Transformations of Glycyrrhizic Acid: The Synthesis of 3-*O*-[β-6′-Desoxy-6′-amino-D-glucopyranosyl (1→2)-β-6″-Amino-D-glucopyranosido]-(3β,20β)-11-oxo-20-methoxycarbonyl-18β-olean-12-en-3-ol

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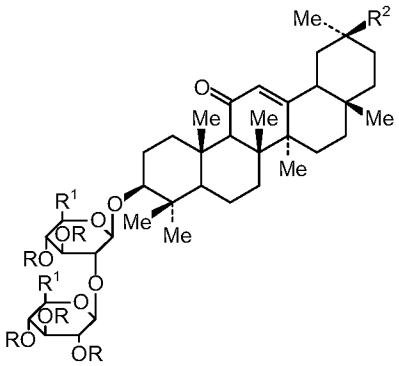
In order to prepare a new triterpene aminoglycoside containing 6-desoxy-6-amino-D-glucopyranosyl groups some transformations of glycyrrhizic acid trimethyl ester have been carried out.

Glycyrrhizic acid (GA), a triterpene glycoside which is the main ingredient of licorice roots (*Glycyrrhiza glabra L.*) and (*Glycyrrhiza uralensis F.*), has a wide range of biological activity (antiinflammatory, antiulcer, antiviral, *etc.*).[1–5]

To develop investigations into directed chemical transformations of GA[6–8] a scheme for the transformation of GA trimethyl ester **2** involving the introduction of NH_2 functions into the carbohydrate chain was used, resulting in the synthesis of the new triterpene 6-desoxy-6-amino-glycoside **7**.†



1 R = H R^1 = R^2 = COOH
2 R = H R^1 = R^2 = COOMe
3 R = H R^1 = CH_2OH R^2 = COOMe
4 R = Ac R^1 = CH_2OAc R^2 = COOMe
5 R = H R^1 = CH_2OMs R^2 = COOMe
6 R = H R^1 = CH_2N_3 R^2 = COOMe
7 R = H R^1 = CH_2NH_2 R^2 = COOMe
8 R = Ac R^1 = CH_2NHAc R^2 = COOMe

† *Experimental procedure. Synthesis of* **3** *and* **4**.

A solution of the trimethyl ester of GA **2** (2 g) in methanol (200 ml) and $NaBH_4$ (KBH_4) (4 g) in water (100 ml) was stirred at 20–22 °C for 8 h, then to the mixture were added glacial acetic acid (15 ml) and cold water (300 ml), and the whole was placed in a refrigerator overnight. The resulting precipitate was filtered, dissolved in ethanol (200 ml) and treated with a cation exchange resin CU-2-8(H^+). The solvent was evaporated *in vacuo*. Glycoside **3** was obtained (2.0 g) and recrystallized from aqueous methanol. The yield was 63.2%, m.p. 205–207 °C, $[\alpha]_D^{20}$ +55° (*c* 0.02, AcOH).

Glycoside **3** (0.2 g) was acetylated with an Ac_2O–pyridine mixture (1:1) (2 ml) at room temperature for 72 h. The yield was 79%, m.p. 148–150 °C; $[\alpha]_D^{20}$ +55° (*c* 0.02, MeOH).

Synthesis of **5**. A mixture of glycoside **3** (1 mmol), pyridine (15 ml) and methanesulfonyl chloride (3 mmol) was stirred at 0 °C for 1 h, stored at 20–22 °C for 5 h, diluted with cold water (50 ml) and extracted with chloroform (25 ml × 3). The organic phase was washed with a 5% HCl solution, water, a 5% $NaHCO_3$ solution and water, then dried ($MgSO_4$) and evaporated *in vacuo*. The resulting precipitate (0.73 g) was chromatographed on a silica gel column ($CHCl_3$–MeOH–H_2O, 100:10:1). The yield was 60%. $[\alpha]_D^{20}$ +58° (*c* 0.02, MeOH).

