Alkylated Steroids. Part 5.[1] Formation of 17β-Acetylenic Steroids from Hindered 20-Oxo-compounds *via* Grignard Derived Enolates

By **Robert T. Logan,* Robert G. Roy,** and **Gilbert F. Woods,** Organon Scientific Development Group, Organon Laboratories Limited, Newhouse, Lanarkshire ML1 5SH, Scotland

Treatment of methyl 3β-acetoxy-16α,17α-dimethyl-5α-androst-9(11)-ene-17-carboxylic acid (1), or 3β-hydroxy-16α,17α-dimethyl-5α-pregn-9(11)-en-20-one (4), with methylmagnesium halide in refluxing anisole gives the 20-yne (3). Similarly 3β-acetoxy-16α,17α-dimethylpregn-5-en-20-one (5) gives the 20-yne (6). The mechanism of the reaction is discussed in terms of the steric hindrance due to the 16- and 17-methyl groups. Acetylenes (3) and (6) are converted into compounds of potential pharmacological interest.

In part 4 [1] we described the isolation and identification of the 16α,17α-dimethyl etianate (1) as one of two major products formed by a Favorskii reaction on the corresponding 16α-methyl-17α-bromo-20-oxopregnane. In pursuance of our interest in 16α,17α-dimethylpregnanes [2,3] of biological interest, the ester (1) was treated with methyl Grignard reagent in an attempt to reconstitute the pregnane side-chain.[4] We now report the outcome of this investigation.

Treatment of the 17-ester (1) with a large excess of methylmagnesium bromide in boiling benzene [4] resulted only in hydrolysis of the 3-acetate group. Under more forcing conditions, the 3-alcohol (2) in refluxing anisole, gave only a trace of the desired pregnen-20-one (4). Instead, the major product was the pregnyne (3) [$\nu_{max.}$ 3 300(C≡CH) and 2 190 cm^{-1} (−C≡C−); and δ 2.1(C≡CH)].

The reaction between Grignard reagents and hindered esters is known to result in the formation of the magnesium salt of the enolised ketones.[5,6] We have previously proposed the intermediacy of such an enolate (B) by the action of methylmagnesium halide on 16α,17α-dimethyl-20-oxopregnanes, in the formation of 16α,17α,-21-trimethylpregnanes.[2] Hence, the formation of the pregnyne (3) is envisaged as arising by pyrolytic cleavage of enolate (B), derived from salt (A). Support for this view was obtained when the 16α,17α-dimethyl-20-oxopregnane (4), treated with methylmagnesium chloride under the forcing conditions described above gave the pregnyne (3) in 71% yield. A similar result was achieved with the 21-bromo-derivative (4a), and in the pregn-5-ene series, the 16α,17α-dimethylpregnenolone acetate (5) gave the pregnyne (6) in 80% yield. The pregnyne (6) was also formed when the dimethylpregnenolone acetate (5) was treated with ethylmagnesium bromide in refluxing anisole. In this case the reaction was complete in *ca.* 1 h, in contrast to the prolonged (20—40 h) reaction times required with methyl Grignard reagent.

Steric hindrance in the ester (1) due to the 16α- and 17α-methyl groups has been demonstrated by its resistance to hydrolysis,[1] and its failure to react with methyl Grignard reagent under conditions in which the 17α-monomethyl pregnane (7) was formed from the corresponding 17α-methyl etianic ester.[4] In order to determine the individual contribution of the 16α- and 17α-methyl groups to the steric hindrance of the 20-carbonyl group, the mono-substitituted derivatives (7) and (10) were treated with methylmagnesium halide in anisole at reflux temperature. The 17α-methylpregnenolone (7) gave an equal mixture of the acetylene (8) and the vinyl compound (9). The latter was probably formed by pyrolysis of the magnesium salt (C) of the carbinol. The 16α-methylpregnenolone (10) gave no acetylenic material, the only product being the expected carbinol (11). The absence of elimination in this case was probably due to the lack of significant steric compression from the 16α-methyl group in the salt (D).

