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Convergent synthesis of sialyl Lewis^{x}-*O*-Core-1 threonine

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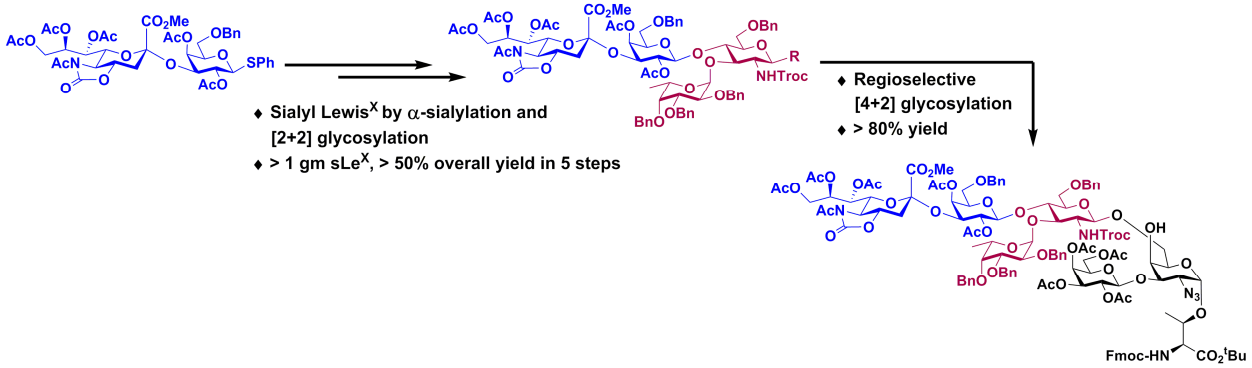
Abstract



Selectins are a class of cell adhesion molecules that play a critical role during the initial steps of inflammation. The N-terminal domain of P-selectin glycoprotein ligand-1 (PSGL-1) binds to all selectins, but with highest affinity to P-selectin. Recent evidence suggests that the blockade of P-selectin/PSGL-1 interactions provides a viable therapeutic option for the treatment of many inflammatory diseases. Herein, we report the total synthesis of threonine bearing sialyl Lewis^X (sLe^X) linked to a Core-1-*O*-hexasaccharide **1**, as a key glycan of the N-terminal domain of PSGL-1. A convergent synthesis using α-selective sialylation and a regioselective [4+2] glycosylation are the key features of this synthesis.

Introduction

During the course of inflammation, homing of leukocytes to vascular endothelial cells and subsequent extravasation represents critical initial features of the evolving immune response.[1-3] The homing of leukocytes is governed by the interactions between cell adhesion molecules and their ligands.[1,4,5] P-, L-, and E-selectin represent a class of Ca^{2+} dependent cell adhesion receptors that are expressed on activated endothelial cells, platelets, and leukocytes. P-selectin glycoprotein ligand-1 (PSGL-1), which is expressed on leukocytes, binds to all three selectins with highest affinity towards P-selectin, followed by L- and E-selectin.[6,7] The interaction of PSGL-1 on leukocytes and P-selectin on endothelial cells initiates a cascade of events that results in the rolling, arrest, and subsequently, the transendothelial migration of leukocytes. Similarly, the interaction of PSGL-1 on leukocytes and P-selectins on activated platelets initiates the formation of platelet-leukocyte aggregates that facilitates the infiltration of leukocytes at sites of injury.[1] Persistent upregulation of selectins leads to excessive trafficking of leukocytes, which may result in tissue damage that underlies a wide range of chronic disorders of innate immunity including atherosclerosis, inflammatory bowel disease, and metabolic syndrome.[8] For these reasons, the blockade of selectin/ligand interactions holds therapeutic potential for these and other conditions including thrombosis and cancer.[9]

The role of P-selectin/PSGL-1 interaction in various inflammatory diseases has motivated the investigation of a number of approaches to block P-selectin/PSGL-1 interactions, albeit with modest success. For instance, while antibody based therapies appear promising, manufacturing cost and the development of antibodies against these biologics limits their effectiveness.[10] There have also been numerous attempts to design small molecule inhibitors by modifying sialyl $Lewis^X$ (sLe^X), a critical binding motif, which has yielded a series of low affinity inhibitors including GMI-1070,[11,12] PSI-697,[13,14] and TBC1269.[15] The interaction between PSGL-1 and P-selectin is governed not only by sLe^X, but by the presence of a neighboring cluster of tyrosine sulfates and the amino terminal peptide backbone.[16,17] Consequently, a number of efforts have been directed towards the synthesis of the N-terminal region of PSGL-1 as a tool compound for drug discovery.

The generation of glycosulfopeptides that mimic PSGL-1 remains limited, in part, by the lack of a scalable chemical synthesis for sLe^X-Core-1-Thr. More specifically, the absence of a facile and scalable synthesis of the sLe^X tetrasaccharide and the Core-1 disaccharide are the key bottlenecks for the generation of sLe^X-Core-1-Thr. While we have developed a scalable process to generate Core-1 diol in multi-gram scale,[18] the design of a scheme for the efficient, large scale synthesis of sLe^X that can be coupled to Core-1 has remained an elusive synthetic target despite attempts by several research groups over past two decades.[19-30] For example, initial reports from Nicolaou[19] and Danishefsky[29] described the synthesis of sLeX in 7 to 9 steps with overall yields ranging from 5% to 20%. More recently, Boons and coworkers reported the synthesis of sLe^X derivative in 7 steps with 35% overall yield, but on a 35 mg scale.[22] Key challenges of sLe^X synthesis include the requirement of an α-(2→3) sialylation and α-(1→3) fucosylation, along with the acid lability of fucose, and the poor reactivity of glucosamine derivatives.[31-35] Moreover, glycosylation of sLe^X donors offers a unique set of challenges. In nature, all sLe^X derivatives are β-linked through an *N*-acetyl glucosamine C1. However, glycosylation using unmodified *N*-acetyl glucosamine donors leads to an inert oxazoline[36,37] and the glycosylation involving a sLe^X donor and a Core-1 diol acceptor is associated with poor regioselectivity. Notably, only two synthetic schemes for C2-*O*-sLeX hexasaccharide have been reported and both are limited by either an absence of control over regio- or diastereoselectivity.[22,38] In particular, the synthesis of a similar structure reported by Kunz and coworkers suffers a major setback at the key [4+2] glycosylation step resulting in an undesired 1→4 linked hexasaccharide as the major product.[38] While improved regioselectivity was observed on a modified mimic of sialyl LewisX[39], significant formation of undesired 1→4 linkage continued to be a major flaw, emphasizing the need for an improved method.

Recently, we have synthesized an analogue of the N-terminal domain of PSGL-1, GSnP-6, which binds to human P-selectin with a K_d of 22 nM.[18] In this approach, we utilized glycosyltransferases to add the terminal galactose, sialic acid, and fucose. In order to produce GSnP-6, as well as other glycosulfopeptide targets of biological interest in large scale, we herein report the

total chemical synthesis of a threonine bearing C2-*O*-sLe^X hexasaccharide **1** (**Fig. 1**). Our synthetic scheme takes advantage of α-selective sialylation using 4-*O*, 5-*N*-oxazolidone protection. An iterative α-selective sialylation forms the desired disaccharide donor with minimum modification followed by convergent synthesis of sLe^X based on [2+2] glycosylation and subsequent coupling to the Core-1 diol.

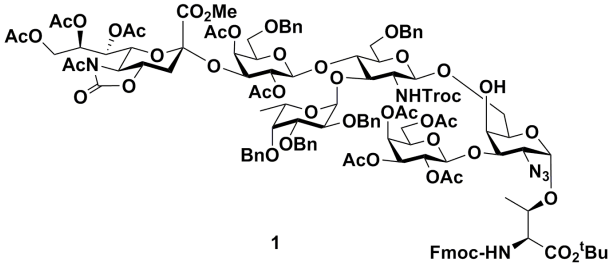


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Fig. 1. Sialyl Lewis^X-*O*-Core-1 threonine **1**.

Results and Discussion

We envisioned that [2+2] glycosylation to generate sLe^X with subsequent [4+2] glycosylation between the sLe^X donor and a Core-1 diol acceptor would be the most efficient route to afford C2-*O*-sLe^X (**Fig. 2**). This approach would allow us to address the challenges posed by α-(1→3) fucosylation and α-(2→3) sialylation during the generation of relatively less complex disaccharides **9** and **16**.

