# A procedure for the preparation of cardioactive steroid precursors: synthesis of 3β-acetoxy-21-hydroxy-5α-pregn-14-en-20-one

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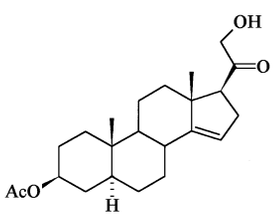
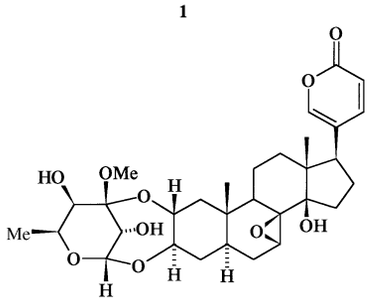
**The efficient preparation of an important precursor in the synthesis of cardioactive steroids is reported. The key step, the introduction of a 21-hydroxy group into a 14,15-dehydropregnane derivative, is accomplished by reaction of the enol ether with dimethyldioxirane.**

Cardiac glycosides have been used since the middle ages for the treatment of congestive heart failure,[1] and digoxin, the most commonly used cardiac glycoside, is still one of the current 10 most used prescription drugs.[2] However, the use of these compounds is severely limited by their extreme toxicity, and digoxin is one of the most toxic drugs on the market. There is accordingly a demand for analogues with diminished toxicity but with enhanced therapeutic activity.

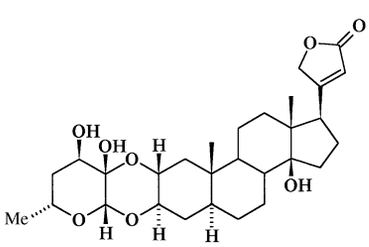
In our program directed towards the synthesis of cardiac glycoside analogues with only the essential substituents on the steroid aglycone (*i.e.* a 14β-hydroxy group and a 17β-unsaturated lactone), but with novel carbohydrate moieties, 3β-acetoxy-21-hydroxy-5α-pregn-14-en-20-one **1** was recognized as a key intermediate. Available methodology would permit the introduction of the lactone ring on C-17, the 14β-hydroxy group and a hydroxy function on C-2, therefore allowing us to prepare cardiac glycosides containing carbohydrate moieties with multiple linkages to the aglycone, as is found for example in cotyledoside **2**[3] and gomphoside **3**.[4] Here we describe an efficient synthesis for **1**.




