Facile Sythesis of Dioscin and Its Analogues

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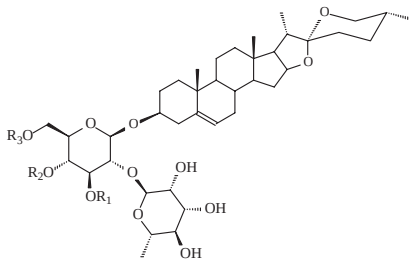
Three representative spirostanol saponins that have typical structure of the sugar moiety, diosgenyl 2,3-di-*O*-α-L-rhamnopyranosyl-β-D-glucopyranoside, diosgenyl 2,4-di-*O*-α-L-rhamnopyranosyl-β-D-glucopyranoside (dioscin), and diosgenyl 2,6-di-*O*-α-L-rhamnopyranosyl-β-D-glucopyranoside, were synthesized in a facile way. An approach to selectively mask the C_3-hydroxyl of diosgenyl 4,6-*O*-benzylidene β-D-glucopyranoside was described. A procedure using cerium(IV) ammonium nitrate for selective removal of *tert*-butyldimethylsilyl group while retaining levulinyl group is afforded.

Saponins, a structurally and biologically diverse class of glycosides, are major component in traditional Chinese medicines.[1] The structure diversity of saponins lies mainly in their sugar moieties.[1] Many studies have disclosed that some biological functions of saponins can be ascribed to the sapogenin and some to the carbohydrate residue,[2] for example diosgenyl glucosides. Dioscin (**2**) displays cardiovascular and antitumor activities.[3] Moreover, recent study had found that diosgenyl 2,3-di-*O*-α-L-rhamnopyranosyl-β-D-glucopyranoside (**1**) also showed stronger anticancer activity.[4] In contrast to the difficulty in isolation of homogeneous saponins from plants, chemical synthesis would provide a realistic route to the availability of saponins. Herein we report a facile way to synthesis dioscin, diosgenyl 2,3-di-*O*-α-L-rhamnopyranosyl-β-D-glucopyranoside and one of their analogue (diosgenyl 2,6-di-*O*-α-L-rhamnopyranosyl-β-D-glucopyranoside) (**3**).

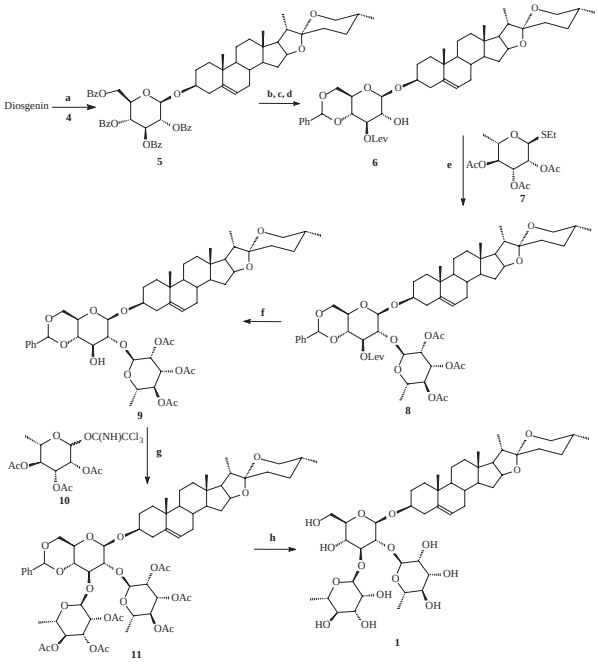
In previous work, it was found that protected ethyl 1-thioglycosides under the promotion of NIS/TMSOTf could be coupled with spirostanol sapogenins in excellent yields.[5] Using this method, diosgenin was glycosylated by ethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**4**)[6] to give a protected diosgenyl glycosides **5** (Scheme 1). The hydrolysis of **5** gave diosgenyl β-D-glucopyranoside[2b] in a yield of 92%. Treatment of the diosgenyl monosaccharide with benzaldehyde dimethyl acetal and a catalytic amount of *p*-toluenesulfonic monohydrate in DMF gave diosgenyl 4,6-*O*-benzylidene β-D-glucopyranoside. The Lev group was introduced by reaction of diosgenyl 4,6-*O*-benzylidene β-D-glucopyranoside with levulinic acid and DCC in the presence of a catalytic amount of DMAP. The desired compound 3-*O*-Lev **6** was afforded in a yield of 73%, although it was quite difficult to selectively mask one of the hydroxyl groups of the 2,3-diol of D-glucopyranose, especially when it was in the β-form.[7] NIS/TMSOTf mediate coupling of ethyl 2,3,4-tri-*O*-acetyl-1-thio-α-L-rhamnopyranose (**7**)[8] with **6**, gave **8** in a yield of 87%. It was anticipated that treatment with hydrazine acetate in CH_2Cl_2/MeOH would cleave the Lev without the effect to other acetyl groups. Indeed, compound **8** was converted into **9** within 2 h in a yield of 90%. Sugar receptor **9** was glycosylated by 2,3,4-tri-*O*-acety-L-rhamnopyranosyl trichloroimidate (**10**)[9] to give the protected diosgenyl trisaccharides **11** in a yield of 92%. Treatment of **11** with 80% HOAc at 70 °C for 5 h, then removal of all of the acetyl groups with MeONa furnished **1** in a yield of 85%.

