Published in final edited form as:

J Carbohydr Chem. 2019 ; 38(2): 109–126. doi:10.1080/07328303.2019.1581889.

Facile Synthesis of Sugar Lactols via Bromine-Mediated Oxidation of Thioglycosides

Shuai Meng, Bishwa Raj Bhetuwal, Padam P. Acharya, Jianglong Zhu*

Department of Chemistry and Biochemistry and School of Green Chemistry and Engineering,
The University of Toledo, 2801 W. Bancroft Street, Toledo, Ohio 43606, United States.

Abstract

Synthesis of a variety of sugar lactols (hemiacetals) has been accomplished in moderate to excellent yields by using bromine-mediated oxidation of thioglycosides. It was found that acetonitrile is the optimal solvent for this oxidation reaction. This approach involving bromine as oxidant is superior to that using *N*-bromosuccinimide (NBS) which produces byproduct succinimide often difficult to separate from the lactol products.

Keywords

sugar lactols; hemiacetals; bromine; oxidation; thioglycosides

Introduction

Glycosyl hydroxides, i.e. sugar lactols or hemiacetals, serve as important glycosyl donors (1-hydroxy glycosyl donors) and synthetic intermediates for chemical synthesis of complex biologically significant carbohydrate molecules.^[1–5] Back in 1890s, sugars lactols were first used as glycosyl donors in the well-known Fischer glycosylation.^[6–7] Recently, Gin^[8–14] and Bennett^[15–16] reported dehydrative glycosylations using 1-hydroxy glycosyl donors. In addition, in 1970s Schmidt pioneered the studies of stereoselective synthesis of oligosaccharides and glycoconjugates via anomeric *O*-alkylation of sugar lactols.^[17–22] Based on Schmidt's work, recently our group^[23–27] and others^[28–33] resurrected the use of anomeric *O*-alkylation for stereoselective construction of challenging glycosidic linkages. Specifically, our group disclosed stereoselective synthesis of several classes of challenging glycosides via anomeric *O*-alkylation of the corresponding sugar hemiacetals, e.g. 2-deoxy- β -glycosides,^[23–24] 2-deoxy- α -glycosides,^[25] as well as β -mannosides.^[26–27] Furthermore, sugar hemiacetals are used as precursors for the preparation of commonly used glycosyl donors, e.g. trichloroacetimidates,^[34] *N*-(phenyl)trifluoroacetimidates,^[35] phosphites and phosphates,^[36–37] or *ortho*-alkynylbenzoates,^[38] carbonates,^[39–42] sulfonates,^[43–44] and glycosyl esters.^[45–46]

Typically, lactols (**2**) are obtained by methanolysis of glycosyl esters (**1**, X = OCOR),^[47–48] hydrolysis of glycosyl halides (**1**, X = halides)^[49–50] or methyl glycosides (**1**, X = OMe),^[51]

*Corresponding author. Tel.: +1 419 530-1501. Jianglong.Zhu@Utoledo.edu.

or oxidation of thioglycosides (**3**)^[52–53] (a and b, Scheme 1). Among those methods, oxidation of readily available and stable thioglycosides (**3**) to lactols is one of the most popular strategies for preparation of sugar hemiacetals and *N*-bromosuccinimide (NBS) is usually employed as the oxidant (b, Scheme 1). Despite its mild nature, the reaction employing NBS generates the byproduct succinimide which oftentimes is difficult to separate from the desired lactol products, especially when the lactols become quite polar. Therefore, our group has been searching for alternative oxidant to facilitate the purification process.

Bromine is often used to oxidize thioglycosides to the corresponding glycosyl bromide donors for the synthesis of various oligosaccharides and glycoconjugates.^[54–57] In addition, there was limited report that sugar hemiacetals can be prepared by bromine-mediated oxidation of thioglycosides via a two-step sequence: 1) bromine-mediated oxidation of thioglycosides in dry dichloromethane to the corresponding glycosyl bromide; 2) hydrolysis of isolated glycosyl bromide.^[58] Use of bromine as oxidant is advantageous as it can avoid the production of difficultly separable byproducts. However, this two-step procedure may not be suitable for carbohydrate substrates containing acid-sensitive protecting groups or free hydroxyl groups. We wondered if it is possible to develop a one-pot oxidation/hydrolysis under suitable conditions for the preparation of sugar hemiacetals from thioglycosides using bromine as the oxidant. In this Communication, we wish to report the facile synthesis of sugar lactols via bromine-mediated oxidation of thioglycosides in a mixture of acetonitrile and water (c, Scheme 1).

Results and Discussion

Phenyl 3,4,6-tri-*O*-benzyl-1-thio- α -D-mannopyranoside (**4**, Table 1) was chosen as the substrate for preparing 3,4,6-tri-*O*-benzyl-D-mannose **5** under bromine-mediated oxidation. It is worth noting that a stock solution of bromine in dichloromethane (5.0 M) was prepared for use instead of pure bromine due to easy handling and safety concerns.^[59] Initially, we used a mixture of acetone and water (10/1, v/v), the solvent system for NBS-mediated oxidation of thioglycosides, for bromine-mediated oxidation. This reaction was sluggish at 0 °C and took 24 hours to complete and 3,4,6-tri-*O*-benzyl-D-mannose **5** was isolated in 83% yield ($\alpha/\beta=3/1$, entry 1, Table 1). The slow reaction rate may be due to that Br₂ is also able to α -brominate acetone, which competes with the oxidation of thioglycosides. Addition of bromine solution at lower temperature followed by warming up to 0 °C did not help (entry 2). Switching to dichloromethane, the solvent used for preparation of glycosyl bromide by bromine oxidation of thioglycosides, did not work well and complex mixtures were obtained (entries 3 and 4). Use of THF as solvent gave similar results as acetone, albeit the reaction was found to be a little faster (entry 5). Finally, we found acetonitrile was the optimal solvent for this reaction which was complete in two hours and gave almost quantitative yield of the corresponding lactol **5** (entry 6). The method was also applied to 0.2 mmol and 1 gram scale of thioglycoside **4** which furnished the desired lactol **5** in 98% and 91% yield, respectively (entry 6). Application of previously reported two-step procedure for this oxidation–hydrolysis only gave 34% yield of the lactol **5** (entry 7). In comparison, use of NBS as the oxidant instead of bromine afforded lactol **5** in 82% yield (entry 8).

With the optimal condition established, the bromine-mediated oxidation of thioglycosides was applied to the synthesis of a variety of sugar hemiacetals (Table 2). In general, sugar hemiacetals were obtained in good to excellent yields. It was also found that both aryl (e.g. phenyl) and alkyl (e.g. ethyl) thioglycosides can be oxidized smoothly to afford the corresponding lactols in good yields (entry 1). Various functional groups, such as carbamate, amide, imide, azide, and carboxylic ester, are tolerated. For thioglycosides containing acid-sensitive protecting groups, such as silyl ethers (entry 2), benzylidene acetals (entries 10–12), and 1,2-diketals (entry 13), solid sodium bicarbonate needs to be added to buffer the acidity of the reaction in order to achieve good yields. Interestingly, methoxyethoxymethyl (MEM) ether was found to be stable in this type of reaction and no sodium bicarbonate was added necessarily (entry 9). Obviously, deoxy sugars, such as 6-deoxy and 2,6-dideoxy sugars, are very reactive substrates towards bromine oxidation (entries 2–4). Sugar substrates with acyl protecting groups, i.e. “disarmed donors”, including thioglycoside of peracetylated *N*-acetyl neuraminic acid (**18**), D-mannose-derived thioglycoside (**30**) and phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio- β -glucopyranoside (**32**), were found to be relatively unreactive and produced corresponding hemiacetals in moderate yields, probably due to the inductive effect. Allowing the reaction to proceed for an additional period of time or adding more Br₂ did not help, probably due to the decomposition of the starting materials or lactols over time (entries 7, 13 and 14).

