Synthesis of 20-Hydroxy-, 20-Amino-, and 20-Nitro-14-hydroxy-21-nor-5β,14β-pregnane C-3 Glycosides and Related Derivatives: Structure-Activity Relationships of Pregnanes That Bind to the Digitalis Receptor

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The preparation of derivatives of 14-hydroxy-21-nor-5β,14β-pregnane and 5β,14β-pregnane C-3 α-L-rhamnosides and tris-β-D-digitoxosides is described. These derivatives, possessing a C-17β $COCH_2OH$, CH_2OH, CO_2H, CO_2Me, CH_2NH_2, or CH_2NO_2 group, bind to the digitalis receptor recognition site of heart muscle as measured in a radioligand binding assay. The 21-norpregnane derivatives consistently show greater binding affinity than the corresponding 20α- and 20β-pregnane analogs. The C-20 nitro rhamnoside is comparable to digitoxin in binding affinity. The 17β-CH_2NO_2 group is the most effective replacement for the unsaturated lactone in the binding assay found so far, showing binding affinity comparable to that of the cardiac glycosides.

Among the naturally occurring cardiac glycosides, the unsaturated γ- and δ-lactone rings are traditionally associated with strong receptor binding and positive inotropy.[1,2] However, strong receptor binding and positive inotropy can also occur on substitution of the lactone with other groups.[2-4] Certain pregnanes bind to the cardiac glycoside recognition site on Na^+,K^+-ATPase and inhibit the enzyme (the sodium pump) in membranes, cells, and tissues.[5] The most potent derivatives identified, thus far, are pregnane C-3 glycosides that are cardiotonic and exert certain potentially useful effects on heart and kidney not shared by the digitalis drugs.[6] Recently we have reported on the receptor binding of a number of 20α and 20β derivatives of 14-hydroxy-5β,14β-pregnane C-3 glycosides and their aglycones.[4] We report here on the synthesis and receptor binding of the corresponding 21-norpregnane C-3 α-L-rhamnoside and β-D-digitoxoside derivatives.

Chemistry

Digitoxigenin α-L-rhamnoside tribenzoate (1) (see Scheme I), prepared as in ref 4, on alkaline hydrolysis yielded evomonoside (digitoxigenin α-L-rhamnoside) (2). Ozonolysis of the rhamnoside 2 and reduction of the ozonide with zinc and acetic acid followed by mild hydrolysis of the intermediate C-21 ester with $KHCO_3$ gave the 21-hydroxymethyl ketone 3.[7] Similar treatment of the cardenolide tribenzoate 1 followed by lithium tri-*tert*-butoxyaluminum hydride (LTBAH) reduction of the hydroxymethyl ketone 4 gave the 20ξ,21-diols. Cleavage of the diols with $NaIO_4$ formed the aldehyde tribenzoate 5. Preparation of the 21-hydroxymethyl ketone 3 and the aldehyde 5 was carried out by methods reported for analogous compounds.[7,8] LTBAH reduction of 5 followed by alkaline hydrolysis of the benzoate esters gave the 20-alcohol 6. Treatment of 5 with hydroxylamine yielded the cis/trans oximes 7a, which on ester hydrolysis gave the oximes 7b. Catalytic reduction of 7b with PtO_2/H_2 in the presence of $CHCl_3$[9] gave the amine hydrochloride 8. Dimethyldioxirane oxidation of the amine salt[10] yielded the nitro derivative 9.

The hydroxymethyl ketone trisdigitoxoside 10 was prepared as described in ref 7 and used to synthesize the derivatives shown in Scheme II by analogous methods to those employed in Scheme I. Thus LTBAH reduction followed by oxidative cleavage gave the noncrystalline aldehyde 11. Formation of the oxime followed by reduction with dissolving sodium metal in *n*-PrOH,[11] with concomitant hydrolysis of the acetate esters, yielded the amine 12. Ozonolysis of the amine gave the nitro derivative 13. LTBAH treatment of the aldehyde 11 followed by triacetate hydrolysis gave the alcohol 16. The carboxylic acid 14 was obtained from $NaIO_4$ oxidation of the hydroxymethyl ketone 10, which on CH_2N_2 treatment yielded the methyl ester 15.