With compound **8** in hand, dioscin (**2**) and diosgenyl 2,6-di-

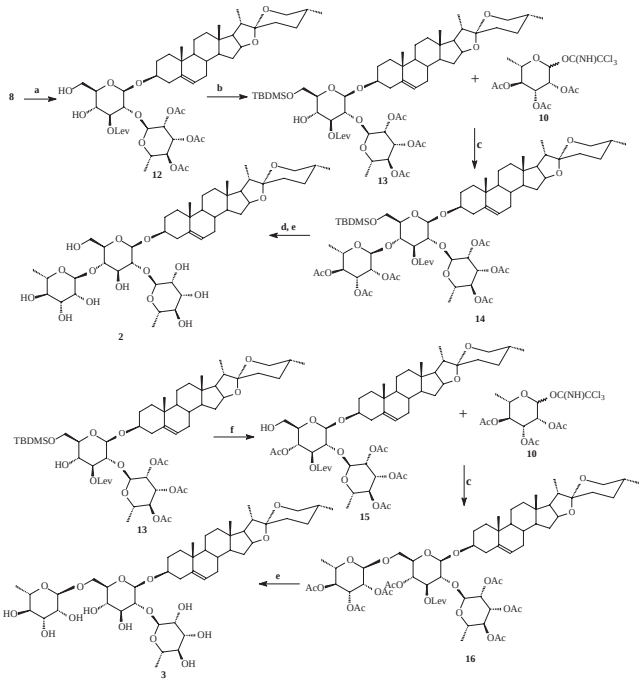


1. R_1 = α-L-rhamnopyranosyl, R_2 = R_3 = H;
2. R_2 = α-L-rhamnopyranosyl, R_1 = R_3 = H;
3. R_3 = α-L-rhamnopyranosyl, R_1 = R_2 = H;

Figure 1. The structure of dioscin and its analogues.



Scheme 1. Reagents and conditions: (a) NIS-TMSOTf, CH_2Cl_2, −15 °C → rt, 94%; (b) 1 mol/L NaOMe in MeOH, reflux, 92%; (c) $PhCH(OMe)_2$, DMF, *p*-TsOH, (d) levulinic acid, DCC, DMAP, CH_2Cl_2, rt, 73%; (e) NIS-TMSOTf, CH_2Cl_2, −30 °C → rt, 87%; (f) H_2NNH_2–HOAc, CH_2Cl_2–MeOH, rt, 90%; (g) $BF_3 \cdot Et_2O$, CH_2Cl_2, −40 °C → rt, 92%; (h) 80% HOAc, 5 h, 70 °C and then MeONa, CH_2Cl_2–MeOH, rt, 85%.



Scheme 2. Reagents and conditions: (a) 80% HOAc, 3 h, 80 °C, 92%; (b) imidazole, DMAP, TBDMSiCl, DMF, rt, 93%; (c) $BF_3 \cdot Et_2O$, CH_2Cl_2, $-40\,^{\circ}C \rightarrow$ rt, 58% for **14**, 80% for **17**; (d) CAN, CH_2Cl_2–MeOH, rt, 95%; (e) 1 mol/L NaOMe in MeOH, rt, 81% for **2**, 89% for **3**; (f) Ac_2O, pyridine, rt, 5 h and then 80% HOAc, 1 h, 70 °C, 78%.

O-α-L-rhamnopyranosyl-β-D-glucopyranoside (**3**) were synthesized as shown in Scheme 2. Treatment of **8** with 80% HOAc at 80 °C for 3 h provided compound **12** in a yield of 92%. In the presence of imidazole, DMAP and TBDMSiCl, the C_6'-OH of **12** was selectively protected and gave compound **13** in a yield of 93%. Though 2.0 equiv. TBDMSiCl of **12** had been used, the product of silylation on C_4'-OH was not found. Using compound **13** as sugar acceptor to couple with sugar donor **10**, protected diosgenyl trisaccharide **14** was afforded in a yield of 58%. The low yield of this glycosylation could be caused by the steric hindrance of the C_4'-OH in **13**. During the process of cleavage TBDMS from **14** in the presence of TBAF in THF, the Lev group was also removed off. The reason was probably contributed to the unstability of Lev to F^- caused by TBAF.[10] Alternatively, treatment with CAN[11] in MeOH/CH_2Cl_2, TBDMS of **14** was cleanly cleaved within 1 h and no loss of the Lev group was observed. The hydrolysis of the intermediate using MeONa/MeOH, dioscin (**2**) was produced in 76% yield of two steps. Acetylation of **13** and then treatment with 80% HOAc at 80 °C for 1 h, furnished **15** in a yield of 78% overall two steps. Glycosylation with sugar donor **10** provided compound **16**. Deprotection of acyl groups with MeONa, afforded target saponin **3** in a yield of 89%.