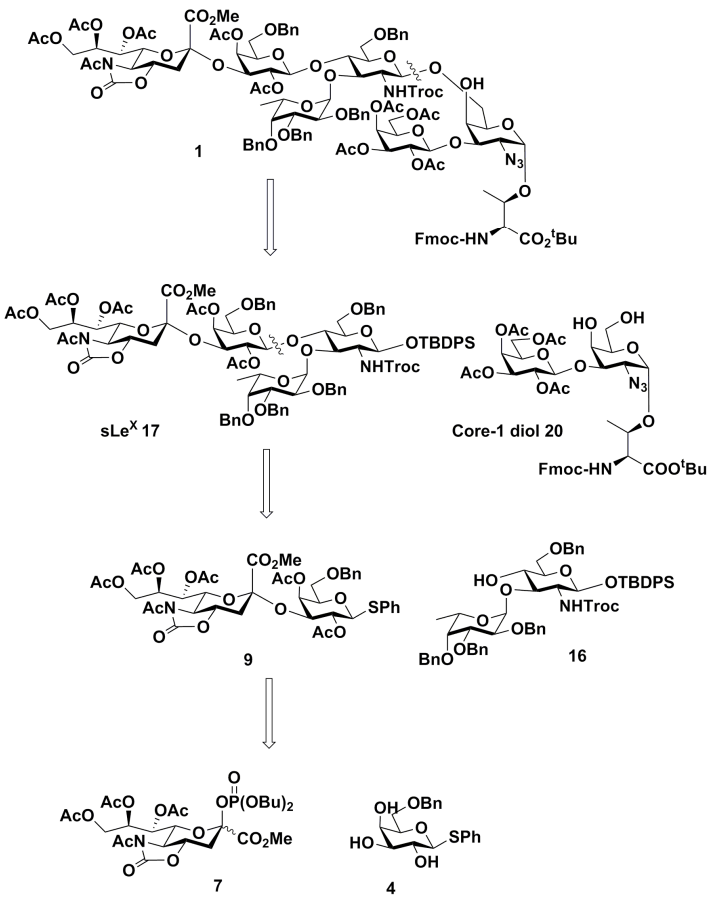
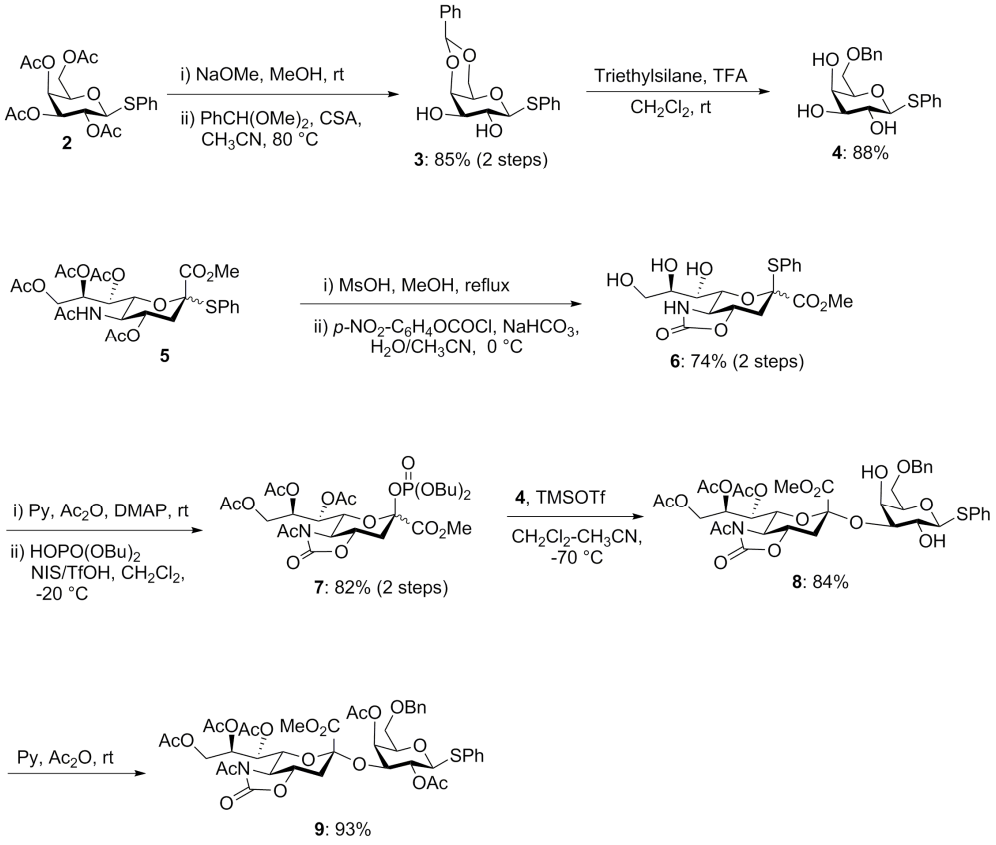


Fig. 2. Retrosynthesis of hexasaccharide **1**.

We began our investigation with a focus on α-(2→3) sialylation, which has often impeded the large scale generation of sLe^X (**Scheme 1**). *N*-Acetyl oxazolidone protected sialoside donors, reported by Crich and coworkers, exhibit excellent α-selectivity.[40,41] Subsequently, Wong and coworkers extended the utility of 5-*N,*4-*O*-oxazolidone protection towards sialoside phosphates for the α-selective iterative glycosylation. As a consequence, α-(2→3) sialylation of the galactosyl acceptor **4** was pursued using sialoside phosphate donor **7**[42] to generate α-(2→3) Sia-Gal disaccharide **8** in one step. The synthesis of galactosyl acceptor **4** was produced from commercially available D-galactose, as reported elsewhere.[43] The commercially available sialoside donor **5** was converted to the oxazolidone protected thioglycoside **6** in two steps. Subsequently, the thioglycoside was converted to its phosphate donor **7** by glycosylation using NIS/TfOH and dibutylphosphate. Iterative glycosylation was

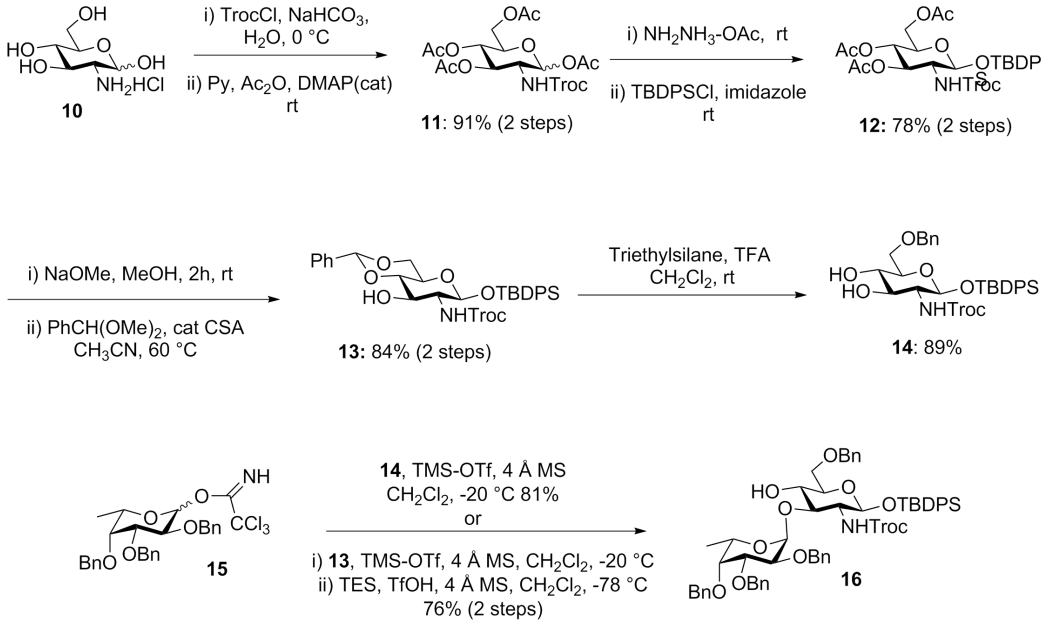
carried out in a 3:1 mixture of dichloromethane and acetonitrile at -70°C using TMS-OTf. The formation of an α-(2→3) linkage was confirmed by the $^{3}J_{C1,H-3ax}$ coupling constant (5.5 Hz) and the chemical shift of *H*-3eq (2.99 ppm), which were in agreement with prior reports.[44,45] Acetylation of the disaccharide using pyridine and Ac_2O resulted in the final disaccharide donor **9**.



Scheme 1. Synthesis of sialylgalactose disaccharide 9.

With successful preparation of the sialic acid-galactose disaccharide donor **9**, we focused on the preparation of the glucosamine-fucose disaccharide acceptor **16** (**Scheme 2**). Anomeric OTBDPS[46] and NHTroc[47] protecting groups were selected due to their compatibility with the subsequent synthesis of more complex analogues. Our initial approach was to fucosylate the diol acceptor **14** regioselectively, as reported by Magnusson and coworkers[27] for a similar acceptor. We sought to bypass regioselective ring opening of 4,6-*O*-benzylidene

acetal, which requires the use of a strong acid in the presence of an acid labile fucose. We initially synthesized Troc-protected glucosamine **12**, followed by deacetylation under Zémplen conditions to afford triol, which was converted *in situ* to 4,6-*O*- benzylidene acetal **13** by treatment with $PhCH(OMe)_2$ and CSA to afford the 3-OH acceptor.[46] Regioselective cleavage of the benzylidene acetal was carried out using triethylsilane and TFA to afford the diol **14**. Glycosylation between **14** and fucose donor **15** was carried out using TMS-OTf at -15°C in CH_2Cl_2 to obtain the disaccharide **16**. However, the purification of the desired

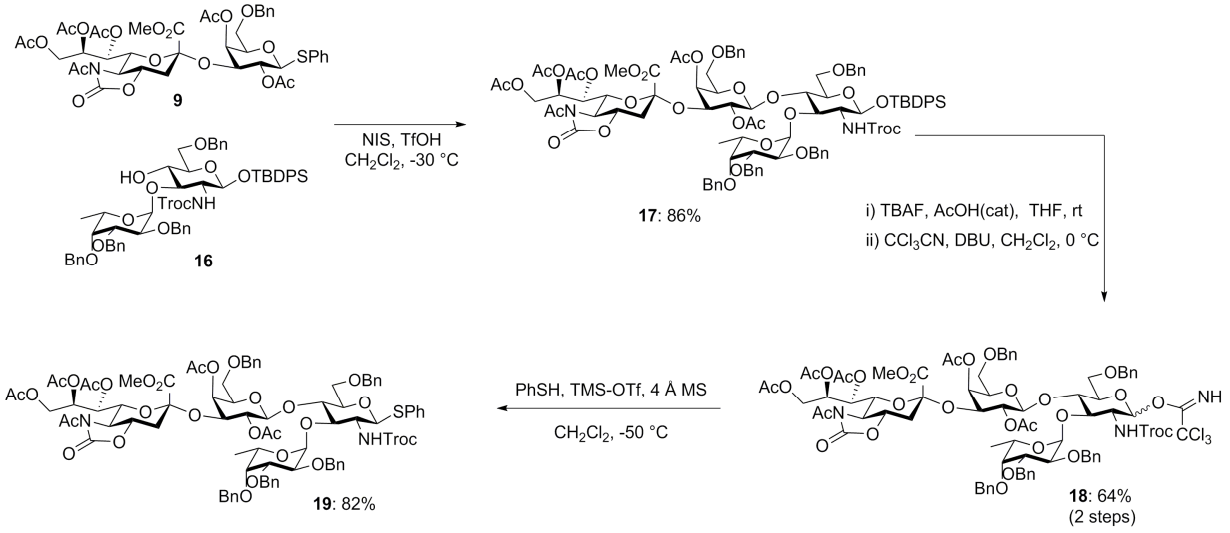


Scheme 2. Synthesis of disaccharide 16.

