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Efficient synthesis of core 2 class glycosyl amino acids by one-pot glycosylation approach ☆

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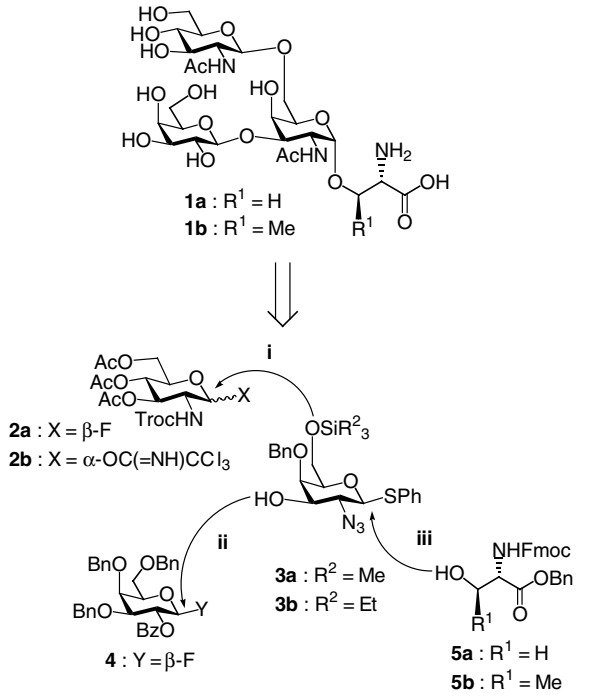
Abstract—We describe the one-pot synthesis of core 2 class branched oligosaccharides initiated by chemo-selective glycosylation of silyl ether. Glycosylation of 6-*O*-silyl-4-benzyl-2-azido-thiogalactoside with glycosyl fluoride provided selectively 6-glycosylated thioglycoside without both O-glycosylation at the 3 position and S-glycosylation. Subsequent coupling of galactosyl fluoride and amino acids afforded the protected branched oligosaccharides in good yields.

Glycoconjugatges on cell surface such as glycoproteins play important roles in biological events.[1] Ligation of the proteins with several saccharides modulate their biological functions. However, it is relatively difficult to elucidate the structure–activity relationships of individual glycoforms as most of the glycoproteins isolated form cultured cells contain several different glycoforms.

Galβ(1 → 3)-[GlcNAcβ(1 → 6)]-GalNAcα(1 → 3)-Ser and -Thr (**1a** and **1b**) are contained in mucin type glycoproteins, and are named core 2 class glycosyl amino acids (Scheme 1).[2] Various di-branched *N*-acetyl galactosaminyl derivatives at their 3 and/or 6 positions are found in related glycoproteins. To elucidate the biological functions of the oligosaccharides, as well as the glycoproteins, chemical tools composed of the corresponding glycosyl amino acids are effective.[3,4] Therefore, an effective methodology for the synthesis of galactosamine derivatives varying not only in the branching saccharides but also in the amino acids, is required.

One-pot sequential glycosylation[5–8] is one of the most effective solution-phase methodologies not only for the high speed synthesis of a target oligosaccharide but also for the combinatorial synthesis of an oligosaccharide library. Most of the methodologies are based on sequential activation of glycosyl donors to provide linear oligosaccharides. Few approaches involve regioselective glycosylation in the sequential glycosylation



Scheme 1. Strategy for the one-pot synthesis of core 2 class amino acids **1**.

Keywords: Glycosyl amino acids; One-pot glycosylation; Glycopeptides; Glycosyl fluorides; Oligosaccharide.

