New Formal Synthesis of (±)-Estrone

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(±)-Estrone is synthesised *via* Torgov's compound by an AB→ABC→ABCD route. The C-ring is constructed by a new Diels–Alder methodology and the D-ring by a novel cyclopentane annulation reaction from a cyclopropanol precursor.

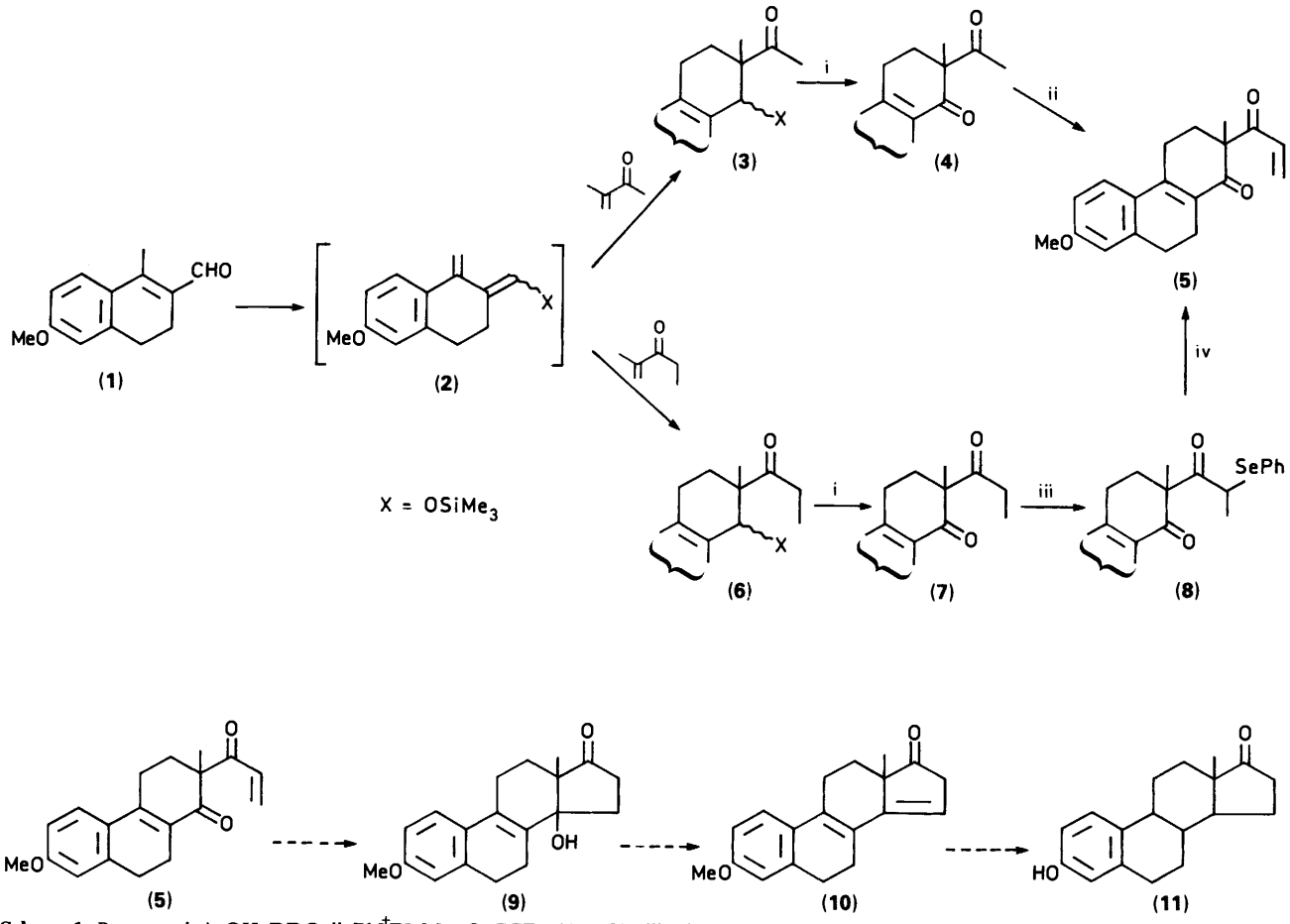
Several methods are known for the synthesis of estrone (**11**), the first estrogenic hormone to be isolated and the starting material for a number of fertility-regulating agents. The latest reported synthesis is by Suginome *et al.*[1] The subject has been reviewed.[2] We now report two synthetic methods,[3,4] in each of which the C-ring is formed by a novel Diels–Alder reaction involving formation of the C(11)–C(12) and C(13)–C(14) bonds and the D-ring by formation of the C(14)–C(15) bond. Torgov's compound (**10**) was the immediate target from which (±)-estrone is commercially available.

