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Pre-activation of fully acetylated dodecyl thioglycosides with BSP-Tf₂O led to efficient glycosylation at low temperature

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Abstract

Fully acetylated dodecyl thioglycosides found to be used as glycosyl donors by activation with 1-benzenesulfinyl piperidine (BSP) and triflic anhydride (Tf₂O) at -78 °C, and the glycosyl acceptor was added to the reaction mixture at the same temperature to furnish various disaccharides and Lewis a (Le^a) trisaccharide in good yields.

Keywords: Dodecyl thioglycosides; 1-Dodecanethiol; Glycosylation; Oligosaccharides

1. Introduction

Thioglycosides are among the most widely used synthetic intermediates in carbohydrate chemistry because of their ease of preparation, shelf stability, and compatibility with numerous protection and deprotection reactions.¹ The most remarkable feature of thioglycosides is that they can be activated as glycosyl donors by treatment with various thiophilic reagents.² Total syntheses of various complex oligosaccharides have been achieved by assembly of the thioglycosyl donors.³ Most of the thioglycosyl donors are derived by protective-group manipulations of fully acetylated thioglycosides, which are readily obtained by Lewis acid catalyzed coupling of the corresponding monosaccharide acetates and thiols.^{1a} Although phenyl and ethyl thioglycosides are well-known as good glycosyl donors, a major disadvantage is the stench these thiols generate during preparation. Even in a closed system or a well-organized draft chamber, the stench of the volatile thiols is pervasive. In the last few years, therefore, odorless methods for preparing thioglycosides have received much attention.⁴ Even earlier, in 1993, Tsuchiya reported⁵ that dodecyl 1-thio- β -maltoside prepared from 1-dodecanethiol was used as a non-ionic detergent for biological applications. Stimulated by this work, we prepared various dodecyl thioglycosides and examined their properties in glycosylation reactions. We have demonstrated

previously that dodecyl thioglycosides of glucose⁶ and *N*-acetylneuraminic acid⁷ showed excellent reactivity as glycosyl donors.^{6b, 6c} It is well known that thioglycosides having *O*-benzoyl or *O*-pivaloyl groups at their 2-positions afford the corresponding 1,2-*trans* glycosides through neighboring group participation. However, application of fully acetylated thioglycoside to glycosylation has been extremely limited. We observed that glycosidation of dodecyl thioglycoside acetate gave a complex mixture of products,^{6a} in which acetyl group of the donor was migrated to the acceptor, suggesting that an orthoester intermediate was formed during the reaction. Similar results were also reported recently.⁸

In complex oligosaccharide synthesis, the glycosyl bromides or trichloroacetimidates with sterically less hindered acetyl groups sometimes played a crucial role in their synthetic strategy.⁹ In order to extend synthetic utility of acetylated thioglycosyl donors, we re-investigated their glycosylation using various thiophilic reagents so far reported. In the course of our studies in oligosaccharide synthesis,^{6, 7} we focused^{6b, 6c} on sulfonium triflate pre-activation procedure of thioglycosides, because it forms highly reactive intermediates like α -glycosyl triflates in the glycosylation process.¹⁰ Although the precise mechanism of the glycosylation is still uncertain, the triflate undergoes glycosylation *via* either transient contact ion pair

mechanism or S_N2-like replacement.¹¹ In this paper, we describe our finding that a trivial modification of the pre-activation method was highly effective to utilize fully acetylated thioglycosides for oligosaccharide synthesis.

2. Results and discussion

According to an established procedure for the preparation of thioglycosides, fully acetylated monosaccharides and 1-dodecanthiol were BF₃ · Et₂O in 1,2-dichloroethane, giving dodecyl thiohexopyranosides **1–6** in more than 80% yields. We next examined glycosylation using these thioglycosides as the donors. It was reported that BSP–Tf₂O pre-activation of fully acetylated 1-thio- α -rhamnopyranoside underwent glycosylation with partially protected serine at –60 °C.^{10b} However, our attempt to apply the conditions to coupling dodecyl 1-thio- α -rhamnoside **1** and a monosaccharide acceptor **7** was unsuccessful, giving several decomposed products of the donor **1** together with an almost quantitative yield unchanged acceptor **7** (see Fig. 1).

TLC monitoring of the reaction suggested that the donor **1** was sufficiently activated by the promoter at –60 °C to produce several decomposed products, and that milder conditions would be necessary for this glycosylation, procedure with acetylated

thioglycosides.

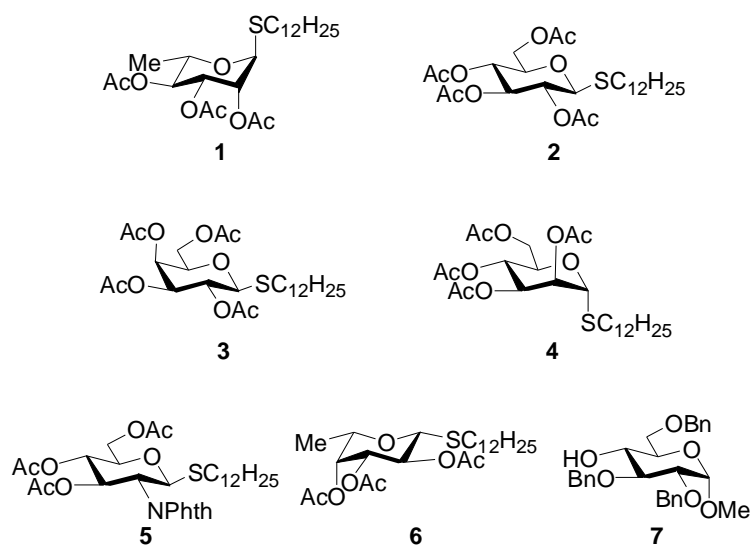
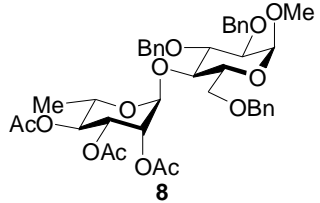
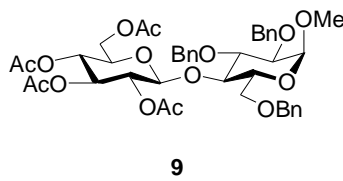
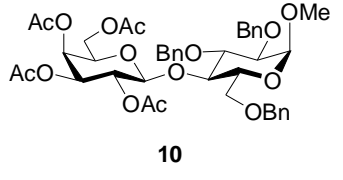
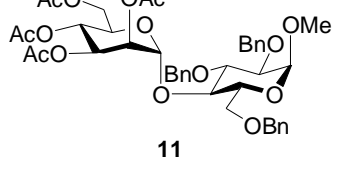
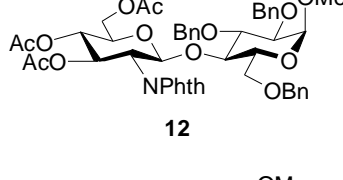
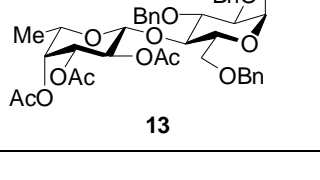


