New Routes to 4-Substituted Steroids: Synthesis of 4-Cyanoprogesterone, a Potent Inhibitor of the Enzyme 5α-Reductase

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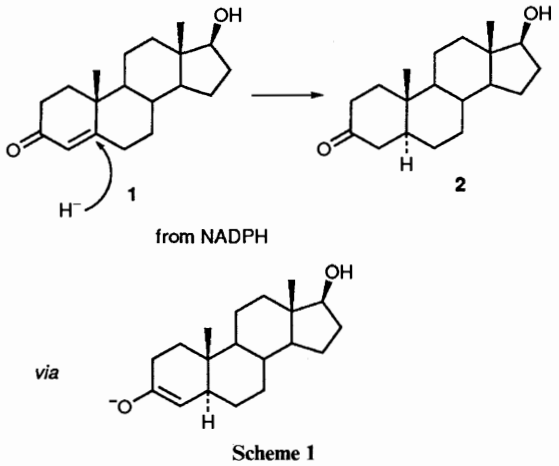
Two new synthetic routes to 4-substituted derivatives of progesterone are described: one involves the palladium-catalysed addition of alkenes to 4-(trifluoromethanesulfonyloxy)progesterone, and the other involves the addition of the anion of acetonitrile to the enol acetate, enol lactone 20-acetoxy-4-oxa-3,5-secopregna-5,17-dien-3-one. This second method provides gram quantities of 4-cyanoprogesterone, which proved to be a potent inhibitor of the enzyme 5α-reductase, and thus of considerable interest as a potential agent for the treatment of benign prostatic hyperplasia and prostatic cancer.

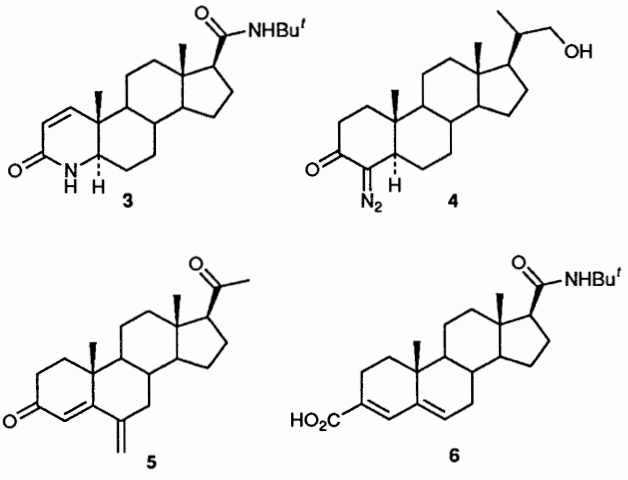
The enzyme 5α-reductase catalyses the conversion of the major male hormone testosterone **1** into dihydrotestosterone **2** *via* the mechanism shown in Scheme 1.[1] This reduction is a key reaction in androgen metabolism since the relative levels of testosterone and dihydrotestosterone are important for the control of, *inter alia*, the male sex drive and the size of the prostate. In particular, increased levels of dihydrotestosterone are implicated in the induction of acne, recession of scalp hair and prostate enlargement in later life. A large percentage of males over the age of 50 years suffer from this last affliction (benign prostatic hyperplasia), and a proportion of these (around 11 000 new cases each year in the UK) eventually suffer from prostatic cancer.



Scheme 1

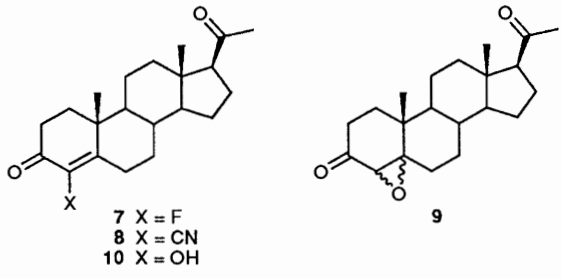
Clearly inhibition of 5α-reductase with a consequent reduction in the production of dihydrotestosterone could represent a viable strategy for the control of prostatic hyperplasia and prostatic cancer, and a number of inhibitors have already been developed. Of these, compounds **3** to **6**[2-5] are the most potent, and compound **3** (K_i 25 nmol dm^{-3}) has recently been introduced as a prescription drug for the treatment of prostatic hyperplasia in the UK and elsewhere.

