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One-Pot Glycosylations in the Synthesis of Human Milk Oligosaccharides

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Human milk oligosaccharides contain a well-defined core structure that makes them interesting synthetic targets for one-pot glycosylation strategies. In this investigation, a one-pot procedure was studied in which a galactose thioglycoside is coupled chemoselectively to a phthalimide-protected glucosamine thioglycoside, and the resulting disaccharide is then coupled to the 3′-position in lactose. Very high yields of the tetrasaccharide product can be obtained when a protected lactosamine thioglycoside is formed in the first coupling. In contrast, it was not possible to extend the one-pot process to the synthesis of the corresponding 3′′-linked structures, due to an inefficient synthesis of the lacto-*N*-biose thioglycoside in the first glycosylation. This is explained by the reactivity difference between the 3- and 4-positions in phthalimide-protected glucosamine. The one-pot procedure has been applied in an efficient synthesis of the pentasaccharide lacto-*N*-neofucopentaose I, which is composed of *N*-acetyllactosamine, lactose, and fucose. On the other hand, a stepwise approach was found to be the preferred synthetic pathway for preparation of the isomeric lacto-*N*-fucopentaose I, which contains a lacto-*N*-biose moiety.

Introduction

Human milk oligosaccharides are a class of structurally distinct glycans that are present in human milk in concentrations ranging from 5 to 25 g/L, depending on the lactational stage.[1] These oligosaccharides are unique to human milk, and they participate in the development and protection of newborn infants.[2] They are not digested by intestinal enzymes, and they reach the large intestine intact, where they stimulate the growth of healthy gut bacteria.[3] Furthermore, human milk oligosaccharides are known to prevent pathogens from binding to their receptors by acting as soluble ligands,[4] and they are believed to serve as nutrients for early brain development in infants.[1] So far, more than 100 different human milk oligosaccharides have been identified, and they share some common structural features.[1] With a few exceptions, they all contain a backbone in which lactose is found at the reducing end (Figure 1). Consecutive elongations with *N*-acetyllactosamine (Galβ1–4GlcNAc) and/or lacto-*N*-biose (Galβ1–3GlcNAc) through β(1→3) and/or β(1→6) linkages then make up the backbone. This is then decorated with α(1→2/3/4) fucose and/or α(2→3/6) sialic acid units to give oligosaccharides containing between 3 and 32 monosaccharides.[2]

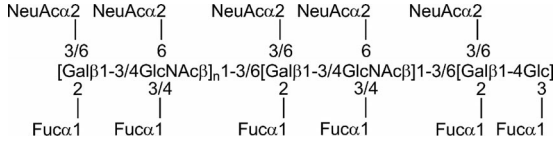

Figure 1. Generic structure of human milk oligosaccharides.

Due to their health benefits for infants, human milk oligosaccharides have attracted significant attention over the past two decades, especially for use as potential additives in infant formulas.[3] Unfortunately, large quantities of these oligosaccharides are not easily available. Microbial and enzymatic approaches have been used to prepare human milk oligosaccharides, but the scale, purity, and cost continue to be a challenge.[5]

Chemical synthesis has also been used, and so far this has led to the preparation of more than 15 different structures ranging from tetrasaccharides to octasaccharides.[6–8] The syntheses can be divided into three categories depending on the structure of the target molecule. The backbone has been assembled by various approaches including solid-phase methods.[6] Fucosylated[7] and sialylated[8] oligosaccharides make up the two other groups. Interestingly, a similar retrosynthetic strategy, in which a lactosamine or a lacto-*N*-biose donor is prepared separately and then coupled to a partially protected lactose acceptor, has been used in the vast majority of the syntheses. A reactivity-based synthesis was first developed recently in which galactose and glucosamine tolyl thioglycosides **1** and **2** were coupled selectively, followed by reaction with lactose acceptor **3** in the same pot to give tetrasaccharide **4** in 40% yield

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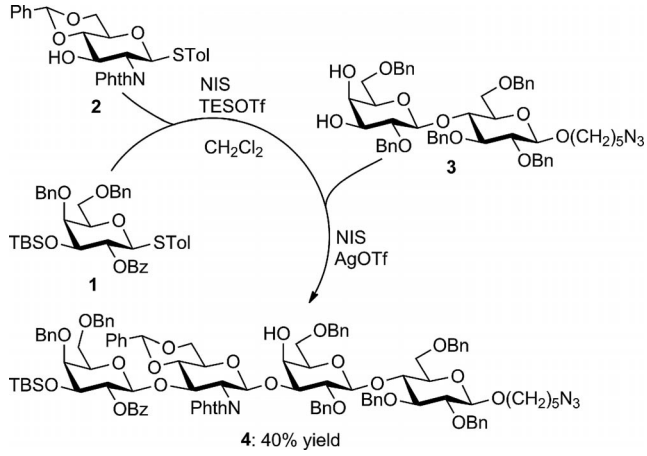
(Scheme 1).[7a] The TBS (*tert*-butyldimethylsilyl) protecting group in donor **1** played an important role in enhancing its reactivity, since the corresponding 3-*O*-benzyl-protected donor gave the tetrasaccharide in only 30% yield in the same sequence.[7a] One-pot glycosylation approaches to oligosaccharides are a valuable way of reducing the number of steps required to assemble a target molecule.[9] Due to the conserved structure of the human milk oligosaccharides, one-pot approaches to this class of glycans may also render the syntheses more flexible, since the separate preparation of lactosamine and lacto-*N*-biose building blocks can be avoided. We decided to further investigate the one-pot approach for assembling the backbone structure, and to explore the scope and limitations of this strategy. In this paper, we report a full account on our synthetic studies towards human milk oligosaccharides, exemplified by the syntheses of lacto-*N*-fucopentaose I and lacto-*N*-neofucopentaose I (Figure 2).



Scheme 1. A reactivity-based one-pot synthesis of the tetrasaccharide backbone.[7a] NIS = *N*-iodosuccinimide; TESOTf = triethylsilyl trifluoromethanesulfonate; Tol = 4-methylphenyl.

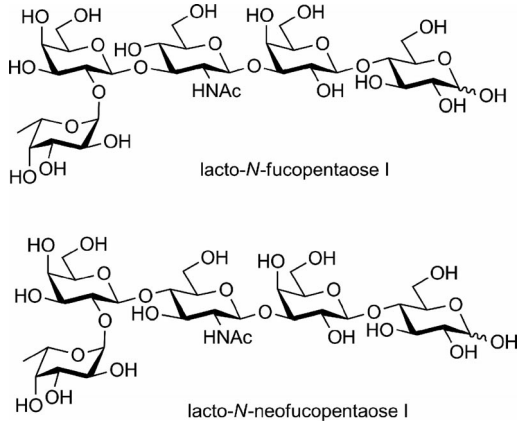


Figure 2. Structures of lacto-*N*-fucopentaose I and lacto-*N*-neofucopentaose I.

Results and Discussion

We have previously used one-pot syntheses for the preparation of several galactans. In that work, we used phenyl thioglycosides as substrates, since they are often crystalline and more easily available on a large scale.[10] Thus for the initial studies, benzylidene-protected glucosamine **5** was selected as the coupling partner, together with partially protected lactose acceptor **6** (Figure 3). The latter was prepared in six straightforward steps from lactose, with a regioselective stannylene-mediated allylation of the 3′-position as the key step.[11] To assemble the backbone tetrasaccharide by a one-pot process, a galactose donor must be identified that couples selectively to **5**. The resulting disaccharide can then react further with **6** in the same mixture. Several easily available galactose thioglycosides **7**–**9** were selected, and their coupling to **5** was investigated (Figure 3). However, regardless of the promoter, these couplings only led to low yields of the desired disaccharide, probably due to an insufficient reactivity difference between the donors and the acceptor.

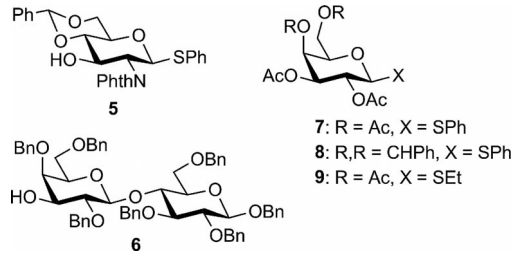
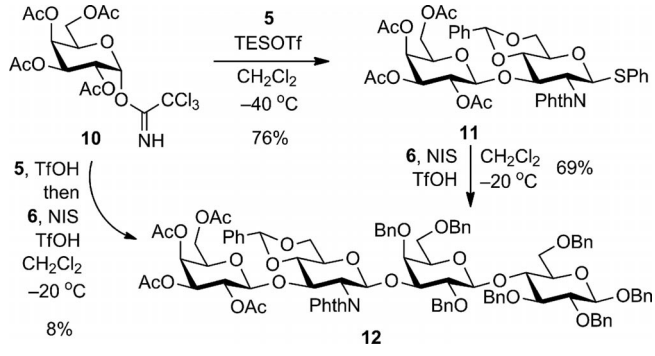


Figure 3. Glycosyl donors and acceptors **5**–**9**.

