Simplified stereoselective synthesis of triterpene 3-*O*-2-deoxy-α-D-glycosides

Oksana B. Flekhter,* Lidiya A. Baltina, Ekaterina V. Vasiljieva and Genrikh A. Tolstikov

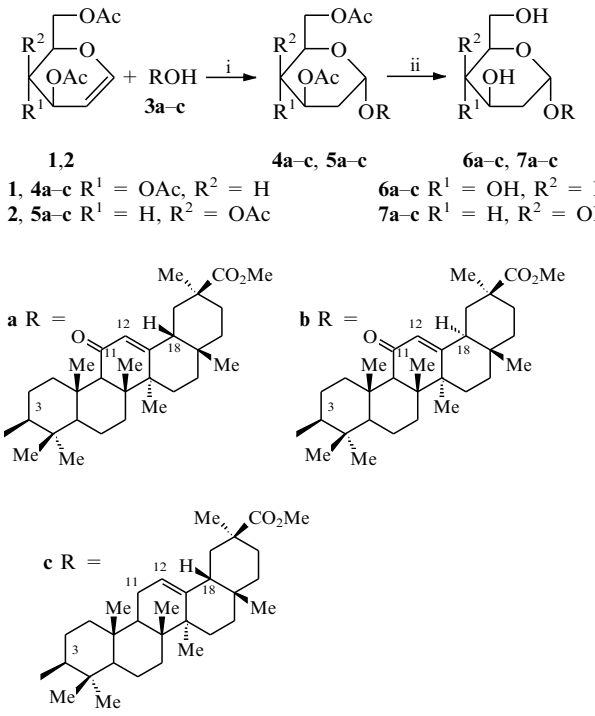
Institute of Organic Chemistry, Ufa Research Centre of the Russian Academy of Sciences, 450054 Ufa, Russian Federation. Fax: +7 3472 356 066; e-mail: root@chemorg.bashkiria.su

3-*O*-2-Deoxy-α-D-glycosides of glycyrrhetic acid derivatives are stereoselectively synthesized *via* electrophilic glycosylation of triterpene alcohols by D-glucal and D-galactal acetates in the presence of anhydrous sulfonic acid cation exchange resins and lithium bromide.

Triterpene glycosides are widely distributed in nature and are known for their diverse biological activity.[1] The synthesis of glycoside analogues from medicinal plants (ginseng, licorice *etc*.) has attracted a great deal of attention over the last few years and compounds of improved pharmacological properties were obtained.[2–4] Earlier[5,6] we carried out an enantiospecific synthesis of the oleanane type triterpene 3-*O*-2-deoxy-α-D-glycosides from biologically active triterpene alcohols and D-glucal acetate in the presence of iodine containing activators *N*-iodosuccinimide (NIS) and di(sym-collidine)iodonium perchlorate (IDCP). The shortcomings of this method are that it is multistage and that it gives unsatisfactory yields since the glycosylation of complex alcohols occurs *via* the formation of 2-deoxy-2-iodo-glycoside intermediates.

Here we report the direct syntheses of triterpene 3-*O*-2-deoxy-α-D-glycosides from triterpene alcohols and acylated glycals in the presence of anhydrous sulfonic acid cation exchange resins and lithium bromide *via* a simplified route without the need to obtain 2-deoxy-2-iodo-glycosides and hence to deiodinate them *via* catalytic hydrogenolysis. The complex biologically active triterpene 2-deoxy-α-D-glycosides were synthesised by the method used by Sabesan and Neira[7] to synthesise 2-deoxy-sugars. 3,4,6-Tri-*O*-acetyl-D-glucal **1** and D-galactal **2** were used as glycosyl donors and the biologically active triterpenoids of licorice root extract, 18β- and 18α-glycyrrhetic acids **3a** and **3b**, 11-deoxo analogue **3c** as methyl esters were used as the alcohol components. The glycosylation was carried out in methylene dichloride–acetonitrile (1 : 1, v/v) with an equimolecular mixture of glycals **1**,**2** and triterpene alcohols **3a**–**c** in the presence of cation exchange resins (KU-2-8, DOWEX-50) in the H^+-form with lithium bromide and anhydrous molecular sieves (4 A) at room temperature. Glycosides **4a**–**c**, **5a**–**c**† were formed after 2–3 h in a 76.9–79.8% yield after chromatographic purification. Deacetylation with a 5% methanolic solution of KOH led to the triterpene 3-*O*-2-deoxy-α-D-glycosides **6a**–**c**, **7a**–**c**‡ in 86.7–88.4% yields (Scheme 1).

