Total Synthesis of 14α-Hydroxyestrone 3-Methyl Ether

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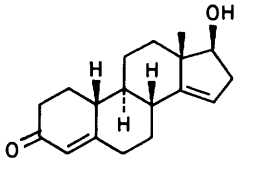
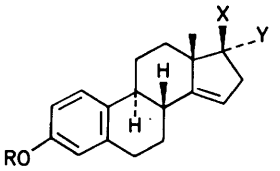
Total synthesis of 14α-hydroxyestrone 3-methyl ether (5) was achieved by the thermolysis of 2-[2-(1,2-dihydro-4-methoxybenzocyclobuten-1-yl)ethyl]-3-hydroxy-2-methyl-3-vinylcyclopentan-1-one (27), obtained by Grignard reaction of 2-[2-(1,2-dihydro-4-methoxybenzocyclobuten-1-yl)ethyl]-2-methylcyclopentane-1,3-dione (26) with vinylmagnesium bromide. An alternative synthesis of (5) started from authentic 14-dehydroestradiol bis-(t-butyldimethylsilyl) ether (28) and proceeded through estradiol-14α,15α-epoxide 3-methyl 17β-t-butyldimethylsilyl bisether (31).

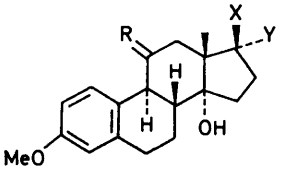
14-DEHYDRO-19-NORTESTOSTERONE (1) derived from 14-dehydroestrone methyl ether (2) and 14-dehydroestradiol 3-methyl ether (3) has been shown to have a high androgenic activity.[1,2] Recently, 14α-hydroxyestrone has been newly identified as an estrogen metabolite,[3-5] and the syntheses of 14α-hydroxy-11-oxoestrone methyl ether (4) and its stereoisomer have received a considerable amount of attention.[6-9] This prompted us to develop a new stereoselective synthesis of 14α-hydroxyestrone methyl ether (5) and 14α-hydroxyestradiol 3-methyl ether (6) which could be an important intermediate for the synthesis of compounds (2) and (3). The synthesis of (4) was also investigated.



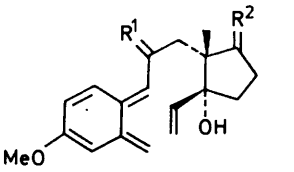
(1)



(2) X,Y = O, R = Me
(3) X = OH, Y = H, R = Me



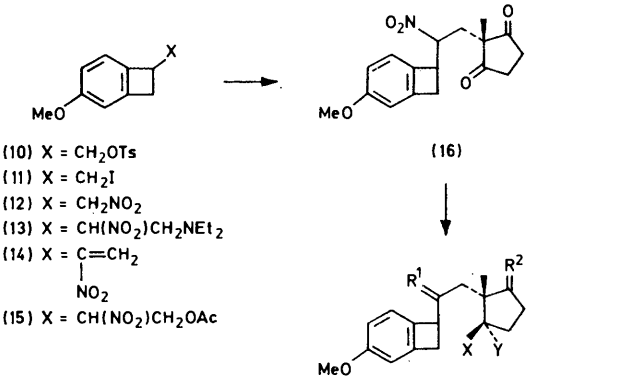
(4) X,Y = R = O
(5) X,Y = O, R = H_2
(6) X = OH, Y = H, R = H_2
(9) X, Y = R = OCH_2CH_2O



(7) $R^1 = H_2$, R^2 = O
(8) $R^1 = R^2 = OCH_2CH_2O$

Subsequent to our initial introduction of thermolysis of benzocyclobutene derivatives into the synthesis of estrone and its derivatives,[10,11] several other workers [12-14] have succeeded in the synthesis of various types of estrone derivatives by use of the same type of reaction. We have also succeeded in the application of this reaction for the asymmetric synthesis of estradiol.[15] For all these cases, where the benzocyclobutene derivatives have no substituents at the geminal position of the vinyl group, we have studied the substituent effect for their thermolysis. We now report the stereoselective synthesis of 14α-hydroxyestrone methyl ether (5) by way of the *o*-quinodimethane (7) generated *in situ* from the thermolysis of the benzocyclobutene (27). The syntheses of 14-dehydroestrone 3-methyl ether (2) and 14-dehydroestradiol 3-methyl ether (3) are described by alternative reaction sequences.

The synthesis of 14α-hydroxy-3-methoxyestra-1,3,-5(10)-triene-11,17-dione (4) was studied first, our plan being based on the intramolecular cycloaddition of the olefinic *o*-quinodimethane (8) generated *in situ* by electrocyclic ring-opening of the benzocyclobutene (19) followed by hydrolysis of the resulting diacetal (9). The preparation of the requisite benzocyclobutene derivative (19) was straightforward. The iodide (11), prepared by treatment of the tosylate (10) [11] with sodium iodide in 90.3% yield, was treated with sodium nitrite in the presence of phloroglucinol in dimethylformamide to give the nitro-compound (12) in 45.7% yield. Mannich reaction of (12) with formaldehyde and diethylamine afforded the Mannich base (13) which was treated with 2-methylcyclopentane-1,3-dione in acetic acid at 60 °C for 7 h to give the nitro-olefin (14), the nitro-acetate (15), and the nitro-diketone (16) in 11.3, 27.7, and 31.2% overall yields, respectively [as mixtures of diastereoisomers in the case of (15) and (16)]. A better yield (44.6%) of the nitro-diketone (16) was obtained by heating the reaction mixture for 13 h. The nitro-