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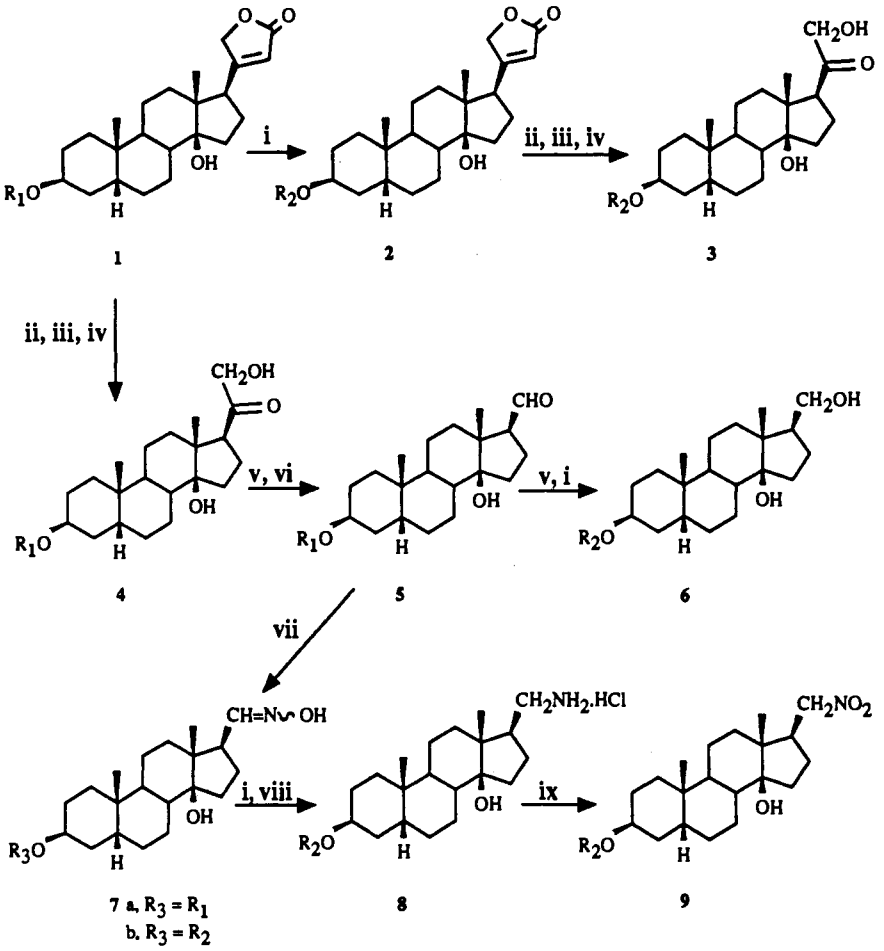
Scheme I[a]



[a] Reagents: i, NH_3/MeOH; ii, O_3/CH_2Cl_2; iii, Zn/HOAc; iv, $KHCO_3/H_2O$/MeOH; v, LTBAH; vi, $NaIO_4$/EtOH; vii, $HONH_2$·HCl/NaOAc/pyridine; viii, $PtO_2/H_2/CHCl_3$/MeOH; ix, dimethyldioxirane/Me_2CO.

Condensation of the aldehyde 5 with nitromethane in the presence of KF[12] gave the C-20 epimeric alcohols 17 (see Scheme III) which on acetylation and treatment with $NaBH_4$ followed by alkaline hydrolysis of the glycoside esters gave the 21-nitropregnane 18.

