Pergamon

Tetrahedron 55 (1999) 5171–5176

TETRAHEDRON

A convenient Synthesis of 18-Hydroxycorticosterone and 18-Hydroxy-11-desoxycorticosterone via Stereospecific Hypoiodination of 20-Hydroxysteroids

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Received 21 January 1999; accepted 1 March 1999

Abstract: 18-Hydroxycorticosterone and 18-hydroxy-11-desoxycorticosterone, were obtained via hypoiodination of 20-hydroxy derivatives. The absolute configurations of the C-20 were established by X-ray, only the 20S alcohols reacted under the hypoiodination conditions.

Keywords: steroid; synthesis; photochemistry; halogenation; crystal structure.

18-Hydroxycorticosterone (18-OH-B) and 18-hydroxy-11-desoxycorticosterone (18-OH-DOC) are precursors of aldosterone, their measurements in plasma are useful in several pathological circumstances. In particular, the measurement of 18-OH-B, corticosterone and aldosterone are used in the diagnosis of corticosterone methyloxydase deficiencies (CMO-I, CMO-II).[1-4] Deoxycorticosterone, 18-OH-DOC and aldosterone represent the hormonal markers which are useful for the differencial diagnosis between malignant and benign adrenal tumors and could also contribute to the diagnosis of adrenal metastasis and other forms of cancer.[5,6]

The reported synthesis of these compounds involve the preparation of 18-hydroxyprogesterone derivatives followed by the introduction of the 21-hydroxyl group in 2 steps.[7,8]

A simple preparation of (18-OH-DOC) **7a** and of (18-OH-B) **7c** based on the direct hypoiodination of 20-hydroxysteroids protected as acetates in position 21 is depicted in the scheme. In the first step, the acetates **1a-b** were reduced by sodium borohydride into a mixture of diols which were not isolated and directly converted by MnO_2 into the diastereoisomeric monoalcohols **2a-3a** and **2b-3b**. The hypoiodination reaction was first achieved on these mixtures. We then observed that only one iodo derivative was formed from each mixture of the diastereoisomers. This led us to separate the diastereoisomers **2-3.** This could be done either by recrystallizing, compounds **3a-b** being less soluble, or by column chromatography **3a-b** migrating faster than **2a-b**. When products **2** and **3** were reacted separately under hypoiodination conditions,[8,9] we observed that only **3a-b** led to the halogenated derivatives **5a-b**.