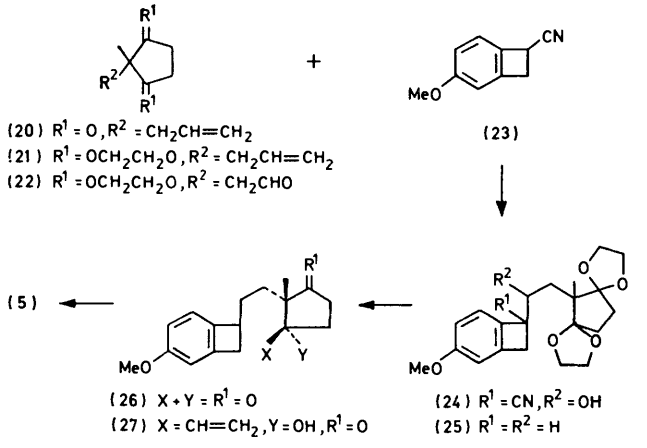


(10) X = CH_2OTs
(11) X = CH_2I
(12) X = CH_2NO_2
(13) X = $CH(NO_2)CH_2NEt_2$
(14) X = $C(=CH_2)NO_2$
(15) X = $CH(NO_2)CH_2OAc$

(16)

(17) X,Y = $R^1 = R^2$ = O
(18) X,Y = O, $R^1 = R^2 = OCH_2CH_2O$
(19) X = $CH=CH_2$, Y = OH; $R^1 = R^2 = OCH_2CH_2O$

SCHEME 1



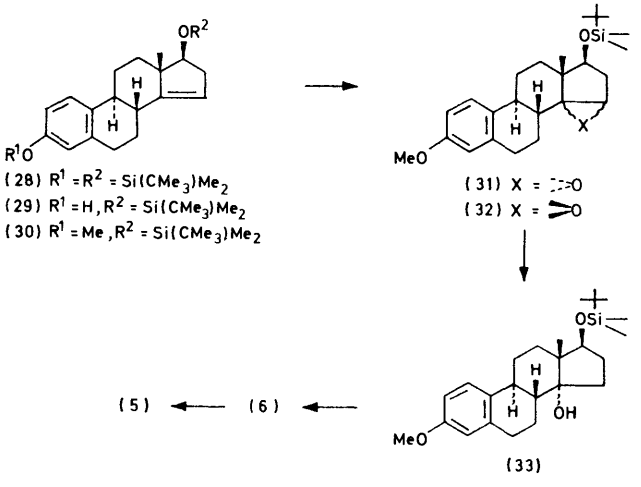
SCHEME 2

diketone (16) thus obtained was transformed into the triketone (17) in 47.5% yield by treatment with titanium trichloride.[16] Next, selective protection of two of the carbonyl groups of the triketone (17) was achieved by heating with ethylene glycol in the presence of a catalytic amount of toluene-*p*-sulphonic acid in benzene to give the monoketone (18) (*m/e* 374) in 51.8% yield, whose i.r. spectrum exhibited the presence of a ketone at 1 735 cm^{-1}. The n.m.r. absorption of the benzylic methine proton adjacent to the carbonyl group, observed for the triketone (17) at δ 4.15 as a triplet with *J* 4 Hz, was shifted upfield for the monoketone (18) and overlapped with the signals due to both the ethylene acetal groups and the methyl protons of methoxy-group. This indicated that the ketone group next to benzylic methine group was acetalized. The two methylene groups on the cyclopentane ring of the triketone (17), observed at δ 2.79 as a singlet, resonated as a multiplet at δ 1.61—2.7 in the case of the monoketone (18), suggesting that one of the two ketone groups on the cyclopentane ring was acetalized. Thus, the structure of the monoketone (18) was confirmed. However, when Grignard reaction of (18) with vinylmagnesium bromide was attempted under various conditions, reactions occurred to give undefined products, with none of the desired compound (19).

The synthesis of 14α-hydroxyestrone 3-methyl ether (5) was next examined. Since the preparation of the benzocyclobutene derivative (19) could not be achieved, we turned our attention towards intramolecular cycloaddition of the benzocyclobutene (27) which was prepared as in Scheme 2. The aldehyde (22) was prepared from the diketone (20) [17] by acetalization with ethylene glycol in the presence of a catalytic amount of toluene-*p*-sulphonic acid to form the diacetal (21), followed by ozonolysis. Condensation of the aldehyde (22) with 1-cyano-4-methoxybenzocyclobutene (23) [18] in the presence of sodium amide in liquid ammonia gave in 66.3% yield the hydroxycyano-compound (24) as a mixture of diastereoisomers. Reaction of (24) with sodium in liquid ammonia and ethanol afforded directly compound (25) (*m/e* 360) in 68% yield, the i.r. spectrum of which lacked absorptions due to cyano- and hydroxy-groups, observed for compound (24) at 2 225 and 3 425 cm^{-1} respectively. Since the Grignard reaction of the monoketone (18) with vinylmagnesium bromide had not been successful, the diketone (26) was used as a starting material. Thus the diketone (26), prepared by reaction of the diacetal (25) with acid, was treated with vinylmagnesium bromide in tetrahydrofuran to afford the key intermediate (27) (*m/e* 300) in 20% yield, which exhibited an i.r. absorption at 1 740 cm^{-1} due to the keto-group and n.m.r. signals at δ 5.0—6.43 due to the vinyl group. Furthermore its methyl group resonated at δ 0.9 as a sharp singlet. The stereochemistry of (27) was deduced from the reaction mechanism, in which the vinyl group might be introduced from the far side from the bulky benzocyclobutenylethyl group. Heating the olefinic compound (27) in *o*-dichlorobenzene at 180 °C for 4 h under a current of nitrogen gave, *via* the *o*-quinodimethane (7), compound (5) (*m/e* 300) in 45% yield, which showed an i.r. absorption at 1 740 cm^{-1}. The n.m.r. signals due to the vinyl group of (27) were not observed for compound (5).

