EPALONS: SYNTHESIS OF 7-NORALLOPREGNANOLONE*

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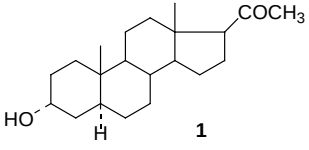
The title compound **2** was prepared from (20*R*)-pregn-5-ene-3β,20-diyl 3-acetate 20-benzoate (**3**) *via* (20*R*)-3β-acetoxy-20-benzoyloxy-5-oxo-5,6-secopregnan-6-oic acid (**5**) and (20*R*)-3β-acetoxy-20-benzoyloxy-7-nor-5β,6α-pregnane-6,5-carbolactone (**6**). An intermediate 7-norpregn-5-ene derivative – (20*R*)-7-norpregn-5-ene-3β,20-diyl 3-acetate 20-benzoate (**7**) – was hydrogenated using diimide *in statu nascendi*. The inversion of configuration at carbon C-3 was carried out *via* (20*R*)-7-nor-5α-pregnane-3β,20-diyl 3-tosylate 20-benzoate (**12**) and (20*R*)-7-nor-5α-pregnane-3α,20-diyl 20-benzoate 3-formate (**13**).

Key words: Steroids; 7-Norsteroids; Epalon; 3α,5α-Tetrahydroprogesterone; $GABA_A$-Modulator; Mitsunobu reaction; NMR spectroscopy, ^1H.

Neurosteroids that positively modulate γ-aminobutyric acid receptors in the brain (*e.g.* 3α-hydroxy-5α-pregnan-20-one (**1**)) induce analgesia, anaesthesia, anxiolysis and sleep[2]. These compounds are assumed to bind relatively open receptor sites by oxygen functionalities at carbons 3 and 20 while the flat lipophilic middle part of their molecule (rings B and C) gets squeezed into a narrow flat hole within the receptor. In our search[3,4] for new ana-



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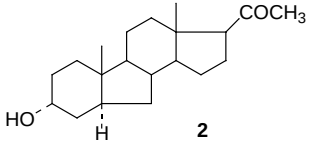


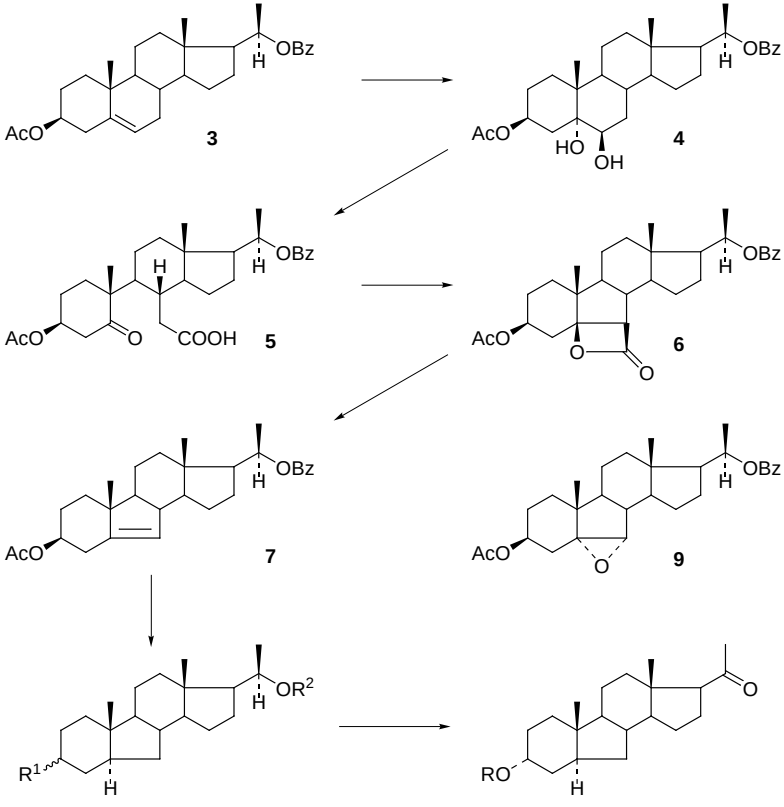
2

logues of compound **1**, we have tried to modify the steroid B ring by making it even flatter which should have a better chance of finding free space within the receptor. Molecular modelling shows that the volume of the B

