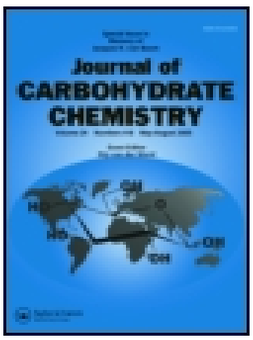

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Facile synthesis of sugar lactols via bromine-mediated oxidation of thioglycosides

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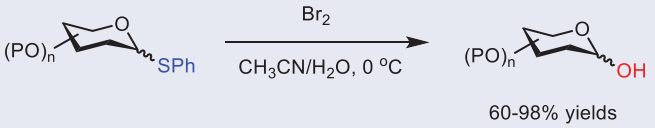
ABSTRACT

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.

GRAPHICAL ABSTRACT



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KEYWORDS
Bromine; hemiacetals; oxidation; sugar lactols; 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

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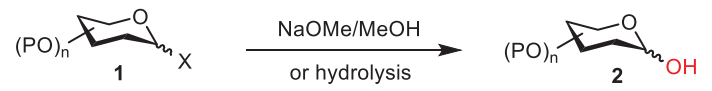
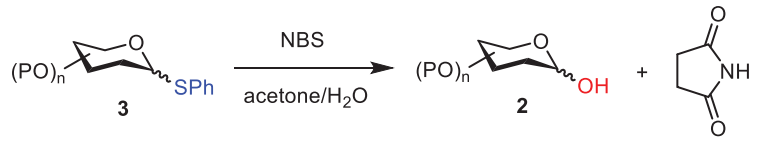
a. Preparation of lactols by methanolysis of glycosyl esters or hydrolysis of halides/methyl glycosides



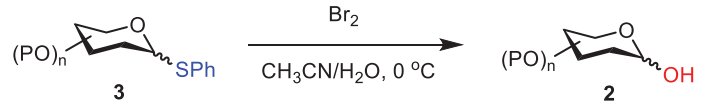
X = OCOR, halides, OMe

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



byproduct succinimide (difficult to separate)

c. This work



Scheme 1. Representative strategies for preparation of sugar lactols.

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] or oxidation of thioglycosides (**3**)[52–53] (a and b, Sch. 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, Sch. 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.

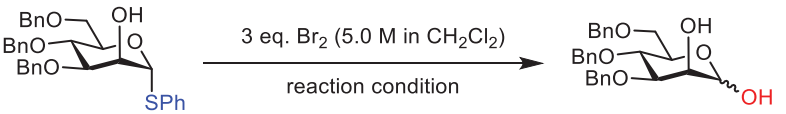
Bromine is often used to oxidize thioglycosides to the corresponding glycosyl bromide donors for the synthesis of various oligosaccharides and glycoconjugates.[54–57] In addition, there was limited report that sugar hemiacetals can be prepared by bromine-mediated oxidation of thioglycosides via a two-step 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, Sch. 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 (α/β = 3/1, entry 1, Table 1). The slow reaction rate may be due to that Br_2 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

Table 1. Synthesis of 3,4,6-tri-*O*-benzyl-D-mannose by bromine-mediated oxidation of corresponding thioglycoside.[a]



4 **5**

Entry	Solvent/Temp/Time[b]	Yield,[c] α/β ratio[d]
1	acetone/H_2O (10/1, v/v), 0 °C, 24 h	83%, 3/1
2	acetone/H_2O (10/1, v/v), −30 to 0 °C, 26 h	79%, 4/1
3	CH_2Cl_2/H_2O (10/1, v/v), −30 to 0 °C, 3.5 h	trace
4	CH_2Cl_2/H_2O (10/1, v/v), 0 °C, 3 h	trace
5	THF/H_2O (10/1, v/v), 0 °C, 12 h	81%, 4/1
6	CH_3CN/H_2O (10/1, v/v), 0 °C, 2 h	97% (98%,[e] 91%[f]), 4/1
7	Br_2, CH_2Cl_2, 0 °C, 0.5 h; then acetone/H_2O (4/1, v/v), RT, 2 h[g]	34%
8	NBS (3.0 eq.), acetone/H_2O (10/1, v/v), 0 °C, 2 h	82%

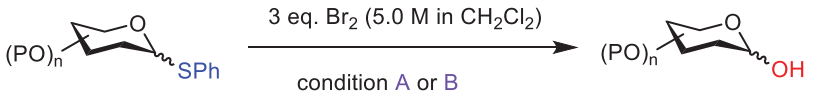
[a]All reactions were performed using 0.1 mmol of phenyl 3,4,6-tri-*O*-benzyl-1-thio-D-mannopyranoside **4** (1.0 eq.) and 60 μL of 5.0 M Br_2 in CH_2Cl_2 (3.0 eq.) in 0.5 mL organic solvent and 50 μL H_2O unless otherwise noted; [b]When TLC showed the substrate was completely consumed; [c]Isolated yield; [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.

