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6,19-Carbon-bridged steroids. Synthesis of 6,19-methano-progesterone

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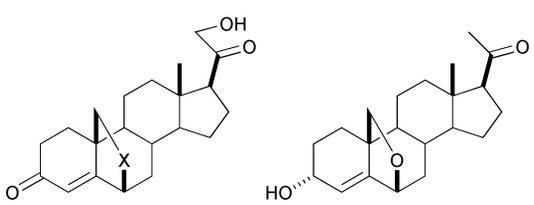
6,19-Methanoprogesterone (**4**) was synthesized in nine steps from the readily available 3β,20β-diacetyloxy-5α-bromo-6,19-oxidopregnane (**5**) in 14% overall yield. The additional carbon atom was introduced by reaction of a C-19 aldehyde with $Ph_3PCHOCH_3$ under salt free conditions and subsequent hydrolysis to give the homologous aldehyde. Intramolecular addition of the newly incorporated carbonyl (C-19a) to the olefinic C-6 in ring B was achieved by means of a Prins reaction with $TiCl_4$ as Lewis acid.

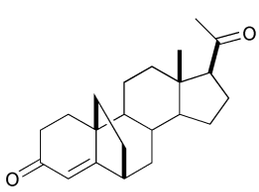
Introduction

Over the past 20 years, the biochemistry of steroids has advanced very rapidly. These developments have been important in the search for new drugs, leading to a renewed interest in these compounds, a large number of which are used in therapy.[1] Many of the natural steroid hormones and synthetic analogues contain a Δ^4-3-keto moiety in their structure, a typical functionality associated to receptor interaction. This moiety, gives ring A a 1α-envelope to 1α half chair conformation. The introduction of a 6,19-oxido bridge into Δ^4-steroids bends the molecule at the A/B ring junction changing the ring A conformation to a 1β-envelope.[2] Some of these bridged steroids have been shown to possess unusual activities; thus the 21-hydroxyprogesterone analogue **1**, is a selective antiglucocorticoid devoid of mineralocorticoid and progestational activities[3] and the pregnanolone analogue **2** is a potent anticonvulsant.[4] 6,19-Sulfur bridges (*e.g.* **3**) give rise to similar activities but with a slightly less torsioned steroid nucleus due to the longer C–S bonds.[5] Introduction of oxygen atoms on the bridging sulfur (*i.e.* sulfoxide and sulfone derivatives) cause major changes in the biological properties.



1 X = O
3 X = S

2



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The incorporation of short carbon atom bridges spanning characteristic positions of the steroid backbone, has been used in the search for new biologically active steroid hormone analogues.[6] Although semiempirical AM1 calculations predict that the overall molecular shape of 6,19-methano-bridged steroids should be very similar to that of the sulfur-bridged analogues,[7] the electronic effects that sulfur, oxygen or other bridging heteroatoms may exert on the observed activities should be absent. This would allow a better assessment of the contribution of overall molecular shape *per se*. Furthermore, compared to oxygen- and sulfur-bridged steroids, carbon bridges are expected to confer better metabolic stability and hence longer half-lives *in vivo*. We now describe the first synthesis of the simplest progesterone derivative, 6,19-methano-progesterone (**4**) starting from commercially available steroids.

Results and discussion

The key steps in the synthesis of **4** were the introduction of an additional carbon atom at C-19 and its cyclization onto C-6.[8] With these guidelines in mind, we used the Wittig olefination with (methoxymethylidene)triphenylphosphorane to introduce a carboxaldehyde group at C-19[9] and the Prins reaction[10] for its intramolecular addition to the olefinic C-6 in ring B. The synthetic sequence starting from 6,19-oxidosteroid **5** is outlined in the Scheme 1; this compound was obtained from commercially available pregnenolone acetate following essentially the procedure described by de Armas *et al.*.[11] Cleavage of the bromoether moiety in **5** with Zn in acetic acid, followed by oxidation of the 19-hydroxy derivative **6** with pyridinium chlorochromate (PCC), gave aldehyde **7** in 68% yield (from **5**). The homologation step was first attempted with (methoxymethylidene)triphenylphosphorane, generated from the corresponding phosphonium salt and *n*-BuLi in THF. It had been claimed that under these conditions, the resulting ylide gave satisfactory yields with similar substrates[12] although, several contradictory reports on related transformations are described in the literature.[13]In our hands, the yield obtained under these conditions did not exceed 35%. We then turned to salt free conditions and, after several attempts, found that a stable (methoxymethylidene)triphenylphosphorane solution resulted from the addition of powdered sodium amide to a suspension of the phosphonium salt in toluene and exposure to ultrasound. The deep red ylide solution, converted **7** into the homologated enol ether **8** in excellent yield (75%).[14] A small amount of 3-deacetylated product was also obtained (*ca.* 16%); acetylation to give **8** increased the overall yield of the Wittig reaction to 90%. The stereochemistry of the newly generated double bond in **8** was evident from the coupling constants between H-19 and H-19a in the ^{1}H NMR spectra. Thus, in the *E*-isomer H-19 and H-19a appeared as two doublets at 4.48 and 6.09 ppm respectively, with a mutual coupling of 13 Hz, while in the *Z*-isomer these hydrogens appeared at 3.88 and 5.91 ppm with a

