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Pre-activation of fully acetylated dodecyl thioglycosides with BSP–Tf_2O led to efficient glycosylation at low temperature

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ABSTRACT

Fully acetylated dodecyl thioglycosides were found to be useful as glycosyl donors by activation with 1-benzenesulfinyl piperidine (BSP) and triflic anhydride (Tf_2O) at −78 °C. The glycosyl acceptor was added to the reaction mixture at the same temperature to furnish various disaccharide, including the protected Lewis a (Le^a) trisaccharide, in good yields.

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 the 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 successfully 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 in a fume hood, 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 and co-workers reported[5] 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 previously demonstrated that dodecyl thioglycosides of glucose[6] and *N*-acetylneuraminic acid[7] showed excellent reactivity as glycosyl donors.[6b,c] It is well known that thioglycosides having *O*-benzoyl or *O*-pivaloyl groups at their 2-positions usually afford the corresponding 1,2-*trans* glycosides through neighboring-group participation. However, application of fully acetylated thioglycosides to glycosylation has been extremely limited. It was observed that glycosidation of dodecyl thioglycoside acetate gave a complex mixture of products[6a,8] in which an acetyl group of the donor migrated the acceptor, suggesting that an orthoester intermediate was formed during the reaction.

In complex oligosaccharide synthesis, glycosyl bromides or trichloroacetimidates with sterically less hindered acetyl groups sometimes played a crucial role in their synthetic strategy.[9] In order to extend the synthetic utility of the acetylated thioglycosyl donors, we re-investigated their glycosylation using various thiophilic reagents that have been reported. In our previous studies in oligosaccharide synthesis,[6,7] we focused[6b,c] on the sulfonium triflate pre-activation procedure for thioglycosides, because it forms highly reactive intermediates like α-glycosyl triflates in the glycosylation process.[10] Although the precise mechanism of this novel method has not yet been established, the triflate intermediate undergoes glycosylation via either a transient contact ion-pair mechanism or an S_N2-like replacement.[11] In this paper, we describe our recent finding that a trivial modification of the pre-activation method is highly effective for formation of 1,2-*trans* glycosides.

2. Results and discussion

According to an established procedure for the preparation of thioglycosides, fully acetylated monosaccharides and 1-dodecanthiol were treated with $BF_3{\cdot}Et_2O$ in 1,2-dichloroethane, giving

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the dodecyl thiohexopyranosides **1**–**6** in good yields. We next examined glycosylation using these thioglycosides as the donors. It was reported that BSP–Tf_2O pre-activation of fully acetylated 1-thio-α-L-rhamnopyranose underwent glycosylation with a partially protected serine derivative at −60 °C.[10b] However, our application of this procedure to coupling dodecyl 2,3,4-tri-*O*-acetyl-1-L-thio-α-rhamnoside (**1**) and a monosaccharide acceptor, methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**7**), was unsuccessful, giving several decomposed products of the donor **1** together with an almost quantitative recovery of unchanged acceptor **7** (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 the acetylated thioglycosides.

Thus, we treated the donor **1** with BSP–Tf_2O at lower temperature of −78 °C, and glycosylation continued at the same temperature, giving known α-linked disaccharide **8**[12] in 87% yield as the sole product. The ^1H NMR spectral data for **8** were consistent with those reported.[12] Furthermore, the configuration of newly generated rhamnosyl linkage in the disaccharides was confirmed to be α-L by measuring the one-bond coupling constant, $J_{C1',H1'}$ 172.5 Hz.

The excellent results of the glycosylation of **1** prompted us to examine the glycosylation of other thioglycoside acetates, D-gluco- **2**, D-galacto- **3**, D-manno- **4**, 2-deoxy-2-phthalimido-D-gluco- **5**, and L-fucopyranoside **6**, with the acceptor **7** using BSP–Tf_2O and a sterically hindered base as the promoter system. However, glycosylation of donors **2** and **4** gave the corresponding disaccharides in low yields. Crich and Smith reported that BSP–Tf_2O promoted glycosylation of benzoylated glucosyl, mannosyl, and xylosyl donors in the presence of sterically hindered base to give orthoesters as major products, while glycosides were obtained in the absence of base.[10b] Therefore, we did not add 2,6-di-*tert*-butyl-4-methylpyridine (DTBM) in the reactions of **1**, **2**, and **4**. Reaction conditions and results of our glycosylation are summarized in Table 1. All reactions were completed within 1 h at −78 °C, giving disaccharides with 1,2-trans configuration in yields of 80–90%. The 1,2-*trans* configurations of the disaccharides **8**–**13** were also confirmed by ^1H and ^{13}C NMR spectroscopy. Although we have not obtained positive evidence, we hypothesized that the glycosylation proceeded through the corresponding dioxocarbenium ion intermediates formed by neighboring-group participation of the 2-*O*-acetyl groups in a manner similar to that for other acetylated donors.

