Efficient Synthesis of a Group of Saponins via Orthogonal Protection–Deprotection Glycosylation

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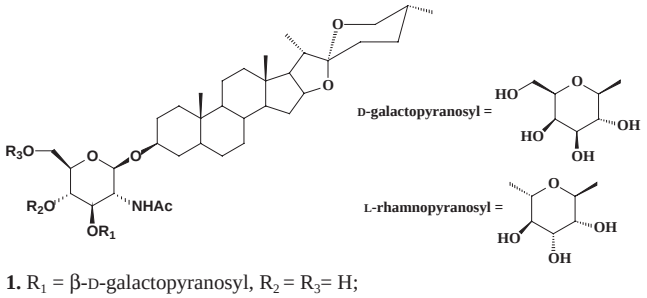
One new building block of tigogenyl glycoside with orthogonal protective groups has been efficiently synthesized. Using the building block as the key synthon, a small library of saponins with branched sugar moieties was built in an efficient way.

It was well-established that natural products are an excellent sources of chemical structures with a broad of promising biological activities, including anticancer activity.[1] Saponins, a structurally and biologically diverse class of natural glycosides present in a wide variety of plants, has been opened as a new field of investigation of potential anticancer compounds.

As a result of the development of various glycosylation procedure, many natural saponins and their analogues have been synthesized.[2] To synthesis the natural glycosides with complicated branched sugar moieties, the new challenge is to increase the efficiency of the oligosaccharide assembly. To tackle this problem, Wong and co-workers developed the strategy of orthogonal protection–deprotection glycosylation and built an oligosaccharide pool in an efficient way.[3]

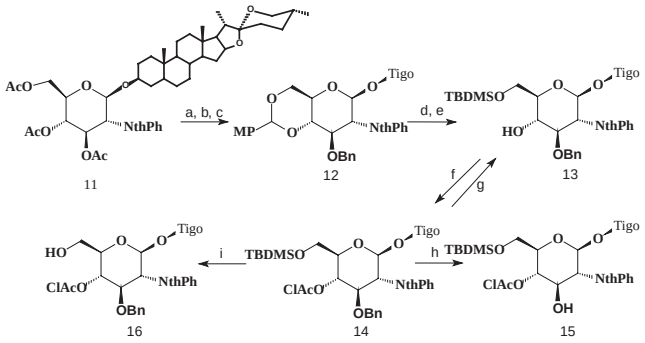
Both natural and synthesized compounds containing glucosamine have been demonstrated with potent bioactivities.[4] In order to study the structur-activity relationship of tigogenyl glycosides, a group of new structurally tigogenyl glycosides having glucosamine was designed (Figure 1) and synthesized by utilization of orthogonal protection–deprotection protocol.

As described in Scheme 1, building block **14** was provided from tigogenyl monosaccharide **11**.[5] Removal of the acetyl groups from **11** gave a triol, which was treated with *p*-methoxybenzaldehyde dimethyl acetal and a catalytic amount of *p*-toluenesulfonic acid monohydrate, then the sterically hindered 3-OH was masked by a benzyl ether to produce **12** in a yield of 73% of three steps. Treatment of **12** with 80% HOAc at 70 °C for 2 h, followed by monosilylation with TBDMS afforded **13**, which was turned into **14** in the presence of chloroacetic anhydride. With the key compound **14** in hand, attentation was turned to examining the orthogonality of the three chosen protective groups. As anticipated, chloroacetyl group was removed off in the presence of thiourea to give **13**. At the condition of H_2/Pd–C, the building block **14** was hydrogenated giving **15**. **14** was treated with CAN leading to clean conversion to **16** in a yield of 80%. Interestingly, during to purify **16** with CH_2Cl_2–MeOH (30:1) and 1% Et_3N as eluent, part of chloroacetyl group in **16** migrated to C_6'. At the same time, under the condition of HOAc–THF–H_2O (3:1:1) at room temperature for 2 h, the silyl ether was removed completely. However, a stimultaneous migration of the chloroacetyl group was observed.



1. R_1 = β-D-galactopyranosyl, R_2 = R_3= H;
2. R_1 = α-L-rhamnopyranosyl, R_2 = R_3 = H;
3. R_2 = β-D-galactopyranosyl, R_1 = R_3 = H;
4. R_2 = α-L-rhamnopyranosyl, R_1 = R_3 = H;
5. R_3 = β-D-galactopyranosyl, R_1 = R_2 = H;
6. R_3 = α-L-rhamnopyranosyl, R_1 = R_2 = H;
7. R_3 = β-D-galactopyranosyl, R_2 = α-L-rhamnopyranosyl, R_1 = H;
8. R_3 = β-D-galactopyranosyl, R_1 = α-L-rhamnopyranosyl, R_2 = H;
9. R_3 = α-L-rhamnopyranosyl, R_2 = β-D-galactopyranosyl, R_1 = H;
10. R_3 = α-L-rhamnopyranosyl, R_1 = β-D-galactopyranosyl, R_2 =H;