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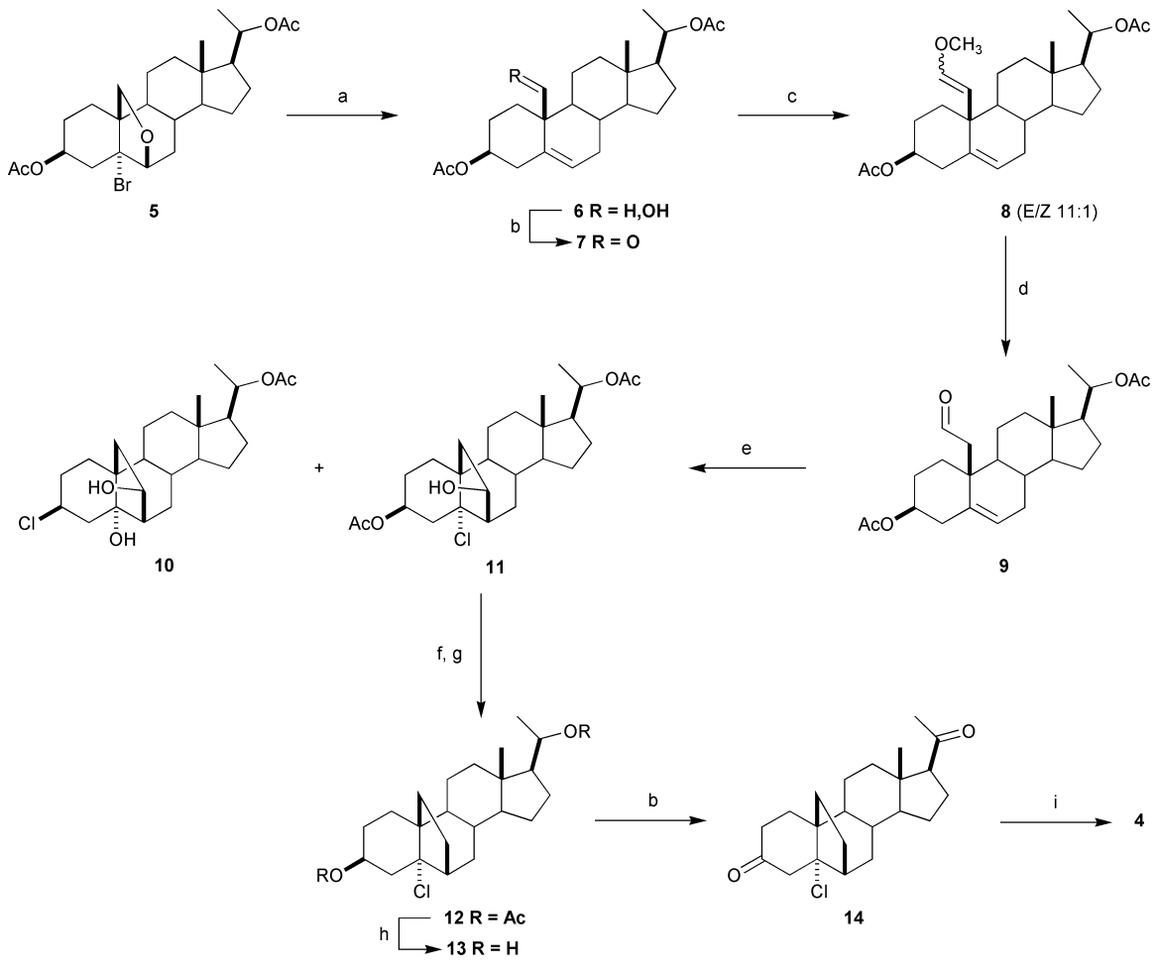
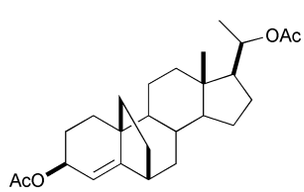


