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Epalons: 6-Substituted Derivatives of 7-Norepiallopregnanolone

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Abstract—The target compounds (3α-hydroxy-5,6-epoxy-7-nor-5α-pregnan-20-one, 3α-hydroxy-5,6β-epoxy-7-nor-5β-pregnan-20-one and 3α-hydroxy-7-nor-5α-pregnane-6,20-dione) were prepared from 5,6β-dihydroxy-20-oxo-5α-pregnan-3β-yl acetate via the corresponding 5,6-seco acid and 3β-acetoxy-20-oxo-7-nor-5β,6α-pregnane-6,5-carbolactone-actone. Intermediate 3β-hydroxy-7-norpregn-5-en-20-one was converted into the corresponding 5α,6α and 5β,6β epoxides. The latter was isomerized into 3β-hydroxy-7-nor-5α-pregnane-6,20-dione. The configuration of the 3β-hydroxy group in these compounds was inverted by Mitsunobu reactions.

In a search[1–4] for new positive modulators of γ-amino-butyric acid receptors of the brain we prepared[5] an analogue of 'epiallopregnanolone' with a flatter B ring, i.e. '7-norepiallopregnanolone' (3α-hydroxy-7-nor-5α-pregnan-20-one, **1**, see Scheme 1). Here we report on the synthesis of analogues containing an additional oxygen atom in the B ring (e.g. compound **2**) which makes the substrates more soluble in body fluids and thus potentially more useful for the treatment of pain, anxiety and sleep disorders.[6–9]

The contraction of the B ring was carried out as previously reported,[10] i.e. from 20-oxopregn-5-en-3β-yl acetate (**3**) via the corresponding 5,6-seco acid **4** (see Scheme 1). Unfortunately, the above oxidation leads mostly to the product of allylic oxidation **5**. The acidic product consisted of an inseparable mixture of the acid sought **4** and the product of the C_{17}–C_{20}-bond cleavage, 20,21-dinor acid **6** (12% according to ^{1}H NMR spectrum). However, if the alkene **3** was first converted into diol **7**, the 5,6-seco steroid production was cleanly carried out under milder conditions.[11] On treatment of acid **4** with benzoyl chloride in pyridine and then on pyrolysis we obtained compounds[10] **8** and **9**.

Epoxidation of 7-norsteroids is known to afford almost exclusively[12] 5α,6α-epoxides. Thus, compound **10** formed on oxidation of alkene **11** with 4-chloroperoxybenzoic acid was ascribed the 5α,6α-epoxide structure. Its treatment with formic acid in the presence of diethyl azodicarboxylate and triphenylphospine produced formate **12** with the reversed configuration at carbon 3. The hydrolysis of the ester grouping in compound **12** led to a 5,7-cyclo analogue of '6-oxa-epiallopregnanolone', compound **13**.

The above inversion of configuration was manifested by the change of multiplicity of the H-3 signal in ^{1}H NMR spectra: compounds **12** and **13** had a narrow multiplet at δ 5.36 and 4.2, respectively (width of signal=15 Hz), in contrast to a broad multiplet of starting alcohol **10** at δ 3.96 (width of signal=35 Hz). The 5β,6β-epoxide **14** was easily prepared from alkene **9** via the corresponding bromohydrin **15** which was generated from compound **9** and hypobromous acid (see Scheme 2). A lipophilic side product was assigned the structure of a 17β-H pregnane derivative **16**: its strongly negative Cotton effect ($\Delta\varepsilon_{287}$ −7.47) contrasts with the positive values for 17α-isomers (e.g. $\Delta\varepsilon_{288}$ +3.57 for compound **11**). The C-17 inversion was also accompanied by the collapse[13] of the triplet of H-17α in the 'normal' pregnane derivatives (e.g. ketone **14**) into a doublet in the 17β-H isomer **16** (see Experimental). The above isomerization at carbon 17 was prevented when the dehydrobromination of bromohydrin **15** was carried out under milder conditions (potassium carbonate at room temperature).

The 5β,6β-epoxides **14** and **17** turned out to be much more acid-sensitive than 5α,6α-epoxide **10**, therefore their NMR and IR spectra had to be quickly measured in freshly purified deuteriochloroform, otherwise the H-6 signal (δ 3.22) was reduced in intensity and a new C=O absorption band at 1732 cm^{-1} emerged.[14] The ease of isomerization corresponds to a lower barrier to the hydride ion migration from C-6 to C-5 in 5β,6β-epoxides (e.g. **14**) in comparison with that of 5α,6α-epoxides (e.g. **10**).

The above acid-sensitivity of 5β,6β-epoxides was utilized in the preparation of 5α-ketone **18** from epoxide **14** and boron trifluoride diethyl etherate.[14] When acetoxy ketone **17** was treated similarly, two by-products **19** and **20** were isolated besides the sought ketone **21**. Their structure assignment was based on spectral evidence (see MS and ^{1}H NMR spectra in Experimental).

Keywords: steroids; Mitsunobu reaction; epoxides; isomerisation; halohydrins.