Structures for the 21-norpregnane derivatives were established from the ^1H and ^{13}C NMR spectra and are in agreement with published data.[3,4,13,14] Structures are consistent with the 17β and not the 17α stereochemistry.[15]

Results and Discussion

We have reported[4] on the synthesis and radioligand binding affinity of 20α and 20β hydroxy, amino, nitro, and related derivatives possessing at C-3 either an α-L-rhamnoside or β-D-digitoxoside.[4] The 20β derivatives proved to have greater binding affinity than the corresponding 20α derivatives in a radioligand binding assay (RBA).[4,16] Similarly the rhamnoside derivatives showed greater binding affinity than the digitoxosides.[4] Comparison of the RBA results (see Table I) for the 21-norpregnane derivatives with the corresponding pregnane analogs[4] showed that they had greater binding affinity than either the 20α or 20β derivatives. Assuming that the polar C-20 group is of major importance for receptor binding affinity the most stable rotamer around the C-17 to C-20 bond can determine the optimum receptor interaction. The 20-methyl group in the pregnanes either restricts rotation about the bond, thereby obstructing optimum interaction of the polar group with the receptor, and/or the 20-methyl group itself sterically hinders receptor binding. Our recent report[15] on the conformation of 20α, 20β, and 21-nor C-20 hydroxy, amino, and nitro pregnane derivatives shows that the polar substituents in 21-nor derivatives take up a conformation closer to that of the less potent 20α rather than the more potent 20β analogs. This inconsistency may result from a lower rotational energy in the 21-norpregnanes, compared with the pregnanes, allowing the C-17 group to take up the 20β orientation with little energy loss compared with the

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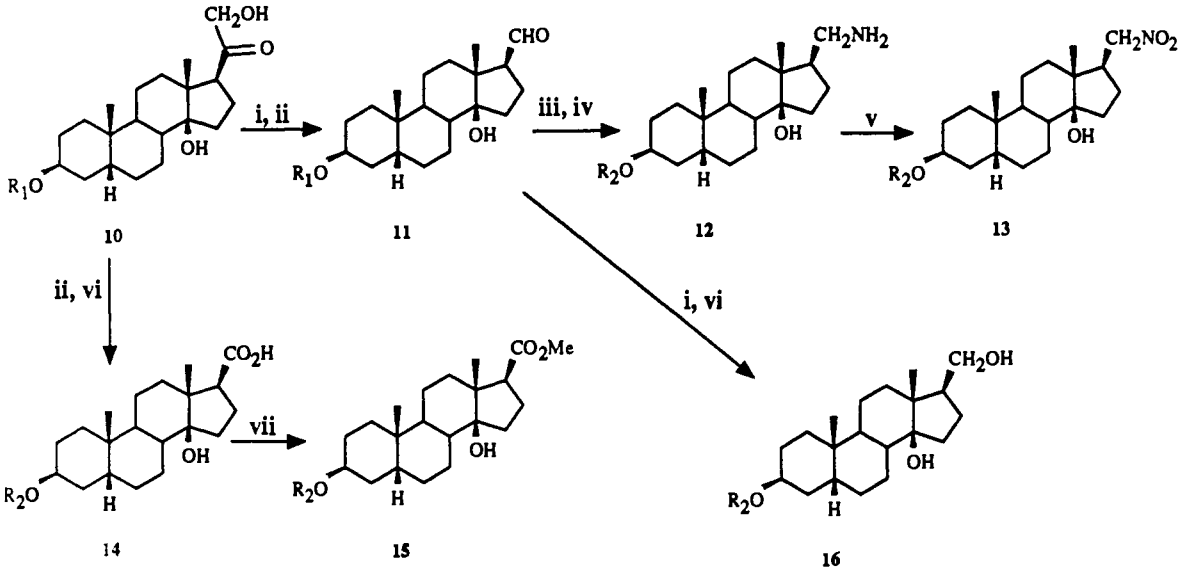
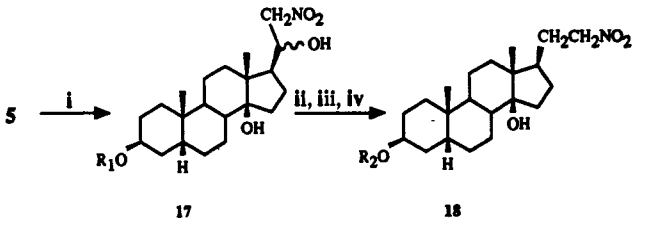
Scheme II[a]