In an earlier paper[5] we described a novel strategy for obtaining the C-ring of an A-ring-aromatic steroid. This involved the starting compound (**1**) which was converted to the diene (**2**) and then condensed with a suitable dienophile. In the present approach it was proposed to convert the diene (**2**), in the first instance, to the intermediate bis-enone (**5**) and then cyclise (**5**) to form the D-ring by an appropriate method [*e.g.* (**5**)→(**9**)→(**10**)→(**11**), Scheme 1].

The bis-enone (**5**) was obtained by two routes, *via* (**3**) and (**6**) (Scheme 1), using the Diels–Alder reaction of the intermediate (**2**) [generated *in situ* from (**1**)] and appropriate dienophiles. Hydrolysis of the silyl group in the Diels–Alder adducts followed by oxidation with 2,3-dichloro-4,5-dicyanobenzoquinone (DDQ) gave the enones (**4**) and (**7**) in overall yields of 81 and 90% respectively from (**1**).

The enone (**4**) was methylenated by a modified Mannich reaction[6] using *N*-methylanilinium trifluoroacetate and paraformaldehyde. The bis-enone (**5**) was obtained in only 10% yield. On the other hand, when the enone (**7**) was subjected to α-selenenylation and oxidative elimination, the bis-enone (**5**) was obtained in 40% overall yield.

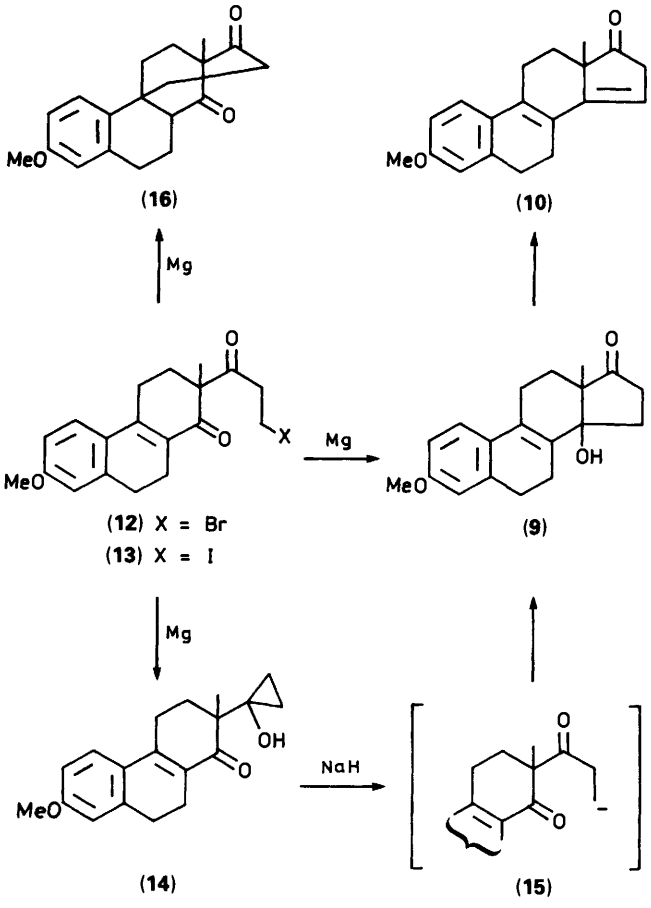
We attempted to convert compound (**5**) to the tetracyclic



Scheme 1. *Reagents:* i, AcOH, DDQ; ii, $PhNH_2Me^+ {}^-O_2CCF_3$, $(CH_2O)_n$; iii, PhSeCl; iv, H_2O_2, AcOH.

compound (**9**) by a radical cyclisation procedure using lithium in liquid ammonia, sodium naphthalenide, Zn–Hg and HCl,[7] Mg–Hg and $TiCl_4$,[8] Zn and Me_3SiCl,[9] and Mg and MgI_2,[10] but these attempts failed.

