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Intermolecular aglycon transfer of ethyl thioglycosides can be prevented by judicious choice of protecting groups

Tong Zhu, Geert-Jan Boons *

Complex Carbohydrate Research Center, University of Georgia, 220 Riverbend Road, Athens, GA 30602-4712, USA

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Abstract

Unexpected intermolecular aglycon transfer occurred in chemoseletive glycosylations using glycosyl fluorides or trichloroacetimidates as glycosyl donors and partially protected thioglycosides as glycosyl acceptors. It is shown that this problem can be addressed by fine-tuning of the reactivity of the anomeric thioalkyl moiety and hydroxyl of the acceptor.

Keywords: Chemoselective glycosylation; Thioglycoside; Oligosaccharide; Lewis antigens

1. Introduction

Oligosaccharides are involved in many vital biological processes [1], and not surprisingly, there is increased demand for efficient methods for their chemical synthesis. The chemical synthesis of complex oligosaccharides requires highly convergent strategies. In such strategies most of the synthetic effort is directed towards the preparation of saccharide building blocks that can be assembled into complex structures using a minimum number of synthetic steps [2]. Alkyl and aryl thioglycosides [3] have emerged as versatile building blocks for convergent oligosaccharide assembly. Due to their excellent chemical stability, anomeric thio groups offer efficient protection of anomeric centers and are stable under many reaction conditions that protecting group chemistry requires for hydroxyl differentiation and manipulation. Thioglycosides can also act as glycosyl acceptors and can be used in combination with a range of different donors including trichloroacetimidates, glycosyl fluorides, bromides, sulfoxides and selenoglycosides [2–4]. In the presence of soft electrophiles, however, thioglycosides can be activated and used as glycosyl donors. These chemical features allow a chemoselective glycosylation strategy whereby a thioglycoside first acts as a glycosyl acceptor and in a subsequent glycosylation as a donor. Such a sequence of reactions is very attractive since time-consuming functional group manipulations at the anomeric center are avoided. Nevertheless, unexpected side reactions may occur when unreactive thioglycosyl acceptors are employed in glycosylations. For example, Leigh and co-workers [5] reported an intermolecular aglycon transfer of ethyl 1-thiorhamnopyranosyl acceptors when Koenigs–Knorr or Helferich glycosylation conditions were employed. Intermolecular

* Corresponding author. Tel.: +1-706-5424401; fax: +1-706-5424412.

E-mail address: gjboons@ccrc.uga.edu (G.-J. Boons).

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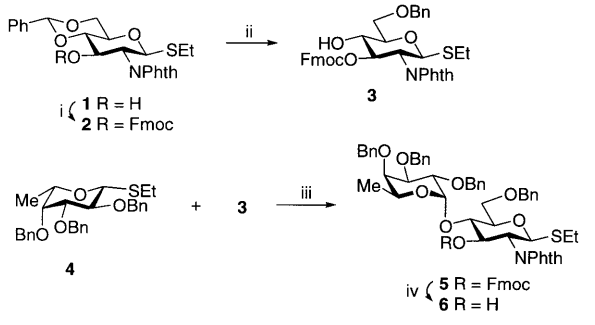
aglycon transfer of a phenyl 1-thiogalactosamide derivative using a trichloroacetimidate donor has also been reported [6,7].

In this paper, we describe an unexpected intermolecular aglycon transfer when a galactosyl fluoride or trichloroacetimidate donor was coupled with a partially protected ethyl 1-thioglucosamine acceptor. It is shown that this undesirable transfer reaction can be avoided by a judicious choice of protecting groups.