In conclusion, an approach for the synthesis of sugar hemiacetals has been developed via bromine-mediated oxidation of thioglycosides in a mixture of acetonitrile/water. Various functional groups and protecting groups are tolerated and a wide range of sugar lactols were obtained in moderate to excellent yields. This method is advantageous as it avoids the production of byproducts difficult to separate.

Experimental

Materials and Methods

Proton and carbon nuclear magnetic resonance spectra (¹H NMR and ¹³C NMR) were recorded on either Bruker 600 (¹H NMR-600 MHz; ¹³C NMR 150) or INOVA 600 (¹H NMR-600 MHz; ¹³C NMR-150 MHz) at ambient temperature with CDCl₃ as the solvent unless otherwise stated. Chemical shifts are reported in parts per million relative to residual protic solvent internal standard CDCl₃: ¹H NMR at δ 7.26, ¹³C NMR at δ 77.36. Data for ¹H NMR are reported as follows: chemical shift, integration, multiplicity (app = apparent, par obs = partially obscure, ovrlp = overlapping, s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet) and coupling constants in Hertz. All ¹³C NMR spectra were recorded with complete proton decoupling. High resolution mass spectra (HRMS) were acquired on a Waters Acuity Premiere XE TOF LC-MS by electrospray ionization. Optical rotations were measured with Autopol-IV digital polarimeter; concentrations are expressed as g/100 mL.

All reagents and chemicals were purchased from Acros Organics, Sigma Aldrich, Fisher Scientific, Alfa Aesar, and Strem Chemicals and used without further purification. THF, methylene chloride, toluene, and diethyl ether were purified by passing through two packed columns of neutral alumina (Innovative Technology). Anhydrous DMF and benzene were

purchased from Acros Organics and Sigma-Aldrich and used without further drying. All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash column chromatography was performed using 200–400 mesh silica gel (Scientific Absorbents, Inc.). Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated.

General procedure for synthesis of sugar lactols by bromine-mediated oxidation of thioglycosides.

General procedure A: Thioglycosides (0.2 mmol) were dissolved by 1.0 mL acetonitrile in a 10 mL flask, followed by the addition of 0.1 mL water. The mixture was stirred at 0 °C for 30 min. 120 μ L of Br₂ (3.0 eq.) solution in CH₂Cl₂ (5.0 M) was added dropwise and then the yellow mixture was stirred at this temperature until the TLC showed that the substrate was completely consumed. Then the mixture was diluted by 5 mL saturated NaHCO₃ aqueous solution and evaporated under reduced pressure to remove acetonitrile. The residue was extracted by CH₂Cl₂ (10 mL $\times$ 3, for lactol **11** 10% *n*-butanol was used together). The organic layers were combined and dried over anhydrous Na₂SO₄. The filtrate was concentrated and purified by flash column chromatography to give the desired lactols.

General procedure B: Thioglycosides (0.2 mmol) were dissolved by 1.0 mL acetonitrile in a 10 mL flask, followed by the addition of 0.1 mL water and 168 mg of NaHCO₃ (10.0 eq.). The mixture was stirred at 0 °C for 30 min. 120 μ L of Br₂ (3.0 eq.) solution in CH₂Cl₂ (5.0 M) was added dropwise and then the yellow mixture was stirred at this temperature until the TLC showed that the substrate was completely consumed. Then the mixture was diluted by 5 mL saturated NaHCO₃ aqueous solution and evaporated under reduced pressure to remove acetonitrile. The residue was extracted by CH₂Cl₂ (10 mL $\times$ 3). The organic layers were combined and dried over anhydrous Na₂SO₄. The filtrate was concentrated and purified by flash column chromatography to give the desired lactol.

3,4,6-Tri-O-benzyl- α/β -D-mannopyranose (5).—Lactol **5** was prepared from thioglycoside **4**^[60] (109 mg, 0.201 mmol) following the general procedure A. The crude reaction mixture was purified by flash column chromatography (Hexanes/EtOAc = 2/1 to CH₂Cl₂/MeOH = 15/1) to give 88.8 mg (0.197 mmol, 98%) of lactol **5** (α/β = 4/1) as colorless syrup. ¹H and ¹³C NMR data of **5** were in agreement with reported ones.^[61]

2,3,4,6-Tetra-O-benzyl- α/β -D-glucopyranose (7).—Lactol **7** was prepared from thioglycoside **6**^[62] (127 mg, 0.201 mmol) following the general procedure A. The crude reaction mixture was purified by flash column chromatography (Hexanes/EtOAc = 5/1 to CH₂Cl₂/MeOH = 20/1) to give 90.8 mg (0.168 mmol, 84%) of lactol **7** (α/β = 2/1) as white solids. ¹H and ¹³C NMR data of **7** were in agreement with reported ones.^[63]

3,4-Di-O-*tert*-butyldimethylsilyl-2,6-dideoxy- α/β -D-glucopyranose (9).—Lactol **9** was prepared from thioglycoside **8**^[64] (93.7 mg, 0.2 mmol) following the general procedure B. The crude reaction mixture was purified by flash column chromatography (Hexanes/EtOAc = 35/1) to give 71.5 mg (0.19 mmol, 95%) of lactol **9** (α/β = 1.4/1) as colorless

symp. $[\alpha]_D^{23} = +61.5$ (*c* 0.1, CHCl₃). **¹H NMR (600 MHz, CDCl₃)** δ 5.28 (d, *J* = 2.9 Hz, 1H), 4.85 (ddd, *J* = 8.8, 6.1, 2.2 Hz, 0.6H), 4.01 (ddd, *J* = 10.5, 7.6, 4.4 Hz, 1H), 3.89 (dq, *J* = 8.5, 6.5 Hz, 1H), 3.69 (dddd, *J* = 10.8, 7.8, 4.6, 1.0 Hz, 0.6H), 3.41 (d, *J* = 6.7 Hz, 0.6H), 3.37 – 3.28 (m, 0.6H), 3.26 – 3.11 (m, 1.6H), 2.81 – 2.60 (m, 1H), 2.24 (ddd, *J* = 12.8, 4.7, 2.2 Hz, 0.6H), 2.16 – 2.01 (m, 1H), 1.68 (ddd, *J* = 13.6, 10.2, 3.6 Hz, 1H), 1.62 – 1.52 (m, 0.6H), 1.31 (d, *J* = 6.4 Hz, 1.8H), 1.26 (d, *J* = 6.5 Hz, 3H), 0.97 – 0.86 (m, 29H), 0.17 – 0.02 (m, 19H). **¹³C NMR (150 MHz, CDCl₃)** δ 93.66, 91.60, 77.90, 77.44, 73.06, 72.86, 70.44, 69.90, 41.82, 39.27, 26.40, 26.37, 26.22, 19.10, 18.78, 18.44, 18.42, 18.22, 18.19, –2.69, –2.79, –2.97, –3.15, –3.81, –3.93, –4.12, –4.26. **ESIHRMS** calculated for C₁₈H₄₀O₄Si₂Na [M+Na]⁺ 399.2363, found 399.2363.

