Simple synthetic approach to 6-oxa steroids. Synthesis of 6-oxa-5β-pregnane-3,20-dione

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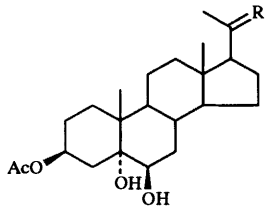
A two-step synthesis of 19-functionalized 6-oxapregnanes from a 5α,6β-dihydroxypregnane is described. Deoxygenation at C-19 afforded a 6-oxapregnane, which was converted into 6-oxa-5β-pregnane-3,20-dione **7**. An insight into the mechanism of formation of the key intermediate, a 5,6-secosteroid, *via* a hypoiodite type reaction is also given.

The synthesis of heterocyclic steroids, is of special interest in view of their physiological properties and the claim that certain heterosteroids possess anabolic, antihormonal, anti-hypercholesterolaemic, vasodilatatory, anticancer, neuro-muscular-blocking, central nervous system depressant and antimicrobial activities.[1] Several patents also describe the pharmacological utility of these compounds.[2]

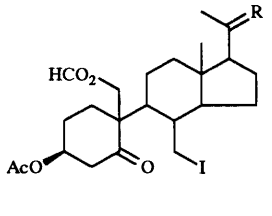
In spite of their significant biological activity, there are few reported syntheses of oxa steroids. Suginome *et al.* have reported the partial and total synthesis of various mono- and dioxa steroids.[3] The key step in these partial syntheses was a β-scission of the alkoxyl radicals generated from steroidal alcohols or lactols derived from cyclic ketones, *via* irradiation of their hypoiodites, to give the corresponding secosteroidal iodoformates. The latter were then converted into the hetero-steroids.

In particular, few methods are available for the preparation of 6-oxa steroids besides those mentioned above. A major route is based on the Torgov's carbocyclic total steroid synthesis for the preparation of 6-aza-, oxa- and thia-estranes.[4,5] Two other methods have been described starting from steroidal precursors with moderate overall yields.[6,7]

The photochemical reaction of 3β-acetoxy-5α,6β-dihydroxypregnan-20-one **1a** with mercury(II) oxide and iodine has



1a R = O
1b R = H, OAc

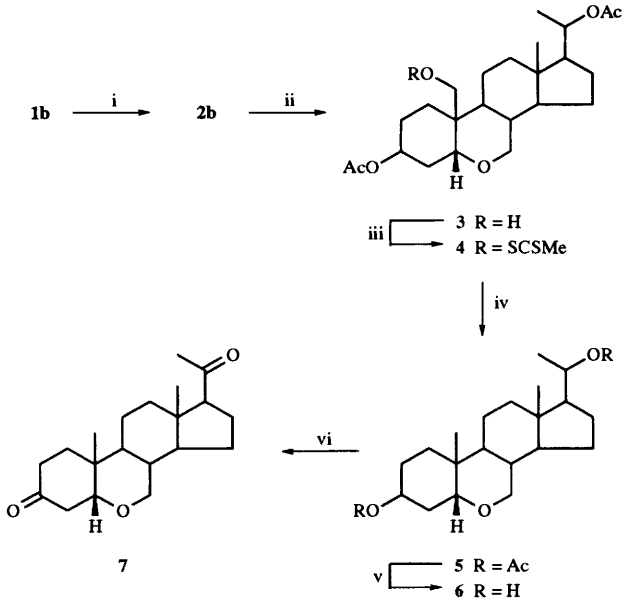


2a R = O
2b R = H, OAc

been described by us to afford in high yield the secosteroid **2a**.[8] This compound has structural features that indicate it would be a suitable precursor for 19-functionalized 6-oxa steroids.

Results and discussion

Scheme 1 outlines the synthesis of the title compound **7** from diol **1b**. This diol can be easily prepared from pregnenolone acetate in *ca.* 70% yield. Treatment of diol **1b** with mercury(II) oxide–iodine ($HgO–I_2$) in carbon tetrachloride under photolytic conditions (3 h, 300 W tungsten lamp) as previously described by us,[8] afforded the key intermediate, secosteroid **2b**. Reaction of the latter compound with sodium borohydride in ethanol gave in a single step the 5βH-6-oxa steroid **3**, as the sole cyclization product in 50% yield from **1b** (see below).