Finally, the synthesis of 14α-hydroxyestrone 3-methyl ether (5), 14-dehydroestrone 3-methyl ether (2), and 14-dehydroestradiol 3-methyl ether (3) was investigated. Although the structure of compound (5) had been deduced from its spectroscopic data and from previous results,[10-15] its stereochemistry could not be determined unambiguously and therefore an alternative synthesis of 14α-hydroxyestrone 3-methyl ether was carried out using 14-dehydroestradiol disilyl ether (28).[19]

The methyl ether (30), synthesized quantitatively by selective hydrolysis of (28) with 10% aqueous sodium hydroxide in methanol followed by methylation of the resulting phenol (29) with dimethyl sulphate in the presence of 40% aqueous potassium hydroxide in acetone, was treated with *m*-chloroperbenzoic acid in methylene dichloride to give the epoxides (31) and (32) in 57.2 and 13.7% yield, respectively. It is known from the n.m.r. spectrum of two epimeric 17β-substituted 14,15-epox-



SCHEME 3

ides [20] that the 18-methyl protons of α-epoxides appear at higher field than those of the β-epimers. In fact, the 18-methyl protons of the epoxide (31) resonated at δ 0.9, with those of the epoxide (32) appearing at δ 1.03. Thus the configurations of the epoxides (31) and (32) were determined to be α and β respectively. This was also supported by the well documented fact that for a 17β-substituted steroid peracid attacks a Δ^{14}-double bond from the rear side to give an α-epoxide [21-23] as the major component.

Reduction of the epoxide (31) with lithium aluminium hydride in ether followed by hydrolysis of the resulting silyl ether (33) with 2N-hydrochloric acid in acetone gave the diol (6) in 59% yield. This was oxidized with Jones reagent to give, in 70.4% yield, 14α-hydroxyestrone methyl ether (5), identical (i.r. and n.m.r. spectra) with the sample obtained by thermolysis of the benzocyclobutene (27) described above.

Thus we could determine the stereochemical course of the thermolysis of the benzocyclobutene (27). Also, treatment of compounds (33) and (6) with 5N-hydrochloric acid in acetone gave the same product (3) in 60.6 and 59.6% yields respectively, Jones oxidation of which afforded ketone (2) in 91.5% yield. In turn, compound (6) was derived from the ketone (5) by sodium borohydride reduction. As compounds (2) and (3) have previously been correlated with 14-dehydro-19-nortestosterone,[1,2] this work also constitutes a total synthesis of 14-dehydro-19-nortestosterone.

EXPERIMENTAL

M.p.s were taken with a Yanagimoto micro-apparatus (MP-S2). I.r. spectra were measured with a Hitachi 215 recording spectrophotometer, n.m.r. spectra with a JEOL JNM-PMX 60 spectrometer, and mass spectra with a Hitachi M-52G and a JEOL D-300 spectrometer.

1,2-Dihydro-1-iodomethyl-4-methoxybenzocyclobutene (11).—A mixture of the tosylate (10) [11] (3.6 g), sodium iodide (5.2 g), and acetone (50 ml) was refluxed for 5 h. After evaporation of the solvent, water (40 ml) was added and the resulting solution extracted with ether. The extract was washed with 5% aqueous sodium thiosulphate and aqueous sodium chloride, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (30 g) with hexane–benzene (1 : 1 v/v) as eluant to give the *iodide* (11) (2.8 g, 90.3%) as an oil (Found: C, 44.15; H, 3.95. $C_{10}H_{11}IO$ requires C, 43.8; H, 4.05%); δ(CCl_4) 2.65 (1 H, dd, *J* 1.5 and 14 Hz, 2-H), 3.25 (1 H, dd, *J* 5 and 14 Hz, 2-H), 3.28—3.87 (3 H, m, 1-H and CH_2I), 3.61 (3 H, s, OMe), and 6.48—7.13 (3 H, m, ArH); *m/e* 274 (M^+).

1,2-Dihydro-4-methoxy-1-nitromethylbenzocyclobutene (12).—The iodide (11) (1.6 g) in anhydrous dimethylformamide (DMF) (3 ml) was added to a solution of sodium nitrite (0.8 g) and anhydrous phloroglucinol (0.94 g) in anhydrous DMF (12 ml) with stirring under nitrogen. Stirring was continued for 2.5 h at 60 °C when the mixture was poured into ice–water (15 ml). The resulting solution was extracted with ether and the combined extracts were washed with water and aqueous sodium chloride, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (20 g) with hexane–benzene (1 : 1 v/v) as eluant to give the *nitro-compound* (12) (0.51 g, 45.7%) as a pale yellow oil (Found: C, 62.2; H, 5.6. $C_{10}H_{11}NO_3$ requires C, 62.15; H, 5.75%), $\nu_{max.}$ ($CHCl_3$) 1 545 and 1 375 cm^{-1} (NO_2); δ(CCl_4) 2.82 (1 H, dd, *J* 1.5 and 14 Hz, 2-H), 3.38 (1 H, dd, *J* 5 and 14 Hz, 2-H), 3.68 (3 H, s, OMe), 3.77—4.23 (1 H, m, 1-H), 4.5 (2 H, d, *J* 8 Hz, CH_2-NO_2), and 6.55—7.07 (3 H, m, ArH); *m/e* 193 (M^+).