R_1 = tris-β-D-digitoxoside tetraacetate R_2 = tris-β-D-digitoxoside

[a] Reagents: i, LTBAH; ii, $NaIO_4$/EtOH; iii, $HONH_2$·HCl/NaOAc/pyridine/EtOH; iv, Na/*n*-PrOH; v, O_3/CH_2Cl_2; vi, NaOH/MeOH; vii, CH_2N_2.

Scheme III[a]



R_1 = α-L-rhamnoside tribenzoate R_2 = α-L-rhamnoside

[a] Reagents: i, CH_3NO_2/KF/*i*-PrOH; ii, Ac_2O/pyridine/DMAP; iii, $NaBH_4$/EtOH; iv, NH_3/MeOH.

Table I. [^{3}H]Ouabain Radioligand Assay Potency of 14-Hydroxy-21-nor-5β,14β-pregnanes and -5β,14β-pregnanes[a,b]

no.	3β	17β	IC_{50}, nM[c]
3	α-L-rhamnoside	$COCH_2OH$	1070
6	α-L-rhamnoside	CH_2OH	360
8	α-L-rhamnoside	CH_2NH_2·HCl	99
9	α-L-rhamnoside	CH_2NO_2	12
12	β-D-digitoxoside	CH_2NH_2	270
13	β-D-digitoxoside	CH_2NO_2	88
14	β-D-digitoxoside	COOH	36000
15	β-D-digitoxoside	COOMe	15000
16	β-D-digitoxoside	CH_2OH	610
18	α-L-rhamnoside	$CH_2CH_2NO_2$	45

[a] IC_{50} represents the concentration that inhibits binding of [^{3}H]ouabain by 50%. [b] Digitoxigenin IC_{50} 8 nM. [c] Average of three to four values.

receptor binding energy in agreement with the Curtin–Hammett principle.[17]

Comparison of the binding affinity of the hydroxymethyl ketone **3** with the hydroxymethyl derivative **6** shows that the hydroxymethyl ketone is less important for binding than the hydroxymethyl group. The C-20 trisdigitoxoside carboxylic acid **14** and its methyl ester **15** were considerably less potent than the hydroxy, amino, and nitro derivatives. The 21-norpregnane hydroxy, amino, and nitro derivatives increase in potency in this order both in the rhamnoside and digitoxoside derivatives. Thus compound **9** > **8** > **6** and compound **13** > **12** > **16**. The nitro rhamnoside **9** (IC_{50} 12 nM) shows receptor binding potency comparable with that of digitoxin (IC_{50} 8 nM). The nitro group therefore is the most effective substitute discovered for the lactone ring of the cardiac glycoside as determined in the RBA. Extension of the C-17 side chain in the nitro derivative by one carbon unit to form the 21-nitropregnane **18** retained high potency (**18**, IC_{50} 45 nM).

Experimental Section

Reactions were monitored by TLC on silica gel (Merck type 60H) and plates developed in EtOAc/PE, acetone/PE, and ether/PE (genins) or 5–10% MeOH/CH_2Cl_2 (glycosides) and visualized by dipping in 5% sulfuric acid/EtOH followed by heating. PE refers to the hydrocarbon fraction bp 35–60 °C. Flash chromatography was carried out on silica gel (Merck type 60 for column chromatography). Elemental analyses for carbon and hydrogen are within ±0.3% of theoretical values. Melting points are uncorrected. RBA measurements were carried out as described in ref 16.