Scheme 1 Reagents and conditions. (a) Zn, AcOH, Pr^{i}OH; (b) PCC, $BaCO_3$, Cl_2CH_2; (c) $CH_3OCHPPh_3$, toluene; (d) 4N HCl, acetone; (e) $TiCl_4$, Cl_2CH_2; (f) 1. CS_2, DBU, DMF; 2. CH_3I; (g) Ph_2SiH_2, AIBN, toluene; (h) $LiAlH_4$, THF; (i) Al_2O_3, Et_2O

coupling of 7 Hz. In the presence of lithium salts, the *E*/*Z* ratio of **8** (determined by ^{1}H NMR) ranged from 1 : 3 to almost 100% of the *Z* isomer; when using salt free conditions, the *E* isomer was the major product (*E*/*Z* ratio *ca.* 11 : 1). Reagent-dependent differences in the stereochemical outcome of Wittig reactions with these and similar reagents, have been described for other steroids;[15] however, the reasons for the stereoselectivity patterns in those cases were not clearly discerned.[16] Transformation of **8** into the homologous aldehyde **9** was first attempted with perchloric acid in diethyl ether (45% yield) and finally carried out using hydrochloric acid in acetone (98% yield).[17]

Titanium tetrachloride has been the Lewis acid of choice for Type II Prins reactions of β,γ-unsaturated aldehydes to give bridged chloroalcohols.[18] Treatment of **9** with $TiCl_4$ in dichloromethane triggered a stereocontrolled intramolecular Prins reaction giving a mixture of 6,19-methano steroids **10** and **11** in a 1:4 ratio.[19] The structures of both compounds were established from ^{1}H and ^{13}C NMR spectra, 2D-NMR experiments and selective irradiation of H-19a in the ^{1}H NMR spectrum of **11**. Diagnostic signals in the ^{1}H NMR spectra of both **10** and **11** were those assigned to H-19a at 4.14 and 4.26 ppm respectively, and the absence of the characteristic resonances of aldehydic and olefinic protons. The 3-chloro-derivative **10** may result from substitution of the allylic acetate group in **15** (the other plausible product of the Prins reaction)[20] and subsequent acid catalyzed addition of water to the highly strained 4,5-double bond during workup. The multiplicity and coupling constants of H-19a ($J_{19a,19pro\text{-}R}$ = 4 Hz, $J_{19a,19pro\text{-}S}$ = 8 Hz and $J_{19a,6}$ ~ 0 Hz) in the ^{1}H NMR spectrum of **11**, allowed assignment of the *R* stereochemistry to C-19a, in accordance with the calculated coupling constants on the AM1 geometry, using the Altona equation.[21] This is the expected stereochemistry for the product on the basis of steric considerations, as the coordination of the Lewis acid at the C-19a carbonyl oxygen, increases steric hindrance. This favours the approach of C19a to C-6, with the more sterically demanding group preferentially placed over the less hindered ring A.



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Removal of the 19a-hydroxyl group in alcohol **11** was achieved using the Barton deoxygenation procedure.[22] The crude mixture of methano-bridged steroids (**10** and **11**),[23] was converted into the 19a-xanthates and treated with diphenylsilane/AIBN in toluene. The 6,19-methanopregnane **12** was obtained in 37% yield (from **8**). The spectroscopic data for this compound (absence of a hydroxymethine resonance at 3.5–4.5 ppm) indicated the success of this reaction. The acetate groups in **12** were removed by reduction with lithium aluminum hydride, and the resulting 3β,20β-diol **13** oxidized to the diketone with PCC (90% yield for the last two steps). Dehydrohalogenation of the latter compound with basic alumina in dichloromethane gave the target compound **4** in 14 % overall yield (from **5**).

Preliminary assays indicate that, as with 6,19-oxidoprogesterone[2] and 6,19-sulfanylprogesterone,[5] 6,19-methanoprogesterone lacks glucocorticoid activity.

Conclusions

The above procedure may be used to introduce 6,19-methano bridges in a variety of steroids. Furthermore, the cyclized intermediate **11** has a functionalized bridging atom, which allows for further derivatization at this position (ester derivatives, ketone, carbon chains, *etc.*).

Experimental

Melting points were taken on a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded in thin films using KBr disks on a Nicolet Magna IR 550 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured in a Bruker AC-200 (200.13 and 50.32 MHz) or AM-500 (500.13 and 125.72 MHz) NMR spectrometer in deuteriochloroform (using TMS as internal standard). The *J* values are given in Hz. Spectra were assigned by analysis of the DEPT, COSY 45, HETCOSY and HMBC spectra and by comparison with those of progesterone.[24] The electron impact mass spectra (EI) were measured in a Shimadzu QP-5000 mass spectrometer at 70 eV or in a VG-Trio 2 at 20 eV, by direct inlet. All solvents used were reagent grade. Solvents were evaporated at *ca.* 45 °C under vacuum. Column chromatography was performed on silica gel Merck 9385 (0.0040–0.0063 mm). TLC analysis was performed on silica gel 60 F254 (0.2 mm thick). The homogeneity of all compounds was confirmed by TLC.