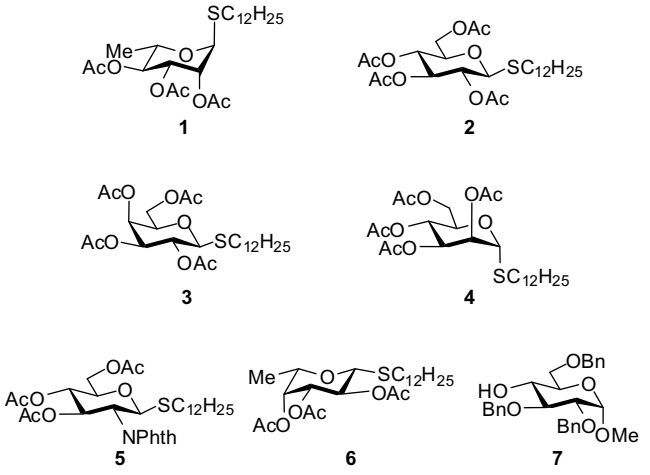
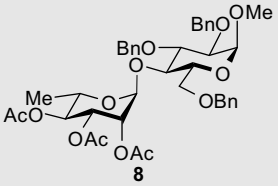
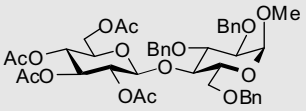
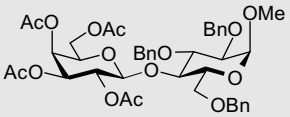
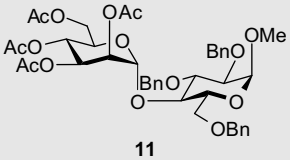
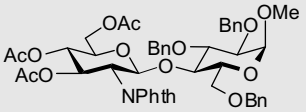
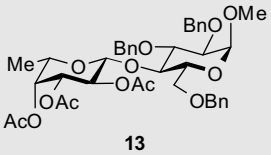


Figure 1. Glycosyl donor (**1**–**6**) and acceptor (**7**) employed in the BSP–Tf_2O-mediated couplings.

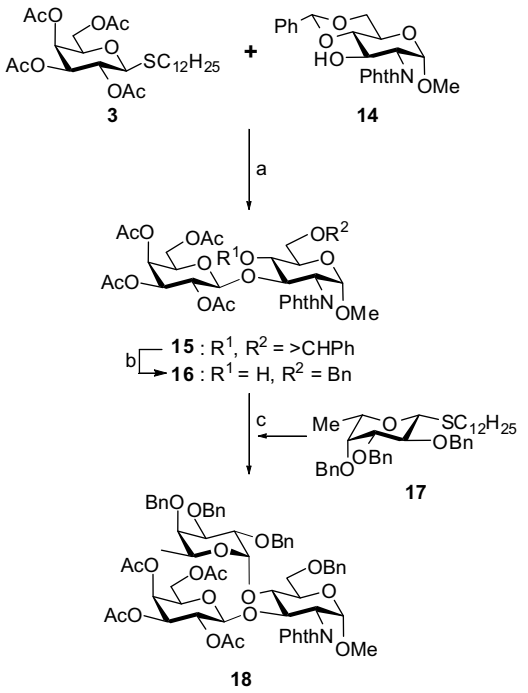
Table 1
Results of BSP–Tf_2O-mediated glycosylation[a]

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

[a] Typically, the dodecyl thioglycoside donors (2.0 equiv with respect to the acceptor) were pre-activated by BSP (1.1 equiv with respect to the donor), Tf_2O (1.4 equiv with respect to the donor), and DTBM (2.0 equiv with respect to the donor) in CH_2Cl_2 at −78 °C, followed by addition of the acceptor at the same temperature.

[b] Reactions were performed without DTBM.