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).

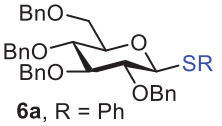
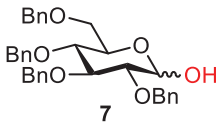
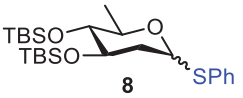
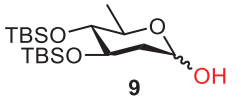
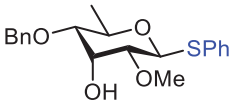
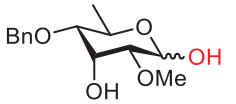
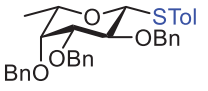
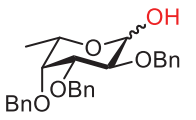
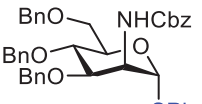
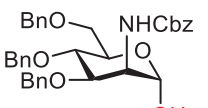
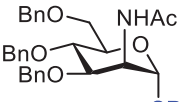
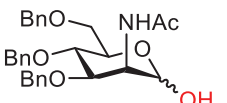
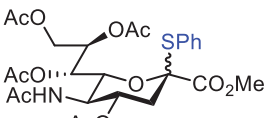
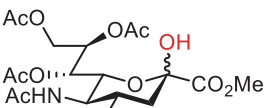
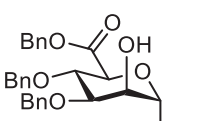
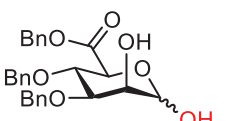
With the optimal condition established, the bromine-mediated oxidation of thioglycosides was applied to the synthesis of a variety of sugar hemiacetals (Table 2). In general, sugar hemiacetals were obtained in good to excellent yields. It was also found that both aryl (e.g. phenyl) and alkyl (e.g. ethyl) 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 Br_2 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.

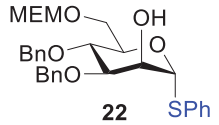
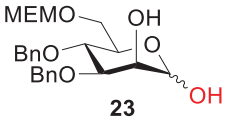
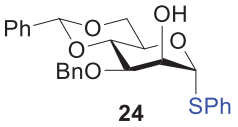
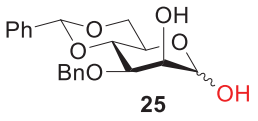
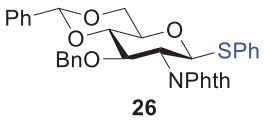
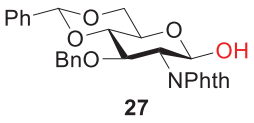
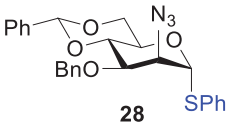
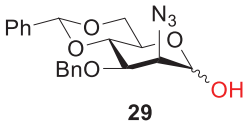
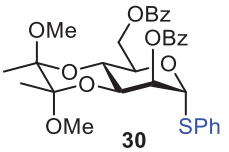
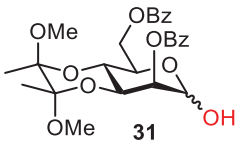
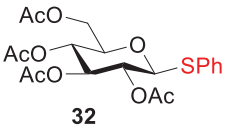
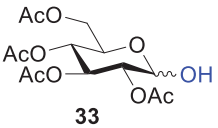
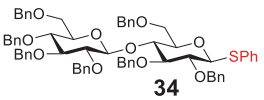
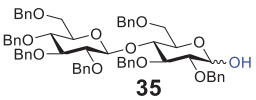
Table 2. Synthesis of various sugar lactols by bromine-mediated oxidation of thioglycosides.[a]



A: Acetonitrile/H_2O (10:1), 0 °C
B: $NaHCO_3$ (10.0 eq.), Acetonitrile/H_2O (10:1), 0 °C

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
8	 **20**	 **21**	75%, 10/1, A, 4 h

(*continued*)

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; ,[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 μL of 5.0 M Br_2 in CH_2Cl_2 (3.0 eq.) in 1 mL acetonitrile and 0.1 mL H_2O at 0 °C; [b]Isolated yield; [c]Determined by ^{1}H NMR; [d]29% of starting material was recovered; [e]4.5 eq. of bromine was used. Trace amount of starting material was recovered; [f]31% of starting material was recovered; [g]The reaction was stirred for 36 hours and 24% of starting material was recovered; [h]NBS (3.0 eq.) was used and the reaction was stirred for 18 hours and 29% of starting material was recovered; [i]64% of starting material was recovered; [j] 24% of starting material was recovered.