(1→3) linked disaccharide from the undesired (1→4) linked disaccharide was challenging, particularly at large scale. As an alternative approach, fucosylation of acceptor **13** was performed followed by regioselective cleavage of the 4,6-*O*-benzylidene acetal. Glycosylation between **13** and **15** was carried out using TMS-OTf at -20°C in CH_2Cl_2. Purification of the resulting disaccharide from excess donor was carried out after regioselective cleavage of benzylidene acetal using TfOH and TES at -78°C in CH_2Cl_2[48]. While other choices were available, the TES/TfOH system was selected to cleave the 4,6-*O*-benzylidene acetal, since the

reaction could be carried out at -78°C and cleavage of fucose was not observed. The structure of disaccharide **16** was confirmed by 1D and 2D NMR spectroscopy (Supporting Information).[38]

Sialyl Lewis^X tetrasaccharide **17** was generated by convergent [2+2] glycosylation between sialylgalactosyl thioglycoside donor **9** and fucosylglucosamine acceptor **16** (**Scheme 3**). The glycosylation was carried out using a NIS/TfOH activation system at -40°C in CH_2Cl_2, which proceeded smoothly to form fully protected sLe^X **17** in 86% yield. NMR spectroscopy revealed that the isolated compound consisted solely of the β-anomeric configuration, which was confirmed by the presence of a large coupling constant ($J_{H1\text{-}H2}$ = 8.4 Hz). To the best of our knowledge, this is the shortest synthesis of sLe^X reported to date. The synthesis of over one gram of fully protected sLe^X was accomplished in 5 steps from the monosaccharide building blocks, with 51% overall yield.



Scheme 3. Synthesis of sialyl Lewis^X.

Subsequently, sLe^X **17** was treated with TBAF and catalytic AcOH to remove the OTBDPS protecting group at the anomeric OH, which was then converted to the imidate donor **18** in two steps using CCl_3CN and DBU in 64% yield. The key [4+2] glycosylation between the sLe^X imidate donor and the Core-1 diol was carried out using TMS-OTf catalyst in CH_2Cl_2 (**Scheme 4**). However, the resulting product consisted of a 3:1 mixture of the desired 1→6 and

the undesired 1→4 linkages. Despite the evaluation of alternate reaction conditions, significant improvement was not observed and attempts to conduct the reaction below -20°C were unsuccessful. This limitation of regioselectivity involving a donor with a participating group and the 4,6-diol system has been previously reported by other groups.[38,49,50] While it is unexpected for the axial 4-OH to react, as proposed by Baumann, it is possible that the 6-OH reacts with the intermediate oxazolinium ion via the exocyclic carbon and upon intramolecular rearrangement forms the 1→4 linked product (**Fig. 3**).[51] To circumvent this limitation, we postulated that a thioglycoside donor would enable glycosylation at a much lower temperature, which would potentially improve regioselectivity. Hence, the imidate donor was converted to its thioglycoside **19** by treatment with TMS-OTf and thiophenol in one step with 82% yield.

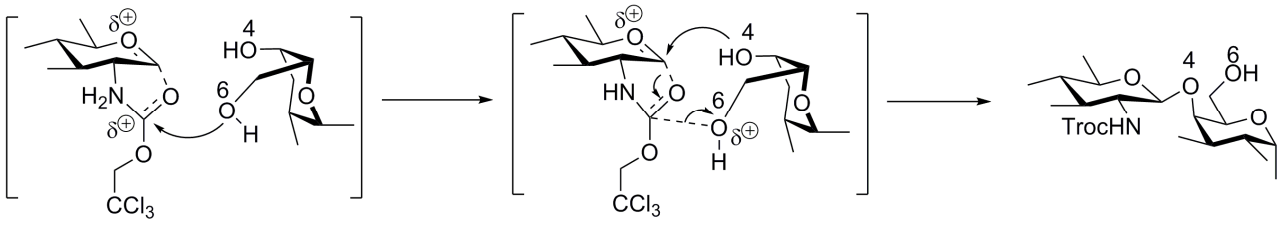
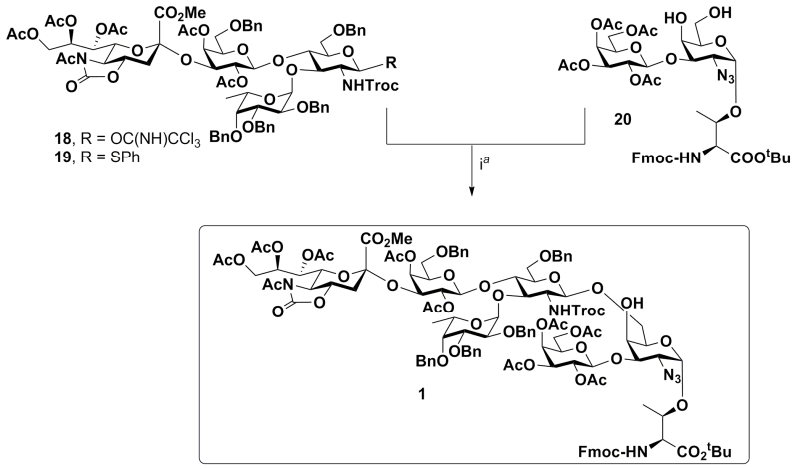


Fig. 3. Speculated mechanism for the formation of the 1→4 linkage.

Table 1 summarizes the results of [4+2] glycosylation to a Core-1 diol acceptor using two sLe^X donors and different promoters under various conditions (**Table 1**). As noted, the sLe^X imidate donor **18** produced a 3:1 mixture of products upon activation using catalytic TMS-OTf in CH_2Cl_2. Use of a less polar solvent, such as a 3:1 mixture of CH_2Cl_2 and toluene, did not improve regioselectivity and further attempts to lower the reaction temperature led to the absence of product, while a higher temperature resulted in the loss of fucose. Studies with the sLe^X thioglycoside donor **19** were initially conducted at -40°C using NIS and TfOH. Higher yield and an improved regioselectivity (10:1) favoring the β-(1→6) linked hexasaccharide was observed (**Table 1**, entry 3). Given the pronounced effect of reaction temperature on selectivity and overall yield, we explored conditions under which reaction temperature was further reduced.

Glycosylation was carried out at -60°C using BSP-Tf_2O along with a bulky base, TTBP (**Table 1**, entry 4). Although only a single isomer was isolated, yield was significantly reduced, which may reflect assisted transfer of a proton by TTBP from glucosamine NHTroc to form an inert oxazoline.



Scheme 4. [4+2] Glycosylation between sLe^X donors and Core-1 diol acceptor. *i* [a] Reaction conditions and yields are listed in Table 1.

Table 1. Conditions for the [4+2] glycosylation between sLe^X donors and Core-1 diol acceptor.

Entry	Donor	Promoter	Solvent	Temperature	Yield (Selectivity)[a]
1	sLe^X-imidate	TMS-OTf	CH_2Cl_2	-15°C	67% (3:1)
2	sLe^X-imidate	TMS-OTf	CH_2Cl_2/Toluene	-15°C	54% (3:1)
3	sLe^X-thioglycoside	NIS/TfOH	CH_2Cl_2	-40°C	82% 10:1
4	sLe^X-thioglycoside	BSP/Tf_2O/TTBP	CH_2Cl_2	-60°C	46% 1→6 only
5	sLe^X-thioglycoside	BSP/Tf_2O	CH_2Cl_2	-60°C	86% 1→6 only

[a]Ratio of 1→6 to 1→4 linked hexasaccharides

The highest yield, with exclusive formation of the β-(1→6) linked hexasaccharide, was observed when [4+2] glycosylation was carried out with a BSP-Tf_2O promoter in the absence of a base (**Table 1**, entry 5). Structural assignments of the final hexasaccharide were performed by

a combination of ^{1}H, ^{13}C, COSY, HSQC, TOCSY, and HMBC (Supporting Information). A downfield ^{13}C shift of $C^{I}6$, HMBC correlation between C^{III}-1 and H^{I}-6, and J_{H1-H2} confirmed formation of the β-(1→6) linkage.