* Part CDIII in the series On Steroids; Part CDII see ref.[1]

ring of the title compound **2** is much reduced in comparison with the parent compound **1**, though some additional changes are also introduced into the molecule. The molecule of its 7 nor analogue **2** is shorter than the original: *e.g.* the distance between oxygen atoms in positions 3 and 20 is shorter in compound **2** than in **1**. Further, the angular methyl groups in the former compound are no longer attached to the skeleton by parallel bonds as they are in compound **1**, where the dihedral angle C19–C10–C13–C18 is about 7°.

Starting with (20*R*)-pregn-5-ene-3β,20-diyl 3-acetate 20-benzoate (**3**, see Scheme 1), we produced a mixture of corresponding 5α,6α- and 5β,6β-



SCHEME 1

epoxides which were cleaved by perchloric acid to a single product – 5α,6β-diol **4**. Its oxidation afforded seco acid **5** which on action of benzoyl chloride in pyridine underwent condensation to a 7-norsteroid derivative **6**. By pyrolysis of the β-lactone **6** the 7-norpregn-5-ene derivative **7** was formed.

Catalytic hydrogenation[5] of 7-norpregn-5-ene compounds leads mainly to 5β-dihydro derivatives. Therefore, diimide reduction[6,7] had to be employed in order to obtain the target 5α-products. Heating of a mixture of alkene **7** and tosylhydrazine in 2,4,6-trimethylpyridine yielded the 5α-dihydro product **8** (88%). When a larger-scale experiment was carried out, the yield was lower. Since both compounds, **7** and **8**, are of the same polarity, the rest of the starting alkene **7** was removed by oxidation[8,9] to epoxide **9** and subsequent chromatography.

Partial hydrolysis of diester **8** was achieved selectively by acid-catalyzed transesterification in methanol and the 3β-alcohol **10** produced was converted[10] into its 3α-isomer **11** either *via* 3β-tosylate **12** by solvolysis or *via* 3α-formate **13** by Mitsunobu reaction. The 3α-hydroxy group was protected by etherification and the (2-methoxyethoxy)methoxy derivative **14** was hydrolyzed and oxidized to compounds **15** and **16**. On treatment with acid, the target 7-norallopregnanolone (**2**) was obtained in a total yield of 18% (*via* 3α-formate **13**) and 11.7% (*via* 3β-tosylate **12**), respectively.

Identity of the compounds prepared was checked by IR and ^{1}H NMR spectra. The opening of the B ring was manifested among other signs by the change of multiplicity of the 3α-proton: due to the loss of rigidity, caused by the A/B ring junction, the 3α-proton lost its axial nature[11] which it revealed in all other 5α-compounds. ^{1}H NMR of the β-lactone **6** had a typical doublet of the 6α-proton at δ 3.19. All 3β-protons in the 7-nor-5α-steroids prepared gave signals of an equatorial proton. CD of the β-lactone **6** corresponded to the characteristics observed earlier[12].

Compound **2** was submitted for biological screening (binding to $GABA_A$ receptors) whose results will be published elsewhere.

EXPERIMENTAL

Melting points were determined on a micro melting point apparatus Boetius (Germany) and are uncorrected. Analytical samples were dried over phosphorus pentoxide at 50 °C/100 Pa. Optical rotations were measured in chloroform ($[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}), IR spectra of chloroform solutions were recorded on a Bruker IFS 88 spectrometer, wavenumbers are given in cm^{-1}. NMR spectra were measured on FT-NMR spectrometer Varian UNITY-200 (at 200 MHz) in $CDCl_3$ with tetramethylsilane as internal reference. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) and width of multiplets

(*W*) in Hz. Unless otherwise stated, the data were interpreted as the first-order spectra. 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. Whenever aqueous solutions of hydrochloric acid, potassium hydrogen carbonate and potassium carbonate are used, their concentration is always 5%. Prior to evaporation on a rotary evaporator in vacuum (bath temperature 50 °C), solutions in organic solvents were dried over anhydrous sodium sulfate.