Evomonoside (2). Evomonoside tribenzoate (**1**) (1 g), prepared from digitoxigenin as described in ref 4, was treated with MeOH (50 mL) and 10% NH_3/MeOH (25 mL) at room temperature for 16 h. After evaporation the residue gave **2** (470 mg, 75%), mp 234–238 °C (lit.[18] mp 238–240 °C) from MeOH/water.

14,21-Dihydroxy-3β-(α-L-rhamnopyranosyloxy)-5β,14β-pregnan-20-one (3). Treatment of **2** (200 mg, 0.39 mmol) in MeOH (5 mL) and CH_2Cl_2 (15 mL) with ozone at −70 °C followed by Zn powder (2 g) and HOAc (2 mL) as described below for **4** gave a residue which was treated with MeOH (20 mL) and $KHCO_3$ (25 mg) in water (6 mL) under Ar for 14 h. Flash chromatographic separation gave on elution with 10% MeOH/CH_2Cl_2 compound **3** (70 mg, 37%), mp 197–201 °C. Anal. ($C_{27}H_{44}O_8$·0.5H_2O) C, H.

14,21-Dihydroxy-3β-[(tri-*O*-benzoyl-α-L-rhamnopyranosyl)oxy]-5β,14β-pregnan-20-one (4). Treatment of **1** (350 mg, 0.42 mmol) in CH_2Cl_2 (100 mL) with ozone at −70 °C for 1 h, when excess ozone was removed by a stream of Ar, and Zn powder (1.75 g) and HOAc (10 mL) were added and the mixture stirred for 2 h while the mixture came to room temperature. The mixture was filtered and the filtrate washed with water and saturated $NaHCO_3$. The residue from evaporation (TLC showed two components) was treated in MeOH (38 mL) with $KHCO_3$ (50 mg in 12 mL of water) and stirred for 14 h when HOAc (2 mL) was added. The residue from evaporation was flash chromato-

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graphed. Elution with 40% acetone/PE gave 4 (228 mg, 68%), mp 198–202 °C from MeOH/water. Anal. ($C_{48}H_{56}O_{11}$) C, H.

14-Hydroxy-3β-[(tri-*O*-benzoyl-α-L-rhamnopyranosyl)-oxy]-21-nor-5β,14β-pregnane-20-carboxaldehyde (5). Ketol 4 (150 mg, 0.185 mmol) in dry ether (20 mL) was stirred with LTBAH (188 mg, 0.74 mmol) under Ar for 1 h. Saturated $NaHCO_3$ (20 mL) was added and the mixture extracted with CH_2Cl_2. Evaporation of the solvent gave a crude product (130 mg, TLC showed one major component) which was dissolved in EtOH (10 mL) and treated with $NaIO_4$ (158 mg, 0.74 mmol) in water (1 mL) for 1 h. Water (50 mL) was added and the mixture extracted with CH_2Cl_2 to give a residue which was separated by flash chromatography on elution with 20% acetone/PE to give 5 (58 mg, 40%), mp 242–246 °C from acetone/PE. Anal. ($C_{47}H_{54}O_{10}\cdot1.5H_2O$) C, H.

14,20-Dihydroxy-3β-(α-L-rhamnosopyranosyloxy)-21-nor-5β,14β-pregnane (6). The aldehyde 5 (400 mg, 0.5 mmol) in anhydrous ether (40 mL) was treated with LTBAH (508 mg, 2.6 mmol) for 1 h. Saturated $NaHCO_3$ (40 mL) was added and the mixture extracted with CH_2Cl_2 to give on evaporation a residue which was dissolved in MeOH and treated with 10% NH_3/MeOH (15 mL) at 0 °C for 14 h. After evaporation the residue was flash chromatographed on silica gel to give 6 on elution with 10% MeOH/CH_2Cl_2 (40 mg, 17%), mp 155–157 °C from acetone/PE. Anal. ($C_{26}H_{44}O_7\cdot0.5H_2O$) C, H.