Figure 1. Glycosyl donor (1–6) and acceptor (7) employed in the BSP–Tf₂O mediated coupling.

Thus, we treated the donor **1** with the promoter at lower temperature of $-78\text{ }^{\circ}\text{C}$ and glycosylation continued at the same temperature, giving the known α -linked disaccharide **8**¹² in 87% yield as a sole product. All ¹H spectral data were consistent with those reported. Furthermore, the configuration of newly generated rhamnosyl linkage of the disaccharides was confirmed by the one bond C1'–H1' coupling constant of **8**, $J_{\text{C1', H2'}} = 172.5\text{ Hz}$. The excellent reacts of coupling between the donor **1** and the acceptor **7** prompted us to examine glycosylation of other thioglycosides. The

Table 1. Results of BSP-Tf₂O mediated glycosylation^b

Entry	Donor	Product	Yield (%)
1	1	 8	87
2	2	 9	89
3 ^a	3	 10	88
4	4	 11	80
5 ^a	5	 12	83
6 ^a	6	 13	84

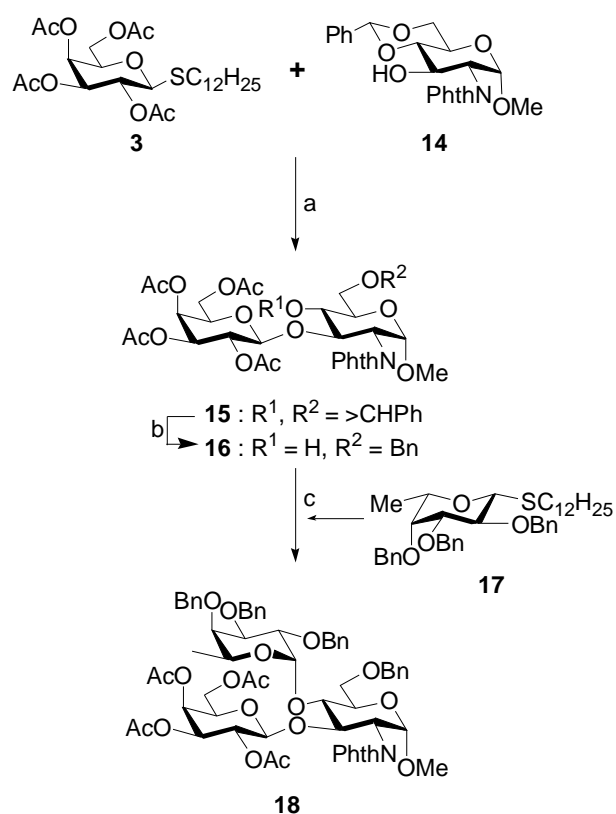
^a DTBM was used as hindered base.

^b All reactions were performed with 2.0 equiv. of donor in CH₂Cl₂.

reactions of gluco- **2**, galacto- **3**, manno- **4**, 2-deoxy-2-phthalimidogluco- **5**, and fuco-pyranoside **6** with the acceptor **7** completed within 1 h at $-78\text{ }^{\circ}\text{C}$, giving disaccharides with 1,2-*trans* configuration in the yields of 80–90%. The results are shown in Table 1. The 1,2-*trans* configurations of the disaccharides **8–13** were also confirmed by ^1H and ^{13}C NMR spectroscopy. We hypothesized that the glycosides were formed directly from the oxocarbenium ion as an intermediate in a neighboring group participation. Since BSP-Tf₂O promoted glycosylation with sterically hindered base of benzoylated glucosyl, mannosyl, and xylosyl donors were reported to give orthoesters as major products,^{10b} we did not add 2,6-di-*tert*-butyl-4-methylpyridine (DTBM) in the reactions of **3**, **5**, and **6**. The yields of isolated disaccharides **10**, **12**, and **13** were more than 80%.

Encouraged by these successful results of disaccharide formation, we turned our attention to the synthesis of Le^a antigen trisaccharide, Fuc- α (1→4)-(Gal- β (1→3))-GlcNAc.^{9a, 9e, 13} In an established synthetic route to the trisaccharide, involves introduction of tetra-O-acetyl- β -D-galactopyranosyl residue at 3-OH group of a D-glucosamine derivative and subsequent α -fucosylation at the 4-OH group of the resulting disaccharide. Although Koenigs–Knorr reaction using fully acetylated galactosyl bromide was used for this synthesis, to the best of our