In conclusion, several key challenges have been addressed in the synthesis of a threonine bearing C2-*O*-sLe^{X} hexasaccharide. The reported scheme, which describes stereoselective sialylation, provides an efficient synthesis for sLe^{X} in high yield. Specifically, convergent synthesis of sLe^{X} in five steps was performed in gram scale with elimination of the formation of any undesired regio- and stereoisomers. Furthermore, conditions were optimized for the regioselective [4+2] glycosylation between sLe^{X} and core-1 diol. A sLe^{X} thioglycoside enabled low temperature glycosylation using a BSP-Tf_2O activation system. As a complex naturally occurring glycan, the synthesis of the C2-*O*-sLe^{X} hexasaccharide provides an opportunity for the creation of tool compounds to probe molecular mechanisms relevant to the development of therapeutic compounds of clinical interest.

Experimental Section

General

All reactions were performed under inert atmosphere of nitrogen or argon, unless otherwise noted. D-Galactose, D-glucosamine hydrochloride, and L-fucose were purchased (Carbosynth LLC, CA). All other reagents were purchased from commercial sources and used directly. All solvents were dried and distilled following standard protocols. All glycosylation reactions were performed in oven dried round bottom flask. Proton nuclear magnetic resonance (^{1}H NMR) and ^{13}C NMR spectra were recorded with a Varian 400-MHz and Bruker 600-MHz spectrometer. High Resolution Mass spectra (HRMS) were acquired using UltraFlex II MALDI/TOF Mass Spectrometer (Bruker Corporation, MA) and Orbitrap Lumos MS (Thermo Fisher Scientific, CA). Thin layer chromatography (TLC) was performed on silica gel matrix with

a 254 nm fluorescent indicator and flash column chromatography purification was performed on Silica Gel 60 (Sigma-Aldrich Corporation, WI).

Phenyl 6-*O*-benzyl-1-thio- β-D-galactopyranoside (4)

TFA (5.0 mL, 64.9 mmol) and triethylsilane (11.0 mL, 68.8 mmol) were added to a solution of galactose diol **3**[43] (4.60 gm, 12.8 mmol) in CH_2Cl_2 (50 mL) at 0°C and stirred at room temperature for 3 h. The reaction was monitored by TLC and upon completion of the reaction, concentrated *in vacuo*. The crude was dissolved in EtOAc (100 mL), washed with satd aq $NaHCO_3$ (2 x 50 mL), brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo.* The crude residue was purified by column chromatography over silica gel using 60% EtOAc in hexanes to obtain a white solid (4.07 gm, 88 %). $[\alpha]_D^{24}$ -32.6 (*c* = 1.0, $CHCl_3$), R_f 0.35 (hexane/EtOAc, 1:4); ^{1}H NMR (400 MHz; CD_3OD) *δ:* 7.58 – 7.50 (m, 2H, Aromatic.), 7.35 – 7.14 (m, 8H, Aromatic.), 4.62 (d, *J* = 9.7 Hz, 1H, H-1), 4.52 (s, 2H, CH_2Ph), 3.87 (d, *J* = 3.3 Hz, 1H, H-4), 3.76 – 3.68 (m, 3H, H-5, 6-CH_2), 3.62 (t, *J* = 9.4 Hz, 1H, H-2), 3.51 (dd, *J* = 9.2, 3.4 Hz, 1H, H-3); ^{13}C NMR (100.5 Hz, CD_3OD) *δ:* 138.3, 134.7, 130.6, 130.6, 128.5, 127.9, 127.4, 127.2, 126.5, 88.7, 88.6, 77.8, 77.7, 74.8, 73.0, 72.9, 72.9, 69.8, 69.4, 69.3; ESI-HRMS m/z calcd for $C_{19}H_{22}O_5SNa$ $[M + Na]^+$ 385.1086, found 385.1074.

Methyl (phenyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-N,4-*O*-carbonyl-3,5-dideoxy-2-thio-D-glycero-β-D-galacto-non-2-ulopyranoside)onate (6)

Sialoside thioglycoside **5** (6.25 g, 10.7 mmol) in methanol (100 mL) was treated with methanesulfonic acid (2.1 mL, 32.1 mmol) and refluxed under N_2 for 24 h. The reaction mixture was quenched with trimethylamine (10 mL) and then concentrated under reduced pressure. The contracted residue and $NaHCO_3$ (4.5 g, 53.5 mmol) were dissolved in CH_3CN (30 mL) and H_2O (60 mL), and cooled to 0°C. 4-Nitrophenyl chloroformate (5.4 g, 26.7 mmol) in CH_3CN (30 mL) was slowly added to the vigorously stirred solution. The reaction mixture was stirred for 3 h at 0°C, after which the aqueous layer was extracted with ethyl acetate (3x100 mL) and the

combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography over silica gel eluting with 10% methanol in ethyl acetate to afford **6** as a white foam (3.16 gm, 74%). The NMR spectra for **6** matched those previously reported.[40,41] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.48 (d, *J* = 7.6 Hz, 2H), 7.38-7.28 (m, 3H), 6.99 (br s, 1H), 4.65 (t, *J* = 11.6, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.02 (br s, 1H), 3.92 (br s, 1H), 3.83-3.66 (m, 3H), 3.59 (s, 3H), 3.55 (t, *J* = 10.4, 1H), 2.85 (d, *J* = 10.0 Hz, 1H), 2.55 – 2.38 (m, 2H), 2.33 (t, *J* = 12.4 Hz, 1H); ^{13}C NMR (100.5 Hz, $CDCl_3$) *δ:* 168.8, 160.7, 136.3, 130.1, 129.0, 128.2, 89.0, 77.6, 75.2, 75.1, 71.2, 70.2, 63.4, 58.4, 58.3, 53.0, 52.9, 36.9.

Dibutyl[(methyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-N,4-*O*-carbonyl-3,5-dideoxy-D-glycero-α/β-D-galacto-non-2-ulopyranosyl)onate] phosphate (7)

Acetic anhydride (30 mL) and DMAP (0.61 gm, 5.0 mmol) were added to a solution of sialoside thioglycoside **6** (2.1 gm, 5.30 mmol) in pyridine (30 mL) and stirred for 48 h. The solvent was then removed and the residue was dissolved in CH_2Cl_2 (100 mL) and successively washed with an aqueous solution of $NaHCO_3$ (3x30 mL), brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was filtered through a silica gel column using 70% ethylacetate in hexanes. The filtrate was concentrated to obtain a white foam. The white foamy residue, dibutylphosphate (2.58 mL, 12.8 mmol) and activated 4 Å molecular sieves (3.1 gm) were stirred in CH_2Cl_2 (50 mL) for 2 h before cooling to -10°C followed by the addition of NIS (1.9 gm, 8.3 mmol) and TfOH (44 µL, 0.5 mmol). The reaction mixture was stirred for 4 h and was then quenched by the addition of trimethylamine (0.3 mL), diluted in CH_2Cl_2 (50 mL), and filtered through a pad of Celite. The filtrate was successively washed with saturated aqueous solution of $Na_2S_2O_3$ (30 mL), $NaHCO_3$ (30 mL), brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel using 50% EtOAc in hexanes to obtain **7** as a yellowish foam (2.74 mg, 82 %). The NMR spectra for **7** matched those previously reported.[42] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* (α-isomer) 5.64 (dd *J* = 8.0, 0.8 Hz,

1H), 5.30-5.25 (m, 1H), 4.73 (dt, *J* = 1.2, 9.6 Hz, 1H), 4.37 (dd, *J* = 12.3, 2.8 Hz, 1H), 4.17-4.03 (m, 6H), 3.85-3.82 (m, 4H), 2.96 (dd, *J* = 4.4, 12.4 Hz, 1H), 2.64 (t, *J* = 12.7 Hz, 1H), 2.45 (s, 3H), 2.47 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H), 2.00 (s, 3H), 1.67-1.63 (m, 4H), 1.42-1.36 (m, 4H), 0.90 (t, *J* = 7.9 Hz, 6H); (β-isomer): 5.63 (dd *J* = 1.2, 4.0 Hz, 1H), 5.23-5.18 (m, 1H), 4.69 (dd, *J* = 2.0, 9.6 Hz, 1H), 4.54 (m, 1H), 4.15 (dd, *J* = 7.2, 12.4 Hz, 1H), 4.10-4.05 (m, 4H), 3.82 (s, 3H), 3.73 (dd, *J* = 9.8, 11.2 Hz, 1H), 2.85 (dd, *J* = 3.6, 12.8 Hz, 1H), 2.47(s, 3H), 2.27 (dt, *J* = 2.4, 12.8 Hz, 1H) 2.08 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H), 1.66-1.61 (m, 4H), 1.39-1.35 (m, 4H), 0.90 (t, *J* = 7.4 Hz, 6H) ^{13}C NMR (100.5 Hz, $CDCl_3$) *δ:* (α-isomer):171.7, 170.5, 170.4, 170.0, 169.9, 167.2, 167.2, 153.4, 98.8, 98.1, 74.1, 71.5, 69.8, 68.1, 68.0, 62.5, 58.3, 53.4, 35.9, 32.1, 32.0, 24.5, 20.9, 20.8, 20.6, 18.6, 18.5, 13.4; (β-isomer): 172.1, 170.5, 170.4, 169.8, 169.6, 165.5, 153.4, 98.8, 98.7, 76.6, 73.9, 72.5, 71.7, 68.5, 68.4, 68.3, 62.8, 58.8, 53.4, 36.0, 32.1, 32.0, 24.6, 20.9, 20.7, 18.5, 13.5.

Methyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranosylonate-(2→3)-phenyl 6-*O*-benzyl-thio-β-D-galactothiopyranoside (8)

Sialoside phosphate donor **7** (700 mg, 1.1 mmol) and galactosyl thioglycoside acceptor **4** (506 mg, 1.4 mmol), along with activated 4 Å molecular sieves (400 mg) were added to a mixture of CH_2Cl_2 and CH_3CN (3:1, 20 mL) and stirred for 2 h at room temperature. The mixture was then cooled to -78°C and stirred for an additional 30 min, before addition of TMS-OTf (200 µL, 1.1 mmol). After stirring for 30 min at -70°C, the reaction mixture was quenched with Et_3N, (0.5 mL), diluted with CH_2Cl_2, and filtered through a pad of Celite. The filtrate was successively washed with water, brine, dried over Na_2SO_4, concentrated *in vacuo*, and the resulting residue was purified by column chromatography over silica gel using 60% EtOAc in hexanes to obtain **8** as a white foam (758 mg, 84%). $[\alpha]_D^{24}$ -42.7 (*c* = 1.0, $CHCl_3$), R_f 0.40 (hexane/EtOAc, 1:3); ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.60-7.57 (m, 2H), 7.34-7.23 (m, 8H), 5.68 (dd, *J* = 1.6, 8.2 Hz, 1H,

H-7'), 5.49 (dt, *J* = 3.2, 6.8 Hz, 1H, H-8'), 4.71 (d, *J* = 9.6 Hz, 1H, H-1), 4.57-4.54 (m, 3H, H-6_a', $PhCH_2$), 4.37 (dd, *J* = 3.2, 12.0 Hz, 1H, H-9'), 4.11 (dd, *J* = 3.0, 9.6 Hz, 1H, H-3), 4.02 (dd, *J* = 6.4, 12.4 Hz, 1H, H-9_b'), 3.96 (dd, *J* = 2.8, 10.8 Hz, 1H, H-4'), 3.81--3.68 (m, 9H, CH_3, H-2, H-4, H-5, H-6a, H-6b, H-5'), 2.99 (dd, *J* = 3.6, 12.4 Hz, 1H, H-3_e), 2.81 (d, *J* = 1.6 Hz, 1H), 2.63 (d, *J* = 3.2 Hz, 1H), 2.49 (s, 3H, OAc), 2.22 (t, *J* = 12.8 Hz, 1H, H-3_a), 2.12 (s, 3H, OAc), 2.11 (s, 3H, OAc), 1.97 (s, 3H, OAc); ^{13}C NMR (100.5 Hz, $CDCl_3$) *δ:* 171.9, 170.7, 170.1, 169.8, 168.2 ($^3J_{C\text{-}1,\ H\text{-}3ax}$ = 5.5 Hz, C-1'), 153.4, 137.9, 133.0, 132.2, 128.7, 128.4, 127.3, 127.6, 137.5, 98.1 (C-2'), 87.7 (C-1), 78.7 (C-3), 76.7 (C-6'), 74.7, 73.6, 71.5 (C-8'), 69.4, 68.8 (C-9'), 68.5, 68.4, 67.5, 63.1 (C-9'), 58.9, 53.2 (C-1'$OOCH_3$), 36.3 (C-3'), 29.6, 24.6, 21.2, 20.9, 20.7; HR-MALDI-ToF/MS m/z calcd for $C_{38}H_{45}NNaO_{17}S$ $[M + Na]^+$ 842.2306, found 842.2341.

Methyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranosylonate-(2→3)-phenyl 2,6-dio-*O*-acetyl-6-*O*-benzyl-1-thio-β-D-galactothiopyranoside (9)

The disaccharide **8** (720 mg, 0.88 mmol) was dissolved in pyridine (8 mL) followed by the addition of Ac_2O (5 mL) and DMAP (40 mg, 0.33 mmol), which was stirred at room temperature for 12 h. The reaction mixture was concentrated and diluted in CH_2CL_2 (50 mL), washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo.* The crude residue was purified by column chromatography over silica gel using 50% EtOAc in hexanes to obtain a white foam (738 mg, 93%). $[\alpha]_D^{24}$ -38.2 (*c* = 1.0, $CHCl_3$), R_f 0.46 (hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.55-7.51 (m, 2H), 7.32-7.22 (m, 8H), 5.64-5.62 (m, 1H, H-7', H-8'), 5.14 (t, *J* = 9.6 Hz, 1H, H-2), 5.00 (d, *J* = 3.2 Hz, 1H, H-4), 4.91 (d, *J* = 10.0 Hz, 1H, H-1), 4.62 (dd, *J* = 3.2, 10.0 Hz, 1H, H-3), 4.51-4.45 (m, 3H, H-9_a',$PhCH_2$), 4.26 (dd, *J* = 1.4, 9.4 Hz, 1H, H-6'), 3.99-3.91 (m, 2H, H-9_b', H-5), 3.86 (dd, *J* = 3.0, 13.2 Hz, 1H, H-4'), 3.82 (s, 3H, CO_2Me), 3.64 (dd, *J* = 9.4, 10.6 Hz, 1H, H-5'), 3.54 (dd, *J* = 6.2, 10.2 Hz, 1H, H-6_a), 3.45 (dd, *J* = 6.2, 10.2 Hz, 1H, H-6_b), 2.92 (dd, *J* = 3.4, 11.8 Hz, 1H, H-3_e'), 2,45 (s, 3H,

OAc), 2.24 (s, 3H, OAc), 2.13 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.05 (s, 3H, OAc), 1.85 (t, *J* = 12.4 Hz, 1H, H-3$_a$'), 1.85 (s, 3H, OAc); ^{13}C NMR (100.5 Hz, $CDCl_3$) *δ:* 171.6, 170.4, 170.2, 169.8, 169.4, 167.4, 153.4, 137.9, 133.4, 131.8, 128.7, 128.3, 127.7, 127.4, 97.5 (C-2'), 85.3 (C-1), 75.8, 75.6, 74.6, 73.4, 73.3, 72.8, 72.1, 68.5, 68.4, 68.2, 68.0, 67.9, 63.3, 59.0, 53.5 (C-1'$OOCH_3$), 36.0, 24.6, 21.4, 21.1, 20.9, 20.8, 20.7, 20.5; HR-MALDI-ToF/MS m/z calcd for $C_{42}H_{49}NNaO_{19}S$ $[M + Na]^+$ 926.2517, found 926.2574.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α/β-D-glucopyranoside (11)

To a solution of D-glucosamine hydrochloride (20 g, 92.8 mmol) in H_2O (250 mL) satd aq $NaHCO_3$ (250 mL) and 2,2,2-trichloroethyl chloroformate (14.05 mL, 102 mmol) were added and stirred vigorously for 18 h at room temperature. The reaction mixture was filtered through a fritted funnel and the white solid was dried under vacuum overnight. A solution of the solid in pyridine (100 mL) was cooled to 0°C, to which Ac_2O (100 mL) was added slowly, followed by DMAP (500 mg, 41 mmol). The solution was warmed to room temperature and stirred for 12 h. The solution was then diluted with CH_2Cl_2 (200 mL), washed with 1M HCl (3 x 100 mL), satd aq $NaHCO_3$ (2 x 100 mL), brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*, to afford glucosamine **11** as a white foam (44.3 g, 91%). The NMR spectra for **11** matched those previously reported.[52] ^{1}H NMR (400 MHz; $CDCl_3$) δ: 6.22 (d, *J* = 3.7 Hz, 1H), 5.38 – 5.06 (m, 4H), 4.87 – 4.68 (m, 2H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.32 – 3.88 (m, 6H), 2.18 – 2.00 (m, 13H); ^{13}C NMR (100.5 Hz, $CDCl_3$) *δ:* 171.2, 170.6, 169.1, 168.5, 154.0, 95.2, 90.4, 90.34, 74.7, 74.6, 70.4, 61.5, 53.2, 20.9, 20.8, 20.7, 20.6, 20.6, 20.5, 20.5; ESI-HRMS m/z calcd for $C_{17}H_{22}Cl_3NO_{11}Na$ $[M + Na]^+$ 544.0156, found 544.0168.

tert-Butyldiphenylsilyl 3,4,6-Tetra-_O_-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonyl-amino)-β-D-glucopyranoside (12)

A solution of **11** (10.3 g, 19.8 mmol) and hydrazinium acetate (1.9 g, 20.6 mmol) in DMF (70 mL) was stirred for 20 min at room temperature. Then the reaction mixture was diluted with EtOAc (400 mL), washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo.* TBDPSCl (8.1 mL, 31.1 mmol) followed by imidazole (2.1 gm, 31.1 mmol) were added to the stirring solution of the crude residue in DMF (50 mL) at room temperature. After 12 h, the reaction mixture was concentrated and diluted in EtOAc (200 mL), washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo.* The crude residue was purified by column chromatography over silica gel using 20% EtOAc in hexanes to obtain **12** as a white foam (11.1 gm, 78%). The NMR spectra for **12** matched those previously reported.[53] ^{1}H NMR (400 MHz; $CDCl_3$) δ: 7.66 (m, 3H), 7.49 – 7.22 (m, 5H), 5.23 (d, *J* = 9.6 Hz, 1H, H-1), 5.13 – 4.90 (m, 2H, H-5, H-3), 4.75 (d, *J* = 12.0 Hz, 1H, 6-CH_2), 4.57 (m, 2H, 6-CH_2, H-4) , 4.06 (dd, *J* = 12.1, 5.7 Hz, 1H, 6-CH_2), 3.99 – 3.79 (m, 2H, H-2,Troc CH_2), 3.40 (m, 1H, Troc CH_2), 1.95 (m, 6H, 2CH_3), 1.89 (s, 3H, CH_3), 1.06 (s, 9H, *t*Bu); ; ^{13}C NMR (100.5 Hz, $CDCl_3$) *δ:* 170.8, 170.5, 169.4, 154.1, 135.9, 135.7, 135.7, 132.7, 132.6, 130.0, 129.9, 129.9, 127.6, 127.4, 96.0, 95.3, 74.6, 74.6, 72.4, 71.5, 62.2, 57.87, 26.7, 26.7, 20.6, 20.6, 20.6, 20.5, 20.5, 19.1; ESI-HRMS m/z calcd for $C_{31}H_{38}Cl_3NO_{10}SiNa$ $[M + Na]^+$ 740.1228, found 740.1241.