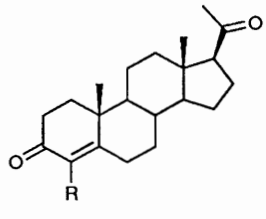
Our involvement in this area arose from work on inhibitors of the enzyme aromatase (for the treatment of breast cancer),[6] and the discovery that 4-fluoroprogesterone **7** was an inhibitor of both aromatase and 5α-reductase at the micromolar level. It appeared reasonable that the electron-withdrawing substituent at C-4 was stabilising the enolic intermediate shown in Scheme 1 and that the compound was thus acting as a competitive inhibitor of 5α-reductase. We decided to prepare other derivatives of progesterone with electron-withdrawing groups



at C-4, and the results of these efforts are the subject of this paper (a preliminary account of this work has been published).[7]

At the commencement of the work, a literature survey revealed one report of a synthesis of 4-cyanoprogesterone[8] **8**, but the synthesis appeared to be rather inefficient and certainly not flexible enough to be used for the synthesis of other 4-substituted steroids. Our initial attempt to introduce a substituent at C-4 was based upon the work of Piers and Fleming[9] involving palladium-catalysed reactions of cyanide with enol trifluoromethanesulfonates (triflates). Reaction of the epoxide mixture **9** with formic acid[6a] provided 4-hydroxypro-

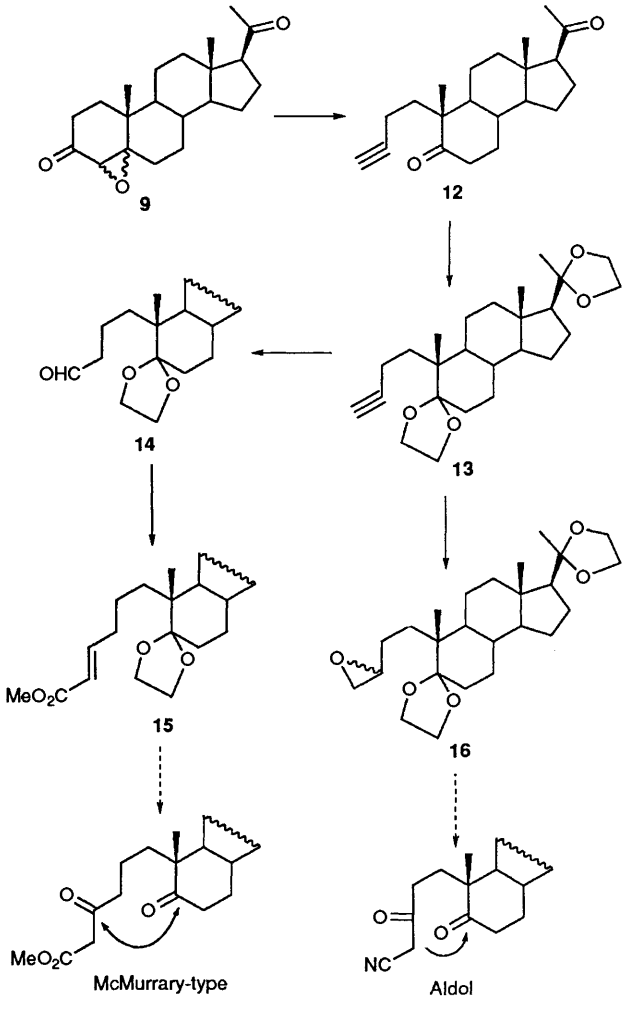




11a R = OSO_2CF_3
11b R = CH=CHCO$_2$Me
11c R = CH=CHPh
11d R = CHO

gesterone **10** in poor yield (*ca.* 40%), although the triflate **11a** could be produced in 70% yield using trifluoromethanesulfonic anhydride and pyridine in dichloromethane. Reaction of this with LiCN in the presence of tetrakis(triphenylphosphine)-palladium(0) and 12-crown-4 (typically in the ratio of 2:5:0.2:0.3) in dry benzene at room temperature led to complete consumption of the triflate and production of an intractable mixture of products. However, reaction of the triflate **11a** with palladium(II) acetate and alkenes (methyl acrylate and styrene) in the presence of triethylamine yielded the 4-substituted steroids **11b** and **11c** in reasonable yields (46 and 86%, respectively). Ozonolysis of **11c** then provided 4-formyl-progesterone **11d** (58%), and this methodology may have general utility for the production of 4-substituted steroids, although not the type of compound we were attempting to prepare.