Formation of the Mannich Base (13) *and Its Reaction with 2-Methylcyclopentane-1,3-dione*.—To a mixture of redistilled diethylamine (0.7 g) and water (0.7 ml), formalin (0.84 ml) was added dropwise with vigorous stirring at room temperature. The mixture was stirred at room temperature for an additional 30 min and then the nitro-compound (12) (1.5 g) was added in one lot under vigorous stirring. After stirring had been continued for 6 h at room temperature, the mixture was diluted with aqueous sodium chloride (20 ml) and extracted with ether. The extract was washed with aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent afforded the Mannich base (13) (2.2 g) as a yellow oil, which was used without further purification. A solution of the crude Mannich base (13) (2.2 g) and 2-methylcyclopentane-1,3-dione (0.95 g) in glacial acetic acid (25 ml) was stirred for 7 h at 60 °C under nitrogen. The mixture was cooled, water (50 ml) was added, and the resulting mixture extracted with benzene. The organic layer was washed with water, 5% aqueous sodium hydrogen carbonate, and sodium chloride aqueous solution, and dried (Na_2SO_4). Removal of the solvent afforded a brown oil, which was chromatographed on silica gel (30 g) with hexane–benzene (1 : 1 v/v) as eluant. Evaporation of the first fraction left a yellow powder, which was recrystallized from ethanol to yield *1-(1,2-dihydro-4-methoxybenzocyclobuten-1-yl)-1-nitroethylene* (14) (0.18 g, 11.3%) as pale yellow needles, m.p. 77—78 °C (Found: C, 64.25; H, 5.3; N, 6.6. $C_{11}H_{11}NO_3$ requires C, 64.4; H, 5.4; N, 6.85%), $\nu_{max.}$ ($CHCl_3$) 1 520 and 1 340 cm^{-1} (NO_2); δ(CCl_4) 2.90 (1 H, dd, *J* 3 and 14 Hz, 2-H), 3.58 (1 H, dd, *J* 6 and 14 Hz, 2-H), 3.71 (3 H, s, OMe), 4.52 br (1 H, s, 1-H), 5.58 and 6.73br (each 1 H, each s, $=CH_2$), and 6.63—7.15 (3 H, m, ArH); *m/e* 205 (M^+). The second fraction afforded *2-(1,2-dihydro-4-methoxybenzocyclobuten-1-yl)-2-nitroethyl acetate* (15) (0.57 g, 27.7%) as a pale yellow oil (Found: C, 59.2; H, 5.5; N, 5.1. $C_{13}H_{15}NO_5$ requires C, 58.85; H, 5.7; N, 5.3%), $\nu_{max.}$ ($CHCl_3$) 1 750 (C=O), 1 557, and 1 370 cm^{-1} (NO_2); δ(CCl_4) 2.01 (3 H, s, O·CO·Me), 2.95 (1 H, dd, *J* 3 and 14 Hz, 2-H), 3.36 (1 H, dd, *J* 5 and 14 Hz, 2-H), 3.63—4.12 (1 H, m, 1-H), 3.70 (1 H, s, OMe), 4.27—4.87 (2 H, m, CH_2OAc), and 6.53—7.13 (3 H, m, ArH); *m/e* 265 (M^+). The third fraction gave *2-[2-(1,2-dihydro-4-methoxybenzocyclobuten-1-yl)-2-nitroethyl]-2-methylcyclopentane-1,3-dione* (16) (0.77 g, 31.2%) as a pale yellow oil (Found: C, 64.2; H, 6.05; N, 4.35. $C_{17}H_{19}NO_5$ requires C, 64.35; H, 6.05; N, 4.4%), $\nu_{max.}$ ($CHCl_3$) 1 720 (C=O), 1 540, and 1 360 cm^{-1} (NO_2); δ(CCl_4) 1.05 (3 H, s, Me), 1.77—4.00 [5 H, m, 1-H, 2-H_2, and $CH(NO_2)CH_2$], 2.70 (4 H, s, $CO{\cdot}CH_2$-$CH_2{\cdot}CO$), 3.68 and 3.70 (3 H, each s, OMe), 4.17—4.77 (1 H, m, $CHNO_2$), and 6.50—7.17 (3 H, m, ArH); *m/e* 317 (M^+).

By the same procedure but with a reaction time of 13 h, the nitro-acetate (15) (0.56 g, 27.2%) and the nitro-diketone (16) (1.1 g, 44.6%) were obtained.

2-[2-(1,2-Dihydro-4-methoxybenzocyclobuten-1-yl)-2-oxoethyl]-2-methylcyclopentane-1,3-dione (17).—A solution of the nitro-diketone (16) (0.68 g) and titanium trichloride (solution in 20% hydrochloric acid; 35 g) in tetrahydrofuran (THF) (50 ml) was stirred for 42 h at room temperature under nitrogen. After addition of water (100 ml), the

mixture was extracted with ether. The extract was washed with water, 5% aqueous sodium hydrogencarbonate and aqueous sodium chloride, and dried (Na_2SO_4). Evaporation left a yellow powder, which was chromatographed on silica gel (20 g) with benzene to afford the *triketone* (17) (0.29 g, 47.5%) as prisms (from hexane–benzene), m.p. 129—130 °C (Found: C, 71.0; H, 6.25. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.35%); $\nu_{max.}$ ($CHCl_3$) 1 729 and 1 700 cm^{-1} (C=O); δ(CCl_4) 0.97 (3 H, s, Me), 2.79 (4 H, s, $CO{\cdot}CH_2CH_2{\cdot}$ CO), 3.18 (2 H, s, $CO{\cdot}CH_2$), 3.27 (2 H, d, *J* 4 Hz, 2-H_2), 3.75 (3 H, s, OMe), 4.15 (1 H, t, *J* 4 Hz), 1-H), and 6.53—7.20 (3 H, m, ArH); *m/e* 286 (M^+).