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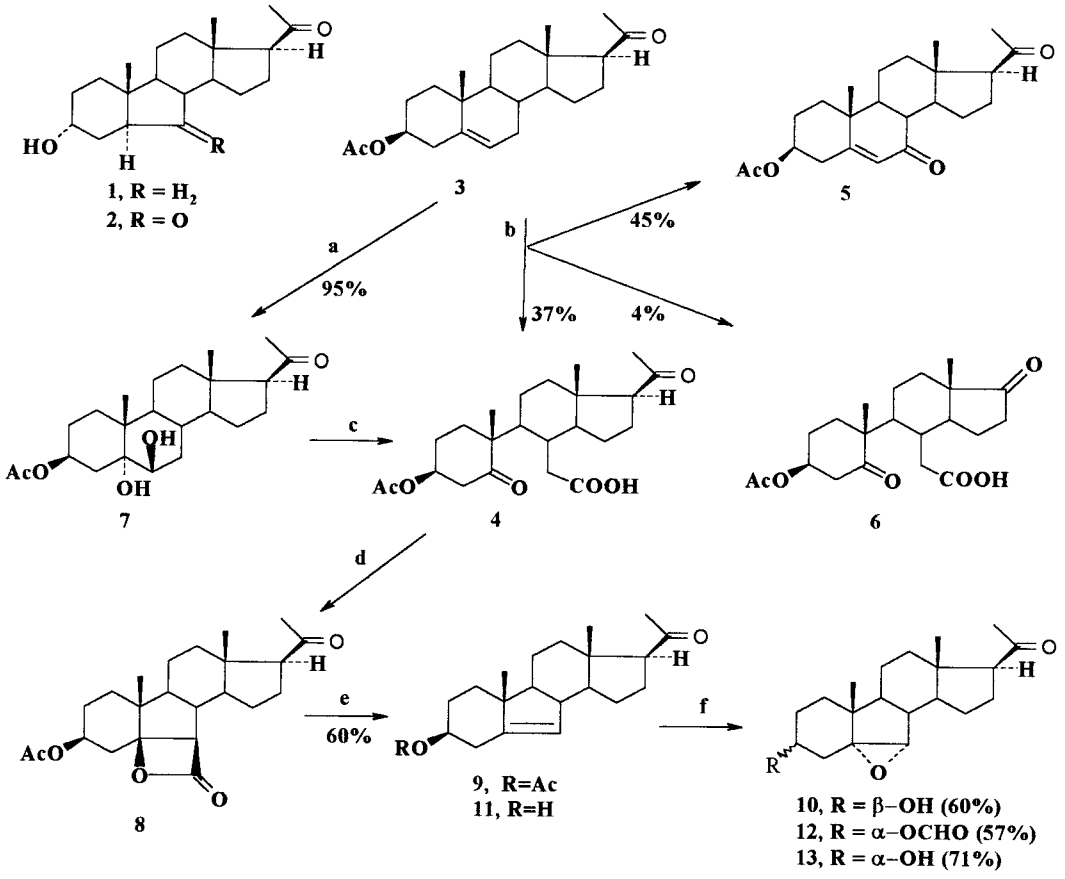


Scheme 1. Reagents: (a) MPA, then $HClO_4$ in THF; (b) CrO_3 in AcOH, 50°C; (c) Jones reagent, acetone, toluene, 50°C; (d) BzCl, py; (e) pyrolysis; (f) DEAD, triphenylphospine and formic acid, then $KHCO_3$ in MeOH.

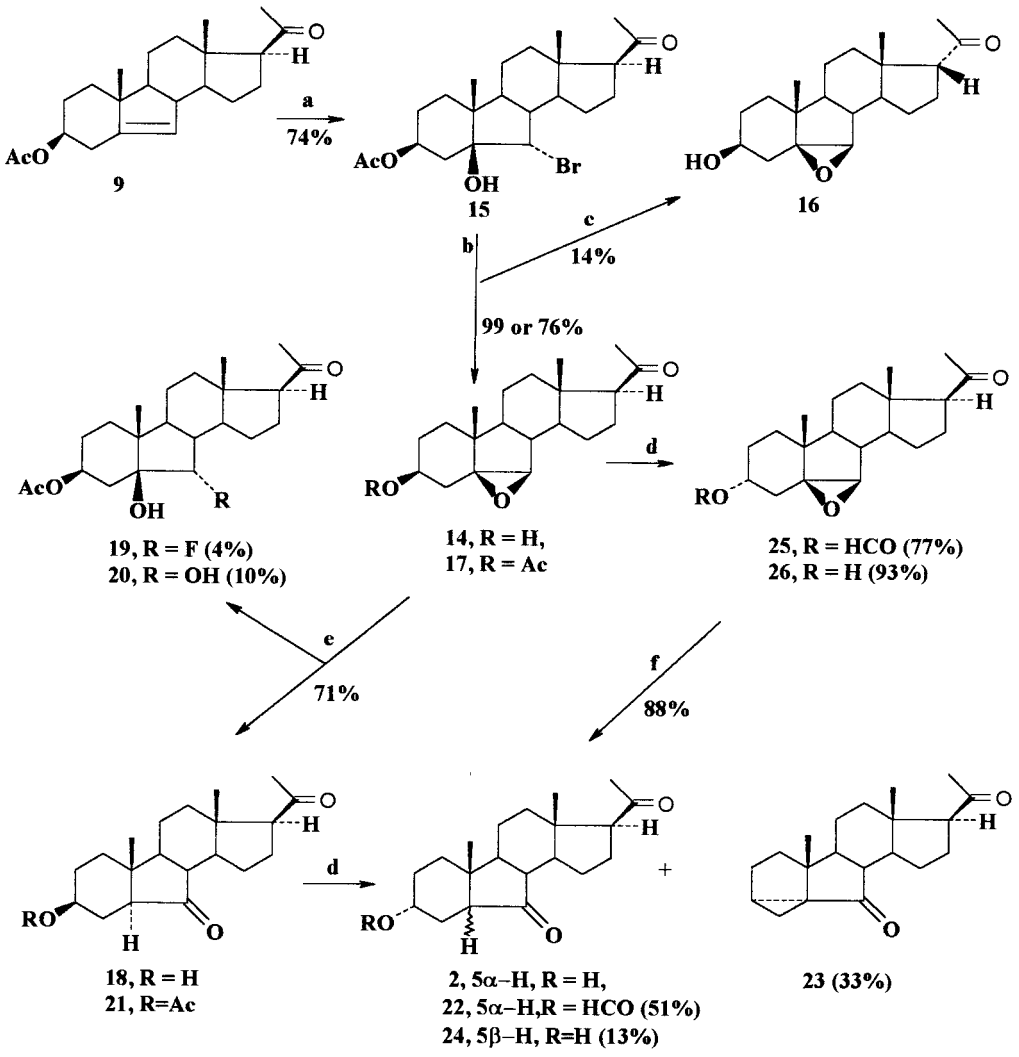
The desired 3α-hydroxy diketone **2** was first prepared from the 3β-hydroxy derivative **18** in low yield by Mitsunobu reaction via formate **22**. The yield was reduced by intramolecular cyclisation leading to cyclopropano-ketone **23** (see Experimental for the IR frequency of C_6=O absorption decreased by conjugation with the cyclopropane ring and for the proton signal of this ring). The efficiency of the sequence was further lessened by lability of 5α-ketones in the 7-nor series: hydrolysis of formate **22** produced not only the expected 3α-alcohol **2** but also a by-product **24**. The latter had a much diminished positive Cotton effect (see the value of $\Delta\varepsilon$ in Experimental) and a wide signal of the 3β proton in its ^{1}H NMR spectrum (further, the 5α-H signal[15] at δ 2.35 disappeared). Both the patterns indicated a configurational change at carbon C-5. A model experiment with ketone **2** showed that alkalinity, needed to hydrolyse the formate grouping, was strong enough to cause the isomerization. Earlier, it was found[16] that 6-oxo-7-nor-5α-steroids could equilibrate to 5β,8β- and even to 5β,8α-isomers. From Morisawa's data[17] on molecular rotation differences we could easily identify the product structures since the conversion into the former isomer was accompanied with a smaller negative difference (ΔM=−299°) than the conversion into the latter one (ΔM=−613°). The ΔM value of compound **24** (−286°) confirmed the 5β,8β-configuration.