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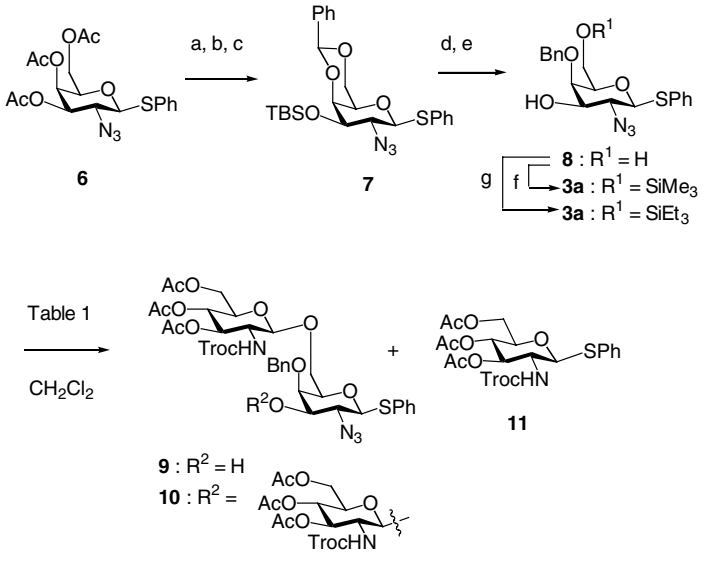
process, and are effective for the synthesis of various branched oligosaccharides.[9] We have already reported a combinatorial one-pot synthesis of linear and branched trisaccharide libraries containing 3,6 branched glucosides and mannosides.[9b] The success of the one-pot synthesis of the branched oligosaccharides depends largely on the selectivity of the regio-selective glycosylation. However, the difference of the reactivity of the 3,6 di-hydroxyl groups of galactoside is not enough to selectively glycosylate at 6 position due to an axial orientated C4 hydroxyl group. Therefore, the one-pot synthesis of 3,6 branched galactosides have not been successful. Herein we describes the one-pot synthesis of core 2 class amino acids **1a** and **1b** involving chemoselective glycosylation of silyl ether at 6 position of galactoside.

Strategy for the one-pot synthesis of **1a** and **1b** is shown in Scheme 1. 6-*O*-Silyl protected 2-azido thiogalactosides **3** was designed as a key intermediate. The silyl ether would promote selective introduction of glycosyl fluoride at the 6 position.[10] The 2-azido substituent of thioglycoside **3** could be effective for the formation of the α-glycosidic linkage to amino acids.[11] The one-pot synthesis would be initiated by (i) chemo-selective glycosylation of the silyl ether in the thiogalactosides **3** with glucosamine **2**. Subsequent (ii) glycosylation of the remaining hydroxyl group at 3 position with galactoside **4**, followed by (iii) coupling with amino acids **5** provides protected glycosyl amino acids. On the basis of our reported branched one-pot glycosylation, there is a different pathways for the coupling of the two fragments **4** and **5** (iii → ii). However, the coupling sequence involves regio-selective glycosylation of the secondary hydroxyl group of threonine **5b** in the presence of the remaining C3 secondary hydroxyl group.

Preparation of thiogalactosamine **3a** and **3b** is shown in Scheme 2. 2-Azido-thioglycoside **6**[12] was converted to 3,6-benzylidene derivative **7** by three steps in 86% yield. Reductive cleavage of the acetal, followed by deprotection of silyl ether provided diol **8** in 62% yield in two steps. Treatment of **8** with TMSCl or TESCl under basic conditions selectively afforded mono-silyl ether **3a** and **3b** in 95% and 92% yields, respectively.

Glycosylation of thioglycosides **3** using glycosyl fluoride **2a**[13c,d] with several activating reagents was examined (Table 1 and Scheme 2). An equivalent of $BF_3{\cdot}OEt_2$ was found to be an effective reagent for glycosylation of trimethyl ether **3a** to give disaccharide **9** in excellent yield (97%) (entry 1). Treatment of **2a** and **3a** with catalytic amounts of $BF_3{\cdot}OEt_2$ provided disaccharide **9** (66% yield) along with formation of small amounts of trisaccharide **10** (2% yield) (entry 2). Glycosylation of the triethylsilyl ether **3b** under the same reaction conditions afforded disaccharide **9** in reduced yield (74%) (entry 3). When diol **8** was used as a glycosyl acceptor for glycosyl fluoride **2a**, significant amounts of thioglycoside **11** and trisaccharide **10** were generated (entry 4). Glycosidation of glycosyl imidate **2b**[13b] with diol **3** in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$ at −78 °C resulted in the yield of disaccharide **9** in 70% yield along with thioglycoside **11** in 12% yield (entry 5). Thioglycoside **11** was generated via S-glycosylation, which is often observed in the chemo-selective glycosylation of thioglycosides with more disarmed donors.[14] These results indicate that the combination of trimethylsilyl ether and a stoichometric amount of $BF_3{\cdot}OEt_2$ is essential for the chemo- and regio-selective glycosylation with glycosyl fluoride **2a**. Boron trifluoride complex with the trimethylsilyl ether would make it more nucleophilic to provide disaccharide **9** without both undesired O- and S-glycosylations.