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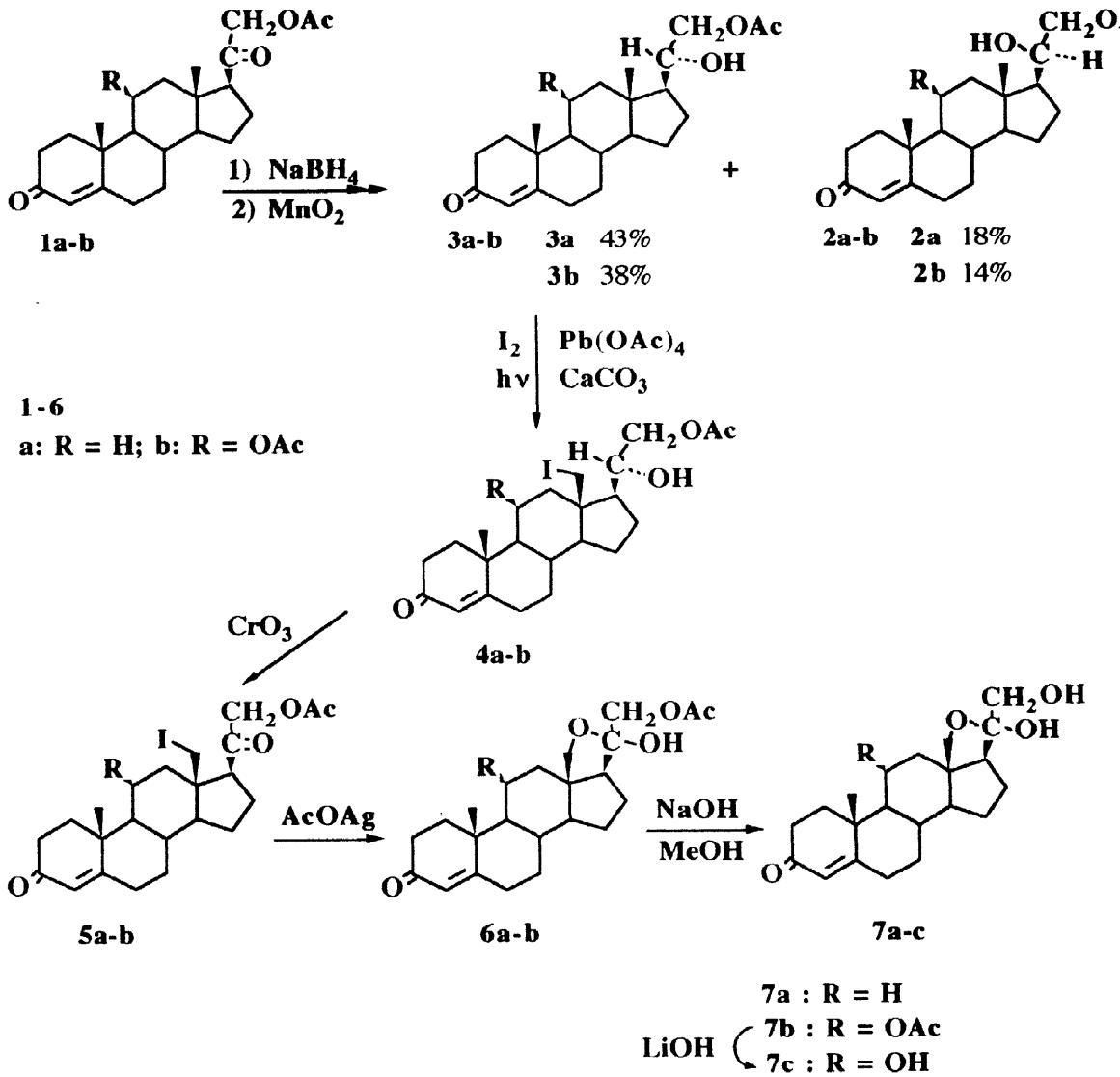
0040-4020/99/$ - see front matter
PII: S0040-4020(99)00187-8



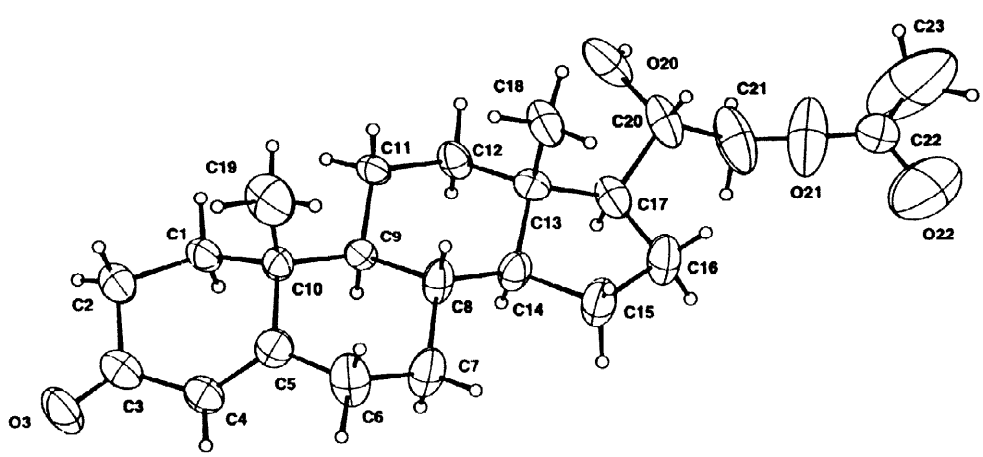


Figure 1: CAMERON[10] plot of the molecular structure of **3a** showing 50% probability displacement ellipsoids.