Encouraged by these successful results of disaccharide formation, we turned our attention to the synthesis of the Lewis a (Le^a) antigen trisaccharide, Fuc-α-(1→4)-(Gal-β-(1→3))-GlcNAc.[9a,e,13] An established synthetic route to the trisaccharide involves the introduction of the tetra-*O*-acetyl-β-D-galactopyranosyl residue at the 3-OH group of a D-glucosamine derivative by a Koenigs–Knorr reaction prior to α-fucosylation at the 4-OH group.[13] This strategy is probably used because of the steric hindrance of the neighboring substituent and/or mismatching between the glycosyl donor and the acceptor.[14] Since thioglycosyl donors have been seldom used for this glycosylation, we were interested in glycosylation between **3** and the acceptor **14** as shown in Scheme 1. By a process similar to the glycosylation described above, **3** was pre-activated with BSP–Tf_2O in dry CH_2Cl_2 at −78 °C in the presence of 4 Å molecular sieves and DTBM, and was subsequently treated with the acceptor **14** at the same temperature. As we expected, this glycosylation proceeded smoothly, and the desired disaccharide **15** was obtained



Scheme 1. Reagents and conditions: (a) BSP, DTBM, Tf_2O, CH_2Cl_2, −78 °C, 1 h, 84%; (b) $NaBH_3CN$, HCl−Et_2O, THF, 0 °C, 30 min, 72%; (c) BSP, DTBM, Tf_2O, CH_2Cl_2, −78 °C, 1 h, 85%.

in an excellent yield of 84%. The anomeric configuration of **15** was confirmed to be β on the basis of its coupling constant ($J_{1',2'}$ 7.8 Hz, H-1′) for the anomeric proton at 4.76 ppm in the ^{1}H NMR spectrum and the chemical shift in ^{13}C NMR spectrum at 100.5 ppm (C-1′). For the next step, the α-fucosylation at the 4-position, the disaccharide **15** was converted into glycosyl acceptor **16** by reductive ring opening of the benzylidene acetal. Thus, **15** was treated with $NaBH_3CN$–HCl in THF at 0 °C, giving the 4-OH derivative **16** in 72% yield. The α-L-fucosylation using the benzylated thioglycoside donor **17** was also successful with BSP–Tf_2O in dry CH_2Cl_2 at −78 °C, giving fully protected Le^a trisaccharide **18** in 85% yield. Both the ^{1}H and ^{13}C NMR spectra, as well as the high-resolution MS spectrum, supported its structure.

In summary, a simple modification of Crich's procedure for the per-activation of thioglycosides was found to result in a dramatically improved ability of fully acetylated thioglycosides to serve as glycosyl donors. On treatment with BSP–Tf_2O at −78 °C, fully acetylated dodecyl thioglycosides coupled with glycosyl acceptors at the same temperature to give various disaccharides and a precursor of Le^a trisaccharide in excellent yields.

3. Experimental

3.1. General methods

All chemicals purchased were of reagent grade, and were used without further purification. Dichloromethane (CH_2Cl_2) and 1,2-dichloroethane were distilled over calcium hydride (CaH_2). Molecular sieves used for glycosylation were 4 Å MS, which were activated at 200 °C under reduced pressure prior to use. Reactions were monitored by thin-layer chromatography (TLC) on a precoated plates of Silica Gel 60F_{254} (layer thickness, 0.25 mm; E. Merck, Germany), which were visualized under UV (254 nm) and/or by spraying with *p*-methoxybenzaldehyde−H_2SO_4−MeOH (1:2:17, v/v). Column chromatography was performed on silica gel (Silica Gel 60; 70−230 mesh ASTM, E. Merck, Darmstadt, Germany).

^{1}H and ^{13}C 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 Me_4Si (δ 0 ppm) in $CDCl_3$. ^{13}C NMR spectra were obtained by using the same NMR spectrometers, and were calibrated with $CDCl_3$ (δ 77.00 ppm). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br d, broad doublet for ^{1}H NMR data. High-resolution mass spectra (HRESI-TOFMS) were measured on a Bruker micro-TOF focus spectrometer.

3.2. Preparation of dodecyl thioglycosides

General procedure: To a solution of per-*O*-acetylated sugar and 1-dodecanethiol (1.1 equiv) in 1,2-dichloroethane (10−20 mL) was added $BF_3{\cdot}OEt_2$ (1.2 equiv) at 0 °C. The temperature was raised to room temperature and stirring was continued. After TLC showed completion of the reaction, the mixture was diluted with $CHCl_3$, poured into ice-water, and stirred for 30 min. The organic layer that separated was successively washed with sat aq $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated. The dodecyl thioglycoside produced was purified by silica gel chromatography (5:1→3:1 hexane–EtOAc, gradient elution).