The bis-enone (**5**) was then converted to the β-bromo diketone (**12**) and an intramolecular Grignard reaction was attempted. Here two possibilities for cyclisation existed: formation of the cyclopropanol (**14**) or the cyclopentanol (**9**) (Scheme 2). Conjugate addition to give (**16**) was also likely. However, the cyclopropanol (**14**) could be readily converted to the tetracyclic compound (**9**) under basic conditions *via* the homoenolate (**15**).

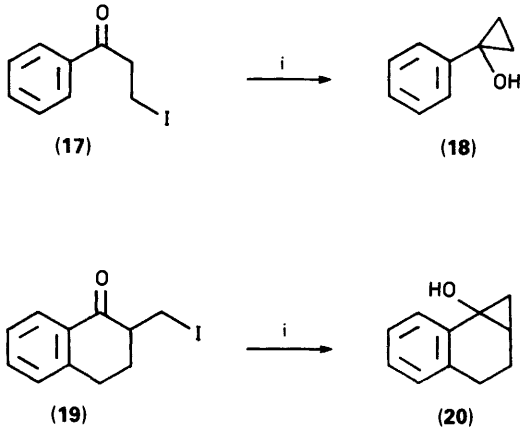


Scheme 2.

The Grignard reaction of (**12**) using ordinary Mg granules, Mg activated by iodine or ethylene dibromide, or even active Mg generated from $MgBr_2$ and potassium gave none of the products (**9**) or (**14**). However, when the corresponding β-iodoketone (**13**) was treated with active Mg, generated from $MgBr_2$ and potassium, the cyclopentanol (**9**) was obtained, but only in 30% yield.

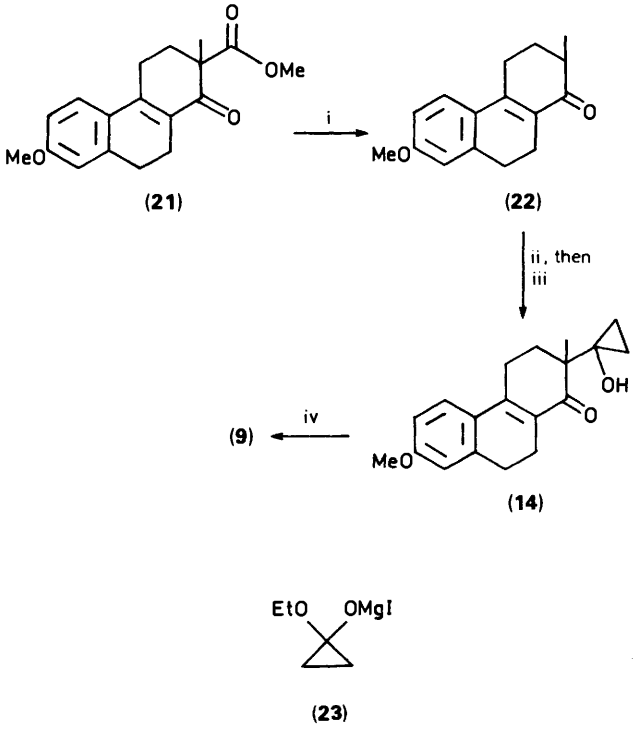
Alternative methods for the cyclisation of (**12**) or (**13**) to give the ring D compound were then considered. The internal addition of carbon radicals, generated by the reaction of Zn and Me_3SiCl with carbonyl groups, to π-bonds has been used by Corey[9] to synthesise cyclic compounds. We attempted to generate the trimethylsilyloxy carbon radical from the β-iodo ketone (**13**) in the hope that an intramolecular alkylation by the carbon bearing the β-iodo substituent would be possible. When the iodo compound (**13**) was treated with Zn and Me_3SiCl in tetrahydrofuran (THF), the cyclopropanol (**14**) was formed in 68% yield. As expected, compound (**14**), on treatment with NaH in THF, gave (**9**) which was then dehydrated with toluene-4-sulphonic acid to give Torgov's compound (**10**) in an overall yield of 61% from (**5**).