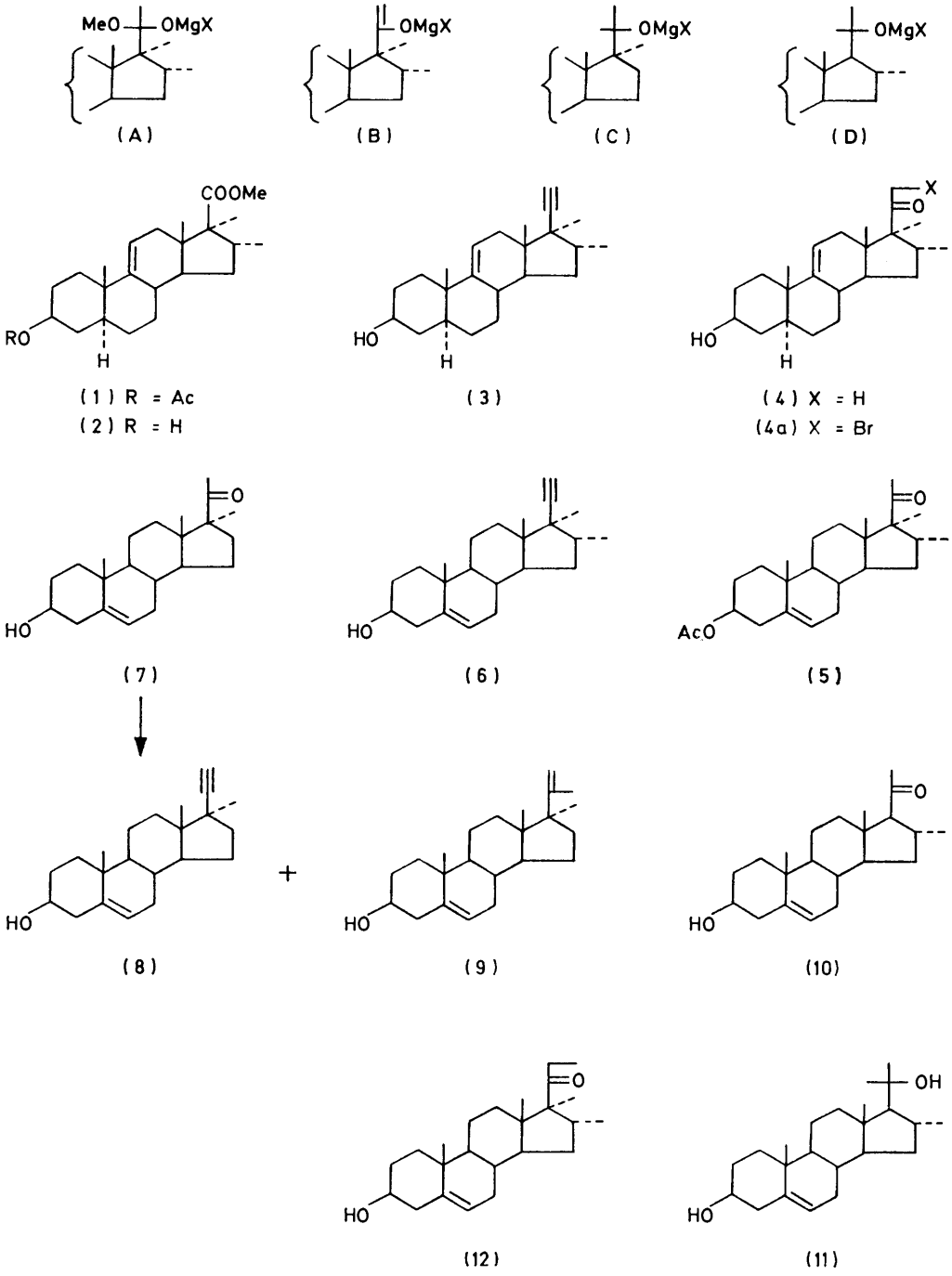
Thus the major contribution to steric hindrance is due to the 17α-methyl group, but the combined effect from both 16α- and 17α-methyl groups is required to prevent completely the alkylation of the 20-carbonyl group. The presence of an additional methyl group at C-21 as in trimethylpregnenolone (12), resulted in the recovery of starting material after prolonged treatment with methyl Grignard reagent in boiling anisole.

The acetylenes (6) and (3) were converted into the products (13), (18), and (21) of potential pharmacological interest, by the routes outlined in Schemes 1 and 2.