knowledge,^{13a} success in coupling between thiogalactosyl donor and 3-position of 2-deoxy-2-phthalinido- β -D-glucofuranosyl acceptor was low for most of the published galactosylations. This is probably due to steric hindrance of the neighboring substituent and/or mismatching between the glycosyl donor and the acceptor.¹⁴ In the first, we undertook to examine glycosylation between **3** and the acceptor **14** as shown in Scheme 1. Similarly to glycosylation described above, **3** was pre-activated with BSP-Tf₂O in dry CH₂Cl₂ at -78 °C in the presence of molecular sieves 4Å and DTBM, and subsequently treated with the acceptor **14** at the same temperature. As we expected, this glycosylation proceeded smoothly and the desired disaccharide **15** was obtained in the yield of 84%. The anomeric configuration of **15** was confirmed to be β -selectivity on the basis of its coupling constant ($J_{1',2'} = 7.8$ Hz, H-1') for anomeric proton at 4.76 ppm in ¹H NMR spectrum and ¹³C NMR 100.5 ppm (C-1'). For the next glycosylation, the disaccharide **15** was converted into glycosyl acceptor **16** by reductive ring opening of the benzylidene acetal. Thus **15** was treated with NaBH₃CN-HCl in THF at 0 °C, giving the 4'-OH derivative **16** in 72% yield. Its α -fucosylation using the benzylated donor **17** was also successful with BSP-Tf₂O in dichloromethane at -78 °C, giving fully protected Le^a trisaccharide **18** in 85% yield.



Scheme 1. Reagents and conditions: (a) BSP, DTBM, Tf₂O, CH₂Cl₂, -78 °C, 1 h, 84%; (b) NaBH₃CN, HCl–Et₂O, THF, 0 °C, 30 min, 72%; (c) BSP, DTBM, Tf₂O, CH₂Cl₂, -78 °C, 1 h, 85%.

In summary, simple modification of Crich's procedure per-activation of thioglycosides found to be dramatically improved the ability of fully acetylated thioglycosides as glycosyl donors. On treatment with BSP–Tf₂O at -78 °C fully acetylated dodecyl thioglycosides and coupling with acceptors at the same temperature underwent smooth glycosylation to give various disaccharides and a precursor of Le^a

trisaccharide in excellent yields.

3. Experimental

3.1. General methods

All chemicals were purchased as reagent grade and used without further purification.

Dichloromethane (CH₂Cl₂) and 1,2-dichloroethane were distilled over calcium hydride (CaH₂). Molecular sieves used for glycosylation were MS4Å, which were activated at 200 °C under reduced pressure prior to use. Reaction monitoring was done with thin-layer chromatography (TLC) on a pre-coated plate of silica gel 60F₂₅₄ plates (layer-thickness, 0.25 mm; E. Merck, Germany), which were visualized under UV (254 nm) and/or by spraying with *p*-methoxybenzaldehyde–H₂SO₄–MeOH (1:2:17, v/v).

Column chromatography was performed on silica gel (Silica gel 60; 70–230 mesh ASTM, Merck, Darmstadt, Germany).

¹H and ¹³C NMR spectra were recorded with a Bruker ASX 300 (300 and 75.1 MHz, respectively) and JEOL ECA 600 (600 and 150 MHz, respectively). Chemical shifts (in ppm) were referenced to tetramethylsilane ($\delta = 0$ ppm) in deuterated chloroform (CDCl₃). ¹³C NMR spectra were obtained by using the same NMR spectrometers and were calibrated with CDCl₃ ($\delta = 77.00$ ppm). Splitting patterns are indicated as s,

singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br d, broad doublet for ^1H NMR data. ESI-TOF HR mass spectra were measured on a Bruker micro TOF focus spectrometer.

3.2. Preparation of dodecyl thioglycosides

General procedure: To a solution per-*O*-acetylated sugar and 1-dodecanethiol (1.1 equiv. to the acetate) in 1,2-dichloroethane (10–20 mL) was added $\text{BF}_3 \cdot \text{OEt}_2$ (1.2 equiv. to the acetate) at 0 °C. The temperature was raised to room temperature and stirring was continued by TLC. After completion of the reaction, the mixture was diluted with CHCl_3 , and added ice-water and stirred for 30 min. The organic layer was successively washed with saturated aqueous (sat. aq.) NaHCO_3 , brine, dried (MgSO_4), filtered, and concentrated. The dodecyl thioglycoside produced was purified by silica gel chromatography (5:1→3:1 hexane–EtOAc, gradient eluant).

3.2.1. Dodecyl 2,3,4-tri-*O*-acetyl-1-thio- α -L-rhamnopyranoside (1)

To a solution of 1,2,3,4-tetra-*O*-acetyl- α -L-rhamnose (1.00 g, 3.01 mmol) was performed according to the general procedure for the synthesis of dodecyl thioglycosides described above to give **1** (1.25 g, 88%) as a colorless syrup; $[\alpha]_{\text{D}}^{20} -95.7$

(*c* 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 5.34 (dd, 1H, *J*_{2,3} = 3.3 Hz, H-2), 5.23 (dd, 1H, *J*_{3,4} = 10.0 Hz, H-3), 5.16 (d, 1H, *J*_{1,2} = 1.5 Hz, H-1), 5.09 (t, 1H, *J*_{4,5} = 9.8 Hz, H-4), 4.23 (m, 1H, H-5), 2.70–2.54 (m, 2H, SCH₂), 2.16, 2.05, 1.98 (3 s, each 3H, acetyl), 1.65–1.22 (m, 23H, SCH₂(CH₂)₁₀CH₃, H-6), 0.88 (t, 3H, *J* = 6.5 Hz, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 170.0, 169.9, 169.8 (C=O), 82.4, 71.6, 71.3, 69.5, 66.9, 31.8, 31.5, 29.5, 29.5, 29.4, 29.3, 29.1, 28.7, 22.6, 20.9, 20.7, 20.6, 17.3, 14.0; Anal. Calcd for C₂₄H₄₂O₇S: C, 60.73; H, 8.92; S, 6.76. Found: C, 60.60; H, 8.90; S, 6.66.