tert-Butyldiphenylsilyl 6-_O_-benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonyl-amino)-β-D-glucopyranoside (14)

Trifluoroacetic acid (2.70 mL, 34.4 mmol) was added to a solution of **13** (4.7 gm, 6.9 mmol) and trimethylsilane (5.48 mL, 34.4 mmol) in CH_2Cl_2 (30 mL) at 0°C. The reaction mixture was then warmed to room temperature and stirred for 3 h. The reaction mixture was subsequently diluted in chloroform (20 mL), washed with a saturated aqueous solution of

$NaHCO_3$ (2 x 20 mL), brine, dried over $MgSO_4$, filtered and concentrated. Purification of the crude residue was performed by column chromatography over silica gel using 45% EtOAc in hexanes as eluent, which afforded diol **14** as a white foam (4.2 gm, 89%). $[\alpha]_D^{24}$ -13.1 (*c* = 1.0, $CHCl_3$), R_f 0.40 (hexane/EtOAc, 2:3); ^{1}H NMR (400 MHz; $CDCl_3$) *δ:* 7.70 (d, *J* = 7.6 Hz, 2H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.36-7.28 (m, 6H), 7.25-7.22 (m, 3H), 4.98 (d, *J* = 7.6 Hz, 1H, NHTroc), 4.70 (d, *J* = 11.6 Hz, 1H, $TrocCH_2$), 4.64 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.50 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.46 (d, *J* = 7.6 Hz, 1H, H-1), 4.43 (d, *J* = 12.0 Hz, 1H, $TrocCH_2$), 3.60-3.54 (m, 4H, H-2, H-4, H-6_a, H-6_b), 3.41 (d, *J* = 10.4 Hz, 1H, H-3), 3.38 (d, *J* = 2.8 Hz, 1H, OH), 3.14 (d, *J* = 4.8 Hz, 1H, H-5), 3.11 (br s, 1H, OH), 1.08 (s, 9H, ^{t}Bu); ^{13}C NMR (100.5 Hz, $CDCl_3$) *δ:* 155.1, 137.8, 136.0, 135.9, 135.8, 132.9, 132.7, 130.1, 129.8, 128.4, 127.7, 127.5, 95.9 (C-1), 95.2 ($TrocCl_3$), 75.1, 75.0, 74.9, 74.1 (C-5), 73.7 (C-3), 72.4 (C-4), 70.0 (C-6), 59.7 (C-2), 26.8, 19.1; HR-MALDI-ToF/MS m/z calcd for $C_{32}H_{38}Cl_3NNaO_7Si$ $[M + Na]^+$ 704.1381, found 704.1384.

tert-Butyldiphenylsilyl (2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl-α-(1→3)]-6-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonyl-amino)-β-D-glucopyranoside (16)

Trichloroacetimidate **15** (2.6 gm, 4.5 mmol), glucosamine acceptor **13** (2.4 gm, 3.5 mmol), and freshly activated 4 Å molecular sieves (3.2 gm) were stirred in distilled CH_2Cl_2 (50 mL) for 1 h at -30°C. TMSOTf (276 µL, 1.5 mmol) was added dropwise and the reaction mixture stirred for 1 h at -20°C. Progress of the reaction was monitored by TLC. Upon consumption of the acceptor, the reaction mixture was quenched with diisopropylethylamine (2 mL). The reaction mixture was diluted with CH_2Cl_2 (100 mL), and filtered through a pad of Celite. The filtrate was successively washed with saturated aqueous solution of $NaHCO_3$ (50 mL), brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was flushed through silica gel using 20% ethyl acetate in hexanes and concentrated to obtain a yellowish foam (4.1 gm). The foamy residue (4.1 gm), Et_3SiH (1.8 mL, 11.4 mmol), and pulverized 4 Å molecular

sieves (12 gm) were stirred in distilled CH_2Cl_2 (50 mL) at room temperature for 1 h and then cooled to -78°C and stirred for another 30 min. TfOH (774 µL, 10.1 mmol) was then added slowly and stirred for 1 h.[48] Upon completion of the reaction as monitored by TLC, Et_3N (5 mL) was added and stirred for another 5 min before warming the reaction mixture to room temperature. The reaction mixture was then diluted with CH_2Cl_2 (100 mL), filtered through Celite, concentrated *in vacuo*. The crude residue was purified by column chromatography over silica gel eluting with 25% ethyl acetate in hexanes to obtain **16** as a white foam (2.95 gm, 76%). $[\alpha]_D^{24}$ -45.5 (*c* = 1.0, $CHCl_3$), R_f 0.30 (hexane/EtOAc, 1:4). ^{1}H NMR (400 MHz; $CDCl_3$) *δ*: 7.76 (dd, *J* = 1.2, 7.8 Hz, 2H), 7.70 (dd, *J* = 1.2, 7.8 Hz, 2H), 7.44-7.26 (m, 26H), 4.97 (d, *J* = 11.2 Hz, 1H, $PhCH_2$), 4.90 (d, *J* = 8.4 Hz, 1H, TrocNH), 4.84-4.70 (m, 5H, H-1', 4 $PhCH_2$), 4.63 (d, *J* = 11.6 Hz, 1H, $PhCH_2$), 4.63 (d, *J* = 11.6 Hz, 1H, $PhCH_2$), 4.58 (d, *J* = 8.0 Hz, 1H, H-1), 4.51 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.45 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.30 (d, *J* = 11.2 Hz, 1H, $PhCH_2$), 4.15-4.07 (m, 1H, H-5'), 4.05 (dd, *J* = 3.4 Hz, 1H, H-2'), 3.94 (dd, *J* = 2.80, 10.0 Hz, H-3'), 3.67-3.59 (m, 4H, H-2, H-6_a, H-6_b, H-4'), 3.52 (t, *J* = 9.0 Hz, 1H, H-4), 3.25 (t, *J* = 8.4 Hz, 1H, H-5), 3.12 (dt, *J* = 3.6,10.0 Hz, 1H, H-3), 1.14 (d, *J* = 6.4 Hz, 3H, Fuc CH_3-6'), 1.10 (s, 9H, ^{t}Bu); ^{13}C NMR (100.5 Hz, $CDCl_3$) *δ*: 154.1, 138.7, 138.5, 138.4, 136.1, 136.0, 133.2, 132.9, 129.9, 129.7, 128.5, 128.4, 128.3, 127.9, 127.7, 127.6, 127.4, 98.9 (C-1'), 95.8 (C-1), 95.4 (Troc-CCl_3), 84.8, 78.9 (C-3'), 77.6, 76.4 (C), 74.9 (C-4'), 73.8 (C-2'), 73.5 (C-3), 73.4, 69.9 (C-4), 69.2 (C-5'), 68.1 (C-6), 58.1 (C-6), 26.8 (^{t}Bu-CH_3), 19.2 (Fuc CH_3-6'), 16.6 (^{t}Bu-C); HR-MALDI-ToF/MS m/z calcd for $C_{59}H_{66}Cl_3NNaO_{11}Si$ $[M + Na]^+$ 1120.3368, found 1120.3359.

***tert*-Butyldiphenylsilyl methyl-5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranosylonate-(2→3)-2,6-di-*O*-acetyl-6-*O*-benzyl-β-D-galactothiopyranosyl-β-(1→4)[2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl-α-(1→3)]-6-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonyl-amino)-β-D-glucopyranoside (17)**