Synthesis of **6**. A mixture of di-*o*-mesylate (2.5 mmol) and NaN_3 (2.5 g) in DMF (50 ml) was stirred at 65–70 °C for 16 h and diluted with cold water (100 ml), then the resulting precipitate was separated and dried. As for **5**, chromatography on a silica gel column resulted in azide **6** (1.23 g). Yield 57.2%. $[\alpha]_D^{20}$ +40° (*c* 0.02, dioxane).

Reduction of the ester groups in the carbohydrate moiety of trimethyl ester **2** with $NaBH_4$ or KBH_4 in aqueous methanol[9] gave the β-D-glucopyranosyl (1→2)-β-D-glucopyranosyl-analogue of GA **3** in 60–62% yield; its structure was confirmed by IR, UV and ^1H and ^{13}C NMR spectroscopy. In the ^{13}C NMR spectrum of the glycoside, signals are displayed due to C=O and methyl in the methoxycarbonyl groups of aglycone (178.78 and 52.39 ppm). The C6′ and C6″ signals of atoms in the carbohydrate moiety of the GA molecule are shifted to high field (63.14 ppm, CH_2OH). Acetylation of glycoside **3** with an acetic anhydride–pyridine mixture (1:1) led to formation of the heptacetate **4** (79%), in the ^1H and ^{13}C NMR spectra of which signals due to seven MeCO groups in the range 1.99–2.15 and 169.21–170.22 ppm, respectively, are evident.

The regioselective mesylation of glycoside **3** with $MeSO_2Cl$ in pyridine at 0 °C gave bis(6′,6″-mesylate) **5**, which was isolated in homogeneous form by column chromatography on

Synthesis of **7** and **8**. A solution of azide **6** (1.2 mmol) in methanol (20 ml) was hydrogenated in the presence of 10% Pd/C for 72 h at room temperature. The solvent was eveporated *in vacuo*, and the resulting precipitate was reprecipitated from chloroform–hexane. Yield 70%. $[\alpha]_D^{20}$ +55° (*c* 0.02, MeOH).

Diamine **7** (0.5 g, 0.6 mmol) was acetylated in an analogous manner to **4**, yield 84.7%; m.p. 174–176 °C (decomp.) (aqueous EtOH). $[\alpha]_D^{20}$ +63° (*c* 0.1, MeOH).

Satisfactory elemental analysis data were obtained for all new compounds.

Spectral data for: **3** IR ν/cm^{-1}: 3600–3200 (OH); 1730 (COOMe); 1660 (C_{11}=O); UV λ_{max}/nm (lg ε) (EtOH) 248 (4.33). ^{13}C NMR (CD_3OD), δ, ppm: 178.78 (C30); 52.39 (C31); 105.34 (C1′); 81.22 (C2′); 78.50 (C3′); 71.94 (C4′); 77.89 (C5′); 63.14 (C6′); 104.53 (C1″); 76.31 (C2″); 78.50 (C3″); 71.54 (C4″); 78.24 (C5″); 63.14 (C6″).

4 IR ν/cm^{-1}: 1760 (OAc); 1670 (C_{11}=O). ^1H NMR ($CDCl_3$), δ, ppm: 0.65; 0.68; 1.03; 1.10; 1.12; 1.36 (21H; 7Me); 1.97; 1.99; 2.02; 2.04; 2.07 (7OAc); 5.63 (=C_{12}H), 3.67 (COOMe). ^{13}C NMR ($CDCl_3$), δ: 103.44 (C1′) ; 77.30 (C2′); 75.28 (C3′); 69.14 (C4′); 71.88 (C5′); 62.04 (C6′); 100.59 (C1″); 71.26 (C2″); 71.44 (C3″); 68.32 (C4″); 73.16 (C5″); 61.84 (C6″).