Scheme 1 *Reagents and conditions:* i, HgO, I_2, CCl_4, *hν*; ii, $NaBH_4$, EtOH; iii, DBU, CS_2, CH_3I, DMF; iv, Bu_3SnH, xylene, reflux; v, LAH, diethyl ether; vi, PCC, $BaCO_3$, molecular sieves (3 Å), CH_2Cl_2

Deoxygenation of the primary (neopentylic) hydroxy group attached at C-10 in compound **3**, was attempted by different methods, ranging from the direct or indirect (*via* iodine) reductive removal of a tosyloxy or mesyloxy group[9] to the widely used radical deoxygenation procedures.[10,11] In spite of the more complicated work-up procedure, the best yield was attained with the thermally initiated Barton reduction of the dithiocarbonate intermediate **4** with tributyltin hydride which is particularly suitable in the case of sterically hindered primary alcohols.[12] Further deacetylation with lithium aluminium hydride and oxidation with pyridinium chlorochromate yielded 6-oxa-5β-pregnane-3,20-dione **7** in 18% yield from **1b**. After the usual work-up, **7** was purified by flash chromatography and its identity confirmed by ^1H and ^{13}C NMR spectroscopy.

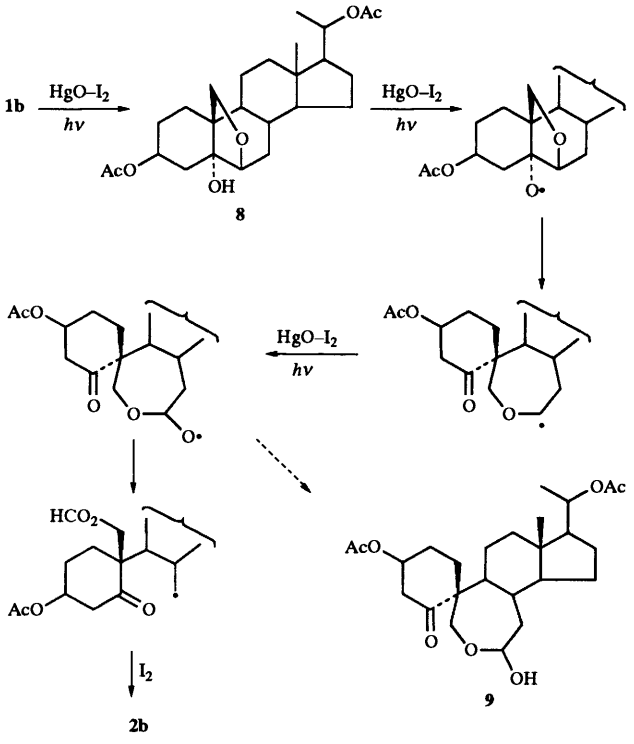
Formation of secosteroid 2b

In a previous publication,[8] we proposed a mechanism for the cleavage reaction of steroidal 5α,6β-diols leading to 5,6-secosteroids like **2a** and **2b**. We now present experimental evidence for this mechanism. TLC analysis of the reaction mixture of diol **1b** with $HgO–I_2$ at different times, revealed the presence of two compounds that were formed transiently. When the reaction was carried out with bis(acetoxy)iodobenzene–

iodine[13] in carbon tetrachloride or dichloromethane† the major product was coincident by TLC with one of the transient species detected in the $HgO–I_2$ reaction. This product was identified by ^1H and ^{13}C NMR and mass spectroscopy as 3β,20β-bis(acetoxy)-5α-hydroxy-6β,19-epoxypregnane **8**. The diagnostic signals in the ^1H NMR spectrum were those assigned to the 19-H_2 (δ 3.78 and 3.86, both doublets, J_{gem} 8.7 Hz) and 6-H^α (δ 3.71, d, J 3.1 Hz). The ^{13}C NMR and mass spectra also agreed with the proposed structure.

When compound **8** was allowed to react under the photolytic conditions used before ($HgO–I_2$, CCl_4, *hν*) the secosteroid **2b** was isolated after a shorter reaction time (2 h); this provided conclusive evidence that compound **8** was a true reaction intermediate. On the other hand, when the reaction of **8** with $HgO–I_2$ was stopped after only 1 h, another product was detected by TLC (coincident with the second transient species observed previously). After work-up and flash chromatography, we isolated this intermediate species which was identified by ^1H and ^{13}C NMR and mass spectroscopy as the *seco*-lactol **9**.

Formation of **8** and **9** from **1b** can be explained by the sequence depicted in Scheme 2, where the initially formed



Scheme 2

5α-hydroxy-6,19-epoxy steroid **8** reacts further by formation of the 5-oxyl radical and cleavage of the 5,6 bond. The carbon radical formed can be oxidized further by the $HgO–I_2$ system,[14] yielding an oxyl-radical which upon work-up gives *seco*-lactol **9**. The course of the reaction continues with the cleavage of the 6,7 bond and the formation of a methylene radical which is finally trapped by iodine affording secosteroid **2b**.