**1**




**2**



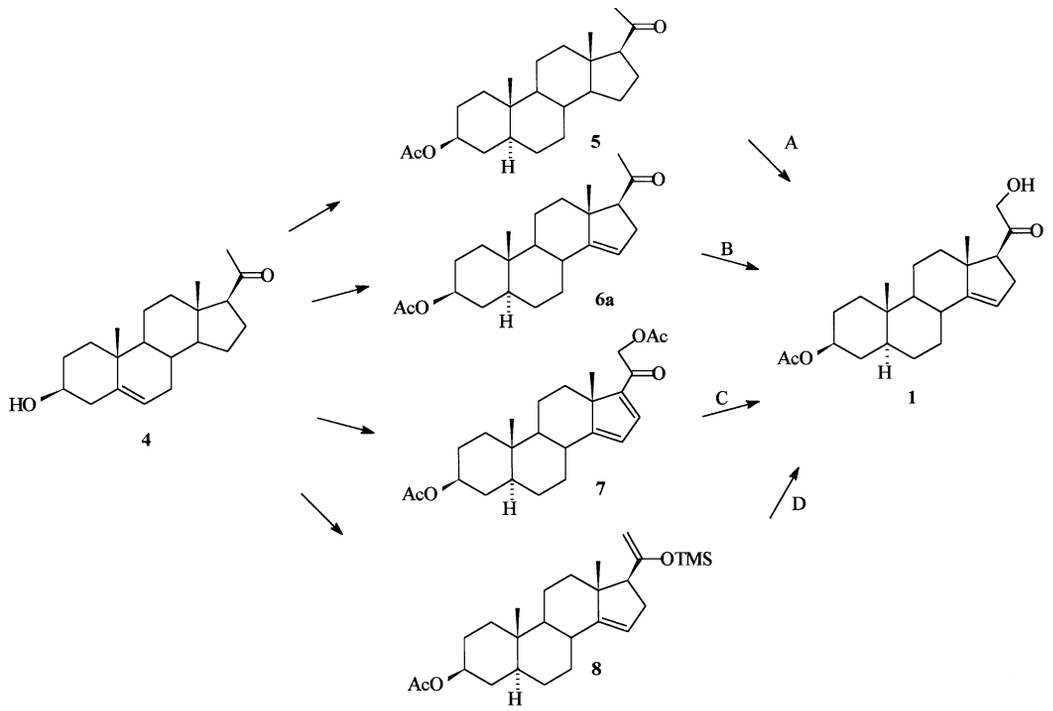

**3**

Different approaches, as summarized in Scheme 1, were considered for the preparation of **1** from pregnenolone **4**. Approaches A, B and C have been published, but in our hands, the reactions gave either low yields or, after careful chromatography of the reaction mixtures on silica gel impregnated with silver nitrate, more products than were reported in the literature. The 'remote functionalisation' method (pathway A) for the introduction of the $\Delta^{14,15}$-double bond, which was effective for the 5β-analogue of **5**,[5] proved to be unsuccessful. Not only was the yield of the reaction low, but an inseparable 1:1 mixture of the 14,15- and the 9,10-unsaturated derivatives was obtained.

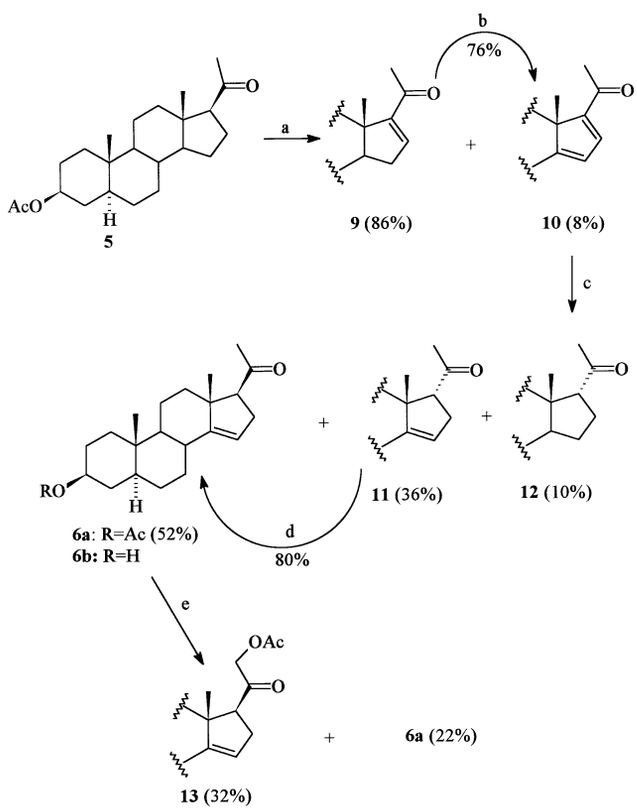
Approach B (Scheme 2), also reported by Kočovský and Stieborová,[6] is based on the acetoxylation of C-21 with lead tetraacetate.[7] The key intermediate **6a** was prepared by a sequence of bromination–elimination reactions,[8,9,10] followed by the palladium(0)-catalysed selective reduction of the 16,17-double bond with diphenysilane.[11] The reduction resulted in the formation of a 3:2 mixture of the 17β- **6a** and the 17α-epimers **11**, as well as a small amount of the fully reduced steroid **12**. The difference in the stereochemistry of the two isomers was reflected in the chemical shifts of 17-H ($\delta$ 2.89 and 3.02, respectively) and 18-H ($\delta$ 0.84 and 1.28, respectively). The $^1$H NMR data reported in the literature[12] did not allow unambiguous differentiation between these two isomers. However, in a NOE experiment, enhancement of the intensity of the 17-Hβ resonance was observed upon irradiation of 18-H, thereby allowing us to assign the structure of **11**. Final proof for the structures was provided by comparing the products obtained by hydrogenation of **6a** and **11** with the hydrogenated product of commercial 17β-pregnenolone. Treatment of **5** with the reagents used in the reduction did not result in any epimerization at C-17, which proved that the two epimers must have formed during the reduction step. The formation of the two stereoisomers **6a** and **11** indicated that the initial complexation of the palladium to the enone was not exclusively from the α-face of **10** (*trans* to the 18-methyl group), but that a substantial degree of complexation from the β-face also occurred.

Base-catalysed equilibration and subsequent acetylation of **11** produced an epimeric mixture from which the required isomer **6a** was isolated in an 80% yield. 3β-Acetoxy-6α-pregn-14-en-20-one **6a** could, therefore, be prepared in an acceptable yield from pregnenolone **4**. However, the final step in this sequence, *i.e.* the oxygenation of C-21 of **6a** with $Pb(OAc)_4$, produced a mixture of compounds from which the required product **13** was isolated in a low yield. Longer reaction times resulted only in the formation of unwanted side products. This approach to the synthesis of **1** was therefore abandoned.