The glycoside structures were assigned by ^{1}H and ^{13}C NMR spectroscopy (^{1}H and ^{13}C NMR spectra were obtained using a Bruker AM-300 spectrometer at 300 and 75.5 MHz) by comparison with literature data for aglycons[8–10] 2-deoxy-α-glycosides.[7,11,12] The chromatographic mobility and physicochemical properties of the newly synthesized compounds were



Scheme 1 *Reagents*: i, cation exchange resin, LiBr, CH_2Cl_2, MeCN; ii, 5% KOH/MeOH.

† *Selected data* for **4a**: $C_{43}H_{64}O_{11}$, decomp. 217–219 °C; $[\alpha]_D^{20}+87\pm3°$ (*c* 0.04, $CHCl_3$); UV (MeOH), λ_{max}/nm: 248.6 (lg ε 3.62); ^{13}C NMR ($CDCl_3$, δ, ppm): 21.8 (C2), 82.8 (C3), 200.3 (C11), 128.6 (C12), 169.3 (C13), 177.0 (C30), 51.9 (C31), 93.2 (C1′), 35.7 (C2′), 69.1 (C3′), 68.3 (C4′), 69.3 (C5′), 62.5 (C6′), 170.1, 170.3, 170.8 (O*C*OCH$_3$), 20.8, 20.9, 21.1 (OCO*C*H$_3$); ^{1}H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 0.80, 0.85, 1.01, 1.12, 1.14, 1.35 (s, 7CH$_3$), 1.20–1.95 (m, CH$_2$, CH of aglycone), 1.80–2.25 (m, 2H, H2′), 2.01, 2.03, 2.08 (s, 3Ac), 2.32 (s, 1H, H9), 2.82 (d, 1H, H18, *J* 13.8), 3.19 (dd, 1H, H3, $J_{3,2e}$ 4.7, $J_{3,2a}$ 11.7), 3.68 (s, 3H, OCH$_3$), 4.00–4.10 (m, 2H, H6′), 4.26 (dd, 1H, H5′, $J_{4',5'}$ 9.7, $J_{5',6'}$ 6.0), 4.99 (t, 1H, H4′, $J_{3',4'}=J_{4',5'}$ 9.7), 5.16 (br. s, 1H, H1′), 5.22–5.38 (m, 1H, H3′), 5.66 (s, 1H, H12).

For **4b**: $C_{43}H_{64}O_{11}$, decomp. 168–170 °C; $[\alpha]_D^{20}+98\pm3°$ (*c* 0.09, $CHCl_3$); UV (MeOH), λ_{max}/nm: 245.6 (lg ε 4.21); ^{13}C NMR ($CDCl_3$, δ, ppm): 21.8 (C2), 82.9 (C3), 199.7 (C11), 124.5 (C12), 165.7 (C13), 178.0 (C30), 51.9 (C31), 93.3 (C1′), 35.7 (C2′), 69.2 (C3′), 68.4 (C4′), 69.3 (C5′), 62.5 (C6′), 169.9, 170.2, 170.7 (O*C*OCH$_3$), 20.8, 20.9, 21.1 (OCO*C*H$_3$); ^{1}H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 0.71, 0.78, 0.84, 0.89, 0.96, 1.12, 1.20 (s, 7CH$_3$), 1.20–2.00 (m, CH$_2$, CH of aglycone), 1.60–2.00 (m, 2H, H2′), 2.01, 2.03, 2.08 (s, 3Ac), 2.15 (s, 1H, H9), 2.70 (d, 1H, H18, *J* 13.6), 3.14 (dd, 1H, H3, $J_{3,2e}$ 3.8, $J_{3,2a}$ 11.2), 3.69 (s, 3H, OCH$_3$), 4.03–4.12 (m, 2H, H6′), 4.22 (dd, 1H, H5′, $J_{4',5'}$ 9.7, $J_{5',6'}$ 6.1), 4.99 (t, 1H, H4′, $J_{3',4'}=J_{4',5'}$ 9.7), 5.16 (br. s, 1H, H1′), 5.20–5.28 (m, 1H, H3′), 5.57 (s, 1H, H12).