The crystal structure of alcohol **3a**, derived from 11-desoxycorticosterone was determined and the configuration of C20 appeared to be S. The structure of compound **3a** is illustrated in figure 1. Correlations could be established by ^{1}H-NMR: chemical shifts and coupling constants of H-20, H-21a and H-21b were similar for **2a** and **2b** on one hand and for **3a** and **3b** on the other hand. In the next step, iodides **5** were oxidized, into the 20-keto derivatives **6**, prior to nucleophilic substitution of the halogen.

Finally, the acetates were removed by saponification. As it can be anticipated, the hydrolysis of the 21-acetate was faster than the 11β-acetate and the mono-acetate **7b** could be isolated. Several saponification conditions were examined and the use of LiOH in methanol proved to be the most effective. From a practical point of view, we found it more convenient to perform the whole sequence from **1** to **5** without purification between steps. Compounds **5** were then easily separated from **1** which resulted from the oxidation of unreacted **2a-b** by column chromatography. Compared to previously reported methods, the presented synthesis is shorter, only one chromatographic separation is required and unreacted **1** formed before removal of the acetates could be recycled.

Aknowledgments We are grateful to Dr J. Osuku Opio for his help during the preparation of the manuscript.

Experimental

Melting points are uncorrected. NMR spectra were recorded on a Bruker 270 MHz spectrometer.

11β,21-Dihydroxy-4-pregnen-3,20-dione 11β,21-diacetate (1b). To a solution of corticosterone 21-acetate in CH_2Cl_2 (9.7 g, 25 mmol, 50 mL) was added 15 mL of acetic anhydride and (0.305 g, 2.5 mmol) of 4-dimethylaminopyridine. The mixture was stirred at room temperature overnight. The solution was washed with H_2O. The organic layer was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel with CH_2Cl_2/MeOH 99:1 to yield 80% of **1b**: M.p. (AcOEt) 112-115 °C. $[\alpha]_D$ = + 130 ° (*c* 0 .1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.80 (3H, s, 18-H), 1.2 (3H, s, 19-H), 2.0 (s, 3H, s, 11-CH_3CO-), 2.1 (3H, s, 21-CH_3CO-), 4.45 and 4.55 (2H, d, *J* = 16 Hz, 21-H), 5.4 (1H, broad s, 11α-H); 5.6 (1H, s, 4-H). ^{13}C NMR ($CDCl_3$): 13.5 (C-18), 18.5, (C-19), 67.2 (C-11), 67.8 (C-21), 121.0 (C-4), 168.0 (C-5), 169.0 and 169.1 (2OCO), 197.0 (C-3), 201.5 (C-20). Analysis calculated for: $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 70.02; H, 7.65.

20-R)-20,21-Dihydroxy-4-pregnen-3-one 21-acetate (2a), (20-R)-11β,20,21-trihydroxy-4-pregnen-3-one 11β,21-diacetate (2b), (20-S)-20,21-dihydroxy-4-pregnen-3-one 21-acetate (3a) and (20-S)-11β,20,21-trihydroxy-4-pregnen-3-one 11β,21-diacetate (3b). Compounds **1** (23.2 mmol) were dissolved in 50 mL of CH_2Cl_2 and 100 mL of MeOH. To this solution was added $NaBH_4$ (4.4 g, 116 mmol) and the mixture was stirred at 0°C for 30 min. Acetic acid was then added to scavenge the excess reagent. The solution was diluted with H_2O and then extracted with ethyl acetate (3x50 mL). The extract was washed with H_2O, dried with Na_2SO_4 and the solvent removed under reduced pressure. The crude products (10 g) were dissolved in 150 mL of CH_2Cl_2, then MnO_2 (80 g, 920 mmol) added and the mixture stirred at room temperature overnight. The salts were eliminated by filtration and evaporation of the solvent gave a crude mixture of diastereoisomers (**2a-b** or **3a-b**) which were either separated by recrystallization from ethyl

