtained by catalytic reduction of **6**.

The uv spectrum (95% EtOH) λ_{max} nm (ε_{max}): 222 (11 455), 323 (20 124).

14β-3-Methoxy-16-bromo-6-oxaestra-1,3,5(10),8-tetraen-7,17-dione ***11b***

A solution of the tetracyclic ketone **11*a*** (0.469 g, 1.57 mmol) in dry THF (15 mL) cooled in an ice-water bath was stirred and bromine (0.25 g) in methylene chloride (5 mL) was added dropwise, keeping the temperature of the reaction mixture below 10°C. The yellow mixture was then stirred for 1 h and the reaction was found to be complete on tlc. The mixture was treated with 10 mL of 5% $NaHCO_3$ and then cold water (50 mL) was added. The product was extracted twice with methylene chloride (100 mL, 50 mL). The combined organic layer was washed once with water and dried. Evaporation of the solvent left yellowish crystals which after column purification gave the bromide **11*b*** (0.49 g, 79%). A sample was recrystallized from benzene to give light yellow crystals melting at 222°C.

Anal. calcd. for $C_{18}H_{17}O_4Br$: C 57.29, H 4.51; found: C 57.15, H 4.56. The ^1H nmr spectrum δ_{TMS} (DMSO-d_6): 1.23 (s, 3H, CH_3—), 1.50–3.30 (complex m, 8H), 3.90 (s, 3H, CH_3O—), 4.73 (m, 1H, C(16)H), 7.00 (m, 2H, aromatic C(2)H and C(4)H), 7.73 (d, J = 10 Hz, 1H, aromatic C(1)H). The ir spectrum ν_{max} (KBr): 1750 (ketone C=O), 1710 (α,β-unsaturated lactone C=O), 1610 (aromatic), 1405, 1280, 1212, 1165, 1100, 1045, 838 cm^{-1}. The mass spectrum *m/e*: 378 (83, M + 2), 376 (83, M^+), 298 (49, M + 2 – HBr), 297 (49, M^+ – Br), 244 (56), 243 (100), 242 (65), 241 (35), 227 (39).

14β-3-Methoxy-6-oxaestra-1,3,5(10),8,15-pentaen-7,17-dione ***6*** *from* ***11b***

A solution of the tetracyclic bromoketone **11*b*** (0.147 g, 0.39 mmol) in dimethylformamide (5 mL) was added to a stirred hot (150°C) suspension of magnesium oxide (0.05 g) in dimethylformamide (20 mL). The mixture was stirred at 150°C for 30 min under nitrogen atmosphere. The red solution was cooled to room temperature and ice-cold 5% HCl (20 mL) was added

and the product extracted with benzene (25 mL) three times. The combined organic layer was washed with 5% $NaHCO_3$ and finally with water and dried. The red solution was decolorized by adding a pinch of activated carbon. Evaporation of the solvent left a purplish residue which after purification on preparative tlc gave the tetracyclic pentaen **6** (0.87 g, 76%) identical with material prepared directly from **5** as previously described.

14β-3-Methoxy-6-oxaestra-1,3,5(10),8-tetraen-7-oxo-17-ol **11***c*

To the solution of the tetracyclic ketone **6** (4.91 g, 16.6 mmol) in benzene (55 mL) was added methanol (55 mL). The solution was cooled in an ice-water bath and sodium borohydride (2.23 g, 55.60 mmol) was added at once. The mixture was stirred for 5 min and the ice-water bath was replaced by a water bath and allowed to warm to room temperature. The yellow mixture was stirred for 2 h and neutralized with ice-cold 5% HCl. The solvent was evaporated under reduced pressure to 1/3 of the original volume. The residue was diluted with ether (150 mL) and washed with water twice. The ethereal layer was dried (anhydrous $MgSO_4$). Evaporation of the solvent gave a quantitative yield of yellow crystalline product **11***c*. Recrystallization in benzene–cyclohexane (1 : 1) gave white crystals, mp 99–101°C.

