Stereoselective synthesis of triterpene 3-*O*-2-deoxy-α-glycosides

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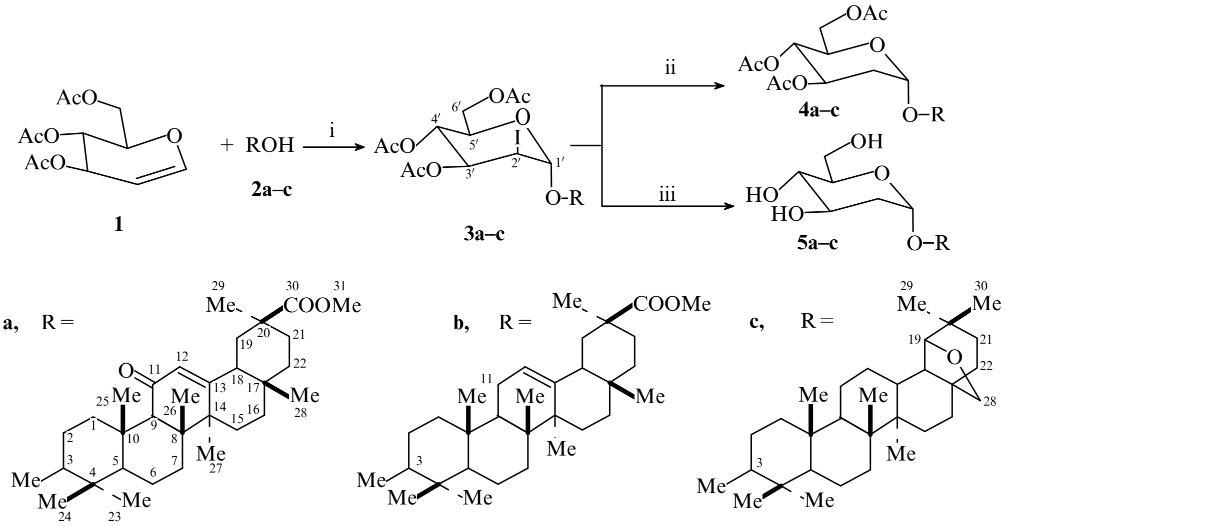
A synthesis of 3-*O*-2-deoxy-α-glycosides of glycyrrhetic acid and allobetulin was carried out by electrophilic glycosylation of triterpene alcohols with D-glucal acetate in the presence of (*sym*-collidin)$_2$IClO$_4$.

A great number plants, of various species, and sea invertebrates contain triterpene glycosides (TG). Natural TGs are known by their high and diverse level of biological activity.[1] A synthesis of TG modelling different natural analogs (*ginseng* and *Glycyrrhizae glabra* glycosides)[2–4] has attracted a great deal of attention over the last few years. An electrophilic glycosylation of alcohols with readily available glycals is a worthwhile method of preparing glycosides.[5–8] 2-Deoxyglycosides are structural units of many major biologically active materials (antibiotics, deoxyribonucleotides, heart glycosides, *etc*.). A synthesis of triterpene 2-deoxyglycosides has not previously been described in the literature.

We have carried out a synthesis of the oleanane-type 3-*O*-2-deoxy-α-glycosides **5a–c** *via* electrophilic glycosylation of triterpene alcohols with D-glucal acetate[9] **1** in the presence of iodonium di(*sym*-collidin) perchlorate[6] (Scheme 1). 18β-Glycyrrhetic acid[10] being one of the main biologically active triterpenoids of licorice roots (*Glycyrrhizae glabra L.* and *G. uralensis F.*), its 11-deoxo-analog, as methyl esters **2a,b**, and allobetulin[11] **2c** from the triterpene fraction of bark (*Betula pendula*) were used as the alcohol components in the synthesis reported here.

The reaction of triterpenoids **2a–c** with glycal **1** proceeds stereoselectively in methylene dichloride at room temperature. A mole ratio of reagents were used in the presence of 4A molecular sieves and (*sym*-collidin)$_2$IClO$_4$ for 4–5 h to give 2-deoxy-2-iodo-α-D-manno-glycosides **3a–c** in 70–80% yield, which were separated by column chromatography on silica gel. Hydride deiodination of the protected 2-iodo-α-glycosides **3a–c** in the presence of 10% Pd/C in ethyl acetate[8] and deacetylation by 5% KOH in methanol[12] led to the triterpene-free 3-*O*-2-deoxy-α-D-arabino-hexopyranosides **5a–c** in yields of 75–80%. Elemental analyses and theoretical computations for all the product compounds are in a good agreement with the proposed structures. The glycoside structure was assigned by ^{1}H and ^{13}C NMR spectroscopy. Signal determination in the spectra of freshly prepared glycosides was carried out on the basis of literature data for 2-deoxy-α-glycosides[8] and *via* a comparison with the spectra of initial compounds. ^{13}C NMR spectra of aglycone fragments of glycosides **3–5** are similar to those for initial triterpenes.[13–15] In the ^{13}C NMR spectra of glycosides **3a–c**[†] signals due to carbinol atoms at C3 were observed at 84.3–84.7 ppm. On going from genins **2a–c** to glycosides **3a–c** the C3 signal was shifted to a lower field (5.3–6.7 ppm). Signals of hydrocarbon atoms at C2′ in the



Scheme 1 *Reagents and conditions:* i, (*sym*-collidin)$_2$IClO$_4$, CH$_2$Cl$_2$, 4A molecular seives; ii, 10% Pd/C, ethyl acetate; iii, 5% KOH–MeOH.