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

1,2,3,4-Tetra-*O*-acetyl-α-L-rhamnopyranose (1.00 g, 3.01 mmol) was treated according to the general procedure described above to give **1** (1.25 g, 88% yield) as a colorless syrup: $[\alpha]_D^{20}$ −95.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 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, SCH_2), 2.16, 2.05, 1.98 (3s, each 3H, acetyl), 1.65−1.22 (m, 23H, $SCH_2(CH_2)_{10}CH_3$, H-6), 0.88 (t, 3H, *J* 6.5 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{24}H_{42}O_7S$: 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)

1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranose (0.78 g, 2.0 mmol) was treated according to the general procedure described above to give **2** (1.00 g, 95% yield) as a colorless solid: $[\alpha]_D^{20}$ −29.2 (*c* 0.12, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 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, SCH_2), 2.10, 2.08, 2.04, 2.03 (4s, each 3H, acetyl), 1.66−1.26 (m, 20H, $SCH_2(CH_2)_{10}CH_3$), 0.88 (t, 3H, *J* 4.1 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{26}H_{44}O_9S$: 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)

1,2,3,4,6-Penta-*O*-acetyl-β-D-galactopyranose (0.78 g, 2.0 mmol) was treated according to the general procedure described above to give **3** (1.05 g, 99% yield) as a colorless solid: $[\alpha]_D^{20}$ −16.0 (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 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, SCH_2), 2.17,

2.16, 2.07, 2.05 (4s, each 3H, acetyl), 1.66–1.26 (m, 20H, $SCH_2(CH_2)_{10}CH_3$), 0.88 (t, 3H, J 4.1 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{26}H_{44}O_9S$: 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)

1,2,3,4,6-Penta-*O*-acetyl-α-D-mannopyranose (2.0 g, 5.0 mmol) was treated according to the general procedure described above to give **4** (2.3 g, 86% yield) as a colorless solid: $[\alpha]_D^{20}$ +76.8 (*c* 0.37, $CHCl_3$); ^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, SCH_2), 2.11, 2.05, 2.03, 1.95 (4s, each 3H, acetyl), 1.66–1.26 (m, 20H, $SCH_2(CH_2)_{10}CH_3$), 0.88 (t, 3H, J 4.1 Hz, CH_2CH_3); ^{13}C 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 $C_{26}H_{44}O_9S$: 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)

1,3,4,6-Tetra-*O*-acetyl-2-phthalimido-2-deoxy-β-D-glucopyranose (2.58 g, 5.42 mmol) was treated according to the general procedure described above to give **5** (2.73 g, 81% yield) as a colorless solid: $[\alpha]_D^{20}$ +22.7 (*c* 2.63, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 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, SCH_2), 2.10, 2.04, 1.87 (3s, each 3H, acetyl), 1.60–1.24 (m, 20H, $SCH_2(CH_2)_{10}CH_3$), 0.88 (t, 3H, J 6.2 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{32}H_{45}NO_9S$: 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)

L-Fucose (2.0 g, 12.2 mmol) was dissolved in Ac_2O (20 mL) and pyridine (20 mL) and was stirred for 12 h. The reaction was quenched by addition of ice-water, and the mixture was stirred overnight and extracted with EtOAc. The organic layer was successively washed with satd aq $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated. Column chromatography (2:1 hexane–EtOAc) yielded 4.0 g (quant) of 1,2,3,4-tetra-*O*-acetyl-L-fucose as a 7:3 mixture of α and β anomers, [(δ 6.36 (d, $J_{1,2}$ 2.19 Hz, H-1α), 5.68 (d, $J_{1,2}$ 8.29 Hz, H-1β)].