20-Amino-14-hydroxy-3β-(α-L-rhamnosopyranosyloxy)-21-nor-5β,14β-pregnane Hydrochloride (8). The aldehyde 5 (200 mg, 0.25 mmol), $HONH_2$·HCl (52 mg, 0.75 mmol), NaOAc·$3H_2O$ (50 mg, 0.37 mmol) and pyridine (1 mL) in EtOH (10 mL) was refluxed for 2 h, poured into icewater, and extracted with CH_2Cl_2. Evaporation gave the cis/trans oximes 7a [^{1}H NMR ($CHCl_3$) δ 7.51 (d, J = 9 Hz (cis)); 6.81 (d, J = 8 Hz (trans)); cis:trans (2:1)]. The cis/trans oximes, obtained as described above (300 mg, 0.61 mmol), were treated with MeOH (20 mL) and 10% NH_3/MeOH (10 mL) for 14 h to give on evaporation 7b. The oximes 7b (50 mg, 0.10 mmol) in MeOH (5 mL) containing $CHCl_3$ (0.3 mL) was hydrogenated at 1 atm with PtO_2 (25 mg) as catalyst for 16 h.[9] The mixture was filtered through a Celite pad and evaporated at room temperature. The residue was triturated with ether to give 8 (33 mg, 65%), mp 217–218 °C from MeOH-ether. Anal. ($C_{26}H_{46}O_6NCl\cdot0.5H_2O$) C, H, N, Cl.

20-Nitro-14-hydroxy-3β-(α-L-rhamnosopyranosyloxy)-21-nor-5β,14β-pregnane (9). To the amine·HCl 8 (60 mg, 0.12 mmol) in MeOH (1 mL) was added 0.1 M dimethyldioxirane in acetone (8 mL), prepared as reported by Adam et al.,[19] and the mixture was stirred for 30 min.[10] On evaporation the residue was flash chromatographed by elution with 50% acetone/PE to give 9 (42 mg, 71%), mp 265–268 °C from MeOH/PE. Anal. ($C_{26}H_{43}O_8N\cdot H_2O$) C, H, N.

20-Amino-14-hydroxy-3β-(tris-β-D-digitoxosyloxy)-21-nor-5β,14β-pregnane (12). To a stirred solution of 10 (600 mg, 0.81 mmol), prepared from digitoxin as described in ref 7, in tetrahydrofuran (100 mL) was added LTBAH (1.36 g, 5.35 mmol). After 15 min the mixture was concentrated, excess aqueous 10% NaOH added, and extracted with CH_2Cl_2 to give a residue which was dissolved in 95% EtOH (30 mL) and $NaIO_4$ (600 mg, 2.8 mmol, in 5 mL of water) added with stirring. After 1 h the mixture was concentrated, diluted with water, and extracted with CH_2Cl_2 to give after flash chromatography on silica gel on elution with 3% MeOH/CH_2Cl_2 the noncrystalline aldehyde 11: ^{1}H NMR ($CHCl_3$) δ 9.72 (d, J = 3.8 Hz (CHO)). The aldehyde 11 (300 mg, 0.43 mmol) in 95% EtOH (20 mL) containing $HONH_2$·HCl (600 mg) and NaOAc·$3H_2O$ (430 mg in 5 mL of water and 7.5 mL of pyridine) was refluxed for 2 h. Extraction with CH_2Cl_2 gave on evaporation the oximes which were dissolved in *n*-PrOH (20 mL) and Na metal (1.2 g) added in portions over 2.5 h to the refluxing solution. Extraction with CH_2Cl_2 gave the amine 12 (86 mg, 37%), mp 239–243 °C from ether/MeOH. Anal. ($C_{38}H_{65}NO_{11}$) C, H, N.