2. Results and discussion

As part of a program to develop fully synthetic tumor vaccines, we embarked on the synthesis of oligosaccharide fragments derived from Lewis antigens. A chemoselective glycosylation strategy was designed where key thioglycoside **3** first acts as an acceptor leading to core Lewis structures. At an appropriate stage, however, the resulting complex thioglycosides can be used as glycosyl donors for glycosylations with Lewis- or lactosyl acceptors to give complex Lewis oligosaccharides. In addition, the 9-fluorenylmethylcarbonyl (Fmoc) group of **3** was selected as an attractive temporary hydroxyl-protecting group because it is remarkably stable under Lewis acid conditions used in glycosylations but can be cleaved under very mild basic conditions without affecting other base-sensitive functionalities [8]. The Fmoc group is also orthogonal with the levulinoyl (Lev) and diethylisopropylsilyl (DEIPS) groups [8], and it is envisaged that these functionalities will be employed for future synthesis of the Lewis antigens.

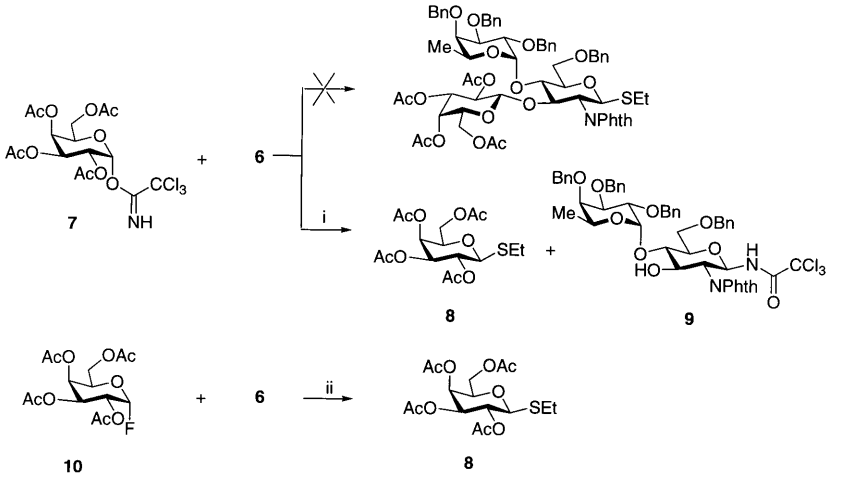


Scheme 1. Reagents and conditions: (i) FmocCl, Py 94%; (ii) $NaCNBH_3$, $HC–Et_2O$, THF, 3 Å MS, 82%; (iii) NIS, TMSOTf, toluene, −5 °C, 4 Å MS, 84%; (iv) Et_3N, DCM, 88%.

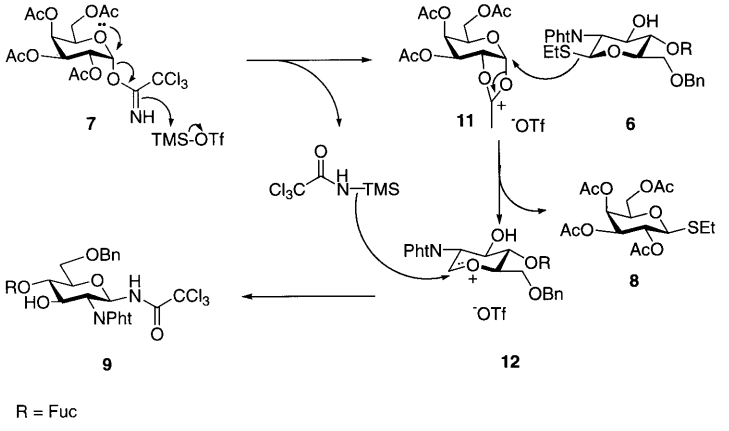
The known thioglycoside **1** [9] was treated with FmocCl in pyridine to give compound **2** in a yield of 94%. The benzylidene acetal of **2** was regioselectively cleaved by treatment with $NaCNBH_3$ and $HCl–Et_2O$ in THF [10] to give compound **3** bearing a C-4 hydroxyl. *N*-Iodosuccinimide (NIS)–trimethylsilyl trifluoromethanesulfonate (TMSOTf) [11] mediated coupling of compound **3** with **4** gave disaccharide **5** as a sole product in a yield of 84%. This glycosylation exploits the higher reactivity of 6-deoxy thioglycosides compared to their 6-hydroxy counterparts [12]. The Fmoc group of compound **5** was efficiently removed by treatment with triethylamine in dichloromethane (Scheme 1). Coupling of acceptor **6** with trichloroacetimidate **7** in the presence of TMSOTf [13] at rt did not afford a trisaccharide, but instead thioglycoside **8** (92% with respect to acceptor) and trichloroacetamide **9** (59%) were isolated. (Scheme 2). A $Cp_2ZrCl_2–AgOTf$ [14] mediated coupling of glycosyl fluoride **10** with disaccharide **6** did not give the desired trisaccharide either, and this reaction also gave thioglycoside **8** and degradation products derived from the glycosyl acceptor.