The resulting acetate (4.0 g, 12.0 mmol) and 1-dodecanethiol (1.0 mL, 3.96 mmol) were stirred in 1,2-dichloroethane (20 mL) at 0 °C. $BF_3{\cdot}OEt_2$ (0.5 mL, 4.32 mmol) was added, and the mixture was stirred for 4 h at this temperature. The reaction mixture was quenched by addition of ice-water and was stirred for 30 min. The organic layer was successively washed with satd aq $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (3:1 hexane–EtOAc) to afford unreacted α-acetate (2.72 g, 68% recovery) and **6** (1.43 g, 84% yield, based on the consumed β-acetate) as a colorless syrup: $[\alpha]_D^{20}$ −16.5 (*c* 0.26, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 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, SCH_2), 2.18, 2.06, 1.99 (3s, each 3H, acetyl), 1.61–1.25 (m, 20H, $SCH_2(CH_2)_{10}CH_3$), 1.22 (d, 3H, J 6.4 Hz, H-6), 0.88 (t, 3H, J 6.5 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{24}H_{42}O_7S$: C, 60.73; H, 8.92; S, 6.76. Found: C, 60.70; H, 8.98; S, 6.86.

3.3. Glycosylation between the donors 1–6 and the acceptor 7

General procedure: A suspension of the dodecyl thioglycosides **1–6** (0.6 mmol, 2.0 equiv), BSP (138.1 mg, 0.66 mmol, 1.1 equiv to thioglycoside), and 4 Å MS (700 mg) was stirred in dry CH_2Cl_2 (6 mL) at room temperature for 30 min under a nitrogen atmosphere. The reaction mixture was cooled to −78 °C, followed by addition of Tf_2O (137 μL, 0.82 mmol, 1.4 equiv to thioglycoside) and was stirred at the same temperature for 15 min. A solution of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**7**, 139.0 mg, 0.3 mmol, 1.0 equiv) in dry CH_2Cl_2 (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 of Et_3N, diluted with $CHCl_3$, and filtered through a pad of Celite. The filtrate was successively washed with satd aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography.

3.3.1. Methyl 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (8)

Dodecyl thiorhamnoside **1** (284.8 mg, 0.6 mmol) was condensed with the glycosyl acceptor **7** (139 mg, 0.3 mmol) in dry CH_2Cl_2 (8 mL) in the presence of BSP (138.1 mg, 0.66 mmol), Tf_2O (137 μL, 0.82 mmol), and 4 Å MS (700 mg) following the general procedure described above. Column chromatography (10:1→6:1 toluene–EtOAc, gradient elution) provided the disaccharide **8** (188 mg, 87% yield). Spectral data for **8** were consistent with those reported previously.[12]

3.3.2. Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (9)

Dodecyl thioglucoside **2** (320 mg, 0.6 mmol) was condensed with the glycosyl acceptor **7** (139 mg, 0.3 mmol) in dry CH_2Cl_2 (8 mL) in the presence of BSP (138.1 mg, 0.66 mmol), Tf_2O (137 μL, 0.82 mmol), and 4 Å MS (700 mg) following the general procedure described above. Column chromatography (7:1→2:1 toluene–EtOAc, gradient elution) provided the disaccharide **9** (210 mg, 88% yield). Spectral data for **9** were consistent with those reported previously.[12,16]

3.3.3. Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (10)

Dodecyl thiogalactoside **3** (320 mg, 0.6 mmol) was condensed with the glycosyl acceptor **7** (139 mg, 0.3 mmol) in dry CH_2Cl_2 (8 mL) in the presence of BSP (138.1 mg, 0.66 mmol), Tf_2O (137 μL, 0.82 mmol), DTBM (246.8 mg, 1.2 mmol), and 4 Å MS (700 mg) following the general procedure described above. Column chromatography (7:1→2:1 toluene–EtOAc, gradient elution) provided the disaccharide **10** (213 mg, 89% yield). Spectral data for **10** were consistent with those reported previously.[3,15]

3.3.4. Methyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (11)

Dodecyl thiomannoside **4** (320 mg, 0.6 mmol) was condensed with the glycosyl acceptor **7** (139 mg, 0.3 mmol) in dry CH_2Cl_2 (8 mL) in the presence of BSP (138.1 mg, 0.66 mmol), Tf_2O (137 μL, 0.82 mmol), and 4 Å MS (700 mg) following the general procedure described above. Column chromatography (10:1→4:1 toluene–EtOAc, gradient elution) provided the disaccharide **11**

(189 mg, 80% yield). Spectral data for **11** were consistent with those reported previously.[12]

3.3.5. Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (12)