For **4c**: $C_{43}H_{66}O_{10}$, mp 223–225 °C; $[\alpha]_D^{20}+78\pm3°$ (*c* 0.04, $CHCl_3$); ^{13}C NMR ($CDCl_3$, δ, ppm): 21.9 (C2), 83.0 (C3), 23.5 (C11), 122.5 (C12), 144.5 (C13), 177.7 (C30), 51.5 (C31), 93.3 (C1′), 35.8 (C2′), 69.3 (C3′), 68.4 (C4′), 69.7 (C5′), 62.6 (C6′); 169.7, 169.9, 170.8 (O*C*OCH$_3$), 20.8, 20.9, 21.1 (OCO*C*H$_3$); ^{1}H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 0.71, 0.76, 0.88, 0.91, 0.94, 1.05, 1.40 (s, 7CH$_3$), 1.20–2.00 (m, CH$_2$,CH of aglycone), 1.60–2.15 (m, 2H, H2′), 1.94, 1.98, 2.02 (s, 3Ac), 3.12 (dd, 1H, H3, $J_{3,2e}$ 3.7, $J_{3,2a}$ 11.5), 3.68 (s, 3H, OCH$_3$), 3.98–4.06 (m, 2H, H6′), 4.21 (dd, 1H, H5′, $J_{4',5'}$ 9.8, $J_{5',6'}$ 6.1), 4.92 (t, 1H, H4′, $J_{3',4'}=J_{4',5'}$ 9.8), 5.12 (d, 1H, H1′, $J_{1',2'e}$ 1.4), 5.22–5.31 (m, 1H, H3′), 5.26 (br. s, 1H, H12).

For **5a**: $C_{43}H_{64}O_{11}$, decomp. 239–241 °C; $[\alpha]_D^{20}+80\pm3°$ (*c* 0.06, $CHCl_3$); UV (MeOH), λ_{max}/nm: 248.2 (lg ε 3.66); ^{13}C NMR ($CDCl_3$, δ, ppm): 21.8 (C2), 82.6 (C3), 200.3 (C11), 128.6 (C12), 169.4 (C13), 177.0 (C30), 51.8 (C31), 93.6 (C1′), 30.7 (C2′), 66.5 (C3′), 66.8 (C4′), 67.0 (C5′), 62.6 (C6′), 170.2, 170.4, 170.6 (O*C*OCH$_3$), 20.8, 20.9, 21.0

also compared with those of glycosides obtained earlier using NIS- and IDCP-methods.[5,6]

The reaction results in α-glycosides which seems bound by steric factors caused by bulk aglycons. β-Anomers were not observed by TLC and NMR. ^{13}C NMR spectra of the aglycone fragments of synthesized glycosides were similar to those of the initial triterpenes. In the ^{13}C NMR spectra of 2-deoxy-glycosides **4**–**7** signals due to carbinol atoms at C-3 were observed at 81.7–83.0 ppm. On going from alcohols **3a**–**c** to the glycosides **4a**–**c**, **5a**–**c** the C-3 signal is shifted to a lower field (3.9–4.7 ppm). The introduction of carbohydrate fragments in triterpenoid molecules also shifted the signals of the α-carbon atoms in aglycon.