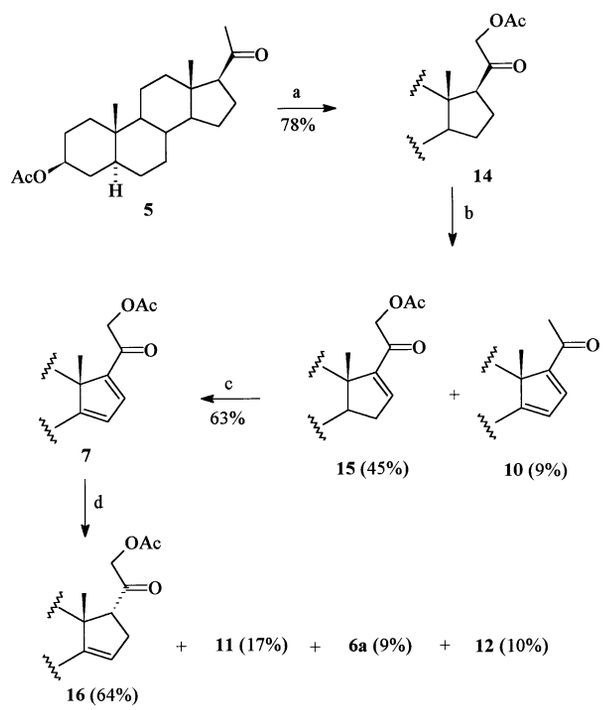
Pathway C (Scheme 3) comprised the same reaction steps as pathway B, but in a different order. The initial acetoxylation proceeded in a high yield, but both the introduction of the




**Scheme 1** Different approaches to the synthesis of **1**. A = Remote functionalization ($PhICl_2$, base), oxidation with $Pb(OAc)_4$; B = oxidation with $Pb(OAc)_4$, selective hydrolysis; C = selective reduction and selective hydrolysis; and D = epoxidation, rearrangement.



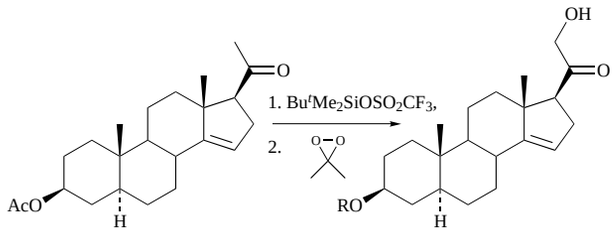

**Scheme 2** *Reagents:* a, (i) $Br_2$, HBr, HOAc and (ii) LiBr, DMF; b, (i) NBS, AIBN, $CCl_4$ and (ii) NaI, $Me_2CO$; c, $Ph_2SiH_2$, $Pd(PPh_3)_4$, $ZnCl_2$, $CHCl_3$; d, (i) $K_2CO_3$ and (ii) $Ac_2O$, Py; e, $Pb(OAc)_4$, $BF_3{\cdot}OEt_2$, MeOH, $C_6H_6$




**Scheme 3** *Reagents:* a, $Pb(OAc)_4$, $BF_3{\cdot}OEt_2$, MeOH, $C_6H_6$; b, (i) $Br_2$, HBr, HOAc and (ii) LiBr, DMF; c, (i) NBS, AIBN, $CCl_4$ and (ii) NaI, $Me_2CO$; d, $Ph_2SiH_2$, $Pd(PPh_3)_4$, $ZnCl_2$, $CHCl_3$

$\Delta^{16,17}$-double bond (to form **15**) and the selective reduction of the 14,16-diene **7** resulted in the formation of unwanted side products. Purification of the products was difficult due to the closely related $R_f$ values of the different compounds. Since the success of a synthesis depends not only on high yields for the individual steps, but also on the ease with which the products can be isolated, this route was also not considered viable for the preparation of cardiac glycosides. Furthermore, compound **16** obtained in the reduction step was not the required isomer, but an epimer with inverted stereochemistry at C-17.

The introduction of the 21-hydroxy group in the presence of the $\Delta^{14}$-double bond *via* the epoxidation of the C-20 enol ether was the most successful approach for the preparation of **1** (Scheme 4). As was described earlier, compound **6a** could be prepared in an acceptable yield from pregnenolone. Although several methods for the preparation of α-hydroxy ketones by the epoxidation of enolates or enol ethers have been described,[13] the choice of reagents for 20-keto steroid substrates




**6a** **1** R = Ac
**17** R = $Me_3SiCH_2CO$

**Scheme 4**

is crucial. Poor yields were obtained by using either LDA–trimethylsilyl chloride[14] or hexamethyldisilazane–trimethylsilyl iodide[15] for the preparation of the enol ether, due to intermolecular aldol condensation reactions. The trimethylsilyl enol ether of **6** was successfully prepared by using the reaction conditions described by Mander and Sethi[16] (*tert*-butyldimethylsilyl trifluoromethanesulfonate, triethylamine). Subsequent epoxidation of the silyl enol ether with dimethyldioxirane[17] and rearrangement of the unstable epoxide to the α-hydroxy ketone proceeded in an excellent yield. A small amount of a side product **17**, which resulted from enolization of the acetate, was also isolated. Since the 3-acetate group will be hydrolysed in a subsequent step, the formation of this product is not detrimental to the yield of the reaction.