The unusual aglycon transfer observed in these reactions was rationalized as follows. The acetoxonium ion **11**, which was formed after activation of glycosyl donor, reacts with the anomeric thio alkyl moiety of **6** instead of its hydroxyl, leading to the formation of β-thioglycoside **8**. The reactive intermediate **12** can either decompose or be trapped by a nucleophile. In the coupling of **6** with **7**, 2,2,2-trichloro-*N*-trimethylsilylacetamide served as a nucleophile to give the trichloroacetamide derivative **9** (Scheme 3).

Our attention was turned to finding a solution for the unwanted transfer. It is well known that the hydroxyl of disaccharide **6** is of low reactivity due to the presence of the bulky phthalimido group at C-2 [15], and this feature may explain the preferred attack at the anomeric thio group. The sterically less demanding trichloroethoxycarbonyl (Troc) was selected as the amino protecting group ensuring higher glycosyl accepting properties of the C-3 hydroxyl of the glucosamine unit. A careful review of previously reported syntheses of

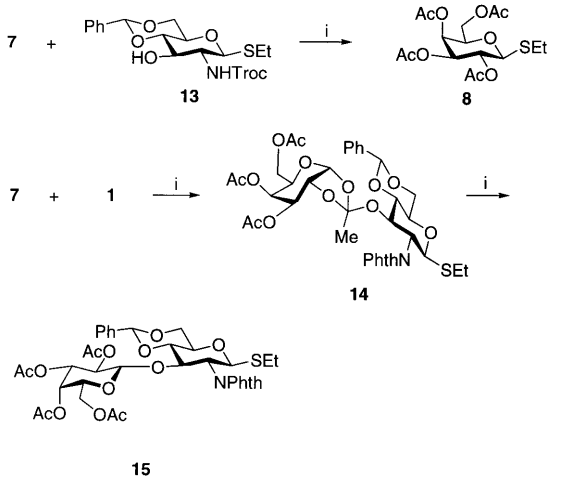


Scheme 2. Reagents and conditions: (i) TMSOTf, 4 Å MS, DCM; (ii) Cp_2ZrCl_2, AgOTf, 4 Å MS, DCM.



Scheme 3. A proposed mechanism for intramolecular aglycon transfer.

Lewis[a] antigens indicated that glucosamine derivatives protected with a 4,6-*O*-benzylidene functionality were most commonly used [16]. Possibly, the C-3 hydroxyl is more accessible because the benzylidene acetal cannot freely rotate and block this position. Furthermore, it is well known that cyclic protecting groups reduce anomeric reactivity [17]. To this end, *N*-Troc protected thioglycoside **13** was employed as a glycosyl acceptor but, unfortunately, coupling with trichloroacetimidate **7** in the presence of TMSOTf did not give the desired product, and again thioglycoside **8** was obtained (yield 93% based on acceptor) (Scheme 4). The outcome of this glycosylation indicated that the anomeric thio moiety is still more nucleophilic than the C-3 hydroxyl. This



Scheme 4. Reagents and conditions: (i) TMSOTf, 4 Å MS, DCM.

observation may be explained by the finding of Wong and co-workers that *N*-Troc protected thioglycosides are approximately 30 times more reactive than their phthalimido analogues [18]. Thus, the reactivity of both the C-3 hydroxyl and the anomeric thio moiety were enhanced still leading to the undesired reaction pathway.