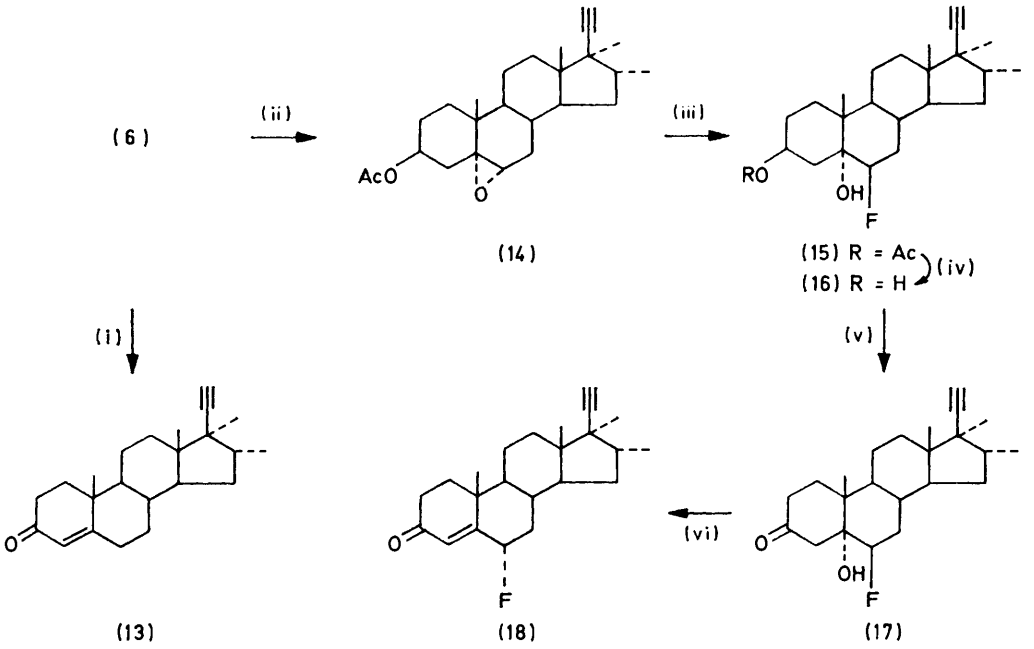
EXPERIMENTAL

M.p.s were taken with a Kofler micro hot-stage apparatus. I.r. spectra were determined with a Perkin-Elmer 457 spectrometer. U.v. spectra were determined for solutions in ethanol with a Perkin-Elmer 402 spectrometer. Optical rotations were measured for solutions in chloroform. G.l.c. was performed with a Hewlett-Packard 5720 chromatograph and quoted retention times are relative to cholestane (t_R 1.0 on SE 30 at 225 °C). ^{1}H N.m.r. spectra were recorded at 60 and 100 MHz with Varian Associates A-60 and XL-100A-12FT spectrometers, respectively. Solutions of products were dried over anhydrous magnesium sulphate. Throughout, ether refers to diethyl ether.

16α,17α-Dimethylpregn-9(11)-en-20-yn-3β-ol (3).—(*a*) *Treatment of methyl 3β-acetoxy-16α,17α-dimethyl-5α-androst-9(11)-ene-17-carboxylic acid* (1) *with methylmagnesium bromide.* A solution of the ester (1) (2.43 g) in dry benzene was added to a stirred ethereal solution of methylmagnesium bromide (75 ml) (from 0.92 g of magnesium). The ether was distilled off and replaced by dropwise addition of dry benzene so that the volume of the solution was maintained at 75 ml.

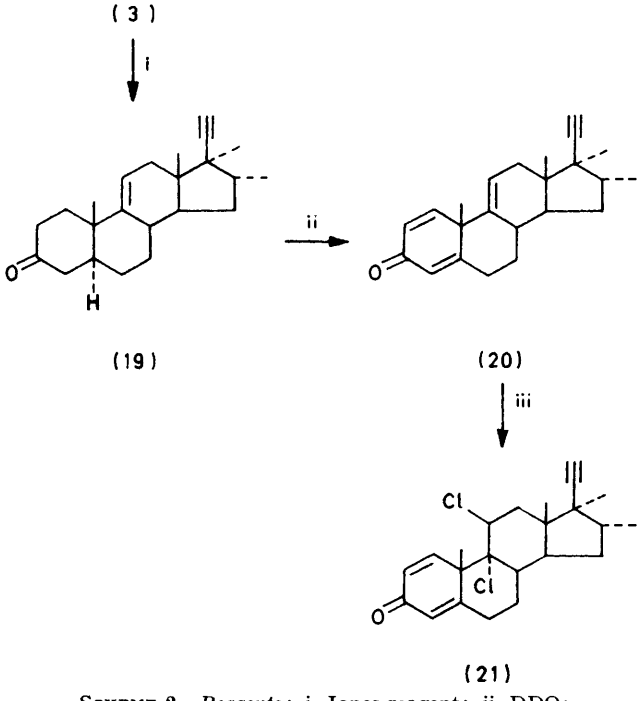


The mixture was stirred under reflux and monitored by t.l.c. After 10.5 h the product consisted mainly of hydrolysed starting material (2). More Grignard reagent (from 3.68 g of magnesium) was added and the solvent was replaced by distillation and simultaneous addition of anisole until the vapour temperature reached 145 °C (final volume *ca.* 100 ml). Periodic samples taken from the stirred refluxing mixture showed (g.l.c.) increasing amounts of a component (t_R 0.48) which constituted *ca.* 90% of the product after 20 h. The reaction mixture was cooled and poured into 5% ammonium chloride solution (500 ml) and the mixture was treated with hydrochloric acid solution (2M; 100 ml). The organic layer was separated and the aqueous solution was extracted with toluene (2 × 100 ml). The combined organic solutions were washed successively with water (50 ml), aqueous sodium hydroxide (1M; 2 × 50 ml), and hydrochloric acid solution (2M; 50 ml), and then steam-distilled to give an aqueous suspension of the product. Extraction into ethyl acetate gave a solution which was washed with water, dried, and evaporated under reduced pressure to give a yellow solid (2.1 g). This solid was dissolved in dichloromethane (20 ml) and the solution was poured on to a short column of alumina.