3β,20β-Diacetyloxy-5α-bromo-6,19-oxidopregnane **5** was obtained from pregnenolone acetate (3β-acetyloxypregn-5-en-20-one) following essentially the procedure described by de Armas *et al.*,[10] by reduction with sodium borohydride in methanol/dichloromethane followed by acetylation to give 3β,20β-diacetyloxypregn-5-ene, formation of the 5,6-bromohydrin with *N*-bromoacetamide and radical cyclization with DIB/I_2 (63% overall yield).

3β,20β-Diacetyloxy-5α-bromo-6,19-oxidopregnane, 5

A sample of *bromoether* **5**, homogeneous by TLC (R_F = 0.55, hexane–ethyl acetate 7 : 3), had mp 150–153 °C (from ethanol–water); (Found C 60.4; H 7.5. $C_{25}H_{37}BrO_5$ requires C 60.4; H 7.5%); ν_{max}(KBr)/cm^{-1} 2945, 1733, 1369, 1248, 1091, 1042; δ_H (200 MHz) 0.67 (3H, s, H-18), 1.15 (3H, d, *J* = 6, H-21), 2.01 (3H, s, acetate), 2.03 (3H, s, acetate), 4.84 (1H, dq, *J* = 10 and 6, H-20), 5.20 (1H, tt, *J* = 11 and 5, H-3); δ_C (50 MHz) 13.0 (C-18), 19.9 (C-21), 21.3 and 21.5 (acetates), 22.5 (C-11), 23.3 (C-7), 23.4 (C-15), 25.5 (C-16), 26.9 (C-2), 32.8 (C-1), 33.2 (C-8), 39.1 (C-12), 41.3 (C-4), 43.0 (C-13), 45.9 (C-10), 48.8 (C-14), 53.8 (C-9), 54.8 (C-17), 67.5 (C-19), 70.0 (C-3), 72.8 (C-20), 74.5 (C-5), 82.2 (C-6), 170.4 and 170.5 (acetates); *m*/*z* (EI, 70 eV): 438 (M^+ − AcOH, 1%), 436 (1), 399 (1), 357 (5), 297 (14), 267 (8), 121 (20), 43 (100).

3β,20β-Diacetyloxy-19-hydroxypregn-5-ene, 6

Zinc powder (0.255 g) was added to a solution of 3β,20β-diacetyloxy-5α-bromo-6,19-oxidopregnane (**5**, 0.100 g, 0.20 mmol) in recently distilled Pr^{i}OH (20 cm^3) and heated to 75 °C. Acetic acid (0.2 cm^3) was added, the mixture was vigorously stirred for 45 min at that temperature, filtered and the solvent evaporated. The resulting residue was taken with dichloromethane, washed with aqueous $NaHCO_3$ and dried with sodium sulfate. Purification by flash chromatography gave *19-hydroxy steroid* **6** (0.059 g, 71%) homogeneous by TLC (R_F = 0.52, hexane–ethyl acetate 7 : 3), mp 70–74 °C (from ethanol-water); (Found C 69.1; H 9.3. $C_{25}H_{38}O_5.H_2O$ requires C 68.8; H 9.2%); δ_H (200 MHz) 0.70 (3H, s, H-18), 1.15 (3H, d, *J* = 6, H-21), 2.02 (3H, s, acetate), 2.03 (3H, s, acetate), 3.72 (1H, d, *J* = 12, Ha-19), 3.84 (1H, d, *J* = 12, Hb-19), 4.64 (1H, tt, *J* = 11 and 5, H-3), 4.84 (1H, dq, *J* = 10 and 6, H-20), 5.76 (1H, dd, *J* = 3 and 2, H-6); δ_C (50 MHz) 12.6 (C-18), 19.8 (C-21), 21.4 and 21.3 (acetates), 21.5 (C-11), 24.0 (C-15), 25.4 (C-16), 28.1 (C-2), 31.2 (C-7), 33.1 (C-1 and C-8), 38.2 (C-4), 39.3 (C-12), 41.5 (C-10), 42.3 (C-13), 50.3 (C-9), 54.9 (C-17), 56.8 (C-14), 62.7 (C-19), 72.8 (C-20), 73.4 (C-3), 127.8 (C-6), 134.7 (C-5), 170.4 (acetates); *m*/*z* (EI, 70 eV) 366 (7), 354 (2), 331 (4), 263 (4), 155 (19), 117 (20), 91 (32), 43 (100).