† **3a**: C$_{43}$H$_{63}$O$_{11}$I M_r = 882.9, amorph; $[\alpha]_D^{20}$ +82° (*c* 0.03, CHCl$_3$); UV (MeOH), λ_{max}/nm: 248.2 (lg *e* 3.59); ^{13}C NMR: (CDCl$_3$, δ, ppm): 22.4 (C2), 84.6 (C3), 200.5 (C11), 128.5 (C12), 169.5 (C13), 177.1 (C30), 51.9 (C31), 98.5 (C1′), 30.9 (C2′), 69.3 (C3′), 67.9 (C4′), 69.7 (C5′), 62.4 (C6′); ^{1}H NMR (CDCl$_3$, δ, ppm): 0.73, 0.79, 0.94, 1.05, 1.07, 1.22 (s, 7CH$_3$), 1.10–1.97 (m, CH$_2$, CH), 1.99, 2.02, 2.03 (s, 3Ac), 2.25 (s, 1H, H9), 2.77 (d, 1H, H18, *J* = 13.7 Hz), 3.15 (dd, 1H, H3, $J_{3,2e}$ = 4.6 Hz, $J_{3,2a}$ = 11.1 Hz), 3.64 (s, 3H, OCH$_3$), 4.00–4.12 (m, 1H, H5′, 2H, H6′), 4.41 (dd, 1H, H2′, $J_{2',1'}$ = 1.1, $J_{2',3'}$ = 4.2 Hz), 4.56 (dd, 1H, H3′, $J_{3',2'}$ = 4.2, $J_{3',4'}$ = 9.5 Hz), 5.23 (d, 1H, H1′, $J_{1',2'}$ = 1.1 Hz), 5.29 (t, 1H, H4′, $J_{4',3'}$ = $J_{4',5'}$ = 9.5 Hz), 5.59 (s, 1H, H12).

3b: C$_{43}$H$_{65}$O$_{10}$I M_r = 868.9, amorph; $[\alpha]_D^{20}$ +75° (*c* 0.02, CHCl$_3$); ^{13}C NMR (CDCl$_3$, δ, ppm): 22.3 (C2), 84.7 (C3), 29.7 (C11), 122.4 (C12), 144.4 (C13), 177.8 (C30), 51.7 (C31), 98.4 (C1′), 31.0 (C2′), 69.3 (C3′), 67.7 (C4′), 69.6 (C5′), 62.3 (C6′); ^{1}H NMR (CDCl$_3$, δ, ppm): 0.75, 0.82, 0.94, 1.10 (s, 7CH$_3$), 1.10–2.00 (m, CH$_2$, CH), 2.05, 2.06, 2.09 (s, 3Ac), 3.20 (dd, 1H, H3, $J_{3,2e}$ = 4.6 Hz, $J_{3,2a}$ = 11.1 Hz), 3.63 (s, 3H, OCH$_3$), 4.15–4.25 (m, 1H, H5′, 2H, H6′), 4.47 (dd, 1H, H2′, $J_{2',1'}$ = 1.0 Hz, $J_{2',3'}$ = 4.1 Hz), 4.61 (dd, 1H, H3′, $J_{3',2'}$ = 4.1 Hz, $J_{3',4'}$ = 9.4 Hz), 5.25 (s, 1H, H12), 5.31 (d, 1H, H1′, $J_{1',2'}$ = 1.0 Hz), 5.37 (t, 1H, H4′, $J_{4',3'}$ = $J_{4',5'}$ = 9.5 Hz).

3c: C$_{42}$H$_{65}$O$_9$I M_r = 840.9, amorph; $[\alpha]_D^{20}$ +54° (*c* 0.04, CHCl$_3$); ^{13}C NMR (CDCl$_3$, δ, ppm): 22.4 (C2), 84.3 (C3), 26.2 (C12), 87.8 (C19), 71.2 (C28), 28.8 (C30), 98.3 (C1′), 31.0 (C2′), 69.2 (C3′), 67.6 (C4′), 69.5 (C5′), 62.3 (C6′); ^{1}H NMR (CDCl$_3$, δ, ppm): 0.79, 0.82, 0.86, 0.92, 0.98, 1.01 (s, 7CH$_3$), 1.00–2.00 (m, CH$_2$, CH), 2.03, 2.05, 2.07 (s, 3Ac), 3.18–3.23 (br. signal, 1H, H3), 3.42 (d, 1H, H28, *J* = 7.9 Hz), 3.50 (s, 1H, H19), 3.76 (d, 1H, H28, *J* = 7.9 Hz), 4.17–4.28 (m, 1H, H5′, 2H, H6′), 4.47 (dd, 1H, H2′, $J_{2',1'}$ = 1.0 Hz, $J_{2',3'}$ = 3.9 Hz), 4.62 (dd, 1H, H3′, $J_{3',2'}$ = 3.9 Hz, $J_{3',4'}$ = 9.3 Hz), 5.30 (d, 1H, H1′, $J_{1',2'}$ = 1.0 Hz), 5.35 (t, 1H, H4′, $J_{4',3'}$ = $J_{4',5'}$ = 9.3 Hz).