A judicious choice of protecting groups is needed to tune the reactivity of the anomeric thio moiety and hydroxyl of the acceptor. An appropriate balance of reactivities may be achieved by employing the phthaloyl as N-protecting group to deactivate the anomeric center of the thioglycoside and a 4,6-*O*-benzylidene acetal to enhance the reactivity of C-3 hydroxyl. Indeed, TMSOTf-mediated coupling of **1** with **7** gave only coupling product **14**, and in this case formation of thioglycoside **8** was not observed. Orthoester **14** was converted easily to disaccharide **15** by TMSOTf-catalyzed rearrangement (Scheme 4). Lewis antigens can be obtained easily from disaccharide **15** by regioselective opening of the benzylidene acetal, followed by glycosylation [19].

In conclusion, it is shown that undesired intermolecular aglycon transfer can be avoided by a careful choice of protecting groups that control anomeric reactivities of glycosyl donor and acceptor and nucleophilicity of the hydroxyl of the acceptor.

3. Experimental

Chemicals were purchased from Aldrich and Fluka and used without further purification. Molecular sieves were activated at 350 °C for 3 h in vacuo. Dichloromethane was distilled from CaH_2 and stored over 4 Å molecular sieves. All the reactions were performed under anhyd conditions and monitored by TLC on Kieselgel 60 F_{254} (E. Merck). Detection was by examination under UV light (254 nm) and by charring with 10% H_2SO_4 in MeOH. Flash chromatography was performed on silica gel (E. Merck, mesh 70–230). Extracts were evaporated under reduced pressure at <40 °C (bath). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300 spectrometer and a Varian Inova 500 spectrometer equipped with Sun workstations. For ^{1}H and ^{13}C NMR spectra recorded in $CDCl_3$, chemical shifts (δ) are given in ppm relative to solvent peaks (^{1}H, δ 7.26; ^{13}C, δ 77.3) as internal standard. Negative-ion matrix-assisted laser-desorption ionization time-of-flight (MALDI-TOF) mass spectra were recorded using an HP-MALDI 2030A instrument with a gentisic acid matrix. Optical rotations were measured on a Jasco P-1020 polarimeter.

*Ethyl 6-*O*-benzyl-3-*O*-(9-fluorenylmethoxycarbonyl)-2-deoxy-2-phthalimido-1-thio-β-*D*-glucopyranoside* (**3**).—To a stirred solution of compound **1** (0.44 g, 1.0 mmol) in pyridine (3 mL) was added FmocCl (0.52 g, 2.0 mmol), and the reaction mixture was stirred at rt for 1 h. Methanol (2 mL) was added, and the solvents were evaporated under reduced pressure. The residue was diluted with CH_2Cl_2 (50 mL) and washed successively with water (2×20 mL) and brine (20 mL). The organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography (silica gel, 1:5, EtOAc–hexanes) to give **2** as a colorless syrup (0.62 g, 94%).

A solution of hydrogen chloride in diethyl ether (2 M, 7 mL) was added to a solution of compound **2** (0.62 g, 0.94 mmol) and sodium cyanoborohydride (0.88 g, 14 mmol) in THF (10 mL) containing 3 Å molecular sieves (300 mg). The mixture was stirred until the evolution of gas had ceased. The reaction mixture was filtered, and the filtrate was co-evaporated with MeOH (3×10 mL). The residue was diluted with CH_2Cl_2 (50 mL) and washed successively with water (2×20 mL) and brine (15 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The resulting syrup was applied to a column of silica gel that was eluted with 1:3 EtOAc–hexanes to give **3** as a white foam (0.51 g, 82%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.84–7.19 (m, 17 H, Ar–H), 5.64 (dd, 1 H, $J_{2,3}$ 10.4, $J_{3,4}$ 10.0 Hz, H-3), 5.50 (d, 1 H, $J_{1,2}$ 10.4 Hz, H-1), 4.64 (AB q, 2 H, J_{AB} 12.1 Hz, OCH_2Ph), 4.46 (t, 1 H, H-2), 4.17 (d, 2 H, J 8.4 Hz, CH_2O (Fmoc)), 3.98–3.78 (m, 5 H, H-4, H-5, H-6a, H-6b, H-9 (Fmoc)), 3.10 (s, 1 H, O*H*), 2.80–2.61 (m, 2 H, SCH_2), 1.23 (t, 3 H, J 7.4 Hz,