The signals of the C-2 atoms of glycosides **4**–**7** were shifted to a higher field (5.1–5.7 ppm). The anomeric carbon atoms at C-1′ of the pyranose residues in the spectra of compounds **4**–**7** resonate at 93.2–93.6 ppm, which provides evidence for the formation of α-glycoside linkages and the axial position of aglycons.[13,14] The α-configuration of glycoside linkages and the diequatorial location of H-1′and H-2′ protons in glycoside molecules **4a**–**c**, **5a**–**c** were confirmed by the presence of a doublet of anomeric protons (H-1′) at a low field (5.12–5.18 ppm) with a small spin–spin coupling constant (SSCC) ($J_{1',2'}$ 1.3 Hz **4b**, 1.4 Hz **4c** and 1.2 Hz **5b**) or by broad singlets for **4a**, **5a**,**c**. Protons H-2′ of glycosides **4a**–**c**, **5a**–**c** resonate at 1.60–2.30 ppm. SSCC values for compounds **4a**–**c** [$J_{3',4'} = J_{4',5'}$ 9.7 (9.8), $J_{5',6'}$ 6.0 (6.1) Hz] demonstrate the axial position of protons H-3′, H-4′ and H-5′. The chemical shifts of protons H-1′–H-6′ and their mutual location in glycosides **4a**–**c** confirm the α-D-arabinohexopyranose configuration and $^4C_1$ (D)-conformation for the carbohydrate rings of these compounds.

The chemical shifts of the protons and their SSCC values [$J_{4',5'} = J_{5',6'}$ 6.2 (6.3) Hz] in the ^{1}H NMR spectra of **5a**–**c** (protons H-4′–H-5′ are equatorial–axial) confirm the α-D-lixo-hexopyranose configuration and $^4C_1$ (D)-conformation of these compounds.

The work was carried out with financial support from the Russian Foundation for Basic Research (project no. 96-03-33240).

References

1 Th. Schopke and K. Hiller, *Pharmazie*, 1990, **45**, 313.
2 L. N. Atopkina, N. F. Samoshina and N. I. Uvarova, *Khim. Prir. Soedin.*, 1989, **6**, 813 [*Chem. Nat. Compd.* (*Engl. Transl.*), 1989, **6**, 690].
3 S. Saito, K. Kuroda, Y. Hayashi, Y. Sasaki, Y. Nagamera, K. Nishida and I. Ishiguro, *Chem. Pharm. Bull.*, 1991, **39**, 2333.
4 S. Saito, S. Sumita, Y. Kanda and Y. Sasaki, *Chem. Pharm. Bull.*, 1994, **42**, 1016.
5 L. A. Baltina, O. B. Flekhter, E. V. Vasil'eva and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 1061 (*Russ. Chem. Bull.*, 1995, **44**, 1979).
6 L. A. Baltina, O. B. Flekhter and E. V. Vasiljieva, *Mendeleev Commun.*, 1996, 63.
7 S. Sabesan and S. Neira, *J. Org. Chem.*, 1991, **56**, 5468.
8 G. A. Tolstikov, L. M. Khalilov, L. A. Baltina, R. M. Kondratenko, A. A. Panasenko and E. V. Vasiljeva, *Khim. Prir. Soedin.*, 1985, **5**, 645 [*Chem. Nat. Compd.* (*Engl. Transl.*), 1985, **5**, 605].
9 H. Duddeck, M. H. A. Elgamal, G. S. Ricca, B. Danieli and G. Palmisano, *Org. Magn. Reson.*, 1978, **11**, 130.
10 G. S. Ricca, B. Danieli and G. Palmisano, *Org. Magn. Reson.*, 1978, **11**, 163.
11 R. W. Friesen and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1989, **111**, 6656.
12 J. Tiem, S. Kopper and J. Schwenther, *Liebigs Ann. Chem.*, 1985, 2135.
13 S. Saito, Sh. Sumita, Y. Kanda and Y. Sasaki, *Chem. Pharm. Bull.*, 1994, **42**, 1016.
14 K. Tori, S. Seo, Y. Yoshimura, H. Arita and Y. Tomita, *Tetrahedron Lett.*, 1977, **2**, 179.