SCHEME 1 *Reagents:* i, $Al(Pr^iO)_3$, cyclohexanone; ii, NaOAc, AcO_2H; iii, HF, BF_3–Et_2O; iv, $HClO_4$; v, Jones reagent; vi, HCl, AcOH

Elution with dichloromethane gave the major component (1.7 g) contaminated with two minor impurities. Elution with ether gave a fraction (0.2 g) containing none of the major component. Recrystallisation of the dichloromethane fraction from methanol, then acetone–n-hexane (twice) gave 16α,17α-*dimethylpregn*-9(11)-*en*-20-*yn*-3β-*ol* (3), m.p. 174 °C, $[\alpha]_D$ −26.7° (*c* 1.0), t_R 0.49; $\nu_{max.}$ (CH_2Cl_2) 3 650(OH), 3 300(C≡CH), and 2 190 cm^{-1} (–C≡C–); δ (CDCl$_3$) 0.95 (6 H, s, 13- and 17α-Me), 1.01 (3 H, s, 10-Me), 1.11 (3 H, d, *J* 7 Hz, 16α-Me), 2.10 (1 H, s, acetylenic-H), 2.33 (1 H, m, 16β-H), 3.55 (1 H, m, 3α-H), and 5.35 (1 H, m, 11-H) (Found: C, 84.35; H, 10.8. $C_{23}H_{34}O$ requires C, 84.6; H, 10.5%).



SCHEME 2 *Reagents:* i, Jones reagent; ii, DDQ; iii, Cl_2

(*b*) *Treatment of* 3β-*hydroxy*-16α,17α-*dimethyl*-5α-*pregn*-9(11)-*en*-20-*one* (4) *with methylmagnesium chloride.* A solution of the 16α,17α-dimethyl compound (4) [3] (35 g) in anisole (1 l) was added to a stirred solution of methylmagnesium chloride (from 45 g of magnesium) in tetrahydrofuran (750 ml) at 20 °C under nitrogen. The tetrahydrofuran was distilled off, anisole being added simultaneously to keep the volume constant, until the vapour temperature reached 145 °C. The reaction mixture (monitored by t.l.c.) was then refluxed for 22 h, cooled, and poured into ice-cold sulphuric acid (1M; 3 l). The organic layer was separated and the aqueous solution was extracted with ether (3 × 200 ml). The combined organic extracts were washed successively with water (3 × 200 ml), 5% potassium carbonate solution (100 ml), then water (100 ml). The washed extracts were distilled under reduced pressure until the mixture became solid. Methanol (150 ml) was added, and the solid acetylene (3) was filtered off (11.9 g). The mother-liquors were evaporated to dryness under reduced pressure and the resulting solid was dissolved in toluene (150 ml) and chromatographed on silica to yield more acetylene (3) (12.9 g; total yield 71%). This material was identical with the product from the reaction between ester (1) and methylmagnesium bromide.

(*c*) *Treatment of* 21-*bromo*-3β-*hydroxy*-16α,17α-*dimethyl*-5α-*pregn*-9(11)-*en*-20-*one* (4a) *with methylmagnesium chloride.* A solution of the 21-bromo-compound (4a) (1.17 g) in tetrahydrofuran (50 ml) was treated with a solution of methylmagnesium chloride (from 3 g of magnesium) in tetrahydrofuran (100 ml). The solvent was replaced with anisole (100 ml) as described in (*b*) above, and the reaction was heated under reflux for 16 h. The crude product was

isolated as described in (*b*) above and chromatographed on silica in n-hexane. Elution with toluene gave the acetylene (3) (0.7 g, 73.7%), m.p. 159—170 °C, shown (g.l.c.) to contain the dimethylpregnene (4) (*ca.* 5%). This impurity (4) persisted after three recrystallisations from methanol.

16α,17α-*Dimethylpregn*-5-*en*-20-*yn*-3β-*ol* (6).—The 16α,17α-dimethylpregnenolone acetate [2] (5) (22 g) was added to a solution of methylmagnesium chloride (from 60 g of magnesium) in tetrahydrofuran (1 l). The solvent was replaced with anisole (1 l) as described in (*b*) above to give a thick gel which was difficult to stir. More anisole (700 ml) was added and the reaction was stirred and refluxed 40 h. The mixture was then cooled, poured into sulphuric acid (1M; 1 l) in crushed ice (1 kg), and the product isolated as described in (*a*) above. Two crops (8.8 g and 1.6 g) were obtained by recrystallisation from methanol, and chromatography of the mother-liquors yielded a further 4.7 g (total 15.1 g, 80%) of 16α,17α-*dimethylpregn*-5-*en*-20-*yn*-3β-*ol* (6), m.p. 152.5—154.5 °C, $[\alpha]_D$ −34.8° (*c*, 1.1), t_R 0.52; $\nu_{max.}$ (CH_2Cl_2) 3 610(OH), 3 310(C≡CH), and 2 100 cm^{-1} (−C≡C−); δ ($CDCl_3$) 0.99 (3 H, d, *J* 7 Hz, 16α-Me), 1.03 (9 H, s, 10-, 13- and 17-Me), 2.07 (1 H, s, acetylenic-H), 2.50 (1 H, m, 16β-H), 3.43 (1 H, m, 3α-H), and 5.34 (1 H, m. 6-H) (Found: C, 84.4; H, 10.7. $C_{23}H_{34}O$ requires C, 84.6; H, 10.5%).