2-O-Methyl-4-O-benzyl-6-deoxy- α/β -D-allopyranose (11).—Lactol **11** was prepared from thioglycoside **10**^[64] (69.7 mg, 0.194 mmol) following the general procedure A. The crude reaction mixture was purified by flash column chromatography (CH₂Cl₂/MeOH = 10/1) to give 46.9 mg (0.175 mmol, 90%) of lactol **11** (α/β = 1/1) as colorless syrup. $[\alpha]_D^{23} = +128.5$ (*c* 0.1, CHCl₃). **¹H NMR (600 MHz, CDCl₃)** δ 7.38 – 7.27 (m, 10H), 5.18 (s, 2H), 4.96 (dd, *J* = 7.9, 3.6 Hz, 1H), 4.68 – 4.64 (m, 2H), 4.55 – 4.51 (m, 2H), 4.45 (m, 1H), 4.39 (t, *J* = 2.9 Hz, 1H), 4.19 (s, 1H), 4.08 (m, 1H), 3.89 (m, 1H), 3.51 (s, 3H), 3.47 (s, 3H), 3.27 (s, 1H), 3.18 (m, 1H), 3.10 – 3.06 (m, 2H), 2.95 (dd, *J* = 7.8, 2.9 Hz, 1H), 2.58 (s, 1H), 1.28 (d, *J* = 6.2 Hz, 3H), 1.26 (d, *J* = 6.2 Hz, 3H). **¹³C NMR (150 MHz, CDCl₃)** δ 137.48, 137.23, 128.70, 128.60, 128.33, 128.14, 128.08, 128.02, 93.68, 91.61, 81.15, 79.87, 79.43, 76.27, 71.52, 71.46, 68.27, 67.53, 65.44, 61.28, 58.16, 56.72, 17.91, 17.76. **ESIHRMS** calculated for C₁₄H₂₀O₅Na [M+Na]⁺ 291.1208, found 291.1213.

2,3,4-Tri-O-benzyl-6-deoxy- α/β -L-galactopyranose (13).—Lactol **13** was prepared from thioglycoside **12**^[65] (108.9 mg, 0.201 mmol) following the general procedure A. The crude reaction mixture was purified by flash column chromatography (Hexanes/EtOAc = 2/1) to give 78.7 mg (0.181 mmol, 90%) of lactol **13** (α/β = 2/1) as colorless syrup. ¹H and ¹³C NMR data of **13** were in agreement with reported ones.^[66]

2-N-(Benzyloxy)carbonyl-3,4,6-tri-O-benzyl-2-deoxy-2-amino- α -D-mannopyranose (15).—Lactol **15** was prepared from thioglycoside **14** (134.4 mg, 0.199 mmol) following the general procedure A. The crude reaction mixture was purified by flash column chromatography (Hexanes/EtOAc = 3/1 to 1/1) to give 109.4 mg (0.187 mmol, 94%) of lactol **15** (α only) as white solids. $[\alpha]_D^{23} = +89.0$ (*c* 0.1, CHCl₃). **¹H NMR (600 MHz, CDCl₃)** δ 7.40 – 7.28 (m, 18H), 7.16 (dd, *J* = 7.0, 2.3 Hz, 2H), 5.34 – 5.28 (m, 1H), 5.26 (d, *J* = 8.8 Hz, 1H), 5.15 (s, 2H), 4.87 (d, *J* = 10.8 Hz, 1H), 4.79 (d, *J* = 11.0 Hz, 1H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.52 (d, *J* = 11.1 Hz, 1H), 4.47 (d, *J* = 12.2 Hz, 1H), 4.45 – 4.38 (m, 2H), 4.18 (d, *J* = 3.9 Hz, 1H), 4.14 (dd, *J* = 9.4, 4.5 Hz, 1H), 4.06 (ddd, *J* = 9.9, 4.8, 2.1 Hz, 1H), 3.66 (dd, *J* = 10.5, 4.8 Hz, 1H), 3.62 (dd, *J* = 10.4, 2.3 Hz, 1H), 3.56 (t, *J* = 9.6 Hz, 1H). **¹³C NMR (150 MHz, CDCl₃)** δ 156.55, 138.24, 138.04, 137.63, 136.29, 128.63, 128.50, 128.44, 128.40, 128.29, 128.26, 128.24, 128.19, 128.02, 127.90, 127.76, 93.83, 77.47, 75.15, 74.29, 73.44, 71.20, 70.31, 68.85, 67.12, 51.54. **ESIHRMS** calculated for C₃₅H₃₇NO₇Na [M+Na]⁺ 606.2468, found 606.2469.

2-N-Acetyl-3,4,6-tri-O-benzyl-2-deoxy-2-amino- α/β -D-mannopyranose (17).—

Lactol **17** was prepared from thioglycoside **16**^[67] (116.6 mg, 0.2 mmol) following the general procedure A. The crude reaction mixture was purified by flash column chromatography (CH₂Cl₂/MeOH=100/1) to give 84.4 mg (0.167 mmol, 84%) of lactol **17** (α/β = 2.5/1) as white solid. ¹H and ¹³C NMR data of **17** were in agreement with reported ones.^[68]

Methyl 4,7,8,9-tetra-O-acetyl-3,5-dideoxy-5-acetamido- α/β -D-glycero-D-galacto-2-nonulopyranosonate (19).—

Lactol **19** was prepared from thioglycoside **18**^[69] (118.0 mg, 0.202 mmol) following the general procedure A. The crude reaction mixture was purified by flash column chromatography (Hexanes/Acetone = 3/2) to give 65.0 mg (0.132 mmol, 65%) of lactol **19** (α/β = 1/10) as white solids with 34.2 mg (29%) of thioglycoside **18** recovered. ¹H and ¹³C NMR data of **19** were in agreement with reported ones.^[70]