3β,20β-Diacetyloxypregn-5-en-19-al, 7

Pyridinium chlorochromate (1.38 g, 6.4 mmol), barium carbonate (0.83 g, 2.4 mmol) and 4 Å molecular sieves (0.64 g) in dry dichloromethane (95 cm^3) were vigorously stirred at room temperature under a nitrogen atmosphere for 15 min and then compound **6** (0.667 g, 1.60 mmol) was added. After 1 h, the reaction mixture was diluted with diethyl ether (50 cm^3), and percolated through silica gel with dichloromethane. Evaporation of the solvent gave *aldehyde* **7** (0.638 g, 96%) homogeneous by TLC (R_F = 0.63 hexane–ethyl acetate 7 : 3), mp 100–105 °C (from *i*-PrOH); (Found C 71.9; H 8.9. $C_{25}H_{36}O_5$ requires C 72.1; H 8.7%); ν_{max} (KBr)/cm^{-1} 2939, 2871, 2368, 1732, 1244, 1032; δ_H (500 MHz) 0.59 (3H, s, H-18), 1.15 (3H, d, *J* = 6, H-21), 2.00 (3H,s, acetate), 2.01 (3H, s, acetate), 4.59 (1H, tt, *J* = 5 and 11, H-3), 4.81 (1H, dq, *J* = 10 and 6, H-20), 5.87 (1H, m, H-6), 9.65 (1H, d, *J* = 1, H-19); δ_C (125 MHz) 12.3 (C-18), 19.9 (C-21), 21.3, 21.5 (acetates), 22.1 (C-11), 24.0 (C-15), 25.4 (C-16), 28.8 (C-2), 30.3 (C-1), 31.3 (C-7), 32.8 (C-8), 39.1 (C-4), 39.5 (C-12), 42.1 (C-13), 48.8 (C-9), 53.6 (C-10), 54.9 (C-17), 55.9 (C-14), 64.5 (C-3), 72.7 (C-20), 128.3 (C-6), 131.7 (C-5), 170.4, 170.6 (acetates), 204.8 (C-19); *m*/*z* (EI, 70 eV) 416 (M^+, 0.1%), 356 (10), 327 (34), 267 (78), 143 (43), 91 (46), 43 (100).

3β,20β-Diacetyloxy-19-(methoxymethylidene)pregn-5-ene, 8

Preparation of the ylide. (Methoxymethylidene)triphenylphosphonium chloride (1.00 g, 2.92 mmol) was suspended in dry toluene (10 cm^3), an excess of finely powdered sodium amide (0.12 g, 3.08 mmol) was added and the mixture sonicated in an ultrasound bath for 30 min. The suspension was then centrifuged and degassed under vacuum (0.5 torr) to give a dark-red solution.

Wittig reaction. To a solution of aldehyde **7**(0.5 g, 1.2 mmol) in dry toluene (0.5 cm^3), the ylide solution (5 cm^3, containing 1.5 mmol of ylide) was added, and the solution was stirred for 16 h under a nitrogen atmosphere. A second portion of ylide solution (5 cm^3) was added and the stirring continued for 16 h. The reaction mixture was directly applied to a silica gel column; elution with hexane–ethyl acetate 9 : 1 gave *enol ether* **8** (0.4 g, 75%) as an *E*/*Z* mixture (11:1 as determined by ^{1}H NMR). An analytical sample of the *E* isomer homogeneous by TLC (R_F = 0.60, hexane–ethyl acetate 7 : 3), had mp 132–136 °C (from Pr^{i}OH); (Found C 72.9; H 9.0. $C_{27}H_{40}O_5$ requires C 72.9; H 9.1%); ν_{max} (KBr)/cm^{-1} 2939, 2360, 1732, 1244, 1034; δ_H (500 MHz) 0.57 (3H, s, H-18), 1.15 (3H, d, *J* = 6, H-21), 2.02 (6H, s, acetates), 3.52 (3H, s, CH_3O), 4.48 (1H, d, *J* = 13, H-19), 4.62 (1H, tt, *J* = 5 and 11, H-3), 4.83 (1H, dq, *J* = 10 and 6, H-20), 5.55 (1H, dd, *J* = 2 and 3, H-6), 6.09 (1H, d, *J* = 13, H-19a); δ_C (125 MHz) 12.3 (C-18), 19.9 (C-21), 21.2 (C-11), 21.3 and 21.5 (acetates), 24.3 (C-15), 25.4 (C-16), 28.1 (C-2), 30.9 (C-8), 31.7 (C-7), 36.5 (C-1), 38.2 (C-12), 39.0 (C-4), 41.2 (C-13 and C-10), 50.2 (C-9), 54.8 (C-17), 55.3 (C-14), 55.9 (CH_3O), 72.8 (C-20), 73.9 (C-3), 106.1 (C-19), 124.7 (C-6), 136.6 (C-5), 150.5 (C-19a), 170.4 and 170.5 (acetates); *m*/*z* (EI, 70 eV): 384 (M^+–AcOH, 22%), 326 (48), 266 (12), 162 (29), 130 (37), 91 (46), 43 (100). An analytical sample of the *Z* isomer homogeneous by TLC (R_F = 0.62, hexane–ethyl acetate 7 : 3), had δ_H (500 MHz) 0.61 (3H, s, H-18), 1.15 (3H, d, *J* = 6, H-21), 2.01 (3H, s, acetate), 2.02 (3H, s, acetate), 3.50 (3H, s, CH_3O), 3.88 (1H, d, *J* = 7, H-19), 4.62 (1H, tt, *J* = 5 and 11, H-3), 4.83 (1H, dq, *J* = 10 and 6, H-20), 5.36 (1H, dd, *J* = 2 and 3, H-6), 5.91 (1H, d, *J* = 7, H-19a).