SCH_2CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.1, 167.4 (2 C, *C*=O, Phth), 155.3 (*C*=O, Fmoc), 143.3, 143.2, 141,3, 141.2, 137.8, 134.4, 134.2, 131.9, 131.4, 128.7, 128.1, 127.8, 127.4, 125.4, 125.3, 123.9, 123.8, 120.1 (24 C, Ar–C), 81.3 (C-1), 78.4 (C-3), 78.3 (C-5), 74.1 (OCH_2Ph), 71.7 (C-4), 70.6 (2 C, CH_2O (Fmoc), C-6), 53.9 (C-2), 46.8 (C-9, Fmoc), 24.5 (SCH_2), 15.3 (SCH_2CH_3). MALDI-TOF MS: *m*/*z* 688 $[M + Na]^+$. Anal. Calcd for $C_{38}H_{35}NO_8S$: C, 68.56; H, 5.30; N, 2.10. Found: C, 68.62; H, 5.19; N, 2.12.

*Ethyl 6-*O*-benzyl-3-*O*-(9-fluorenylmethoxycarbonyl)-2-deoxy-2-phthalimido-4-*O*-(2,3,4-tri-*O*-benzyl-α-*L*-fucopyranosyl)-1-thio-β-*D*-glucopyranoside* (**5**).—A solution of compound **4** (48 mg, 0.10 mmol) and **3** (44 mg, 0.066 mmol) in toluene (3 mL) was stirred in the presence of 4 Å molecular sieves (100 mg, powdered) for 15 min. The mixture was cooled (-5 °C), and NIS (25 mg, 0.11 mmol) and TMSOTf (0.5 μL, 2.8 μmol) were added. After 5 min, the reaction mixture was diluted with CH_2Cl_2 (40 mL) and filtered, and the filtrate was washed successively with aq sodium thiosulfate (15%, 25 mL), water (20 mL) and brine (15 mL). The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The crude product was purified by silica gel column chromatography (1:3 EtOAc–hexanes) to give **5** as a colorless syrup (60 mg, 84%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.74–7.17 (m, 32 H, Ar–H), 5.59 (dd, 1 H, $J_{2,3}$ 10.0, $J_{3,4}$ 8.7 Hz, H-3), 5.43 (d, 1 H, $J_{1,2}$ 10.5 Hz, H-1), 5.09 (d, 1 H, $J_{1',2'}$ 3.6 Hz, H-1′), 4.89, 4.56 (AB q, 2 H, J_{AB} 11.4 Hz, OCH_2Ph), 4.79, 4.63 (AB q, 2 H, J_{AB} 11.4 Hz, OCH_2Ph), 4.75, 4.68 (AB q, 2 H, J_{AB} 12.3 Hz, OCH_2Ph), 4.43 (t, 1 H, H-2), 4.40 (AB q, 2 H, J_{AB} 12.3 Hz, OCH_2Ph), 4.05 (dd, 1 H, *J* 7.8 10.5 Hz, C*H*O (Fmoc)), 4.00 (dd, 1 H, $J_{2',3'}$ 10.0 Hz, H-2′), 3.95–3.75 (m, 7 H, H-6a, H-4, H-5′, C*H*O (Fmoc), H-3′, H-5, H-6b), 3.71 (t, 1 H, *J* 7.3 Hz, H-9 (Fmoc)), 3.57 (s, 1 H, H-4′), 2.73–2.59 (m, 2 H, SCH_2), 1.17 (t, 3 H, *J* 7.3 Hz, SCH_2CH_3), 0.96 (d, 3 H, *J* 6.4 Hz, H-6′). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.0, 167.2 (2 C, *C*=O, Phth), 154.9 (*C*=O, Fmoc), 143.3, 143.2, 141.2, 141.0, 138.8, 138.7, 138.6, 134.3, 134.0, 131.9, 131.2, 128.8, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.4, 125.4, 125.3, 123.7, 123.5, 119.9 (42 C, Ar–C), 100.1 (C-1′), 80.8 (C-1), 79.7 (C-5), 79.5 (C-3′), 78.0 (C-3), 77.7 (C-4′), 76.9 (C-4), 76.6 (C-2′), 75.1 (OCH_2Ph), 74.3 (OCH_2Ph), 73.5 (OCH_2Ph), 73.0 (OCH_2Ph), 70.4 (CH_2O, Fmoc), 69.3 (C-6), 67.8 (C-5′), 54.4 (C-2), 46.6 (C-9, Fmoc), 24.2 (SCH_2), 16.8 (C-6′), 15.4 (SCH_2CH_3). MALDI-TOF MS: *m*/*z* 1104.3 $[M + Na]^+$. Anal. Calcd for $C_{65}H_{63}NO_{12}S$: C, 72.14; H, 5.87; N, 1.29. Found: C, 72.28; H, 6.02; N, 1.17.