The one-pot synthesis of glycosyl amino acids **1a** and **1b** is illustrated in Scheme 3. Chemo-selective glycosylation of **3a** with **2a** in the presence of $BF_3{\cdot}OEt_2$, followed by sequential coupling of the remaining secondary hydroxyl groups of **9** with glycosyl fluoride **4** in the presence of

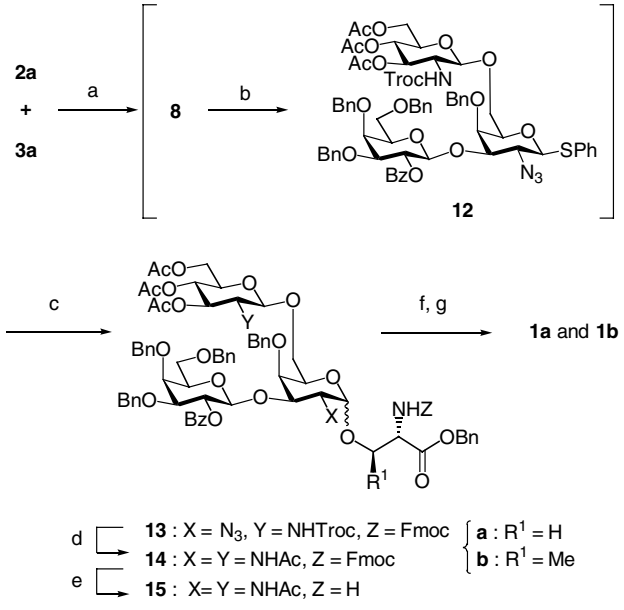


Scheme 2. Reagents and conditions: (a) NaOMe, MeOH; (b) $PhCH(OMe)_2$, CSA, DMF, 80 °C; (c) TBSCl, imidazole, DMF, 86% in three steps; (d) $BH_3{\cdot}THF$, Bu_2BOTf; (e) 40% aq HF, CH_3CN, 62% in two steps; (f) TMSCl, Et_3N, CH_2Cl_2, 95%; (g) TESCl, Et_3N, CH_2Cl_2, 92%.

Table 1. Chemo-selective glycosylation of **3a**, **3b** and **8** with **2**

Entry	Donor (equiv)[a]	Acceptor	$BF_3{\cdot}Et_2O$ (equiv)[b]	Temperature (°C)	Yield of **9** (%)	Yield of **10** (%)	Yield of **11** (%)
1	**2a** (1.40)	**3a**	1.00	0	97	—	—
2	**2a** (1.40)	**3a**	0.50	0	66	2	2
3	**2a** (1.40)	**3b**	1.00	0	74	9	Trace
4	**2a** (1.10)	**8**	1.00	0	48	12	12
5	**2b** (1.10)	**8**	0.05	−78	70	Trace	12

[a] Based on the acceptor **3a**, **3b** or **8**.
[b] Based on the donor **2a** or **2b**.



Scheme 3. Reagents and conditions: (a) **2a** (1.40 equiv), **3a** (1.00 equiv), $BF_3{\cdot}OEt_2$ (2.25 equiv), CH_2Cl_2, MS4A, 0 °C; (b) **4** (1.45 equiv), $ZrCp_2Cl_2$, AgOTf, 0 °C; (c) **5a** or **5b** (1.50 equiv), NIS, TfOH, −50 °C, toluene–CH_2Cl_2 (1:1), 75% for **13a**, and 68% for **13b** in one-pot three steps; (d) Zn dust, THF, AcOH, Ac_2O, 0 °C, 87% for **14a-α**, and 89% for **14b-α**; (e) piperazinomethyl polystylene, THF, rt, 82% for **15a-α** and 93% for **15b-α**; (f) $Pd(OH)_2$, THF, MeOH, H_2O; (g) 0.1 N NaOH, MeOH, rt, 96% for **1a** and 93% for **1b** in two steps.

$ZrCp_2Cl_2$/AgOTf[15] provided **12**. Subsequent glycosidation of thioglycoside **12** with amino acids **5a** and **5b** by NIS/TfOH[16] in toluene–CH_2Cl_2 (1:1) provided the amino acids **13a** and **13b** in 75% ($\alpha/\beta = 63/37$) and 68% ($\alpha/\beta = 60/40$) yields, respectively.[17] Further examination of the α-selective glycosidation of **12** using several solvents and additives unfortunately did not result in better reaction conditions applicable to the one-pot three-step reaction. Separation of the α/β mixture of **13a** and **13b** was performed by preparative thin layer chromatography for **13a** and by column chromatography on silica gel for **13b** to give the corresponding pure isomers **13a-α**, **13a-β**, **13b-α** and **13b-β**.

