Efficient Synthesis of a Pregnane-type Steroid. Total Synthesis of (+)-5α-Dihydropregnenolone [(+)-3β-Hydroxy-5α-pregnan-20-one]

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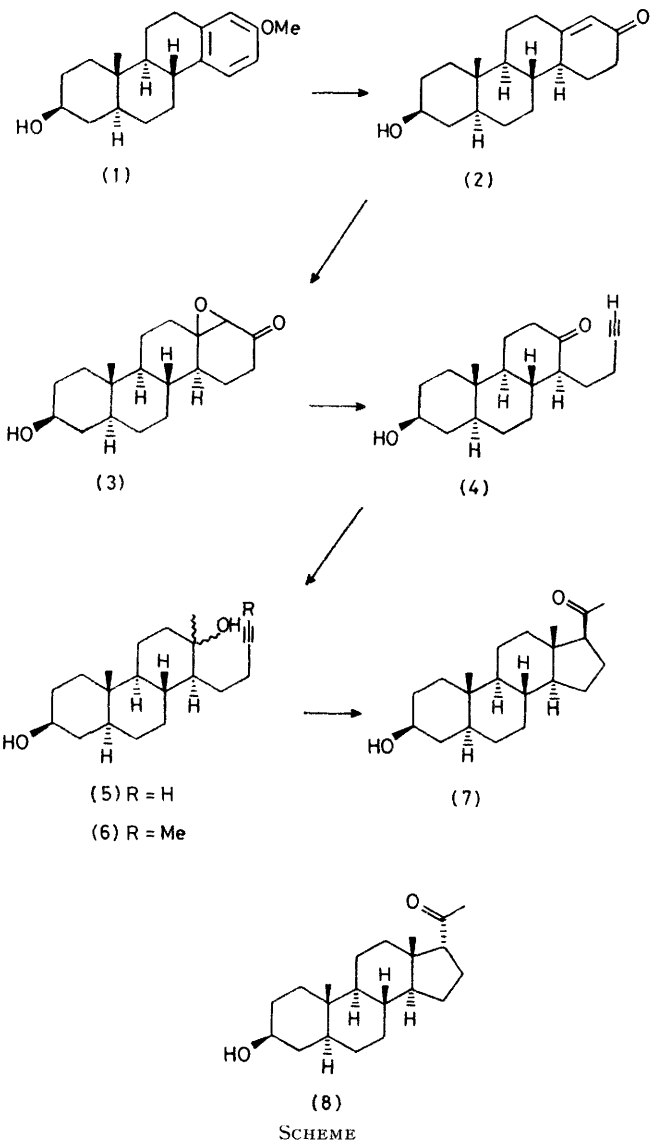
An efficient total synthesis of the title compound (7) was carried out by acetylene-cation cyclisation of a 1-(pent-3-ynyl)perhydro-2-phenanthrol (6) which was prepared from a ring-D-aromatic steroid (1) *via* Eschenmoser ring-opening of its 13,17a-epoxy-17-oxo-derivative (3).