*Ethyl 6-*O*-benzyl-2-deoxy-2-phthalimido-4-*O*-(2,3,4-tri-*O*-benzyl-α-*L*-fucopyranosyl)-1-thio-β-*D*-glucopyranoside* (**6**).—Triethylamine (1 mL) was added to a solution of compound **5** (60 mg, 0.055 mmol) in CH_2Cl_2 (2 mL). After stirring for 2 h, TLC analysis (1:2 EtOAc–hexanes) indicated the completion of the reaction. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (1:3 EtOAc–hexanes) to give **6** as a colorless syrup (42 mg, 88%). $[\alpha]_D^{25}$ $-21.4°$ (*c* 0.2, CH_2Cl_2). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.90–7.26 (m, 24 H, Ar–H), 5.33 (d, 1 H, $J_{1,2}$ 10.1 Hz, H-1), 5.00 (d, 1 H, $J_{1',2'}$ 3.8 Hz, H-1′), 4.97, 4.63 (AB q, 2 H, J_{AB} 11.5 Hz, OCH_2Ph), 4.85, 4.76 (AB q, 2 H, J_{AB} 11.5 Hz, OCH_2Ph), 4.79, 4.68 (AB q, 2 H, J_{AB} 12.0 Hz, OCH_2Ph), 4.44 (AB q, 2 H, J_{AB} 12.0 Hz, OCH_2Ph), 4.37 (dd, 1 H, $J_{2,3}$ 10.1 Hz, $J_{3,4}$ 8.6 Hz, H-3), 4.28 (t, 1 H, H-2), 4.08 (dd, 1 H, $J_{2',3'}$ 10.6 Hz, H-2′), 4.05 (q, 1 H, $J_{5',6'}$ 6.2 Hz, H-5′), 3.96 (d, 1 H, $J_{5,6a}$ 10.1 Hz, H-6a), 3.90 (dd, 1 H, $J_{3',4'}$ 2.4 Hz, H-3′), 3.82 (dd, 1 H, $J_{5,6b}$ 5.3 Hz, H-6b), 3.76 (dd, 1 H, H-5), 3.67 (d, 1 H, H-4′), 3.55 (dd, 1 H, $J_{4,5}$ 9.1 Hz, H-4), 2.78–2.63 (m, 2 H, SCH_2), 1.24 (t, 3 H, *J* 7.2 Hz, SCH_2CH_3), 1.09 (d, 3 H, H-6′). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.5, 168.0 (2 C, *C*=O, Phth), 138.9, 138.7, 138.5, 134.2, 132.0, 128.6, 128.5, 128.4, 128.1, 128.0, 127.8, 127.7, 127.6, 124.0, 123.3 (30 C, Ar–C), 100.2 (C-1′), 82.8 (C-4), 81.0 (C-1), 79.1 (C-3′), 79.0 (C-5), 77.7 (C-4′), 76.1 (C-2′), 75.3 (OCH_2Ph), 74.0 (OCH_2Ph), 73.5 (OCH_2Ph), 73.4 (OCH_2Ph), 71.8 (C-3), 69.5 (C-6), 68.4 (C-5′), 55.5 (C-2), 24.2 (SCH_2), 17.1 (C-6′), 15.4 (SCH_2CH_3). MALDI-TOF MS: *m*/*z* 882.0 $[M + Na]^+$. Anal. Calcd for $C_{50}H_{53}NO_{10}S$: C, 69.83; H, 6.21; N, 1.63. Found: C, 69.59; H, 6.16; N, 1.72.