Stereochemistry of the reductive cyclization of secosteroid 2b

The structure of the oxa steroid **3** and its stereochemistry at position 5 were confirmed by ^1H and ^{13}C NMR (proton decoupled and DEPT). The ^1H NMR spectra presented a singlet for one angular methyl at δ 0.70 (13-H_3C) and a doublet for the 20-H_3C at δ 1.25 as well as singlets for the two acetoxy groups. The protons on C-19 appeared as an AB quartet at δ 3.51 and 4.02 (J_{gem} 11 Hz). The 5-H^β resonance was observed at δ 4.15 as a double doublet and the 3-H^α appeared as an unresolved multiplet at δ 5.19. The ^{13}C NMR spectrum of **3** gave conclusive evidence on the structure of this compound. Only 20 resonances were observed (besides those of the acetyloxy groups). Five carbon resonances (two methylene and three methines) assigned to C-3, -5, -7, -19 and -20 were observed in the range δ 64.2 to 72.7, typical of oxygen bonded carbons. Two methyl carbon resonances appeared at δ 12.8 (C-18) and 19.9 (C-21).

Table 1 Calculated[15] and observed vicinal coupling constants for relevant hydrogens in ring A of 5-H^β-oxa steroid **3**

H,H	Dihedral angle[a] (deg)	$^3J_{H-H}$(obs.)/Hz	$^3J_{H-H}$(calc.)/Hz
3α,4α	47.39	3.2	3.5
3α,4β	−67.39	*ca.* 2.5	2.9
4α,5β	−162.68	12.5	10.1
4β,5β	−48.21	5.2	5.9

[a] From PM3 calculations.

The assignment of the absolute configuration at C-5 in compound **3** was deduced from its ^1H NMR spectrum, based on the coupling constants between 5-H and the hydrogens at position 4 and, of the latter hydrogens with 3-H^α (position 3 had a fixed configuration throughout the synthetic transformations). The primary evidence of an A/B *cis* fusion, was given by the resonance of 3-H, which appeared as a broad signal ($W_{1/2}$ 9.1 Hz) typical of an equatorial hydrogen. The axial hydrogen at position 4, identified by its large coupling constant with 5-H (also axial), was clearly visible at δ 2.30 as a double double doublet; the other couplings observed for the axial 4-H were the geminal coupling (13.8 Hz) and a 3.2 Hz coupling with 3-H which corresponded to an axial–equatorial J. This arrangement, only possible in an A/B *cis* steroid, had J values which agreed with those calculated using the Altona equation[15] for the steroid in which the configuration was 5-H^β (Table 1).

Final confirmation of the stereochemistry at C-5 was carried out on compound **5** based on the NOESY spectrum, as all the oxapregnanes synthesized had identical configuration at this position. This experiment gave us clear evidence of the *cis*-fusion of rings A and B, showing strong NOEs between 5-H and the hydrogens of the 10-methyl group and between 4-H^α and 7-H^α (Fig. 1).

The closure of secosteroid **2b** to the usually less stable *cis*-juncture of the A/B rings in oxa steroid **3**, prompted us to analyse by molecular modelling using the PM3 semiempirical method, the two possible ring A conformations of the intermediate 19-hydroxy secosteroid for each of the rotamers around the C(9)–C(10) bond (Table 2).‡ Fig. 2 shows the two most stable conformers found, which have ring A in a conformation analogous to that found in 5β-steroids (*i.e.* $^1C_4$) in agreement with the NMR data for **2b** (*i.e.* 3-H resonance observed as a broad signal with $W_{1/2}$ 9 Hz). These conformers, have the rest of the steroid moiety (rings C, D and side chain) bound to C-10 in an axial orientation blocking attack of the hydride from the α face on C-5, thus reduction yields stereoselectively the 5α-alcohol (probably with participation of the 19-hydroxy group) which cyclizes to the oxa steroid **3** with the 5-H^β configuration.

† Diol **1b** dissolves only with difficulty in CCl_4 (especially if it has been recrystallized); the use of CH_2Cl_2 allowed us to work in more concentrated solutions and did not alter the course of the reaction.

‡ Conversion of the 19-formate to the 19-hydroxy secosteroid takes place in the first stages of the reaction with sodium borohydride.

Table 2 Relative energies of the possible conformations of the 19-hydroxy analogue of secosteroid **2b**, from PM3 calculations (AMPAC 4.5)

Ring A conformation	C(19)–C(10)–C(9)–H(9) (deg)	Relative energy (kcal mol^{-1})[a]
$^1C_4$	177.33	0.00
$^1C_4$	34.30	0.84
$^1C_4$	−39.31	2.81
$^4C_1$	145.50	10.70
$^4C_1$	55.36	1.65
$^4C_1$	−82.49	4.41

[a] 1 cal = 4.184 J.