From these results, it is clear that the more classical approaches to the synthesis of **1** (Schemes 2 and 3) were unsuccessful, but that the sequence illustrated in Scheme 4 offers a short, efficient route for the preparation of 21-hydroxy-$\Delta^{14}$-steroids, compounds that are versatile intermediates for the preparation of cardioactive steroids.

## Experimental

Mps were determined on a Kofler hot-plate apparatus and are uncorrected. IR Spectra were obtained as dilute solutions in spectroscopic grade chloroform using a Perkin-Elmer 881 instrument. $^1$H (200 MHz) and $^{13}$C (50 Hz) NMR data were recorded on a Varian VXR 200 NMR spectrometer in $CDCl_3$ solution with tetramethylsilane as internal standard; *J* values are given in Hz. Mass spectra were recorded on a Finnigan-MAT 8200 spectrometer at an electron impact of 70 eV. Column chromatography was performed with silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM, neat or impregnated with $AgNO_3$) and thin layer chromatography with Whatman silica gel 60 A K6F (neat or impregnated with $AgNO_3$).

### Reduction of 3β-acetoxy-5α-pregna-14,16-dien-20-one 10

3β-Acetoxy-5α-pregna-14,16-dien-20-one **10** (375 mg, 1.05 mmol), prepared from 3β-acetoxy-5α-pregnan-20-one according to methods described in the literature,[8–10] diphenylsilane (388 mg, 2.10 mmol) and zinc chloride (33 mg, 0.24 mmol) were dissolved in $CHCl_3$ (3 ml). $Pd(PPh_3)_4$ (60 mg, 0.05 mmol) and triphenylphosphine (40 mg, 0.15 mmol) were added to the reaction mixture which was then stirred at 25 °C for 18 h. The solution was filtered through a short silica gel column ($CHCl_3$) and the residue obtained after removal of the solvent was subjected to column chromatography on silica gel impregnated with silver nitrate (hexane–EtOAc, 4:1). The products isolated were 3β-acetoxy-5α,17α-pregnan-20-one **12** ($R_f$ 0.41 on $SiO_2$–$AgNO_3$, 35 mg, 9%), 3β-acetoxy-5α,17β-pregn-14-en-20-one **6a** ($R_f$ 0.30 on $SiO_2$–$AgNO_3$, 195 mg, 52%) and 3β-acetoxy-5α,17α-pregn-14-en-20-one **11** ($R_f$ 0.21 on $SiO_2$–$AgNO_3$, 135 mg, 36%).

**3β-Acetoxy-5α-pregn-14-en-20-one 6a.** This compound had mp 127–129 °C (EtOAc), $[\alpha]_D^{20}$ +29 (*c* 1.13 in $CHCl_3$) (lit.,[18] mp 127–129 °C, $[\alpha]_D$ +35); $\nu_{max}(CHCl_3)/cm^{-1}$ 3033, 1685, 1563, 1546, 1511, 1459, 1233, 1222, 1031, 801 and 676; $\delta_H$ 0.83 (3 H, s, 19-H), 0.84 (3 H, s, 18-H), 1.99 (3 H, s, OAc), 2.13 (3 H, s, 21-H), 2.72 (1 H, m, 8-H), 2.89 (1 H, dd, *J* 10 and 8, 17-H), 4.67 (1 H, m, 3-H) and 5.12 (1 H, q, *J* 2, 15-H); $\delta_C$ 11.9 (C-19), 18.6 (C-18), 21.4 (OCO*C*H$_3$), 21.8 (C-11), 27.3 (C-2), 28.2 (C-6), 29.9 (C-16), 31.2 (C-21), 31.3 (C-7), 33.9 (C-4), 34.8 (C-8), 35.7 (C-10), 36.7 (C-1), 42.0 (C-12), 44.2 (C-5), 48.2 (C-13), 53.7 (C-9), 65.4 (C-17), 73.5 (C-3), 116.8 (C-15), 151.8 (C-14), 170.5 (O*C*OCH$_3$) and 209.2 (C-20); *m*/*z* 358 ($M^+$, 65%), 343 (11), 315 (16), 255 (71), 161 (19), 147 (31), 135 (27) and 43 (100).