In an alternative route, the epoxide isomerization to ketone and the Mitsunobu reaction were swapped (i.e. an alkaline hydrolysis of the formate was realized in epoxide **25** which was followed with the Lewis acid treatment of epoxide **26**). In this way, the diketone **2** was produced without complications.

The binding of the target compounds **2**, **13** and **26** to the $GABA_A$ receptor, measured through effects on [^{3}H]muscimol and [^{35}S]TBPS binding, will be published elsewhere.

Experimental

General. Whenever aqueous solutions of hydrochloric acid, potassium hydrogen carbonate and potassium carbonate were used, their concentration was always 5%. Prior to evaporation on a rotary evaporator in vacuo (bath temperature 50°C), solutions in organic solvents were dried over anhydrous sodium sulfate. Thin-layer chromatography (TLC) was performed on silica gel (ICN Biochemicals), preparative TLC (PLC) was carried out on 200×200 mm plates coated with an 0.7 mm thick layer of the same material. For column chromatography, silica gel 60–120 μm was used. Analytical samples were dried over phosphorus pentoxide at 50°C/100 Pa. Melting points were determined on a micro melting point apparatus (Boetius, Germany) and are uncorrected. Optical rotations were measured in chloroform ($[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}), IR spectra were recorded on a Bruker IFS 88 spectrometer, proton NMR spectra were measured on a Varian UNITY-200 FT-NMR spectrometer (at



Scheme 2. Reagents: (a) NBS, $HClO_4$; (b) K_2CO_3 or KOH, MeOH; (c) KOH, MeOH; (d) DEAD, triphenylphosphine, HCOOH, then $KHCO_3$, MeOH; (e) $BF_3{\cdot}Et_2O$.

200 MHz) in $CDCl_3$ with tetramethylsilane as internal reference. Chemical shifts of selected signals are given in ppm (δ-scale), coupling constants and width of multiplets in Hz. Unless otherwise stated, the data were interpreted as the first-order spectra.

3α-Hydroxy-7-nor-5α-pregnane-6,20-dione (2). *(a) By hydrolysis.* A solution of potassium hydrogencarbonate (75 mg, 0.75 mmol) in water (1 mL) was added to a boiling solution of formate **22** (90 mg, 0.26 mmol) in methanol (9 mL). After 5 min, the solution was evaporated to dryness in vacuo. The residue was partitioned between water and chloroform, the organic layer was dried over sodium sulfate and concentrated in vacuo. PLC (two plates, benzene–ethyl acetate 1:1, double development) yielded the title compound **2** (50 mg, 73%) as white crystals, mp 166–167°C (acetone); [Found: C, 75.21; 9.69. $C_{20}H_{30}O_3$ requires C, 75.43; 9.50%]; $[\alpha]_D$=+188 (*c* 1.1, $CHCl_3$). ν_{max} ($CHCl_3$) 3613, 3505, 999, 986 (OH); 1729, 1701, 1360 (C=O) cm^{-1}. Circular dichroism: $\Delta\varepsilon_{296}$ +6.38 (methanol); δ_H (200 MHz, $CDCl_3$) 4.22 (1H, p, *J*=2.7 Hz, *H*-3), 2.51 (1H, t, *J*=9.0 Hz, *H*-17α), 2.35 (1H, dd, *J*=12.2, 2.4 Hz, *H*-5), 2.15 (3H, s, 3×*H*-21), 0.83 (3H, s, 3×*H*-19), 0.63 (3H, s, 3×*H*-18), besides white crystals of **3α-hydroxy-7-nor-5β-pregnane-6,20-dione** (**24**, 9 mg, 13%), mp 162–164°C (acetone–heptane); $[\alpha]_D$=+98 (*c* 0.8, $CHCl_3$). Circular dichroism: $\Delta\varepsilon_{292}$ +2.54 (methanol); δH (200 MHz, $CDCl_3$) 3.75–3.56 (1H, m, *H*-3), 2.51 (1H, t, *J*=9.0 Hz, H-17α), 2.15 (3H, s, 3×*H*-21), 0.99 (3H, s, 3×*H*-19), 0.62 (3H, s, 3×*H*-18).