To circumvent the chemoselectivity problem, imidate donor **10** was studied next, and with this donor, glycosylation with **5** could be achieved in good yield (Scheme 2). The resulting disaccharide (i.e., **11**) was subsequently coupled with lactose acceptor **6** to give tetrasaccharide **12** in 69% yield. Unfortunately, when the two steps were combined in a one-pot sequence, the overall yield of **12** dropped to a mere 8%. This is presumably due to inhibition of the second coupling by the trichloroacetamide formed in the first step. As a result, imidate donors were abandoned, and attention turned back to thioglycoside donors.



Scheme 2. Synthesis of tetrasaccharide **12**.

Thus, a more reactive thioglycoside donor was needed, and the recently presented donors with 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl protection,[12] such as **13**, were therefore considered (Figure 4). Thioglycoside **13** was prepared in eight steps from galactose, with the formation and rearrangement

of a 1,2-orthoester as the key steps.[13] However, to our disappointment, the coupling between **13** and **5** in the presence of NIS and AgOTf led to only a 28% yield of the desired disaccharide.

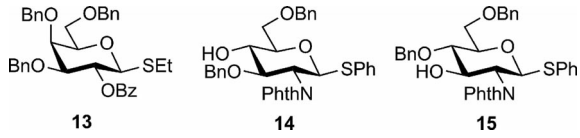
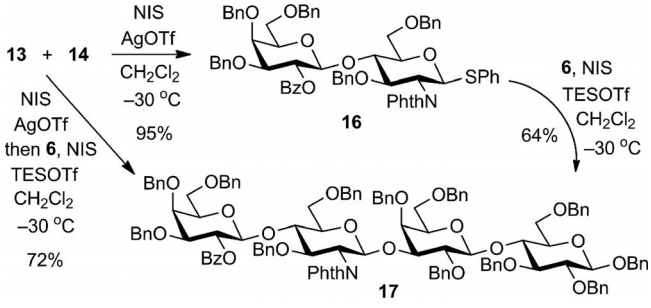


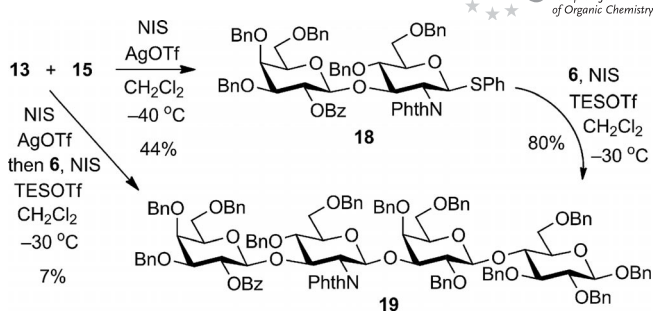
Figure 4. Glycosyl donors and acceptors **13**–**15**.

As a result, it was decided to change the benzylidene acetal in **5** to two benzyl ethers, which would also make it possible to address the two different glycosidic linkages in the backbone. Accordingly, thioglycosides **14** and **15** (Figure 4) were prepared from **5**, and the chemoselective couplings with **13** were investigated. Gratifyingly, the glycosylation of **14** with **13** gave a remarkable 95% yield of disaccharide **16** (Scheme 3), which was very promising for the one-pot synthesis. Further coupling with lactose acceptor **6** was uneventful, and gave tetrasaccharide **17** in 64% yield. Indeed, when the two steps were combined in a one-pot process, the overall yield of **17** was a satisfying 72%, a higher yield than that obtained over the two-step sequence. The same experiments were carried out with thioglycoside **15**, which first reacted with donor **13** to give disaccharide **18** in 44% yield (Scheme 4). Although this was an improvement over the coupling between **13** and **5**, it was not possible to increase this yield further by modifying the conditions. These results illustrate the known observation that the 3-position in phthalimide-protected β-glucosamines is the least reactive.[14] Further reaction with lactose acceptor **6** gave tetrasaccharide **19** in 80% yield, but when a one-pot sequence was run in this case, the overall yield of **19** was only 7%. Thus, the one-pot strategy may be used for the synthesis of the backbone with the β(1→4) linkage, but the β(1→3) linkage is more difficult, due to a moderate yield in the first coupling.



Scheme 3. Sequential and one-pot synthesis of tetrasaccharide **17**.

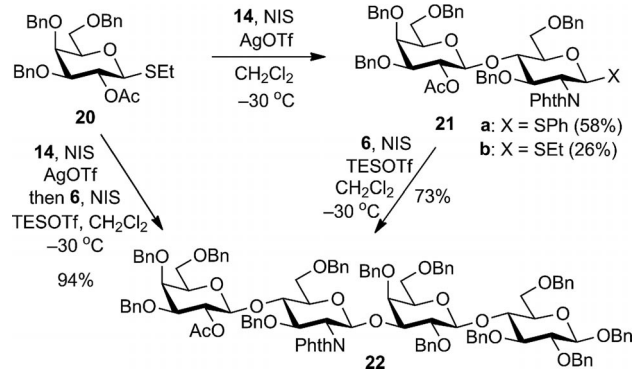
Attempts to remove the benzoate selectively from **17** and **19** under Zemplén conditions were unsuccessful, since the deprotections were accompanied by ring-opening and cleavage of the phthalimide. Complete removal of both the benzoate and the phthalimido group could be achieved with hydrazine in ethanol at reflux (for **17**), or under Zemplén conditions at room temperature (for **19**). Although selective



Scheme 4. Sequential and one-pot synthesis of tetrasaccharide **19**.

N-acetylation can be carried out with amino alcohols, these results made us reconsider the use of the 2-benzoate in the galactose donor. A 2-acetate may be a better choice, since it can usually be removed in the presence of a phthalimide, and may also give a better coupling yield due to a lower steric demand.

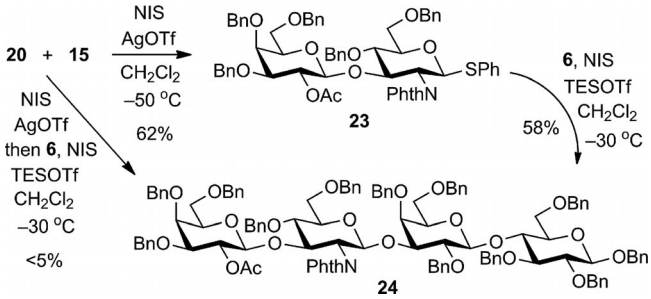
Consequently, the corresponding donor (i.e., **20**) was prepared in six steps from galactose.[13b] Chemoselective glycosylation with acceptor **14** gave disaccharide **21** in 58% yield, together with 26% of the corresponding ethyl thioglycoside (Scheme 5). Aglycon transfer of thiols is a known side-reaction in some glycosylations with thioglycosides, and is hard to predict,[15] but it came as a surprise that the transfer was much more pronounced with acetate donor **20** than with benzoate donor **13**. However, it was not a major concern, since both thioglycosides would undergo a subsequent glycosylation reaction. Therefore, the mixture was treated with lactose acceptor **6**, and tetrasaccharide **22** was isolated in 73% yield. When the two glycosylations were carried out in a one-pot sequence, the overall yield increased to a gratifying 94%.



Scheme 5. Sequential and one-pot synthesis of tetrasaccharide **22**.

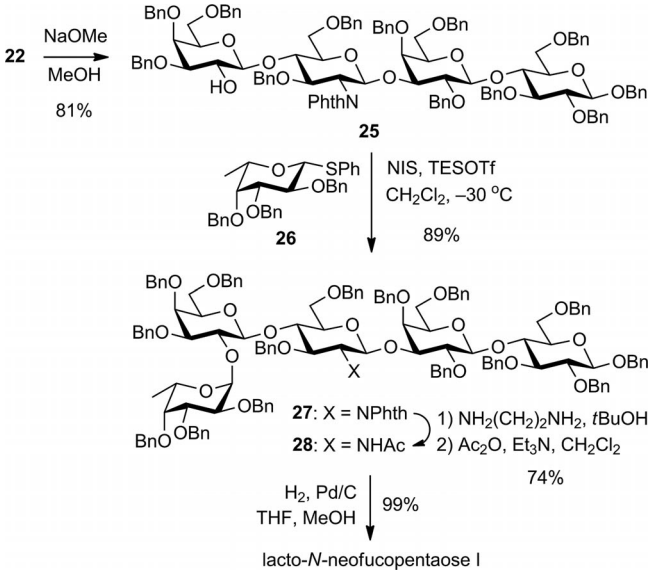
The same series of reactions was carried out with thioglycoside **15**, where the first glycosylation produced disaccharide **23** in 62% yield, together with 14% of the corresponding ethyl thioglycoside (Scheme 6). Again, the reaction was accompanied by significant aglycon transfer, but the coupling yield with acetate donor **20** was noticably better than that obtained with benzoate **13**. Further glycosylation between disaccharides **23** and **6** gave tetrasaccharide **24** in 58% yield. Unfortunately, when the two glycosylations were carried out in a one-pot sequence, tetrasaccharide **24**

was only obtained in trace amounts, and could not be sufficiently purified. This result together with the coupling in Scheme 5 clearly illustrate that the backbone with the β(1→3) linkage cannot be assembled by the present one-pot approach, but must be prepared in a stepwise manner.