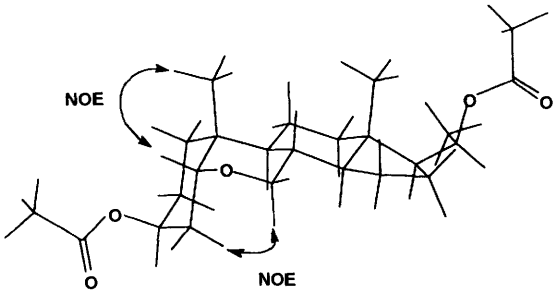


Fig. 1 Observed NOEs on 6-oxa-5β-pregnane **5**

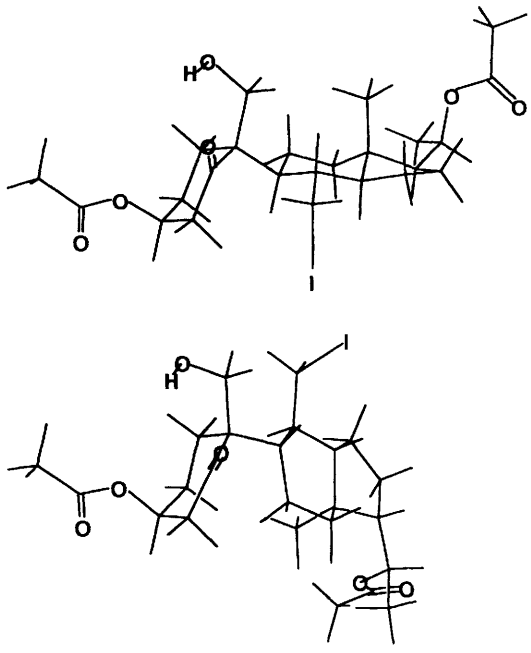


Fig. 2 Most stable conformers of the 19-hydroxy analogue of secosteroid **2b** as predicted by PM3 calculations (see Table 2)

Conclusions

In conclusion, a simple method for the conversion of a 5α,6β-steroidal diol into 19-functionalized 6-oxa steroids with a *cis* A/B fusion, is described based on the stereospecific reductive cyclization of iodo secosteroid **2b**. Deoxygenation at position 19 using the Barton procedure affords 10-Me oxa steroids. The synthesis of the 6-oxa analogue of 5β-pregnane-3,20-dione has been achieved by this procedure.

Experimental

Mps were taken on a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded in KBr pellets or thin films using KBr disks on a Nicolet Magna IR 550 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were measured at 200.13 and 50.32 MHz in a Bruker AC-200 NMR spectrometer in deuteriochloroform (using tetramethylsilane as internal standard). *J* Values are given in Hz. Electron impact mass spectra (EI) were measured in a VG Trio 2 mass spectrometer at 70 eV by direct inlet. FAB mass spectra and electron impact high resolution mass spectra (HRMS) were obtained in a VG ZAB BEQQ mass spectrometer. Semiempirical calculations were performed with AMPAC 4.5 (Semichem, USA). All solvents used were reagent grade. Solvents were evaporated at *ca.* 45 °C under reduced pressure.

3β,20β-Diacetoxy-5α,6β-dihydroxypregnane **1b** was prepared from pregnenolone (3β-hydroxypregn-5-en-20-one) acetate in 70% yield, as a single product, by reduction with sodium cyanoborohydride in methanol to the 20-alcohol followed by acetylation, epoxidation with *m*-chloroperbenzoic acid and acid hydrolysis of the epoxide mixture with tetrahydrofuran and aqueous sulfuric acid.[8]