The *N*-phthaloyl glucosamine derivative **5** (372 mg, 0.6 mmol) was condensed with the glycosyl acceptor **7** (418 mg, 0.9 mmol) in dry CH_2Cl_2 (8 mL) in the presence of BSP (138.1 mg, 0.66 mmol), Tf_2O (137 μL, 0.82 mmol), DTBM (246.8 mg, 1.2 mmol), and 4 Å MS (700 mg) following the general procedure described above. Column chromatography (10:1→2:1 toluene–EtOAc, gradient elution) provided the disaccharide **12** (220 mg, 83% yield) as a colorless syrup: $[\alpha]_D^{22}$ +18.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): 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, PhC*H*$_2$), 4.91 (d, 1H, *J* 11.6 Hz, PhC*H*$_2$), 4.68 (d, 1H, *J* 12.7 Hz, PhC*H*$_2$), 4.55 (d, 1H, *J* 12.1 Hz, PhC*H*$_2$), 4.50 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 4.35 (d, 1H, *J* 11.5 Hz, PhC*H*$_2$), 4.33 (d, 1H, *J* 12.0 Hz, PhC*H*$_2$), 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 (3s, 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; HRESIMS: *m/z* $[M+Na]^+$ calcd for $C_{48}H_{51}NO_{15}Na$: 904.3151; found: 904.3143.

3.3.6. Methyl 2,3,4-tri-*O*-acetyl-β-L-fucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (13)

Dodecyl thiofucoside **6** (284.8 mg, 0.6 mmol) was condensed with the glycosyl acceptor **7** (139 mg, 0.3 mmol) in dry CH_2Cl_2 (8 mL) in the presence of BSP (138.1 mg, 0.66 mmol), Tf_2O (137 μL, 0.82 mmol), DTBM (246.8 mg, 1.2 mmol), and 4 Å MS (700 mg) following the general procedure described above. Column chromatography (10:1→5:1 toluene–EtOAc, gradient elution) provided the disaccharide **13** (183 mg, 84% yield) as a colorless syrup: $[\alpha]_D^{22}$ +22.1 (*c* 1.00, $CHCl_3$); ^{1}H 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, PhC*H*$_2$), 4.93 (dd, 1H, $J_{3',4'}$ 10.4 Hz, H-3′), 4.76 (d, 1H, *J* 12.1 Hz, PhC*H*$_2$), 4.69 (d, 1H, *J* 9.9 Hz, PhC*H*$_2$), 4.64 (d, 1H, *J* 11.6 Hz, PhC*H*$_2$), 4.62 (d, 1H, $J_{1,2}$ 3.3 Hz, H-1), 4.61 (d, 1H, *J* 11.6 Hz, PhC*H*$_2$), 4.53 (d, 1H, *J* 12.1 Hz, PhC*H*$_2$), 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; HRESIMS: *m/z* $[M+Na]^+$ calcd for $C_{40}H_{48}O_{13}Na$: 759.2987; found: 759.2963.

3.4. Synthesis of fully protected Le^a trisaccharide 18

3.4.1. Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-α-D-glucopyranoside (15)

To a stirred suspension containing the thiogalactosyl donor **3** (320 mg, 0.6 mmol), BSP (138.1 mg, 0.66 mmol), DTBM (216.8 mg, 1.2 mmol), and 4 Å MS (700 mg) in dry CH_2Cl_2 (6 mL) at −78 °C under a nitrogen atmosphere was added Tf_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 the same temperature for 1 h, and the reaction was quenched by addition of Et_3N. The mixture was diluted with $CHCl_3$ and filtered through a pad of Celite. The filtrate was successively washed with satd aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (5:1→2:1 toluene–EtOAc, gradient elution) to provide **15** (372 mg, 84% yield) as a colorless syrup: $[\alpha]_D^{21}$ +62.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97–7.21 (m, 9H, CH_{arom}), 5.59 (s, 1H, PhC*H*), 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 (4s, each, 3H, acetyl); ^{13}C NMR (75 MHz, $CDCl_3$): 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; HRESIMS: *m/z* $[M+Na]^+$ calcd for $C_{36}H_{39}NO_{16}Na$: 764.2161; found: 764.2178.