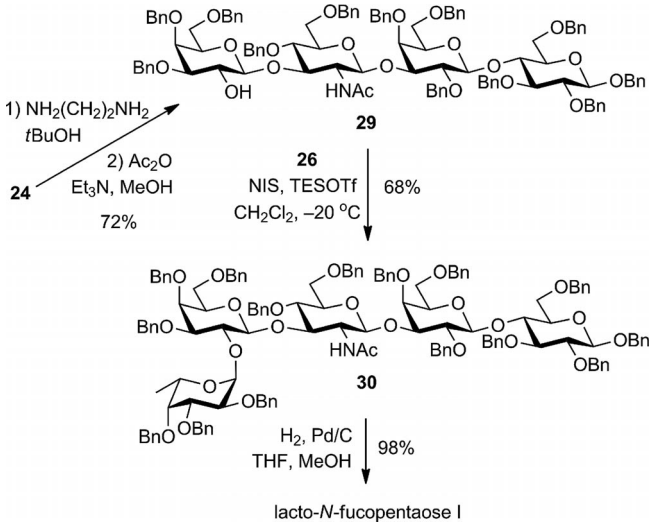
Scheme 6. Sequential and one-pot synthesis of tetrasaccharide **24**.

Tetrasaccharides **22** and **24** were both converted into the target human milk oligosaccharides by four similar transformations. Selective removal of the acetate in **22** could now be carried out in a good yield under Zemplén conditions without affecting the phthalimide (Scheme 7). Subsequent glycosylation with fucose thioglycoside **26** gave pentasaccharide **27** in high yield, although the product was contaminated by small amounts of an impurity, which could not be removed before the next step. Cleavage of the phthalimido group followed by *N*-acetylation and hydrogenolysis of the benzyl ethers then gave lacto-*N*-neofucopentaose I. Only two previous syntheses of lacto-*N*-neofucopentaose I are known, and in those syntheses, the final deprotections were not carried out.[7d,7i] Compared to these two earlier syntheses, the present synthesis offers a significant reduction in the total number of steps.



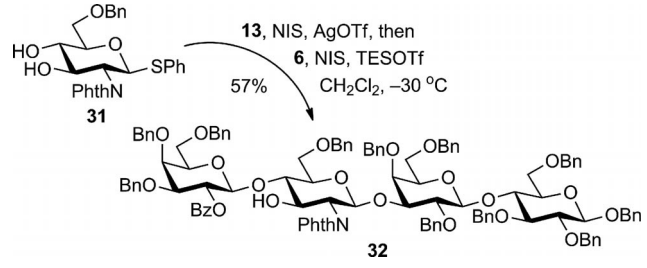
Scheme 7. Final steps in the synthesis of lacto-*N*-neofucopentaose I.

In the same way, isomer **24** was also subjected to deprotection with sodium methoxide in methanol. In this case, however, both the acetate and the phthalimide were removed under the basic conditions, similarly to what was observed with benzoate **19**. The reaction was very slow, and we therefore decided to use ethylene diamine instead, followed by selective *N*-acetylation to give alcohol **29** (Scheme 8). Glycosylation with fucose donor **26** then gave pentasaccharide **30**, which was deprotected to give lacto-*N*-fucopentaose I.



Scheme 8. Final steps in the synthesis of lacto-*N*-fucopentaose I.

Since the 3-position in glucosamine is the least reactive, it may be possible to perform a selective glycosylation at the 4-position in a 3,4-unprotected substrate. Indeed, when glucosamine thioglycoside **31** was submitted to the one-pot process, tetrasaccharide **32** was obtained in 57% overall yield (Scheme 9). The position of the new interglycosidic linkage was verified by NMR spectroscopy, where the HMBC spectrum showed a correlation between C-1′′′ and H-4′′. Unfortunately, it was not possible to glycosylate **32** with fucose donor **26**; this resulted only in decomposition of the donor and recovery of the acceptor. Hence, the lower reactivity of the 3-position favors the one-pot reaction with **31** at position 4, but limits the synthetic value of the resulting product (i.e., **32**). Similar results were obtained with acetate donor **20** and glucosamine acceptor **31**, and this approach is therefore not useful for synthesis of another human milk oligosaccharide.



Scheme 9. One-pot synthesis of tetrasaccharide **32**.

Conclusions

In summary, we have described a one-pot process for assembling the lactosamine–lactose backbone in human milk

oligosaccharides, in which galactose and glucosamine thioglycosides are first coupled chemoselectively followed by glycosylation with lactose. The transformation gives a higher yield of the tetrasaccharide than the stepwise approach, and it has been applied in the synthesis of lacto-*N*-neofucopentaose I. The one-pot process could not be extended to the corresponding lacto-*N*-biose–lactose backbone, due to a more difficult coupling in the first step. In this case, the stepwise approach is still the favored pathway, as shown with the synthesis of lacto-*N*-fucopentaose I.

Experimental Section

General Remarks: All reactions were carried out under an argon atmosphere. Molecular sieves (MS) were flame dried before use. Dichloromethane was dried with 4 Å MS. Phenyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**5**),[16] benzyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**6**),[11] 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate (**10**),[7j] ethyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (**13**),[13a] phenyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**14**),[17] ethyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (**20**),[13b] phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (**26**),[16] and phenyl 6-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**31**)[18] were synthesized according to literature procedures. TLC was carried out on aluminum plates coated with silica gel 60. The plates were visualized with UV light or by dipping into a solution of cerium(IV)sulfate (2.50 g) and ammonium molybdate (6.25 g) in sulfuric acid (10%; 250 mL) followed by heating. Purification was carried out with HPLC grade solvents by flash chromatography on silica gel (Merck 40–63 micron) or by dry column chromatography[19] on silica gel (Merck 15–40 micron). Reverse-phase chromatography was carried out on silica gel (YMC–C_{18}, 120 Å, 5–10–20 μm). NMR spectra were recorded with a Varian Mercury 300, a Bruker Ascend 400, or a Varian Unity Inova 500 instrument. Chemical shifts were calibrated using the residual solvent signal in $CDCl_3$ (δ_H = 7.26 ppm, δ_C = 77.16 ppm) or tetramethylsilane. HRMS analyses were carried out with an Agilent 1100 LC system equipped with a diode array detector and a Luna C_{18} column (3 μm, 50 mm × 2 mm). The LC was coupled to a Micromass LCT orthogonal time-of-flight mass spectrometer equipped with lock mass probe and operating in positive electrospray mode.

Phenyl 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (11): Imidate **10** (423 mg, 0.86 mmol) and thioglycoside **5** (300 mg, 0.61 mmol) were coevaporated with toluene (2× 5 mL), and then dissolved in CH_2Cl_2 (18 mL). The mixture was cooled to –40 °C, and TESOTf (27.7 μL, 0.12 mmol) was added. The reaction was stirred overnight, during which time it reached room temperature. Then Et_3N (171 μL, 1.23 mmol) was added. The stirring was continued for an additional 15 min, then the mixture was filtered through Celite and concentrated. The residue was purified by flash chromatography (EtOAc/heptane, 1:1) to give compound **11** (380 mg, 76%) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.88–7.75 (m, 4 H), 7.50–7.43 (m, 2 H), 7.40–7.31 (m, 5 H), 7.28–7.21 (m, 3 H), 5.57 (s, 1 H), 5.56 (d, J = 10.8 Hz, 1 H, 1-H), 5.18 (d, J = 2.9 Hz, 1 H, 4-H), 4.96 (dd, J = 10.4, 8.1 Hz, 1 H), 4.79–4.68 (m, 2 H), 4.54 (d, J = 7.9 Hz, 1 H, 1′-H), 4.44–4.32 (m, 2 H), 4.01 (dd, J = 10.8, 8.2 Hz, 1 H), 3.88–3.76 (m, 3 H), 3.72 (dd, J = 9.7, 4.4 Hz, 1 H), 3.45 (dd, J = 7.9, 6.2 Hz, 1 H), 2.06 (s, 3 H), 1.90 (s, 3 H), 1.83 (s, 3 H), 1.50 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 170.0, 170.0, 168.9, 163.7, 136.8, 132.7, 131.2, 129.3, 128.9, 128.3, 128.2, 126.0, 101.4, 100.3, 84.1, 80.7, 76.5, 70.9, 70.4, 70.2, 69.1, 68.5, 66.5, 60.7, 54.2, 20.6, 20.5, 20.4, 20.0 ppm. NMR spectroscopic data are consistent with literature values.[20]