THE stereocontrolled synthesis of *trans*-fused hydrindane derivatives has recently attracted much attention [1-4] mainly due to the fact that the steroidal nucleus incorporates such a ring system. From among the available methods, acetylene-cation cyclisation has proved to be the most promising with regard to construction of the *trans*-hydrindane portion of 20-keto-steroids.[5-7] The key intermediates in this synthetic route are acetylenic alcohols and their stereoselective synthesis is thus of prime importance for exploitation of the method. Taking advantage of a facile stereoselective and asymmetric synthesis of ring-D-aromatic steroids developed by us,[8,9] we now report an efficient synthesis of the acetylenic alcohol (6), starting from (+)-3-hydroxy-17-methoxy-D-homo-18-nor-5-androsta-13,15,17-triene (1),[9] and its cyclisation to (+)-5α-dihydropregnenolone [(+)-3β-hydroxy-5α-pregnan-20-one] (7). Reduction of (1) with lithium in liquid ammonia and tetrahydrofuran in the presence of t-butyl alcohol, and treatment of the product with 10% hydrochloric acid in methanol produced the enone (2). This product was identical (i.r. and n.m.r. spectra) to an authentic racemic sample [10] indicating it to have the stereochemistry depicted in formula (2). Conversion into the epoxide (3) was achieved on treatment of (2) with 30% hydrogen peroxide in 10% aqueous sodium hydroxide and methanol. The acetylenic ketone (4) resulting from Eschenmoser ring-opening of the epoxide (3), using toluene-*p*-sulphonyl hydrazide in acetic acid and dichloromethane, was treated with methyl-lithium in tetrahydrofuran to give the acetylenic alcohol (5). Methylation of the terminal acetylene group by treatment with methyl iodide in the presence of lithium amide in liquid ammonia and tetrahydrofuran produced the requisite acetylenic alcohol (6) in which all the chiral centres, other than that at C-2, are already fixed. Treatment of (6) with a mixture of trifluoroacetic acid and trifluoroacetic anhydride and hydrolysis of the resulting enol trifluoroacetate with 10% potassium hydroxide afforded 5α-dihydropregnenolone (7), identical to an authentic sample (obtained by recrystallizing commercially available material) in all aspects except for the value of the optical rotation ($[\alpha]_D$ +85.0° *vs.* +93.0° for the authentic sample) which indicated the optical purity of our product to be 91.4%, *i.e.* the enantiomeric excess to be 95.7%. Equilibration of (7), effected by treatment with potassium t-butoxide, produced a mixture of (7) and the diastereoisomer (8). Although the presence of the isomer (8) in the crude cyclisation product was recognised from comparison of the n.m.r. spectra, the C-13-diastereoisomeric compound was not detected.



SCHEME

EXPERIMENTAL

M.p.s were taken with a Yanagimoto micro-apparatus (MP-52). I.r. spectra were obtained with a Hitachi 215

recording spectrophotometer and n.m.r. spectra with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are reported as δ values relative to internal tetramethylsilane. Mass spectra were recorded on a Hitachi RMU-7 spectrometer. All optical rotations were measured in chloroform solution at 20 °C on a JASCO-PIP-SL polarimeter using a 1-dm cell.

(−)-3β-*Hydroxy*-D-*homo*-18-*nor*-5α-*androst*-13(17a)-*en*-17-*one* (2).—To a stirred solution of lithium (49 mg) in liquid ammonia (100 ml), anhydrous t-butyl alcohol (50 ml), and anhydrous tetrahydrofuran (50 ml) at −33 °C was added a solution of the ether (1) (185 mg) in anhydrous tetrahydrofuran (5 ml). Stirring was continued for 5 h at −33 °C and to the reaction mixture was then added ethanol. After evaporation of the solvent, saturated ammonium chloride solution (100 ml) was added and the resulting mixture was extracted with benzene (×3). The combined extracts were washed with saturated sodium chloride solution and dried (Na_2SO_4). After removal of the solvent the residue was dissolved in methanol (20 ml). This solution was treated with 10% hydrochloric acid (1 ml), and the mixture stirred for 4 h at room temperature under nitrogen. The mixture was diluted with water (50 ml) and then extracted with benzene (×3). The combined benzene extracts were washed with saturated sodium hydrogencarbonate solution and saturated sodium chloride solution and dried (Na_2SO_4). Evaporation afforded a yellow gum which was chromatographed on silica gel (4 g) using dichloromethane as eluant to give, after recrystallisation from acetone, the *enone* (2) (124 mg, 70.5%) as needles, m.p. 188—189 °C (Found: C, 78.55; H, 9.4. $C_{19}H_{28}O_2 \cdot 0.2H_2O$ requires C, 78.15; H, 9.80%); *m/e* 288 (M^+); $\nu_{max.}$ ($CHCl_3$) 3 600 (OH) and 1 660 cm^{-1} (C=O); δ($CDCl_3$) 0.74 (3 H, s, Me), 3.20—4.00 (1 H, m, 3-H), and 5.86br (1 H, s, 17a-H); $[\alpha]_D^{20}$ −37.3° (*c* 0.51).