The new method for cyclopropanol synthesis, using the reaction of a β-halogenoketone with Zn and Me_3SiCl, is a general one. Thus, 3-iodopropiophenone (**17**), on treatment with Zn and Me_3SiCl, furnished the phenylcyclopropanol (**18**). Similarly 2-iodomethyl-1-tetralone (**19**) furnished the cyclopropanol (**20**) (Scheme 3).



Scheme 3. *Reagents:* i, Zn, Me_3SiCl.

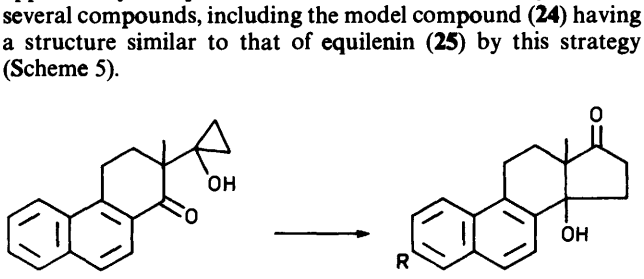
The formation of the tetracyclic compound (**9**) *via* the cyclopropanol (**14**) prompted us to investigate the direct synthesis of (**14**) from the tricyclic enone (**22**) and convert it to (**9**). Cyclopropanone itself is unstable but the magnesium salt of its hemiketal is stable and has been used as a cyclopropanone equivalent. Thus the magnesium salt (**23**) has been condensed with, *e.g.*, phenyl-lithium,[11] Ph–C≡C–MgBr,[12] or the lithium enolate of cyclohexanone[13] to yield the corresponding cyclopropanol derivatives. A new synthesis of estrone was then considered (Scheme 4) based on this approach.



Scheme 4. *Reagents:* i, AcOH; ii, LDA; iii, compound (**23**); iv, NaH.

The tricyclic β-ketoester (**21**) was obtained by our earlier procedure.[5] Hydrolysis and decarboxylation of (**21**) gave the tricyclic enone (**22**). The enone (**22**) was condensed with (**23**) using lithium di-isopropylamide (LDA) as a base. The cyclopropanol (**14**) was obtained in 73% yield.

Cyclopentanone annulation *via* a cyclopropanol is of general applicability. Helquist and co-workers[14] have also synthesised several compounds, including the model compound (**24**) having a structure similar to that of equilenin (**25**) by this strategy (Scheme 5).



(**24**) R = H
(**25**) R = OH

Scheme 5.

Experimental

M.p.s were determined for samples in capillaries on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 337 instrument and ^{1}H NMR spectra for solutions in deuteriochloroform on a Jeol FX 90 Q or a Perkin-Elmer R-32 (90 MHz) spectrometer with tetramethylsilane as internal standard. Elemental analyses were performed on a Hosli C, H analyser. HPLC was done using a Jobin-Yvon high performance liquid chromatograph. Solvents were dried and purified by standard procedures.

Diels–Alder Reactions.—A mixture of the aldehyde (**1**) (5.0 g, 25 mmol), triethylamine (9.7 ml, 70 mmol), the dienophile (45 mmol), and chlorotrimethylsilane (7.6 ml, 60 mmol) in dry benzene (60 ml) was refluxed for 40 h with constant stirring. All the volatile materials were evaporated off *in vacuo* and the resulting syrup was chromatographed on silica gel using 1% EtOAc–hexane as eluant to give the Diels–Alder adducts (**3**) or (**6**).

