A Facile Synthesis of Neosaccharides: 2,6′-and 3,6′-Ether-Linked Sugars

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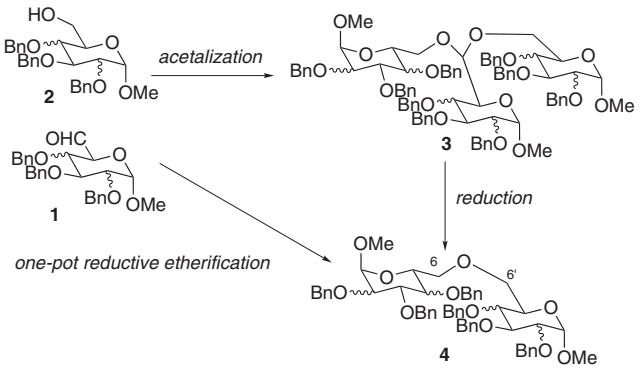
Abstract: A novel synthesis of the 2,6′-O-linkage of methyl α-D-glucoside and methyl α-D-mannoside was developed based on an acetalization–reduction approach. Utilizing this approach, the 3,6′-O-linkage of methyl α-D-glucosides was also obtained. It is noteworthy that the reductive etherification of secondary alcohols and the C6-aldehyde of carbohydrates proceeded efficiently.

Key words: carbohydrate, acetals, ethers, reductions, regioselectivity

Since coyolosa was isolated as the first 6,6′-ether-linked pyranose,[1] its unique structure[2] along with its strong hypoglycemic activity prompted us to develop an efficient method to link sugars via ether bonds.[3] Recently, we reported an efficient synthesis of 6,6′-ether-linked pyranoses utilizing an acetalization–reduction approach (Scheme 1).[4]

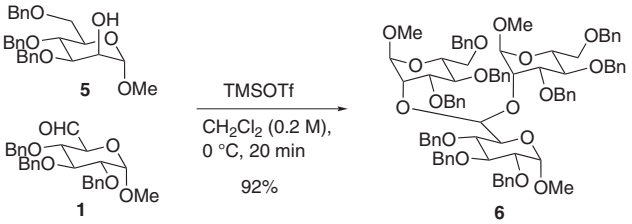
In this method, the C6-aldehyde of **1** reacted with the C6-alcohol of **2** under mild acid-catalyzed conditions to give the intermediate acetal derivative **3**, which was successively reduced to furnish 6,6′-ether-linked pyranosides (neo-6,6′-*O*-saccharides); a one-pot reductive etherification[5] was also established.



Scheme 1 Synthesis of the neo-6,6′-*O*-saccharide **4**.

Such successful results led us to pursue the prospect of achieving a novel connection between a secondary alcohol (C2, C3) and the aldehyde (C6) of pyranosides via acetalization–reduction.

We applied the previous procedure to the acetalization of the C6-aldehyde **1** and the secondary alcohol of methyl α-D-mannoside **5**.[6] An excess amount of α-D-mannoside **5** was reacted with **1** in the presence of three equivalents of TMSOTf to give the acetal derivative **6** in excellent yield.



Scheme 2 Acetalization of aldehyde **1** with alcohol **5** catalyzed by TMSOTf.

It is noteworthy that the axial C2-OH reacted smoothly to form the relatively stable acetal, which was easily separated by silica gel column chromatography. We next examined the reduction step. Initial attempts to reduce the acetal **6** with triethylsilane (TESH) in the presence of TMSOTf provided the desired ether-linked sugar **7** in moderate yield, reactions at the anomeric positions resulted in complicated byproducts (Table 1, entry 3). We reasoned that the bulky TESH barely attacked the crowded C6-acetal, which was composed of two secondary alcohols, but reduced less crowded anomeric acetals. This rationalization led us to examine various reducing agents. While the reaction with an excess amount of $LiAlH_4$–$AlCl_3$ or BH_3·THF–TMSOTf did not proceed, BH_3·SMe_2–TMSOTf produced **7** in 51% yield. Although borane reagents appeared hopeful, further improvement was not achieved, and we reconsidered the reductive cleavage with alkylsilane reagents.