Further elution with hexane–ethyl acetate 6 : 4 gave 20β-acetyloxy-3β-hydroxy-19-(methoxymethylidene)pregn-5-ene (0.077 g, 16%) as an *E*/*Z* mixture (5 : 1 as determined by ^{1}H NMR), which upon acetylation (acetic anhydride/pyridine) gave **8** (0.079 g, 93%).

3β,20β-Diacetyloxypregn-5-en-19-carboxaldehyde, 9

4 M hydrochloric acid (0.8 cm^3) was added to a solution of enol ether **8** (0.200 g, 0.449 mmol) in acetone (8 cm^3), and the resultant mixture was stirred for 16 h under a nitrogen atmosphere. The solvent was evaporated and water was added. Extraction with dichloromethane gave a mixture of products that was then dissolved in dichloromethane (1 cm^3) and acetylated with acetic anhydride (0.6 cm^3) and pyridine (0.6 cm^3) for 16 h at room temperature. Extractive workup gave *aldehyde* **9** (0.19 g, 98%), homogeneous by TLC (R_F = 0.44, hexane–ethyl acetate 7 : 3); ν_{max} (KBr)/cm^{-1} 2938, 1726, 1384, 1248, 1034; δ_H (500 MHz) 0.57 (3H, s, H-18), 1.15 (3H, d, *J* = 6, H-21), 2.01 (3H, s, acetate), 2.04 (3H, s, acetate), 2.33 (1H, d, *J* = 15, Ha-19), 2.71 (1H, d, *J* = 15, Hb-19), 4,68 (1H, tt, *J* = 5 and 11, H-3), 4.82 (1H, dq, *J* = 10 and 6, H-20), 5.55 (1H, t, *J* = 3, H-6), 9.76 (1H, dd, *J* = 1 and 5, H-19a); δ_C (125 MHz) 12.4 (C-18), 19.9 (C-21), 21.3 and 21.4 (acetates), 21.5 (C-11), 24.0 (C-15), 25.3 (C-16), 27.6 (C-2), 31.3 (C-7), 32.7 (C-8), 36.6 (C-1), 38.2 (C-4), 39.1 (C-12), 40.5 (C-10), 42.2 (C-13), 45.5 (C-19), 50.5 (C-9), 54.8 (C-17), 56.7 (C-14), 72.8 (C-20), 73.2 (C-3), 125.6 (C-6), 135.6 (C-5), 170.3 and 170.4 (acetates), 203.9 (C-19a); *m*/*z* (EI, 70 eV) 370 (M$^+$ − AcOH, 3%), 326 (19), 266 (8), 142 (21), 43 (100). Attempts to recrystallize this compound were unsuccessful, resulting in extensive decomposition.

3β,20β-Diacetyloxy-5-chloro-19a-hydroxy-6,19-methano-pregnane, 11

To a stirred solution of **9** (0.32 g, 0.744 mmol) in dry dichloromethane (11 cm^3) at −70 °C was added a solution of $TiCl_4$ (1 cm^3) in dichloromethane (10 cm^3) under a nitrogen atmosphere. The reaction mixture was stirred at −30 °C for 2 h, Pr^{i}OH–water 1 : 3 (12 cm^3) was added and the resulting solution was further stirred at 0 °C for 15 min. The organic layer was washed with water and aqueous $NaHCO_3$, dried, filtered and concentrated to give a mixture of *6,19-methano steroids* **10** and **11** (1:4 by ^{1}H NMR). An analytical sample of **10** had R_F = 0.43 (hexane–ethyl acetate 6:4); δ_H (500 MHz) 0.64 (3H, s, H-18), 1.13 (3H, d, *J* = 6, H-21), 1.56 (1H, dd, *J* = 4 and 14, H-19$_{proR}$), 2.01 (3H, s, acetate), 2.26 (1H, dd, *J* = 8 and 14, H-19$_{proS}$), 2.50 (1H, br s, H-6), 4.14 (1H, dd, *J* = 4 and 8, H-19a), 4.61 (1H, tt, *J* = 5 and 11, H-3), 4.83 (1H, dq, *J* = 11 and 6, H-20); δ_C (125 MHz) 12.9 (C-18), 19.9 (C-21), 21,5 (acetate), 22.4 (C-11), 23.5 (C-15), 25.4 (C-16), 28.3 (C-1), 31.1 (C-2), 31.9 (C-7), 33.3 (C-8), 39.1 (C-12), 40.0 (C-4), 42.9 (C-19 and C-13), 45.2 (C-14), 50.1 (C-10), 54.7 (C-17), 54.9 (C-9), 55.3 (C-6), 55.9 (C-3), 72.6 (C-20), 77.6 (C-19a), 95.5 (C-5), 170.4 (acetate); *m*/*z* (EI, 20 eV) 388 (M$^+$–HCl, 1%), 370 (388-H_2O, 18), 326 (370-C_2H_4O, 100), 266 (326 − AcOH, 57), 198 (26), 161 (44), 141 (55), 116 (60).