3β,20β-Bis(acetoxy)-19-formyloxy-7-iodo-6-nor-5,7-seco-pregnan-5-one 2b

To a solution of diol **1b** (0.400 g, 0.92 mmol) in freshly distilled carbon tetrachloride (66 cm^3) were added mercury(II) oxide (2.06 g, 9.51 mmol) and iodine (3.16 g, 12.5 mmol). The solution was then irradiated with a 300 W tungsten lamp (5000 lm) for 3.5 h while being vigorously stirred at room temperature. After filtration the solution was diluted with dichloromethane, washed with aqueous sodium thiosulfate and water, dried and then evaporated to dryness, yielding crude *secosteroid* **2b** (0.517 g, 98%). This product could not be crystallized,§ an analytical sample was purified by preparative TLC (hexane–ethyl acetate 7:3); ν_{max}(KBr)/cm^{-1} 1728 (C=O, esters), 1704 (C=O, ketone), 1438 (CH_2–I), 1247 (C–O, acetate), 1163 (C–O, formate), 1028 and 1021; δ_H 0.70 (3 H, s, 13-H_3C), 1.15 (3 H, d, *J* 6, 20-H_3C), 2.02 (3 H, s, acetate), 2.03 (3 H, s, acetate), 2.58 (1 H, br d, J_{gem} 15.0, 4-H^a), 3.13 (1 H, dd, $J_{7a,8}$ 2.7, J_{gem} 10.9, 7-H^a), 3.39 (1 H, dd, $J_{7b,8}$ 1.9, J_{gem} 10.9, 7-H^b), 3.63 (1 H, dd, $J_{4\beta,3}$ 4.3, J_{gem} 15.0, 4-H^B), 4.31 (1 H, d, J_{gem} 11.8, 19-H^a), 4.52 (1 H, d, J_{gem} 11.8, 19-H^b), 4.83 (1 H, m, 20-H), 5.41 (1 H, br s, 3-H) and 8.11 (1 H, s, formate); δ_C 13.2 (C-18), 17.2 (C-7), 19.7 (C-21), 21.2 (acetate), 21.4 (acetate), 23.2 (C-11¶), 23.4 (C-15¶), 24.8 (C-16¶), 25.0 (C-1¶), 28.8 (C-2), 37.6 (C-9), 38.9 (C-12), 40.0 (C-8), 41.6 (C-13), 41.2 (C-4), 53.7 (C-10), 54.7 (C-14), 54.8 (C-17), 64.7 (C-19), 72.5 (C-3), 72.5 (C-20), 160.7 (formate), 170.1 (acetate), 170.2 (acetate) and 212.2 (C-5); *m/z* (FAB, 3-nitrobenzyl alcohol) 577 (M + 1, 36%), 517 (M + 1 − AcOH, 92), 457 (M + 1 − 2AcOH, 54), 389 (M + 1 − HI, 52), 373 (55) and 303 (100) (Found M − HOAc, 516.1359. $C_{23}H_{33}O_5I$ requires *M*, 516.1372; Found: M − HOAc − HI, 388.2248. $C_{23}H_{32}O_5$ requires *M*, 388.2249).

3β,20β-Bis(acetoxy)-19-hydroxy-6-oxa-5β-pregnane 3

To a solution of the crude secosteroid **2b** (0.5 g) in absolute ethanol (67 cm^3) cooled to 0 °C, was added sodium borohydride (0.123 g, 3.21 mmol). The solution was stirred at 0 °C for 2 h and then at room temperature for another 2 h, acidified (pH 5–6) with hydrochloric acid (1 mol dm^{-3}), and then neutralized with 10% aqueous sodium hydrogen carbonate. The solution was concentrated under reduced pressure to a volume of 25 cm^3, diluted with water and extracted with diethyl ether. The extract was washed with water, dried and then evaporated to dryness. Chromatography on silica gel with ethyl acetate–hexane as eluent yielded 19-*hydroxy oxa steroid* **3** (0.190 g, 52%)

§ Attempts to recrystallize this compound were unsuccessful due to its instability.

¶ Assignments may be interchanged.

homogeneous by TLC; ν_{max}(KBr)/cm^{-1} 3443 (OH), 1734 (C=O), 1244 (C–O), 1151, 1070, 1047 and 1028; δ_H 0.70 (3 H, s, 13-H$_3$C), 1.15 (3 H, d, J 6.0, 20-H$_3$C); 2.01 (3 H, s, acetate), 2.05 (3 H, s, acetate), 2.30 (1 H, ddd, $J_{4\alpha,3}$ 3.2, $J_{4\alpha,5}$ 12.5, J_{gem} 13.8, 4-H$^{\alpha}$), 3.34 (1 H, t, J_{gem} ~ $J_{7\alpha,8}$ 11.5, 7-H$^{\alpha}$), 3.51 (1 H, d, J_{gem} 11.0, 19-H^{a}), 3.57 (1 H, dd, $J_{7\beta,8}$ 5.2, J_{gem} 11.5, 7-H$^{\beta}$), 4.02 (1 H, d, J_{gem} 11.0, 19-H^{b}), 4.15 (1 H, dd, $J_{5,4\beta}$ 5.2, $J_{5,4\alpha}$ 12.5, 5-H$^{\beta}$); 4.83 (1 H, m, 20-H) and 5.19 (1 H, br s, 3-H); δ_C 12.8 (C-18), 19.9 (C-21), 20.2 (C-11), 21.3 (acetate), 21.5 (acetate), 22.9 (C-1), 23.3 (C-15), 24.1 (C-16), 25.7 (C-2), 27.8 (C-4), 34.7 (C-8), 38.4 (C-9), 39.1 (C-10), 39.5 (C-12), 42.8 (C-13), 52.3 (C-14), 54.5 (C-17), 64.2 (C-19), 66.7 (C-7), 70.5 (C-5), 71.4 (C-3), 72.7 (C-20), 170.4 (acetate) and 170.5 (acetate); m/z (FAB, 1-sulfanylglycerol) 423 (M + 1, 15%), 363 (M + 1 − AcOH, 49), 361 (40), 345 (20), 331 (22), 303 (19), 285 (18), 271 (15), 267 (15) and 91 (100). Acetylation with Ac_2O–pyridine gave the 19-*acetate*, mp 162–163 °C (from acetone–hexane) (Found: C, 67.2; H, 8.7. $C_{26}H_{40}O_7$ requires C, 67.2; H, 8.7%).