As shown in Table 1, the reaction with bulky triphenylsilane and triisopropylsilane gave mixtures of unidentified products with an excess amount of **5**, which may be attributed to over-reduction of the acetal carbon (Table 1, entries 1 and 2). This over-reduction means that both acetal bonds are cleaved simultaneously by the bulky silane to give two equivalents of **5**.[7] The less hindered diethylmethylsilane (DEMSH), dimethylethylsilane (DMESH), and trimethylsilane (TMSH) reacted well (Table 1, entries 4, 6, and 8), but the use of diethylsilane (DESH) proved to be less effective. Under optimized conditions, acetal **6** was treated with DMESH (14.4 equiv) in the presence of TMSOTf (4.8 equiv) at –20 °C for two hours to afford the 2,6′-ether-connected sugar **7** in 83% yield (Table 1, entry 7).

Having established a method for the connection of the aldehyde of **1** to the secondary alcohol **5**, we then examined

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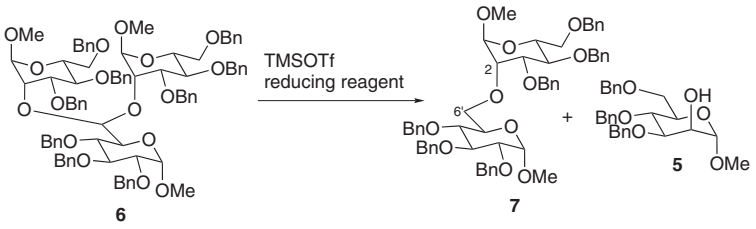
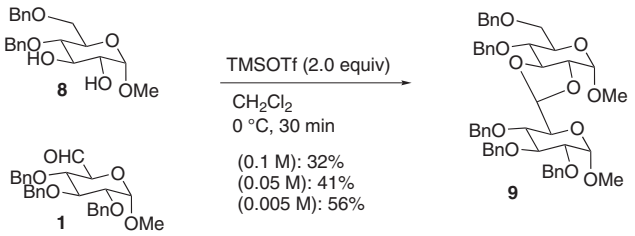
Table 1 Reduction of Acetal **6**[a]



Entry	Reagent	Time (h)	Yield of **7** (%)[b]	Yield of **5** (%)[c]
1	triphenylsilane	4	0	156
2	triisopropylsilane	4	0	145
3	TESH	4	53	104
4	DEMSH	4.5	73	96
5	DESH	3	47	100
6	DMESH	2.5	78	97
7[d]	DMESH	2	83	107
8	TMSH	3	70	108

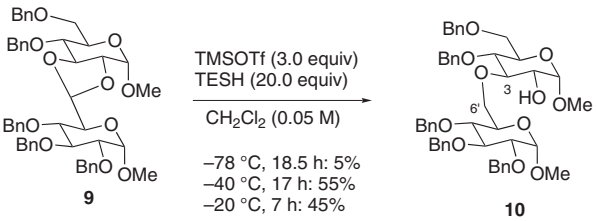
[a] Reagents: the substrate was treated with TMSOTf (4.8 equiv) and silane reagent (9.6 equiv) in CH_2Cl_2 at –20 °C.
[b] Isolated yield.
[c] Isolated yield of **5** based on **6**.
[d] DMESH (14.4 equiv) was used.

the acetalization of **1** with methyl α-D-glucoside **8**[8] (Scheme 3). In this case a cyclic acetal should form, however, one potential issue was the regioselectivity of the reduction of the cyclic acetal, which might afford the ether-linked sugars as a mixture of regioisomers.



Scheme 3 Synthesis of the cyclic acetal **9**.

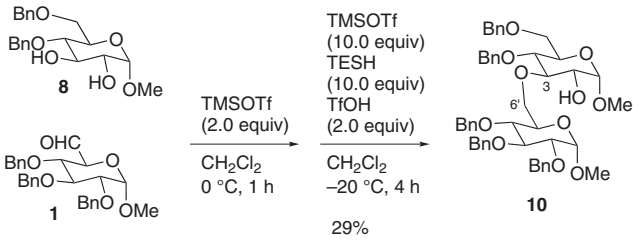
Initially we looked at the formation of the cyclic acetal **9**. Reaction of one of the hydroxyl groups of the 2,3-diol **8** with the C6-aldehyde of **1** furnishes a hemi-acetal. The second step, formation of the desired cyclic acetal, is not a simple task. There are two possible acetals which can form: the desired cyclic acetal **9**, which would result from intramolecular attack of the remaining hydroxyl group on the hemi-acetal or a non-cyclic acetal which would result from attack of a second molecule of **8** on the hemi-acetal. We focused on the concentration of the solution as we wished to avoid intermolecular acetalization. While intermolecular acetal formation proceeded under the usual conditions (0.1 M solution), it was found that intramolecular acetalization dominated under more dilute conditions. Reaction of aldehyde **1** with diol **8** (10 equiv) at high dilution (0.005 M) afforded the desired cyclic acetal **9** in 56% yield. It had been anticipated that the cyclic acetal derivative **9**, which was composed of a 2,3-*trans*-diol, would be unstable. However, we found that **9** was so stable that it could be isolated.[9]



Scheme 4 Regioselective reduction of the cyclic acetal **9** with TESH–TMSOTf.