**3β-Acetoxy-5α,17α-pregn-14-en-20-one 11.** This compound had mp 103–104 °C (EtOAc), $[\alpha]_D^{20}$ +81 (*c* 1.14 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3749, 3026, 2956, 2880, 2420, 2337, 1747, 1706, 1567, 1539, 1528, 1233, 1219 and 669; $\delta_H$ 0.83 (3 H, s, 19-H), 1.28 (3 H, s, 18-H), 1.99 (3 H, s, 23-H), 2.13 (3 H, s, 21-H), 2.32 (1 H, m, 16-H), 2.67 (1 H, m, 16-H), 3.02 (1 H, dd, *J* 9 and 6, 17-H), 4.65 (1 H, m, 3-H) and 5.10 (1 H, q, *J* 2, 15-H); $\delta_C$ 12.0 (C-19), 21.4 (OCO*C*H$_3$), 21.4 (C-11), 26.2 (C-18), 27.4 (C-2), 28.3 (C-6), 30.1 (C-16), 31.6 (C-21), 32.2 (C-7), 33.9 (C-4), 34.7 (C-12), 34.8 (C-8), 35.8 (C-10), 36.5 (C-1), 44.3 (C-5), 50.4 (C-13), 54.9 (C-9), 62.1 (C-17), 73.5 (C-3), 116.5 (C-15), 151.6 (C-14), 170.6 (O*C*OCH$_3$) and 210.1 (C-20); *m*/*z* 358.2483 ($M^+$, $C_{23}H_{34}O_3$ requires 358.2508), 358 (100%), 343 (22), 315 (23), 283 (25), 255 (99), 213 (17), 100 (78) and 43 (75).

**3β-Acetoxy-5α,17α-pregnan-20-one 12.** This compound had mp 109 °C (EtOAc), $[\alpha]_D^{20}$ −6 (*c* 1.33 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1733, 1713, 1546, 1226, 1219, 913 and 680; $\delta_H$ 0.76 (3 H, s, 19-H), 1.18 (3 H, s, 18-H), 1.97 (s, 23-H), 2.09 (3 H, s, 21-H), 2.66 (1 H, t, *J* 9, 17-H) and 4.65 (1 H, m, 3-H); $\delta_C$ 12.1 (C-19), 21.0 (C-11), 21.4 (OCO*C*H$_3$), 23.0 (C-18), 23.3 (C-16), 24.2 (C-15), 27.3 (C-2), 28.1 (C-12), 28.7 (C-6), 31.7 (C-21), 32.0 (C-7), 33.7 (C-8), 34.0 (C-4), 35.4 (C-10), 36.8 (C-1), 44.0 (C-13), 44.4 (C-5), 54.9 (C-9), 52.4 (C-14), 64.5 (C-17), 73.6 (C-3), 170.5 (O*C*OCH$_3$) and 210.0 (C-20); *m*/*z* 360.2681 ($M^+$, $C_{23}H_{36}O_3$ requires 360.2664), 360 (12%), 300 (16), 217 (30), 215 (19), 84 (86) and 43 (100).

### Epimerization of 3β-acetoxy-5α,17α-pregn-14-en-20-one 11

A mixture of **11** (542 mg, 1.51 mmol), $K_2CO_3$ (2.0 g, 14 mmol) in methanol (25 ml), $CHCl_3$ (13 ml) and water (3 ml) was stirred for 48 h at 25 °C after which the reaction mixture was diluted with water (20 ml) and extracted with $CH_2Cl_2$ (3 × 30 ml). The combined extracts were evaporated to dryness, column chromatography (hexane–EtOAc, 2:1) of the residue on silica gel impregnated with $AgNO_3$ yielding starting material (42 mg) and 3β-hydroxy-5α,17β-pregn-14-en-20-one **6b** (381 mg, 80%). Acetylation of the latter with acetic anhydride and pyridine yielded **6a** in a quantitative yield.

### 3β,21-Diacetoxy-5α-pregn-14-en-20-one 13

A solution of **6a** (96 mg, 0.27 mmol), $Pb(OAc)_4$ (210 mg, 0.48 mmol) and boron trifluoride–diethyl ether (600 mg, 4.2 mmol) in benzene (1.5 ml) and MeOH (0.2 ml) was stirred at room temperature for 4 h after which it was diluted with saturated brine (4 ml) and extracted with diethyl ether (3 × 5 ml). The organic extract was evaporated to dryness and the residue purified by column chromatography on silica gel using hexane–EtOAc (4:1) as eluent to give starting material (21 mg, 22%) and 3,21-*diacetoxy*-5α-*pregn*-14-*en*-20-*one* **13** (36 mg, 32%), mp 140–143 °C (EtOAc), $[\alpha]_D^{20}$ +50 (*c* 1.02 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3972, 3749, 3053, 3026, 2372, 1817, 1741, 1730, 1720, 1702, 1689, 1654, 1563, 1546, 1511, 1383, 1424, 1268, 1237, 1222, 1212, 805, 735 and 673; $\delta_H$ 0.81 (3 H, s, 19-H), 0.86 (3 H, s, 18-H), 2.00 (3 H, s, OAc), 2.15 (3 H, s, OAc), 2.85 (1 H, m, 17-H), 4.56 (1 H, d, *J* 17, 21-H), 4.64 (1 H, m, 3-H), 4.72 (1 H, d, *J* 17, 21-H) and 5.11 (1 H, q, *J* 2, 15-H); $\delta_C$ 11.9 (C-19), 18.6 (C-18), 20.5 (OAc), 21.4 (OAc), 21.8 (C-11), 27.3 (C-2), 28.1 (C-6), 29.9 (C-16), 31.16 (C-7), 33.8 (C-4), 34.8 (C-8), 35.6 (C-10), 36.7 (C-1), 41.8 (C-12), 44.1 (C-5), 49.0 (C-13), 53.6 (C-9), 60.8 (C-17), 69.0 (C-21), 73.5 (C-3), 116.7 (C-15), 151.9 (C-14), 170.3 (OAc), 170.7 (OAc) and 203.7 (C-20); *m*/*z* 416.2595 ($M^+$, $C_{25}H_{36}O_5$ requires 416.2563), 416