An analytical sample of **11** had R_F = 0.25 (hexane–ethyl acetate 6:4); mp 110–115 °C (from ethanol–water); (Found C 66.6; H 8.4. $C_{26}H_{39}ClO_5$ requires C 66.9; H 8.4%); ν_{max} (KBr)/cm^{-1} 3415, 2938, 2360, 1733, 1255, 1084, 1034; δ_H (500 MHz) 0.63 (3H, s, H-18), 1.14 (3H, d, *J* = 6, H-21), 1.78 (1H, dd, *J* = 4 and 15, H-19$_{proR}$), 1.98 (1H, dd, *J* = 8 and 15, H-19$_{proS}$), 2.00 (3H, s, acetate), 2.01 (3H, s, acetate), 2.06 (1H, br s, H-6), 4.26 (1H, dd, *J* = 4 and 8, H-19a), 4.83 (1H, dq, *J* = 11 and 6, H-20), 5.15 (1H, tt, *J* = 5 and 11, H-3); δ_C (125 MHz) 13.0 (C-18), 19.9 (C-21), 21.4 and 21.5 (acetates), 22.1 (C-11), 23.5 (C-15), 25.5 (C-16), 25.9 (C-1), 26.8 (C-2), 30.4 (C-7), 34.0 (C-8), 36.6 (C-19), 39.1 (C-12), 41.5 (C-4), 43.1 (C-10), 47.6 (C-14), 48.0 (C-13), 54.1 (C-6 and C-9), 54.9 (C-17), 70.4 (C-19a), 72.7 (C-20), 73.4 (C-3), 82.3 (C-5), 170.4 and 170,5 (acetates); *m*/*z* (EI, 20 eV) 406 (M$^+$–AcOH, 26%), 370 (406-HCl, 34), 362 (370-C_2H_4O, 57), 326 (406 − HCl–C_2H_4O, 100), 266 (326 − AcOH, 87), 197 (23), 142 (40), 117 (34).

3β,20β-Diacetyloxy-5α-chloro-6,19-methanopregnane, 12

To a solution of the crude mixture of **10** and **11** obtained above (0.300 g) in dimethylformamide (2.53 cm^3), were added DBU (0.361 cm^3, 2.42 mmol) and CS_2 (3.35 cm^3) under a nitrogen atmosphere. The mixture was stirred at room temperature for 90 min and methyl iodide (6.21 cm^3) was added. After 90 min, excess methyl iodide was evaporated under a nitrogen stream, and the mixture was washed with $KHSO_4$ and evaporated. The residue (0.216 g) was dissolved in dry toluene (3.1 cm^3) and diphenylsilane (0.163 cm^3, 0.885 mmol) was added under a nitrogen atmosphere. The resulting solution was heated to 90 °C and treated with ten portions of 0.336 cm^3 of a solution of AIBN in toluene (0.044 g cm^{-3}) at 30 min intervals. After a further 30 min the mixture was evaporated to give, after purification by flash chromatography, *methano steroid* **12** (0.125 g, 37%, three steps) homogeneous by TLC (R_F = 0.49, hexane–ethyl acetate 8:2); mp 121–124 °C (from ethanol–water); (Found C 69.0; H 8.7. $C_{26}H_{39}ClO_4$ requires C 69.2; H 8.7); ν_{max} (KBr)/cm^{-1} 2945, 1740, 1369, 1241, 1091, 1035; δ_H (500 MHz) 0.65 (3H, s, H-18), 1.14 (3H, d, *J* = 6, H-21), 2.00 (3H, s, acetate), 2.01 (3H, s, acetate), 4.84 (1H, dq, *J* = 10 and 6, H-20), 5.16 (1H, tt, *J* = 5 and 11, H-3); δ_C (125 MHz) 13.0 (C-18), 19.9 (C-21), 21.5 and 21.4 (acetates), 22.1 (C-11), 23.7 (C-15), 24.3 (C-19), 25.6 (C-16), 25.7 (C-19a), 25.9 (C-1), 27.0 (C-2), 32.4 (C-7), 33.2 (C-8), 39.3 (C-12), 41.3 (C-4), 43.0 (C-10), 45.5 (C-6), 45.7 (C-13), 48.3 (C-14), 54.2 (C-9), 55.0 (C-17), 70.2 (C-3), 72.8 (C-20), 82.7 (C-5), 170.3 and 170.5 (acetates);*m*/*z* (EI, 70 eV) 450 (M$^+$, 0.14%), 414 (M − HCl, 0.7%), 330 (14), 137 (37), 119 (42), 55 (87), 43 (100).