Reduction of the acetal using TESH–TMSOTf was then examined (Scheme 4). The reaction proceeded very slowly at –78 °C, although we were delighted to find the 3,6′-ether-linked sugar **10** as the sole product. At –40 °C, reduction of the cyclic acetal **9** proceeded with specific cleavage of the 2,6′ connection, giving the 3,6′-ether-linked sugar **10** in 55% yield.[10] Unfortunately, an attempt to reduce the cyclic acetal at –20 °C resulted in over-reduced mixtures, which decreased the yield of **10**. It should be noted that a 2,6′-ether-linked sugar has never been observed even at high temperatures. Although there is limited information on the specificity for the 3,6′-ether-linked sugar, Hung et al. reported similar results: the 2,3-*O*-ben-

zylidene acetal of methyl α-D-glucoside was reduced by TMSOTf–TESH regioselectively to give the 3-*O*-benzyl product.[11] We postulate that the 2,6′-acetal bond is more reactive than the 3,6′-acetal bond, also the C2-alcohol of methyl α-D-glucoside may be influenced by the α-methoxy group at the anomeric position which decreases its nucleophilicity and hence the 2,6′-acetal bond would be cleaved.



Scheme 5 One-pot acetalization–reduction of the aldehyde **1** with the diol **8** using TESH in the presence of TMSOTf–TfOH.

The one-pot etherification of aldehyde **1** with diol **8** was further examined. Acetalization in the presence of TMSOTf was carried out at 0 °C for one hour, and subsequent addition of TESH and TMSOTf to this system converted the acetal into **10** in 19% yield. Surveying the conditions, we found that the addition of TfOH to this system provided a better result (29%). Although the effect caused by the combination of Lewis acid and Brönsted acid[12] in this system was not fully explained, it might be useful for the development of other reaction systems.

In conclusion, we have established a novel and efficient method for the synthesis of 2,6′-ether-linked sugars based on reductive etherification using TMESH as the reducing agent. We also developed the acetalization of the 2,3-diol and the C6-aldehyde of pyranoside and its regioselective reductive cleavage to produce a 3,6′-ether-linked sugar. This is the first application of the reductive etherification of secondary alcohols and the C6-aldehyde in pyranosides. Work concerning the connection of other sugars by an ether linkage using similar concepts is in progress.

Melting points were determined with a Yanagimoto micro melting point apparatus and were uncorrected. IR spectra were measured with a JASCO FT/IR-8000 spectrometer. HRMS-FAB were taken with a JEOL SX-102A. ^{1}H NMR and ^{13}C NMR spectra were recorded at 600 MHz with a JEOL GSX-600 spectrometer using TMS as an internal standard. Chemical shifts were reported in ppm downfield from TMS. Optical rotations were measured on a JASCO DIP-370 in a 1-dm cell. Analytical and preparative TLC was conducted on pre-coated TLC plates (silica gel 60 F_{254}, Merck). Column chromatography was performed using Merck silica gel 60N (100–210 μm). All anhydrous solvents were purified according to standard methods.