2-*Acetyl*-7-*methoxy*-2-*methyl*-1-*trimethlsilyloxy*-1,2,3,4,9,10-*hexahydrophenanthrene* (**3**) was an oil (8.0 g, 90%) (Found: C, 70.2; H, 8.4. $C_{21}H_{30}O_3Si$ requires C, 70.35; H, 8.4%); ν_{max}(neat) 1 710 cm^{-1} (C=O); ^{1}H NMR δ (CCl_4) 0.09 (9 H, s, $SiMe_3$); 0.96, 1.13 (3 H, s, 2-Me, two configurations), 1.7–1.95 (2 H, m, 3-H), 1.95–2.6 (4 H, m, 4-H, 10-H), 2.08, 2.1 (3 H, s, COMe, two configurations), 2.6–2.84 (2 H, m, 9-H), 3.72 (3 H, s, OMe), 4.02 and 4.60 (1 H, s, 1-H, two configurations), 6.5–6.67 (2 H, m, 6-H, 8-H), and 6.96 and 7.05 (1 H, d, *J* 9 Hz, 5-H).

7-*Methoxy*-2-*methyl*-2-*propionyl*-1-*trimethylsilyloxy*-1,2,3,4,9,10-*hexahydrophenanthrene* (**6**) was an oil (8.83 g, 95%) (Found: C, 71.2; H, 8.6. $C_{22}H_{32}O_3Si$ requires C, 70.9; H, 8.7%); ν_{max}(neat) 1 705 cm^{-1} (C=O); ^{1}H NMR (CCl_4) δ 0.09 (9 H, s, $SiMe_3$), 0.97, 1.15 (3 H, s, 2-Me, two configurations), 1.02 (3 H, t, *J* 7 Hz, 2-$COCH_2Me$), 1.7–2.0 (2 H, m, 3-H), 2.0–2.6 (6 H, m, 4-H, 10-H, 2-$COCH_2$Me), 2.6–2.85 (2 H, m, 9-H), 3.76 (3 H, s, OMe), 4.07 and 4.66 (1 H, s, 1-H, two configurations), 6.53–6.70 (2 H, m, 6-H, 8-H), and 7.07 (1 H, d, *J* 9 Hz, 5-H).

Hydrolysis and Oxidation of Diels–Alder Adducts.—A stirred solution of the Diels–Alder adduct (**3**) or (**6**) (8 mmol) in dry ether (70 ml) was cooled in an ice bath and glacial acetic acid (5 ml) added. DDQ (1.2 equiv.) was then added in small portions during 30 min. The mixture was stirred for 1 h at 0 °C and 2 h at 25 °C; decantation of the supernatant liquid yielded a red ethereal solution. The residue was washed with ether. The combined ethereal solution was washed successively with water, aqueous $NaHCO_3$, and water, and dried (Na_2SO_4). Evaporation and chromatography of the residue on silica gel with 20% EtOAc–hexane as eluant yielded the ketone.

2-*Acetyl*-7-*methoxy*-2-*methyl*-3,4,9,10-*tetrahydrophenanthren*-1(2H)-*one* (**4**) was an oil (2.04 g, 90%) (Found: C, 76.1; H, 7.2. $C_{18}H_{20}O_3$ requires C, 76.0; H, 7.1%); ν_{max}(neat) 1 710 and 1 645 cm^{-1} (ketone and α,β-unsaturated ketone); ^{1}H NMR (CCl_4) δ 1.3 (3 H, s, 2-Me), 1.6–2.04 (2 H, m, 3-H), 2.1 (3 H, s, COMe), 2.46–2.92 (6 H, m, 4-H, 9-H, 10-H), 3.86 (3 H, s, OMe), 6.66–6.82 (2 H, m, 6-H, 8-H), and 7.32 (1 H, d, *J* 9 Hz, 5-H).

7-*Methoxy*-2-*methyl*-2-*propionyl*-3,4,9,10-*tetrahydrophenanthren*-1(2H)-*one* (**7**) was an oil, (2.26 g, 95%) (Found: C, 76.3; H, 7.3. $C_{19}H_{22}O_3$ requires C 76.5; H, 7.4%); ν_{max}(neat) 1 710 (ketone) and 1 640 cm^{-1} (α,β-unsaturated ketone); ^{1}H NMR (CCl_4) δ 0.95 (3 H, t, *J* 7 Hz, OCH_2Me), 1.3 (3 H, s, 2-Me), 1.6–2.1 (2 H, m, 3-H), 2.1–2.83 (8 H, m, 4-H, 9-H, 10-H, $COCH_2$Me), 3.8 (3 H, s, Me), 6.6–6.75 (2 H, m, 6-H, 8-H), and 7.25 (1 H, d, *J* 9 Hz, 5-H).