(−)-13,17a-*Epoxy*-3β-*hydroxy*-D-*homo*-18-*nor*-5α-*androstan*-17-*one* (3).—To a stirred solution of the enone (2) (439 mg) in methanol (1 ml) at 0 °C was added 30% hydrogen peroxide (3 drops) and 10% aqueous sodium hydroxide (3 drops). After stirring for 15 min at 0 °C, the mixture was diluted with ice-cold water (50 ml) and extracted with benzene (×3). The combined extracts were washed with saturated sodium chloride solution and dried (Na_2SO_4). Removal of the solvent gave a colourless gum, which was chromatographed on silica gel (10 g) with chloroform as eluant to afford the *epoxide* (3) (441 mg, 95.2%) as an oil (Found: M^+, 304.207 3. $C_{19}H_{28}O_3$ requires *M*, 304.203 8); $\nu_{max.}$ ($CHCl_3$) 3 600 (OH) and 1 700 cm^{-1} (C=O); δ($CDCl_3$) 1.08 (3 H, s, Me), 3.07 (1 H, s, 17a-H), and 3.25—4.00 (1 H, m, 3-H); $[\alpha]_D^{20}$ −38.0° (*c* 0.335).

(−)-1-(*But*-3-*ynyl*)-7β-*hydroxy*-4bβ-*methyl*-3,4,4aα,4b,5,6,7,8,8a,9,10,10aβ-*dodecahydrophenanthren*-2(1H)-*one* (4).—A solution of the epoxide (3) (320 mg) and toluene-*p*-sulphonyl hydrazide (195 mg) in acetic acid–dichloromethane (5 ml; 1 : 1 v/v) was stirred for 10 min at −20 °C, stored at −20 °C for 20 h and then stirred for 4 h at room temperature. The mixture was diluted with water (50 ml) and extracted with benzene (×3). The extract was washed with saturated sodium hydrogencarbonate solution and saturated sodium chloride solution and dried (Na_2SO_4). Removal of the solvent gave a yellow gum which was chromatographed on silica gel (7 g) using dichloromethane as eluant to afford the *acetylenic ketone* (4) (170 mg, 59.0%) as an oil (Found: M^+, 288.212 5. $C_{19}H_{28}O_2$ requires *M*, 288.209 0); $\nu_{max.}$ ($CHCl_3$) 3 600 (OH), 3 310 (−C≡CH), and 1 700 cm^{-1} (C=O); δ($CDCl_3$) 0.76 (3 H, s, Me) and 3.33—4.00 (1 H, m, 3-H); $[\alpha]_D^{20}$ −6.87° (*c* 0.495).

(−)-1-(*But*-3-*ynyl*)-7β-*hydroxy*-2,4bβ-*dimethyl*-1,2,3,4,4aα,5,6,7,8,8a,9,10,10aβ-*tetradecahydro*-2-*phenanthrol* (5).—To a stirred solution of the acetylenic ketone (4) (200 mg) in anhydrous tetrahydrofuran (50 ml) at 0 °C was added methyl-lithium (20 ml; 1.5M solution in ether) and the mixture was stirred for 1 h at 0 °C. After addition of water (1 ml) and evaporation of the solvent, water (50 ml) was added to the residue and the resulting mixture was extracted with benzene (×3). The combined benzene extract was washed with saturated sodium chloride solution and dried (Na_2SO_4). Removal of the solvent and chromatography of the residue on silica gel (5 g) using chloroform as eluant gave the *acetylenic alcohol* (5) (166 mg, 78.7%) as an oil (Found: M^+, 304.241 3. $C_{20}H_{32}O_2$ requires *M*, 304.240 2); $\nu_{max.}$ ($CHCl_3$) 3 600 (OH) and 3 310 cm^{-1} (−C≡CH); δ($CDCl_3$) 0.81 (3 H, s, Me), 1.20 (3 H, s, Me), and 3.21—4.00 (1 H, m, 3-H), $[\alpha]_D^{20}$ −10.8° (*c* 0.5).