Compound 6

To a mixture of **1** (51.3 mg, 0.11 mmol) and **5** (517 mg, 1.11 mmol) in CH_2Cl_2 (0.56 mL) was added TMSOTf (60.5 μL, 0.334 mmol) at 0 °C. The resulting solution was stirred for 20 min. The reaction was quenched with a sat. solution of $NaHCO_3$ (30 mL), and extracted with CH_2Cl_2 (200 mL). The combined organic phase was dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The residual oil was initially purified by chromatography (toluene–EtOAc, 3:1) and the excess of **5** was recovered (372 mg, 0.801 mmol). Further chromatographic purification (toluene–*i*-Pr_2O, 2:3) of the remaining material afforded **6** (141 mg, 0.102 mmol, 92%); $[\alpha]_D^{19}$ +3.39 (*c* 0.84, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.32–7.11 (m, 45 H), 5.11 (d, *J* = 11.3 Hz, 1 H), 5.03 (s, 1 H), 4.98 (d, *J* = 1.7 Hz, 1 H), 4.87 (d, *J* = 10.4 Hz, 1 H), 4.84 (d, *J* = 10.5 Hz, 1 H), 4.76–4.70 (m, 5 H), 4.65–4.63 (m, 3 H), 4.59 (d, *J* = 12.1 Hz, 1 H), 4.56–4.47 (m, 6 H), 4.44 (d, *J* = 10.7 Hz, 1 H), 4.28 (d, *J* = 11.8 Hz, 1 H), 4.17 (d, *J* = 11.8 Hz, 1 H), 3.99–3.94 (m, 2 H), 3.91 (dd, *J* = 9.6, 9.6 Hz, 1 H), 3.85–3.83 (m, 3 H), 3.74–3.68 (m, 6 H), 3.63 (d, *J* = 10.2 Hz, 1 H), 3.40–3.38 (m, 2 H), 3.24 (s, 3 H), 3.23–3.22 (6 H, m).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 139.6, 138.7, 138.6, 138.5, 138.3, 138.2, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 126.8, 110.6, 103.0, 100.1, 98.0, 82.0, 79.9, 79.4, 78.0, 77.2, 76.0, 75.9, 75.6, 75.5, 75.1, 75.0, 74.4, 73.5, 73.4, 73.2, 73.1, 72.2, 72.0, 71.7, 69.6, 69.3, 55.3, 54.8, 54.4.

HRMS (FAB-NBA, NaI): *m*/*z* calcd for $C_{84}H_{92}O_{17}Na$: 1395.6232; found: 1395.6250.

Compound 7

To a solution of **6** (50 mg, 0.0364 mmol) in CH_2Cl_2 (0.49 mL) was added TMSOTf (31.7 μL, 0.175 mmol) and DMESH (69.2 μL, 0.524 mmol) successively at –78 °C. The resulting solution was stirred for 2 h at –20 °C. The reaction was quenched with a sat. aq solution of $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (200 mL). The combined organic phase was dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The residual oil was initially purified by chromatography (toluene–EtOAc, 4.5:1) and the excess of **5** was recovered (18.1 mg, 0.0389 mmol). Chromatographic purification (toluene–EtOAc, 15:1) of the remaining material afforded **7** (27.5 mg, 0.0302 mmol, 83%); $[\alpha]_D^{20}$ +3.02 (*c* 0.84, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.04 (m, 30 H), 4.95 (d, *J* = 10.7 Hz, 1 H), 4.83–4.77 (m, 5 H), 4.72–4.68 (m, 2 H), 4.65–4.62 (m, 3 H), 4.54 (d, *J* = 3.6 Hz, 1 H), 4.49 (d, *J* = 12.1 Hz, 1 H), 4.35–4.31 (m, 2 H), 3.96 (dd, *J* = 9.5, 9.1 Hz, 1 H), 3.90 (dd, *J* = 9.6, 9.3 Hz, 1 H), 3.86 (dd, *J* = 9.6, 2.8 Hz, 1 H), 3.78 (dd, *J* = 2.8, 1.9 Hz, 1 H), 3.75–3.64 (m, 6 H), 3.51 (dd, *J* = 9.5, 3.6 Hz, 1 H), 3.33 (s, 3 H), 3.31 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.9, 138.4, 138.2, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 99.9, 98.2, 82.1, 80.9, 79.9, 77.7, 77.6, 75.7, 75.1, 75.0, 73.5, 73.3, 72.4, 71.7, 71.2, 70.6, 69.2, 55.1, 54.6.

HRMS (FAB-NBA, NaI): *m*/*z* calcd for $C_{56}H_{62}O_{11}Na$: 933.4190; found: 933.4185.

Compound 9

To a mixture of **1** (500 mg, 1.08 mmol) and **8** (4.04 g, 10.8 mmol) in CH_2Cl_2 (216 mL) was added TMSOTf (392 μL, 2.16 mmol) at 0 °C. The resulting solution was stirred for 30 min. The reaction was quenched with a sat. solution of $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (200 mL). The combined organic phase was dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The residual oil was initially purified by chromatography (toluene–EtOAc, 2:1) and the excess of **8** was recovered. Chromatographic purification (hexane–Et_2O, 3:2) of the remaining material afforded **9** (497 mg, 0.607 mmol, 56%); $[\alpha]_D^{17}$ +87.7 (*c* 1.12, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.39–7.23 (m, 25 H), 5.55 (d, *J* = 1.6 Hz, 1 H), 5.11 (d, *J* = 3.0 Hz, 1 H), 4.98 (d, *J* = 10.9 Hz, 1 H), 4.87 (d, *J* = 10.7 Hz, 1 H), 4.83 (d, *J* = 10.9 Hz, 1 H), 4.81 (d, *J* = 12.4 Hz, 1 H), 4.80 (d, *J* = 11.4 Hz, 1 H), 4.71 (d, *J* = 12.4 Hz, 1 H), 4.65 (d, *J* = 3.7 Hz, 1 H), 4.64 (d, *J* = 10.7 Hz, 1 H), 4.61 (d, *J* = 12.2 Hz, 1 H), 4.54 (d, *J* = 11.4 Hz, 1 H), 4.50 (d, *J* = 12.2 Hz,