7-*Methoxy*-2-*methyl*-2-(α-*phenylselenopropionyl*)-3,4,9,10-*tetrahydrophenanthren*-1(2H)-*one* (**8**).—A solution of the ethyl diketone (**7**) (0.894 g, 3 mmol) in dry CH_2Cl_2 (60 ml) and PhSeCl (0.63 g, 3.3 mmol) were stirred at 25 °C for 20 h. The mixture was then washed with aqueous $NaHCO_3$ and water, and dried (Na_2SO_4). Concentration and chromatography of the residue on silica gel using benzene as eluant provided the *seleno ketone* (**8**) (0.6 g, 44%) as an oil (Found: C, 66.2; H, 5.8. $C_{25}H_{26}O_3Se$ requires C, 66.2; H, 5.8%); ν_{max}(neat) 1 700 (ketone) and 1 640 cm^{-1} (α,β-unsaturated ketone); ^{1}H NMR ($CDCl_3$) δ 1.27 (3 H, d, *J* 7 Hz, PhSeCH*Me*), 1.41 (3 H, s, 2-Me), 1.55–2.05 (2 H, m, 3-H), 2.2–2.8 (6 H, m, 4-H, 9-H, 10-H), 3.7 (3 H, s, OMe), 4.16 (1 H, q, *J* 7 Hz, PhSeC*H*CO), 6.54–6.7 (2 H, m, 6-H, 8-H), 7.1–7.3 (4 H, m, 5-H, PhSe), and 7.45 (2 H, dd, *J* 8 and 4 Hz, SePh).

2-*Acryloyl*-7-*methoxy*-2-*methyl*-3,4,9,10-*tetrahydrophenanthren*-1(2H)-*one* (**5**).—Aqueous H_2O_2 (30%; 0.4 ml, 4 mmol) was added dropwise to an ice-cold solution of the selenide (**8**) (0.6 g, 1.3 mmol) and acetic acid (0.3 ml). Stirring for 1 h at 20 °C followed by washing with aqueous $NaHCO_3$ and water, drying (Na_2SO_4), and concentration provided the *bis-enone* (**5**) (0.335 g, 90%), as an oil (Found: C, 77.0; H, 6.8. $C_{19}H_{20}O_3$ requires C, 77.0; H, 6.8%); ν_{max}(neat) 1 690 and 1 645 cm^{-1} (α,β-unsaturated ketone); ^{1}H NMR ($CDCl_3$) δ 1.4 (3 H, s, 2-Me), 1.75–2.10 (2 H, m, 3-H), 2.5–2.95 (6 H, m, 4-H, 9-H, 10-H), 3.85 (3 H, s, OMe), 5.65 (1 H, dd, *J* 9 and 4 Hz, vinyl), 6.32 (1 H, dd, *J* 18 and 4 Hz, vinyl), 6.6 (1 H, dd, *J* 18 and 9 Hz vinyl), 6.73–6.88 (2 H, m, 6-H, 8-H), and 7.35 (1 H, d, *J* 9 Hz, 5-H).

2-(β-*Iodopropionyl*)-7-*methoxy*-2-*methyl*-3,4,9,10-*tetrahydrophenanthren*-1(2H)-*one* (**13**).—A solution of the bis-enone (**5**) (0.5 g, 1.7 mmol) in benzene (10 ml) was vigorously stirred with aqueous HI (57%; 1.15 ml, 5 mmol) for 2 h. The benzene layer was separated, washed with $NaHCO_3$ and water, and dried (Na_2SO_4). Evaporation *in vacuo* gave (**13**) as a yellow solid (0.715 g, 100%); ν_{max}(neat) 1 715 (ketone) and 1 650 cm^{-1} (α,β-unsaturated ketone); ^{1}H NMR ($CDCl_3$) δ 1.37 (3 H, s, 2-Me), 1.6–2.10 (2 H, m, 3-H), 2.45–2.95 (8 H, m, 4-H, 9-H, 10-H, $COCH_2$), 3.10–3.35 (2 H, m, CH_2I), 3.84 (3 H, s, OMe), 6.7–6.85 (2 H, m, 6-H, 8-H), and 7.35 (1 H, d, *J* 9 Hz, 5-H). This highly unstable compound was used directly in the next step.