(b) By isomerisation. A solution of epoxide **26** (36 mg, 0.11 mmol) in tetrahydrofuran (3 mL) was treated with boron trifluoride diethyl etherate (0.005 mL, 0.004 mmol) as in the preparation of compound **18**. The title compound **2** (32 mg), identical with the above product, was produced in 88% yield.

3β-Acetoxy-5,20-dioxo-5,6-seco-5β-pregnan-6-oic acid (4). (a) Jones reagent[11] (91 mL) was added to a solution of diol **7** (37.9 g, 96.6 mmol) in a mixture of acetone (760 mL) and toluene (200 mL) under stirring at 50°C. After 2 h, an excess of the reagent was reduced with propan-2-ol and solvents were evaporated in vacuo. The residue was dissolved in dichloromethane and washed subsequently with a saturated aqueous solution of oxalic acid and

water. The extract was dried over sodium sulfate and evaporated. Part (84 mg) of the oily *title compound* (38.0 g, 97%) was purified for analysis by PLC (2 plates, benzene–ether 1:1). The product failed to crystallize from common solvents (earlier reported sample[18] was not characterized). $[\alpha]_D$=+90 (*c* 1.2, $CHCl_3$); [Found: C, 69.86; H, 8.57. $C_{23}H_{34}O_6$ requires C, 67.96; H, 8.43%]; ν_{max} ($CHCl_3$) 3525 (COOH-monomer), 3032, 2684, 1421, 1291 (COOH-dimer); 1733, 1249, 1025 (AcO, COOH); 1704 (C=O) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.45–5.34 (1H, m, *H*-3), 3.21 (1H, dd, *J*=14.9 Hz, 4.3, *H*-4α), 2.13 (3H, s, 3×*H*-21), 2.02 (3H, s, CH_3COO), 1.05 (3H, s, 3×*H*-19), 0.65 (3H, s, 3×*H*-18).

(b) A solution of chromium trioxide (4.0 g, 40.0 mmol) in aqueous acetic acid (50%, 20 mL) was added into a stirred solution of alkene **3** (4.5 g, 12.55 mmol) in acetic acid (50 mL) during 1 h at 50°C. After an additional hour at this temperature, an excess of the oxidizing agent was reduced with methanol (30 mL) and the solvent was evaporated at 45°C in vacuo. The dry residue was partitioned between ether and water, the combined ethereal extracts were washed with water and dried and concentrated in vacuo. The residue was dissolved in acetone (7 mL) applied on a silica gel column (200 g). A mixture of chloroform and 2-propanol (98:2) eluted the ketone **5** (2.124 g, 45%); ν_{max} ($CHCl_3$) 1730, 1366, 1035 (AcO); 1701, 1360 ($COCH_3$); 1671, 1633 (C=C–CO) cm^{-1} (the spectrum was identical with that of an authentic sample[19]). More polar fractions gave the *title compound* **4** (1.892 g, 37%) as colourless oil; ^{1}H NMR spectrum proves the presence of 3β-acetoxy-5,20-dioxo-5,6-secoandrostan-6-oic acid (**6**, 12%). For comparison, the compound **6** was prepared from 17-oxo-androst-5-en-3β-yl acetate according to Ref. 20 δ_H (200 MHz, $CDCl_3$) 5.42–5.33 (1H, m, *H*-3), 3.23 (1H, dd, *J*=14.9, 4.3 Hz, *H*-4α), 2.01 (3H, s, CH_3COO), 1.07 (3H, s, 3×*H*-19), 0.89 (3H, s, 3×*H*-18).

5,6β-Dihydroxy-20-oxo-5α-pregnan-3β-yl acetate (7). Compound **7** was prepared according to Ref. 21 by epoxidation of 20-oxopregn-5-en-3β-yl acetate (**3**) and hydration of the mixture of 5α,6α- and 5β,6β-epoxides. The hydration was modified as follows: a mixture of epoxides **3** (54 g, 0.15 mol) was dissolved in tetrahydrofuran (245 mL) and treated with perchloric acid (7%, 54 mL) at room temperature (20 h) and then at 0°C (6 h). A white precipitate of the *title compound* **7** (43.1 g, 73%) was filtered off, an additional crop (12.9 g, 22%) was obtained on precipitation of the mother liquor with brine.

3β-Acetoxy-20-oxo-7-nor-5β,6α-pregnane-6,5-carbolactone (8). Oxo acid **4** (12.7 g, 31.24 mmol) was cyclised by treatment with benzoyl chloride (12 mL) in pyridine (50 mL) according to Ref. 10. The *title compound* **8** (5.85 g, 48%), a colourless oil, was found identical with the authentic sample. ν_{max} ($CHCl_3$) 1819, 1086 (β-lactone); 1729, 1252, 1021 (AcO); 1703 ($COCH_3$) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.08–4.93 (1H, m, *H*-3), 3.19 (1H, d, *J*=7.3 Hz, *H*-6), 2.53 (1H, t, *J*=9.0 Hz, *H*-17), 2.13 (3H, s, 3×*H*-21), 2.06 (3H, s, CH_3COO), 1.47 (3H, s, 3×*H*-19), 0.66 (3H, s, 3×*H*-18).