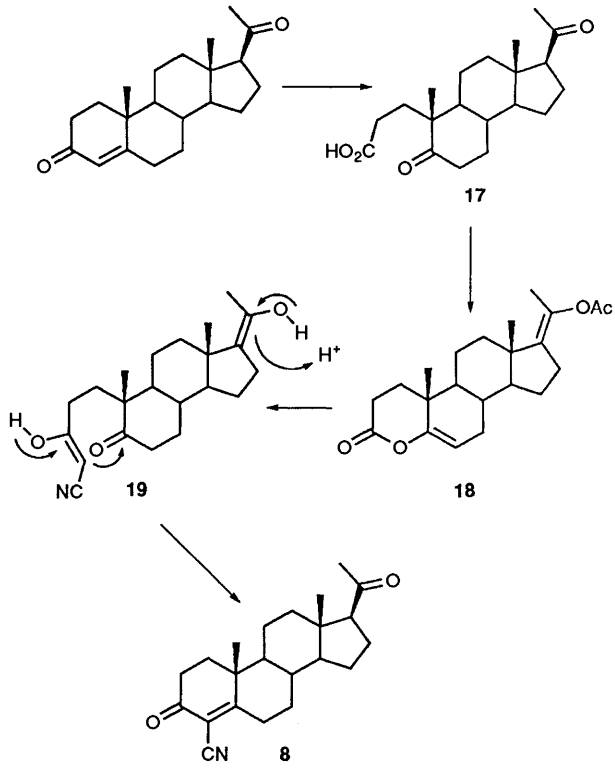
Our second potential route to 4-substituted derivatives of progesterone is shown in Scheme 2, and involved an initial



Scheme 2

cleavage of the A-ring of epoxide **9** using the Eschenmoser method[10] to produce the keto alkyne **12** (85% isolated yield on the 10 g scale). This was converted into the diketal **13** prior to hydroboration with disiamylborane and production of the diketal aldehyde **14** (52%). Treatment of this with (methoxy-carbonylmethylene)triphenylphosphorane yielded the expected unsaturated ester **15** (50% yield). Alternatively, partial hydrogenation of the alkyne **12** (Lindlar catalyst, 95%) followed by treatment with *m*-chloroperbenzoic acid yielded the epoxide **16** (35% yield). The low yields of many of these conversions discouraged us from attempting further reactions in the planned sequence (Scheme 2).

Our third route proved successful and is shown in Scheme 3.



Scheme 3

Ozonolysis of progesterone followed by oxidative work-up (H_2O_2–NaOH) produced the diketo acid **17** (80–90% yield on 10 g scale), and this was converted into the enol acetate, enol lactone **18** using a mixture of acetic anhydride and acetyl chloride (*ca.* 50% on the 5 g scale). Finally, addition of 2 equiv. of the anion from acetonitrile [BuLi, tetrahydrofuran (THF), −78 °C], followed by addition of potassium *tert*-butoxide and *tert*-butyl alcohol yielded the desired 4-cyanoprogesterone **8** (40–45% on the 5 g scale). A proposed mechanism for this interesting conversion is shown in Scheme 3, and it is particularly interesting to note that there was no evidence for the production of steroids with the α-stereochemistry at C-17. This presumably implies that protonation in the conversion of enol **19** into ketone **8** by *tert*-butyl alcohol occurs exclusively from the α-face. The overall three-step reaction sequence has been carried out routinely on the 5–10 g scale, and although there is clearly room for optimisation (overall yield *ca.* 20%), the process is operationally very simple.