Anal. calcd. for $C_{18}H_{20}O_4$: C 72.60, H 6.67; found: C 72.90, H 6.64. The mass spectrum *m/e*: 300 (100, M^+), 282 (27, $M^+ - H_2O$), 267 (52, $M^+ - (CH_3$ and $H_2O)$), 243 (72), 241 (40), 240 (21), 227 (19). The ^1H nmr spectrum δ_{TMS} ($CDCl_3$): 1.07 (s, 3H, CH_3—), 1.83 (s, 1H, —OH), 1.40–3.00 (complex m, 9H), 3.90 (s, 3H, CH_3O—), 4.10 (t, J = 8 Hz, 1H, 17αH), 6.82–7.00 (m, 2H, aromatic C(2)H and C(4)H), 7.53 (d, J = 8 Hz, 1H, aromatic C(1)H). The ir spectrum ν_{max} (KBr): 3320 (broad OH), 1710 (lactone C=O), 1615 (aromatic), 1520, 1285, 1170, 840, 685 cm^{-1}.

14β-3-Methoxy-6-oxaestra-1,3,5(10),8-tetraen-7-oxo-17-ethylene Acetal **11***d*

To a solution of the tetraen dione **11***a* (200 mg, 0.67 mmol) in dry benzene (20 mL) was added ethylene glycol (2 mL), and a catalytic amount of *p*-toluenesulfonic acid monohydrate. The mixture was refluxed for 2.5 h and water was removed with aid of a Dean–Stark trap. The mixture was then washed with 5% $NaHCO_3$ (2 × 15 mL) and worked up in the usual manner. The residue was concentrated in benzene (5 mL) and filtered without suction through silica gel (10 g). The adsorbent was washed with ethyl acetate (50 mL) and the combined washings were evaporated under reduced pressure to give a white crystalline ketal **11***d* (210 mg, 95%), homogeneous on tlc.

The ^1H nmr spectrum δ_{TMS}: 0.97 (s, 3H, CH_3—), 1.59–3.18 (complex m, 9H), 3.93 (s, 3H, CH_3O—), 3.98 (s, 4H, OCH_2CH_2O), 6.78–7.56 (m, 3H, aromatic). The ir spectrum ν_{max} (KBr): 1710 (C=O), 1610, 1281, 1199 cm^{-1}.

14β-3-Methoxy-5,7-dihydroxy-5,6-seco-6-oxaestra-1,3,5(10)-trien-17-one **12** *from* **11**d

Into a two-necked 1 litre round-bottomed flask ammonia (600 mL) was condensed using a Dewar condenser. Excess lithium (619 mg, 88.42 mmol), cut into small pieces, was added against a countercurrent of N_2. The resulting deep blue solution was stirred vigorously for 15 min. Tetracyclic tetraen **11***d* (7.56 g, 22.11 mmol) was added at once from a dropping funnel under N_2 atmosphere. The blue mixture was stirred for another 30 min and then quenched with excess ammonium chloride (5 g). Ammonia was allowed to evaporate in a stream of N_2 and a white residue was obtained. Residual ammonia was removed under reduced pressure. The residue was treated with 5% NaOH (180 mL) and stirred to dissolve the phenolic product. The undissolved material was filtered and washed with water until the washings were not basic, affording the ethylene ketal of **13***b* (1.39 g, 17%), *vide infra*. The basic layer was washed with ether (2 × 30 mL) and after acidification, the product was extracted with ether (3 × 30 mL). After the usual work up, the residue was deketalized to afford a less soluble tricyclic ketone **12** (5.29 g, 79%). An analytical sample recrystallized in acetone melted at 226–228°C.

Anal. calcd. for $C_{18}H_{24}O_4$: C 71.05, H 7.89; found: C 70.93, H 7.64. The mass spectrum *m/e*: 304 (100, M^+), 286 (7, $M - H_2O$), 164 (26), 163 (61), 150 (64), 137 (25). The ^1H nmr spectrum δ_{TMS} ($CDCl_3$ + DMSO-d_6): 1.20 (s, 3H, CH_3—), 1.33–3.58 (complex m, 14H), 3.73 (s, 3H, CH_3O—), 6.21–7.00 (m, 3H, aromatic), 8.90 (s, 1H, phenolic —OH). The ir spectrum ν_{max} (KBr): 3420–3100 (broad —OH), 1720 (C=O), 1614, 1520 cm^{-1}.