20-Oxo-7-norpregn-5-en-3β-yl acetate (9). β-Lactone **8** (5.85 g, 15.1 mmol) was heated to 190°C according to Ref. 10 The *title compound* **9** (3.09, 60%) was found identical with the authentic sample. ν_{max} ($CHCl_3$) 1727, 1250 (AcO); 1699 ($COCH_3$); 1635 (C=C) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.39 (1H, bs, *H*-6), 4.72–4.55 (1H, m, *H*-3), 2.64 (1H, ddd, *J*=13.7, 4.9, 1.8 Hz, *H*-4α), 2.14 (3H, s, 3×*H*-21), 2.04 (3H, s, CH_3COO), 0.90 (3H, s, 3×*H*-19), 0.64 (3H, s, 3×*H*-18).

3β-Hydroxy-5,6α-epoxy-7-nor-5α-pregnan-20-one (10). Compound **11** (850 mg, 2.81 mmol) was treated with 4-chloroperoxybenzoic acid (550 mg, 3.19 mmol) in dichloromethane (20 mL) at 0°C. After 2 h, the mixture was washed with the potassium hydrogencarbonate solution and water. After evaporation of the solvent, crystallization yielded the *title compound* **10** (610 mg, 70%), mp 220–221°C (dichloromethane–heptane); $[\alpha]_D$=+13 (*c* 1.1, $CHCl_3$); [Found: C, 75.23; H, 9.60. $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.50%]; ν_{max} ($CHCl_3$) 3611, 3463, 1034 (OH); 1699, 1358 ($COCH_3$); 1386 (CH_3) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.05–3.87 (1H, m, *H*-3), 3.28 (1H, s, *H*-6β), 2.56 (1H, t, *J*=9.0 Hz, *H*-17), 2.13 (3H, s, 3×*H*-21), 0.90 (3H, s, 3×*H*-19), 0.60 (3H, s, 3×*H*-18). Thin layer chromatography of the mother liquor (7 plates, benzene–ethyl acetate 2:1, double development) yielded an additional crop of the α-epoxide **10** (134 mg, 15%).

3β-Hydroxy-7-norpregn-5-en-20-one (11). Acetate **9** (877 mg, 2.55 mmol) was treated with potassium carbonate (2.0 g, 14.47 mmol) at room temperature in aqueous methanol (4%, 50 mL) under nitrogen. After 2 h, the mixture was filtered, the filtrate was concentrated to a quarter of its volume and diluted with brine (50 mL). The precipitate of the title compound **11** was taken up in chloroform, washed with water and dried. After evaporation in vacuo, the residue (690 mg, 92%) crystallized from toluene to yield white crystals. Mp 133–135°C, undepressed on admixture of the authentic sample. $[\alpha]_D$=−26 (*c* 1.4, $CHCl_3$). Circular dichroism: $\Delta\varepsilon_{288}$=+3.57 (methanol); ν_{max} ($CHCl_3$) 3608, 3464, 1036 (OH); 1698, 1385, 1358 ($COCH_3$); 1635 (C=C) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.39 (1H, bs, *H*-6), 3.67–3.49 (1H, m, *H*-3), 2.62 (1H, ddd, *J*=13.7, 4.9, 1.8 Hz, *H*-4α), 2.13 (3H, s, 3×*H*-21), 0.89 (3H, s, 3×*H*-19), 0.64 (3H, s, 3×*H*-18).

5,6α-Epoxy-20-oxo-7-nor-5α-pregnan-3α-yl formate (12). A solution of alcohol **10** (467 mg, 1.47 mmol) in toluene (90 mL) was heated until azeotropic mixture (30 mL) distilled off. A solution of triphenylphosphine (900 mg, 3.43 mmol) in toluene (30 mL) was added to this solution under stirring. The reaction mixture was stirred at 0°C for 10 min and then diethyl azodicarboxylate (30 drops, 3.7 mmol) was added. After additional 20 min, formic acid (9 drops, 4.3 mmol) was dripped in. The solution was left aside for 18 h. A precipitate formed was filtered off and washed with toluene, the filtrate was applied on a column of silica gel (40 mL). Toluene–ether (10:1) eluted the title compound **12** which crystallized from a mixture of heptane and acetone. Mp 161–162°C (304 mg, 57%); $[\alpha]_D$=+43 (*c* 1.2, $CHCl_3$); [Found: C, 72.7; H, 8.69. $C_{21}H_{30}O_4$ requires C, 72.80; H, 8.73%]; ν_{max} ($CHCl_3$) 1716, 1194, 926 (formate); 1701, 1358 ($COCH_3$); 1387 (CH_3) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.08 s, 1 H (*H*COO), 5.40–5.32 (1H, m, *H*-3),

3.21 (1H, s, *H*-6β), 2.58 (1H, t, *J*=9.0 Hz, *H*-17), 2.37 (1H, ddd, *J*=15.0, 3.4, 0.9 Hz, *H*-4), 2.13 (3H, s, 3×*H*-21), 0.89 (3H, s, 3×*H*-19), 0.61 (3H, s, 3×*H*-18). Further fractions yielded the starting compound (**10**, 99 mg, 21%).