3.2.2. Dodecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**2**)

To a solution of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (0.78 g, 2.0 mmol) was performed according to the general procedure for the synthesis of dodecyl thioglycosides described above to give **2** (1.00 g, 95%) as a colorless solid; [α]_D²⁰ –29.2 (*c* 0.12, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 5.24 (t, 1H, *J*_{3,4} = 9.3 Hz, H-3), 5.10 (t, 1H, *J*_{4,5} = 9.5 Hz, H-4), 5.05 (t, 1H, *J*_{2,3} = 9.4 Hz, H-2), 4.49 (d, 1H, *J*_{1,2} = 10.0 Hz, H-1), 4.26 (dd, 1H, *J*_{5,6b} = 4.9 Hz, H-6b), 4.05 (dd, 1H, *J*_{5,6a} = 2.2 Hz, *J*_{6a,6b} = 12.4 Hz, H-6a), 3.75–3.65 (m, 1H, H-5), 2.76–2.60 (m, 2H, SCH₂), 2.10, 2.08, 2.04, 2.03 (4 s, each 3H, acetyl), 1.66–1.26 (m, 20H, SCH₂(CH₂)₁₀CH₃), 0.88 (t, 3H, *J* = 4.1 Hz, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 171.1, 170.7, 169.9, 169.9 (C=O), 84.2, 76.4,

74.5, 70.5, 68.9, 62.8, 32.4, 30.6, 30.2, 30.1, 30.1, 29.9, 29.7, 29.3, 23.2, 21.2, 21.1, 14.6; Anal. Calcd for C₂₆H₄₄O₉S: C, 58.62; H, 8.33; S, 6.02. Found: C, 58.55; H, 8.46; S, 6.17.

3.2.3. Dodecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (3)

To a solution of 1,2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranose (0.78 g, 2.0 mmol) was performed according to the general procedure for the synthesis of dodecyl thioglycosides described above to give **3** (1.05 g, 99%) as a colorless solid; $[\alpha]_{\text{D}}^{20} -16.0$ (*c* 0.30, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 5.43 (d, 1H, *J*_{4,5} = 3.3 Hz, H-4), 5.27 (t, 1H, *J*_{2,3} = 10.0 Hz, H-2), 5.04 (dd, 1H, *J*_{3,4} = 10.0 Hz, H-3), 4.47 (d, 1H, *J*_{1,2} = 9.9 Hz, H-1), 4.25–4.05 (m, 2H, H-6a, 6b), 3.94–3.91 (m, 1H, H-5), 2.73–2.65 (m, 2H, SCH₂), 2.17, 2.16, 2.07, 2.05 (4 s, each 3H, acetyl), 1.66–1.26 (m, 20H, SCH₂(CH₂)₁₀CH₃), 0.88 (t, 3H, *J* = 4.1 Hz, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 170.4, 170.2, 170.1, 169.5 (C=O), 84.2, 74.3, 71.9, 67.3, 61.4, 31.9, 30.9, 30.2, 29.7, 29.6, 29.5, 29.3, 29.2, 28.8, 22.6, 20.8, 20.6, 20.6, 14.1; Anal. Calcd for C₂₆H₄₄O₉S: C, 58.62; H, 8.33; S, 6.02. Found: C, 58.65; H, 8.35; S, 6.05.

3.2.4. Dodecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (4)

To a solution of 1,2,3,4,6-tetra-*O*-acetyl- α -D-mannopyranose (2.0 g, 5.0 mmol) was performed according to the general procedure for the synthesis of dodecyl thioglycosides described above to give **4** (2.3 g, 86%) as a colorless solid; $[\alpha]_{\text{D}}^{20} +76.8$ (*c* 0.37, CHCl₃); ¹H NMR (300 MHz, acetone): δ 5.38 (br d, 1H, H-1), 5.31 (dd, 1H, $J_{2,3} = 3.2$ Hz, H-2), 5.23 (t, 1H, $J_{4,5} = 9.5$ Hz, H-4), 5.19 (dd, 1H, $J_{3,4} = 9.9$ Hz, H-3), 4.41–4.33 (m, 1H, H-5), 4.24 (dd, 1H, $J_{5,6a} = 5.8$ Hz, $J_{6a,6b} = 12.1$ Hz, H-6a), 4.10 (dd, 1H, $J_{5,6b} = 2.4$ Hz, H-6b), 2.79–2.60 (m, 2H, SCH₂), 2.11, 2.05, 2.03, 1.95 (4 s, each 3H, acetyl), 1.66–1.26 (m, 20H, SCH₂(CH₂)₁₀CH₃), 0.88 (t, 3H, $J = 4.1$ Hz, CH₂CH₃); ¹³C NMR (75 MHz, acetone): δ 170.1, 170.0, 169.8, 169.7 (C=O), 82.6, 82.4, 76.4, 71.1, 69.9, 69.5, 66.5, 62.8, 32.1, 31.5, 31.1, 22.8, 20.2, 20.1, 20.0, 13.8; Anal. Calcd for C₂₆H₄₄O₉S: C, 58.62; H, 8.33; S, 6.02. Found: C, 58.63; H, 8.38; S, 6.06.

3.2.5. Dodecyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio- β -D-glucopyranoside

(**5**)

To a solution of 1,3,4,6-tetra-*O*-acetyl-2-phthalimido-2-deoxy- β -D-glucopyranoside (2.58 g, 5.42 mmol) was performed according to the general procedure for the synthesis of dodecyl thioglycosides described above to give **5** (2.73 g, 81%) as a colorless solid; $[\alpha]_{\text{D}}^{20} +22.7$ (*c* 2.63, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.89–7.74 (m, 5H, CH_{arom}),

5.83 (t, 1H, $J_{3,4} = 9.2$ Hz, H-3), 5.46 (d, 1H, $J_{1,2} = 10.6$ Hz, H-1), 5.18 (t, 1H, $J_{4,5} = 9.4$ Hz, H-4), 4.39 (t, 1H, $J_{2,3} = 10.4$ Hz, H-2), 4.31 (dd, 1H, $J_{5,6a} = 4.8$ Hz, $J_{6a,6b} = 8.2$ Hz, H-6a), 4.17 (dd, 1H, $J_{5,6b} = 2.1$ Hz, H-6b), 3.93–3.85 (m, 1H, H-5), 2.67–2.62 (m, 2H, SCH₂), 2.10, 2.04, 1.87 (3 s, each 3H, acetyl), 1.60–1.24 (m, 20H, SCH₂(CH₂)₁₀CH₃), 0.88 (t, 3H, $J = 6.2$ Hz, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 170.7, 170.1, 169.5, 167.8, 167.2 (C=O), 134.4, 134.3, 131.6, 131.2, 123.7, 81.4, 77.2, 77.0, 76.6, 75.9, 71.5, 68.8, 62.3, 53.7, 31.9, 30.3, 29.6, 29.5, 29.3, 29.1, 28.7, 22.7, 20.8, 20.7, 20.5, 14.1; Anal. Calcd for C₃₂H₄₅NO₉S: C, 62.01; H, 7.32; N, 2.26; S, 5.17. Found: C, 61.84; H, 7.20; N, 2.27; S, 5.26.