8α,14β-3-Methoxy-6-oxaestra-1,3,5(10)-trien-7,17-dione **13**b

The ketal of **13***b*, the minor product of Na/NH_3 reduction of **11***d*, was deketalized by dissolving it in acetone (20 mL) and adding a catalytic amount of *p*-toluenesulfonic acid. The solution was stirred at room temperature overnight. Acetone was evaporated and the pinkish residue, in a minimum amount of benzene, was filtered without suction and washed with ethyl acetate to afford white crystalline tetracyclic ketone **13***b* in 90% yield. An analytical sample recrystallized from benzene melted at 204°C.

Anal. calcd. for $C_{18}H_{20}O_4$: C 72.00, H 6.66; found: C 72.05, H 6.65. The mass spectrum *m/e*: 300 (100, M^+), 204 (43), 203 (97), 202 (84), 174 (52). The ^1H nmr spectrum δ_{TMS} ($CDCl_3$): 1.19 (s, 3H, CH_3—), 1.33–3.21 (complex m, 11H), 3.80 (s, 3H, CH_3O—), 6.60–6.76 (m, 2H, aromatic C(2)H and C(4)H), 7.10 (d, J = 8 Hz, 1H, aromatic C(1)H). The ir spectrum ν_{max} (KBr): 1771 (lactone C=O), 1732 (ketone C=O), 1630, 1596 cm^{-1}.

8α,14β-3-Methoxy-7-hydroxy-6-oxaestra-1,3,5(10)-trien-17-one **13**a *from* **12**

To a stirred solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (2.60 g, 8.82 mmol) in dimethylsulfoxide (25 mL) was added the tricyclic dihydroxytriene **12** (4.10 g, 13.5 mmol) in dimethylsulfoxide (2 mL). Concentrated H_2SO_4 (5 mL) was added slowly keeping the temperature below 70°C. The mixture was cooled, poured into crushed ice-water mixture, and extracted with chloroform (2 × 50 mL). The organic layer was washed with 5% NaOH (2 × 20 mL) and water (3 × 30 mL). The usual work up afforded a brown residue which was purified via a column of silica gel (125 g). Elution with ethyl acetate – cyclohexane (2:5) gave pure white crystalline hemiacetal **13***a* (3.50 g, 86%), mp 192°C (recrystallized from ethyl acetate).

Anal. calcd. for $C_{18}H_{22}O_4$: C 71.52, H 7.28; found: C 71.69, H 7.29. The mass spectrum *m/e*: 302 (64, M^+), 163 (100), 150 (77), 137 (30), 124 (91). The ^1H nmr spectrum δ_{TMS} ($CDCl_3$): 0.97 (s, 3H, CH_3—), 1.32–3.33 (complex m, 11H), 3.59 (d, J = 4.4 Hz, 1H, —OH), 3.80 (s, 3H, CH_3O—), 5.53 (t, J = 4 Hz, 1H, —OCHO—), 6.40–6.63 (m, 2H, aromatic C(2)H and C(4)H), 7.10 (d, J = 8 Hz, 1H, aromatic C(1)H). The ir spectrum ν_{max} (KBr): 3370 (OH), 1715 (C=O), 1612, 1575, 1504 cm^{-1}.

14β-3-Methoxy-6-oxaestra-1,3,5(10),7-tetraen-17-one **14**a *from* **13**b

A solution of the tetracyclic hemiacetal **13***b* (120 mg, 3.97 mmol) in dry benzene (10 mL) was treated with a catalytic amount of *p*-toluenesulfonic acid monohydrate (50 mg). The solution was refluxed for 1 h and water was removed azeotropically with a Dean–Stark trap. The mixture was cooled and diluted with benzene (20 mL), washed with 5% $NaHCO_3$ (30 mL) and water (2 × 20 mL). The usual work up afforded a pure oily vinyl ether **14***a* in quantitative yield. An analytical sample was crystallized from cyclohexane to give white crystals, mp 76–85°C.