3α-Hydroxy-5,6α-epoxy-7-nor-5α-pregnan-20-one (13). Formate **12** (120 mg, 0.35 mmol) was treated with potassium hydrogencarbonate (120 mg, 1.20 mmol) in aqueous methanol (90%, 12 mL) under stirring at room temperature. After 24 h, the solution was concentrated in vacuo, and diluted with brine (20 mL). A precipitate of the *title compound* **13** was filtered off, washed with water and dried. Crystallization yielded compound **13** (78 mg, 71%) as white crystals, mp 131–132°C (acetone–heptane); $[\alpha]_D$=+14 (*c* 1.0); [Found: C, 75.37; H, 9.53. $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.50%]; ν_{max} ($CHCl_3$) 3575, 1024, 984 (OH); 1700, 1358 ($COCH_3$); 1386 (CH_3) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.23–4.15 (1H, m, *H*-3), 3.24 (1H, s, *H*-6β), 2.59 (1H, t, *J*=9.0 Hz, *H*-17), 2.37 (1H, dd, *J*=15.4, 3.9 Hz, *H*-4), 2.14 (3H, s, 3×*H*-21), 0.87 (3H, s, 3×*H*-19), 0.61 (3H, s, 3×*H*-18).

3β-Hydroxy-5,6β-epoxy-7-nor-5β-pregnan-20-one (14). *(a) At elevated temperature*. Bromohydrin **15** (275 mg, 0.62 mmol) was treated with a boiling solution of potassium carbonate (3 g, 21.7 mmol) in aqueous methanol (80%, 50 mL) under nitrogen. After 2 h, the solution was concentrated in vacuo, diluted with brine (100 mL) and a white crystalline precipitate of the *title compound* **14** was extracted with dichloromethane. The extract was washed with water, dried and evaporated. The epoxide **14** crystallized from acetone–heptane, mp 171–173°C (118 mg, 59%); $[\alpha]_D$=+71 (*c* 1.0, $CHCl_3$); [Found: C, 74.45; H, 9.59. $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.50%]; ν_{max} ($CHCl_3$) 3609, 3482, 1039 (OH); 1700, 1388, 1358 ($COCH_3$); 1233 (epoxide) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.01–3.83 (1H, m, *H*-3), 3.20 (1H, s, *H*-6), 2.53 (1H, t, *J*=8.3 Hz, *H*-17), 2.12 (3H, s, 3×*H*-21), 0.89 (3H, s, 3×*H*-19), 0.59 (3H, s, 3×*H*-18).

(b) At room temperature. A solution of potassium carbonate (720 mg, 5.21 mmol) in water (3 mL) was added to a solution of bromohydrin **15** (67 mg, 0.15 mmol) in methanol (10 mL). The mixture was left under nitrogen. After 24 h, the solution was concentrated in vacuo to a half, a product, precipitated on addition of brine (20 mL), was extracted with dichloromethane and washed with water and dried. The white solid (48 mg, 99%) had ^1H NMR spectrum identical with that of the *title compound* **14**.

6α-Bromo-5-hydroxy-20-oxo-7-nor-5β-pregnan-3β-yl acetate (15). *N*-Bromo acetamide (140 mg, 1.0 mmol) was added to a solution of alkene **9** (300 mg, 0.87 mmol) in dioxane (3 mL) and perchloric acid (1 M, 0.3 mL) at +15°C. After 30 min, a saturated solution of sodium hydrogensulfite was added. The precipitate of the title compound **15** was filtered off, dissolved in chloroform and washed with water and dried. The product (227 mg, 59%) crystallized from methanol, additional crop of white crystals (56 mg, 15%) was obtained by PLC of the mother liquor on 3 PLC plates in benzene–ether 3:1. Mp 144–145°C; $[\alpha]_D$=+26 (*c* 1.2, $CHCl_3$); [Found: C, 59.51; H, 7.39. $C_{22}H_{33}BrO_4$ requires C, 59.86; H, 7.54%]; ν_{max} ($CHCl_3$) 3581, 1017 (OH); 1738, 1250, 1230, 1045 (OAc); 1700 (C=O); 595 (Br) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.35−5.24 (1H, m, *H*-3), 4.34 (1H, d, *J*=6.1 Hz, *H*-6), 2.56 (1H, t, *J*=9.3 Hz, *H*-17), 2.14 (3H, s, 3×*H*-21), 2.07 (3H, CH_3COO), 0.95 (3H, s, 3×*H*-19), 0.68 (3H, s, 3×*H*-18).

3β-Hydroxy-5,6β-epoxy-7-nor-5β,17β-pregnan-20-one (16). The mother liquor of the above example (sub a, 68 mg) was chromatographed using 3 PLC plates in benzene–ethyl acetate, 1:1. The polar component was identical with the above epoxide **14** (33 mg, additional 17%), the less polar component is the *title compound* **16** (27 mg, 14%), mp 175–176°C (white crystals from acetone–heptane), ν_{max} ($CHCl_3$) 3610, 3480, 1037 (OH); 1700, 1382, 1359 ($COCH_3$) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.01–3.83 (1H, m, *H*-3), 3.20 (1H, s, *H*-6), 2.80 (1H, d, *J*=7.5 Hz, *H*-17β), 2.14 (3H, s, 3×*H*-21), 0.86 (6H, s, 3×*H*-19 and 3×*H*-18). Circular dichroism: $\Delta\varepsilon_{287}$ −7.47 (methanol); *m/z* (EI): 318 (M+, 100), 300 (26), 285 (14), 257 (20), 248 (28); HRMS (EI): found 318.2181. $C_{20}H_{30}O_3$ requires 318.2195.