acetate or by column chromatography using CH_2Cl_2/MeOH 99:1 (v/v) as eluent. Compound **1a** yielded 68% of **2a-3a** and compound **1b** yielded 65% of **2b-3b** (isolated yields of **2-3** are shown in scheme). **2a**: M.p(AcOEt) = 137-142 °C. $[\alpha]_D$ = + 91° (*c* 0 .02, $CHCl_3$). ^1H NMR ($CDCl_3$): 0.71 (3H, s, 18-H), 1.2 (3H, s, 19-H), 2.1 (3H, s, 21-CH_3CO-), 3.55 (1H, dd, J_{gem} = 12 Hz, $J_{H21a-H20}$ = 4 Hz, 21-H_a), 3.8 (1H, d, *J* = 12 Hz, 21-H_b), 4.91 (1H, m, 20-H), 5.72 (1H, s, 4-H). ^{13}C NMR ($CDCl_3$): 10.2 (C-18), 15.4 (C-19), 66.7 (C-21), 70.6 (C-20), 121.9 (C-4), 168.9 (C-5), 169.1 (OCO), 197.3 (C-3). Analysis calculated for: $C_{23}H_{34}O_4$: C, 73.79; H, 9.09. Found: C, 73.65; H, 9.15. **2b**: M.p(AcOEt) = 161-162 °C. $[\alpha]_D$ = + 108 ° (*c* 0.01, $CHCl_3$). ^1H NMR ($CDCl_3$): 0.78 (3H, s, 18-H), 1.24 (3H, s, 19-H), 2.0 (3H, s, 11-CH_3CO-), 2.05 (3H, s, 21-CH_3CO-), 3.45 (1H, dd, J_{gem} = 12 Hz, $J_{H21a-H20}$ = 4 Hz, 21-H_a), 3.7 (1H, d, J = 12 Hz, 21-H_b), 4.8 (1H, m, 20-H), 5.28 (1H, broad s, 11α-H), 5.61 (1H, s, 4-H). ^{13}C NMR ($CDCl_3$): 12.9 (C-18), 18.7 (C-19), 66.6 (C-11), 67.9 (C- 21), 70.3 (C-20), 120.9 (C-4), 167.9 (C-5), 169.2 and 169.3 (2OCO), 197.2 (C-3). Analysis calculated for $C_{25}H_{36}O_6$: C, 69.44; H, 8.33. Found: C, 69.17; H, 8.45. **3a**: M.p(AcOEt) = 155-161 °C. $[\alpha]_D$ = + 135° (*c* 0.02, $CHCl_3$). ^1H NMR ($CDCl_3$): 0.83 (3H, s, 18-H), 1.2 (3H, s, 19-H), 2.11 (3H, s, 21-CH_3CO-), 3.8 (1H, m, 20-H), 3.9 (1H, dd, J_{gem} = 12 Hz, $J_{H21a-H20}$ = 8 Hz, 21-H_a), 4.19 (1H, d, J = 12 Hz, 21-H_b), 5.74 (1H, s, 4-H). ^{13}C NMR ($CDCl_3$): 12.0 (C-18), 17.1, (C-19), 68.5 (C-21), 72.3 (C-20), 123.6 (C-4), 170.8 (C-5), 170.9 (OCO), 199.1 (C-3). Analysis calculated for $C_{23}H_{34}O_4$: C, 73.79 ; H, 9.09. Found: C, 73.56 ; H, 9.13. **3b**: M.p(AcOEt)= 147-151°C. $[\alpha]_D$ = + 93° (*c* 0.02, $CHCl_3$). ^1H NMR ($CDCl_3$): 0.87 (3H, s, 18-H), 1.24 (3H, s, 19-H), 2.0 (3H, s, 11-CH_3CO-), 2.05 (3H, s, 21-CH_3CO-), 3.7 (1H, m, 20-H), 3.8 (1H, dd, J_{gem} = 12 Hz, $J_{H21a-H20}$ = 8 Hz, 21-H_a), 4.08 (1H, d, *J* = 12 Hz, 21-H_b), 5.35 (1H, broad s, 11α-H), 5.61 (1H, s, 4-H). ^{13}C NMR ($CDCl_3$): 14.8 (C-18), 21.0, (C-19), 69.0 (C-11), 70.0 (C-21), 72.6 (C-20), 123.0 (C-4), 170.0 (C-5), 171.0 (2OCO), 199.0 (C-3). Analysis calculated for $C_{25}H_{36}O_6$: C, 69.44; H, 8.33. Found: C, 69.21; H, 8.44.