(14%), 356 (49), 343 (17), 313 (10), 255 (19), 161 (23), 159 (14), 147 (24), 145 (18), 135 (17), 133 (16), 131 (14), 121 (16), 119 (19), 108 (15), 107 (35), 105 (30), 95 (19), 93 (39), 91 (28), 81 (30), 79 (21), 67 (17), 55 (20) and 43 (100).

**3β,21-Diacetoxy-5α-pregn-16-en-20-one 15**

3β,21-Diacetoxypregnan-20-one **14** was prepared from 3β-acetoxy-5α-pregnan-20-one according to methods described in the literature.[7] HBr (47%; 0.5 ml) and subsequently $Br_2$ (14 ml) were added dropwise to a solution of **14** (867 mg, 2.07 mmol) in AcOH (40 ml) at 40 °C. After the addition was completed, the solution was stirred for 20 min, poured into water (45 ml), and extracted with diethyl ether (3 × 20 ml). The combined extracts were dried ($Na_2SO_4$) and evaporated. The residue was dissolved in DMF (3 ml) and LiBr (227 mg) was added to the solution which was then stirred at 95 °C for 30 min. After cooling, the mixture was applied directly to a silica column. Elution with hexane–EtOAc (4:1) yielded 3β-acetoxy-5α-pregna-14,16-diene-20-one **10** (64 mg, 9%) and 3β,21-diacetoxy-5α-pregn-16-en-20-one **15** (388 mg, 45%).

**3β-Acetoxy-5α-pregna-14,16-dien-20-one 10.** This compound had mp 172–173 °C, $[\alpha]_D^{20}$ +332 (*c* 1.00 in $CHCl_3$) (lit.,[19] mp 181 °C, $[\alpha]_D$ +370); $\nu_{max}(CHCl_3)/cm^{-1}$ 3026, 1741, 1702, 1660, 1633, 1546, 1525, 1511, 1233, 1215, 1031 and 673; $\delta_H$ 0.91 (3 H, s, 19-H), 1.13 (3 H, s, 18-H), 1.98 (3 H, s, OAc), 2.27 (3 H, s, 21-H), 2.43 (1 H, td, *J* 13 and 3, H-12), 4.65 (1 H, m, 3-H), 5.95 (1 H, t, *J* 2, 15-H) and 7.18 (1 H, d, *J* 2, 16-H); $\delta_C$ 12.2 (C-19), 18.7 (C-19), 20.8 (C-11), 21.3 (OCO*C*H$_3$), 26.6 (C-21), 27.4 (C-2), 28.0 (C-6), 29.3 (C-7), 33.8 (C-4), 36.1 (C-8), 36.2 (C-10), 36.3 (C-1), 37.1 (C-12), 44.3 (C-5), 53.5 (C-13), 58.2 (C-9), 73.4 (C-3), 118.0 (C-15), 141.8 (C-16), 154.6 (C-14), 170.5 (O*C*OCH$_3$), 174.0 (C-17) and 192.5 (C-20); *m*/*z* 356 ($M^+$, 19%), 313 (10), 234 (21), 91 (41), 68 (44), 43 (78) and 41 (100).