3.2.6. Dodecyl 2,3,4-tri-*O*-acetyl-1-thio- β -L-fucopyranoside (**6**)

To a solution of 1,2,3,4-tetra-*O*-acetyl- β -L-fucopyranose (3.23 g, 9.72 mmol) was performed according to the general procedure for the synthesis of dodecyl thioglycosides described above to give dodecyl thioglycoside **6** (3.83 g, 83%) as a colorless syrup; $[\alpha]_D^{20} -16.5$ (*c* 0.26, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 5.27 (d, 1H, $J_{4,5} = 3.2$ Hz, H-4), 5.21 (t, 1H, $J_{2,3} = 9.9$ Hz, H-2), 5.04 (dd, 1H, $J_{3,4} = 10.0$ Hz, H-3), 4.44 (d, 1H, $J_{1,2} = 9.9$ Hz, H-1), 3.81 (dd, 1H, $J_{5,6} = 12.7$ Hz, H-5), 2.72–2.64 (m, 2H, SCH₂), 2.18, 2.06, 1.99 (3 s, each 3H, acetyl), 1.61–1.25 (m, 20H,

SCH₂(CH₂)₁₀CH₃), 1.22 (d, 3H, *J* = 6.4 Hz, H-6), 0.88 (t, 3H, *J* = 6.5 Hz, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 170.4, 169.8, 169.4 (C=O), 83.6, 73.1, 72.3, 70.4, 67.3, 31.9, 29.8, 29.6, 29.6, 29.5, 29.3, 29.2, 28.8, 22.7, 20.8, 20.7, 20.6, 16.4, 14.1; Anal. Calcd for C₂₄H₄₂O₇S: C, 60.73; H, 8.92; S, 6.76. Found: C, 60.70; H, 8.98; S, 6.86.

3.3. Glycosylation of donors 1–6 with acceptor 7

General procedure: A solution of the dodecyl thioglycoside 1–6 (0.6 mmol, 2.0 equiv. to acceptor), BSP (138.1 mg, 0.66 mmol, 1.1 equiv. to thioglycoside), DTBM (246.8 mg, 1.2 mmol, 2.0 equiv. to thioglycoside), and MS4Å (700 mg) was stirred in dry CH₂Cl₂ (6 mL) at room temperature for 30 min under nitrogen atmosphere. The reaction mixture was cooled to –78 °C, followed by addition of Tf₂O (137 μL, 0.82 mmol, 1.4 equiv. to thioglycoside) and stirred at this temperature for 15 min. Then a solution of glycosyl acceptor 7 (139.0 mg, 0.3 mmol, 1.0 equiv.) in dry CH₂Cl₂ (2 mL) was slowly added to the resulting mixture for 10 min. The reaction mixture was stirred at this temperature for 1 h, quenched by addition Et₃N and diluted CHCl₃. The reaction mixture was filtered through a pad of Celite, the filtrate was successively washed with sat. aq. NaHCO₃, brine, dried (MgSO₄), and concentrated. The residue was purified by column chromatography.

Known disaccharides (**8**,¹² **9**,^{12, 16} **10**,^{13, 15} **11**¹²) gave data consistent with literature values.

3.3.1. Methyl 4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranosyl)-2,3,6-tri-*O*-benzyl- α -D-glucopyranoside (**12**)

The *N*-phthaloyl protected glucosamine derivative **5** (372 mg, 0.6 mmol) was condensed with methyl 2,3,6-tri-*O*-benzyl- α -D-glucopyranoside **7** (139 mg, 0.3 mmol) following the general procedure for the glycosylation procedure described above. Column chromatography (10:1→2:1 toluene–EtOAc, gradient eluant) provided the **12** (220 mg, 83%) as a colorless syrup; $[\alpha]_{\text{D}}^{22} +18.3$ (*c* 1.00, CHCl₃); ¹H NMR (600 MHz, CDCl₃): δ 7.83–7.21 (m, 19H, CH_{arom}), 5.69 (t, 1H, $J_{3',4'} = 9.8$ Hz, H-3'), 5.63 (d, 1H, $J_{1',2'} = 8.8$ Hz, H-1'), 5.11 (t, 1H, $J_{4',5'} = 9.4$ Hz, H-4'), 4.99 (d, 1H, $J = 11.5$ Hz, PhCH₂), 4.91 (d, 1H, $J = 11.6$ Hz, PhCH₂), 4.68 (d, 1H, $J = 12.7$ Hz, PhCH₂), 4.55 (d, 1H, $J = 12.1$ Hz, PhCH₂), 4.50 (d, 1H, $J_{1,2} = 3.8$ Hz, H-1), 4.35 (d, 1H, $J = 11.5$ Hz, PhCH₂), 4.33 (d, 1H, $J = 12.0$ Hz, PhCH₂), 4.25 (dd, 1H, $J_{2',3'} = 10.4$ Hz, H-2'), 4.07 (dd, 1H, $J_{5',6'a} = 3.8$ Hz, $J_{6'a,6'b} = 12.4$ Hz, H-6'a), 3.98 (t, 1H, $J_{4,5} = 9.0$ Hz, H-4), 3.88 (t, 1H, $J_{3,4} = 9.3$ Hz, H-3), 3.80 (dd, 1H, $J_{5',6'b} = 1.8$ Hz, H-6'b), 3.58–3.53 (m, 1H, H-5'), 3.45 (dd, 1H, $J_{2,3} = 9.6$ Hz, H-2), 3.44–3.41 (m, 2H, H-6a, 6b), 3.37–3.32 (m, 1H, H-5), 3.26 (s, 3H, OMe),