6,19-Methanopregn-4-ene-3,20-dione, 4

Diacetate **12** (0.032 g, 0.07 mmol) was stirred with lithium aluminum hydride (0.048 g, 1.3 mmol) in dry diethyl ether (0.7 cm^3) for 90 min under a nitrogen atmosphere. Ethyl acetate was added and the mixture was washed with aqueous $KHSO_4$and extracted with diethyl ether to give *diol* **13** (0.025 g, 97%) homogeneous by TLC (R_F = 0.43, hexane–ethyl acetate 1:1); δ_H (200 MHz) 0.77 (3H, s, H-18), 1.12 (3H, d, *J* = 6, H-21), 3.70 (1H, dq, *J* = 10 and 6, H-20), 4.05 (1H, tt, *J* = 5 and 11, H-3); δ_C (125 MHz) 12.7 (C-18), 22.0 (C-11), 23.2 (C-21), 23.7 (C-19a), 24.1 (C-19), 25.4 (C-16), 25.6 (C-1), 26.1 (C-15), 30.2 (C-2), 32.3 (C-7), 32.9 (C-8), 39.6 (C-12), 42.9 (C-10), 44.6 (C-4), 45.4 (C-6 and C-13), 48.2 (C-14), 54.0 (C-17), 54.1 (C-9), 66.2 (C-20), 70.1 (C-3), 83.5 (C-5).

Compound **13** (0.059 g, 0.15 mmol) was oxidized with pyridinium chlorochromate as described above yielding *diketone* **14** (0.051 g, 93%) homogeneous by TLC (R_F = 0.61, hexane–ethyl acetate 1:1); δ_H (200 MHz) 0.67 (3H, s, H-18), 2.12 (3H, s, H-21), 2.57 (1H, d, *J* = 15, H-4β), 2.86 (1H, d, *J* = 15, H-4α); δ_C (125 MHz) 13.8 (C-18), 22.2 (C-11), 22.8 (C-19a), 23.9 (C-15), 25.8 (C-16), 25.9 (C-19), 28.4 (C-2), 31.5 (C-21), 32.0 (C-7), 33.2 (C-8), 36.8 (C-1), 38.8 (C-12), 44.6 (C-10), 44.8 (C-6), 46.0 (C-13), 48.3 (C-14), 51.5 (C-4), 54.9 (C-9), 63.5 (C-17), 83.6 (C-5), 207.8 (C-20), 209.5 (C-3). A solution of diketone **14** (0.050 g, 0.138 mmol) in dichloromethane (2.8 cm^3) was stirred for 3 h in the presence of aluminum oxide (0.3 g). Filtration, evaporation of the solvent and purification by flash chromatography, gave *6,19-methanoprogesterone* **4** (0.035 g, 70%) homogeneous by TLC (R_F = 0.40 hexane–ethyl acetate 6:4); (Found C 81.1; H 9.3. $C_{22}H_{30}O_2$ requires C 80.9; H 9.3%); ν_{max}(KBr)/cm^{-1} 2930, 1740, 1697, 1661, 1447, 1248, 1077, 1034; mp 125–127 °C (from ethanol–water); δ_H (500 MHz) 0.69 (3H, s, H-18), 1.30 (1H, m, H-7α), 1.34 (1H, dt, *J* = 4 and 13, H-19$_{proS}$), 1.63 (1H, m, H-19a$_{proS}$), 1.72 (1H, td, *J* = 8 and 14, H-1β), 1.75 (1H, m, H-7β), 2.00 (1H, tt, *J* = 6 and 13,

H-19a$_{proR}$), 2.12 (3H, s, H-21), 2.23 (1H, ddd, J = 5, 3 and 14, H-1α), 2.25 (1H, m, H-2α), 2.29 (1H, m, H-2β), 2.79 (1H, ddd, J = 2, 4 and 6, H-6), 5.75 (1H, s, H-4); δ_C (125 MHz) 13.8 (C-18), 23.0 (C-16), 23.3 (C-19a), 23.4 (C-11), 24.1 (C-15), 30.8 (C-1), 31.4 (C-21), 32.6 (C-19), 33.9 (C-2 and C-8), 38.6 (C-12), 41.2 (C-7), 42.9 (C-6), 44.8 (C-13), 45.3 (C-10), 51.6 (C-9), 55.3 (C-14), 63.3 (C-17), 115.8 (C-4), 181.1 (C-5), 199.7 (C-3), 209.2 (C-20); *m/z* (EI, 70 eV): 326 (M^+, 23%), 284 (16), 241 (16), 147 (17), 135 (34), 43 (100).

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