3.4.2. Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→3)-6-*O*-benzyl-2-deoxy-2-phthalimido-α-D-glucopyranoside (16)

Sodium cyanoborohyride (211 mg, 3.36 mmol) was added to a stirring solution of the disaccharide **15** (208 mg, 0.18 mmol) in anhyd. THF (5 mL) containing 4 Å MS (500 mg). A solution of HCl in Et_2O (2 M) was added dropwise until the evolution of gas ceased. After stirring for an additional 30 min, the mixture was filtered through Celite and washed successively with satd aq $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated. The crude mixture was purified by column chromatography (5:1→2:1 toluene–EtOAc, gradient elution) to give acceptor **16** as a colorless syrup (149 mg, 72% yield): $[\alpha]_D^{22}$ +93.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): 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, PhC*H*$_2$), 4.63 (d, 1H, *J* 12.1 Hz, PhC*H*$_2$), 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 (4s, each, 3H, acetyl); ^{13}C NMR (75 MHz, $CDCl_3$): 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; HRESIMS: *m/z* $[M+Na]^+$ calcd for $C_{36}H_{41}NO_{16}Na$: 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 dry MeOH (15 mL), and methanolic 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 (H^+). Subsequent removal of the resin by filtration and evaporation of the solvent gave a white solid. The dry product was further treated with benzyl bromide (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 the reaction was quenched with MeOH and aq NH_4OH (25%, w/v), which was then coevaporated with toluene (20 mL × 3). The crude product was diluted with EtOAc (100 mL), and the organic layer was washed with satd aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residual

syrup was purified by column chromatography (10:1→3:1 hexane–EtOAc, gradient elution) to give the benzylated thiofucoside **17** as a colorless solid (1.9 g, 93% yield): $[\alpha]_D^{22}$ +9.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58–7.11 (m, 15H, CH_{arom}), 5.03 (d, 1H, *J* 10.4 Hz, PhC*H*$_2$), 4.90 (d, 1H, *J* 10.1 Hz, PhC*H*$_2$), 4.79 (d, 1H, *J* 10.1 Hz, PhC*H*$_2$), 4.75 (s, 2H, PhC*H*$_2$), 4.69 (d, 1H, *J* 11.8 Hz, PhC*H*$_2$), 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, SC*H*$_2$), 1.66–1.18 (m, 23H, $SCH_2(CH_2)_{10}CH_3$, H-6), 0.88 (t, 3H, *J* 6.5 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 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; HRESIMS: *m/z* $[M+Na]^+$ calcd for $C_{39}H_{54}O_4SNa$: 641.3635; found: 641.3607.

3.4.4. Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→3)-[2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→4)-]-6-*O*-benzyl-2-deoxy-2-phthalimido-α-D-glucopyranoside (18)

To a stirred suspension of **17** (241 mg, 0.39 mmol), BSP (90.0 mg, 0.43 mmol), DTBM (177 mg, 0.86 mmol), and 4 Å MS (500 mg) in dry CH_2Cl_2 (5.0 mL) at −78 °C under a nitrogen atmosphere was added Tf_2O (88 μL, 0.52 mmol). The reaction mixture was stirred for 15 min, after which time disappearance of **17** was detected by TLC. A solution of the acceptor **16** (191 mg, 0.26 mmol) in dry CH_2Cl_2 (2.0 mL) was then added dropwise. The reaction mixture was stirred at the same temperature for 1 h, and the reaction was quenched by addition of Et_3N. The mixture was then diluted with $CHCl_3$ and filtered through a pad of Celite. The filtrate was successively washed with satd aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (5:1→1:1 hexane–EtOAc, gradient elution) to provide the fully protected trisaccharide **18** (252 mg, 85% yield) as a colorless syrup: $[\alpha]_D^{21}$ +28.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): 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, PhC*H*$_2$), 4.98 (dd, 1H, $J_{2',3'}$ 10.4 Hz, H-2′), 4.89 (d, 1H, *J* 11.6 Hz, PhC*H*$_2$), 4.84 (s, 2H, PhC*H*$_2$), 4.83 (d, 1H, *J* 11.5 Hz, PhC*H*$_2$), 4.87–4.81 (m, 1H, H-5″), 4.66 (d, 1H, *J* 11.5 Hz, PhC*H*$_2$), 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, PhC*H*$_2$), 4.36 (d, 1H, *J* 12.1 Hz, PhC*H*$_2$), 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 (4s, each, 3H, acetyl), 1.29 (d, 3H, *J* 6.6 Hz, H-6″); ^{13}C NMR (75 MHz, $CDCl_3$): 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; HRESIMS: *m/z* $[M+Na]^+$ calcd for $C_{63}H_{69}NO_{20}Na$: 1182.4305; found: 1182.4316.

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