The availability of gram quantities of 4-cyanoprogesterone meant that comprehensive biological evaluation could be undertaken (at the Cancer Research Campaign Laboratories at Sutton, Surrey), and these experiments will be reported in full in a separate paper. However, it is worth noting that both *in vitro* and *in vivo* compound **8** exhibited marked inhibitory activity against the enzyme 5α-reductase (0.05 and 0.5 μmol, respectively), and it is clearly worth preparing other compounds of this type for biological evaluation. This work is underway.

Experimental

IR spectra were recorded on a Perkin-Elmer 881 double beam grating spectrometer using sodium chloride cells and chloroform solutions unless otherwise stated. ^{1}H NMR spectra were recorded at 220 MHz using a Perkin-Elmer R34 instrument,

and at 400 MHz *via* the SERC NMR Service at the University of Warwick in deuteriochloroform solution using tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded using a JEOL FX90Q spectrometer. *J* Values are quoted in Hz. M.p.s were obtained using an Electrothermal digital melting point apparatus and are uncorrected.

Reactions requiring anhydrous conditions were carried out under a static nitrogen atmosphere using oven dried glassware. THF was dried over molecular sieves and distilled from sodium–benzophenone prior to use. All other reagents and solvents were used as supplied without further purification. Flash chromatography was performed using Sorbosil™ C60 silica gel. Light petroleum refers to the fraction with b.p. 40–60 °C unless otherwise stated.

4(α,β),5-*Epoxypregnane*-3,20-*dione* **9**.—Hydrogen peroxide (30%; 100 cm^3) and aq. sodium hydroxide (4 mol dm^{-3}; 10 cm^3) were added dropwise and at the same time to a solution of progesterone (25.00 g, 0.08 mol) in ethanol (500 cm^3) at 0 °C, whilst maintaining the temperature at 0 °C and the pH between 8 and 9. After *ca.* 7 h further aq. NaOH (20 cm^3) was added. The reaction mixture was stored at 0 °C for 3 days, subsequently poured into iced water (1 dm^3), and the resulting white precipitate extracted with dichloromethane. The organic extract was evaporated and recrystallisation of the resulting solid from acetone–hexane yielded a mixture of the two title epoxides (22.84 g, 87%; α:β, 1:3); m.p. (α,β-epimers) 130–132 °C; ν_{max}/cm^{-1} 1692 (C=O) and 856 (C–O); δ_H(400 MHz; $CDCl_3$) 0.61 and 0.62, 1.03 and 1.12, 2.08 and 2.09 (each 3 H, s, 18-, 19- and 21-CH_3 of α,β-epimers, respectively) and 2.95 and 3.00 (1 H, s, 4-H of β,α-epimers, respectively); δ_C(22.49 MHz; $CDCl_3$) 209.16, 209.05 (C-20), 206.61, 206.55 (C-3), 70.03, 69.82 (C-5), 63.42, 63.25 (C-4), 62.66 and 62.47 (C-17) (Found: C, 76.4; H, 9.2. $C_{21}H_{30}O_3$ requires C, 76.33; H, 9.15%).

4-*Hydroxyprogesterone* **10**.—A solution of progesterone epoxide mixture **9** (19.16 g, 58 mmol) dissolved in formic acid (90%; 170 cm^3) was heated under reflux for 1.25 h. The reaction mixture was poured into hot water (800 cm^3) and then left to cool to room temperature. The precipitate was filtered off, washed with water and then dissolved in dichloromethane (300 cm^3). The organic layer was washed with brine (2 × 100 cm^3) and saturated aq. sodium hydrogen carbonate (2 × 100 cm^3), dried ($MgSO_4$) and then evaporated. The residue was dissolved in a little dichloromethane and crystallised from methanol (250 cm^3) to give the title compound **10** as colourless crystals; m.p. 205–215 °C (lit.,[8] 221–227 °C); δ_H(220 MHz, $CDCl_3$) 0.64, 1.14 and 2.10 (each 3 H, s, 18-, 19- and 21-CH_3, respectively), 2.46–2.62 (3 H, m), 2.92–3.10 (1 H, m) and 6.08 (1 H, s, OH exchangeable).