(20*R*)-5,6β-Dihydroxy-5α-pregnane-3β,20-diyl 3-Acetate 20-Benzoate (**4**)

A solution of peracetic acid in acetic acid (21%, 40 ml, 110.5 mmol) was added to a mixture of (20*R*)-pregn-5-ene-3β,20-diyl 3-acetate 20-benzoate[13] (**3**, 26.0 g, 55.7 mmol) in chloroform (130 ml) and sodium hydrogenphosphate heptahydrate (14.0 g, 52.23 mmol). The mixture was stirred at room temperature for 5 h and then it was diluted with chloroform, washed with water and the potassium hydrogencarbonate solution and water. The solvent was evaporated, the residue was dissolved in a mixture of dioxane and acetone (2 : 1, 1 000 ml) and treated with aqueous perchloric acid (6%, 100 ml, 59.7 mmol) at room temperature. After 4 h, the solution was concentrated in vacuum to a quarter of its volume and compound **4** (24.8 g, 89%) precipitated on addition of brine (100 ml). An analytical sample crystallized from methanol at –60 °C; m.p. 123–126 °C, $[\alpha]_D$ –40 (*c* 0.9). IR: 3 621, 3 595, 3 464, 1 049, 963 (OH); 1 709 (C=O); 1 603, 1 451, 1 119 (arom.); 1 263, 1 254, 1 049 (C–O). ^{1}H NMR: 8.05 m, 2 H (H-2′ and H-6′); 7.60 t, 1 H (*J* = 7.2, H-4′); 7.49 t, 2 H (*J* = 7.3, H-3′ and H-5′); 5.14 m, 2 H (*W* = 44.0, H-3 and H-20); 3.54 s, 1 H (*W* = 16, H-6); 2.02 s, 3 H (CH_3CO); 1.26 d, 3 H (*J* = 6.1, H-21); 1.14 s, 3 H (3 × H-19); 0.68 s, 3 H (3 × H-18). For $C_{30}H_{42}O_6$ (498.7) calculated: 72.26% C, 8.49% H; found: 72.19% C, 8.54% H.

(20*R*)-3β-Acetoxy-20-benzoyloxy-5-oxo-5,6-secopregnan-6-oic Acid (**5**)

Jones reagent (2.4 ml, 2.63 mmol) was added to a stirred solution of diol **4** (1.0 g, 2.0 mmol) in acetone (30 ml) within 1 h at 50 °C. After additional 1 h at room temperature, the excess of the oxidizing agent was reduced by addition of methanol (6 ml) and the solvent was evaporated at 45 °C in vacuum. The dry residue was partitioned between ether and water, combined ethereal extracts were washed with water and passed through a column of anhydrous sodium sulfate and silica gel. Eluates were concentrated in vacuum to give 690 mg (67%) of noncrystalline acid **5**; $[\alpha]_D$ +63 (*c* 1.0). IR: 3 520 (COOH, monomer); 2 864, 2 633, 2 561 (COOH, dimer); 1 732, 1 264, 1 252 (AcO); 1 706 (C=O); 1 603, 1 451, 1 277, 964 (benzoate). ^{1}H NMR: 8.06 d, 2 H (*J* = 7.7, H-2′ and H-6′); 7.54 t, 1 H (*J* = 7.2, H-4′); 7.46 t, 2 H (*J* = 7.3, H-3′ and H-5′); 5.39 m, 1 H (*W* = 23.0, H-3); 5.15 m, 1 H (*W* = 36, H-20); 3.22 dd, 1 H (*J*(3α,4α) = 4.3, *J*(4α,4β) = 18.5, H-4α); 2.01 s, 3 H (CH_3CO); 1.26 d, 3 H (*J* = 6.1, 3 × H-21); 1.01 s, 3 H (3 × H-19); 0.70 s, 3 H (3 × H-18). For $C_{30}H_{40}O_7$ (512.6) calculated: 70.29% C, 7.86% H; found: 70.21% C, 7.80% H.