3β,20β-Bis(acetoxy)-6-oxa-5β-pregnane 5

6-Oxapregnane **3** (0.3 g, 0.71 mmol) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (0.434 g, 2.84 mmol) were dissolved in dry *N*,*N*-dimethylformamide (3.6 cm^3). Carbon disulfide (4.0 cm^3) was added and the reaction mixture was stirred for 45 min at room temperature. After addition of methyl iodide (7.8 cm^3) stirring was continued for a further 45 min at room temperature and the reaction mixture was then evaporated. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried and then evaporated to dryness. Chromatography on silica gel with ethyl acetate–hexane as eluent yielded 3β, 20β-*bis*(*acetoxy*)-19-(*methylsulfanylthiocarbonyloxy*)-6-*oxa*-5β-*pregnane* **4** (0.256 g, 70%); δ_H 0.67 (3 H, s, 13-H$_3$C), 1.15 (3 H, d, J 6.0, 20-H$_3$C), 2.00 (3 H, s, acetate), 2.04 (3 H, s, acetate), 2.35 (1 H, ddd, $J_{4\alpha,3}$ 3.0, $J_{4\alpha,5}$ 12.1, J_{gem} 14.7, 4-H$^{\alpha}$), 2.58 (3 H, s, SCH$_3$), 3.33 (1 H, t, J_{gem} ~ $J_{7\alpha,8}$ 11.4, 7-H$^{\alpha}$), 3.60 (1 H, dd, $J_{7\beta,8}$ 4.9, J_{gem} 11.4, 7-H$^{\beta}$), 4.14 (1 H, dd, $J_{5,4\beta}$ 4.8, $J_{5,4\alpha}$ 12.1, 5-H$^{\beta}$), 4.78 (1 H, d, J_{gem} 10.9, 19-H^{a}), 4.86 (1 H, d, J_{gem} 19-H^{b}), 4.83 (1 H, m, 20-H) and 5.21 (1 H, br s, 3-H).

Tributyltin hydride (1.082 g, 3.35 mmol) in xylene (16 cm^3) was added during 2 h to the dithiocarbonate **4** (0.240 g, 0.47 mmol) in xylene (16 cm^3) at 150 °C under nitrogen. After heating for a further 14 h, the solvent was evaporated and the residue was partitioned between hexane (100 cm^3) and acetonitrile (100 cm^3). The acetonitrile layer was separated and washed with hexane (3 × 50 cm^3) and evaporated to dryness. Chromatography on silica gel with ethyl acetate–hexane as eluent yielded *oxapregnane* **5** (0.121 g, 63.5%); mp 114–115 °C (from ethanol–water) (Found: C, 70.6; H, 9.4. $C_{24}H_{38}O_5$ requires C, 70.9; H, 9.4%); ν_{max}(KBr)/cm^{-1} 1734 (C=O), 1254 and 1238 (C–O), 1191, 1162, 1089, 1078 and 1034; δ_H 0.65 (3 H, s, 13-H$_3$C), 1.11 (3 H, s, 10-H$_3$C), 1.15 (3 H, d, J 6, 20-H$_3$C), 2.01 (3 H, s, acetate), 2.04 (3 H, s, acetate), 2.32 (1 H, ddd, $J_{4\alpha,3}$ 3.1, $J_{4\alpha,5}$ 12.4, J_{gem} 13.5, 4-H$^{\alpha}$), 3.30 (1 H, t, J_{gem} ~ $J_{7\alpha,8}$ 11.2, 7-H$^{\alpha}$), 3.56 (1 H, dd, $J_{7\beta,8}$ 5.0, J_{gem} 11.2, 7-H$^{\beta}$), 3.69 (1 H, dd, $J_{5,4\beta}$ 4.9, $J_{5,4\alpha}$ 12.4, 5-H$^{\beta}$), 4.83 (1 H, m, 20-H) and 5.20 (1 H, br s, 3-H); δ_C 12.7 (C-18), 20.0 (C-19), 20.5 (C-11), 21.4 (acetate), 21.5 (acetate), 22.8 (C-21), 23.4 (C-15), 24.5 (C-16), 25.8 (C-2), 29.3 (C-1), 28.0 (C-4), 34.7 (C-8), 35.5 (C-10), 38.8 (C-9), 39.3 (C-12), 42.8 (C-13), 51.7 (C-14), 54.7 (C-17), 64.8 (C-7), 71.1 (C-3), 72.8 (C-20), 76.5 (C-5), 170.4 (acetate) and 170.5 (acetate); m/z (EI) 346 (M$^+$ − AcOH, 100%), 331 (17), 271 (8.6), 111 (30) and 43 (68).