**3β,21-Diacetoxy-5α-pregn-16-en-20-one 15.** This compound had mp 121–122 °C (EtOAc), $[\alpha]_D^{20}$ +31 (*c* 1.44 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3033, 2344, 1793, 1730, 1706, 1567, 1539, 1515, 1226, 1215 and 673; $\delta_H$ 0.84 (3 H, s, 19-H), 0.89 (3 H, s, 18-H), 2.00 (3 H, s, OAc), 2.16 (3 H, s, OAc), 2.31 (2 H, m, 15-H), 4.67 (1 H, m, 3-H), 4.84 (1 H, d, *J* 16, 21-H), 5.01 (1 H, d, *J* 16, 21-H) and 6.71 (1 H, dd, *J* 5 and 2, 16-H); $\delta_C$ 12.1 (C-19), 16.0 (C-18), 20.9 (C-11), 20.4 (OCO*C*H$_3$), 21.4 (OCO*C*H$_3$), 27.3 (C-2), 28.4 (C-6), 31.8 (C-7), 32.5 (C-15), 33.7 (C-8), 34.0 (C-4), 34.5 (C-12), 35.7 (C-10), 36.5 (C-1), 44.8 (C-5), 46.7 (C-13), 54.7 (C-9), 55.8 (C-14), 65.6 (C-21), 73.5 (C-3), 143.8 (C-16), 152.1 (C-17), 170.2 (O*C*OCH$_3$), 170.5 (O*C*OCH$_3$) and 190.5 (C-20); *m*/*z* 416.2571 ($M^+$, $C_{25}H_{36}O_5$ requires 416.2563), 415 (3%), 401 (3), 374 (8), 356 (20), 343 (100), 315 (15), 255 (7), 161 (11), 147 (9), 133 (8), 121 (16), 119 (10), 107 (20), 105 (16), 95 (12), 93 (18), 91 (16), 81 (16), 79 (12), 67 (11), 55 (11) and 43 (50).

**3β,21-Diacetoxy-5α-pregna-14,16-dien-20-one 7**

A mixture of **15** (264 mg, 0.63 mmol), *N*-bromosuccinimide (NBS) (300 mg, 1.68 mmol) and azoisobutyronitrile (AIBN) (150 mg) in dry $CCl_4$ (30 ml) was refluxed for 1.5 h and then evaporated. The residue was dissolved in dry acetone (30 ml) and NaI (600 mg, 4 mmol) was added to the mixture which was then refluxed for 3 h. After this it was evaporated and the residue suspended in saturated aqueous $Na_2S_2O_3$. Extraction with $CH_2Cl_2$ (3 × 30 ml), evaporation of the organic extract and chromatography of the residue (hexane–EtOAc, 4:1) yielded 3β,21-*diacetoxy*-5α-*pregna*-14,16-*dien*-20-*one* **7** (165 mg, 63%), mp 119 °C (EtOAc), $[\alpha]_D^{20}$ +391 (*c* 0.96 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3081, 3033, 1747, 1737, 1706, 1674, 1657, 1521, 1511, 1236, 1229, 1219, 1208, 1031 and 673; $\delta_H$ 0.90 (3 H, s, 19-H), 1.16 (3 H, s, 18-H), 1.99 (3 H, s, OAc), 2.15 (3 H, s, OAc), 2.25 (1 H, m, 8-H), 2.43 (1 H, td, *J* 2, 12-H), 4.65 (1 H, m, 3-H), 5.00 (2 H, s, 21-H), 5.98 (1 H, t, *J* 2, 15-H) and 7.25 (1 H, d, *J* 2, 16-H); $\delta_C$ 12.2 (C-19), 18.7 (C-18), 20.5 (OCO*C*H$_3$), 20.8 (C-11), 21.4 (OCO*C*H$_3$), 27.4 (C-2), 28.0 (C-6), 29.3 (C-7), 33.8 (C-4), 36.2 (C-8), 36.4 (C-1), 36.4 (C-10), 37.2 (C-12), 44.3 (C-5), 54.3 (C-13), 58.2 (C-9), 65.4 (C-21), 73.3 (C-3), 118.2 (C-15), 141.2 (C-16), 150.8 (C-14), 170.4 (O*C*OCH$_3$), 170.5 (O*C*OCH$_3$), 175.1 (C-17) and 186.3 (C-20); *m*/*z* 414.2383 ($M^+$, $C_{25}H_{34}O_5$ requires 414.2406), 414 (16%), 341 (100), 85 (38), 83 (54), 49 (15), 47 (33) and 43 (21).

**Reduction of 3β,21-diacetoxy-5α-pregna-14,16-dien-20-one 7**

Compound **7** (75 mg, 0.18 mmol), diphenylsilane (69 mg, 0.37 mmol) and zinc chloride (8 mg, 0.06 mmol) were dissolved in $CHCl_3$ (1.5 ml) and $Pd(PPh_3)_4$ (14 mg, 0.012 mmol) and triphenylphosphine (9 mg, 0.034 mmol) were added to the reaction mixture. After this had been stirred at 25 °C for 18 h, it was filtered through a short silica gel column ($CHCl_3$) and the residue obtained after evaporation of the eluent was subjected to column chromatography on silica gel impregnated with silver nitrate (hexane–EtOAc, 4:1). The products isolated were 3β,21-diacetoxy-5α,17α-pregn-14-en-20-one **16** ($R_f$ 0.65; 48 mg, 64%) and a mixture (26 mg) of 3β-acetoxy-5α,17α-pregn-14-en-20-one **11** (17%), 3β-acetoxy-5α-pregn-14-en-20-one **6a** (9%) and 3β-acetoxy-5α,17α-pregnan-20-one **12** (10%).