1,1-*Ethylenedioxy*-2-[2,2-*ethylenedioxy*-2-(1,2-*dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*ethyl*]-2-*methylcyclopentan*-3-*one* (18).—A solution of the triketone (17) (1.05 g), ethylene glycol (0.51 g), and toluene-*p*-sulphonic acid (30 mg) in dry benzene (50 ml) was refluxed for 13 h under nitrogen using a water separator. After cooling, the mixture was washed with 5% aqueous sodium hydrogencarbonate and aqueous sodium chloride, dried (Na_2SO_4), and evaporated to give an oily residue which was chromatographed on silica gel (30 g) with benzene to give the *diacetal* (18) (0.71 g, 51.8%) as an oil (Found: C, 67.55; H, 7.05. $C_{21}H_{26}O_6$ requires C, 67.35; H, 7.0%); $\nu_{max.}$ ($CHCl_3$) 1 735 cm^{-1} (C=O); δ(CCl_4) 1.00 (3 H, s, Me), 1.61—2.7 (6 H, m, 3 × CH_2), 3.03 (2 H, distorted d, *J* 3 Hz, 2-H_2), 3.70 (3 H, s, OMe), 3.4—4.0 (5 H, m, OCH_2CH_2O and 1-H), 3.90 (4 H, s, OCH_2CH_2O), and 6.50—7.10 (3 H, m, ArH); *m/e* 374 (M^+).

2-*Allyl*-1,1;3,3-*bisethylenedioxy*-2-*methylcyclopentane* (21).—A solution of the diketone (20) (20 g), ethylene glycol (40 g), and toluene-*p*-sulphonic acid (1 g) in dry benzene (400 ml) was refluxed for 48 h using a water separator. After cooling, the mixture was washed with 5% aqueous sodium hydrogencarbonate and aqueous sodium chloride, and dried (Na_2SO_4). Evaporation left a yellow oil, which was subjected to distillation to give the *diacetal* (21) (12.2 g, 38.7%) as an oil, b.p. 86—92 °C at 1 mmHg (Found: C, 64.6; H, 8.6. $C_{13}H_{18}O_4$ requires C, 65.0; H, 8.4%); δ(CCl_4) 1.0 (3 H, s, Me), 1.7 (4 H, s, CH_2CH_2), 2.23 (2 H, d, *J* 6 Hz, $CH_2CH{=}CH_2$), 3.7—4.2 (8 H, m, 2 × OCH_2CH_2O), and 4.8—6.4 (3 H, m, $CH{=}CH_2$); *m/e* 240 (M^+).

1,1;3,3-*Bisethylenedioxy*-2-*methylcyclopentane*-2-*acetaldehyde* (22).—Through a solution of the diacetal (21) (20 g) in methanol (100 ml) at −78 °C was bubbled ozone to give a saturated solution, to which dimethyl sulphide (20 ml) was added. The mixture was diluted with water (300 ml) and extracted with ether and the extract was washed with water and aqueous sodium chloride, and dried (Na_2SO_4). Evaporation left an oil, which was chromatographed on neutral alumina (grade III, 300 g) to give the *aldehyde* (22) (13.66 g, 67.8%) as an oil (Found: C, 59.25; H, 7.35. $C_{12}H_{18}O_5$ requires C, 59.5; H, 7.5%), $\nu_{max.}$ ($CHCl_3$) 1 740 cm^{-1} (C=O); δ(CCl_4) 1.15 (3 H, s, Me), 1.86 (4 H, s, CH_2CH_2), 2.25 (2 H, d, *J* 3 Hz, CH_2CHO), 3.9 (8 H, s, 2 × OCH_2CH_2O), and 9.7 (1 H, t, *J* 3 Hz, CH_2CHO); *m/e* 242 (M^+).

1,1;3,3-*Bisethylenedioxy*-2-[2-(1,2-*dihydro*-1-*cyano*-4-*methoxybenzocyclobuten*-1-*yl*)-2-*hydroxyethyl*]-2-*methylcyclopentane* (24).—To a stirred solution of the benzocyclobutene (23) [18] (11.6 g) and sodium amide [from sodium (3.36 g)] in liquid ammonia a solution of the aldehyde (22) (18 g) in anhydrous THF (50 ml) was added dropwise at −78 °C. After stirring had been continued for 30 min at the same temperature, the mixture was treated with an excess of crystalline ammonium chloride and the solvent removed to give a reddish residue which was diluted with aqueous ammonium chloride. The resulting mixture was extracted with ether, and the extract was washed with aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent afforded a reddish gum, which was chromatographed on neutral alumina (grade III, 500 g) with benzene–ethyl acetate (10 : 5 v/v) as eluant to give compound (24) (19.4 g, 66.3%) as a mixture of diastereoisomers, one part of which was subjected to careful chromatography on neutral alumina (grade III) using ethyl acetate–hexane (1 : 2 v/v) as eluant to afford one of the diastereoisomers as *prisms*, m.p. 162—163 °C (from benzene–hexane) (Found: C, 65.65; H, 6.65; N, 3.5. $C_{22}H_{27}NO_6$ requires C, 65.8; H, 6.8; N, 3.5%), $\nu_{max.}$ ($CHCl_3$) 3 425 (OH) and 2 225 cm^{-1} (C≡N); δ($CDCl_3$) 1.1 (3 H, s, Me), 1.9 (4 H, s, CH_2CH_2), 1.9—2.3 [2 H, m, $CH_2CH(OH)$], 3.55br (2 H, s, 2-H_2), 3.8 (3 H, s, OMe), 3.7—4.2 [9 H, m, $CH(OH)$ and 2 × OCH_2-CH_2O], and 6.7—7.3 (3 H, m, ArH): *m/e* 401 (M^+).