4-(*Trifluoromethylsulfonyloxy*)*progesterone* **11a**.—A solution of **10** (4.87 g, 14.7 mmol) and pyridine (2 cm^3, 25 mmol) in dry dichloromethane (70 cm^3) was added to a solution of trifluoromethanesulfonic anhydride (2.5 cm^3, 15 mmol) in dry dichloromethane (50 cm^3) at 0 °C. The mixture was stirred for 2 h at 0 °C and then poured into water (100 cm^3). The organic layer was separated, washed with water (2 × 250 cm^3), dried ($MgSO_4$) and then evaporated. The residue was purified by filtration on silica gel with dichloromethane–ethyl acetate (5:1) as eluent (R_f 0.74, SiO_2, dichloromethane–ethyl acetate, 5:1). Crystallisation from diethyl ether gave the title compound **11a** (4.83 g, 71%) as colourless crystals; m.p. 118–119 °C; ν_{max}/cm^{-1} 2944 (C–H), 1698 (C=O), 1410 and 1142; δ_H(220 MHz; $CDCl_3$) 0.68, 1.28 and 2.13 (each 3 H, s, 18-, 19- and 21-CH_3, respectively), 2.50–2.62 (3 H, m) and 2.92 (1 H, dt, *J* 13.2, 3.5, 2-H); δ_C(22.49 MHz; $CDCl_3$) 208.8 (C-20), 188.4 (C-3), 159.7 (C-4), 139.5 (C-5), 118.7 (CF_3), 31.7 (C-21), 17.6 (C-19) and 13.3(C-18)(Found: C, 57.1; H, 6.35; S, 6.9. $C_{22}H_{29}F_3O_5S$ requires C, 57.13; H, 6.35; S, 6.93%); *m/e* 480 ($M + NH_4^+$, 100%).

4-(2-*Methoxycarbonylvinyl*)*progesterone* **11b**.—Compound **11a** (1.57 g, 3.4 mmol) methyl acrylate (0.35 cm^3, 4 mmol), triethylamine (0.9 cm^3) and palladium acetate (17.8 mg, 0.08 mmol) in dry dimethylformamide (15 cm^3) were stirred at 60 °C for 2 h. Diethyl ether (20 cm^3) and water (100 cm^3) were added, and the organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water, dried ($MgSO_4$) and then evaporated to afford crude **11b** (1.40 g) as a yellow oil. This was purified by flash chromatography on silica gel with dichloromethane–ethyl acetate 5:1 as eluent (R_f 0.60), SiO_2, dichloromethane–ethyl acetate, 5:1) and crystallised from diethyl ether to give the title compound **11b** (0.63 g, 46%) as colourless crystals; m.p. 140–144 °C; ν_{max}/cm^{-1} 2945 (C–H), 1701 (C=O), 1677 (C=C), 1438, 1295 and 1174; δ_H(220 MHz; $CDCl_3$) 0.68, 1.24 and 2.12 (each 3 H, s, 18-, 19- and 21-CH_3, resectively), 2.40–2.62 (3 H, m), 2.95 (1 H, dt, *J* 15.4, 3.5, 2-H), 3.76 (3 H, s, OCH_3) and AB-signal (δ_A 7.47, δ_B 6.36, J_{AB} 15.4, 2 H, vinyl H) (Found: C, 75.1; H, 8.6. $C_{25}H_{34}O_4$ requires C, 75.34; H, 8.60%); *m/e* 398 (M^+), 366 ($M^+ - CH_3OH$), 339 ($M^+ - CO_2CH_3$) and 131 (100%).