Transformation of **13a-α** and **13b-α** to **1a** and **1b** is as follows. The simultaneous reduction of the azido and Troc groups of **13a-α** and **13b-α**,[13a] followed by acetylation provided the corresponding *N*-acetyl derivatives **14a-α** and **14b-α** in 87% and 89% yields. Complete deprotection of **14a-α** and **14b-α** was accomplished in three steps involving removal of the Fmoc group by solid-supported piperazine,[18] to provide the corresponding amines **15a-α** and **15b-α** in 82% and 93% yields. Hydrogenolysis of the benzyl ethers and ester, followed by hydrolysis of the benzoate provided the fully deprotected core 2 trisaccharides **1a** and **1b** in 96% and 93% yields, respectively. Their analytical data (^1H and ^{13}C NMR, MS) were identical with those previously reported.[3a,b]

In conclusion, we have demonstrated an effective one-pot synthesis of the core 2 class branched glycosyl amino acids **1a** and **1b** initiated by chemo-selective glycosylation of the trimethylsilyl ether of **4a** with glycosyl fluoride **2a** in the presence of $BF_3{\cdot}Et_2O$. Boron trifluoride complex with the trimethylsilyl ether would enhance the nucleophilicity of the silyl ether. This methodology would be effective for the synthesis of branched oligosaccharide libraries.

Supporting information available. Experimental procedures for synthesis and full characterization for all compounds.