1,1;3,3-*Bisethylenedioxy*-2-[2-(1,2-*dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*ethyl*]-2-*methylcyclopentane* (25).—To a stirred solution of the benzocyclobutene (24) (7.4 g) in absolute ethanol (1 ml), anhydrous THF (100 ml), and liquid ammonia (200 ml) was added sodium (1.65 g) at −78 °C and the resulting solution stirred for 30 min at the same temperature. After addition of an excess of crystalline ammonium chloride followed by evaporation of the solvent, the residue was diluted with saturated aqueous ammonium chloride and extracted with ether. The extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent afforded a reddish gum, which was chromatographed on neutral alumina (grade III, 200 g) using hexane–ethyl acetate (4 : 1 v/v) as eluant to give (25) (5.6 g, 84.1%) as a *viscous syrup* (Found: C, 70.2; H, 7.8. $C_{21}H_{28}O_5$ requires C, 69.95, H, 7.85%); δ(CCl_4) 1.0 (3 H, s, Me), 1.6 (2 H, d, *J* 3 Hz, CH_2), 1.8 (4 H, s, $CHCH_2$), 2.45—2.9 (2 H, m, CH_2), 3.1—3.5 (3 H m, CH_2 and CH), 3.74 (3 H, s, OMe), 3.7—4.1 (8 H, m, 2 × OCH_2-CH_2O), and 6.6—7.15 (3 H, m, ArH); *m/e* 360 (M^+).

2-[2-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*ethyl*]-2-*methylcyclopentane*-1,3-*dione* (26).—A mixture of the diacetal (25) (2 g), 10% aqueous hydrochloric acid (1 ml), and THF (10 ml) was stirred for 30 min at room temperature. After addition of saturated aqueous sodium hydrogencarbonate (20 ml), the solution was extracted with ether. The extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent left a yellow oil, which was chromatographed on silica gel (30 g) with benzene as eluant to afford the *diketone* (26) (1.421 g, 94%) as an oil (Found: C, 74.95; H, 7.1. $C_{17}H_{20}O_3$ requires C, 74.95; H, 7.4%); $\nu_{max.}$ ($CHCl_3$) 1 720 cm^{-1} (C=O); δ(CCl_4) 1.05 (3 H, s, Me), 1.35—2.00 (4 H, m, 2 × CH_2), 2.7 (4 H, s, $COCH_2CH_2CO$), 3.0—3.7 (3 H, m, 1-H and 2-H_2), 3.75 (3 H, s, OMe), and 6.55—7.1 (3 H, m, ArH); *m/e* 272 (M^+).

2-[2-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*ethyl*]-3-*hydroxy*-2-*methyl*-3-*vinylcyclopentan*-1-*one* (27).—To a solution of vinylmagnesium bromide [from magnesium (240 mg) and vinyl bromide (1.1 g)] in anhydrous THF (30 ml) was added dropwise a solution of the diketone (26) (1.617 g) in anhydrous THF (10 ml) at 0 °C under stirring. After the stirring had been continued for 1 h at room temperature, saturated aqueous ammonium chloride was added and the resulting solution extracted with ether. The extract was washed with saturated aqueous sodium

chloride and dried (Na_2SO_4). Evaporation afforded a brown oil, which was chromatographed on silica gel (20 g) with benzene as eluant to give compound (27) (353 mg, 20%) as a syrup; $\nu_{max.}$ ($CHCl_3$) 1 740 cm^{-1} (C=O); δ(CCl_4) 0.9 (3 H, s, Me), 3.73 (3 H, s, OMe), 5.0—6.43 (3 H, m, CH=CH_2), and 6.55—7.1 (3 H, m, ArH); *m/e* 300 (M^+).

14α-*Hydroxyestrone* 3-*Methyl Ether* (5).—A solution of compound (27) (60 mg) in *o*-dichlorobenzene (3 ml) was heated at 180 °C for 4 h under a current of nitrogen. After evaporation of the solvent the residue was chromatographed on silica gel (2 g) with benzene–ethyl acetate (100 : 1 v/v) as eluant to give (5) (27 mg, 45%) as *prisms*, m.p. 195—196 °C (from carbon tetrachloride) (Found: C, 73.25; H, 7.7. $C_{19}H_{24}O_3$,0.33H_2O requires C, 73.05; H, 8.15%), $\nu_{max.}$ ($CHCl_3$) 1 740 cm^{-1} (C=O); δ($CDCl_3$) 1.03 (3 H, s, Me), 3.8 (3 H, s, OMe), 6.76 (1 H, d, *J* 3 Hz, ArH), 6.83 (1 H, dd, *J* 3 and 8 Hz, ArH), and 7.33 (1 H, d, *J* 8 Hz, ArH); *m/e* 300 (M^+).