Treatment of 3β-*Acetoxy*-16α,17α-*dimethylpregn*-5-*en*-20-*one* (5) *with Ethylmagnesium Bromide*.—A solution of the acetate (5) (2 g) in anisole (40 ml) was added dropwise to a stirred, distilling solution of ethylmagnesium bromide (from 5.8 g of magnesium) in ether (154 ml). The remaining ether was replaced with anisole as described in (*b*) above until the vapour temperature reached 150 °C. After 1 h at this temperature, only a trace of the 3-hydroxy-derivative of starting material remained (t.l.c.). The reaction was cooled to room temperature, then poured into ice–water (400 ml) containing sulphuric acid (2.5M; 40 ml). The product was extracted into toluene (3 × 50 ml) and the organic extracts were steam-distilled until the distillate became clear. The residue in the aqueous phase was extracted into ether and the organic solution was dried and evaporated to a gum which crystallised with time. This product was purified on preparative h.p.l.c. to give the pregnyne (6) (1.65 g) identical (g.l.c., i.r., n.m.r.) with the material described above.

Treatment of 3β-*Hydroxy*-17α-*methylpregn*-5-*en*-20-*one* (7) *with Methylmagnesium Chloride*.—A solution of the steroid (7) (2 g) in anisole (40 ml) was added dropwise to a distilling solution of methylmagnesium chloride (from 6 g of magnesium) in tetrahydrofuran (152 ml). Distillation was continued and anisole added until the vapour temperature reached 150 °C at a final volume of *ca.* 100 ml. The reaction was heated under reflux for 24 h at which time *ca.* 20% of the starting material remained (t.l.c.). More methylmagnesium chloride (from 6 g Mg) in tetrahydrofuran (152 ml) was added dropwise and the tetrahydrofuran then distilled off and replaced with anisole as before. After a further 24 h the reaction was cooled and poured into ice–water (500 ml) containing sulphuric acid (2.5M; 80 ml). The product was isolated by extraction and steam-distillation as before. The resulting brown solid was filtered off, dried *in vacuo* and purified by preparative h.p.l.c. This material, which showed a single spot on t.l.c., was shown (g.l.c.) to be a mixture (1 : 1) of two components. Several crystallisations from ether–n-hexane, then methanol gave 17α,20-*dimethylpregna*-5,20-*dien*-3β-*ol* (9), m.p. 164.5—165 °C, $[\alpha]_D$ +89.3° (*c*, 0.7), t_R 0.68; $\nu_{max.}$ (CH_2Cl_2) 3 610(OH) and 1 630 cm^{-1} (−C=C−); δ ($CDCl_3$) 0.7 (3 H, s, 17α-Me), 1.03 and 1.05 (6 H, 2 × s, 10- and 13-Me), 1.79 (3 H, s, 20-Me), 3.5br (1 H, m, 3α-H), 4.74 (2 H, s, 21-H_2), and 5.35 (1 H, m, 6-H) (Found: C, 83.8; H, 11.0. $C_{23}H_{36}O$ requires C, 84.1; H, 11.0%).

The mother liquors were evaporated to dryness (1.35 g) and dissolved in ethyl acetate (70 ml). This solution was treated with 1% silver nitrate solution (70 ml) and the resulting two-phase mixture was shaken at room temperature for 18 h. The white precipitate which formed was filtered off and the aqueous layer was separated. The solid and the aqueous phase were combined and treated with hydrochloric acid (5M; 30 ml) and ethyl acetate. The mixture was shaken at room temperature for 5 h, until all the solid had dissolved. The organic layer was separated and the aqueous phase was extracted (2×) with ethyl acetate. The combined organic phases were washed with 5% sodium carbonate solution, then water, and dried. Evaporation gave a solid (0.64 g) which was recrystallised from dichloromethane–methanol to give 17α-*methylpregn*-5-*en*-20-*yn*-3β-*ol* (8), m.p. 109—114 °C, $[\alpha]_D$ −38° (*c*, 0.95), t_R 0.43; $\nu_{max.}$ (KCl) 3 300(OH) and 2 110 cm^{-1} (−C≡CH); δ ($CDCl_3$) 1.01 (3 H, s, 13-Me), 1.09 (3 H, s, 17-Me), 1.23 (3 H, s, 10-Me), 2.15 (1 H, s, C≡CH), 3.5 br (1 H, m, 3α-H), and 5.4 (1 H, m, 6-H) (Found: M^+, 312.2420. $C_{22}H_{32}O$ requires *M*, 312,2453).

Treatment of 3β-*Hydroxy*-16α-*methylpregn*-5-*en*-20-*one* (10) *with Methylmagnesium Chloride*.—A solution of the steroid (10) (3 g) in anisole (60 ml) was added dropwise to a distilling solution of methylmagnesium chloride (from 9 g of magnesium) in tetrahydrofuran (230 ml). The tetrahydrofuran was replaced with anisole as described above and the reaction was stirred at reflux temperature (150 °C) for 45 min. The reaction was cooled and poured into ice–water (800 ml) containing sulphuric acid (2.5M; 80 ml). The resulting product was extracted into toluene. The organic phase was separated and steam-distilled until the distillate was clear. The resulting brown gum was dissolved in toluene and the solution was washed with water, dried, and evaporated under reduced pressure. The product (3.2 g) was purified by preparative h.p.l.c. to give 16α,20-*dimethylpregn*-5-*ene*-3β,20-*diol* (11), m.p. 161—165 °C (from dichloromethane–methanol), $[\alpha]_D$ −71.3° (*c*, 0.68), t_R 0.91; $\nu_{max.}$ (KCl) 3 440(OH) and 1 667 cm^{-1} (−C=C−); δ ($CDCl_3$) 0.88 (3 H, s, 13-Me), 1.01 (3 H, s, 10-Me), 1.11 (3 H, d, *J* 7 Hz, 16α-Me), 1.28 and 1.32 (6 H, 2s, 2 × 20-Me), 3.5br (1 H, m, 3α-H) and 5.37 (1 H, m, 6-H) (Found: C, 80.0; H, 11.2; M^+, 346.2882. $C_{23}H_{38}O_2$ requires C, 79.7; H, 11.05%; *M*, 346.2872).