spectra of 2-iodoglycosides **3a–c** were observed at 30.9–31.0 ppm, in the spectra of protected 2-deoxyglycosides **4a–c**[‡] at 35.1–35.7 ppm and in the spectra of free glycosides **5a–c**[§] at 38.1–38.6 ppm. Anomeric hydrogen atoms at C1′ of the carbohydrate residues in the spectra of **3a–c** resonate at 98.3–98.5 ppm and at 93.4–93.5 ppm in the spectra of glycosides **5a–c**,[13–15] which provides evidence for the existence of an α-glycosidic linkage.[16] The α-configuration of the glycosidic linkage was confirmed by a doublet of anomeric proton H1′ in the ^{1}H NMR spectra at 5.27 ppm with a spin–spin coupling constant (SSCC) of $J_{H1',H2'} = 1.1$ Hz. The H2′ proton signal was observed at 4.4 ppm as a doublet of doublets with SSCCs of $J_{H2',H1'} = 1.1$ Hz and $J_{H2',H3'} = 4.0$ Hz. The small value of SSCC for both H1′ and H2′ protons demonstrates their diequatorial position and, hence, the α-glycosidic linkage and axial position of iodine atom. In the ^{13}C NMR spectra in the regime NOE of **3a–c**, the geminal constant value $^2J_{C1',H2'}$ is small (< 1 Hz), which confirms an axial position of the aglycone.[17] Thus, glycosides **3a–c** were found to be of α-D-manno-configuration and in a $^4C_1$(D) conformation. The formation of α-D-manno-glycosides has been observed during the glycosylation of steroid alcohols by glycals[8] and a synthesis of disaccharides.[6]

‡ **4a**: $C_{43}H_{64}O_{11}$ M_r = 757.0, amorph; $[\alpha]_D^{20}$ + 87° (*c* 0.04, $CHCl_3$); UV (MeOH), λ_{max}/nm: 248.2 (lg ε 3.66); ^{13}C NMR ($CDCl_3$, δ, ppm): 21.8 (C2), 87.2 (C3), 93.2 (C1′), 35.1 (C2′), 69.3 (C3′), 68.3 (C4′), 69.7 (C5′), 62.5 (C6′).

4b: $C_{43}H_{66}O_{10}$ M_r = 743.0, amorph; $[\alpha]_D^{20}$ + 78° (*c* 0.04, $CHCl_3$); ^{13}C NMR ($CDCl_3$, δ, ppm): 21.9 (C2), 83.0, (C3),93.2(C1′), 35.7 (C2′), 69.3 (C3′), 68.4 (C4′), 69.7 (C5′), 62.6 (C6′).

4c: $C_{42}H_{66}O_9$ M_r = 715.0, amorph; $[\alpha]_D^{20}$ + 56° (*c* 0.07, $CHCl_3$); ^{13}C NMR ($CDCl_3$, δ, ppm): 21.9 (C2), 82.8 (C3), 93.2 (C1′), 35.6 (C2′), 69.3 (C3′), 68.3 (C4′), 69.7 (C5′), 62.5 (C6′).

§ **5a**: $C_{37}H_{58}O_8$ M_r = 630.9, decomp. 210–212 °C; $[\alpha]_D^{20}$ + 95° (*c* 0.02, $CHCl_3$); UV (MeOH), λ_{max}/nm: 248.0 (lg ε 3.81); ^{13}C NMR ($CDCl_3$, δ, ppm): 21.7 (C2), 81.7(C3), 93.4 (C1′), 38.1 (C2′), 72.0 (C3′), 69.2 (C4′), 72.5 (C5′), 62.2 (C6′).

5b: $C_{37}H_{60}O_7$ M_r = 616.9, decomp. 214–216 °C; $[\alpha]_D^{20}$ + 83° (*c* 0.05, $CHCl_3$); ^{13}C NMR ($CDCl_3$, δ, ppm): 21.8 (C2), 82.0 (C3), 93.5 (C1′), 38.3 (C2′), 71.9 (C3′), 69.3 (C3′), 69.3 (C4′), 72.5 (C5′), 62.1 (C6′).

5c: $C_{36}H_{60}O_6$ M_r = 588.9, decomp. 202–204 °C; $[\alpha]_D^{20}$ + 61° (*c* 0.06, $CHCl_3$); ^{13}C NMR ($CDCl_3$, δ, ppm): 21.9 (C2), 82.0 (C3), 93.5 (C1′), 38.6 (C2′), 71.9 (C3′), 69.3 (C4′), 72.8 (C5′), 62.5 (C6′).

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Received: Moscow, 3rd July 1995
Cambridge, 14th August 1995; Com. 5/04610F