1.98, 1.97, 1.82 (3 s, each, 3H, acetyl); ^{13}C NMR (75 MHz, CDCl_3): δ 170.1, 170.6, 169.8 (C=O), 131.8, 129.4, 128.7, 128.7, 128.5, 128.2, 127.8, 127.7, 127.5, 127.3, 125.7, 124.0, 98.4, 97.7, 80.6, 79.8, 75.9, 75.1, 73.8, 73.2, 72.0, 71.2, 69.7, 68.8, 68.6, 61.9, 55.8, 55.7, 21.1, 21.0, 20.8; HRMS-ESI: m/z $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{48}\text{H}_{51}\text{NO}_{15}\text{Na}$: 904.3151; Found: 904.3143.

3.3.2. Methyl 4-*O*-(2,3,4-tri-*O*-acetyl- β -L-fucopyranosyl)-

2,3,6-tri-*O*-benzyl- α -D-glucopyranoside (**13**)

The compound **6** (284.8 mg, 0.6 mmol) was condensed with methyl 2,3,6-tri-*O*-benzyl- α -D-glucopyranoside **7** (139 mg, 0.3 mmol) following the general procedure for the glycosylation procedure described above. Column chromatography (10:1 \rightarrow 5:1 toluene–EtOAc, gradient eluant) provided the **13** (183 mg, 84%) as a colorless syrup; $[\alpha]_{\text{D}}^{22} +22.1$ (c 1.00, CHCl_3); ^1H NMR (600 MHz, CDCl_3): δ 7.43–7.21 (m, 15H, CH_{arom}), 5.16 (d, 1H, $J_{4',5'} = 3.7$ Hz, H-4'), 5.15 (t, 1H, $J_{2',3'} = 9.7$ Hz, H-2'), 5.01 (d, 1H, $J_{1',2'} = 8.2$ Hz, H-1'), 4.99 (d, 1H, $J = 9.9$ Hz, PhCH_2), 4.93 (dd, 1H, $J_{3',4'} = 10.4$ Hz, H-3'), 4.76 (d, 1H, $J = 12.1$ Hz, PhCH_2), 4.69 (d, 1H, $J = 9.9$ Hz, PhCH_2), 4.64 (d, 1H, $J = 11.6$ Hz, PhCH_2), 4.62 (d, 1H, $J_{1,2} = 3.3$ Hz, H-1), 4.61 (d, 1H, $J = 11.6$ Hz, PhCH_2), 4.53 (d, 1H, $J = 12.1$ Hz, PhCH_2), 3.90 (t, 1H, $J_{3,4} = 8.8$ Hz, H-3), 3.86 (t, 1H,

$J_{4,5} = 9.4$ Hz, H-4), 3.80 (dd, 1H, $J_{5,6b} = 1.6$ Hz, H-6b), 3.74–3.69 (m, 1H, H-5), 3.63 (dd, 1H, $J_{5,6a} = 4.4$ Hz, $J_{6a,6b} = 10.7$ Hz H-6a), 3.57 (dd, 1H, $J_{5',6'} = 12.9$ Hz, H-5'), 3.53 (dd, 1H, $J_{2,3} = 9.3$ Hz, H-2), 3.38 (s, 3H, OMe), 2.16, 2.06, 1.99 (3 s, each, 3H, acetyl), 1.03 (d, 3H, $J = 6.6$ Hz, H-6'); ^{13}C NMR (75 MHz, CDCl_3): δ 171.1, 170.6, 170.0 (C=O), 138.9, 138.6, 138.3, 129.5, 129.2, 129.0, 128.8, 128.7, 128.6, 128.6, 128.5, 127.9, 127.8, 100.7, 98.1, 82.4, 80.5, 77.2, 76.5, 74.3, 73.9, 73.7, 71.8, 70.8, 69.8, 69.7, 69.4, 69.1, 21.4, 21.2, 16.5; HRMS-ESI: m/z $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{40}\text{H}_{48}\text{O}_{13}\text{Na}$: 759.2987; Found: 759.2963.

3.4. Synthesis of fully protected Le^a trisaccharides **18**

3.4.1. Methyl 3-*O*-(2,3,4,6-tetra-*O*-acetyl- β -D-galactopyranosyl)-

4,6-*O*-benzylidene-2-deoxy-2-phthalimido- α -D-glucopyranoside (**15**)

To a stirred solution containing the dodecyl thiogalactosyl donors **3** (320 mg, 0.6 mmol), BSP (138.1 mg, 0.66 mmol), DTBM (216.8 mg, 1.2 mmol), and MS4Å (700 mg) in dry CH_2Cl_2 (6 mL), at -78 °C under a nitrogen atmosphere, was added TiF_2O (137 μL , 0.82 mmol). After 15 min, a solution of the glycosyl acceptor **14** (370.0 mg, 0.9 mmol) in dry CH_2Cl_2 was added. The reaction mixture was stirred at this temperature for 1 h, quenched by addition Et_3N and diluted CHCl_3 . The reaction mixture was filtered through a pad of Celite, the filtrate was successively washed with sat. aq. NaHCO_3 ,