16α,17α-*Dimethylpregn*-4-*en*-20-*yn*-3-*one* (13).—A solution of 16α,17α-dimethylpregn-5-en-20-yn-3β-ol (6) (3 g) in toluene (120 ml) containing aluminium isopropoxide (1.5 g) and cyclohexanone (30 ml) was distilled slowly for 45 min. The reaction was shown (t.l.c.) to be incomplete. Toluene (60 ml), aluminium isopropoxide (0.75 g), and cyclohexanone (15 ml) were added and distillation was continued for a further 30 min. Rochelle salt (potassium sodium tartrate) solution (25%; 50 ml) was added to the cooled reaction mixture which was then steam-distilled to remove volatile impurities. The resulting solid was filtered off, dried (2.64 g), treated with charcoal in acetone, and recrystallised twice from methanol to give 16α,17α-*dimethylpregn*-4-*en*-20-*yn*-3-*one* (13) (1.68 g), m.p. 148—150 °C; $[\alpha]_D$ +101.2° (*c*, 1.0), t_R 0.70; $\nu_{max.}$ (CH_2Cl_2) 3 310(C≡CH), 2 100(−C≡C−), 1 670

(3-C=O) and 1 616 cm^{-1} (4-C=C); $\lambda_{max.}$ 240 nm (ε 15 500); δ ($CDCl_3$) 0.98 (3 H, d, *J* 7 Hz, 16α-Me), 1.04 (6 H, s, 13- and 17-Me), 1.20 (3 H, s, 10-Me), 2.08 (1 H, s, acetylenic-H), and 5.71br (1 H, s, 4-H) (Found: C, 85.0; H, 10.2. $C_{23}H_{32}O$ requires C, 85.1; H, 9.9%).

5α,6α-*Epoxy*-16α,17α-*dimethylpregn*-20-*yn*-3β-*yl Acetate* (14).—A solution of 16α,17α-dimethylpregn-5-en-20-yn-3β-ol (6) (7.6 g) in chloroform (76 ml) was cooled to 5 °C and treated dropwise over 15 min with a solution of sodium acetate (2.28 g) in peracetic acid (22.8 ml). After 40 min, sodium sulphite solution (5%) was added until the reaction gave a negative test with starch iodide paper. Water (200 ml) was added and the organic layer was separated. The aqueous layer was extracted with chloroform (2 × 30 ml) and the combined organic extracts were washed with aqueous sodium carbonate (5%) until just alkaline, and then with water until neutral; they were then dried and evaporated to dryness. The resulting solid was dissolved in pyridine (10 ml) and acetic anhydride (10 ml) was added. This reaction was left overnight at room temperature and then poured onto crushed ice. The solid product was filtered off, washed well with water, and dried (8.3 g). One recrystallisation from dichloromethane–methanol gave the *epoxide* (14) (5.92 g) m.p. 207—210 °C, $[\alpha]_D$ −66.1° (*c*, 1.3), t_R 1.13; $\nu_{max.}$ 3 300(C≡CH), 2 100(−C≡C−), 1 735(OAc), and 1 235 cm^{-1} (OAc); δ ($CDCl_3$) 0.96 (3 H, d, 16α-Me), 1.02 (3 H, s, 17α-Me), 1.10 (3 H, s, 13-Me), 1.37 (3 H, s, 10-Me), 2.0 (3 H, s, OAc), 2.06 (1 H, s, acetylenic-H), 2.86 (1 H, d, $J_{6\beta,7\alpha}$ 4 Hz, 6β-H), and 4.95 (1 H, m, 3α-H) (Found: M^+, 384.2652. $C_{25}H_{36}O_3$ requires *M*, 384.2664).