1 H), 4.06 (dd, *J* = 9.6, 9.5 Hz, 1 H), 3.99 (dd, *J* = 9.5, 9.3 Hz, 1 H), 3.87 (dd, *J* = 9.5, 9.4 Hz, 1 H), 3.82 (dd, *J* = 10.2, 1.6 Hz, 1 H), 3.76 (dd, *J* = 10.7, 3.8 Hz, 1 H), 3.71 (dd, *J* = 10.7, 2.2 Hz, 1 H), 3.64–3.61 (m, 3 H), 3.53 (dd, *J* = 9.5, 3.7 Hz, 1 H), 3.46 (s, 3 H), 3.40 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.6, 138.1, 137.9, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 103.0, 97.8, 97.6, 82.1, 79.8, 79.2, 78.5, 75.9, 75.8, 75.6, 75.1, 73.5, 73.2, 72.6, 71.4, 70.0, 68.1, 55.5, 54.9.

HRMS (FAB-NBA, NaI): *m*/*z* calcd for $C_{49}H_{54}O_{11}Na$: 841.3522; found: 841.3543.

Compound 10

To a solution of **9** (37.0 mg, 0.0452 mmol) in CH_2Cl_2 (0.90 mL) was added TMSOTf (24.6 μL, 0.136 mmol) and TESH (144 μL, 0.904 mmol) successively at –78 °C. The resulting solution was stirred for 17 h at –40 °C. The reaction was quenched with a sat. solution of $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (200 mL). The combined organic phase was dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The residual oil was purified by chromatography (toluene–EtOAc, 3:1) to afford **10** (20.3 mg, 0.0247 mmol, 55%).

One-Pot Synthesis of 10

To a mixture of **1** (40.0 mg, 0.087 mmol) and **8** (324 mg, 0.87 mmol) in CH_2Cl_2 (1.73 mL) was added TMSOTf (31.3 μL, 0.17 mmol) at 0 °C. The resulting solution was stirred for 1 h and then TMSOTf (157 μL, 0.87 mmol), TESH (138 μL, 0.87 mmol), and TfOH (15.3 μL, 0.17 mmol) were added successively at –78 °C. After stirring at –20 °C for 4 h, the reaction was quenched with a sat. solution of $NaHCO_3$ (30 mL), and extracted with CH_2Cl_2 (200 mL). The combined organic phase was dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The residual oil was purified by chromatography (toluene–Et_2O, 1:1) to afford **10** (20.9 mg, 0.0255 mmol, 29%); $[\alpha]_D^{20}$ +58.7 (*c* 0.95, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.35–7.05 (m, 25 H), 4.96 (d, *J* = 11.0 Hz, 1 H), 4.87 (d, *J* = 11.0 Hz, 1 H), 4.81–4.79 (m, 2 H), 4.77 (d, *J* = 12.1 Hz, 1 H), 4.73 (d, *J* = 10.9 Hz, 1 H), 4.68 (d, *J* = 3.6 Hz, 1 H), 4.66–4.63 (m, 3 H), 4.50 (d, *J* = 12.1 Hz, 1 H), 4.44 (d, *J* = 10.9 Hz, 1 H), 4.33 (dd, *J* = 11.8, 2.2 Hz, 1 H), 3.97 (dd, *J* = 9.4, 8.8 Hz, 1 H), 3.88 (dd, *J* = 11.8, 2.2, Hz 1 H), 3.77–3.71 (m, 4 H), 3.69–3.65 (m, 3 H), 3.56–3.54 (m, 2 H), 3.41 (s, 3 H), 3.35 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.7, 138.1, 138.0, 137.9, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.6, 127.5, 99.2, 98.2, 86.1, 81.8, 80.2, 77.3, 75.7, 75.1, 74.7, 73.5, 72.8, 71.5, 71.0, 70.3, 68.5.

HRMS (FAB-NBA, NaI): *m*/*z* calcd for $C_{49}H_{56}O_{11}Na$: 843.3720; found: 843.3726.

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References

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