18-Iodo-20,21-dihydroxy-4-pregnen-3-one 21-acetate (4a) and 18-iodo-11β,20,21-trihydroxy-4-pregnen-3-one 11β,21-diacetate (4b). Into a 1 L two-neck round-bottom flask, with a 150 W lamp (Heraus TQ 150, cooled by the circulation of water within the jacked system) immersed inside the reactor, was dissolved compounds **3** (16.2 mmol) in 350 mL of benzene/cyclohexane 1/1 v/v, iodine (3.9 g, 15.4 mmol), $Pb(AcO)_4$ (4.8 g, 11 mmol) and $CaCO_3$ (6.4 g, 64.8 mmol). The reaction was carried out by irradiation at rt for 3 h. The mixture was filtred through celite, the residue was washed with AcOEt and the organic layer washed once with 5% aqueous $Na_2S_2O_3$ and water, then dried with anhydrous Na_2SO_4. After the removal of the solvents under reduced pressure, the crude products were chromatographed on silica gel with $CHCl_3$/MeOH 99.6:0.4 to afford **4a** in 70% yield or **4b** in 65% yield. **4a**: M.p(iPrOH) = 105-108 °C. $[\alpha]_D$ = + 125° (*c* 0 .013, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.13 (3H, s, 19-H), 2.02 (3H, s, 21-CH_3CO-), 3.09 and 3.3 (2H, d, *J* = 11 Hz, 18-H); 3.88 (1H, dd, J_{gem} = 12 Hz, $J_{H21a-H20}$ = 8 Hz, 21-H_a), 4.1 (1H, d, *J* = 12, 21-H), 4.15 (1H, broad s, 20-H), 5.68 (1H, s, 4-H). ^{13}C NMR ($CDCl_3$): 9.37 (C-18), 17.5, (C-19), 67.8 (C-21), 60.5 (C-20), 124.4 (C-4), 170.3 (C-5), 171.3 (OCO), 199.4 (C-3). Analysis calculated for $C_{23}H_{33}O_4I$: C, 55.20; H, 6.62. Found: C, 54.92; H, 6.84. **4b**: M.p(iPrOH) = 121-123°C. $[\alpha]_D$ = + 115° (*c* 0 .01, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.2 (3H, s, 19-H), 2.0 (3H, s, 11-CH_3CO-), 2.1 (3H, s, 21-CH_3CO-), 3.18 and 3.55 (2H, d, *J* = 11 Hz, 18-H); 3.71 (1H, dd, J_{gem} = 12 Hz, $J_{H21a-H20}$ = 8 Hz, 21-H_a), 4.08 (1H, d, *J* = 12, 21-H), 4.2 (1H, broad s, 20-H), 5.41 (1H, broad s, 11α-H), 5.6 (1H, s, 4-H). ^{13}C NMR ($CDCl_3$): 9.34 (C-18),