3β-*Acetoxy*-6β-*fluoro*-16α,17α-*dimethylpregn*-20-*yn*-5α-*ol* (15).—The epoxide (14) (5.5 g), suspended in dry diglyme (55 ml) at room temperature was treated with boron trifluoride–ether (5.36 ml) and a diglyme solution of hydrogen fluoride (9.82M; 1.64 ml). The reaction was stirred for 15 min, by which time all the steroid was in solution, and then poured into water (400 ml) containing sodium acetate (5.5 g). The resulting solid was filtered off and dried (5.78 g). Recrystallisation from acetone–n-hexane gave the *fluoro-compound* (15), m.p. 220—221 °C, $[\alpha]_D$ −40.1° (*c*, 1.0), t_R 1.17; $\nu_{max.}$ (CH_2Cl_2) 3 590, 3 440(OH), 3 310(C≡CH), 2 100(−C≡C−), 1 730(OAc), and 1 243 cm^{-1} (OAc); δ ($CDCl_3$) 0.95 (3 H, d, *J* 7 Hz, 16α-Me), 1.02 (6 H, s, 13- and 17-Me), 1.12 (3 H, d, *J* 5 Hz, 10-Me), 2.00 (3 H, s, OAc), 2.05 (1 H, s, acetylenic-H), 2.35 (1 H, m, 16β-H), 4.19 (1 H, dt, $J_{6\alpha,F}$ 50 Hz, $J_{6\alpha,7}$ 3 Hz, 6α-H), and 5.12 (1 H, m, 3α-H) (Found: C, 73.9; H, 9.2; F, 4.6. $C_{25}H_{37}FO_3$ requires C, 74.2; H, 9.2; F, 4.7%).

6β-*Fluoro*-16α,17α-*dimethylpregn*-20-*yne*-3β,5α-*diol* (16).—A suspension of the 3β-acetate (15) (5.25 g) in methanol (260 ml) was treated with perchloric acid solution (72%; 5.25 ml) at room temperature. After 21 h the reaction mixture was poured into water (700 ml) containing ice (500 g) and the resulting solid was filtered off, washed with water until free of acid, and then dried to give the *diol* (16) (4.75 g), m.p. 205—208 °C (from acetone–n-hexane then ether–n-hexane), $[\alpha]_D$ −29.5° (*c*, 1.4); $\nu_{max.}$ (CH_2Cl_2) 3 680, 3 500(OH), 3 310(C≡CH), and 2 100 cm^{-1} (−C≡C−); δ (C_5D_5N) 0.91 (3 H, d, 16α-Me), 1.03 (3 H, s, 17α-Me), 1.10 (3 H, s, 13-Me), 1.27 (3 H, d, *J* 4 Hz, 10-Me), 2.69 (1 H, s, acetylenic-H), 4.55 (1 H, d, *J* 50 Hz, 6α-H), and 4.73br (1 H, m, 3α-H) (Found: M^+, 362.2623. $C_{23}H_{35}FO_2$ requires *M*, 362.2621).

6β-*Fluoro*-5α-*hydroxy*-16α,17α-*dimethylpregn*-20-*yn*-3-*one* (17).—A solution of the diol (16) (4.25 g) in acetone (210 ml) was cooled to 5 °C and treated dropwise with Jones reagent (7M; 3.66 ml). After a few minutes the excess of reagent was destroyed by the addition of methanol (5 ml). Water (1 l) was added and the product was filtered off, washed with water, and dried to give the 3-*ketone* (17) (3.95 g), m.p. 223—226 °C (from ether–n-hexane), $[\alpha]_D$ 0° (*c*, 1.0); $\nu_{max.}$ (CH_2Cl_2) 3 580, 3 460(OH), 3 310(C≡CH), 2 100(−C≡C−), and 1 712 cm^{-1} (3-C=O); δ ($CDCl_3$) 0.97 (3 H, d, *J* 7 Hz, 16α-Me), 1.02 (6 H, s, 13- and 17-Me), 1.27 (3 H, d, *J* 4 Hz, 10-Me), 2.07 (1 H, s, acetylenic-H), and 4.23 (1 H, dt, $J_{6\alpha,F}$ 50 Hz, $J_{6\alpha,7}$ 3 Hz, 6α-H) (Found: C, 76.6; H, 9.3; F, 5.6. $C_{23}H_{33}FO_2$ requires C, 76.6; H, 9.2; F, 5.3%).

6α-*Fluoro*-16α,17α-*dimethylpregn*-4-*en*-20-*yn*-3-*one* (18).—A solution of the 3-ketone (17) (3.4 g) in glacial acetic acid (170 ml) containing hydrogen chloride gas was left for 18 h at 20 °C then poured into ice-cold water (1 l). The resulting solid was filtered off, washed with water, and dried to give 6α-*fluoro*-16α,17α-*dimethylpregn*-4-*en*-20-*yn*-3-*one* (18) (3.08 g), m.p. 180—183 °C (from methanol), $[\alpha]_D$ +86.5° (*c*, 0.8), t_R 0.74; $\lambda_{max.}$ 236 nm (ε 15 400); $\nu_{max.}$ (CH_2Cl_2) 3 305(C≡CH), 2 100(−C≡C−), 1 680(3-C=O), and 1 624 cm^{-1} (4-C=C); δ ($CHCl_3$) 0.97 (3 H, d, *J* 7 Hz, 16α-Me), 1.03 (6 H, s, 13- and 17-Me), 1.19 (3 H, s, 10-Me), 2.09 (1 H, s, acetylenic-H), 4.4—4.9br, 5.2—5.7br (1 H, 2 multiplets, main coupling *ca.* 50 Hz, 6β-H), and 6.06br (1 H, s, 4-H) (Found: C, 80.6; H, 9.1; F, 5.6. $C_{23}H_{31}FO$ requires C, 80.7; H, 9.1; F, 5.55%).