Reaction of (**13**) *with Active Magnesium.*—Active magnesium was prepared according to the literature procedure[15] from

magnesium (0.175 g). The β-iodo ketone (**13**) (0.143 g, 0.3 mmol) in dry THF (10 ml) was added during 2 h to a vigorously stirred suspension of active Mg under nitrogen at 0 °C. Stirring for 45 min, quenching with saturated NH_4Cl (15 ml), extraction with CH_2Cl_2 (5 × 5 ml) drying (Na_2SO_4), concentration, and HPLC of the residue on silica gel with 25% EtOAc–hexane as eluant gave 14-hydroxy-3-methoxyestra-1,3,5(10),8-tetraen-17-one (**9**) (0.03 g, 30%); m.p. 133–134 °C (from Et_2O); ν_{max}(Nujol) 3 460 (OH) and 1 740 cm^{-1} (ketone); ^1H NMR ($CDCl_3$) δ 1.1 (3 H, s, 13-Me), 1.8–2.9 (13 H, m, 6-H, 7-H, 11-H, 12-H, 15-H, 16-H, exchangeable 14-OH), 3.8 (3 H, s, OMe), 6.75 (2 H, m, 2-H, 5-H), and 7.15 (1 H, d, *J* 9 Hz, 1-H).

Reaction of (**13**) *with Zinc and Trimethylsilyl Chloride.*—A solution of (**13**) (0.285 g, 0.68 mmol) and Me_3SiCl (0.5 ml, 4 mmol) in dry THF (10 ml) was added to a vigorously stirred refluxing suspension of Zn (0.9 g, 13.5 mmol) in dry THF (30 ml) under nitrogen during 2 h. The mixture was then cooled, the THF layer decanted off, and the residual Zn washed with THF (10 ml). The combined THF solution was then evaporated, and the residue taken up in CH_2Cl_2, washed with water, and dried (Na_2SO_4). Concentration followed by HPLC on silica gel using 30% EtOAc–hexane as eluant gave the ethyl diketone (**7**) (0.04 g, 20%) and 2-(1-*hydroxycyclopropyl*)-7-*methoxy*-2-*methyl*-3,4,9,10-*tetrahydrophenanthren*-1(2H)-*one* (**14**) (0.136 g, 68%) as an oil (Found: C, 76.3; H, 7.3. $C_{19}H_{22}O_3$ requires C, 76.5; H, 7.4%); ν_{max}(neat) 3 425 (OH) and 1 640 cm^{-1} (ketone); ^1H NMR ($CDCl_3$) δ 0.52 and 0.6 (2 H, br s, cyclopropyl), 1.2 (3 H, s, 2-Me), 1.5–2.83 (8 H, m, 4 × CH_2), 3.72 (1 H, br s, exchangeable, OH), 3.8 (3 H, s, OMe), 6.63–6.76 (2 H, m, 6-H, 8-H), and 7.26 (1 H, d, *J* 9 Hz, 5-H).