Received: Moscow, 7th June 1996
Cambridge, 19th July 1996; Com. 6/04069A

(OCO*C*H$_3$); ^{1}H NMR (CDCl$_3$, δ, ppm, *J*/Hz): 0.80, 0.82, 1.01, 1.13, 1.16, 1.35 (s, 7CH$_3$), 1.25–1.95 (m, CH$_2$, CH of aglycone), 1.70–2.30 (m, 2H, H2′), 1.99, 2.04, 2.14 (s, 3Ac), 2.31 (s, 1H, H9), 2.83 (d, 1H, H18, *J* 13.6), 3.20 (dd, 1H, H3, $J_{3,2e}$ 4.5, $J_{3,2a}$ 11.3), 3.69 (s, 3H, OCH$_3$), 4.07–4.12 (m, 2H, H6′), 4.27 (t, 1H, H5′, $J_{4',5'} = J_{5',6'}$ 6.3), 5.17 (br. s, 1H, H1′), 5.22–5.33 (m, 1H, H3′), 5.36 (br. s, 1H, H4′), 5.66 (s, 1H, H12).

For **5b**: $C_{43}H_{64}O_{11}$, decomp. 185–187 °C; $[\alpha]_D^{20} + 125 \pm 4°$ (*c* 0.06, CHCl$_3$); UV (MeOH), λ_{max}/nm: 246.4 (lg ε 4.23); ^{13}C NMR (CDCl$_3$, δ, ppm): 22.0 (C2), 82.8 (C3), 200.0 (C11), 124.2 (C12), 166.0 (C13), 178.9 (C30), 51.9 (C31), 93.5 (C1′), 30.9 (C2′), 66.6 (C3′), 66.9 (C4′), 67.1 (C5′), 62.4 (C6′), 169.9, 170.2, 170.3 (O*C*OCH$_3$), 20.8, 20.9, 21.1 (OCO*C*H$_3$); ^{1}H NMR (CDCl$_3$, δ, ppm, *J*/Hz): 0.70, 0.87, 0.96, 1.12, 1.19, 1.36 (s, 7CH$_3$), 1.15–2.00 (m, CH$_2$, CH of aglycone), 1.60–2.00 (m, 2H, H2′), 1.98, 2.05, 2.11 (s, 3Ac), 2.21 (s, 1H, H9), 2.69 (d, 1H, H18, *J* 13.7), 3.17 (dd, 1H, H3, $J_{3,2e}$ 4.0, $J_{3,2a}$ 11.3), 3.69 (s, 3H, OCH$_3$), 4.07–4.11 (m, 2H, H6′), 4.28 (t, 1H, H5′, $J_{4',5'} = J_{5',6'}$ 6.2), 5.18 (d, 1H, H1′, $J_{1',2'e}$ 1.2), 5.22–5.30 (m, 1H, H3′), 5.35 (br. s, 1H, H4′), 5.57 (s, 1H, H12).

For **5c**: $C_{43}H_{66}O_{10}$, mp 200–202 °C; $[\alpha]_D^{20} + 79 \pm 3°$ (*c* 0.05, CHCl$_3$); ^{13}C NMR (CDCl$_3$, δ, ppm): 21.8 (C2), 82.9 (C3), 23.5 (C11), 122.5 (C12), 144.4 (C13), 177.7 (C30), 51.6 (C31), 93.2 (C1′), 30.8 (C2′), 66.5 (C3′), 66.9 (C4′), 67.0 (C5′), 62.5 (C6′), 169.8, 170.2, 170.8 (O*C*OCH$_3$), 20.8, 20.9, 21.1 (OCO*C*H$_3$); ^{1}H NMR (CDCl$_3$, δ, ppm, *J*/Hz): 0.77, 0.81, 0.89, 0.95, 0.96, 1.00, 1.12 (s, 7CH$_3$), 1.15–2.00 (m, CH$_2$, CH of aglycone), 1.60–2.00 (m, 2H, H2′), 1.99, 2.05, 2.17 (s, 3Ac), 3.20 (dd, 1H, H3, $J_{3,2e}$ 4.0 Hz, $J_{3,2a}$ 11.0), 3.68 (s, 3H, OCH$_3$), 4.02–4.15 (m, 2H, H6′), 4.28 (t, 1H, H5′, $J_{4',5'} = J_{5',6'}$ 6.3), 5.18 (br. s, 1H, H1′), 5.21–5.30 (m, 1H, H3′), 5.27 (br. s, 1H, H12), 5.35 (br. s, 1H, H4′).