4-(2-*Phenylvinyl*)*progesterone* **11c**.—A mixture of compound **11a** (2.97 g, 6.4 mmol), triethylamine (0.8 cm^3, 5.7 mmol), styrene (0.75 cm^3, 6.6 mmol), palladium acetate (57.4 mg, 0.26 mmol), triphenylphosphine (31.4 mg, 0.12 mmol) in dry dimethylformamide (30 cm^3) was stirred at 60–70 °C for 1.5 h. The reaction mixture was poured into water (50 cm^3) and extracted with diethyl ether (3 × 75 cm^3). The combined organic phases were washed with brine (4 × 50 cm^3), dried ($MgSO_4$) and then evaporated. The residue was purified by flash chromatography on silica gel with diethyl ether–light petroleum (4:1) as eluent (R_f 0.36), SiO_2, diethyl ether–light petroleum, 4:1). Crystallisation from diethyl ether–light petroleum gave the title compound **11c** (2.37 g, 86%) as pale yellow crystals; m.p. 150–151 °C; ν_{max}/cm^{-1} 3017 (C–H), 1701 (C=O) and 1665 (C=C); δ_H(220 MHz; $CDCl_3$) 0.67, 1.24 and 2.11 (each 3 H, s, 18-, 19- and 21-CH_3, respectively), 2.42–2.64 (3 H, m), 3.10 (1 H, dt, *J* 13.2, 3.5, 2-H), AB-signal (δ_A 6.82, δ_B 6.66, J_{AB} 15.4, 2 H, vinyl H) and 7.14–7.52 (5 H, m, Ar-H) (Found: C, 83.4; H, 8.72. $C_{29}H_{36}O_2$ requires C, 83.61; H, 8.71%); *m/e* 416 (M^+) and 91 (100%).

4,5-*Secopregn*-3-*yne*-5,20-*dione* **12**.—To a solution of 4(α,β),-5-epoxypregnane-3,20-dione **9** (10.00 g, 0.03 mol) in absolute ethanol (150 cm^3) at 40 °C was added toluene-*p*-sulfonohydrazide (1.1 equiv., 6.20 g). The solution immediately turned yellow and a precipitate formed. After *ca.* 2 h the precipitate dissolved and the reaction was allowed to proceed for a further 5 h until the solution turned colourless. The reaction mixture was subsequently treated with diethyl ether and water, the organic layer was concentrated, and then the product was extracted into dichloromethane. This crude product was chromatographed on a silica column with diethyl ether–light petroleum (1:1) as eluent and 4,5-secopregn-3-yne-5,20-dione **12** (7.89 g, 0.026 mol, 85%) was isolated; m.p. 148–150 °C; ν_{max}/cm^{-1} 3306 (C≡C–H), 2252 (C≡C) and 1700 (C=O); δ_H(220 MHz; $CDCl_3$) 0.65, 1.05 and 2.09 (each 3 H, s, 18-, 19- and 21-CH_3, respectively) and 2.51 (1 H, m, terminal C–H); δ_C(22.49 MHz; $CDCl_3$) 213.8 (C-5), 208.8 (C-20), 84.8 (C-4) and 67.9 (C-3) (Found: C, 80.4; H, 9.7. $C_{21}H_{30}O_2$ requires C, 80.21; H, 9.62%).

5,5;20,20-*Bis*(*ethylenedioxy*)-4,5-*secopregn*-3-*yne* **13**.—4,5-Secopregn-3-yne-5,20-dione **12** (2.00 g, 6.37 mmol), toluene-*p*-sulfonic acid (100 mg) and ethylene glycol (20 cm^3) in benzene (120 cm^3) were heated under reflux with water separation for

18 h. The mixture was washed with aq. 5% sodium hydrogen carbonate and saturated aq. sodium chloride, then dried and the solvents evaporated. The yellow oily residue was chromatographed on a silica column (elution with 60% diethyl ether in light petroleum) to give the title compound **13** (1.41 g, 55%); m.p. 151–153 °C; ν_{max}/cm^{-1} 3268 (C≡C–H); δ_H(400 MHz; $CDCl_3$) 0.75, 0.96 and 1.27 (each 3 H, s, 18-, 19- and 21-CH_3, respectively) and 3.94 (8 H, br m, 2 × OCH_2CH_2O); δ_C(22.49 MHz; $CDCl_3$) 113.7 (C-5), 111.8 (C-20), 86.4 (C-4) and 67.2 (C-3) (Found: C, 74.5; H, 9.7. $C_{25}H_{38}O_4$ requires C, 74.59; H, 9.51%).