20-Nitro-14-hydroxy-3β-(tris-β-D-digitoxosyloxy)-21-nor-5β,14β-pregnane (13). A stream of ozone was passed through the amine 12 (142 mg, 0.20 mmol) in CH_2Cl_2 (50 mL) cooled in an solid CO_2 bath at −70 °C for 2.5 h. Excess ozone was removed in a stream of N_2 and the residue from evaporation flash chromatographed on silica gel. Elution with 3% MeOH/CH_2Cl_2 gave 13 (50 mg, 34%), mp 246–249 °C from ether. Anal. ($C_{38}H_{63}NO_{13}$) C, H.

14-Hydroxy-3β-(tris-β-D-digitoxosyloxy)-21-nor-5β,14β-pregnane-20-carboxylic Acid (14). To a stirred solution of 10 (515 mg, 0.70 mmol), prepared from digitoxin as described in ref 7, in 95% EtOH (20 mL) was added $NaIO_4$ (1.06 g, 5.0 mmol, in 8 mL of water). After 1 h the mixture was concentrated, diluted with water, and extracted with CH_2Cl_2 to give a product which was dissolved in 0.235 M methanolic NaOH (20 mL), refluxed for 1 h, cooled, neutralized with HOAc, and extracted with CH_2Cl_2 to give the acid 14 (228 mg, 55%), mp 235–237 °C from $CHCl_3$/acetone. Anal. ($C_{38}H_{62}O_{13}$) C, H.

14,20-Dihydroxy-3β-(tris-β-D-digitoxosyloxy)-21-nor-5β,14β-pregnane-20-carboxylic Acid Methyl Ester (15). To the acid 14 (183 mg, 0.25 mmol) in MeOH (20 mL) was added ethereal CH_2N_2 until a yellow color persisted followed by evaporation and recrystallization from $CHCl_3$/acetone to give the methyl ester 15 (153 mg, 82%), mp 254–257 °C. Anal. ($C_{39}H_{64}O_{13}$) C, H.

14,20-Dihydroxy-3β-(tris-β-D-digitoxosyloxy)-21-nor-5β,14β-pregnane (16). To 11 (140 mg, 0.20 mmol) in tetrahydrofuran (20 mL) was added LTBAH (318 mg, 1.25 mmol). After 15 min the solution was diluted with water and extracted with CH_2Cl_2 to give a residue which was dissolved in 0.1 M methanolic NaOH (20 mL) and refluxed for 1 h. CH_2Cl_2 extraction gave the alcohol 16 (65 mg, 46%), mp 247–249 °C from $CHCl_3$/acetone. Anal. ($C_{38}H_{64}O_{12}$) C, H.

14,20-Dihydroxy-21-nitro-3β-(α-L-rhamnopyranosyloxy)-5β,14β-pregnane (18). The aldehyde 5 (1.1 g, 1.3 mmol), nitromethane (400 mg, 6.4 mmol, freshly distilled), and KF (94 mg, 1.0 mmol) were stirred in dry 2-PrOH (20 mL) for 14 h.[11] After evaporation the residue was flash chromatographed on silica gel. Elution with 20% acetone/PE gave 17, as a noncrystalline fraction (460 mg). Compound 17 (250 mg, 0.30 mmol), acetic anhydride (1 mL), and 4-(dimethylamino)pyridine (DMAP) (10 mg) in dry ether (5 mL) was stirred for 14 h. Ether (50 mL) and excess aqueous $NaHCO_3$ was added to give on evaporation a residue which was dissolved in MeOH (4 mL), and $NaBH_4$ (80 mg) was added. After stirring for 1 h, water was added and the mixture extracted with CH_2Cl_2 to give a residue which was treated with MeOH (5 mL) and 10% NH_3/MeOH (5 mL) for 14 h. After evaporation of the solvent, the residue was flash chromatographed. Elution with 7.5% MeOH/CH_2Cl_2 gave the 21-nitro derivative 18 (32 mg, 21%), mp 227–229 °C from acetone/ether/PE. Anal. ($C_{27}H_{45}O_8N$) C, H, N.

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Supplementary Material Available: Tables containing ^{1}H and ^{13}C NMR spectral data (5 pages). Ordering information is given on any current masthead page.

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