Benzyl 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (12): Compound **11** (921 mg, 1.12 mmol) and lactose derivative **6** (939 mg, 0.96 mmol) were dissolved in CH_2Cl_2 (15 mL), the mixture was cooled to –20 °C, and then NIS (280 mg, 1.25 mmol) and TfOH (8.5 μL, 0.10 mmol) were added. After 1 h, Et_3N was added. The mixture was stirred for 15 min, and then it was filtered through Celite and concentrated. The residue was purified by flash chromatography (EtOAc/heptane, 1:2) to give compound **12** (1.13 g, 0.67 mmol, 69%) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.76 (br. s, 1 H), 7.59 (br. s, 1 H), 7.58–7.50 (m, 2 H), 7.46–7.19 (m, 35 H), 7.17–7.06 (m, 3 H), 6.91 (dd, J = 6.6, 2.5 Hz, 2 H), 5.63 (s, 1 H), 5.45 (d, J = 8.5 Hz, 1 H), 5.21 (d, J = 3.2 Hz, 1 H), 5.06–4.95 (m, 2 H), 4.93–4.81 (m, 4 H), 4.78–4.67 (m, 2 H), 4.61–4.20 (m, 13 H), 4.19–4.01 (m, 2 H), 3.99–3.79 (m, 6 H), 3.73 (dd, J = 9.7, 4.7 Hz, 1 H), 3.64–3.57 (m, 1 H), 3.56–3.46 (m, 4 H), 3.43–3.27 (m, 5 H), 2.93 (d, J = 10.0 Hz, 1 H), 2.08 (s, 3 H), 1.94 (s, 3 H), 1.86–1.83 (m, 3 H), 1.49 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 170.0, 170.0, 168.7, 139.1, 138.9, 138.5, 138.4, 138.3, 138.1, 137.4, 136.9, 128.4, 128.3, 128.3, 128.2, 128.2, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.7, 127.7, 127.6, 127.6, 127.4, 127.3, 127.0, 126.8, 126.0, 126.0, 102.4, 102.3, 101.4, 100.3, 99.8, 82.9, 81.5, 81.1, 80.9, 78.8, 76.3, 75.8, 75.4, 75.2, 75.0, 75.0, 74.9, 74.7, 73.7, 73.3, 72.9, 72.9, 70.9, 70.7, 70.2, 68.9, 68.0, 67.5, 67.0, 66.5, 66.0, 60.7, 55.7, 20.6, 20.5, 20.4, 20.0 ppm. HRMS: calcd. for $C_{96}H_{99}NO_{26}$ $[M + H]^+$ 1682.6528; found 1682.6554.

General Procedure for One-pot Glycosylation: A super-armed galactose donor and a glucosamine acceptor were dissolved in CH_2Cl_2 (1 mL/100 mg reactants), and the solution was stirred under argon with 4 Å MS for 1 h. The mixture was cooled to –30 °C, and NIS (1.15 equiv.) and AgOTf (cat.) were added. The mixture was stirred for 15 min, after which time TLC revealed full conversion of the acceptor (toluene/acetone, 9:1). Then a solution of lactose acceptor **6** in CH_2Cl_2 (0.5 mL/0.1 mmol) was added together with NIS (1.05 equiv.) and TESOTf (0.1 equiv.). The mixture was stirred for 40 min, after which time TLC showed full conversion of the acceptor. The reaction was quenched with Et_3N. The mixture was stirred for 15 min, and then filtered through Celite and concentrated. The residue was purified by chromatography.

General Procedure for NIS/AgOTf Glycosylation: A super-armed galactose donor and a glucosamine acceptor were dissolved in CH_2Cl_2 (1 mL/100 mg reactants), and the solution was stirred under argon with 4 Å MS for 1 h. The mixture was cooled to the temperature indicated, and then NIS (1.15 equiv.) and AgOTf (cat.) were added. The mixture was allowed to stir for 40 min, after which time TLC showed full conversion of the acceptor (toluene/acetone, 9:1). The reaction was quenched with Et_3N. The mixture was stirred for 15 min, and then filtered through Celite and concentrated. The residue was purified by chromatography.

General Procedure for NIS/TESOTf Glycosylation: A donor and lactose acceptor **6** were dissolved in CH_2Cl_2 (1 mL /100 mg reactants), and the solution was stirred under argon with 4 Å MS for 1 h. The mixture was cooled to –30 °C, and then NIS (1.15 equiv.)

and TESOTf (0.1 equiv.) were added. The mixture was allowed to stir for 40 min, after which time TLC showed full conversion of the acceptor (toluene/acetone, 9:1). The reaction was quenched with Et_3N. The mixture was stirred for 15 min, and then filtered through Celite and concentrated. The residue was purified by chromatography.

Phenyl 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-3,6-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (16): Synthesized by the general NIS/AgOTf procedure using **13** (117 mg, 0.19 mmol) and **14** (103 mg, 0.18 mmol). Purified by flash chromatography (toluene/acetone, 15:1) to give **16** (188 mg, 95%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07–7.94 (m, 2 H), 7.82 (d, J = 5.3 Hz, 1 H), 7.73–7.55 (m, 4 H), 7.53–7.41 (m, 2 H), 7.39–7.08 (m, 26 H), 7.03–6.94 (m, 2 H), 6.91–6.82 (m, 2 H), 5.67 (dd, J = 10.0, 7.9 Hz, 1 H), 5.44 (d, J = 10.3 Hz, 1 H), 5.06–4.82 (m, 2 H), 4.73–4.54 (m, 4 H), 4.53–4.44 (m, 2 H), 4.41–4.20 (m, 5 H), 4.08–3.99 (m, 2 H), 3.75–3.62 (m, 1 H), 3.61–3.40 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 167.6, 165.3, 139.0, 138.6, 138.2, 138.0, 134.1, 134.0, 133.4, 132.6, 132.5, 131.9, 131.8, 130.1, 129.3, 129.0, 128.9, 128.7, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.0, 125.6, 123.7, 123.6, 101.1, 83.7, 80.0, 79.2, 78.4, 77.8, 75.1, 74.7, 73.7, 73.6, 72.8, 72.7, 71.6, 68.4, 68.2 ppm.

Benzyl 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (17): Synthesized by the general NIS/TESOTf procedure using **16** (116 mg, 0.10 mmol) and **6** (111 mg, 0.11 mmol). Purified by dry column chromatography (acetone/toluene, 0 to 75% in steps of 5%) to give **17** (132 mg, 64%) as a colorless oil. In addition, synthesized by the general one-pot glycosylation procedure using **13** (124 mg, 0.21 mmol), **14** (110 mg, 0.19 mmol), and **6** (184 mg, 0.19 mmol). Purified by flash column chromatography (acetone/toluene, 1:19) to give **17** (270 mg, 72%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99 (d, J = 7.4 Hz, 2 H), 7.62 (t, J = 7.4 Hz, 2 H), 7.48 (t, J = 7.7 Hz, 3 H), 7.39–7.10 (m, 53 H), 7.07 (t, J = 7.3 Hz, 2 H), 6.94 (d, J = 6.8 Hz, 2 H), 6.90–6.76 (m, 5 H), 5.67 (dd, J = 9.8, 8.1 Hz, 1 H), 5.30 (d, J = 8.3 Hz, 1 H), 5.04 (d, J = 11.4 Hz, 1 H), 4.99 (d, J = 11.6 Hz, 1 H), 4.94 (d, J = 12.1 Hz, 1 H), 4.91–4.81 (m, 3 H), 4.73–4.62 (m, 3 H), 4.60–4.52 (m, 4 H), 4.52–4.19 (m, 14 H), 4.16 (d, J = 11.9 Hz, 1 H), 4.06 (t, J = 9.2 Hz, 1 H), 4.04–3.97 (m, 2 H), 3.95 (d, J = 1.8 Hz, 1 H), 3.83 (t, J = 9.0 Hz, 1 H), 3.70 (dd, J = 10.9, 3.3 Hz, 1 H), 3.55 (dd, J = 10.1, 2.6 Hz, 1 H), 3.53–3.24 (m, 14 H), 2.92 (d, J = 7.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9, 167.8, 165.2, 139.5, 139.1, 139.0, 138.8, 138.7, 138.6, 138.4, 138.4, 138.3, 138.0, 137.8, 137.7, 133.5, 133.2, 131.3, 130.0, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 127.5, 127.2, 127.1, 126.8, 126.7, 126.5, 123.1, 102.5, 102.5, 100.9, 99.7, 83.0, 82.1, 81.7, 79.9, 78.8 77.8, 77.4, 76.9, 76.1, 75.5, 75.1, 75.1, 74.8, 74.8, 74.6, 74.5, 74.1, 73.6, 73.6, 73.4, 73.3, 73.0, 73.0, 72.6, 72.6, 71.4, 70.9, 68.3, 68.1, 68.1, 67.7, 56.4 ppm. HRMS: calcd. for $C_{123}H_{121}NO_{23}$ $[M + Na]^+$ 2002.8222; found 2002.8191.