Anal. calcd. for $C_{18}H_{20}O_3$: C 76.06, H 7.04; found: C 76.10, H 6.98. The mass spectrum *m/e*: 284 (62, M^+), 269 (22, $M - CH_3$),

188 (55), 187 (90), 86 (23), 85 (67), 84 (38), 83 (100). The ^{1}H nmr spectrum δ_{TMS} ($CDCl_3$): 1.10 (s, 3H, CH_3—), 1.32–3.50 (complex m, 10H), 3.77 (s, 3H, CH_3O—), 6.40–6.72 (m, 3H, aromatic and vinylic), 7.07 (d, J = 8 Hz, aromatic at C(1)H). The ir spectrum ν_{max} (KBr): 1735 (C=O), 1680 (C=C—O), 1620, 1580 cm^{-1}.

3-Hydroxy-6-oxaestra-1,3,5(10),7-tetraen-17-one **14**b *from* **14**a *and from* **13**

(*a*) To an ice-water cooled solution of boron tribromide (0.72 mL, 7.47 mmol) in dry dichloromethane under N_2 (3 mL) was added slowly a solution of methyl ether **14***a* (753 mg, 2.49 mmol) in dry dichloromethane (6 mL) via a syringe. The mixture was stirred at 0°C for an hour and a yellow precipitate was observed to form. The yellow mixture was further stirred at room temperature for another hour and then quenched with ether (10 mL) and water (5 mL). The mixture was extracted with ether and the ether layer was washed with 5% sodium hydroxide solution to extract the phenolic product. After acidification of the basic aqueous layer and extraction with ether, the dried organic layer on evaporation gave a crude product. Crystallization from ethyl acetate afforded the product **14***b* (412 mg), plus mother liquors which upon chromatography on silica gave additional 103 mg of product. The total yield was 615 mg (92%), mp 160–164°C.

(*b*) In one step the hemiacetal **13***a* (502 mg, 1.66 mmol) was demethylated and dehydrated as described above (*a*) to afford **14***b* (369 mg, 85%).

Anal. calcd. for $C_{17}H_{18}O_3$: C 75.56, H 6.67; found: C 75.52, H 6.69. The mass spectrum *m/e*: 270 (68, M^+), 255 (28, $M-15$), 213 (10), 174 (72), 173 (100). The ^{1}H nmr spectrum δ_{TMS} ($CDCl_3$): 1.10 (s, 3H, CH_3—), 1.32–3.50 (complex m, 10H), 3.5 (complex m, 1H, benzylic), 6.38–6.70 (m, 4H, aromatic C(2)H and C(4)H, vinylic C(7)H and phenolic), 7.00 (d, J = 8 Hz, 1H, aromatic C(1)H). The ir spectrum ν_{max} (KBr): 3380 (broad, OH), 1720 (C=O), 1680 (O—C=C), 1620 and 1595 cm^{-1} (aromatic).

Determination of Uterotrophic Activity of **9**b, **9**c, ***10***a, ***10***b, ***10***c, *and* **14**a

Immature 21-day old Sprague–Dawley rats weighing 30–40 g were obtained from Canadian Breeding Laboratories, St. Constant, Quebec. The animals were housed in an air-conditioned room 24 to 25°C, 45 to 50% humidity, and given Purina Chow and water *ad libitum*. Test substances (0.01–10 μg per rat) were administered subcutaneously in 0.2 mL sesame oil. Control animals received vehicle only. The work was divided into four experiments, each with control group and three groups receiving fixed amounts of 17β-estradiol (0.02, 0.1, 0.5 μg per rat) as standard.

The rats (10 per group) received three daily injections, and were sacrificed by cervical dislocation 24 h after the last injection. The uteri were excised free of fat and mesentery blotted and weighed to the nearest milligram on a torsion balance.

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