5,5;20,20-*Bis*(*ethylenedioxy*)-4,5-*secopregnan*-4-*al* **14**.—Disiamylborane [$(Me_2CHCHMe_2)_2BH$] was prepared in a 100 cm^3 flask. A static pressure of nitrogen was maintained until after the oxidation. The flask was immersed in an ice–salt bath and the temperature lowered to −10 °C. A solution of 5,5;20,20-bis(ethylenedioxy)-4,5-secopregn-3-yne **13** (1.207 g, 3 mmol) in THF (5 cm^3) was added as rapidly as possible while maintaining the temperature below 10 °C. The cold bath was removed and the reaction mixture allowed to come to room temp., and stirred for 5 h to complete the hydroboration. The reaction mixture was cooled to 0 °C and the product was oxidised at 0 °C by the addition of hydrogen peroxide (2 cm^3, 15%), maintaining the pH of the solution at approximately pH ~8 by the controlled addition of sodium hydroxide (2 mol dm^{-3}; 1.5 cm^3). After oxidation, the reaction mixture was neutralised and the organic phase was subsequently extracted into dichloromethane, dried over anhydrous sodium sulfate, and then the solvent was evaporated. An oily, colourless residue (1.15 g, 2.74 mmol) (91% crude yield) was obtained which was then chromatographed on a silica column (elution with 70% diethyl ether in light petroleum) and 5,5;20,20-bis(ethylenedioxy)-4,5-secopregnan-4-al **14** was isolated (0.66 g, 52% yield); m.p. 159–161 °C; ν_{max}/cm^{-1} 2720 (OC–H) and 1700 (C=O); δ_H(220 MHz, $CDCl_3$) 0.76, 0.98 and 1.20 (each (3 H, s, 18-, 19- and 21-CH_3, respectively), 3.95 (8 H, br m, 2 × OCH_2CH_2O) and 9.76 (1 H, s, CHO); δ_C(22.49 MHz; $CDCl_3$) 202.9 (4-CHO), 113.7 (C-5) and 111.8 (C-20) (Found: C, 71.2; H, 9.6%; M^+, 420.2870. $C_{25}H_{40}O_5$ requires C, 71.39; H, 9.59%; *M*, 420.2876).

Wittig Product **15**.—To a solution of 5,5;20,20-bis(ethylenedioxy)-4,5-secopregnan-4-al **14** (315 mg, 0.75 mmol) in dichloromethane (5 cm^3) was added the reagent (methoxycarbonylmethylene)triphenylphosphorane ($Ph_3P{=}CHCO_2Me$) (1.1 equiv.) dissolved in dichloromethane. The reaction mixture was stirred at room temp. for 3 h and then refluxed for 1.5 h. Finally, it was stirred at room temp. for a further 48 h. The product was then extracted into dichloromethane and the organic extract was evaporated. The crude oily product was subsequently chromatographed (elution with 50% diethyl ether to light petroleum to give the pure Wittig product **15** (179 mg, 50%); ν_{max}/cm^{-1} 3040 (C=C–H), 1720 (C=O) and 1190 (C–O); δ_H(220 MHz; $CDCl_3$) 0.59, 0.94 and 1.23 (each 3 H, s, 18-, 19- and 21-CH_3, respectively), 3.71 (3 H, s, OCH_3), 3.95 (8 H, br m, 2 × OCH_2CH_2O), 5.83 (1 H, dt, J_{AB} 15, J_{BX} ~1, H_B) and 6.91 (1 H, dt, J_{AB} 15, J_{AX} ~5, H_A); δ_C(22.49 MHz; $CDCl_3$) 175.1 (CO_2), 149.8 (C-5), 120.8 (C-4), 111.8 (C-20), 113.8 (C-5) and 51.2 (OCH_3) (Found: C, 70.4; H, 9.4. $C_{28}H_{44}O_6$ requires C, 70.54; H, 9.31%).