(20*R*)-3β-Acetoxy-20-benzoyloxy-7-nor-5β,6α-pregnane-6,5-carbolactone (**6**)

Oxo acid **5** (22.3 g, 43.5 mmol) was dried by azeotropic distillation with toluene, dissolved in pyridine (80 ml) and the solution was cooled to 0 °C. Benzoyl chloride (25 ml, 215.0 mmol) was added and the mixture was allowed to stand at room temperature. After 24 h, it

was poured onto ice (300 ml), the precipitate was extracted with ethyl acetate (3 × 150 ml) and washed with a cold solution of sodium hydroxide (0 °C, 2%) and water. The solvent was removed in vacuum and chromatography of the residue on silica gel (250 g, toluene) yielded the β-lactone **6** (19.4 g, 90%); $[\alpha]_D$ +10 (*c* 1.2). Circular dichroism: $\Delta\varepsilon_{227}$ +0.33, $\Delta\varepsilon_{243}$ –0.70 (methanol). IR: 1 819 (β-lactone); 1 726, 1 254, 1 038 (AcO); 1 709, 1 288, 1 275, 962, 714 (benzoate); 1 603, 1 315, 1 108, 1 027 (arom.). ^{1}H NMR: 8.05 m, 2 H (H-2′ and H-6′); 7.60 t, 1 H (*J* = 7.2, H-4′); 7.49 t, 2 H (*J* = 7.3, H-3′ and H-5′); 5.18 m, 1 H (*W* = 36, H-20); 5.00 m, 1 H (*W* = 35, H-3); 3.19 d, 1 H (*J*(6α,8β) = 13.7, H-7); 2.05 s, 3 H (CH_3CO); 1.28 d, 3 H (*J* = 6.2, 3 × H-21); 0.97 s, 3 H (3 × H-19); 0.70 s, 3 H (3 × H-18). For $C_{30}H_{38}O_6$ (494.6) calculated: 72.85% C, 7.74% H; found: 72.76% C, 7.73% H.

(20*R*)-7-Norpregn-5-ene-3β,20-diyl 3-Acetate 20-Benzoate (**7**)

A solution of compound **6** (18.4 g, 37.2 mmol) in toluene (200 ml) was heated at reflux temperature under nitrogen for 95 h and then the solvent was evaporated in vacuum. Chromatography of the residue on silica gel (250 g, toluene) gave 13.1 g (78%) of compound **7**; m.p. 117–118 °C (methanol), $[\alpha]_D$ –73 (*c* 1.1). IR: 3 072, 3 064, 3 028, 3 012 (C=C–H); 1 727, 1 602, 1 585, 1 279, 961 (benzoate); 1 708 (C=O); 1 252, 1 027 (acetate); 1 653 (C=C). ^{1}H NMR: 8.05 m, 2 H (H-2′ and H-6′); 7.60 t, 1 H (*J* = 7.2, H-4′); 7.49 t, 2 H (*J* = 7.3, H-3′ and H-5′); 5.40 bs, 1 H (*W* = 10.0, H-6); 5.18 m, 1 H (*W* = 36, H-20); 4.64 m, 1 H (*W* = 35, H-3); 2.63 ddd, 1 H (*J*(4α,4β) = 13.7, *J*(4α,3α) = 4.9, *J*(4α,6) = 1.8, H-4α); 2.04 s, 3 H (CH_3CO); 0.86 s, 3 H (3 × H-19); 0.64 s, 3 H (3 × H-18). MS, *m*/*z* (%): 450 (M^+, 0.2), 406 (0.6), 390 (15), 268 (65), 253 (19), 239 (11). For $C_{29}H_{38}O_4$ (450.6) calculated: 77.30% C, 8.50% H; found: 77.24% C, 8.47% H.