18-Iodo-21-hydroxy-4-pregnen-3,20-dione 21-acetate (5a) and 18-iodo-11β,21-dihydroxy-4-pregnen-3,20-dione 11β,21-diacetate (5b). The iodides **4** (3.6 mmol) were dissolved in 20 mL of acetone and 13.5 mL of CH_2Cl_2. To this solution was added 3.5 mL of Jones reagent (3.5 g CrO_3 in 10 mL H_2O and 2.9 mL concentred sulphuric acid) and the mixture stirred at 0° C for 30 min. After this time, the excess reagent was neutralized with 4 mL of MeOH. The solution was diluted with H_2O then extracted with AcOEt to afford **5a** in 92% yield and **5b** in 90%. **5a** ^{1}H NMR ($CDCl_3$): 1.15 (3H, s, 19-H), 2.12 (3H, s, 21-CH_3CO-), 3.15 and 3.14 (2H, d, J = 11 Hz, 18-H), 4.13 and 4.8 (d, 2H, J = 16 Hz, 21-H), 5.7 (1H, s, 4-H). ^{13}C NMR ($CDCl_3$): 8.8 (C-18), 17.4 (C-19), 70.3 (C-21), 124.5 (C-4), 169.9 (C-5), 170.4 (OCO), 199.3 (C-3), 203.5 (C-20). Calculated for $C_{23}H_{31}O_4I$, 55.42; H, 6.22. Found: C, 55.25; H, 6.46. **5b** ^{1}H NMR ($CDCl_3$): 1.2 (3H, s, 19-H), 2.1 (3H, s, 11-CH_3CO-), 2.11 (3H, s, 21-CH_3CO-), 3.2 and 3.5 (2H, d, J = 11 Hz, 18-H), 4.58 and 4.78 (d, 2H, J = 16 Hz, 21-H), 5.46 (1H, broad s, 11α-H), 5.64 (1H, s, 4-H). ^{13}C NMR ($CDCl_3$): 9.1 (C-18), 18.9 (C-19), 66.1 (C-11), 68.1 (C-21), 121.3 (C-4), 167.6 (C-5), 168.3 (2OCO), 196.6 (C-3), 200.8 (C-20). Calculated for $C_{25}H_{33}O_6I$: C, 53.96; H, 5.97. Found: C, 53.75; H, 6.09.

18,21-Dihydroxy-4-pregnen-3,20-dione 21-diacetate (6a) and 11β,18,21-trihydroxy-4-pregnen-3,20-dione 11β,21-diacetate (6b). Compounds **5** (1.8 mmol) were dissolved in 4 mL of dioxane then 0.7 mL of H_2O, silver acetate (0.547 g, 3.28 mmol) added and the mixture was refluxed for 4 h. The mixture was filtered through celite and the solid residue was washed with EtOAc. The filtrate was washed with H_2O then dried. The crude product was purified by chromatography on silica gel with CH_2Cl_2/MeOH 99:1 to yield 75% **6a** or 72% of **6b**. **6a**: $[\alpha]_D$ = + 89° (c 0 .01, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.09 (3H, s, 19-H), 2.08 (3H, s, 21-CH_3CO-), 3.71 and 3.78 (2H, d, J = 10 Hz, 18-H), 4.11 and 4.25 (2H, d, J = 12 Hz, 21-H), 5.69 (1H, s, 4-H). ^{13}C NMR ($CDCl_3$): 17.6 (C-19), 67.2 (C-21), 73.8 (C-18), 106.0 (C-20), 124.2 (C-4), 170 (C-5), 171 (OCO), 199.5 (C-3). Calculated for $C_{23}H_{32}O_5$: C, 71.13; H, 8.30. Found: C, 71.05; H, 8.32. **6b**: $[\alpha]_D$ = + 137° (c 0 .01, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.2 (3H, s, 19-H), 2.1 (3H, s, 11-CH_3CO-), 2.12 (3H, s, 21-CH_3CO-), 3.78 and 3.85 (2H, d, J = 10 Hz, 18-H), 4.1 and 4.23 (2H, d, J = 12 Hz, 21-H), 5.45 (1H, broad s, 11α-H), 5.65 (1H, s, 4-H). ^{13}C NMR ($CDCl_3$): 18.7 (C-19), 65.0 (C-11), 67.9 (C-21), 71.5 (C-18), 103.0 (C-20), 120.8 (C-4), 167.8 (C-5), 168.4 (2OCO), 196.9 (C-3). Calculated for $C_{25}H_{34}O_7$: C, 67.24; H, 7.62. Found: C, 67.09; H, 7.64.