20-Oxo-5,6β-epoxy-7-nor-5β-pregnan-3β-yl acetate (17). Epoxide **14** (270 mg, 0.75 mmol) was treated with acetic anhydride (1.0 mL, 10.6 mmol) in pyridine (1.0 mL) at room temperature. After 18 h, the mixture was poured onto ice, the precipitate of the *title compound* was extracted with ether, the extract was washed with the solution of potassium hydrogen carbonate and water and dried with sodium sulfate. The solvent was evaporated, the residue was dissolved in toluene (10 mL) and repeatedly evaporated to remove traces of pyridine. The product **17** (285 mg, 93%), a colourless oil, failed to crystallize from common solvents. $[\alpha]_D$=+56 (*c* 0.9, $CHCl_3$); [Found: C, 73.19; H, 9.11. $C_{22}H_{32}O_4$ requires C, 73.30; H, 8.95%]; ν_{max} ($CHCl_3$) 1729, 1252, 1030 (AcO); 1702, 1361 ($COCH_3$) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.03–4.87 (1H, m, *H*-3), 3.20 (1H, s, *H*-6), 2.52 (1H, d, *J*=9.1 Hz, *H*-17), 2.12 (3H, s, 3×*H*-21), 2.05 (3H, s, CH_3COO), 0.89 (3H, s, 3×*H*-19), 0.59 (3H, s, 3×*H*-18).

3β-Hydroxy-7-nor-5α-pregnane-6,20-dione (18). A solution of epoxide **14** (85 mg, 0.27 mmol) in a mixture of ether (4 mL) and tetrahydrofuran (1.5 mL) was treated with boron trifluoride diethyl etherate (0.01 mL, 0.08 mmol) at room temperature. After 3 h, the reaction was stopped by the solution of potassium hydrogencarbonate and the product was extracted with ether and washed with water. The extract was dried and concentrated in vacuo. The residue was purified by PLC (3 plates, benzene–ethyl acetate, 1:1), the major component represented the *title compound* **18** (63 mg, 74%) which crystallized from acetone–heptane as white crystals. Mp 181–183°C; $[\alpha]_D$=+170 (*c* 1.1, $CHCl_3$); [Found: C, 75.40; H, 9.53. $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.50% H]; ν_{max} ($CHCl_3$) 3610, 3458, 1054 (OH); 1732 (C=O); 1701, 1357 ($COCH_3$); 1390, 1385, 1377 (CH_3) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.76–3.58 (1H, m, *H*-3), 2.50 (1H, t, *J* 9.0 Hz, *H*-17), 2.14 (3H, s, 3×*H*-21), 0.89 (3H, s, 3×*H*-19), 0.63 (3H, s, 3×*H*-18).

Reaction of epoxide 17 with boron trifluoride etherate

Epoxide **17** (220 mg, 0.61 mmol) was dissolved in ether (12 mL) and treated with boron trifluoride diethyl etherate

(0.02 mL, 0.16 mmol) at room temperature. The mixture was worked up as in the preparation of diketone **18**. Thin-layer chromatography (6 plates, benzene-ethyl acetate, 2:1) of the residue yielded:

6,20-Dioxo-7-nor-5α-pregnan-3β-yl acetate (**21**, 175 mg, 71%), mp 89–90°C (white crystals from acetone–heptane); $[\alpha]_D$=+55 (*c* 1.1, $CHCl_3$). Circular dichroism: $\Delta\varepsilon_{296}$=+4.55 (methanol); [Found: C, 73.22; H, 8.97. $C_{22}H_{32}O_4$ requires C, 73.30; H, 8.95%]; ν_{max} ($CHCl_3$) 1729 (C=O); 1702, 1357($COCH_3$); 1252, 1030 (C–O) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.79–4.61 (1H, m, *H*-3), 2.50 (1H, s, *J*=8.9 Hz, *H*-17), 2.14 (3H, s, 3×*H*-21), 2.04 (3H, s, C*H*$_3$COO), 0.89 (3H, s, 3×*H*-19), 0.63 (3H, s, 3×*H*-18), and

5-Hydroxy-6α-fluoro-20-oxo-7-nor-5α-pregnan-3β-yl acetate (**19**, 8 mg, 4%), mp 185–6°C (white crystals from acetone–heptane), ν_{max} ($CHCl_3$) 3612, 3487, 1047 (OH); 1729 (AcO); 1700, 1363, 1032 ($COCH_3$); 1378, 1363 (CH_3) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.27–5.08 (1H, s, *H*-3), 3.80 (1H, dd, *J*=25.3, 4.9 Hz, *H*-6), 2.58 (1H, t, *J*=8.8 Hz, *H*-17), 2.14 (3H, s, 3×*H*-21), 2.04 (3H, s, C*H*$_3$COO), 1.01 (3H, s, 3×*H*-19), 0.64 (3H, s, 3×*H*-18); *m/z*: 380 (M^+, 24), 362 (M^+-H_2O, 40), 358 (46), 343 (42), 300 (81), 283 (100); HRMS (EI): found: 380.2333. $C_{22}H_{33}O_4F$ requires 380.2363, and

5,6α-Dihydroxy-20-oxo-7-nor-5α-pregnan-3β-yl acetate (**20**, 24 mg, 10%), mp 173–176°C (white crystals from methanol); δ_H (200 MHz, $CDCl_3$) 5.14 (1H, p, *J*=2.6 Hz, *H*-3), 4.12 (1H, d, *J*=7.0 Hz, *H*-6), 3.50 (1H, d, *J*=7.2 Hz, *H*-4), 2.50 (1H, t, *J*=8.8 Hz, *H*-17), 2.14 (3H, s, 3×*H*-21), 2.07 (3H, s, C*H*$_3$COO, 1.07 (3H, s, 3×*H*-19), 0.67 (3H, s, 3×*H*-18); m/z: 360 (M^+-H_2O, 7), 300 (100), 285 (23), 267 (7).