brine, dried (MgSO₄), and concentrated. The residue was purified by column chromatography (5:1→2:1 toluene–EtOAc, gradient eluant) provided the **15** (372 mg, 84%) as a colorless syrup; $[\alpha]_D^{21} +62.4$ (*c* 1.00, CHCl₃); ¹H NMR (600 MHz, CDCl₃): δ 7.97–7.21 (m, 9H, CH_{arom}), 5.59 (s, 1H, PhCH), 5.45 (t, 1H, *J*_{3,4} = 9.2 Hz, H-3), 5.21 (d, 1H, *J*_{4',5'} = 3.4 Hz, H-4'), 4.96 (t, 1H, *J*_{2',3'} = 9.4 Hz, H-2'), 4.81 (dd, 1H, *J*_{3',4'} = 10.4 Hz, H-3'), 4.77 (d, 1H, *J*_{1,2} = 3.3 Hz, H-1), 4.76 (d, 1H, *J*_{1',2'} = 7.8 Hz, H-1'), 4.47 (dd, 1H, *J*_{2,3} = 10.7 Hz, H-2), 4.30 (dd, 1H, *J*_{5,6b} = 4.4 Hz, H-6b), 4.07–3.97 (m, 2H, H-6a, 6'b), 3.88–3.75 (m, 3H, H-4, 5, 6'a), 3.54–3.47 (m, 1H, H-5'), 3.32 (s, 3H, OMe), 2.05, 1.94, 1.85, 1.74 (4 s, each, 3H, acetyl); ¹³C NMR (75 MHz, CDCl₃): δ 170.8, 170.6, 170.5, 169.7 (C=O), 168.9, 168.3, 137.6, 134.8, 134.5, 132.8, 132.4, 129.8, 129.5, 128.9, 128.7, 126.6, 123.9, 102.2, 100.5, 99.6, 82.2, 72.9, 71.9, 71.8, 71.6, 71.3, 69.5, 69.4, 67.2, 62.9, 61.3, 56.0, 55.5, 21.1, 21.0, 20.9; HRMS-ESI: *m/z* [M+Na]⁺ Calcd for C₃₆H₃₉NO₁₆Na: 764.2161; Found: 764.2178.

3. 4.2. Methyl 3-*O*-(2,3,4,6-tetra-*O*-acetyl- β -D-galactopyranosyl)-

6-*O*-benzyl-2-deoxy-2-phthalimido- α -D-glucopyranoside (**16**)

Sodium cyanoborohydrate (211 mg, 3.36 mmol) was added to a solution of disaccharide **15** (208 mg, 0.18 mmol) in anhydrous THF (5 mL) containing MS4Å (500 mg). A 2

M solution of HCl in Et₂O was added dropwise until the evolution of gas ceased. After an additional 30 min, the mixture was filtered through Celite and washed sequentially with sat. aq. NaHCO₃, brine, dried (MgSO₄), filtered, and concentrated. The crude mixture was purified by column chromatography (5:1→2:1 toluene–EtOAc, gradient eluant) gave acceptor **16** as a colorless syrup (149 mg, 72%); [α]_D²² +93.6 (*c* 1.00, CHCl₃); ¹H NMR (600 MHz, CDCl₃): δ 7.95–7.25 (m, 9H, CH_{arom}), 5.33 (d, 1H, $J_{4',5'} = 2.8$ Hz, H-4'), 5.21 (t, 1H, $J_{3,4} = 9.9$ Hz, H-3), 5.12 (t, 1H, $J_{2',3'} = 8.8$ Hz, H-2'), 4.92 (dd, 1H, $J_{3',4'} = 10.4$ Hz, H-3'), 4.79 (d, 1H, $J_{1,2} = 3.3$ Hz, H-1), 4.72 (d, 1H, $J_{1',2'} = 8.2$ Hz, H-1'), 4.65 (d, 1H, $J = 12.6$ Hz, PhCH₂), 4.63 (d, 1H, $J = 12.1$ Hz, PhCH₂), 4.40 (dd, 1H, $J_{2,3} = 10.7$ Hz, H-2), 4.23 (s, 1H, OH), 4.18–4.11 (m, 2H, H-6'a, 6'b), 4.06–4.02 (m, 1H, H-5'), 3.89–3.82 (m, 2H, H-5, 6a), 3.76 (dd, 1H, $J_{5,6b} = 4.9$ Hz, H-6b), 3.68 (t, 1H, $J_{4,5} = 9.4$ Hz, H-4), 3.32 (s, 3H, OMe), 2.13, 2.04, 1.88, 1.07 (4 s, each, 3H, acetyl); ¹³C NMR (75 MHz, CDCl₃): δ 171.1, 170.7, 170.5, 169.2, 168.9, 168.8 (C=O), 138.9, 135.1, 134.8, 134.7, 132.9, 131.4, 128.9, 128.1, 124.4, 123.9, 100.7, 99.1, 79.8, 75.5, 74.0, 71.8, 71.7, 71.5, 70.1, 69.7, 69.2, 67.6, 62.1, 55.8, 55.3, 21.2, 21.1, 19.6; HRMS-ESI: *m/z* [M+Na]⁺ Calcd for C₃₆H₄₁NO₁₆Na: 743. 2425; Found: 743.2403.

3.4.3. Dodecyl 2,3,4-tri-*O*-benzyl-1-thio- β -L-fucopyranoside (**17**)

Dodecyl 2,3,4-tri-*O*-acetyl-1-thio- β -L-fucopyranoside **6** (1.4 g, 2.9 mmol) was dissolved in MeOH (15 mL) and NaOMe (25%, w/v, 0.2 mL) was added. The solution was stirred at room temperature for 2 h and neutralized with amberlite IR 50. Subsequent removal of resin by filtration and removal of solvent in vacuum gave a white solid. The product was further treated with BnBr (1.6 mL, 13.1 mmol) and NaH (60% in mineral oil, 13.1 mmol) in DMF at 0 °C. The reaction mixture was stirred at room temperature for 3 h and quenched with MeOH and NH₄ (25%, w/v), which was coevaporated with toluene (20 mL x 3). The crude product diluted with EtOAc (100 mL). The organic layer was washed with sat. aq. NaHCO₃, brine, dried (MgSO₄), and concentrated. The crude mixture was purified by column chromatography (10:1→3:1 hexane–EtOAc, gradient eluant) gave **17** as a colorless solid (1.9 g, 93%); $[\alpha]_D^{22} +9.3$ (*c* 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.58–7.11 (m, 15H, CH_{arom}), 5.03 (d, 1H, *J* = 10.4 Hz, PhCH₂), 4.90 (d, 1H, *J* = 10.1 Hz, PhCH₂), 4.79 (d, 1H, *J* = 10.1 Hz, PhCH₂), 4.75 (s, 2H, PhCH₂), 4.69 (d, 1H, *J* = 11.8 Hz, PhCH₂), 4.36 (d, 1H, *J*_{1,2} = 9.6 Hz, H-1), 3.81 (t, 1H, *J*_{2,3} = 9.4 Hz, H-2), 3.60 (d, 1H, *J*_{4,5} = 2.4 Hz, H-4), 3.55 (dd, 1H, *J*_{3,4} = 9.2 Hz, H-3), 3.46 (dd, 1H, *J*_{5,6} = 12.9 Hz, H-5), 2.81–2.59 (m, 2H, SCH₂), 1.66–1.18 (m, 23H, SCH₂(CH₂)₁₀CH₃, H-6), 0.88 (t, 3H, *J* = 6.5 Hz, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 139.2, 139.0, 138.9, 129.0, 129.0, 128.9, 128.7, 128.6, 128.3,