Benzyl (3,4-di-O-benzyl- α/β -D-mannopyranose) uronate (21).—

Lactol **21** was prepared from thioglycoside **20** (106.3 mg, 0.191 mmol) following the general procedure A. The crude reaction mixture was purified by flash column chromatography (Hexanes/EtOAc = 2/1 to CH₂Cl₂/MeOH = 15/1) to give 66.5 mg (0.143 mmol, 75%) of lactol **21** (α/β = 10/1) as white solids. $[\alpha]_D^{23}$ = +35.3 (*c* 0.1, CHCl₃). ¹H NMR (600 MHz, CDCl₃) δ 7.34 – 7.25 (m, 15H), 7.23 – 7.20 (m, 2H), 5.38 (t, *J* = 4.1 Hz, 1H), 5.17 (d, *J* = 12.1 Hz, 0.1H), 5.12 (d, *J* = 12.1 Hz, 1H), 5.04 (d, *J* = 12.2 Hz, 1H), 4.83 (d, *J* = 9.8 Hz, 0.1H), 4.71 (d, *J* = 11.0 Hz, 0.1H), 4.68 (d, *J* = 11.2 Hz, 1H), 4.66 – 4.61 (m, 0.2H), 4.58 – 4.55 (m, 3H), 4.52 (d, *J* = 6.8 Hz, 1H), 4.44 (t, *J* = 10.5 Hz, 0.1H), 4.15 (t, *J* = 7.0 Hz, 1H), 4.10 (t, *J* = 8.1 Hz, 0.1H), 4.05 (d, *J* = 8.0 Hz, 0.1H), 4.00 (s, 0.1H), 3.95 (t, *J* = 3.7 Hz, 1H), 3.92 (dd, *J* = 7.1, 3.2 Hz, 1H), 3.65 (d, *J* = 4.7 Hz, 1H), 2.63 (d, *J* = 5.4 Hz, 1H). ¹³C NMR (150 MHz, CDCl₃) δ 169.60, 169.43, 137.82, 137.74, 137.62, 137.39, 135.19, 135.03, 128.74, 128.72, 128.70, 128.67, 128.64, 128.54, 128.49, 128.25, 128.11, 127.99, 127.97, 127.91, 127.89, 94.43, 93.82, 79.86, 78.21, 75.42, 75.30, 74.57, 74.33, 74.03, 72.50, 72.42, 72.11, 68.94, 67.93, 67.64, 67.37. ESIHRMS calculated for C₂₇H₂₈O₇Na [M+Na]⁺ 487.1733, found 487.1732.

3,4-Di-O-benzyl-6-O-(methoxyethoxy)methyl- α/β -D-mannopyranose (23).—

Lactol **23** was prepared from thioglycoside **22** (109.8 mg, 0.203 mmol) following the general procedure A. The crude reaction mixture was purified by flash column chromatography (Hexanes/EtOAc = 1/1 to CH₂Cl₂/MeOH = 15/1) to give 74.1 mg (0.165 mmol, 81%) of lactol **23** (α/β = 2.5/1) as colorless syrup. $[\alpha]_D^{23}$ = +91.0 (*c* 0.1, CHCl₃). ¹H NMR (600 MHz, CDCl₃) δ 7.39 – 7.27 (m, 14H), 5.27 (d, *J* = 1.7 Hz, 1H), 4.92 (d, *J* = 10.9 Hz, 0.4H), 4.89 (d, *J* = 11.0 Hz, 1H), 4.77 – 4.66 (m, 6.4H), 4.63 (d, *J* = 10.9 Hz, 0.4H), 4.59 (d, *J* = 11.0 Hz, 1H), 4.11 (ddd, *J* = 9.3, 6.7, 2.1 Hz, 1H), 4.06 (dd, *J* = 3.3, 1.8 Hz, 2H), 4.01 (dd, *J* = 3.3, 1.2 Hz, 0.4H), 3.97 (dd, *J* = 9.1, 3.2 Hz, 1H), 3.87 – 3.59 (m, 8H), 3.56 – 3.49 (m, 3H), 3.43 (ddd, *J* = 9.8, 4.7, 2.3 Hz, 0.4H), 3.35 (d, *J* = 5.7 Hz, 4.2H). ¹³C NMR (150 MHz, CDCl₃) δ 138.34, 138.24, 137.94, 137.72, 128.66, 128.63, 128.53, 128.49, 128.12, 128.03, 127.98, 127.96, 127.92, 127.91, 127.82, 96.32, 96.17, 94.21, 93.88, 81.73, 79.84,

75.19, 75.13, 74.92, 74.46, 73.99, 72.04, 71.93, 71.80, 70.59, 68.97, 68.64, 68.33, 67.16, 67.10, 67.08, 59.07, 59.04. **ESIHRMS** calculated for $C_{27}H_{32}O_8Na$ $[M+Na]^+$ 471.1995, found 471.1978.

3-O-Benzyl-4,6-O-[(R)-phenylmethylene]- α/β -D-mannopyranose (25).—Lactol **25** was prepared from thioglycoside **24**^[71] (91.4 mg, 0.203 mmol) following the general procedure B. The crude reaction mixture was purified by flash column chromatography (Hexanes/Acetone = 2/1 to CH_2Cl_2 /MeOH = 20/1) to give 52.3 mg (0.146 mmol, 72%) of lactol **25** (α/β = 2/1) as colorless syrup. 1H and ^{13}C NMR data of **25** were in agreement with reported ones.^[26]

3-O-Benzyl-4,6-O-[(R)-phenylmethylene]-2-deoxy-2-phthalimido- β -D-glucopyranose (27).—Lactol **27** was prepared from thioglycoside **26**^[72] (113.6 mg, 0.196 mmol) following the general procedure B. The crude reaction mixture was purified by flash column chromatography (Hexanes/Acetone = 4/1 to 1/1) to give 61.2 mg (0.126 mmol, 64%) of lactol **27** (β only) as white solids. 1H and ^{13}C NMR data of **27** were in agreement with reported ones.^[73]

3-O-Benzyl-4,6-O-[(R)-phenylmethylene]-2-deoxy-2-azido- α/β -D-mannopyranose (29).—Lactol **29** was prepared from thioglycoside **28**^[74] (95 mg, 0.2 mmol) following the general procedure B. The crude reaction mixture was purified by flash column chromatography (Hexanes/EtOAc = 7/1) to give 47 mg (0.122 mmol, 61%) of lactol **29** (α/β = 1.4/1) as colorless syrup. $[\alpha]_D^{23}$ = +34.0 (*c* 0.1, $CHCl_3$). **1H NMR (600 MHz, $CDCl_3$)** δ 7.49 (ddd, *J* = 7.3, 3.8, 1.8 Hz, 3H), 7.43 – 7.27 (m, 14H), 5.63 (s, 1H), 5.61 (s, 0.7H), 5.17 (dd, *J* = 3.4, 1.5 Hz, 1H), 4.95 – 4.90 (m, 1.7H), 4.80 – 4.71 (m, 2.4H), 4.32 (dd, *J* = 10.5, 4.9 Hz, 0.7H), 4.23 (dd, *J* = 10.3, 4.9 Hz, 1H), 4.19 (dd, *J* = 9.7, 3.7 Hz, 1H), 4.13 (t, *J* = 9.5 Hz, 1H), 4.08 – 4.00 (m, 3.5H), 3.87 (dd, *J* = 9.6, 3.7 Hz, 0.7H), 3.82 (td, *J* = 10.3, 2.2 Hz, 1.7H), 3.60 (d, *J* = 11.7 Hz, 0.7H), 3.36 (td, *J* = 9.7, 4.9 Hz, 0.7H), 2.78 (d, *J* = 3.5 Hz, 1H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 138.11, 137.76, 137.47, 137.29, 129.19, 129.11, 128.67, 128.56, 128.41, 128.37, 128.13, 127.90, 127.78, 127.66, 126.17, 126.12, 101.75, 101.67, 94.15, 93.28, 79.28, 78.61, 77.57, 75.29, 73.50, 73.45, 68.83, 68.50, 67.13, 65.09, 64.07, 62.99. **ESIHRMS** calculated for $C_{20}H_{21}N_3O_5Na$ $[M+Na]^+$ 406.1379, found 406.1379.