Experimental

Materials and Methods

Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on either Bruker 600 (^{1}H NMR-600 MHz; ^{13}C NMR 150) or INOVA 600 (^{1}H NMR-600 MHz; ^{13}C NMR-150 MHz) at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. Chemical shifts are reported in parts per million relative to residual protic solvent

internal standard CDCl3: ^{1}H NMR at δ 7.26, ^{13}C NMR at δ 77.16. Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (app = apparent, par obsc = partially obscure, ovrlp = overlapping, s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet) and coupling constants in Hertz. All ^{13}C 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 μL of Br_2 (3.0 eq.) solution in CH_2Cl_2 (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 $NaHCO_3$ aqueous solution and evaporated under reduced pressure to remove acetonitrile. The residue was extracted by CH_2Cl_2 (10 mL × 3, for lactol **11** 10% *n*-butanol was used together). The organic layers were combined and dried over anhydrous Na_2SO_4. 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 $NaHCO_3$ (10.0 eq.). The mixture was stirred at 0 °C for 30 min. 120 μL of Br_2

(3.0 eq.) solution in CH_2Cl_2 (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 $NaHCO_3$ aqueous solution and evaporated under reduced pressure to remove acetonitrile. The residue was extracted by CH_2Cl_2 (10 mL × 3). The organic layers were combined and dried over anhydrous Na_2SO_4. 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 CH_2Cl_2/MeOH = 15/1) to give 88.8 mg (0.197 mmol, 98%) of lactol **5** (α/β = 4/1) as colorless syrup. ^{1}H and ^{13}C 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 CH_2Cl_2/MeOH = 20/1) to give 90.8 mg (0.168 mmol, 84%) of lactol **7** (α/β = 2/1) as white solids. ^{1}H and ^{13}C 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 syrup. $[\alpha]_D^{23}$ = +61.5 (*c* 0.1, $CHCl_3$). **^{1}H NMR (600 MHz, $CDCl_3$)** 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). **^{13}C NMR (150 MHz, $CDCl_3$)** 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 $C_{18}H_{40}O_4Si_2Na$ $[M+Na]^+$ 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 (CH_2Cl_2/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, $CHCl_3$). **^{1}H NMR (600 MHz, $CDCl_3$)** 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). **^{13}C NMR (150 MHz, $CDCl_3$)** 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 $C_{14}H_{20}O_5Na$ $[M+Na]^+$ 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. ^{1}H and ^{13}C 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, $CHCl_3$). **^{1}H NMR (600 MHz, $CDCl_3$)** 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). **^{13}C NMR (150 MHz, $CDCl_3$)** 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 $C_{35}H_{37}NO_7Na$ $[M+Na]^+$ 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 (CH_2Cl_2/MeOH = 100/1) to give 84.4 mg (0.167 mmol, 84%) of lactol **17** (α/β = 2.5/1) as white solid. ^{1}H and ^{13}C 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. ^{1}H and ^{13}C 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 CH_2Cl_2/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, $CHCl_3$). **^{1}H NMR (600 MHz, $CDCl_3$)** 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). **^{13}C NMR (150 MHz, $CDCl_3$)** 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 $C_{27}H_{28}O_7Na$ $[M+Na]^+$ 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 CH_2Cl_2/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, $CHCl_3$). **^{1}H NMR (600 MHz, $CDCl_3$)** 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). **^{13}C NMR (150 MHz, $CDCl_3$)** 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. ^{1}H 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. ^{1}H 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, $CHCl_3$). **^{1}H 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, $CHCl_3$). **^{1}H 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, $CDCl_3$)** 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 $C_{26}H_{20}O_{10}Na$ $[M + Na]^+$ 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. ^{1}H and ^{13}C 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-beznyl-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. ^{1}H and ^{13}C NMR data of **35** were in agreement with reported ones.[78]

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