(20*R*)-7-Nor-5α-pregnane-3β,20-diyl 3-Acetate 20-Benzoate (**8**)

Method A. A mixture of alkene **7** (207 mg, 0.46 mmol) and tosylhydrazine (610 mg, 3.28 mmol) was heated in 2,4,6-trimethylpyridine (3.0 ml) at 150 °C. After 3 h, the solvent was evaporated, the residue was dissolved in ether and the ethereal solution was washed successively with the solution of hydrochloric acid, water and the solution of potassium carbonate and water. The solution was then dried with anhydrous sodium sulfate and the solvent was evaporated. Thin layer chromatography of the residue (4 PLC plates, benzene–ether 10 : 1) gave compound **8** (182 mg, 88%); m.p. 144–145 °C (methanol), $[\alpha]_D$ –37 (*c* 1.0). IR: 3 092, 3 072, 3 064, 1 603, 1 585, 1 451, 1 120 (arom.); 1 709, 1 285, 972 (benzoate); 1 709, 1 249, 1 042 (AcO). ^{1}H NMR: 8.04 m, 2 H (*W* = 16, H-2′ and H-6′); 7.79 m, 1 H (*W* = 20, H-4′); 7.44 m, 2 H (*W* = 20, H-3′ and H-5′); 5.15 m, 1 H (*W* = 36, H-20); 4.72 m, 1 H (*W* = 39, H-3); 2.02 s, 3 H (CH_3CO); 1.27 d, 3 H (*J* = 6.1, H-21); 0.70 s, 3 H (3 × H-19); 0.66 s, 3 H (3 × H-18). For $C_{29}H_{40}O_4$ (452.6) calculated: 76.95% C, 8.91% H; found: 76.70% C, 9.03% H.

Method B. Alkene **7** (3.09 g, 6.86 mmol) was treated with tosylhydrazine (9.7 g, 52.1 mmol) in 2,4,6-trimethylpyridine (50 ml) as above. The product was dissolved in dichloromethane (30 ml) and treated with 3-chloroperoxybenzoic acid (0.5 g, 2.9 mmol) at room temperature. After 3 h, the solution was washed with the potassium carbonate solution and water and concentrated in vacuum on a rotary evaporator. The solution was applied on a column of silica gel (100 g). A mixture of ligroin–toluene (2 : 1) eluted compound **8** (2.5 g, 81%) identical with the above described sample. Further fractions yielded (20*R*)-5,6α-epoxy-7-nor-5α-pregnane-3β,20-diyl 3-acetate 20-benzoate (**9**, 0.55 g, 17%); m.p. 204–206 °C

(methanol), $[\alpha]_D$ –52 (*c* 0.9). ^{1}H NMR: 8.04 m, 2 H (*W* = 16, H-2′ and H-6′); 7.55 m, 1 H (*W* = 20, H-4′); 7.44 m, 2 H (*W* = 20, H-3′ and H-5′); 5.15 m, 1 H (*W* = 36, H-20); 4.98 m, 1 H (*W* = 39, H-3); 3.27 s, 1 H (H-6); 2.03 s, 3 H (CH_3CO); 1.27 d, 3 H (*J* = 6.1, H-21); 0.86 s, 3 H (3 × H-19); 0.64 s, 3 H (3 × H-18). For $C_{29}H_{38}O_5$ (466.6) calculated: 74.65% C, 8.21% H; found: 74.59% C, 8.18% H.

(20*R*)-3β-Hydroxy-7-nor-5α-pregnan-20-yl Benzoate (**10**)