6,20-Dioxo-7-nor-5α-pregnan-3α-yl formate (22). 3β-Hydroxy derivative **18** (108 mg, 0.34 mmol) was treated with triphenyl phosphine (240 mg, 0.92 mmol) and diethyl azodicarboxylate (7 drops, 1.0 mmol) as in the preparation of compound **12**. The *title compound* **22** (60 mg, 51%) crystallized from acetone–heptane as white crystals. Mp 177–178°C, $[\alpha]_D$+173 (c 1.1, $CHCl_3$); [Found: C, 72.78; H, 8.80. $C_{21}H_{30}O_4$ requires C, 72.80; H, 8.73%]; ν_{max} ($CHCl_3$) 1732 (sh, C_6=O), 1720 and 1191, 1164 (HCOO), 1703 and 1359 (OAc) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.32 (1H, p, *J*=2.6 Hz, *H*-3), 2.50 (1H, t, *J*=8.8 Hz, *H*-17), 2.15 (3H, s, 3×*H*-21), 0.87 (3H, s, 3×*H*-19), 0.64 (3H, s, 3×*H*-18).

A side product was isolated (3α,5-cyclo-7-nor-5α-pregnane-6,20-dione, **23**, 34 mg, 33%) as white crystals. Mp 202–203°C (acetone); $[\alpha]_D$=+57 (*c* 1.0, $CHCl_3$); [Found: C, 75.45; H, 9.61. $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.50%]; ν_{max} (CCl_4) 1708, 1356 (CH_3C=O), 1723 (C_6=O), 3066, 3029, 2990 (sh), 1025 (cyclopropane) cm^{-1}; *m/z*: 300 (M^+, 100), 282 (12), 256 (8), 230 (9), 215 (48), 55 (44), 43 (64); δ_H (200 MHz, $CDCl_3$) 2.50 (1H, t, *J*=8.8 Hz, *H*-17), 2.15 (3H, s, 3×*H*-21), 1.00 (3H, s, 3×*H*-19), 0.93 (1H, t, *J*=4.7 Hz, *H*-4), 0.66 (3H, s, 3×*H*-18).

5,6β-Epoxy-20-oxo-7-nor-5β-pregnan-3α-yl formate (25). From a solution of alcohol **14** (164 mg, 0.51 mmol) in benzene (15 mL), azeotropic mixture (10 mL) was distilled off. A solution of triphenylphosphine (300 mg, 1.14 mmol) in a mixture of benzene and tetrahydrofuran (20 mL, 1:1) was added to this solution under stirring. After 5 min, the reaction mixture was cooled to 0°C and diethyl azodicarboxylate (10 drops, 1.11 mmol) was added. After additional 10 min, formic acid (3 drops, 1.43 mmol) was dripped in. The mixture was left aside for 18 h, then a precipitate was filtered off and washed with toluene. The filtrate was concentrated in vacuo and applied on four PLC plates which were developed with toluene–ether (9:1). The major zone gave 137 mg (77%) of the title compound **25** as white crystals, mp 139–140°C (heptane–acetone); $[\alpha]_D$=+73 (*c* 1.2, $CHCl_3$); [Found: C, 72.82; H, 8.77. $C_{21}H_{30}O_4$ requires C, 72.80; H, 8.73%]; ν_{max} ($CHCl_3$) 1719, 1169 (formate); 1704, 1358 ($COCH_3$); 1387 (CH_3) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.06 (1H, s, *H*COO), 5.40–5.27 (1H, m, *H*-3), 3.22 (1H, s, *H*-6), 2.59 (1H, t, *J*=9.0 Hz, *H*-17), 2.13 (3H, s, 3×*H*-21), 0.88 (3H, s, 3×*H*-19), 0.61 (3H, s, 3×*H*-18).

3α-Hydroxy-5,6β-epoxy-7-nor-5β-pregnan-20-one (26). A solution of sodium methoxide in methanol (0.87 M, 0.3 mL) was added to a solution of formate **25** (83 mg, 0.24 mmol) in methanol (3 mL). After 2 min, the mixture was diluted with brine (12 mL) and cooled to −15°C to yield the *title compound* **26** (71 mg, 93%) as white crystals. Mp 188–189°C (acetone), $[\alpha]_D$=+72 (*c* 0.9, $CHCl_3$); [Found: C, 75.26; H, 9.55. $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.50%]; Circular dichroism: $\Delta\varepsilon_{288}$=+4.47 (methanol); ν_{max} ($CHCl_3$) 3610, 3400, 1031 (OH); 1700, 1358 ($COCH_3$) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.27–4.15 (1H, m, *H*-3), 3.23 (1H, s, *H*-6), 2.58 (1H, t, *J*=9.0 Hz, *H*-17), 2.14 (3H, s, 3×*H*-21), 0.85 (3H, s, 3×*H*-19), 0.60 (3H, s, 3×*H*-18).

Equilibration of 3α-hydroxy-7-nor-5α-pregnane-6,20-dione (2). Potassium hydrogencarbonate (160 mg) was dissolved in water (2.7 mL). One tenth of this solution (0.16 mmol) was added to a solution of compound **2** (27 mg, 0.08 mmol) in methanol (2.5 mL). The mixture was held at 70°C for 15 min, then it was diluted with brine and the product was extracted with chloroform. The extract was concentrated in vacuo and the two components were separated by PLC (one plate) in benzene-ethyl acetate (1:1). The more polar one (9 mg, 33%) was found identical with 5β,8β-ketone **24**. The less polar component (**2**, 10 mg, 37%) was the starting material.

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