Estra-1,3,5(10),14-*tetraene*-3,17β-*diol* 17-*t*-*Butyldimethylsilyl Ether* (29).—To a solution of estra-1,3,5(10),14-tetraene-3,17β-diol bis-(t-butyldimethylsilyl ether) (28) (500 mg) in acetone (20 ml) was added 10% aqueous sodium hydroxide (0.3 ml) in small portions with stirring at room temperature. The mixture was stirred for a further 3 h at room temperature. After addition of saturated aqueous ammonium chloride (1 ml) followed by evaporation of the acetone, the residue was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent gave an oil, which was chromatographed on silica gel (5 g) with hexane to give the *phenol* (29) (325 mg, 84.3%) as needles, m.p. 166—167 °C (from hexane) (Found: C, 75.0; H, 9.45. $C_{24}H_{36}O_2Si$ requires C, 75.0; H, 9.45%); $\nu_{max.}$ ($CHCl_3$) 3 600 cm^{-1} (OH); δ($CDCl_3$) 0.06 (6 H, s, $SiMe_2$), 0.90 (9 H, s, $SiCMe_3$), 0.98 (3 H, s, Me), 1.30—3.10 (12 H, m, 5 × CH_2 and 2 × CH), 4.03 (1 H, t, *J* 8 Hz, 17-H), 5.19 (1 H, m, 15-H), 6.53—6.72 (2 H, m, 2- and 4-H), and 7.11br (1 H, s, 1-H); *m/e* 384 (M^+).

Estra-1,3,5(10),14-*tetraene*-3,17β-*diol* 17-*t*-*Butyldimethylsilyl* 3-*Methyl Bisether* (30).—To a solution of the phenol (29) (300 mg) in acetone (20 ml) was added dropwise 40% aqueous potassium hydroxide (0.15 ml) and dimethyl sulphate (0.1 ml) at room temperature with stirring, and the resulting mixture was stirred for 1.5 h. After addition of saturated aqueous ammonium chloride followed by evaporation of the acetone, the residue was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Evaporation afforded an oil, which was chromatographed on silica gel (5 g) with hexane as eluant to give the *methyl ether* (30) (250 mg, 80.4%) as needles, m.p. 89—90 °C (from methanol), $[\alpha]_D$ +113.5° (*c* 0.008, $CHCl_3$) (Found: C, 75.0; H, 9.9. $C_{25}H_{38}O_2Si$ requires C, 75.3; H, 9.6%); δ($CDCl_3$) 0.05 (6 H, s, $SiMe_2$), 0.90 (9 H, s, $SiCMe_3$), 1.00 (3 H, s, Me), 1.20—3.20 (12 H, m, 5 × CH_2 and 2 × CH), 3.78 (3 H, s, OMe), 4.04 (1 H, t, *J* 8 Hz, 17-H), 5.15—5.50 (1 H, m, >C=CH), and 6.53—7.19 (3 H, m, ArH); *m/e* 398 (M^+).

Epoxidation of Compound (30).—To a solution of the olefin (30) (190 mg) in dry dichloromethane (20 ml) was added in small portions *m*-chloroperbenzoic acid (100 mg) at room temperature and the mixture stirred for 2 h at room temperature. After addition of saturated aqueous sodium hydrogencarbonate the organic layer was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Evaporation left an oil which was chromatographed on silica gel (5 g) using hexane–benzene (1 : 1 v/v) as eluant. The first fraction afforded the α-*epoxide* (31) (113 mg, 57.2%) as needles, m.p. 118—119 °C (from methanol), $[\alpha]_D$ +78.0° (*c* 0.006, $CHCl_3$) (Found: C, 72.25; H, 9.45. $C_{25}H_{38}O_3Si$ requires C, 72.4; H, 9.25%); δ(CCl_4) 0.03 (6 H, s, $SiMe_2$), 0.90 (12 H, s, Me and $SiCMe_3$), 1.20—3.10 (12 H, m, 5 × CH_2 and 2 × CH), 3.43br (1 H, s, 15-H), 3.63—3.82 (1 H, m, 17-H), 3.80 (3 H, s, OMe), and 6.44—7.15 (3 H, m, ArH); *m/e* 414 (M^+). The second fraction yielded the β-*epoxide* (32) (27 mg, 13.7%) as needles, m.p. 76—79 °C, (from methanol) (Found: C, 71.6; H, 9.3. $C_{25}H_{38}O_3Si$, 0.33MeOH requires C, 71.55; H, 9.3%); δ(CCl_4) 0.30 (6 H, s, $SiMe_2$), 0.90 (9 H, s, $SiCMe_3$), 1.03 (3 H, s, Me), 1.20—3.00 (12 H, m, 5 × CH_2 and 2 × CH), 3.25br (1 H, s, 15-H), 3.5—3.8 (1 H, m, 17-H), 3.70 (3 H, s, OMe), and 6.4—7.1 (3 H, m, ArH); *m/e* 414 (M^+).

Estra-1,3,5(10)-*triene*-3,14α,17β-*triol* 17-t-*Butyldimethylsilyl* 3-*Methyl Bisether* (33).—A solution of the epoxide (31) (100 mg) in dry ether (5 ml) was added to a suspension of lithium aluminium hydride (100 mg) in dry ether (20 ml) at room temperature and the stirring continued for 5 h at room temperature. After addition of water followed by evaporation of the ether, the residue was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent afforded an oil, which was chromatographed on silica gel (2 g) using hexane–benzene (1 : 1 v/v) as eluant to give the *hydroxy-compound* (33) (65 mg, 64.7%) as prisms, m.p. 121—122 °C (from hexane), $[\alpha]_D$ +67.1° (*c* 0.007, $CHCl_3$) (Found: C, 72.3; H, 9.9. $C_{25}H_{40}O_3Si$ requires C, 72.05; H, 9.7%); δ(CCl_4) 0.04 (6 H, s, $SiMe_2$), 0.87 (3 H, s, Me), 0.90 (9 H, s, $SiCMe_3$), 1.20—3.15 (14 H, m, 6 × CH_2 and 2 × CH), 3.71 (3 H, s, OMe), 4.31 (1 H, t, *J* 6 Hz, 17-H), and 6.45—7.13 (3 H, m, ArH); *m/e* 416 (M^+).