(−)-7β-*Hydroxy*-2,4bβ-*dimethyl*-1-(*pent*-3-*ynyl*)-1,2,3,4,4aα,5,6,7,8,8a,9,10,10aβ-*tetradecahydro*-2-*phenanthrol* (6).—To a stirred solution of lithium amide [from lithium (48 mg) and excess of liquid ammonia] and the acetylenic alcohol (5) (122 mg) in liquid ammonia (50 ml) and anhydrous tetrahydrofuran (15 ml) at −33 °C was added methyl iodide (0.3 ml). After stirring for 5 h at −33 °C, the mixture was treated with an excess of solid ammonium chloride and the solvent was evaporated off. The reddish residue was diluted with saturated ammonium chloride solution and the resulting mixture was extracted with benzene (×3). The combined extracts were washed with saturated sodium chloride solution and dried (Na_2SO_4). Removal of the solvent afforded a reddish gum which was chromatographed on silica gel (5 g) using chloroform as eluant to give the *alcohol* (6) (81 mg, 63.9%) as an oil (Found: M^+, 318.258 5. $C_{21}H_{34}O_2$ requires *M*, 318.255 9); $\nu_{max.}$ ($CHCl_3$) 3 600 cm^{-1} (OH); δ($CDCl_3$) 0.61 (3 H, s, Me), 1.20 (3 H, s, Me), 1.77 (3 H, s, Me), and 3.33—4.00 (1 H, m, 3-H); $[\alpha]_D^{20}$ −14.8° (*c* 0.705).

Cyclisation of (6).—To a mixture of trifluoroacetic acid (1.5 ml) and trifluoroacetic anhydride (0.75 ml) at −18 °C was added the acetylenic alcohol (6) (32 mg) and the resulting mixture was stirred for 2 h at −18 °C. After evaporation of the solvent, the residue was dissolved in ethanol (5 ml) and the solution treated with 10% ethanolic potassium hydroxide (1 ml) and then stirred for 4 h at room temperature. After evaporation of the solvent, the residue was extracted with benzene (×3). The extract was washed with saturated sodium chloride solution and dried (Na_2SO_4). Evaporation gave a yellow gum which was chromatographed on silica gel (1 g) using benzene as eluant to afford, after recrystallisation from benzene, (+)-3β-hydroxy-5α-pregnan-20-one (7) (8 mg, 24.9%) as needles, m.p. 193—195 °C (lit.,[11] 192—195 °C); $\nu_{max.}$ ($CHCl_3$) 3 600 (OH), and 1 720 cm^{-1} (C=O); δ($CDCl_3$) 0.60 (3 H, s, Me), 0.81 (3 H, s, Me), 2.12 (3 H, s, Me), and 3.35—4.20 (1 H, m, 3-H), $[\alpha]_D^{20}$ +85.0° (*c* 0.04). Further elution with benzene gave a mixture of (7) and (8) [1 : 2 (n.m.r.)] (12 mg, 37.4%); $\nu_{max.}$ ($CHCl_3$) 3 600 (OH) and 1 720 cm^{-1} (C=O); δ($CDCl_3$) 0.60 and 0.90 (each s, Me), 0.81 (s, Me), 2.11 and 2.12 (each s, Me), and 3.35—4.20 (1 H, m, 3-H); *m/e* 318.

Equilibration of (+)-3β-*Hydroxy*-5α-*pregnan*-20-*one* (7) *using Potassium t-Butoxide*.—To a stirred solution of potassium t-butoxide [prepared from potassium (185 mg)] in t-butyl alcohol (50 ml) was added a solution of the

hydroxy-ketone (7) (900 mg) in absolute t-butyl alcohol (10 ml) and the mixture was refluxed for 18 h under nitrogen. After evaporation of the solvent, the residue was diluted with water (100 ml) and the resulting mixture was extracted with benzene. The benzene extract was washed with saturated sodium chloride solution and dried (Na_2SO_4). Removal of the solvent and chromatography of the residue on silica gel (20 g) using benzene as eluant gave a mixture of (7) and (8) [3 : 2 (n.m.r.)] (785 mg, 87.2%) as an oil, identical to the mixture of (7) and (8) obtained above [i.r. ($CHCl_3$) and n.m.r. ($CDCl_3$) spectra except for the integration of each signal].

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