Hydrochloric acid (37%, 1.7 ml) was added to a solution of acetate **8** (1.73 g, 3.82 mmol) in chloroform (8.5 ml) and methanol (85.0 ml). After 18 h at room temperature, the solution was concentrated in vacuum to 25 ml and diluted with brine (100 ml). The precipitate was filtered off, washed with water and dried. Compound **10** (1.51 g, 96%) crystallized from methanol; m.p. 180–181 °C, $[\alpha]_D$ –51 (*c* 1.1). IR: 3 611, 1 048, 1 009 (OH); 1 706, 1 603, 1 451, 1 285, 1 273, 1 070 (benzoate). ^{1}H NMR: 8.05 m, 2 H (*W* = 16, H-2′ and H-6′); 7.73 m, 1 H (*W* = 20, H-4′); 7.44 m, 2 H (*W* = 20, H-3′ and H-5′); 5.14 m, 1 H (*W* = 36, H-20); 3.63 m, 1 H (*W* = 39, H-3); 1.27 d, 3 H (*J* = 6.1, H-21); 0.69 s, 3 H (3 × H-19); 0.66 s, 3 H (3 × H-18). For $C_{27}H_{38}O_3$ (410.6) calculated: 78.98% C, 9.33% H; found: 80.01% C, 9.26% H.

(20*R*)-3α-Hydroxy-7-nor-5α-pregnan-20-yl Benzoate (**11**)

Method A. A solution of tosylate **12** (1.68 g, 3.0 mmol) in DMF (50 ml) was added to a stirred suspension of sodium nitrite (16.8 g, 247.0 mmol) in hot DMF (130 °C, 130 ml). After 25 h, the solution was cooled and a product was precipitated with a saturated aqueous solution of ammonium carbonate (350 ml). A precipitate was filtered off, washed with water and purified by chromatography on a column of silica gel (50 g). Toluene eluted 835 mg (68%) of compound **11**; $[\alpha]_D$ –28 (*c* 1.1). IR: 3 615, 1 273, 994 (OH); 1 706, 1 603, 1 452, 1 315, 1 286, 1 120, 1 070, 714 (benzoate). ^{1}H NMR: 8.06 m, 2 H (*W* = 16, H-2′ and H-6′); 7.79 m, 1 H (*W* = 20, H-4′); 7.44 m, 2 H (*W* = 20, H-3′ and H-5′); 5.15 m, 1 H (*W* = 32, H-20); 4.10 m, 1 H (*W* = 16, H-3); 1.27 d, 3 H (*J* = 6.1, H-21); 0.66 s, 3 H (3 × H-19); 0.63 s, 3 H (3 × H-18). For $C_{27}H_{38}O_3$ (410.6) calculated: 78.98% C, 9.33% H; found: 78.90% C, 9.24% H.

Method B. Formate **13** (188 mg, 0.43 mol) was dissolved in boiling methanol (18 ml) and a solution of potassium hydrogencarbonate (100 mg, 100.0 mmol) in water (2 ml) was added. After 5 min, the solvent was evaporated in vacuum and the residue was diluted with water (20 ml). The precipitate formed was extracted with ether, the extract was washed with water and concentrated in vacuum. The product (139 mg, 79%) was identical with the sample prepared by the method *A*.

(20*R*)-7-Nor-5α-pregnane-3β,20-diyl 3-Tosylate 20-Benzoate (**12**)

4-Methylbenzenesulfonyl chloride (8.4 g, 44.1 mmol) was added to a cold (0 °C) solution of alcohol **10** (1.6 g, 3.9 mmol) in pyridine (15 ml). After 56 h standing at room temperature, the mixture was poured onto ice (50 g) and the precipitate was extracted with dichloromethane. The extract was washed with the solution of hydrochloric acid, water, potassium hydrogencarbonate, water and concentrated in vacuum. The oily product **12** (1.54 g, 70%) failed to crystallize from common solvents. IR: 1 706, 1 285, 1 273, 714 (benzoate); 1 354, 1 175, 931, 579, 557 (SO_3); 1 601, 1 452, 1 315, 1 188 (arom.). ^{1}H NMR: 8.04 m, 2 H (*W* = 16, H-2 and H-6, benzoate); 7.79 d, _ H (*J* = 8.4, H-2 and H-6, tosylate); 7.55 t, 1 H (*J* = 7.6, H-4, benzoate); 7.46 m, 2 H (*W* = 20, H-3 and H-5, benzoate); 7.32 d, 2 H (*J* = 8.4, H-3 and

H-5, tosylate); 5.13 m, 1 H (*W* = 36, H-20); 4.44 m, 1 H (*W* = 39, H-3); 2.45 s, 3 H ($C\mathbf{H}_3C_6H_4$); 1.26 d, 3 H (*J* = 6.1, H-21); 0.66 s, 3 H (3 × H-19); 0.63 s, 3 H (3 × H-18). For $C_{34}H_{44}O_5S$ (564.8) calculated: 72.31% C, 7.85% H, 5.68% S; found: 72.32% C, 7.99% H, 5.30% S.