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17. Procedure for the one-pot synthesis of the protected oligosaccharide **12a**: A mixture of **2a** (1.40 equiv), **4a** (1.00 equiv) and pulverized activated MS-4A in dry CH_2Cl_2 was stirred at room temperature for 10 min under argon to remove trace amounts of water. Then the reaction mixture was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (2.25 equiv) was added to the reaction mixture. After 30 min, a solution of **5** (1.45 equiv), azeotroped three times with toluene, in dry CH_2Cl_2 was added to the reaction mixture at 0 °C. After 10 min, a dichloromethane solution of $ZrCp_2(OTf)_2$, prepared from $ZrCp_2Cl_2$ (2.90 equiv) and silver trifluoromethanesulfonate (5.80 equiv), was added to the reaction mixture. After stirring at the same temperature for 1 h, the reaction mixture was cooled to −50 °C. A solution of **6a** (1.50 equiv), azeotroped three times with toluene, in dry CH_2Cl_2 and dry toluene was added to the reaction mixture. After 10 min, *N*-iodosuccinimide (2.00 equiv) and a catalytic amount of trifluoromethanesulfonic acid was added to the reaction mixture at −50 °C. After stirring at the same temperature for 1.5 h, the reaction mixture was neutralized with triethylamine and filtered through a pad of Celite. The filtrate was poured into a mixture of saturated aq $NaHCO_3$ and saturated aq $Na_2S_2O_3$ with cooling. The aqueous layer was extracted with two portions of ethyl acetate. The combined extracts were washed with a mixture of saturated aq $NaHCO_3$ and saturated aq $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was chromatographed on silica gel and further purified by gel permeation chromatography (GPC) to give **12a-α** and **12a-β** (75% yield, α:β = 63:37). Spectra of **12a-α**: $[\alpha]_D^{25}$ +32.9° (*c* 1.07, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, 2H), 7.74 (m, 2H), 7.56 (m, 2H), 7.14–7.45 (m, 34H), 6.13 (d, 1H, $J = 6.8$ Hz), 6.14 (d, 1H, $J = 7.2$ Hz), 5.74 (dd, 1H, $J = 8.2$ Hz, $J = 8.2$ Hz), 5.58 (dd, 1H, $J = 9.7$ Hz, $J = 10.1$ Hz), 5.22 (d, 1H, $J = 12.1$ Hz), 5.13 (d, 1H, $J = 12.6$ Hz), 5.05 (d, 1H, $J = 11.6$ Hz), 4.94 (d, 1H, $J = 10.6$ Hz), 4.93 (dd, 1H, $J = 9.2$ Hz, $J = 9.2$ Hz), 4.77 (d×2, 2H, $J = 7.7$ Hz), 4.40–4.74 (m, 11H), 4.32 (m, 1H), 4.22 (m, 1H), 4.18 (dd, 1H, $J = 3.9$ Hz, $J = 7.7$ Hz), 4.00 (br s, 1H), 3.97 (m, 2H), 3.92 (br s, 1H), 3.87 (dd, 1H, $J = 1.9$ Hz, $J = 10.6$ Hz), 3.49–3.72 (m, 9H), 3.21 (ddd, 1H, $J = 6.8$ Hz, $J = 7.6$ Hz, $J = 9.2$ Hz), 1.98, 1.93, 1.91 (3s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.0, 169.5×2, 165.3, 155.8, 153.8, 143.7, 143.5, 141.2, 141.2, 138.4, 138.2, 137.4, 134.9, 132.8, 130.1, 129.7, 128.8, 128.6, 128.5, 128.3, 128.2, 128.0, 128.0, 127.8, 127.7, 127.6, 127.4, 127.1, 127.1, 125.0, 120.0, (103.0, 99.8, 98.8 (anomeric)), 95.6, 79.5, 77.5, 77.2, 75.3, 74.5, 74.1, 73.5, 72.7, 71.9, 71.8, 71.3, 70.9, 70.2, 69.6, 68.9, 68.7, 68.2, 67.7, 67.1, 62.0, 59.0, 56.9, 54.3, 47.0, 29.6, 20.5; IR (solid) 3333, 2927, 2110, 1747, 1733, 1534, 1454, 1236, 1071, 795, 741, 699 cm^{-1}; MS (FAB) calcd for $C_{87}H_{89}Cl_3N_5O_{24}$ $[M+H]^+$ 1695, found 1695; Spectra of **12a-β**: $[\alpha]_D^{25}$ −2.1° (*c* 1.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, 2H), 7.75 (d, 2H), 7.04–7.54 (m, 34H), 6.15 (d, 1H, $J = 9.2$ Hz), 5.73 (d, 1H, $J = 9.7$ Hz, $J = 10.1$ Hz), 5.62 (d, 1H, $J = 8.2$ Hz), 5.41 (d, 1H, $J = 13.0$ Hz), 5.15 (d, 1H, $J = 13.0$ Hz), 5.13 (dd, 1H, $J = 8.7$ Hz, $J = 11.6$ Hz), 5.05 (d, 1H, $J = 11.6$ Hz), 5.00 (d, 1H, $J = 11.6$ Hz), 4.95 (dd, 1H, $J = 9.2$ Hz, $J = 10.1$ Hz), 4.79 (d, 1H, $J = 12.1$ Hz), 4.72 (d, 1H, $J = 7.7$ Hz), 4.69 (d, 1H, $J = 12.6$ Hz), 4.65 (m, 3H), 4.63 (d, 1H, $J = 11.6$ Hz), 4.60 (d, 1H, $J = 11.6$ Hz), 4.56 (d×2, 2H, $J = 12.6$ Hz), 4.38 (m, 2H), 4.31 (d, 1H, $J = 10.7$ Hz), 4.23–4.30 (m, 2H), 4.11–4.18 (m, 3H), 4.02 (br s, 1H, $J = 1.4$ Hz), 3.92 (m, 1H), 3.55–3.82 (m, 9H), 3.40 (dd, 1H), 3.31 (dd, 1H, $J = 2.0$ Hz, $J = 10.7$ Hz), 3.03 (m, 1H), 2.04, 1.97, 1.94 (3s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.3, 169.4, 165.3, 155.8, 154.3, 143.8, 143.7, 141.2, 138.5, 137.9, 137.6, 135.0, 132.9, 130.1, 129.7, 129.3, 128.7, 128.6, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 125.3, 125.2, 119.9, (102.9, 102.8, 101.9 (anomeric)), 95.8, 80.0, 79.6, 75.2, 74.7, 74.6, 74.4, 74.3, 73.7, 73.6, 72.9, 72.3, 72.0, 71.9, 71.2, 69.9, 68.6, 67.5, 62.8, 61.8, 54.9, 54.5, 20.7, 20.6; IR (solid) 3436, 2928, 2113, 1734, 1454, 1233, 1072, 1028, 740, 699 cm^{-1}; MS (FAB) calcd for $C_{87}H_{89}Cl_3N_5O_{24}$ $[M+H]^+$ 1695, found 1695.
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