Disaccharide **9** (720 mg, 0.78 mmol), disaccharide **16** (1.05 gm, 0.96 mmol), and freshly activated 4 Å molecular sieves (800 mg) were stirred in freshly distilled CH_2Cl_2 (15 mL) for 1 h at room temperature. The reaction mixture was cooled to -40°C before adding NIS (511 mg, 1.8 mmol) and TfOH (8.9 µL, 0.1 mmol). Upon consumption of the donor, as determined by TLC, the reaction mixture was quenched with diisopropylethylamine (2 mL). The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and filtered through Celite. The filtrate was successively washed with saturated aqueous solution of $Na_2S_2O_3$ (20 mL), $NaHCO_3$ (20 mL), brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by chromatography over silica gel using 50% EtOAc in hexanes to obtain sLe^X **17** as a white foam (1.23 gm 86%). $[\alpha]_D^{24}$ -22.5 (*c* = 1.0, $CHCl_3$), R_f 0.52 (hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 6.8 Hz, 2H), 7.60 (d, *J* = 6.4 Hz, 2H), 7.44-7.15 (m, 31H), 5.68 (dd, *J* = 2.0, 8.4 Hz, 1H, H-7'''), 5.56-5.52 (m, 1H, H-8'''), 5.27 (dd, *J* = 2.6, 7.8 Hz, 1H, NHTroc), 5.23 (d, *J* = 3.6 Hz, 1H, H-1'), 5.03 (d, *J* = 3.2 Hz, 1H, H-4''), 4.95 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.92 (d, *J* = 10.4 Hz, 1H, $PhCH_2$), 4.87 (d, *J* = 10.8 Hz, 1H, H-1), 4.76 (d, *J* = 8.4 Hz, 1H, H-1''), 4.79 (d, *J* = 11.6 Hz, 1H, $PhCH_2$), 4.72 (d, *J* = 11.6 Hz, 1H, $PhCH_2$), 4.68-4.52 (m, 4H, $PhCH_2$), 4.49 (dd, *J* = 3.8, 6.6 Hz, 1H, H-3''), 4.39-4.25 (m, 5H, $PhCH_2$, H-9_a'''), 4.19 (dd, *J* = 2.0, 10.0 Hz, 1H, H-6'''), 4.09 (dd, *J* = 3.4, 10.2 Hz, 1H, H-2'), 4.04-3.91 (m, 5H, H-9_b''', h-4'''), 3.80 (s, 3H, CO_2Me), 3.76 (dd, *J* = 6.0, 7.2 Hz, 1H), 3.66 (dd, *J* = 3.4, 11.4 Hz, 1H), 3.61-3.53 (m, 3H, H-6_a, H-6_a'', H-5'''), 3.46 (dd, *J* = 5.2, 9.2 Hz, 1H), 3.42 (d, *J* = 11.2 Hz, 1H, H-6_b''), 3.39 (d, *J* = 11.6 Hz, 1H, H-6_b), 3.28 (t, *J* = 8.8 Hz, 1H), 3.06 (d, *J* = 8.0 Hz, 1H, H-3'), 2.85 (dd, *J* = 3.4, 11.8 Hz, 1H, H-3_e'''), 2.45 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H), 1.93 (s, 3H), 1.84 (t, *J* = 12.4 Hz, 1H, H-3_a'''), 1.83 (s, 3H), 1.19 (d, *J* = 6.4 Hz, 3H, Me-5'), 1.03 (s, 9H, ^{t}Bu); ^{13}C NMR (100.5 Hz, $CDCl_3$) δ: 171.4, 170.5, 170.2, 169.6, 169.2, 169.0, 167.1, 153.5, 139.0, 138.7, 138.6, 138.5, 137.8, 135.9, 135.8, 133.5, 132.9, 129.7, 129.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.5, 127.4, 127.3, 127.1, 127.0, 126.9, 99.3 (C-1''), 97.7 (C-2'''), 97.1 (C-1'), 95.2 (C-1), 94.8 (CCl_3), 79.8, 77.9 (C-3'), 75.9 (C-2'), 75.3 (C-6'''), 74.7, 74.4, 74.3, 74.1, 73.5, 73.2 (C-7'''), 73.1, 73.0,

72.2, 71.8, 71.4, 70.3, 68.2 (C-8'''), 68.0, 67.9, 67.3 (C-4''), 66.4, 62.5 (C-9'''), 61.1, 59.1 (C-2), 53.4 (C-1'''$OOCH_3$), 35.9 (C-3'''), 29.5, 28.4, 24.5, 21.3, 20.9, 20.8, 20.7, 20.6, 19.1 (^{t}Bu), 16.7 (Me-5'); HR-MALDI-TOF/MS m/z calcd for $C_{95}H_{109}Cl_3N_2NaO_{30}Si$ $[M + Na]^+$ 1913.5798, found 1913.5811.

Methyl-5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranosylonate-(2→3)-2,6-di-*O*-acetyl-6-*O*-benzyl-β-D-galactothiopyranosyl-β-(1→4)[2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl-α-(1→3)]-6-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonyl-amino)-β-D-glucopyranoside-1-trichloroacetimidiate (18)

sLe^X tetrasaccharide **17** (1.2 gm, 0.63 mmol) was dissolved in THF (50 mL) and was cooled to 0°C. TBAF solution in THF (1N, 660 µL, 0.66 mmol) and acetic acid (25 µL) were added and stirred for 48 h at room temperature. Upon completion of the starting material, as determined by TLC, the solvent was removed *in vacuo,* and the crude reaction mixture was filtered through silica gel using EtOAc. The filtrate was concentrated and dried overnight *in vacuo*. The solid residue was dissolved in CH_2Cl_2 (12 mL) and cooled to 0°C. Trichloroacetonitrile (660 µL, 3.3 mmol) and DBU (48 µL, 0.3 mmol) were added dropwise to the reaction mixture and stirred for 1 h at room temperature. Upon completion of the reaction, the solvent was removed at 10°C and the crude was purified by column chromatography over silica gel using 40% EtOAc in hexanes. Product **18** was obtained as a white foam (729 mg 64%). $[\alpha]_D^{24}$ -65.1 (*c* = 1.0, $CHCl_3$), R_f 0.51 (hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.63 (d, *J* = 2.0 Hz, 1H, CCl_3C=NH), 7.37-7.26 (m, 20H), 7.24-7.20 (m, 5H), 6.67 (d, *J* = 6.4 Hz, 1H), 6.56 (s, 1H), 5.72 (dd, *J* = 2.0, 9.2 Hz, 1H), 5.63 (dd, *J* = 5.2, 8.8 Hz, 1H), 5.30 (s, 1H), 5.02 (d, *J* = 11.2 Hz, 1H), 5.00 (d, *J* = 9.6 Hz, 1H), 4.91 (d, *J* = 12.0 Hz, 1H), 4.90 (d, *J* = 12.0 Hz, 1H), 4.86 (d, *J* = 10.0 Hz, 1H), 4.83 (d, *J* = 8.8 Hz, 1H), 4.82 (d, *J* = 9.0 Hz, 1H), 4.67 (d, *J* = 5.2 Hz, 1H), 4.64 (d, *J* = 95.2 Hz, 1H), 4.50 (dd, *J* = 1.6, 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.49

(dt, *J* = 1.6, 10.0 Hz, 1H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.37(t, *J* = 11.2 Hz, 1H), 4.35 (d, *J* = 12.8 Hz, 1H), 4.28 (d, *J* = 11.6 Hz, 1H), 4.24-4.14 (m, 3H), 4.12-3.95 (m, 5H), 3.92-3.85 (m, 3H), 3.82 (s, 1H), 3.81 (s, 3H, COOMe), 3.76 (d, *J* = 6.4 Hz, 1H), 3.61-3.56 (m, 2H), 3.46 (dd, *J* = 5.0, 9.4 Hz, 1H), 3.33 (t, *J* = 8.8 Hz, 1H), 2.88 (dd, *J* = 3.0, 11.8 Hz, 1H, H-3_e'''), 2.46 (s, 3H), 2.12 (s, 3H), 2.09 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.94 (s, 3H), 1.86 (t, *J* = 12.4 Hz, 1H, H-3_a'''), 1.15 (d, *J* = 6.4 Hz, 3H, Me-5'); ^{13}C NMR (100.5 Hz, $CDCl_3$) *δ*: 171.4, 170.5, 170.3, 169.9, 169.2, 169.1, 160.1, 154.4, 153.5, 138.8, 138.7, 138.4, 138.0, 137.8, 128.5, 128.4, 128.4, 128.2, 128.1, 128.0, 127.7, 127.5, 127.4, 127.3, 127.2, 127.1, 99.6, 98.6, 97.7, 95.5, 94.3, 91.1, 79.6, 77.9, 75.9, 74.8, 74.6, 74.5, 74.2, 74.1, 73.9, 73.3, 73.1, 73.0, 72.3, 71.8, 71.7, 70.6, 68.1, 68.0, 67.9, 67.3, 67.3, 62.7, 59.1, 55.0, 53.4 (C-1'''$OOCH_3$), 35.9, 24.5, 21.3, 21.0, 20.9, 20.8, 20.7, 16.7 (CH_3-5'); HR-MALDI-TOF/MS m/z calcd for $C_{79}H_{91}Cl_3N_2NaO_{30}$ $[(M - C_2Cl_3N) + Na]^+$ 1675.4620, found 1675.4663.

Methyl-5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranosylonate-(2→3)-2,6-di-*O*-acetyl-6-*O*-benzyl-β-D-galactothiopyranosyl-β-(1→4)[2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl-α-(1→3)]-6-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonyl-amino)-β-D-1-thio-glucopyranoside (19)

sLe^X imidate **18** (718 mg, 0.4 mmol), thiophenol (82 µL, 0.8 mmol), and 4 Å molecular sieves (900 mg) were dissolved in CH_2Cl_2 (20 mL) and stirred for 1 h at room temperature before cooling to -78°C. TMS-OTf (14.4 µL, 0.08 mmol) was added slowly and the reaction mixture was warmed to -50°C and stirred for 1 h. The reaction was then quenched by the addition of triethylamine (1 mL) and warmed to room temperature. The mixture was then diluted with CH_2Cl_2 (50 mL) and filtered through a pad of Celite. The filtrate was successively washed with saturated aqueous solution of $NaHCO_3$ (20 mL), brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography over silica gel using 40% EtOAc in hexanes to obtain **19** as a white foam (572 mg 82%). $[\alpha]_D^{24}$ -68.8 (*c* = 1.0,