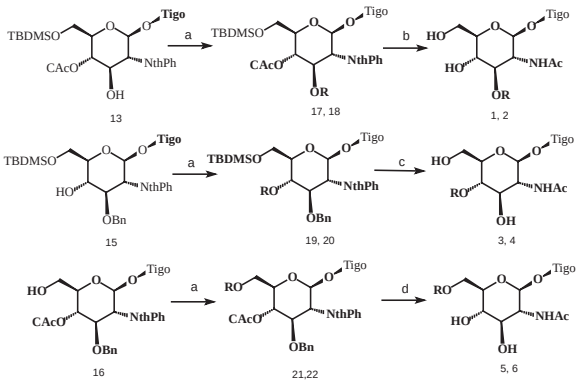
Figure 1. Small library of tigogenyl glycosides.



Scheme 1. Reagents and conditions: a) 0.1 mol L^{-1} MeONa–MeOH, reflux, 87%. b) *p*-methoxybenzaldehyde dimethyl acetal, *p*-TsOH, DMF, 50 °C, 82%. c) BnBr, NaH, DMF, 73%. d) 80% HOAc, 70 °C, 89%. e) TBDMSiCl, DMAP, imidazole, DMF, 94%. f) $ClAc_2O$, pyridine, 62%. g) thiourea, CH_2Cl_2, 73%. h) H_2, 10% Pd/C, CH_2Cl_2–EtOH, 73%. i) CAN, CH_2Cl_2–MeOH, 80%.

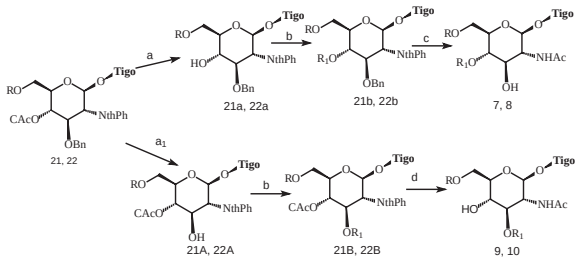
When three sugar receptors **13**, **15**, and **16** were prepared, six tigogenyl disaccharides were synthesized in an efficient way described as in shown Scheme 2. Using 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate[6] as the sugar donor to couple with **13**, **15**, and **16** were afforded **17**, **19**, and **21**, respectively. Using the methods described above, TBDMS group and Bn were efficiently removed off. Treatment of the three intermediates with hydrazine hydrate and then Ac_2O–MeOH, furnished the target saponins **1**, **3**, and **5**. Using a similar way with 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl trichloroacetimidate[7] as donor, disaccharide saponin **2**, **4**, and **6** were prepared from **13**, **15**, and **16**, respectively.

As shown in Scheme 3 as the example, saponins with complete branched sugar moieties were synthesized in an efficient



17, **19**, **21**: R = 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl;
1, **3**, **5**: R = β-D-galactopyranosyl
18, **20**, **22**: R = 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl,
2, **4**, **6**: R = α-L-rhamnopyranosyl

Scheme 2. Reagents and conditions: a) $BF_3 \cdot Et_2O$, CH_2Cl_2, 4 Å MS, $-40\,^{\circ}C \rightarrow$ rt, 75% for **17**, 65% for **18**, 89% for **19**, 87% for **20**, 46% for **21**, 55% for **20**. b) (i). CAN, CH_2Cl_2–MeOH; (ii). 85% $NH_2 \cdot NH_2 \cdot H_2O$, CH_2Cl_2–EtOH, reflux (iii). Ac_2O–MeOH, rt; 43% for **1**, 47% for **2** over three steps. c) (i). H_2, 10% Pd/C, CH_2Cl_2–MeOH; (ii). CAN, CH_2Cl_2–MeOH; (iii). 85% $NH_2 \cdot NH_2 \cdot H_2O$, CH_2Cl_2–EtOH, reflux (iv). Ac_2O–MeOH, rt; 37% for **3** and 33% for **4** over four steps. d) (i). H_2, 10% Pd/C, CH_2Cl_2–MeOH; (ii). 85% $NH_2 \cdot NH_2 \cdot H_2O$, CH_2Cl_2–EtOH, reflux (iii). Ac_2O–MeOH, rt. 41% for **5** and 39% for **6** over three steps.