16α,17α-*Dimethylpregn*-9(11)-*en*-20-*yn*-3-*one* (19).—A solution of 16α,17α-dimethylpregn-9(11)-en-20-yn-3β-ol (3) (12.9 g) in acetone (250 ml), and dichloromethane (100 ml) was cooled to 0 °C and treated dropwise with Jones reagent (7M; 12.2 ml). Methanol (10 ml) was added to destroy the excess of reagent, and the reaction mixture was poured into water (1.5 l). The organic layer was separated and the aqueous solution was extracted with dichloromethane (2 × 100 ml). The combined organic extracts were washed with water (3 × 50 ml), dried, and evaporated to dryness to give the 3-*ketone* (19) (11.9 g), m.p. 219—220 °C (from acetone and dichloromethane), $[\alpha]_D$ +3.3° (*c*, 0.96), t_R 0.53; $\nu_{max.}$ (CH_2Cl_2) 3 310(C≡CH), 2 100(−C≡C−), and 1 715 cm^{-1} (3-C=O); δ ($CDCl_3$) 0.97 (3 H, s, 13-Me), 1.02 (3 H, s, 17α-Me), 1.00 (3 H, d, *J* 7 Hz, 16α-Me), 1.16 (3 H, s, 10-Me), 2.10 (1 H, s, acetylenic-H), and 5.4 (1 H, m, 11-H) (Found: C, 85.0; H, 10.2. $C_{23}H_{32}O$ requires C, 85.1; H, 9.9%).

16α,17α-*Dimethylpregna*-1,4-9(11)-*trien*-20-*yn*-3-*one* (20).—A solution of the saturated 3-ketone (19) (7.5 g) in toluene (250 ml) and acetic acid (7.5 ml) was treated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (11.6 g, 2.2 mol equiv.) and the reaction was stirred and heated under reflux for 18 h. The reaction mixture was cooled and evaporated to low volume under reduced pressure and the mixture was poured on to a column (8 in × 1 in) of alumina. Elution with ether gave the crude product (5.5 g) which was treated with charcoal in acetone and recrystallised from acetone–n-hexane to give the *triene* (20), m.p. 181—183 °C, $[\alpha]_D$ −26.4° (*c*, 0.7), t_R 0.65; $\lambda_{max.}$ 239 nm (ε 13 860); $\nu_{max.}$ (CH_2Cl_2) 3 310(C≡CH), 3 050(−C=CH), 2 100(−C≡C−), 1 676(3-C=O), 1 628(4-C=C), and 1 608 cm^{-1} (1-C=C); δ ($CDCl_3$) 0.98 (3 H, s, 13-Me), 1.00 (3 H, d, *J* 7 Hz, 16α-Me), 1.05 (3 H, s, 17α-Me), 1.40 (3 H, s, 10-Me), 2.11 (1 H, s, acetylenic-H), 5.56 (1 H, d, *J* 6 Hz, 11-H), 6.06 (1 H, d, *J* 2 Hz, 4-H), 6.25 (1 H, dd, $J_{2,1}$ 10 Hz, $J_{2,4}$ 2 Hz, 2-H), and 7.19 (1 H, d, $J_{1,2}$ 10 Hz, 1-H) (Found: C, 85.9; H, 8.9%; M^+, 320.2124. $C_{23}H_{28}O$ requires C, 86.2; H, 8.8%; *M*, 320.2140).

9α,11β-*Dichloro*-16α,17α-*dimethylpregna*-1,4-*dien*-20-*yn*-3-*one* (21).—A solution of the triene (20) (1.0 g) in carbon tetrachloride (50 ml) at 3—4 °C was treated dropwise with a

solution of chlorine in carbon tetrachloride (1.0M; 6.6 ml). After 5 min the solvent was removed by evaporation under reduced pressure at room temperature and the product was crystallised from ether to give the *dichloro-compound* (21) (0.26 g), m.p. 245—247 °C from ether, $[\alpha]_D$ +139.4° (*c*, 0.66); $\lambda_{max.}$ 237 nm (ε 1 390); $\nu_{max.}$ (CH_2Cl_2) 3 310(C≡CH), 2 100(–C≡C–), 1 670(3-C=O), 1 634(4-C=C), and 1 612 cm^{-1} (1-C=C); δ ($CDCl_3$) 1.01 (3 H, d, *J* 7 Hz, 16α-Me), 1.07 (3 H, s, 17α-Me), 1.38 (3 H, s, 13-Me), 1.74 (3 H, s, 10-Me), 2.11 (1 H, s, acetylenic-H), 4.76 (1 H, m, 11-H), 6.05 br (1 H, s, 4-H), 6.36 (1 H, dd, $J_{2,1}$ 10 Hz, $J_{2,4}$ 2 Hz, 2-H), and 7.19 (1 H, d, $J_{1,2}$ 10 Hz, 1-H) (Found: C, 70.55; H, 7.3; Cl, 18.9%; M^+, 390.1520. $C_{23}H_{28}Cl_2O$ requires C, 70.6; H, 7.2; Cl, 18.1%; *M*, 390.1517).

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