Estra-1,3,5(10)-*triene*-3,14α,17β-*triol* 3-*Methyl Ether* (6).—To a solution of the silyl ether (33) (30 mg) in acetone (10 ml), 2N-hydrochloric acid (0.45 ml) was added in small portions with stirring at 0 °C and the stirring continued for 7 h at the same temperature. After addition of saturated aqueous sodium hydrogencarbonate, the solvent was removed to give a residue which was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried (Na_2SO_4), and evaporated to leave a yellow oil, which was subjected to preparative t.l.c. using benzene–ethyl acetate (1 : 1 v/v) as eluant to give the *alcohol* (6) (16 mg, 73.5%) as needles, m.p. 164—165 °C (from benzene) (Found: C, 74.55; H, 8.65. $C_{19}H_{26}O_3$, 0.1H_2O requires C, 74.7; H, 8.7%); $\nu_{max.}$ ($CHCl_3$) 3 620 cm^{-1} (OH); δ($CDCl_3$) 0.90 (3 H, s, Me), 1.20—3.15 (14 H, m, 6 × CH_2 and 2 × CH), 3.77 (3 H, s, OMe), 4.46 (1 H, t, *J* 6 Hz, 17-H), and 6.55—7.30 (3 H, m, ArH); *m/e* 302 (M^+).

14α-*Hydroxyestrone* 3-*Methyl Ether* (5).—To a solution of the alcohol (6) (10 mg) in acetone (2 ml) was added Jones reagent (0.2 ml) at 0 °C and the resulting mixture was stirred at this temperature for 30 min. After dilution with water (5 ml), the resultant solution was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Evaporation left a pale yellow oil, which was subjected to preparative t.l.c. using hexane–ethyl acetate (1 : 1 v/v) as eluant to give the ketone (5) (7 mg, 70.4%) as needles, m.p. 175—176 °C (from carbon tetrachloride), $[\alpha]_D$ +152.5° (*c* 0.008, $CHCl_3$); *m/e* 300 (M^+), identical (i.r., n.m.r.) with the sample obtained from the thermolysis of benzocyclobutene (27).

To a solution in methanol (3 ml) of the ketone (5) (5 mg) obtained above was added in small portions sodium borohydride (2 mg) and the mixture stirred for 4 h at room temperature. After removal of the solvent, the residue was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Evaporation afforded a powder, which was recrystallized from benzene to give compound (6) (3 mg, 59.6%) as needles, m.p. 164—165 °C, identical (i.r., n.m.r., mixed m.p.) with the sample obtained from the silyl ether (33).

Estra-1,3,5(10),14-tetraene-3,17β-diol 3-Methyl Ether (3).—To a solution of the silyl ether (33) (50 mg) in acetone (20 ml) was added in small portions with stirring at room temperature 5N-hydrochloric acid (0.15 ml) and the mixture stirred for 3.5 h at the same temperature. After addition of saturated aqueous sodium hydrogencarbonate, the solvent was evaporated to leave an oil, which was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent yielded an oil, which was chromatographed on silica gel (1 g) using benzene to give *compound* (3) (22 mg, 60.6%) as needles, m.p. 112—114 °C (from hexane) [lit.,[2] 112—114 °C] (Found: C, 79.35; H, 8.6. $C_{19}H_{24}O_2,0.17H_2O$ requires C, 79.4; H, 8.55%); $\nu_{max.}$ ($CHCl_3$) 3 625 cm^{-1} (OH); δ(CCl_4) 0.98 (3 H, s, Me), 1.20—3.20 (12 H, m, 5 × CH_2 and 2 × CH), 3.71 (3 H, s, OMe), 4.00 (1 H, t, *J* 8 Hz, 17-H), 5.14br (1 H, s, >C=CH), and 6.42—7.11 (3 H, m, ArH); *m/e* 284 (M^+).

A solution of compound (6) (10 mg) in acetone (5 ml) was also treated with 5N-hydrochloric acid (0.1 ml) by the same procedure as above to give compound (3) (6 mg, 63.7%), identical (i.r., n.m.r., mixed m.p.) with the sample obtained from compound (33).

14-*Dehydroestrone Methyl Ether* (2).—To a solution of compound (3) (11 mg) in acetone (2 ml) at 0 °C was added Jones reagent (0.2 ml) and the reaction mixture stirred for 20 min at the same temperature. After dilution with water (5 ml), the solution was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution and dried (Na_2SO_4). Removal of the solvent afforded an oil, which was chromatographed on silica gel (500 mg) with benzene as eluant to yield the *ketone* (2) (10 mg, 91.5%) as needles, m.p. 101—102 °C (from hexane) (lit.,[1] m.p. 100—102 °C), $[\alpha]_D$ +348° (*c* 0.001, $CHCl_3$) (Found: C, 80.9; H, 7.65. $C_{19}H_{22}O_2$ requires C, 80.8; H, 7.85%); $\nu_{max.}$ ($CHCl_3$) 1 738 cm^{-1} (C=O); δ(CCl_4) 1.14 (3 H, s, Me), 1.2—3.2 (12 H, m, 5 × CH_2 and 2 × CH), 3.74 (3 H, s, OMe), 5.60br (1 H, s, >C=CH), and 6.50—7.25 (3 H, m, ArH); *m/e* 282 (M^+).

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