In conclusion, regioselective protection C_3-hydroxyl of diosgenyl 4,6-*O*-benzylidene β-D-glucopyranoside by levulinyl group enables compound **8** to be produced in a better yield. Taken **8** as the synthon, three sugar acceptors **9**, **13**, and **15** were gotten respectively in high yields. Therefore, dioscin and its analogues were facilely prepared in satisfactory overall yields.

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References and Notes

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12 The spectral data of **1**: ^{1}H NMR (500 MHz, pyridine-d_5): 5.86 (brs, 1H, H-1‴), 5.79 (brs, 1H, H-1″), 5.29 (d, $J = 4.5$ Hz, 1H, H-6), 4.90–4.83 (m, 3H), 4.80–4.76 (m, 2H), 4.55–4.20 (m, 4H), 4.34–4.27 (m, 3H), 4.16 (t, $J = 8.5$ Hz, 1H), 4.07–4.03 (m, 2H), 3.91–3.87 (m, 1H), 3.79–3.77 (m, 1H), 3.58–3.46 (m, 2H), 2.74–2.64 (m, 2H), 2.08–1.99 (m, 2H), 1.93 (m, 1H), 1.73 (d, $J = 6.0$ Hz, 3H), 1.64 (d, $J = 5.5$ Hz, 3H), 1.13 (d, $J = 7.0$ Hz, 3H), 1.02 (s, 3H), 0.81 (s, 3H), 0.67 (d, $J = 5.0$ Hz, 3H). ^{13}C NMR (75 MHz, pyridine-d_5): 140.73, 121.81, 109.23, 103.84, 102.61, 99.86, 87.41, 81.09, 78.40, 78.08, 77.75, 73.80, 73.57, 72.81, 72.62, 72.51(2C), 70.58, 69.87, 66.84, 62.87, 62.24, 56.61, 50.24, 41.95, 40.44, 39.83, 38.64, 37.46, 37.10, 32.29, 32.20, 31.81, 31.66, 30.58, 30.04, 29.25, 21.08, 19.37, 18.66, 18.41, 17.31, 16.32, 15.02. ESI-MS: 891.6 $(M + Na)^+$. HRMS (FAB-MS): calcd for $C_{45}H_{72}O_{16}Na$ $(M + Na)^+$: 891.4718, found: 891.4725.
13 The spectral data of **2** as reported before: C.-C. Zou, S.-J. Hou, Y. Shi, P.-S. Lei, and X.-T. Liang, *Carbohydr. Res.*, **338**, 721 (2003).
14 The spectral data of **3**: ^{1}H NMR (500 MHz, pyridine-d_5): 6.35 (brs, 1H, H-1‴), 5.48 (brs, 1H, H-1″), 5.30 (d, $J = 4.5$ Hz, 1H, H-6), 4.98–4.95 (m, 2H), 4.81 (d, $J = 3.5$ Hz, 1H), 4.63–4.61 (dd, $J = 3.5$, 9.0 Hz, 1H), 4.59–4.48 (m, 4H), 4.37–4.32 (m, 2H), 4.24–4.16 (m, 2H), 4.06 (m, 1H), 3.97–3.92 (m, 2H), 3.59–3.48 (m, 3H), 2.80–2.70 (m, 2H), 2.22 (m, 1H), 1.77 (d, $J = 6.5$ Hz, 3H), 1.63 (d, $J = 6.0$ Hz, 3H), 1.13 (d, $J = 7.0$ Hz, 3H), 1.00 (s, 3H), 0.80 (s, 3H), 0.68 (d, $J = 5.0$ Hz, 3H). ^{13}C NMR (75 MHz, pyridine-d_5): 140.84, 121.63, 109.21, 102.41, 102.17, 100.83, 81.07, 79.53, 78.69, 78.01, 76.55, 74.06, 73.98, 72.79, 72.68, 72.51, 72.22, 71.80, 69.77, 69.51, 67.91, 66.81, 62.84, 56.52, 50.12, 41.91, 40.39, 39.79, 39.16, 37.45, 37.04, 32.17, 31.77, 31.61, 30.55, 30.33, 29.95, 29.57, 29.21, 21.02, 19.35, 18.64, 17.30, 16.29, 15.02. ESI-MS: 891.6 $(M + Na)^+$, HRMS (FAB-MS): calcd for $C_{45}H_{72}O_{16}Na$ $(M + Na)^+$: 891.4718, found: 891.4697.

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