5 IR ν/cm^{-1}: 3600–3200 (OH); 1730 (COOMe); 1660 (C_{11}=O); 1180–1200 (SO_2). ^{13}C NMR ($CDCl_3$ + CD_3OD), δ: 106.29 (C1′); 79.80 (C2′); 75.56 (C3′); 72.93 (C4′); 77.55 (C5′); 70.81 (C6′); 40.80 (C7′); 105.05 (C1″); 74.92 (C2″); 76.37 (C3″); 70.95 (C4″) ; 78.13 (C5″); 70.56 (C6″); 40.80 (C7″).

6 IR ν/cm^{-1}: 3600–3200 (OH); 2120 (N_3); 1730 (COOMe); 1660 (C_{11}=O). UV λ_{max}/nm (lg ε) (MeOH): 245 (3.93). ^{13}C NMR (CD_3OD), δ: 105.11 (C1′); 82.89 (C2′); 76.54 (C3′); 72.35 (C4′); 79.49 (C5′); 52.50 (C6′); 104.98 (C1″); 75.87 (C2″); 77.60 (C3″); 71.90 (C4″); 78.17 (C5″); 52.39 (C6″).

7 IR ν/cm^{-1}: 3600–3200 (OH, NH_2); 1730 (COOMe); 1660 (C_{11}=O); UV λ_{max}/nm (lg ε) (MeOH): 248 (3.93). ^{13}C NMR (CD_3OD), δ: 104.96 (C1′); 81.36 (C2′); 76.16 (C3′); 72.64 (C4′) ; 78.13 (C5′); 52.43 (C6′); 103.55 (C1″); 75.91 (C2″); 77.66 (C3″); 71.53 (C4″); 78.12 (C5″); 52.43 (C6″).

8 IR ν/cm^{-1}: 1760 (OAc); 1670 (C_{11}=O); 1570 (NHAc). ^1H NMR ($CDCl_3$), δ: 0.65; 0.68; 1.03; 1.10; 1.12; 1.36 (s, 7Me, 21H); 1.97; 1.99; 2.02; 2.04; 2.07 (s, 7OAc); 2.31 (s, H-C9); 2.76 (d, *J* 13.2 Hz, H-C18); 3.08 (t, *J* 7.6 Hz, H_e-H-C1); 3.8 (dd, H-C2′); 4.02 (d, *J* 12 Hz, H-C5′, H-C5″); 4.25–5.3 (H-C1″, H-C3, H-C2″, H-C3′, H-C3″, H-C4′, H-C4″); 5.64 (s, H-C12).

silica gel in 60% yield. In the ^{13}C NMR spectrum of mesylate **5**, the signals of the C-6′ and C-6″ atoms are shifted to low field by ~7 ppm in comparison with the spectrum of the initial glycoside **3**. Additional resonance signals due to carbon atoms of the $MeSO_2$ groups appear at 40.80 ppm.

Nucleophilic substitution of mesylate **5** with NaN_3 in DMF at 65–70 °C yielded 57% bis-(6′,6″-desoxy-6′,6″-azide) **6** after chromatographic purification. In the IR spectrum of azide **6** an intense absorption maximum of N_3 groups is observed (2120 cm^{-1}). In the ^{13}C NMR spectrum the signals of the $MeSO_2$ groups disappear, and the signals of C6′- and C6″-atoms shift to high field by ~9 ppm in comparison with the spectrum of the initial glycoside **3**.

The reduction of bis(6-desoxy-6-azide) **6** with H_2 in methanol in the presence of 10% Pd/C led to the formation of bis(6-desoxy-6-amino)glycoside **7** (yield 70%), which then yielded the full acetate **8** (85%). The reduction of N_3 groups was determined by the disappearance of the absorption maximum (2120 cm^{-1}) in the IR spectrum of compound **6**. In the carbohydrate part of the ^{13}C NMR spectrum of 6-aminoglycoside **7** there are CH_2NH_2 group signals at 52.43 ppm. In the ^1H NMR spectrum of the full acetate **8** there are signals due to seven MeCO groups and in the IR spectrum an absorption maximum at 1570 cm^{-1} (NHAc) is exhibited.

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