2,6-Di-O-benzoyl-3,4-O-[(1S,2S)-1,2-dimethoxy-1,2-dimethyl-1,2-ethanediyl]- α/β -D-mannopyranose (31).—Lactol **31** was prepared from thioglycoside **30** (119.3 mg, 0.201 mmol) following the general procedure B. The crude reaction mixture was purified by flash column chromatography (Hexanes/EtOAc = 4/1 to 1/1) to give 60.9 mg (0.121 mmol, 60%) of lactol **31** (α/β > 20/1) as colorless syrup with 37.1 mg (31%) of thioglycoside **30** recovered. $[\alpha]_D^{23}$ = +123.5 (*c* 0.1, $CHCl_3$). **1H NMR (600 MHz, $CDCl_3$)** δ 8.08 – 8.02 (m, 4H), 7.60 – 7.52 (m, 2H), 7.38 (q, *J* = 7.7 Hz, 4H), 5.39 (dd, *J* = 4.0, 1.6 Hz, 1H), 5.34 (dd, *J* = 3.0, 1.7 Hz, 1H), 4.62 (dd, *J* = 12.0, 2.2 Hz, 1H), 4.56 (dd, *J* = 12.0, 3.5 Hz, 1H), 4.48 (t, *J* = 10.2 Hz, 1H), 4.38 (dd, *J* = 10.3, 3.0 Hz, 1H), 4.34 (dt, *J* = 10.0, 2.8 Hz, 1H), 3.69 (dd, *J* = 4.0, 1.6 Hz, 1H), 3.29 (s, 3H), 3.19 (s, 3H), 1.29 (s, 3H), 1.24 (s, 3H). **^{13}C NMR (150 MHz,**

CDCl₃ δ 166.59, 166.10, 133.23, 133.21, 130.27, 130.06, 129.97, 129.75, 128.51, 128.49, 100.39, 100.10, 92.98, 71.56, 68.99, 65.86, 63.48, 62.67, 48.28, 48.05, 17.86, 17.76.
ESIHRMS calculated for C₂₆H₂₀O₁₀Na [M+Na]⁺ 525.1737, found 525.1743.

2,3,4,6-Tetra-O-acetyl- α/β -D-glucopyranose (33).—Lactol **33** was prepared from thioglycoside **32**^[75] (88.6 mg, 0.201 mmol) following the general procedure A. The crude reaction mixture was purified by flash column chromatography (Hexanes/Acetone = 2/1) to give 26.9 mg (0.077 mmol, 38%) of lactol **33** (α/β = 4/1) as colorless syrup with 21.3 mg (24%) of thioglycoside **32** recovered. ¹H and ¹³C NMR data of **33** were in agreement with reported ones.^[76]

2,3,6-Tri-O-benzyl-4-O-(2,3,4,6-tetra-O-benzyl- β -D-galactopyranosyl)- α/β -D-glucopyranose (35).—Lactol **35** was prepared from thioglycoside **34**^[77] (207.0 mg, 0.194 mmol) following the general procedure A. The crude reaction mixture was purified by flash column chromatography (Hexanes/EtOAc = 3/1) to give 163.0 mg (0.167 mmol, 86%) of lactol **35** (α/β = 2/1) as white solids. ¹H and ¹³C NMR data of **35** were in agreement with reported ones.^[78]

Acknowledgements

We are grateful to National Science Foundation (CHE-1464787), National Institutes of Health Common Fund Glycosciences Program (U01GM125289), and The University of Toledo for supporting this research.

Funding

National Science Foundation [CHE-1464787]; National Institutes of Health Common Fund Glycosciences Program [U01GM125289].

References

- [1]. Koto S; Sato T; Morishima N; Zen S The glucosylation of several alcohols with tetra-*O*-benzyl- α -D-glucopyranose and a mixture of *p*-nitrobenzenesulfonyl chloride, silver trifluoromethanesulfonate, and triethylamine. *Bull. Chem. Soc. Jpn* 1980, 53, 1761–1762.
- [2]. Susaki H Glycosidation with 1-hydroxy sugars as glycosyl donors promoted by trimethylsilyl chloride and zinc triflate. *Chem. Pharm. Bull* 1994, 42, 2.
- [3]. Suda S; Mukaiyama T Stereoselective synthesis of 1,2-trans-ribofuranosides from 1-hydroxy sugars by the use of [1,2-benzenediolato(2-)-*O,O'*]oxotitanium and trifluoromethanesulfonic anhydride. *Chem. Lett* 1991, 431–434.
- [4]. Uchiro H; Mukaiyama T Trityl salt catalyzed stereoselective glycosylation of alcohols with 1-hydroxyribofuranose. *Chem. Lett* 1996, 79–80.
- [5]. Inanaga J; Yokoyama Y; Hanamoto T Catalytic *O*-glycosylation and *S*-glycosylation of 1-hydroxy sugars. *J. Chem. Soc., Chem. Commun* 1993, 1090–1091.
- [6]. Izumi M; Fukase K; Kusumoto S TMSCl as a mild and effective source of acidic catalysis in Fischer glycosidation and use of propargyl glycoside for anomeric protection. *Biosci. Biotechnol. Biochem* 2002, 66, 211–214. [PubMed: 11866111]
- [7]. Fischer E Ueber die glucoside der alkohole. *Chem. Ber* 1893, 26, 2400–2412.
- [8]. Garcia BA; Poole JL; Gin DY Direct glycosylations with 1-hydroxy glycosyl donors using trifluoromethanesulfonic anhydride and diphenyl sulfoxide. *J. Am. Chem. Soc* 1997, 119, 7597–7598.
- [9]. Garcia BA; Gin DY Dehydrative glycosylation with activated diphenyl sulfonium reagents. Scope, mode of *C*(1)-hemiacetal activation, and detection of reactive glycosyl intermediates. *J. Am. Chem. Soc* 2000, 122, 4269–4279.