**3β,21-Diacetoxy-5α,17α-pregn-14-en-20-one 16.** This compound had mp 143–145 °C (EtOAc), $[\alpha]_D^{20}$ +44 (*c* 0.97 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3860, 3033, 2380, 1754, 1657, 1511 and 1260; $\delta_H$ 0.83 (3 H, s, 19-H), 1.28 (3 H, s, 18-H), 4.65 (1 H, m, 3-H), 4.73 (1 H, d, *J* 17, 21-H) and 5.10 (q, *J* 2, 15-H); $\delta_C$ 12.0 (C-19), 20.5 (C-11), 21.3 (OAc), 21.4 (OAc), 26.0 (C-18), 27.3 (C-2), 28.3 (C-6), 32.2 (C-7), 33.8 (C-4), 34.6 (C-8), 35.0 (C-12), 30.1 (C-16), 35.8 (C-10), 36.5 (C-1), 44.3 (C-5), 51.1 (C-13), 54.8 (C-9), 57.5 (C-17), 69.1 (C-21), 73.5 (C-3), 116.3 (C-15), 151.6 (C-14), 170.2 (OAc), 170.6 (OAc) and 204.8 (C-20); *m*/*z* 416.2543 ($M^+$, $C_{25}H_{36}O_5$ requires 416.2563), 416 (12%), 356 (65), 343 (22), 314 (10), 313 (10), 255 (16), 173 (8), 161 (20), 159 (13), 149 (11), 147 (24), 145 (16), 135 (16), 133 (16), 131 (13), 121 (16), 119 (18), 107 (30), 105 (25), 95 (20), 93 (32), 91 (25), 81 (29), 79 (19), 55 (24) and 43 (100).

**3β-Acetoxy-21-hydroxy-5α-pregn-14-en-20-one 1**

TMSOTf (77 mg, 0.35 mmol) was added dropwise to a solution of **6a** (103 mg, 0.28 mmol) and triethylamine (58 mg, 0.57 mmol) in $CH_2Cl_2$ (1 ml) at −78 °C. The mixture was stirred for 40 min and then diluted with water (10 ml) and extracted with diethyl ether (3 × 10 ml). The combined extracts were evaporated under reduced pressure and the residue (124 mg) was dissolved in acetone (0.5 ml) to which a solution of dimethyldioxirane[20] (0.09 M; 3.6 ml, 0.33 mmol) was added. The mixture was stirred for 16 h at room temperature after which it was evaporated under reduced pressure. The residue was purified by column chromatography (hexane–EtOAc, 6:1) to yield 3β-acetoxy-21-hydroxy-5α-pregn-14-en-20-one **1** (91 mg, 85%), mp 122–124 °C (EtOAc), $[\alpha]_D^{20}$ +29 (*c* 1.09 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3040, 2379, 1720, 1657, 1511, 1268, 1219, 798 and 673; $\delta_H$ 0.83 (6 H, s, 18, 19-H), 2.01 (3 H, s, OAc), 2.30 (1 H, m, 16-H), 2.78–2.90 (1 H, m, 16α, 17-H), 3.27 (1 H, t, *J* 5, OH), 4.19 (1 H, d, *J* 15, 21-H), 4.20 (1 H, d, *J* 15, 21-H), 4.66 (1 H, m, 8-H) and 5.14 (1 H, br s, 15-H); $\delta_C$ 11.9 (C-19), 18.7 (C-18), 21.4 (OCO*C*H$_3$), 21.7 (C-11), 27.3 (C-2), 28.1 (C-6), 29.9 (C-16), 31.0 (C-7), 33.8 (C-4), 34.9 (C-8), 35.7 (C-10), 36.7 (C-1), 41.8 (C-12), 44.1 (C-5), 49.0 (C-13), 53.7 (C-9), 60.7 (C-17), 69.3 (C-21), 73.5 (C-3), 116.6 (C-15), 152.0 (C-14), 170.6 (O*C*OCH$_3$) and 210.15 (C-20); *m*/*z* 374.2495 ($M^+$, $C_{23}H_{34}O_4$ requires 374.2457), 374 (20%), 343 (31), 315 (9), 255 (39), 161 (32), 159 (17), 147 (31), 145 (23), 143 (12), 135 (13), 133 (21), 131 (20), 129 (10), 121 (23), 119 (27), 117 (21), 107 (53), 105 (48), 95 (28), 93 (66), 91 (51), 81 (51), 79 (39), 77 (21), 73 (41), 67 (32), 55 (46) and 43 (100).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