Phenyl 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→3)-4,6-di-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (18): Synthesized by the general NIS/AgOTf procedure using **13** (118 mg, 0.20 mmol) and **15** (110 mg, 0.19 mmol). Purified by dry column chromatography (acetone/toluene, 0 to 50% in steps of 2.5%) to give **18** (94 mg, 44%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, J = 7.4 Hz, 2 H), 7.62–7.56 (m, 3 H), 7.53 (t, J = 7.4 Hz, 1 H), 7.33 (t, J = 7.7 Hz, 3 H), 7.29–6.94 (m, 28 H), 6.91 (d, J = 7.3 Hz, 2 H), 5.50–5.39 (m, 1 H), 5.31 (d, J = 10.5 Hz, 1 H), 5.02 (d, J = 10.7 Hz, 1 H), 4.84 (d, J = 11.4 Hz, 1 H), 4.78 (dd, J = 10.1, 7.8 Hz, 1 H), 4.53–4.37 (m, 6 H), 4.28–4.20 (m, 3 H), 4.15 (d, J = 11.7 Hz, 1 H), 3.85 (d, J = 2.3 Hz, 1 H), 3.74 (d, J = 10.7 Hz, 1 H), 3.69 (dd, J = 10.7, 4.3 Hz, 1 H), 3.63–3.56 (m, 2 H), 3.39 (t, J = 8.1 Hz, 1 H), 3.34–3.25 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 138.7, 138.68, 138.4, 138.1, 137.5, 134.1, 133.0, 132.8, 131.8, 131.5, 130.4, 130.1, 128.9, 128.5, 128.4, 128.3, 128.3, 128.1, 128.1, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 127.3, 100.8, 84.0, 80.3, 79.4, 77.9, 77.3, 74.9, 74.8, 73.6, 73.5, 73.4, 72.9, 72.5, 71.7, 69.3, 67.9, 55.1 ppm. HRMS: calcd. for $C_{68}H_{63}NO_{12}S$ $[M + Na]^+$ 1140.3963; found 1140.3955.

Benzyl 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→3)-4,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (19): Synthesized by the general NIS/TESOTf procedure using **18** (126 mg, 0.11 mmol) and **6** (104 mg, 0.11 mmol). Purified by dry column chromatography (acetone/toluene, 0 to 75% in steps of 5%) to give **19** (170 mg, 80%) as a colorless oil. In addition, synthesized by the general one-pot glycosylation procedure using **13** (124 mg, 0.21 mmol), **15** (110 mg, 0.19 mmol), and **6** (184 mg, 0.19 mmol). Purified by flash column chromatography (acetone/toluene, 1:19) to give **19** (27 mg, 7%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (dd, J = 8.2, 1.2 Hz, 2 H), 7.59–7.53 (m, 1 H), 7.41–7.02 (m, 62 H), 7.00–6.94 (m, 2 H), 6.88–6.81 (m, 2 H), 5.51 (dd, J = 9.9, 7.9 Hz, 1 H), 5.22 (d, J = 8.4 Hz, 1 H), 5.12 (d, J = 10.6 Hz, 1 H), 4.99–4.81 (m, 6 H), 4.69 (d, J = 10.9 Hz, 1 H), 4.58–4.40 (m, 10 H), 4.36–4.11 (m, 10 H), 3.97 (d, J = 2.9 Hz, 1 H), 3.94 (d, J = 2.6 Hz, 1 H), 3.86–3.65 (m, 6 H), 3.53–3.28 (m, 12 H), 3.25 (d, J = 9.4 Hz, 1 H), 2.92–2.84 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 139.5, 139.1, 138.8, 138.7, 138.7, 138.7, 138.5, 138.3, 138.2, 138.1, 137.7, 137.6, 133.6, 132.7, 131.1, 130.3, 130.0, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.2, 128.1, 128.1, 128.1, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.7, 127.6, 127.6, 127.6, 127.5, 127.3, 127.2, 126.8, 126.4, 102.5, 102.5, 100.7, 99.6, 83.0, 81.7, 81.5, 80.3, 78.7, 77.5, 76.7, 76.3, 76.0, 75.5, 75.1, 75.1, 75.0, 75.0, 74.8, 74.8, 73.8, 73.7, 73.5, 73.4, 73.3, 73.3, 73.1, 72.9, 72.9, 71.7, 70.9, 69.5, 68.6, 67.9, 67.6, 56.4 ppm. HRMS: calcd. for $C_{123}H_{121}NO_{23}$ $[M + Na]^+$ 2002.8222; found 2002.8276.

Phenyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (21a) and Ethyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (21b): Synthesized by the general NIS/AgOTf procedure using **20** (113 mg, 0.21 mmol) and **14** (110 mg, 0.19 mmol). Purified by dry column chromatography (acetone/toluene, 0 to 60% in steps of 3%) to give **21a** (87 mg, 44%), **21b** (10 mg), and a mixture of the two (7:11, 72 mg).

Data for **21a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (d, J = 6.7 Hz, 1 H), 7.78–7.60 (m, 3 H), 7.43–7.12 (m, 25 H), 7.03–6.90 (m, 2 H), 6.90–6.75 (m, 3 H), 5.51 (d, J = 10.0 Hz, 1 H), 5.36 (dd, J = 10.1, 7.9 Hz, 1 H), 4.91 (d, J = 11.6 Hz, 1 H), 4.84 (d, J = 12.2 Hz, 1 H), 4.73–4.62 (m, 2 H), 4.55–4.45 (m, 4 H), 4.42 (d, J = 12.2 Hz, 1 H), 4.36–4.21 (m, 4 H), 4.02–3.95 (m, 1 H), 3.93 (d, J = 2.5 Hz, 1 H), 3.84–3.74 (m, 2 H), 3.60 (d, J = 10.0 Hz, 1 H), 3.49–3.33 (m, 4 H), 2.00 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.4, 168.1, 167.5, 138.9, 138.8, 138.3, 138.2, 138.1, 134.0, 133.9, 132.6, 132.4, 131.8, 131.8, 128.9, 128.6, 128.5, 128.5, 128.2, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.8, 127.5, 127.4, 126.9, 123.6, 123.5, 100.9, 83.6, 80.5, 79.5, 78.1, 77.8, 77.4, 77.2, 76.9, 74.9, 74.6, 73.6, 73.4, 72.8, 72.1, 71.8, 68.2, 54.9, 21.2 ppm. HRMS: calcd. for $C_{63}H_{61}NO_{12}S$ $[M + Na]^+$ 1078.3807; found 1078.3806.

Data for **21b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84–7.64 (m, 4 H), 7.40–7.15 (m, 20 H), 7.02–6.76 (m, 5 H), 5.36 (dd, *J* = 10.0, 8.0 Hz, 1 H), 5.22 (d, *J* = 10.0 Hz, 1 H), 4.97–4.80 (m, 2 H), 4.77–4.62 (m, 2 H), 4.54–4.19 (m, 9 H), 4.08–3.97 (m, 1 H), 3.93 (d, *J* = 2.6 Hz, 1 H), 3.85–3.71 (m, 2 H), 3.59 (t, *J* = 9.4 Hz, 1 H), 3.49–3.32 (m, 4 H), 2.75–2.52 (m, 2 H), 2.01 (s, 3 H) 1.17 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5, 168.0, 167.7, 138.9, 138.9, 138.3, 138.2, 138.1, 133.9, 132.6, 131.8, 128.9, 128.6, 128.5, 128.5, 128.2, 128.0, 127.9, 127.9, 127.8, 127.4, 127.4, 126.9, 123.5, 123.4, 100.8, 81.2, 80.4, 79.5, 78.0, 77.8, 74.8, 74.5, 73.6, 73.6, 73.4, 72.7, 72.1, 71.7, 68.2, 54.9, 24.0, 21.2, 15.1 ppm. HRMS: calcd. for $C_{63}H_{61}NO_{12}S$ [M + Na]$^+$ 1030.3807; found 1030.3809.

Benzyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (22): Synthesized by the general NIS/TESOTf procedure using a mixture of **21a/21b** (300 mg, ca. 0.284 mmol) and **6** (215 mg, 0.221 mmol). Purified by flash column chromatography (EtOAc/heptane, 1:2) to give **22** (310 mg, 73%) as a colorless oil. In addition, synthesized by the general one-pot glycosylation procedure using **20** (686 mg, 1.3 mmol), **14** (620 mg, 1.1 mmol), and **6** (1.00 g, 1.0 mmol). Purified by flash column chromatography (EtOAc/heptane, 1:2) to give **22** (1.86 g, 94%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.04 (m, 58 H), 6.94–6.76 (m, 6 H), 5.37 (m, 2 H), 5.07 (d, *J* = 11.4 Hz, 1 H), 4.95–4.82 (m, 5 H), 4.72–4.62 (m, 3 H), 4.57–4.22 (m, 18 H), 4.17 (d, *J* = 11.9 Hz, 1 H), 4.06–3.98 (m, 3 H), 3.93 (d, *J* = 2.7 Hz, 1 H), 3.88–3.83 (m, 1 H), 3.82–3.74 (m, 2 H), 3.63–3.57 (m, 1 H), 3.54 (dd, *J* = 9.8, 3.0 Hz, 1 H), 3.53–3.31 (m, 12 H), 2.98–2.88 (m, 1 H), 2.01 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.4, 139.6, 139.2, 139.0, 138.9, 138.8, 138.6, 138.5, 138.5, 138.2, 138.2, 138.1, 137.7, 133.5, 128.6, 128.4, 128.4, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.0, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.7, 127.6, 127.6, 127.5, 127.4, 127.3, 127.2, 126.9, 126.8, 126.6, 102.6, 101.0, 99.9, 83.1, 82.1, 81.8, 80.5, 78.9, 78.0, 76.8, 76.8, 76.1, 75.6, 75.2, 75.2, 74.9, 74.9, 74.8, 74.6, 74.2, 73.8, 73.6, 73.4, 73.4, 73.2, 73.1, 72.8, 72.1, 71.8, 71.0, 68.4, 68.4, 68.2, 67.8, 56.5, 21.2 ppm. MS: *m*/*z* = 1940.8 [M + Na]$^+$. NMR spectroscopic data are consistent with literature values.[7i]

Phenyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→3)-4,6-di-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (23): Synthesized by the general NIS/AgOTf procedure using **15** (150 mg, 0.26 mmol) and **20** (167 mg, 0.31 mmol). Purified by dry column chromatography (acetone/toluene, 0 to 50% in steps of 2.5%) to give **23** (171 mg, 62%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94–7.72 (m, 4 H), 7.48–7.01 (m, 30 H), 5.44 (d, *J* = 10.5 Hz, 1 H), 5.31 (dd, *J* = 10.1, 7.9 Hz, 1 H), 5.04 (d, *J* = 10.3 Hz, 1 H), 4.92 (d, *J* = 11.3 Hz, 1 H), 4.85–4.73 (m, 1 H), 4.63 (d, *J* = 12.0 Hz, 1 H), 4.60–4.18 (m, 8 H), 4.14 (d, *J* = 7.9 Hz, 1 H), 3.88 (d, *J* = 2.7 Hz, 1 H), 3.85–3.77 (m, 2 H), 3.71–3.60 (m, 2 H), 3.48 (t, *J* = 10.0 Hz, 1 H), 3.40–3.30 (m, 2 H), 3.10 (dd, *J* = 10.1, 2.7 Hz, 1 H), 2.02 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 168.6, 167.2, 138.7, 138.4, 138.3, 138.0, 137.8, 134.4, 132.6, 132.0, 129.1, 128.9, 128.5, 128.4, 128.4, 128.3, 128.2, 128.0, 128.0, 128.0, 127.8, 127.7, 127.6, 127.5, 127.3, 127.2, 125.4, 123.6, 100.8, 83.7, 80.2, 79.4, 77.6, 76.7, 75.2, 74.7, 73.5, 73.5, 73.4, 72.6, 71.5, 71.3, 69.1, 67.7, 55.1, 21.0 ppm. HRMS: calcd. for $C_{63}H_{61}NO_{12}S$ [M + Na]$^+$ 1078.3807; found 1078.3820.

Benzyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→3)-4,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (24): Synthesized by the general NIS/TESOTf procedure using **23** (270 mg, 0.26 mmol) and **6** (207 mg, 0.21 mmol). Purified by dry column chromatography (EtOAc/toluene, 0 to 33% in steps of 1.65%) to give **24** (240 mg, 58%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72–7.52 (m, 2 H), 7.47–7.01 (m, 60 H), 6.96–6.80 (m, 2 H), 5.31–5.21 (m, 2 H), 5.08–4.99 (m, 2 H), 4.94–4.79 (m, 5 H), 4.69 (d, *J* = 10.9 Hz, 1 H), 4.63–4.39 (m, 9 H), 4.38–4.14 (m, 10 H), 4.08 (d, *J* = 7.9 Hz, 1 H), 4.01 (d, *J* = 2.8 Hz, 1 H), 3.93–3.75 (m, 5 H), 3.70 (ddd, *J* = 9.9, 4.6, 1.8 Hz, 1 H), 3.66–3.60 (m, 1 H), 3.53–3.43 (m, 4 H), 3.43–3.24 (m, 8 H), 3.04 (dd, *J* = 10.1, 2.7 Hz, 1 H), 2.90 (ddd, *J* = 9.9, 3.4, 1.7 Hz, 1 H), 1.92 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 139.6, 139.2, 138.8, 138.8, 138.5, 138.4, 138.3, 138.1, 137.9, 137.8, 133.9, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 128.1, 128.0, 128.0, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 127.6, 127.6, 127.6, 127.5, 127.3, 127.2, 126.9, 126.4, 102.6, 102.5, 100.8, 99.5, 83.2, 81.7, 81.7, 80.4, 78.8, 77.1, 76.8, 76.3, 76.1, 75.6, 75.3, 75.2, 75.1, 75.0, 74.9, 74.8, 73.9, 73.8, 73.6, 73.4, 73.4, 73.3, 73.2, 72.7, 71.6, 71.4, 70.9, 69.5, 68.5, 67.8, 67.7, 56.6, 21.0 ppm. HRMS: calcd. for $C_{118}H_{119}NO_{23}$ [M + Na]$^+$ 1940.8065; found 1940.8030.

Benzyl 3,4,6-Tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (25): Compound **22** (1.55 g, 0.81 mmol) was dissolved in CH_2Cl_2 (10 mL), and a solution of NaOMe [from Na (40 mg, 1.74 mmol) and MeOH (100 mL)] was added. The mixture was stirred at room temperature for 48 h, then it was quenched with Amberlite IR 120 H$^+$. It was stirred for an additional 2 h, then it was filtered and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane, 1:3) to give **25** (1.23 g, 81%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49–6.77 (m, 64 H), 5.37 (d, *J* = 8.4 Hz, 1 H), 5.06 (d, *J* = 11.4 Hz, 1 H), 4.92–4.81 (m, 5 H), 4.73–4.67 (m, 2 H), 4.65–4.60 (m, 2 H), 4.58–4.44 (m, 8 H), 4.38 (d, *J* = 12.3 Hz, 1 H), 4.35–4.11 (m, 10 H), 4.08 (dd, *J* = 11.3, 3.5 Hz, 1 H), 4.02–3.81 (m, 6 H), 3.72 (ddd, *J* = 9.9, 3.2, 1.9 Hz, 1 H), 3.59–3.26 (m, 13 H), 2.92 (ddd, *J* = 9.9, 3.6, 1.7 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.5, 139.2, 139.0, 138.9, 138.8, 138.7, 138.5, 138.5, 138.3, 138.0, 138.0, 137.7, 133.5, 128.6, 128.5, 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 126.9, 126.8, 126.5, 123.2, 103.6, 102.6, 102.5, 100.0, 83.1, 82.1, 82.0, 81.8, 79.0, 78.4, 78.1, 76.8, 76.1, 75.6, 75.2, 75.2, 74.9, 74.8, 74.7, 74.6, 74.1, 73.8, 73.6, 73.6, 73.5, 73.2, 73.1, 72.9, 72.4, 72.3, 70.9, 68.8, 68.4, 68.4, 67.8, 56.6 ppm. HRMS: calcd. for $C_{116}H_{117}NO_{22}$ [M + Na]$^+$ 1898.7959; found 1898.7934.