- [10]. Nguyen HM; Poole JL; Gin DY Chemoselective iterative dehydrative glycosylation. *Angew. Chem., Int. Ed* 2001, 40, 414–417.
- [11]. Kim YJ; Gin DY Synthesis of the trisaccharide portion of the immunologic adjuvant QS-21A via sulfonium-mediated oxidative and dehydrative glycosylation. *Org. Lett* 2001, 3, 1801–1804. [PubMed: 11405715]
- [12]. Nguyen HM; Chen Y; Duron SG; Gin DY Sulfide-mediated dehydrative glycosylation. *J. Am. Chem. Soc* 2001, 123, 8766–8772. [PubMed: 11535081]
- [13]. Gin D Dehydrative glycosylation with 1-hydroxy donors. *J. Carbohydr. Chem* 2002, 21, 645–665.
- [14]. Boebel TA; Gin DY Probing the mechanism of sulfoxide-catalyzed hemiacetal activation in dehydrative glycosylation. *J. Org. Chem* 2005, 70, 5818–5826. [PubMed: 16018673]
- [15]. Nogueira JM; Nguyen SH; Bennett CS Cyclopropenium cation promoted dehydrative glycosylations using 2-deoxy- and 2,6-dideoxy-sugar donors. *Org. Lett* 2011, 13, 2814–2817. [PubMed: 21548642]
- [16]. Nogueira JM; Bylsma M; Bright DK; Bennett CS Reagent-controlled α -selective dehydrative glycosylation of 2,6-dideoxy- and 2,3,6-trideoxy sugars. *Angew. Chem., Int. Ed* 2016, 55, 10088–10092.
- [17]. Schmidt RR; Michel J Direct *O*-glycosyl trichloroacetimidate formation - nucleophilicity of the anomeric oxygen atom. *Tetrahedron Lett* 1984, 25, 821–824.
- [18]. Schmidt RR New methods for the synthesis of glycosides and oligosaccharides—are there alternatives to the Koenigs-Knorr method? *Angew. Chem., Int. Ed* 1986, 25, 212–235.
- [19]. Schmidt RR Recent developments in the synthesis of glycoconjugates. *Pure Appl. Chem* 1989, 61, 1257–1270.
- [20]. Schmidt RR; Klotz W Glycoside bond formation via anomeric *O*-alkylation: how many protective groups are required? *Synlett* 1991, 168–170.
- [21]. Tsvetkov YE; Klotz W; Schmidt RR Disaccharide synthesis via anomeric *O*-alkylation. *Liebigs Ann. Chem* 1992, 371–375.
- [22]. Schmidt RR The anomeric *O*-alkylation and the trichloroacetimidate method - versatile strategies for glycoside bond formation. *Frontiers in Natural Product Research* 1996, 1 (Modern Methods in Carbohydrate Synthesis), 20–54.
- [23]. Zhu D; Baryal KN; Adhikari S; Zhu J Direct synthesis of 2-deoxy- β -glycosides via anomeric *O*-alkylation with secondary electrophiles. *J. Am. Chem. Soc* 2014, 136, 3172–3175. [PubMed: 24476042]
- [24]. Li X; Woodward J; Hourani A; Zhu D; Ayoub S; Zhu J Synthesis of the 2-deoxy trisaccharide glycal of antitumor antibiotics landomycins A and E. *Carbohydr. Res* 2016, 430, 54–58. [PubMed: 27196313]
- [25]. Zhu D; Adhikari S; Baryal KN; Abdullah BN; Zhu J Stereoselective synthesis of α -Digitoxosides and α -Boiviniosides via chelation-controlled anomeric *O*-alkylation. *J. Carbohydr. Chem* 2014, 33, 438–451.
- [26]. Nguyen H; Zhu D; Li X; Zhu J Stereoselective construction of β -mannopyranosides by anomeric *O*-Alkylation: Synthesis of the trisaccharide core of *N*-linked glycans. *Angew. Chem., Int. Ed* 2016, 55, 4767–4771.
- [27]. Bhetuwal BR; Woodward J; Li X; Zhu J Stereoselective β -mannosylation via anomeric *O*-alkylation: Concise synthesis of β -D-Xyl-(1 $\rightarrow$ 2)- β -D-Man-(1 $\rightarrow$ 4)- α -D-Glc-OMe, a trisaccharide oligomer of the hyriopsis schlegelii glycosphingolipid. *J. Carbohydr. Chem* 2017, 36, 162–172.
- [28]. Lubineau A; Escher S; Alais J; Bonnaffé D Stereoselectivity control in anomeric *O*-alkylation. Application to the synthesis of C2 symmetric glycoconjugates. *Tetrahedron Lett.* 1997, 38, 4087–4090.
- [29]. Trewartha G; Burrows JN; Barrett AGM Glycosidation via conjugate addition of anomeric alkoxides to nitroalkenes and nitrosoalkenes. *Tetrahedron Lett.* 2005, 46, 3553–3556.
- [30]. Ryan DA; Gin DY Ring-opening of aziridine-2-carboxamides with carbohydrate *C1-O*-nucleophiles. Stereoselective preparation of α - and β -*O*-glycosyl serine conjugates. *J. Am. Chem. Soc* 2008, 130, 15228–15229. [PubMed: 18950157]
- [31]. Morris WJ; Shair MD Stereoselective synthesis of 2-deoxy- β -glycosides using anomeric *O*-alkylation/arylation. *Org. Lett* 2009, 11, 9–12. [PubMed: 19061365]

- [32]. Pertel SS; Gorkunenko OA; Kakayan ES; Chirva VJ Synthesis of 1,2-cis- and 1,2-trans-glycosides of 2-acetamido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranose by anomeric *O*-alkylation. *Carbohydr. Res* 2011, 346, 685–688. [PubMed: 21320702]
- [33]. Li X; Berry N; Saybolt K; Ahmed U; Yuan Y Stereoselective β -mannosylation via anomeric *O*-alkylation: Formal synthesis of potent calcium signal modulator acremomannolipin A. *Tetrahedron Lett.* 2017, 58, 2069–2072.
- [34]. Schmidt RR; Michel J Facile synthesis of α -*O*-glycosyl and β -*O*-glycosyl imidates - preparation of glycosides and disaccharides. *Angew. Chem., Int. Ed* 1980, 19, 731–732.
- [35]. Yu B; Tao HC Glycosyl trifluoroacetimidates. Part 1: Preparation and application as new glycosyl donors. *Tetrahedron Lett.* 2001, 42, 2405–2407.
- [36]. Sim MM; Kondo H; Wong CH Synthesis of dibenzyl glycosyl phosphites using dibenzyl *N,N*-diethylphosphoramidite as phosphitylating reagent: an effective route to glycosyl phosphates, nucleotides, and glycosides. *J. Am. Chem. Soc* 1993, 115, 2260–2267.
- [37]. Garcia BA; Gin DY Synthesis of glycosyl-1-phosphates via dehydrative glycosylation. *Org. Lett* 2000, 2, 2135–2138. [PubMed: 10891249]
- [38]. Li Y; Yang Y; Yu B An efficient glycosylation protocol with glycosyl ortho-alkynylbenzoates as donors under the catalysis of Ph_3PAuOTf . *Tetrahedron Lett.* 2008, 49, 3604–3608.
- [39]. Babu RS; O'Doherty GA A palladium-catalyzed glycosylation reaction: the de novo synthesis of natural and unnatural glycosides. *J. Am. Chem. Soc* 2003, 125, 12406–12407. [PubMed: 14531673]
- [40]. Babu RS; Zhou M; O'Doherty GA De novo synthesis of oligosaccharides using a palladium-catalyzed glycosylation reaction. *J. Am. Chem. Soc* 2004, 126, 3428–3429. [PubMed: 15025462]
- [41]. Mishra B; Neralkar M; Hotha S Stable alkynyl glycosyl carbonates: Catalytic anomeric activation and synthesis of a tridecasaccharide reminiscent of mycobacterium tuberculosis cell wall lipoarabinomannan. *Angew. Chem., Int. Ed* 2016, 55, 7786–7791.
- [42]. Yu X; O'Doherty GA De novo synthesis in carbohydrate chemistry: From furans to monosaccharides and oligosaccharides. *ACS Symposium Series* 2008, 990 (Chemical Glycobiology), 3–28.
- [43]. Issa JP; Lloyd D; Steliotes E; Bennett CS Reagent controlled β -specific dehydrative glycosylation reactions with 2-deoxy-sugars. *Org. Lett* 2013, 15, 4170–4173. [PubMed: 23906042]
- [44]. Issa JP; Bennett CS A reagent-controlled $\text{S}_{\text{N}}2$ -glycosylation for the direct synthesis of β -linked 2-deoxy-sugars. *J. Am. Chem. Soc* 2014, 136, 5740–5744. [PubMed: 24670112]
- [45]. Barrett AGM; Bezuidenhout BCB A convenient stereoselective Synthesis of α -glycosyl esters. *Heterocycles* 1989, 28, 209–212.
- [46]. Lim D; Fairbanks AJ Selective anomeric acetylation of unprotected sugars in water. *Chem. Sci* 2017, 8, 1896–1900. [PubMed: 28553480]
- [47]. Deng LH; Tsybina P; Gregg KJ; Mosi R; Zandberg WF; Boraston AB; Vocadlo DJ Synthesis of 4-methylumbelliferyl α -D-mannopyranosyl-(1 $\rightarrow$ 6)- β -D-mannopyranoside and development of a coupled fluorescent assay for GH125 exo- α -1,6-mannosidases. *Biorg. Med. Chem* 2013, 21, 4839–4845.
- [48]. El-Badri MH; Willenbring D; Tantillo DJ; Gervay-Hague J Mechanistic studies on the stereoselective formation of β -mannosides from mannosyl iodides using α -deuterium kinetic isotope effects. *J. Org. Chem* 2007, 72, 4663–4672. [PubMed: 17539683]
- [49]. Singhamahapatra A; Sahoo L; Paul KJV; Varghese B; Loganathan D Improved synthesis of per-*O*-acetylated Cl hydroxyglycopyranose and structural study as non-covalent organic framework. *Tetrahedron Lett.* 2013, 54, 6121–6124.
- [50]. Pilgrim W; Murphy PV $\text{SnCl}(4)$ - and $\text{TiCl}(4)$ -catalyzed anomerization of acylated *O*- and *S*-glycosides: analysis of factors that lead to higher α : β anomer ratios and reaction rates. *J. Org. Chem* 2010, 75, 6747–6755. [PubMed: 20836488]
- [51]. Peng RG; VanNieuwenhze MS Construction of the DEF-ring system of nogalamycin and menogaril via an efficient Suzuki-Miyaura reaction. *Tetrahedron Lett.* 2017, 58, 2236–2239.