$CHCl_3$), R_f 0.49 (hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (dd, *J* = 1.2, 7.2 Hz, 2H), 7.39 (dd, *J* = 1.2, 6.8 Hz, 2H), 7.35-7.27 (m, 18H), 7.24-7.17 (m, 8H), 5.68 (dd, *J* = 1.8, 8.6 Hz, 1H), 5.66 (dd, *J* = 2.4, 12.0 Hz, 1H), 5.62 (dd, *J* = 2.0, 8.0 Hz, 1H), 5.21 (d, *J* = 3.2 Hz, 1H), 5.09-5.03 (m, 2H), 4.99 (dd, *J* = 8.4, 9.6 Hz, 1H), 4.96 (d, *J* = 11.6 Hz, 1H), 4.82 (d, *J* = 10.8 Hz, 1H), 4.79 (d, *J* = 10.0 Hz, 1H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 12.4 Hz, 1H), 4.64 (d, *J* = 11.6 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.58 (d, *J* = 6.0 Hz, 1H), 4.56 (dd, *J* = 2.4, 10.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.43-4.35 (m, 3H), 4.29 (d, *J* = 12.0 Hz, 1H), 4.22 (dd, *J* = 2.2, 9.4 Hz, 1H), 4.16 (t, *J* = 7.8 Hz, 1H), 4.09 (dd, *J* = 3.4, 10.2 Hz, 1H), 4.03 (dd, *J* = 6.0, 12.0 Hz, 1H), 3.97 (t, *J* = 8.0 Hz, 1H), 3.93 (dd, *J* = 3.2, 12.4 Hz, 1H), 3.89 (dd, *J* = 2.6, 11.8 Hz, 1H), 3.87-3.82 (m, 3H), 3.82 (s, 3H), 3.80 (t, *J* = 7.0 Hz, 1H), 3.66-3.60 (m, 2H), 3.57 (br s, 1H), 3.47 (dd, J = 5.4, 9.4 Hz, 1H), 3.30 (t, J = 8.8 Hz, 1H), 2.90 (dd, J = 3.0, 7.8 Hz, 1H), 2.46 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.89 (s, 3H), 1.86 (t, J = 11.8 Hz, 1H), 1.18 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100.5 Hz, $CDCl_3$) δ: 171.5, 170.5, 170.4, 169.7, 169.4, 169.3, 167.2, 153.7, 153.5, 138.5, 138.7, 138.5, 138.4, 137.8, 132.5, 128.8, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 99.4, 97.7, 97.5, 95.5, 84.7 (C-1), 79.9, 79.3, 77.5, 75.9, 74.5, 74.4, 74.3, 74.0, 73.9, 73.2, 73.1, 73.0, 72.9, 72.0, 71.4, 68.8, 68.2, 67.9, 67.2, 66.7, 62.8, 59.1, 56.9, 53.4 (C-1'''$OOCH_3$), 35.9, 24.6, 21.4, 20.9, 20.7, 20.6, 16.7; HR-MALDI-TOF/MS m/z calcd for $C_{85}H_{95}Cl_3N_2NaO_{29}S$ $[M + Na]^+$ 1767.4704, found 1767.4704.

N^{α}-(Fluoren-9-ylmethoxycarbonyl)-*O*-(Methyl-5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranosylonate-(2→3)-O-(2,4-di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-*O*-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)-6-*O*-benzyl-2-deoxy-1-thio-2-(2,2,2-trichloroethoxycarbonyl-amino)-β-D-glucopyranosyl]-(1→6)-[(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→3)-*O*-2-azido-2-deoxy-α-D-galactopyranosyl]-L-threonine *tert*-butyl ester (1)

Method A: sLe^X thioglycoside **19** (523 mg, 0.30 mmol), Core-1 diol **20** (373 mg, 0.41 mmol), and freshly activated 4 Å molecular sieves (600 mg) were stirred in freshly distilled CH_2Cl_2 (8 mL) for 1 h at room temperature. The reaction mixture was cooled to -60°C before adding BSP (79 mg, 0.37 mmol) and Tf_2O (57 µL, 0.33 mmol). Upon consumption of the donor, as determined by TLC, the reaction mixture was quenched with diisopropylethylamine (2 mL). The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and filtered through a pad of Celite. The filtrate was successively washed with saturated aqueous solution of $NaHCO_3$ (20 mL), brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography over silica gel with 60% EtOAc in hexanes to obtain hexasaccharide **1** as a white foam (619 mg, 81%).

Method B: sLe^X thioglycoside **19** (506 mg, 0.29 mmol), Core-1 diol **20** (365 mg, 0.40 mmol), and freshly activated 4 Å molecular sieves (400 mg) were stirred in freshly distilled CH_2Cl_2 (8 mL) for 1 h at room temperature. The reaction mixture was cooled to -40°C before adding NIS (137 mg, 0.61 mmol) and TfOH (4.4 µL, 0.05 mmol). Upon consumption of the donor, as determined by TLC, the reaction mixture was quenched with diisopropylethylamine (2 mL). The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and filtered through a pad of Celite. The filtrate was successively washed with saturated aqueous solution of $Na_2S_2O_3$ (20 mL), $NaHCO_3$ (20 mL), brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography over silica gel, eluting with 60% EtOAc in hexanes to

obtain hexasaccharide **1** as a white foam (621 mg 84%). $[\alpha]_D^{24}$ -12.7 (*c* = 1.0, $CHCl_3$), R_f 0.36 (hexane/EtOAc, 1:4) ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 7.79 (d, *J* = 7.4 Hz, 2H, Fmoc H), 7.66 (d, *J* = 7.2 Hz, 2H, Fmoc H), 7.45-7.38 (m, 4H, Fmoc H), 7.35--7.20 (m, 25H, 5 Bn), 5.72 (d, *J* = 7.8 Hz, 1H, NHTroc), 5.69 (dd, *J* = 2.0, 8.8 Hz, 1H, H-7''''), 5.67 (d, *J* = 10.4 Hz, 1H, FmocNH), 5.64-5.61 (m, 1H, H-8''''), 5.40 (d, *J* = 3.2 Hz, 1H, H-4'), 5.31 (dd, *J* = 8.2, 10.4 Hz, 1H, H-2'), 5.24 (br s, 1H, H-1'''), 5.08-4.92 (m, 5H, H-1, H-2, H-3', H-4'''', $PhCH_2$), 4.82 (d, *J* = 10.2, 1H, H-1''), 4.80 (d, *J* = 7.8 Hz, 1H, H-1''''), 4.79 (d, *J* = 12.6 Hz, 1H, $PhCH_2$) 4.85-4.77 (m, 3H, H-1', H-1'', $PhCH_2$), 4.76-4.60 (m, 10H, H-3'''', H-1'''', 4$PhCH_2$), 4.53 (dd, *J* = 3.2, 9.8 Hz, 1H, H-6a), 4.50 (dd, *J* = 3.4, 5.2 Hz, 1H), 4.48 (br s, 1H), 4.42 (d, *J* = 12.2 Hz, 1H, FmocCH_2), 4.42-4.26 (m, 7H, TrocCH_2,Thr H-2, H-6, TrocCH_2, Thr H-1, FmocCH), 4.22 (dd, *J* = 2.2, 9.5 Hz, 1H, H-6''''), 4.14 (d, *J* = 7.4 Hz, 1H), 4.12 (d, *J* = 5.4 Hz, 1H), 4.11-4.09 (m, 2H), 4.07 (dd, *J* = 6.0, 10.8 Hz, 1H), 4.05-3.87 (m, 8H), 3.83 (s, 3H), 3.82-3.72 (m, 4H, CH_3-1'''', H-6a), 3.69-3.64 (m, 1H), 3.61 (t, *J* = 10.6 Hz, 1H), 3.60 (s, 1H), 3.50 (dd, *J* = 4.4, 9.7 Hz, 1H), 3.42-3.35 (m, 1H), 3.32 (t, *J* = 8.8 Hz, 1H), 2.90 (dd, *J* = 3.5, 11.8 Hz, 1H, H-3$_e$''''), 2.48 (s, 3H), 2.19 (s, 3H), 2.16 (s, 3H), 2.13 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.90 (s, 3H), 1.88 (t, *J* = 12.0 Hz, 1H, H-3$_a$), 1.53 (s, 9H, ^{t}Bu), 1.29 (d, *J* = 6.4 Hz, 3H, Thr-CH_3), 1.20 (d, *J* = 6.4 Hz, 3H, CH_3-5'''); ^{13}C NMR (150.5 Hz, $CDCl_3$) *δ*: 171.6, 170.6, 170.5, 170.3, 170.2, 169.8, 169.7, 169.6, 169.4, 169.2, 169.2, 156.9, 153.7, 153.5, 143,9, 143.8, 141.3, 138.7, 138.6, 138.3, 137.7, 128.5, 128.3, 128.2, 127.8, 127.7, 127.6, 127.4, 127.1, 127.1, 125.3, 120.0, 100.6 (C-1''''), 100.2, (C-1'), 100.1 (C-1''), 99.5 (C-1), 97.6 (C-1'''), 97.3 (C-2''''), 95.6 (Troc-CCl_3), 83.0, 80.0 (C-6''''), 77.5, 76.4 (C-5''''), 75.9, 75.2 (C-9''''), 74.6 (C-3''), 74.3 (C-5''), 73.8 (C-5'), 73.1 (C-7''''), 73.0, 72.9, 72.0, 71.8, 71.3 (C-3'), 71.0 (C-3''''), 70.8, 70.3, 69.1 (C-6), 68.8, 68.2 (C-2''''), 67.9, 67.7 (C-8''''), 67.4 (C-6'), 67.1 (C-6''''), 66.8 (C-6''), 62.8, 61.2, 59.3 (C-5''''), 59.0 (C-2), 58.4 (C-2''), 53.5 (C-1''''), 47.1 (FmocCH), 35.9 (C-3''''), 29.7, 28.1, 24.7, 22.8, 21.4,21.1, 21.0, 20.8, 20.7, 19.2 (Thr-CH_3), 16.8 (C-6'''); HR-MALDI-TOF/MS m/z calcd for $C_{122}H_{143}Cl_3N_6NaO_{47}$ $[M + Na]^+$ 2571.7947, found 2571.7983.

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Supporting Information Available

Copies of ^{1}H, ^{13}C, and 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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