128.2, 128.1, 128.0, 85.7, 85.0, 78.9, 76.9, 76.3, 75.0, 73.4, 32.5, 31.2, 30.4, 30.3, 30.2, 30.1, 29.9, 29.8, 29.5, 23.2, 17.8, 14.7; HRMS-ESI: m/z $[M+Na]^+$ Calcd for $C_{39}H_{54}O_4SNa$: 641.3635; Found: 641.3607.

3.4.4. Methyl 3-*O*-(2,3,4,6-tetra-*O*-acetyl- β -D-galactopyranosyl)-6-*O*-benzyl-4-*O*-(2,3,4-tri-*O*-benzyl- α -L-fucopyranosyl)-2-deoxy-2-phthalimido- α -D-glucopyranoside (18)

Tf₂O (88 μ L, 0.52 mmol) was added to a stirred solution of **17** (241 mg, 0.39 mmol), BSP (90.0 mg, 0.43 mmol), DTBM (177 mg, 0.86 mmol), and MS4Å (500 mg) in dry CH₂Cl₂ (5.0 mL) at -78 °C under a nitrogen atmosphere. The reaction mixture was stirred for 15min, after disappearance of **17** detected by TLC, a solution of the acceptor **16** (191 mg, 0.26 mmol) in dry CH₂Cl₂ (2.0 mL) was added dropwise. The reaction mixture was stirred at this temperature for 1 h, quenched by addition Et₃N and diluted CHCl₃. The reaction mixture was filtered through a pad of Celite, the filtrate was successively washed with sat. aq. NaHCO₃, brine, dried (MgSO₄), and concentrated. The residue was purified by column chromatography (5:1→1:1 hexane–EtOAc, gradient eluant) provided the **18** (252 mg, 85%) as a colorless syrup; $[\alpha]_D^{21} +28.8$ (c 1.00, CHCl₃); ¹H NMR (600 MHz, CDCl₃): δ 7.91–7.19 (m, 24H, CH_{arom}), 5.33 (dd, 1H,

$J_{3,4} = 10.4$ Hz, H-3), 5.24 (d, 1H, $J_{1'',2''} = 3.3$ Hz, H-1''), 5.12 (d, 1H, $J_{4',5'} = 3.8$ Hz, H-4'), 4.99 (d, 1H, $J = 12.1$ Hz, PhCH₂), 4.98 (dd, 1H, $J_{2',3'} = 10.4$ Hz, H-2'), 4.89 (d, 1H, $J = 11.6$ Hz, PhCH₂), 4.84 (s, 2H, PhCH₂), 4.83 (d, 1H, $J = 11.5$ Hz, PhCH₂), 4.87–4.81 (m, 1H, H-5''), 4.66 (d, 1H, $J = 11.5$ Hz, PhCH₂), 4.65 (d, 1H, $J_{1,2} = 3.3$ Hz, H-1), 4.53 (dd, 1H, $J_{3',4'} = 10.4$ Hz, H-3'), 4.48 (dd, 1H, $J_{2,3} = 10.4$ Hz, H-2), 4.44 (d, 1H, $J_{1',2'} = 8.1$ Hz, H-1'), 4.42 (d, 1H, $J = 12.1$ Hz, PhCH₂), 4.36 (d, 1H, $J = 12.1$ Hz, PhCH₂), 4.25 (t, 1H, $J_{2'',3''} = 10.1$ Hz, H-2''), 4.16 (dd, 1H, $J_{5',6'a} = 3.8$ Hz, $J_{6'a,6'b} = 9.9$ Hz, H-6'a), 4.15–3.91 (m, 5H, H-4, 6a, 6b, 6'b, 3''), 3.83–3.76 (m, 2H, H-5', 4''), 3.61–3.54 (m, 1H, H-5), 3.21 (s, 3H, OMe), 2.01, 1.83, 1.81, 1.73 (4 s, each, 3H, acetyl), 1.29 (d, 3H, $J = 6.6$ Hz, H-6'') ; ¹³C NMR (75 MHz, CDCl₃): δ 170.7, 170.5, 170.4, 169.6, 169.5, 169.0, 139.3, 139.2, 139.0, 138.4, 135.3, 135.0, 132.5, 131.4, 129.1, 129.0, 128.9, 128.8, 128.5, 128.2, 128.1, 128.0, 127.9, 127.6, 124.4, 123.8, 99.4, 99.2, 98.0, 81.3, 76.9, 76.2, 75.4, 74.4, 74.0, 73.7, 73.3, 73.0, 72.9, 72.8, 71.6, 70.9, 70.6, 69.9, 68.6, 68.1, 67.0, 66.7, 61.0, 60.4, 56.5, 55.8, 55.4, 21.2, 21.0, 20.8, 17.4, 14.7; HRMS-ESI: m/z [M+Na]⁺ Calcd for C₆₃H₆₉NO₂₀Na: 1182.4305; Found: 1182.4316.

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