- [52]. Gomez AM; Company MD; Agocs A; Uriel C; Valverde S; Lopez JC Synthesis of 2,3 : 4,6-di-O-isopropylidene-D-allopyranose from D-glucose. *Carbohydr. Res* 2005, 340, 1872–1875. [PubMed: 15979053]
- [53]. Yamamoto K; Yakushiji F; Matsumaru T; Ichikawa S Total Synthesis of Tunicamycin V. *Org Lett* 2018, 20, 256–259. [PubMed: 29256622]
- [54]. Singh Y; Wang T; Geringer SA; Stine KJ; Demchenko AV Regenerative glycosylation. *J. Org. Chem* 2018, 83, 374–381. [PubMed: 29227649]
- [55]. Emmadi M; Khan N; Lykke L; Reppe K; S GP; Lisboa MP; Wienhold SM; Witzenrath M; Pereira CL; Seeberger PHA *Streptococcus pneumoniae* type 2 oligosaccharide glycoconjugate elicits opsonic antibodies and is protective in an animal model of invasive pneumococcal disease. *J. Am. Chem. Soc* 2017, 139, 14783–14791. [PubMed: 28945368]
- [56]. Lu X; Kovac P Chemical synthesis of the galacturonic acid containing pentasaccharide antigen of the *O*-specific polysaccharide of *Vibrio cholerae* O139 and its five fragments. *J. Org. Chem* 2016, 81, 6374–6394. [PubMed: 27452084]
- [57]. Hederos M; Konradsson P Synthesis of the trypanosoma cruzi LPPG heptasaccharyl myo-inositol. *J. Am. Chem. Soc* 2006, 128, 3414–3419. [PubMed: 16522122]
- [58]. Paulsen H; Heume M; Nurnberger H Synthesis of branched nonasaccharide sequence of bisected structure of *N*-glycoproteins. *Carbohydr. Res* 1990, 200, 127–166. [PubMed: 2379203]
- [59]. At large scale, bromine may be used directly for this reaction via slow addition.
- [60]. Sanapala SR; Kulkarni SS Chemical synthesis of asparagine-linked archaeal *N*-glycan from *Methanothermobacter fervidus*. *Chem. Eur. J* 2014, 20, 3578–3583. [PubMed: 24616211]
- [61]. Jonke S; Liu K-G; Schmidt, R. R. Solid-phase oligosaccharide synthesis of a small library of *N*-glycans. *Chem. Eur. J* 2006, 12, 1274–1290. [PubMed: 16273561]
- [62]. France RR; Rees NV; Wadhawan JD; Fairbanks AJ; Compton RG Selective activation of glycosyl donors utilising electrochemical techniques: a study of the thermodynamic oxidation potentials of a range of chalcoglycosides. *Org. Biomol. Chem* 2004, 2, 2188–2194. [PubMed: 15280954]
- [63]. Zeng J; Vedachalam S; Xiang S; Liu X-W Direct *C*-glycosylation of organotrifluoroborates with glycosyl fluorides and its application to the total synthesis of (+)-Varitriol. *Org. Lett* 2011, 13, 42–45. [PubMed: 21114334]
- [64]. Acharya PP; Baryal KN; Reno CE; Zhu J Synthesis of *S*-linked trisaccharide glycal of derhodinosylurdamycin A: Discovery of alkyl thiocyanate as an efficient electrophile for stereoselective sulfenylation of 2-deoxy glycosyl lithium. *Carbohydr. Res* 2017, 448, 103–109. [PubMed: 28645002]
- [65]. Li C-Y; Liu G-J; Dua W; Zhang Y; Xing G-W A novel *O*-fucosylation strategy preactivated by (*p*-Tol)₂SO/Tf₂O and its application for the synthesis of Lewis blood group antigen Lewis^a. *Tetrahedron Lett.* 2017, 58, 2109–2112.
- [66]. Matwiejuk M; Thiem J New method for regioselective glycosylation employing saccharide oxyanions. *Eur. J. Org. Chem* 2011, 5860–5878.
- [67]. Arihara R; Kakita K; Suzuki N; Nakamura S; Hashimoto S Glycosylation with 2-acetamido-2-deoxyglycosyl donors at a low temperature: Scope of the non-oxazoline method. *J. Org. Chem* 2015, 80. [PubMed: 25384731]
- [68]. Ayadi E; Czernecki S; Xie J Convenient preparation of perbenzylated 2-azido and 2-*N*-acetylamino-2-deoxy-D-hexono-1,5-lactones by oxidation of the corresponding lactols. *J. Carbohydr. Chem* 1996, 15, 191–199.
- [69]. Liao GC; Zhou ZF; Guo ZW Synthesis and immunological study of α-2,9-oligosialic acid conjugates as anti-group C meningitis vaccines. *Chem. Commun* 2015, 51, 9647–9650.
- [70]. Nagorny P; Fasching B; Li X; Chen G; Aussedat B; Danishefsky SJ Toward fully synthetic homogeneous β-human follicle-stimulating hormone (β-hFSH) with a biantennary N-linked dodecasaccharide. synthesis of β-hFSH with chitobiose units at the natural linkage sites. *J. Am. Chem. Soc* 2009, 131, 5792–5799. [PubMed: 19341309]
- [71]. Ohira S; Yamaguchi Y; Takahashi T; Tanaka H The chemoselective *O*-glycosylation of alcohols in the presence of a phosphate diester and its application to the synthesis of oligomannosylated phosphatidyl inositols. *Tetrahedron* 2015, 71, 6602–6611.