6-Oxa-5β-pregnane-3,20-dione 7

The diacetate **5** (0.1 g, 0.25 mmol) in dry diethyl ether (9.5 cm^3) was stirred with lithium aluminium hydride (0.1 g, 2.6 mmol) for 6 h under nitrogen. The reaction mixture was treated successively with ethyl acetate and 10% aqueous hydrochloric acid. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were washed with aqueous sodium hydrogen carbonate and water, dried and then evaporated to dryness, yielding *diol* **6** (0.075 g, 95%); δ_H 0.77 (3 H, s, 13-H$_3$C), 1.11 (3 H, s, 10-H$_3$C); 1.14 (3 H, d, J 6, 20-H$_3$C), 2.32 (1 H, ddd, $J_{4\alpha,3}$ 3.1, $J_{4\alpha,5}$ 12.2, J_{gem} 13.4, 4-H$^{\alpha}$), 3.31 (1 H, t, J_{gem} ~ $J_{7\alpha,8}$ 11.4, 7-H$^{\alpha}$), 3.56 (1 H, dd, $J_{7\beta,8}$ 5.1, J_{gem} 11.4, 7-H$^{\beta}$), 3.72 (1 H, m, 20-H) 3.79 (1 H, dd, $J_{5,4\beta}$ 4.8, $J_{5,4\alpha}$ 12.2, 5-H$^{\beta}$) and 4.26 (1 H, br s, 3-H).

Pyridinium chlorochromate (0.38 g, 1.76 mmol), barium carbonate (0.22 g, 1.13 mmol) and 3 Å molecular sieves (0.15 g) in dry dichloromethane (2.0 cm^3) were vigorously stirred at room temperature for 20 min and then the diol **6** (0.068 g, 0.21 mmol) in dry dichloromethane (3.0 cm^3) was added. After a further 4 h, the reaction mixture was diluted with diethyl ether, percolated through Florisil, eluting with diethyl ether and dichloromethane and then evaporated to dryness. Chromatography on silica gel with ethyl acetate–hexane as the eluent yielded *diketone* **7** (0.054 g, 80%); mp 153–154 °C (from diisopropyl ether) (Found: C, 75.2; H, 9.8. $C_{20}H_{30}O_3$ requires C, 75.4; H, 9.5%); ν_{max}(KBr)/cm^{-1} 1716 and 1709 (C=O) and 1077 (C-O-C); δ_H 0.67 (3 H, s, 13-H$_3$C), 1.16 (3 H, s, 10-H$_3$C); 2.13 (3 H, s, 20-H$_3$C), 2.41 (1 H, ddd, $^4J_{4\beta,2\beta}$ 1.9, $J_{4\beta,5}$ 5.6, J_{gem} 14.7, 4-H$^{\beta}$), 3.05 (1 H, dd, $J_{4\alpha,5}$ 11.4, J_{gem} 14.7, 4-H$^{\alpha}$), 3.35 (1 H, t, J_{gem} ~ $J_{7\alpha,8}$ 11.5, 7-H$^{\alpha}$), 3.67 (1 H, dd, $J_{7\beta,8}$ 5.1, J_{gem} 11.5, 7-H$^{\beta}$) and 3.71 (1 H, dd, $J_{5,4\beta}$ 5.6, $J_{5,4\alpha}$ 11.4, 5-H$^{\beta}$); δ_C 13.5 (C-18), 20.4 (C-11), 21.8 (C-19), 23.3 (C-15), 23.6 (C-16), 31.5 (C-21), 31.9 (C-1), 34.6 (C-8), 35.2 (C-10), 36.4 (C-2), 38.8 (C-12), 39.5 (C-9), 40.7 (C-4), 44.4 (C-13), 52.6 (C-14), 63.1 (C-17), 64.8 (C-7), 79.7 (C-5), 208.9 (C-20) and 209.8 (C-3); m/z (EI) 318 (M$^+$, 34%), 300 (M − H$_2$O, 76), 261 (13), 248 (10), 233 (12), 215 (8), 55 (49) and 43 (100).