Benzyl 2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (27): NIS (112 mg, 0.50 mmol) and TESOTf (13 mg, 0.049 mmol) were added to a mixture of **25** (711 mg, 0.38 mmol), **26** (253 mg, 0.48 mmol), and 4 Å MS in CH_2Cl_2 (7 mL) at –30 °C. The mixture was stirred for 20 min, then the reaction was quenched with Et_3N. The mixture was stirred for 15 min, then it was filtered through Celite and concentrated in vacuo. Purification by flash column chromatography (acetone/toluene, 1:24) gave **27** (657 mg, 89%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (br. s, 1 H), 7.52 (br. s, 1 H), 7.39–7.04 (m, 70 H), 6.93–6.80 (m, 5 H), 6.75 (t, *J* = 7.3 Hz, 2 H), 5.73 (d, *J* = 3.8 Hz, 1 H), 5.38 (d, *J* = 7.9 Hz, 1 H), 5.10 (d, *J* = 11.4 Hz, 1 H), 4.97 (d, *J* = 11.5 Hz, 1 H), 4.94–4.16 (m, 34 H), 4.15–3.99 (m, 4 H), 3.95 (d, *J* = 2.5 Hz, 1 H), 3.94–3.75 (m, 5 H), 3.64 (dd, *J* = 9.7, 2.8 Hz, 1 H), 3.59 (dd, *J* = 9.8,

2.9 Hz, 1 H), 3.57–3.29 (m, 12 H), 3.00–2.90 (m, 1 H), 1.39 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.5, 139.1, 138.9, 138.9, 138.8, 138.7, 138.6, 138.6, 138.5, 138.4, 138.2, 138.2, 138.1, 137.7, 133.6, 131.3, 128.6, 128.6, 128.5, 128.4, 128.4, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.2, 128.1, 128.1, 128.0, 129.0, 127.8, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.4, 127.3, 127.3, 127.2, 127.0, 126.9, 126.5, 126.3, 123.2, 102.5, 102.5, 100.9, 100.2, 97.7, 84.1, 83.1, 82.5, 81.8, 79.4, 78.9, 78.2, 76.8, 76.8, 76.7, 76.1, 75.8, 75.8, 75.6, 75.3, 75.2, 75.0, 75.0, 74.7, 74.5, 74.3, 73.9, 73.7, 73.6, 73.5, 73.3, 73.2, 73.1, 72.7, 72.4, 72.3, 71.0, 70.9, 68.8, 68.5, 68.3, 67.8, 66.6, 56.5, 17.0 ppm. MS: *m*/*z* = 2314.8 [M + Na]$^+$. NMR spectroscopic data are consistent with literature values.[7i]

Benzyl 2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (28): A mixture of **27** (475 mg, 0.207 mmol) and ethylenediamine (5.7 mL, 0.085 mmol) in *t*BuOH (25 mL) was stirred at 100 °C for 16 h. The volatiles were removed in vacuo, and the residue was coevaporated with toluene (2× 10 mL) and ethanol (10 mL). The residue was dissolved in CH_2Cl_2 (6 mL), and acetic anhydride (2 mL, 0.021 mol), Et_3N (4 mL), and DMAP (4-dimethylaminopyridine; 25 mg, 0.21 mmol) were added at 0 °C. The mixture was stirred at room temperature for 15 h. The residue was diluted with EtOAc (50 mL), then washed with saturated aqueous $NaHCO_3$ (2× 30 mL) and H_2O (40 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (deactivated with Et_3N; EtOAc/toluene, 1:9) to give **28** (336 mg, 74%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.00 (m, 75 H), 5.71 (d, *J* = 3.6 Hz, 1 H), 5.10 (d, *J* = 8.3 Hz, 1 H), 5.05–4.97 (m, 2 H), 4.96–4.87 (m, 5 H), 4.83–4.71 (m, 5 H), 4.70–4.17 (m, 24 H), 4.07–3.91 (m, 5 H), 3.86 (d, *J* = 10.4 Hz, 1 H), 3.81–3.33 (m, 19 H), 3.30–3.23 (m, 1 H), 1.47 (s, 3 H), 1.27 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 139.5, 139.2, 139.1, 138.9, 138.9, 138.8, 138.7, 138.6, 138.5, 138.3, 138.2, 138.0, 137.7, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 127.5, 127.4, 127.4, 127.3, 127.2, 126.9, 126.3, 102.7, 102.6, 101.8, 101.1, 97.6, 84.1, 83.0, 81.9, 81.9, 80.1, 79.4, 78.5, 78.1, 77.5, 77.2, 76.8, 76.6, 76.4, 75.9, 75.8, 75.7, 75.6, 75.3, 75.2, 75.0, 75.0, 74.8, 74.7, 74.3, 73.7, 73.6, 73.6, 73.5, 73.3, 73.3, 73.2, 72.7, 72.5, 72.4, 71.2, 71.0, 68.9, 68.3, 68.3, 68.3, 66.5, 56.4, 23.3, 17.0 ppm. HRMS: calcd. for $C_{137}H_{145}NO_{25}$ [M + H]$^+$ 2205.0178; found 2226.0173.

Benzyl 3,4,6-Tri-*O*-benzyl-β-D-galactopyranosyl-(1→3)-2-acetamido-4,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (29): A mixture of **22** (301 mg, 0.162 mmol) and ethylenediamine (4.7 mL, 0.070 mmol) in *t*BuOH (20 mL) was stirred at 100 °C for 16 h. The volatiles were removed in vacuo, and the residue coevaporated with toluene (2× 10 mL) and ethanol (10 mL). The residue was dissolved in ethanol (4.5 mL), and acetic anhydride (1.5 mL, 0.016 mol) and Et_3N (3 mL) were added at 0 °C. The mixture was stirred at room temperature for 15 h. The residue was diluted with EtOAc (40 mL), then washed with saturated aqueous $NaHCO_3$ (2× 20 mL) and H_2O (30 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (deactivated with Et_3N; EtOAc/heptane, 2:3) to give **29** (209 mg, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.11 (m, 60 H), 5.09 (d, *J* = 8.6 Hz, 1 H), 5.04–4.87 (m, 7 H), 4.80–4.32 (m, 19 H), 4.28–4.20 (m, 2 H), 4.15 (d, *J* = 7.5 Hz, 1 H), 4.03–3.85 (m, 5 H), 3.85–3.58 (m, 9 H), 3.57–3.43 (m, 6 H), 3.42–3.34 (m, 2 H), 3.34–3.27 (m, 2 H), 1.55 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 139.4, 139.4, 139.2, 139.0, 138.7, 138.6, 138.5, 138.3, 138.2, 138.2, 137.6, 128.7, 128.7, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.4, 127.3, 127.3, 126.5, 104.3, 102.6, 102.5, 101.5, 83.0, 81.8, 81.7, 81.4, 81.1, 80.8, 76.7, 76.5, 76.4, 75.6, 75.2, 75.2, 75.1, 75.1, 74.8, 74.8, 74.6, 73.9, 73.6, 73.6, 73.6, 73.6, 73.5, 73.5, 72.5, 71.8, 71.0, 69.4, 68.6, 68.4, 68.2, 56.1, 23.2 ppm. HRMS: calcd. for $C_{110}H_{117}NO_{21}$ [M + Na]$^+$ 1810.8010; found 1810.7994.

Benzyl 2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-β-*D*-galactopyranosyl-(1→3)-2-acetamido-4,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (30): NIS (17 mg, 0.077 mmol) and TESOTf (1.9 mg, 0.0077 mmol) were added to a mixture of **29** (100 mg, 0.056 mmol), **26** (38 mg, 0.073 mmol), and 4 Å MS in CH_2Cl_2 (1.5 mL) at –20 °C. The mixture was left to reach 10 °C, then the reaction was quenched with Et_3N. The mixture was stirred for 15 min, then it was filtered through Celite and concentrated in vacuo. Purification by flash column chromatography (deactivated with Et_3N; acetone/toluene, 1:9) gave **30** (84 mg, 68%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–6.96 (m, 75 H), 5.60 (d, *J* = 3.7 Hz, 1 H), 5.06 (d, *J* = 11.1 Hz, 2 H), 4.99 (d, *J* = 10.6 Hz, 1 H), 4.95–4.34 (m, 31 H), 4.26 (d, *J* = 11.8 Hz, 1 H), 4.19 (dd, *J* = 9.5, 7.6 Hz, 1 H), 4.05 (dd, *J* = 10.5, 2.5 Hz, 1 H), 4.02–3.91 (m, 5 H), 3.89 (d, *J* = 1.4 Hz, 1 H), 3.87–3.37 (m, 18 H), 3.33–3.22 (m, 1 H), 1.63 (s, 3 H), 1.20 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 139.7, 139.6, 139.3, 139.2, 138.9, 138.7, 138.7, 138.4, 138.3, 138.3, 138.1, 137.6, 129.0, 128.8, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.2, 128.2, 128.1, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 127.5, 127.3, 127.2, 127.2, 127.1, 126.4, 126.3, 102.7, 102.5, 102.0, 101.6, 98.2, 84.0, 83.0, 81.8, 81.5, 80.2, 79.3, 78.1, 78.0, 77.5, 77.2, 77.1, 76.8, 76.6, 76.4, 75.7, 75.6, 75.3, 75.3, 75.2, 75.1, 75.1, 75.0, 74.8, 74.7, 74.1, 73.7, 73.6, 73.6, 73.5, 73.5, 73.4, 72.8, 72.4, 72.0, 71.2, 71.0, 69.5, 68.9, 68.4, 68.3, 66.4, 55.8, 23.6, 16.8 ppm. HRMS: calcd. for $C_{137}H_{145}NO_{25}$ [M + H]$^+$ 2205.0178; found 2205.0132.