- [72]. Gampe CM; Tsukamoto H; Wang TS; Walker S; Kahne D Modular synthesis of diphospholipid oligosaccharide fragments of the bacterial cell wall and their use to study the mechanism of moenomycin and other antibiotics. *Tetrahedron* 2011, 67, 9771–9778. [PubMed: 22505780]
- [73]. Chiara JL; Garcia A; Cristobal-Lumbroso G Ketone-imide versus ketone-oxime reductive cross-coupling promoted by samarium diiodide: new mechanistic insight gained from a failed aminocyclopentitol synthesis. *J. Org. Chem* 2005, 70, 4142–4151. [PubMed: 15876107]
- [74]. Litjens REJN; Leeuwenburgh MA; van der Marel GA; van Boom JH A novel approach towards the stereoselective synthesis of 2-azido-2-deoxy- β -D-mannosides. *Tetrahedron Lett.* 2001, 42, 8693–8696.
- [75]. D'Angelo KA; Taylor MS Borinic acid catalyzed stereo- and regioselective couplings of glycosyl methanesulfonates. *J. Am. Chem. Soc* 2016, 138, 11058–11066. [PubMed: 27533523]
- [76]. Baddeley TC; Harrison WTA; Howie RA; Skakle JMS; Wardell JL Co-crystallised α - and β -anomers of 2,3,4,6-tetra-acetyl-D-glucopyranose, in which the α - and β -Anomers are randomly distributed in the hydrogen-bonded chains of molecules. *J. Chem. Crystallogr* 2007, 37, 853–858.
- [77]. McGarvey GJ; LeClair CA; Schmidtman BA Studies on the stereoselective synthesis of C-allyl glycosides. *Org Lett* 2008, 10, 4727–4730. [PubMed: 18826234]
- [78]. Yamanoi T; Misawa N; Matsuda S; Watanabe M Preparation of partially benzylated mono-, di-, and trisaccharides by selective cleavage of the β -fructofuranosidic linkage in fully benzylated sucrose and sucrose-related oligosaccharides under acidic conditions. *Carbohydr. Res* 2008, 343, 1366–1372. [PubMed: 18423585]

- a. Preparation of lactols by methanolysis of glycosyl esters or hydrolysis of halides/methyl glycosides

- b. Preparation of lactols by NBS-mediated oxidation/hydrolysis of thioglycosides

- c. This work

byproduct succinimide
(difficult to separate)

Scheme 1.

Representative strategies for preparation of sugar lactols.

Table 1.

Synthesis of 3,4,6-tri-*O*-benzyl-D-mannose by bromine-mediated oxidation of corresponding thioglycoside.^a

Entry	Solvent/Temp/Time ^b	Yield, ^c α/β ratio ^d
1	acetone/H ₂ O (10/1, v/v), 0 °C, 24 h	83%, 3/1
2	acetone/H ₂ O (10/1, v/v), -30 to 0 °C, 26 h	79%, 4/1
3	CH ₂ Cl ₂ /H ₂ O (10/1, v/v), -30 to 0 °C, 3.5 h	trace
4	CH ₂ Cl ₂ /H ₂ O (10/1, v/v), 0 °C, 3 h	trace
5	THF/H ₂ O (10/1, v/v), 0 °C, 12 h	81%, 4/1
6	CH ₃ CN/H ₂ O (10/1, v/v), 0 °C, 2 h	97% (98%, ^e 91% ^f), 4/1
7	Br ₂ , CH ₂ Cl ₂ , 0 °C, 0.5 h; then acetone/H ₂ O (4/1, v/v), RT, 2 h ^g	34%
8	NBS (3.0 eq.), acetone/H ₂ O (10/1, v/v), 0 °C, 2 h	82%

^a All reactions were performed using 0.1 mmol of phenyl 3,4,6-tri-*O*-benzyl-1-thio-D-mannopyranoside **4** (1.0 eq.) and 60 μ L of 5.0 M Br₂ in CH₂Cl₂ (3.0 eq.) in 0.5 mL organic solvent and 50 μ L H₂O unless otherwise noted;

^b When TLC showed the substrate was completely consumed;

^c Isolated yield;

^d Determined by ¹H NMR;

^e Isolated yield obtained on 0.2 mmol scale.

^f Isolated yield on a 1 gram scale.

^g see reference 58.

Table 2.

Synthesis of various sugar lactols by bromine-mediated oxidation of thioglycosides.^a

Entry	Thioglycosides	Lactols	Yield, ^b α/β ratio, ^c Reaction Condition, Time
1	 6a , R = Ph 6b , R = Et	 7	84%, 2/1 from 6a , A, 2 h; 86%, 2/1 from 6b , A, 2 h
2	 8	 9	95%, 1.4/1, B, 1 h
3	 10	 11	90%, 1/1, A, 2 h
4	 12	 13	93%, 2/1, A, 2 h
5	 14	 15	94%, α only, A, 2 h
6	 16	 17	84%, 2.5/1, A, 2 h
7	 18	 19	66%, ^d 1/10, A, 12 h; 63%, ^e 1/10, A, 12 h

A: Acetonitrile/H₂O (10:1), 0 °C

B: NaHCO₃ (10.0 eq.), Acetonitrile/H₂O (10:1), 0 °C

Entry	Thioglycosides	Lactols	Yield, ^b α/β ratio, ^c Reaction Condition, Time
8			75%, 10/1, A, 4 h
9			81%, 2.5/1, A, 3 h
10			15%, 2/1, A, 2 h; 72%, 2/1, B, 3 h
11			64%, β only, B, 5 h
12			61%, 1.4/1, B, 5 h
13			60%, ^f >20/1, B, 18 h; 55%, ^g >20/1, B, 36 h; 59% ^h
14			20%, ⁱ 4/1, 2 h; 38%, ^j 4/1, 12 h
15			86%, 2/1, 3 h

^a All reactions were performed using 0.2 mmol of thioglycosides (1.0 eq.) and 120 μ L of 5.0 M Br₂ in CH₂Cl₂ (3.0 eq.) in 1 mL acetonitrile and 0.1 mL H₂O at 0 °C;

^b Isolated yield;

^c Determined by ¹H NMR;

^d29% of starting material was recovered;

^e4.5 eq. of bromine was used. Trace amount of starting material was recovered;

^f31% of starting material was recovered;

^gThe reaction was stirred for 36 hours and 24% of starting material was recovered;

^hNBS (3.0 eq.) was used and the reaction was stirred for 18 hours and 29% of starting material was recovered;

ⁱ64% of starting material was recovered;

^j24% of starting material was recovered.