3β,20β-Bis(acetoxy)-5α-hydroxy-6β,19-epoxypregnane 8

A solution of diol **1b** (0.100 g, 0.23 mmol) in freshly distilled carbon tetrachloride (21 cm^3) containing bis(acetoxy)iodobenzene (0.084 g, 0.25 mmol) and iodine (0.063 g, 0.25 mmol) was irradiated with a 300 W tungsten lamp for 85 min at room temperature. The reaction mixture was then poured into water and extracted with diethyl ether. The organic layer was washed successively with sodium thiosulfate and water, dried and then evaporated to dryness. Chromatography on silica gel with ethyl acetate–hexane as eluent yielded *hydroxy ether* **8** (0.070 g, 70%); mp 201–203 °C (from acetone) (Found: C, 69.2; H, 9.07. $C_{25}H_{38}O_6$ requires C, 69.09; H, 8.81); ν_{max}(KBr)/cm^{-1} 3423 (OH), 1728 (C=O), 1240 (C–O, acetate), 1078, 1039 and 1023; δ_H 0.67 (3 H, s, 13-H$_3$C), 1.14 (3 H, d, J 6, 20-H$_3$C), 2.01 (3 H, s, acetate), 2.04 (3 H, s, acetate), 3.71 (1 H, d, $J_{6\alpha,7}$ 3.1, 6-H$^{\alpha}$), 3.78 (1 H, d, J_{gem} 8.7, 19-H^{a}), 3.86 (1 H, d, J_{gem} 8.7, 19-H^{b}), 4.87 (1 H, m, 20-H) and 4.99 (1 H, m, 3-H); δ_C 12.8 (C-18), 19.8 (C-21), 21.3 (acetate), 21.4 (acetate), 22.1 (C-11), 23.5 (C-16 ¶), 23.6 (C-15 ¶), 25.4 (C-7), 27.1 (C-2), 31.0 (C-1), 33.0 (C-8), 38.6 (C-12 ¶), 39.2 (C-4 ¶), 42.9 (C-13), 44.1 (C-10) 44.4 (C-9), 54.0 (C-14), 54.9 (C-17), 68.8 (C-19), 69.8 (C-3), 72.8 (C-20), 76.9 (C-5), 81.3 (C-6), 170.1 (acetate) and 170.4 (acetate); m/z (FAB 1-sulfanylglycerol) 433 (M − 1, 9.5%), 375 (27), 373 (M − 1 − AcOH, 35), 316 (19), 315 (83), 313 (22), 297 (43), 267 (19.5) and 121 (100).

3β,20β-Bis(acetoxy)-6α-hydroxy-6β,19-epoxy-5,6-seco-pregnan-5-one 9

To a solution of hydroxy ether **8** (0.174 g, 0.41 mmol) in freshly distilled carbon tetrachloride (28 cm^3) were added HgO (0.890 g, 4.11 mmol) and I_2 (1.33 g, 5.26 mmol). The solution was then irradiated with a 300 W tungsten lamp for 1 h while being vigorously stirred at room temperature. After filtration, the solution was diluted with dichloromethane, washed with

aqueous sodium thiosulfate and water, dried and then evaporated to dryness. Chromatography on silica gel with ethyl acetate–hexane as eluent yielded *lactol* **9** (0.021 g, 11%), an analytical sample was purified by preparative TLC (hexane–ethyl acetate 1:1) (Found: M − AcOH − H_2O, 372.2297. $C_{23}H_{32}O_4$ requires *M*, 372.2301; Found: M − AcOH − HCOH, 360.2295. $C_{22}H_{32}O_4$ requires *M* 360.2301); ν_{max}(film)/cm^{-1} 3435 (OH), 1728 (C=O, acetate), 1668 (C=O, ketone), 1246 (C–O, acetate) and 1026 (C–O–C); δ_H 0.62 (3 H, s, 13-H_3C), 1.14 (3 H, d, *J* 6, 20-H_3C), 1.99 (3 H, s, acetate), 2.04 (3 H, s, acetate), 2.43 (1 H, dd, $J_{4a,3}$ 8.7, J_{gem} 16.8, 4-H^a), 2.69 (1 H, dd, $J_{4b,3}$ 5.6, J_{gem} 16.8, 4-H^b), 3.59 (1 H, d, J_{gem} 13.0, 19-H^a), 3.83 (1 H, d, J_{gem} 13.0, 19-H^b), 4.83 (1 H, m, 20-H), 5.05 (1 H, m, 3-H) and 5.14 (1 H, dd, $J_{6,7a}$ 5.1, $J_{6,7b}$ 9.2, 6-H); δ_C 12.1 (C-18), 19.7 (C-21), 20.9 (C-11), 21.1 (acetate), 21.4 (acetate), 24.1 (C-15), 24.7 (C-16), 25.5 (C-1¶), 25.8 (C-2¶), 32.7 (C-8), 38.4 (C-12), 39.1 (C-7), 41.6 (C-13), 45.0 (C-4) 50.4 (C-9), 54.3 (C-14), 54.9 (C-17), 56.4 (C-10), 62.5 (C-19), 69.8 (C-3), 72.5 (C-20), 95.6 (C-6), 170.1 (acetate), 170.4 (acetate) and 211.0 (C-5); *m/z* (EI) 372 (M$^+$ − AcOH − H_2O, 8.6%), 360 (M − AcOH − HCOH, 25), 342 (5), 161 (21), 126 (26), 125 (29), 109 (40) and 43 (100).

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