Benzyl 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-6-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (32): Synthesized by the general one-pot glycosylation method using **13** (120 mg, 0.20 mmol), **31** (83 mg, 0.17 mmol), and **6** (164 mg, 0.17 mmol). Purified by flash column chromatography (EtOAc/heptane, 1:2) to give **32** (183 mg, 57%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–7.94 (m, 2 H), 7.69–6.81 (m, 62 H), 5.65 (dd, *J* = 10.0, 8.0 Hz, 1 H), 5.35 (d, *J* = 8.4 Hz, 1 H), 4.98 (d, *J* = 11.4 Hz, 1 H), 4.92 (d, *J* = 11.7 Hz, 1 H), 4.89–4.75 (m, 3 H), 4.68–4.36 (m, 11 H), 4.31–4.13 (m, 8 H), 4.12–3.99 (m, 3 H), 3.96–3.84 (m, 3 H), 3.84–3.75 (m, 1 H), 3.67–3.25 (m, 17 H), 2.94–2.84 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 165.2, 139.5, 139.1, 138.7, 138.6, 138.5, 138.4, 138.3, 138.1, 137.7, 137.4, 137.4, 134.6, 133.7, 133.5, 133.4, 131.5, 130.2, 130.1, 129.9, 129.9, 129.1, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.7, 127.7, 127.7, 127.6, 127.6, 127.5, 127.2, 127.2, 127.1, 126.9, 126.6, 123.2, 102.5, 102.4, 102.1, 99.7, 83.0, 82.3, 82.1, 81.7, 79.8, 78.9, 76.8, 76.0, 75.5, 75.1, 75.1, 74.8, 74.6, 74.2, 74.0, 73.8, 73.7, 73.3, 73.1, 73.1, 73.1, 72.2, 72.1, 71.8, 70.9, 69.4, 68.7, 68.7, 68.4, 67.7, 56.6 ppm. HRMS: calcd. for $C_{116}H_{115}NO_{23}$ [M + Na]$^+$ 1912.7752; found 1912.7687.

α-L-Fucopyranosyl-(1→2)-β-D-galactopyranosyl-(1→3)-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→3)-β-D-galactopyranosyl-(1→4)-β-

D-glucopyranose (Lacto-*N*-fucopentaose I): A solution of **30** (30 mg, 0.014 mmol) in THF (1 mL) and MeOH (1 mL) was flushed thoroughly with argon, and then Pd/C (5%; 16 mg, 0.0075 mmol) and TFA (trifluoroacetic acid; 0.05 mL, 0.65 μmol) were added. The mixture was stirred under a hydrogen atmosphere (balloon) at room temperature for 16 h, then it was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by reverse-phase dry column chromatography (CH_2Cl_2/MeOH, 0 to 100% in steps of 10%) to give lacto-*N*-fucopentaose I (11.5 mg, 98%) as an amorphous solid. ^{1}H NMR (400 MHz, D_2O): δ = 5.22 (d, J = 3.7 Hz, 0.4 H, 1α-H), 5.19 (d, J = 4.0 Hz, 1 H, 1′′′′-H), 4.70–4.58 (m, 2.6 H, 1β-H, 1′′′-H, 1′′-H), 4.42 (d, J = 7.8 Hz, 1 H, 1′-H), 4.29 (q, J = 6.6 Hz, 1 H, 5′′′′-H), 4.14 (d, J = 3.2 Hz, 1 H, 4′-H), 4.04–3.44 (m, 27 H), 3.28 (t, J = 8.5 Hz, 0.6 H, 2β-H), 2.05 (s, 3 H), 1.23 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 174.2, 103.2 (C-1′′), 102.9 (C-1′), 100.2 (C-1′′′), 99.5 (C-1′′′′), 95.7 (C-1β), 91.8 (C-1α), 81.5, 78.2, 78.1, 77.1, 76.6, 75.2, 75.0, 74.8, 74.3, 73.8, 73.5, 71.8, 71.3, 71.1, 70.2, 69.4, 69.1, 68.6, 68.4, 68.0, 66.5, 61.1, 60.9, 60.4, 60.0, 55.9, 22.1, 15.2 ppm. MS: m/z = 860.6 $[M + Li]^+$. ^{1}H NMR spectroscopic data are consistent with literature values.[21]

α-L-Fucopyranosyl-(1→2)-β-D-galactopyranosyl-(1→4)-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→3)-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose (Lacto-*N*-neofucopentaose I): A solution of **28** (140 mg, 0.064 mmol) in THF (5 mL) and MeOH (5 mL) was flushed thoroughly with argon, and then Pd/C (5%; 78 mg, 0.037 mmol) and TFA (0.1 mL, 0.0013 mmol) were added. The mixture was stirred under a hydrogen atmosphere (balloon) at room temperature for 16 h, then it was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by reverse-phase dry column chromatography (CH_2Cl_2/MeOH, 0 to 100% in steps of 10%) to give lacto-*N*-neofucopentaose I (53 mg, 99%) as an amorphous solid. ^{1}H NMR (400 MHz, D_2O): δ = 5.30 (d, J = 2.6 Hz, 1 H, 1′′′′-H), 5.22 (d, J = 3.7 Hz, 0.4 H, 1α-H), 4.70 (d, J = 8.4 Hz, 1 H, 1′′-H), 4.66 (d, J = 8.0 Hz, 0.6 H, 1β-H), 4.55 (d, J = 7.8 Hz, 1 H, 1′′′-H), 4.44 (d, J = 7.8 Hz, 1 H, 1′-H), 4.21 (q, J = 6.6 Hz, 1 H, 5′′′′-H), 4.14 (d, J = 3.2 Hz, 1 H, 4′-H), 4.01–3.54 (m, 25 H), 3.50–3.42 (m, 1 H), 3.32–3.23 (m, 0.6 H, 2β-H), 2.04 (s, 3 H), 1.22 (d, J = 6.6 Hz, 3 H, 6′′′′-H) ppm. ^{1}H NMR spectroscopic data are consistent with literature values.[22] ^{13}C NMR (100 MHz, D_2O): δ = 174.9, 102.9 (C-1′), 102.7 (C-1′′), 100.2 (C-1′′′), 99.4 (C-1′′′′), 95.7 (C-1β), 91.8 (C-1α), 81.9, 78.3, 78.2, 76.4, 75.8, 75.2, 75.1, 74.8, 74.8, 74.3, 73.8 (C-2β), 73.5, 72.0, 71.6, 71.4, 71.1, 70.1, 70.0, 69.6, 69.1, 68.3 (C-4′), 68.2, 66.9 (C-5′′′′), 61.1, 60.9, 60.0, 60.0, 55.4, 22.2, 15.3 ppm. MS: m/z = 860.6 $[M + Li]^+$. ^{1}H NMR spectroscopic data are consistent with literature values.[22]

Supporting Information (see footnote on the first page of this article): Synthesis of thioglycoside **15** from **5**, as well as copies of ^{1}H and ^{13}C NMR spectra for all products.

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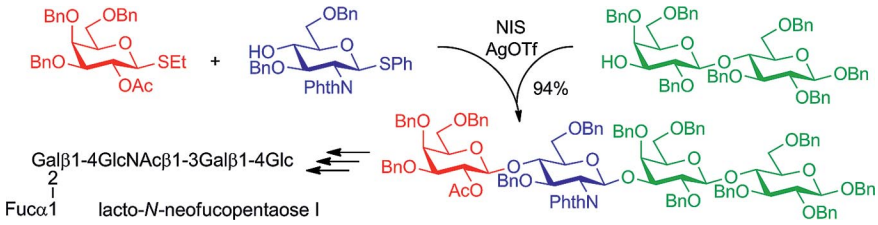

A one-pot glycosylation strategy has been developed for assembling the lactosamine–lactose backbone in human milk oligosaccharides, and applied in a concise synthesis of lacto-*N*-neofucopentaose I.

Keywords: Carbohydrates / Oligosaccharides / Glycosylation / Thioglycosides