N-Trichloroacetyl-6-O-benzyl-2-deoxy-2-phthalimido-4-O-(2,3,4-tri-O-benzyl-α-L-fuco-pyranosyl)-β-D-glucopyranosylamine (**9**).—To a mixture of **7** (34 mg, 0.07 mmol) and **6** (40 mg, 0.046 mmol) in CH_2Cl_2 (2 mL) in the presence of 4 Å molecular sieves (100 mg, powdered) was added TMSOTf (0.5 μL, 2.8 μmol) at rt. After 5 min Et_3N was added for neutralization, and the mixture was diluted with CH_2Cl_2 (40 mL). The molecular sieves were removed by filtration, and the filtrate was concentrated under reduced pressure. Silica gel column chromatography (1:3 EtOAc–hexanes), followed by size-exclusion chromatography (LH-20, 1:1 MeOH–CH_2Cl_2) gave compound **8** as a white solid (16 mg, 92%) and **9** as a white foam (26 mg, 59%).

Analytical data for compound **9**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.88–7.18 (m, 25 H, 24 Ar–H, N*H*), 5.74 (dd, 1 H, $J_{1,2}$ 10.3 Hz, $J_{1,NH}$ 9.3 Hz, H-1), 5.00 (d, 1 H, $J_{1',2'}$ 3.9 Hz, H-1′), 4.95, 4.60 (AB q, 2 H, J_{AB} 11.3 Hz, OCH_2Ph), 4.82, 4.75 (AB q, 2 H, J_{AB} 11.8 Hz, OCH_2Ph), 4.79, 4.65 (AB q, 2 H, J_{AB} 11.8 Hz, OCH_2Ph), 4.70 (dd, 1 H, $J_{2,3}$ 10.3 Hz, $J_{3,4}$ 8.8 Hz, H-3), 4.38 (AB q, 2 H, J_{AB} 12.3 Hz, OCH_2Ph), 4.21 (t, 1 H, H-2), 4.08 (dd, 1 H, $J_{2',3'}$ 10.3 Hz, H-2′), 4.05 (q, 1 H, $J_{5',6'}$ 6.4 Hz, H-5′), 3.91 (dd, 1 H, $J_{3',4'}$ 2.5 Hz, H-3′), 3.85–3.81 (m, 3 H, H-6a, H-6b, H-5), 3.67 (d, 1 H, H-4′), 3.63 (t, 1 H, $J_{4,5}$ 8.8 Hz, H-4), 1.08 (d, 3 H, H-6′). Selected ^{13}C NMR ($CDCl_3$, 125 MHz): δ 100.2 (C-1′), 81.7 (C-4), 79.0 (C-3′), 78.2 (C-1), 77.5 (C-4′), 76.7 (C-5), 75.7 (C-2′), 75.1 (O*C*H_2Ph), 73.8 (O*C*H_2Ph), 73.5 (O*C*H_2Ph), 73.4 (O*C*H_2Ph), 69.7 (C-3), 68.4 (C-6), 68.3 (C-5′), 55.8 (C-2), 16.7 (C-6′). MALDI-TOF MS: m/z 983.2 $[M + Na]^+$. Anal. Calcd for $C_{50}H_{49}Cl_3N_2O_{11}$: C, 62.54; H, 5.14; N, 2.92. Found: C, 62.38; H, 5.17; N, 2.88.

Ethyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-3-O-(2,3,4,6-tetra-O-acetyl-β-D-galacto-pyranosyl)-1-thio-β-D-glucopyranoside (**15**).—A solution of **7** (60 mg, 0.12 mmol) and **1** (44 mg, 0.1 mmol) in CH_2Cl_2 (3 mL) was stirred in the presence of 4 Å molecular sieves (100 mg, powdered) for 15 min. The mixture was cooled (0 °C), and TMSOTf (0.5 μL, 2.8 μmol) was added. After 5 min TLC analysis (1:1 EtOAc–hexanes) showed that compound **1** was consumed, and Et_3N (0.1 mL) was then added. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and filtered, and the filtrate was washed successively with satd aq $NaHCO_3$ (25 mL), water (20 mL) and brine (15 mL). The organic phase was dried ($MgSO_4$) and filtered, the filtrate was concentrated in vacuo. Purification of the residue by silica gel column chromatography (1:2 EtOAc–hexanes) gave **14** as a colorless syrup (77 mg, containing 5% of **15**), which was dissolved in dry CH_2Cl_2 (2 mL). Molecular sieves (4 Å, 100 mg) were added, and the mixture was stirred at rt for 30 min. TMSOTf (1 μL, 5.6 μmol) was added, and the mixture was stirred for 16 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and filtered, and the filtrate was concentrated in vacuo. The crude product was applied to a silica gel column that was eluted with 1:2 EtOAc–hexanes to give compound **15** as a white foam (41 mg, 53%). $[\alpha]_D^{25}$ −20.4° (*c* 0.3, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.94–7.34 (m, 9 H, arom), 5.57 (s, 1 H, PhC*H*), 5.28 (d, 1 H, *J* 9.7 Hz, H-1), 5.19 (d, 1 H, $J_{3',4'}$ 3.4 Hz, H-4′), 4.98 (dd, 1 H, $J_{1',2'}$ 7.8 Hz, $J_{2',3'}$ 10.2 Hz, H-2′), 4.77 (t, 1 H, $J_{2,3}$, $J_{3,4}$ 9.7 Hz, H-3), 4.73 (dd, 1 H, H-3′), 4.55 (d, 1 H, H-1′), 4.42–4.37 (m, 2 H, H-2, H-6′a), 4.03 (dd, 1 H, $J_{5',6'a}$ 8.3 Hz, $J_{6'a,6'b}$ 11.2 Hz, H-6′a), 3.85–3.80 (m, 3 H, H-4, H-6b, H-6′b), 3.70 (ddd, 1 H, H-5), 3.48 (ddd, 1 H, H-5′), 2.76–2.57 (m, 2 H, SCH_2), 2.07, 1.91, 1.84, 1.57 (4 s, 12 H, Ac), 1.18 (t, 3 H, *J* 7.3 Hz, SCH_2CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.4–123.4 (18 C, *C*=O, Ar–C), 101.7, 100.6, 82.0, 81.2, 76.7, 71.3, 70.9, 70.6, 69.5, 68.9, 66.9, 61.1, 54.5, 24.2, 21.0, 20.9, 20.8, 20.4, 15.1. MALDI-TOF MS: m/z 794 $[M + Na]^+$. Anal. Calcd for $C_{37}H_{41}NO_{15}S$: C, 57.58; H, 5.35; N, 1.81. Found: C, 57.83; H, 5.04; N, 1.66.

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