21, **21a**, **21A**: R = 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl;
21b, **21B**: R = 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl, R_1 = 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl,
7, **9**: R = β-D-galactopyranosyl, R_1 = α-L-rhamnopyranosyl;[8,10]
22, **22a**, **22A**: R = 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl
22b, **22B**: R = 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl, R_1 = 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl
8, **10**: R = α-L-rhamnopyranosy, R_1 = β-D-galactopyranosyl[9,11]

Scheme 3. Reagents and conditions: a) thiourea, CH_2Cl_2, 73%. b) $BF_3 \cdot Et_2O$, CH_2Cl_2, 4 Å MS, $-40\,^{\circ}C \rightarrow$ rt, 65% for **21b**, 63% for **22b**, 79% for **21B**, 62% for **22B**. c) (i). H_2, 10% Pd/C, CH_2Cl_2–MeOH; (ii). 85% $NH_2 \cdot NH_2 \cdot H_2O$, CH_2Cl_2–EtOH, reflux (iii). Ac_2O–MeOH, rt; 51% for **7** and 47% for **8** over three steps. d) (i). 85% $NH_2 \cdot NH_2 \cdot H_2O$, CH_2Cl_2–EtOH, reflux (ii). Ac_2O–MeOH, rt, 68% for **9** and 72% for **10** over two steps.

way. With the synthon **21** in hand, sugar receptors **21a** and **21A** were furnished. Using 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl trichloroacetimidate as the sugar donor to couple with **21a** and **21A**, trisaccharide saponins **21b** and **21B** were afforded respectively. By deprotection of **21b** and **21B**, target saponins **7** and **9** were produced. According to the same procedure, **8** and **10** were synthesized from **22**.

In a summary, the tactics of orthogonal protection–deprotection glycosylation was fist used to synthesized branched saponins, which was proved to be an efficient way to build the library of saponins.

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8 The spectral data of **7**: ^{13}C NMR (75 MHz, pyridine-d_5) δ 170.4, 109.2, 105.4, 103.1, 100.1, 81.1, 80.7, 78.0, 76.9, 75.2, 75.1, 74.1, 73.8, 72.6, 72.4, 72.2, 70.5, 70.1, 68.8, 66.8, 63.0, 62.1, 58.4, 56.3, 55.0, 54.3, 44.5, 41.9, 40.7, 40.1, 37.1, 35.7, 35.2, 32.3, 32.0, 31.7, 30.5, 29.9, 29.2, 28.9, 23.6, 21.2, 18.4, 17.3, 16.5, 15.0, 12.2. FAB-MS (m/z): 950.6 $(M + Na)^+$ HRMS (FAB-MS) m/z: calcd for $C_{47}H_{77}NO_{17}Na$ $(M + Na)^+$ 950.5089, found: 950.5114.
9 The spectral data of **8**: ^{13}C NMR (75 MHz, pyridine-d_5) δ 170.8, 109.2, 105.9, 102.2, 100.3, 82.5, 80.0, 78.4, 77.0, 74.9, 74.8, 73.8, 73.6, 72.6, 72.2, 69.8, 69.6, 67.2, 66.7, 62.8, 61.8, 57.0, 56.2 (2 × C, overlap), 54.1, 44.5, 41.8, 40.6, 39.9, 36.9, 35.6, 35.0, 32.2 (2 × C, overlap), 31.9, 31.6, 30.4, 29.8, 29.1, 28.7, 23.4, 21.1, 18.5, 17.2, 16.4, 14.9, 12.1. FAB-MS (m/z): 950.4 $(M + Na)^+$ HRMS (FAB-MS) m/z: calcd for $C_{47}H_{77}NO_{17}Na$ $(M + Na)^+$ 950.5089, found: 950.5099.
10 The spectral data of **9**: ^{13}C NMR (75 MHz, pyridine-d_5) δ 170.2, 109.1, 105.8, 103.2, 99.8, 82.3, 81.0, 77.9, 76.9, 75.2, 73.7, 72.6, 72.5, 72.4, 70.6, 70.1, 69.7, 66.7, 62.9, 62.2, 57.2, 56.3, 56.0, 54.2, 44.4, 41.9, 40.6, 40.0, 37.0, 35.6, 35.1, 35.0, 34.8, 32.2, 32.0, 31.5, 30.5, 29.9, 29.1, 28.8, 23.3, 21.1, 18.4, 17.3, 16.5, 14.9, 12.2. FAB-MS (m/z): 950 $(M + Na)^+$ HRMS (FAB-MS) m/z: calcd for $C_{47}H_{77}NO_{17}Na$ $(M + Na)^+$ 950.5089, found: 950.5126.
11 The spectral data of **10**: ^{13}C NMR (75 MHz, pyridine-d_5) δ 171.3, 109.1, 105.8, 102.6, 99.9, 86.0, 81.0, 78.1, 77.3, 76.1, 75.0, 73.9, 72.2, 72.3, 70.4, 70.0, 69.8, 68.0, 66.8, 62.9, 62.0, 56.6, 56.3, 54.2, 44.4, 41.4, 40.7, 40.0, 37.0, 35.7, 35.1, 35.0, 32.3, 32.0, 31.7, 31.5, 30.5, 29.9, 29.2, 28.9, 23.7, 21.2, 18.6, 17.4, 16.5, 15.0, 12.2. FAB-MS (m/z): 950.5 $(M + Na)^+$ HRMS (FAB-MS) m/z: calcd for $C_{47}H_{77}NO_{17}Na$ $(M + Na)^+$ 950.5089, found: 950.5126.

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