5,20-*Dioxo*-4-*nor*-3,5-*secopregnan*-3-*oic Acid* **17**.—A solution of progesterone (10.00 g, 31.8 mmol) in dichloromethane–ethyl acetate (2:1; 150 cm^3) was oxidised by passing ozone through the solution at −78 °C. The progress of the reaction was monitored by TLC. As soon as the progesterone had reacted (TLC analysis after 3 h) the solvents were evaporated. The residue was dissolved in glacial acetic acid and hydrogen peroxide (30%; 12.5 cm^3) was added and the solution left at room temp. overnight. The solvents were then removed under reduced pressure and the residue taken up in diethyl ether and extracted with aq. sodium hydroxide (2 mol dm^{-3}). This extract was acidified with concentrated hydrochloric acid and the resulting crystalline precipitate filtered off and dried. On recrystallisation from acetone–hexane the title product **17** was obtained (9.50 g, 89%); m.p. 177–179 °C; ν_{max}/cm^{-1} 3354 (O–H), 1734 (C=O), 1702 (C=O) and 1293 (C–O); δ_H(400 MHz; $CDCl_3$) 0.66, 1.10 and 2.11 (each 3 H, s, 18-, 19- and 21-CH_3, respectively) and 2.53 (2 H, m, 2-H); δ_C(22.49 MHz; $CDCl_3$) 214.4 (C-20), 209.2 (C-5), 179.4 (C-3) and 63.2 (C-17) (Found: C, 71.7; H, 9.0. $C_{20}H_{30}O_4$ requires C, 71.82; H, 9.04%).

20-*Acetoxy*-4-*oxa*-3,5-*secopregna*-5,17-*dien*-3-*one* **18**.—5,20-Dioxo-4-nor-3,5-secopregnan-3-oic acid **17** (3.00 g, 8.96 mmol) was dissolved in acetic anhydride (20 cm^3) and acetyl chloride (10 cm^3) and the mixture was heated under gentle reflux under an inert atmosphere in moisture-free conditions for 28 h. The solvents were then evaporated under reduced pressure at 50 °C and the brown crystalline residue was chromatographed over silica (elution with diethyl ether) giving the title product (1.44 g, 45%); m.p. 170–171 °C; ν_{max}/cm^{-1} 1751 (C=O), 1743 (C=O), 1685 (C=C), 1161 (C–O), 1734 (C=O) and 1227 (C–O); δ_H(400 MHz; $CDCl_3$) 0.92, 1.11 and 1.88 (each 3 H, s, 18-, 19- and 21-CH_3, respectively), 2.09 (3 H, s, acetate CH_3), 2.61–2.64 (2 H, m, 2-H) and 5.26 (1 H, dd, 6-H); δ_C(22.49 MHz; $CDCl_3$) 168.9 (ester C=O), 168.3 (C-3), 154.2 (C-5), 136.9 (C-17), 136.4 (C-20) and 105.3 (C-6) (Found: C, 73.1; H, 8.5. $C_{22}H_{30}O_4$ requires C, 73.71; H, 8.43%).

4-*Cyanopregn*-4-*ene*-3,20-*dione* **8** (4-*Cyanoprogesterone*).—A solution of acetonitrile (4 mmol) in THF (5 cm^3) was cooled to −78 °C and BuLi (4 mmol) was added dropwise. The solution was stirred for 30 min prior to the addition of 20-acetoxy-4-oxa-3,5-secopregna-5,17-dien-3-one **18** (2 mmol). After 1 h at −78 °C and 2 h at room temp., *tert*-butyl alcohol (10 cm^3) containing potassium *tert*-butoxide (6 mmol) was added, and the solution was stirred for 16 h at room temp. The products were extracted into dichloromethane and then purified by silica chromatography eluting with 90% of diethyl ether to light petroleum. It was further recrystallised from acetone–diethyl ether (4:1) to give 4-cyanoprogesterone **8** (0.29 g, 42%); m.p. 210–212 °C (lit.,[8] 214–217 °C); ν_{max}/cm^{-1} 2233 (C≡N), 1697 (C=O), 1685 (C=O) and 1586 (C=C); δ_H(400 MHz; $CDCl_3$) 0.70, 1.27 and 2.14 (each 3 H, s, 18-, 19- and 21-CH_3, respectively), 3.07 (1 H, dm, *J* 15.3, 6-α-H); δ_C(22.49 MHz; $CHCl_3$) 208.8 (C-20), 192.0 (C-3), 183.4 (C-5), 113.9 (C-4) and 112.3 (CN) (Found: C, 77.6; H, 8.85; N, 4.2%; M^+, 339.2187. $C_{22}H_{30}O_4$ requires C, 77.84; H, 8.61; N, 4.13%; *M*, 339.2198).

Acknowledgements

We thank the Cancer Research Campaign for generous funding of this work.

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Paper 3/04733D
Received 6*th August* 1993
Accepted 15*th September* 1993