‡For **6a**: 3-*O*-2-deoxy-α-D-arabinohexopyranoside of 18β-glycyrrhetic acid methyl ester, decomp. 211 °C; $[\alpha]_D^{20} + 97 \pm 3°$ (*c* 0.08, CHCl$_3$); lit.[5,6]: decomp. 210–212 °C; $[\alpha]_D^{20} + 95°$ (*c* 0.02, CHCl$_3$).

For **6b**: 3-*O*-2-deoxy-α-D-arabinohexopyranoside of 18α-glycyrrhetic acid methyl ester, $C_{37}H_{58}O_8$, decomp. 140–142 °C; $[\alpha]_D^{20} + 113 \pm 4°$ (*c* 0.09, CHCl$_3$); UV (MeOH), λ_{max}/nm: 245.8 (lg ε 4.27); ^{13}C NMR (CDCl$_3$, δ, ppm): 21.8 (C2), 81.9 (C3), 199.9 (C11), 124.3 (C12), 165.9 (C13), 178.9 (C30), 52.0 (C31), 93.5 (C1′), 38.9 (C2′), 72.0 (C3′), 69.5 (C4′), 73.3 (C5′), 62.8 (C6′).

For **6c**: 3-*O*-2-deoxy-α-D-arabinohexopyranoside of 11-deoxo-18β-glycyrrhetic acid methyl ester, decomp. 213–215 °C; $[\alpha]_D^{20} + 84 \pm 3°$ (*c* 0.07, CHCl$_3$); lit.[5,6]: decomp. 214–216 °C; $[\alpha]_D^{20} + 83°$ (*c* 0.05, CHCl$_3$).

For **7a**: 3-*O*-2-deoxy-α-D-lyxo-hexopyranoside of 18β-glycyrrhetic acid methyl ester $C_{37}H_{58}O_8$, decomp. 226–228 °C; $[\alpha]_D^{20} + 88 \pm 3°$(*c* 0.05, CHCl$_3$); UV (MeOH), λ_{max}/nm: 248.2 (lg ε 3.89); ^{13}C NMR (CDCl$_3$, δ, ppm): 21.7 (C2), 81.8 (C3), 200.4 (C11), 128.6 (C12), 169.4 (C13), 177.0 (C30), 51.8 (C31), 93.6 (C1′), 33.3 (C2′), 65.9 (C3′), 69.6 (C4′), 70.2 (C5′), 64.3 (C6′).

For **7b**: 3-*O*-2-deoxy-α-D-lyxohexopyranoside of 18α-glycyrrhetic acid methyl ester, $C_{37}H_{58}O_8$, decomp. 163–166 °C; $[\alpha]_D^{20} + 108 \pm 4°$ (*c* 0.06, CHCl$_3$); UV (MeOH), λ_{max}/nm: 246.2 (lg ε 4.20); ^{13}C NMR (CDCl$_3$, δ, ppm): 21.7 (C2), 81.8 (C3), 199.3 (C11), 124.1 (C12), 165.9 (C13), 178.9 (C30), 51.9 (C31), 93.5 (C1′), 33.5 (C2′), 65.8 (C3′), 69.7 (C4′), 70.00 (C5′), 64.0 (C6′).

For **7c**: 3-*O*-2-deoxy-α-D-lyxohexopyranoside of 11-deoxo-18β-glycyrrhetic acid methyl ester, $C_{37}H_{60}O_7$, mp 189–191 °C; $[\alpha]_D^{20} + 82 \pm 3°$ (*c* 0.06, CHCl$_3$); ^{13}C NMR (CDCl$_3$, δ, ppm): 21.8 (C2), 81.9 (C3), 23.6 (C11), 122.6 (C12), 144.5 (C13), 177.8 (C30), 51.7 (C31), 93.5 (C1′), 33.6 (C2′), 66.7 (C3′), 69.5 (C4′), 70.2 (C5′), 64.9 (C6′).