(20*R*)-7-Nor-5α-pregnane-3α,20-diyl 20-Benzoate 3-Formate (**13**)

A solution of 3β-alcohol **10** (250 mg, 0.61 mmol) and triphenylphosphine (393 mg, 1.5 mmol) in toluene (20 ml) was heated until 10 ml of an azeotropic mixture was distilled off. The mixture was cooled in an ice bath and diethyl azodicarboxylate (261 mg, 1.5 mmol) was added under stirring. After 5 min, 3 drops of formic acid (98%, 66 mg, 1.43 mmol) were added. The ice bath was removed and the mixture was left aside for 3 h. The precipitate formed was filtered off and washed with toluene, the filtrate was concentrated in vacuum and applied onto a column of silica gel. Toluene eluted formate **13** (250 mg, 94%); m.p. 178–179 °C (acetone–heptane), $[\alpha]_D$ –16 (*c* 1.1). IR: 1 709, 1 452, 1 285, 1 273, 1 070, 714 (benzoate); 1 709, 1 206, 1 173 (formate). ^{1}H NMR: 8.06 m, 3 H (*W* = 16, overlapping signals of HCOO, H-2′ and H-6′); 7.79 m, 1 H (*W* = 20, H-4′); 7.44 m, 2 H (*W* = 20, H-3′ and H-5′); 5.23 m, 1 H (*W* = 15, H-3); 5.15 m, 1 H (*W* = 36, H-20); 1.27 d, 3 H (*J* = 6.1, H-21); 0.66 s, 6 H (3 × H-19 and 3 × H-18). For $C_{28}H_{38}O_4$ (438.6) calculated: 76.68% C, 8.73% H; found: 76.96% C, 8.93% H.

(20*R*)-3α-[(2-Methoxyethoxy)methoxy]-7-nor-5α-pregnan-20-yl Benzoate (**14**)

N,*N*-Diisopropylethylamine (1 ml, 5.74 mmol) and (2-methoxyethoxy)methyl chloride (0.4 ml, 3.50 mmol) were added to a solution of compound **11** (606 mg, 1.48 mmol) in dichloromethane (6 ml). After 3 h, the mixture was washed with a solution of citric acid (5%, 20 ml), water, the potassium hydrogencarbonate solution, and water. The solvent was concentrated in vacuum yielding compound **14** (748 mg, 96%); m.p. 80–82 °C (acetone–heptane), $[\alpha]_D$ –10 (*c* 1.1). IR: 2 824, 1 378, 1 176, 1 106, 1 043 (MEM); 1 705, 1 603, 1 585, 1 491, 1 452, 1 315, 1 285, 1 273, 1 120, 1 070, 1 027, 974, 714 (benzoate). ^{1}H NMR: 8.06 m, 2 H (*W* = 16, H-2′ and H-6′); 7.55 m, 1 H (*W* = 20, H-4′); 7.43 m, 2 H (*W* = 20, H-3′ and H-5′); 5.14 m, 1 H (*W* = 34, H-20); 4.74 s, 2 H (OCH_2O), 3.92 t, 1 H (*J* = 2.7, H-3); 3.70 m and 3.56 m, 4 H (*W* = 19.0, $O(CH_2)_2O$); 3.40 s, 3 H (OCH_3); 1.27 d, 3 H (*J* = 6.3, H-21); 0.65 s, 3 H (3 × H-19); 0.64 s, 3 H (3 × H-18). For $C_{31}H_{46}O_5 \cdot 0.5\ Me_2CO$ (527.8) calculated: 73.97% C, 9.36% H; found: 73.10% C, 9.52% H.