18,21-Dihydroxy-4-pregnen-3,20-dione (7a) and 11β,18,21-trihydroxy-4-pregnen-3,20-dione 11β-acetate (7b). Compounds **6** (0.45 mmol) were dissolved in 10 mL of MeOH, 5 mL of 1N NaOH were added. The solution was stirred at rt. After 30 min, the solvent was evaporated. The crude product was then diluted in EtOAc (30 mL) and washed with 10 mL of H_2O then dried. Evaporation of the solvent gave the **7a** or **7b** in 90% yield. **7a**: M.p. (iPrOH) = 158-160°C. $[\alpha]_D$ = + 142° (c 0 .01, $CHCl_3$). ^{1}NMR ($CDCl_3$): 1.08 (3H, s, 19-H), 3.58 and 3.61 (2H, d, J = 10 Hz, 21-H), 3.75 and 3.78 (2H, d, J = 9 Hz, 18-H), 5.68 (1H, s, 4-H). ^{13}C NMR ($CDCl_3$): 17.6 (C-19), 72.2 (C-21), 73.1 (C-18), 105.7 (C-20), 124.5 (C-4), 169.8 (C-5), 199.6 (C-3). Analysis calculated for $C_{21}H_{30}O_4$: C, 72.83; H, 8.67. Found: C, 72.65; H, 8.81. **7b**: $[\alpha]_D$ = + 111° (c 0 .01, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.2 (3H, s, 19-H), 2.0 (3H, s, 11-CH_3CO-). 3.65 and 3.75 (2H, d, J = 10 Hz, 21-H), 3.78 (2H, s, 18-H), 5.4 (1H, broad, 11α-H), 5.65 (1H, s, 4-H). ^{13}C NMR ($CDCl_3$): 19.1 (C-19), 63.8 (C-11), 68.0 (C-21), 71.5 (C-18), 104.0 (C-20), 121.0 (C-4), 168.0 (C-5), 169.0 (OCO), 197.0 (C-3). Analysis calculated for $C_{23}H_{32}O_6$: C, 68.32; H, 7.97. Found: C, 68.15; H, 8.11.

11β,18,21-Trihydroxy-4-pregnen-3,20-dione (7c). Compound **7b** (0.100 g, 0.3 mmol) in 5 mL MeOH was treated with LiOH (0.072 g, 3 mmol) at rt overnight. The product was extracted with EtOAc, washed with H_2O and purified by column chromatography with CH_2Cl_2-MeOH 95:5 in 70% yield. **7c**: M.p. (AcOEt)= 150-155°C. $[\alpha]_D$ = + 122° (*c* 0 .01, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.36 (3H, s, 19-H), 3.6 and 3.76 (2H, d, *J* = 10 Hz, 21-H), 3.74 and 4.2 (2H, d, *J* = 9 Hz, 18-H), 4.35 (1H, broad s, 11α-H), 5.61 (1H, s, 4-H). ^{13}C NMR ($CDCl_3$): 18.5 (C-19), 65.0 (C-11), 60.0 (C-21), 71.0 (C-18), 105.0 (C-20), 120.8 (C-4), 167.5 (C-5), 197.1 (C-3). Analysis calculated for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.48; H, 8.63.

Crystal structure of (20-S)-20,21-dihydroxy-4-pregnen-3-one 21-acetate (3a). A suitable crystal of **3a**, measuring 0.400 mm x 0.350 mm x 0.450 mm, was investigated on a Philips PW1100 diffractometer (Cu Kα radiation, λ = 1.5418 Å, graphite monochromator). Crystal data: $C_{23}H_{34}O_4$, M = 374.5, monoclinic, space group $P2_1$, Z = 2 with two independent molecules (A and B) in the asymmetric unit, a = 9.348 (5) Å, b = 18.597 (9) Å, c = 12.865 (9) Å, b = 110.18 (5)°, V = 2099 (2) $Å^3$, Dcalc = 1.19 $g.cm^{-3}$; reflections up to 2θ = 55° of which 2405 with F > 4σ(F) were kept in refinement calculations. The structure was solved by direct methods using SHELXS86[11a] and refined with SHELXL93.[11b] Convergence was reached at R = 0.105. The residual electron density in the final difference Fourier map shows no features up to 0.41 $e.Å^{-3}$.

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