7-*Methoxy*-2-*methyl*-3,4,9,10-*tetrahydrophenanthren*-1(2H)-*one* (**22**): *Hydrolysis of the Oxo Ester* (**21**).—A solution of the oxo ester (**21**)[5] (3.5 g) in acetic acid (15 ml), 12M HCl (1.5 ml), and water (1.5 ml) was refluxed on a steam bath for 6 h. The mixture was then diluted with water and extracted with ether (3 × 30 ml). The combined ether extract was washed successively with aqueous sodium hydrogen carbonate and water, and dried (Na_2SO_4). Solvent was removed under reduced pressure to give a crude compound, which on recrystallization from methanol provided the ketone (**22**) (2.1 g, 75%), m.p. 65 °C (lit.,[16] m.p. 65–66 °C) (Found: C, 79.0; H, 7.4. Calc. for $C_{16}H_{18}O_2$: C, 79.3; H, 7.5%); ν_{max}(Nujol) 1 665 cm^{-1} (ketone); ^1H NMR ($CDCl_3$) δ 1.2 (3 H, d, *J* 7 Hz, 2-Me), 1.7–2.9 (9 H, m, 4 × C*H*$_2$, 2-H), 3.8 (3 H, s, OMe), 6.68–6.80 (2 H, m, 6-H, 8-H), and 7.35 (1 H, d, *J* 9 Hz, 5-H).

2-(1-*Hydroxycyclopropyl*)-7-*methoxy*-2-*methyl*-3,4,9,10-*tetrahydrophenanthren*-1(2H)-*one* (**14**).—The ketone (**22**) (200 mg, 6.8 mmol) was stirred with LDA (5 mmol) in THF (10 ml) at 0 °C under nitrogen for 1.5 h. The mixture was then rapidly added, by syringe, to the magnesium salt of the hemiketal (**23**)[11] (10 mmol) obtained as a suspension in dry ether (25 ml). The mixture was immediately refluxed for 15 min. Quenching with saturated ammonium chloride (10 ml), extraction with ether, drying with Na_2SO_4, and evaporation followed by preparative HPLC of the residue on silica gel and with 30% EtOAc–hexane as eluant furnished the cyclopropanol (**14**) as a yellow viscous liquid (180 mg, 73%) (Found: C, 76.3; H, 7.3% having IR and NMR data identical with those of the sample prepared from (**13**).

14-*Hydroxy*-3-*methoxyestra*-1,3,5(10),8-*tetraen*-17-*one* (**19**).—To a stirred suspension of sodium hydride (0.02 g, excess) in dry THF (10 ml), a solution of the cyclopropanol (**14**) (0.66 g) in dry THF was added slowly under nitrogen at 0 °C. The mixture was allowed to reach room temperature and stirred for a further 4 h. It was then quenched with cold water and the THF evaporated off. The residue was extracted with dichloromethane (2 × 10 ml). The combined extract was washed with water and dried (Na_2SO_4). Removal of solvent and crystallization from ether furnished the *hydroxycyclopentanone* (**9**) (0.055 g, 90%); m.p. 133–134 °C (from ether) (Found: C, 76.2; H, 7.3. $C_{19}H_{22}O_3$ requires C, 76.5; H, 7.4%); ν_{max} 3 460 (OH) and 1 740 cm^{-1} (ketone); ^1H NMR ($CDCl_3$) δ 1.1 (3 H, s, 13-Me), 1.8–2.9 (13 H, m, 6 × CH_2, exchangeable 14-OH), 3.8 (3 H, s, OMe), 6.75 (2 H, m, 2-H, 5-H), and 7.15 (1 H, d, *J* 9 Hz, 1-H).

3-*Methoxyestra*-1,3,5(10),8,14-*pentaen*-17-*one* (**10**) (*Torgov's Compound*).—A solution of the hydroxycyclopentanone (**9**) (0.05 g) in dry benzene (15 ml) was refluxed for 2 min in the presence of toluene-4-sulphonic acid as catalyst. The solution was cooled and filtered through a short pad of alumina. Removal of solvent furnished Torgov's compound (**10**) (0.048 g, 100%), m.p. 111–112 °C (from ether) (lit.,[17] m.p. 113–115 °C) (Found: C, 81.2; H, 7.0. Calc. for $C_{19}H_{20}O_2$: C, 81.4; H, 7.2%); ν_{max} 1 745 cm^{-1} (ketone); ^1H NMR ($CDCl_3$) δ 1.13 (3 H, s, 13-Me), 1.5–3.44 (10 H, m, 5 × CH_2), 3.76 (3 H, s, OMe), 5.8 (1 H, m, 15-H), 6.64–6.76 (2 H, m, 2-H, 4-H), and 7.19 (1 H, d, *J* 9 Hz, 1-H).

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