(20*R*)-3α-[(2-Methoxyethoxy)methoxy]-7-nor-5α-pregnan-20-ol (**15**)

Benzoate **14** (331 mg, 0.63 mmol) was refluxed in a 0.87 M solution of sodium methoxide in methanol (3.5 ml). After 8 h, the solvent was evaporated in vacuum, the residue was diluted with brine (20 ml) and the precipitate formed was extracted with methylene dichloride. The extract was washed with water and concentrated on a rotary evaporator. The residue (compound **15**, 248 mg, 95%) failed to crystallize from common solvents; $[\alpha]_D$ –22 (*c* 1.2). IR: 3 610, 3 472 (OH); 2 823, 1 458 (OCH_3); 1 184, 1 133, 1 099, 1 043 (C–O). ^{1}H NMR: 4.74 s, 2 H (OCH_2O); 3.92 m, 1 H (*W* = 12.8, H-3); 3.75 m, 1 H (*W* = 34, H-20); 3.70 m and 3.56 m (4 H, *W* = 19.0 and 19.0, $O(CH_2)_2O$); 3.40 s, 3 H (OCH_3); 1.14 d, 3 H (*J* = 6.3, H-21); 0.74 s, 3 H (3 × H-19); 0.68 s, 3 H (3 × H-18). For $C_{24}H_{42}O_4$ (394.6) calculated: 73.05% C, 10.73% H; found: 72.95% C, 10.78% H.

3α-[(2-Methoxyethoxy)methoxy]-7-nor-5α-pregnan-20-one (**16**)

A solution of 20-hydroxy derivative **15** (114 mg, 0.29 mmol) in acetone (2 ml) was treated with the Jones reagent (7 drops) at room temperature. After 5 min, methanol (1 ml) and then the potassium hydrogencarbonate solution (1 ml) were added before the solvent was evaporated. The residue was extracted with ether, the extract was washed with water and concentrated in vacuum. Product **16** (99 mg, 88%) crystallized from methanol at –60 °C; m.p. 31–33 °C, $[\alpha]_D$ +60 (*c* 1.1). IR: 2 823, 1 101, 1 043 (MEM); 1 697, 1 358 ($COCH_3$). ^{1}H NMR: 4.70 s, 2 H (OCH_2O); 3.93 t, 1 H (*J* = 2.6, H-3); 3.70 m and 3.57 m, 4 H (*W* = 17.0 and 17.0, $O(CH_2)_2O$); 3.40 s, 3 H (OCH_3); 2.13 s, 3 H (H-21); 0.68 s, 3 H (3 × H-19); 0.60 s, 3 H (3 × H-18). For $C_{24}H_{40}O_4$ (392.6) calculated: 73.43% C, 10.27% H; found: 73.36% C, 10.19% H.

3α-Hydroxy-7-nor-5α-pregnan-20-one (**2**)

A solution of compound **16** (90 mg, 0.23 mmol) in aqueous tetrahydrofuran (91%, 5 ml) was treated with hydrochloric acid (0.5 ml) at room temperature. After 24 h, the solution was diluted with toluene (10 ml) and concentrated in vacuum to one half of its volume. The mixture was partitioned between toluene and water, the organic layer was washed with water, the solvent was evaporated in vacuum and the residue crystallized from acetone–heptane (49 mg, 70%). PLC of mother liquor (1 plate, benzene–ether 3 : 1) afforded an additional crop (12 mg; the overall yield 87%); m.p. 148–149 °C, $[\alpha]_D$ +74 (*c* 0.7). IR: 3 616, 1 000, 984 (OH); 1 696, 1 358 ($COCH_3$). ^{1}H NMR: 4.11 m, 1 H (*W* = 17, H-3); 2.56 t, 1 H (*J* = 8.9, H-17); 2.13 s, 3 H (H-21); 0.67 s, 3 H (3 × H-19); 0.61 s, 3 H (3 × H-18). For $C_{20}H_{32}O_2$ (304.5) calculated: 78.90% C, 10.59% H; found: 78.86% C, 10.61% H.

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