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Integrating ReSET with Glycosyl Iodide Glycosylation in Step-Economy Syntheses of Tumor-Associated Carbohydrate Antigens and Immunogenic Glycolipids  
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*Supporting Information

ABSTRACT: Carbohydrates mediate a wide range of biological processes, and understanding these events and how they might be influenced is a complex undertaking that requires access to pure glycoconjugates. The isolation of sufficient quantities of carbohydrates and glycolipids from biological samples remains a significant challenge that has redirected efforts toward chemical synthesis. However, progress toward complex glycoconjugate total synthesis has been slowed by the need for multiple protection and deprotection steps owing to the large number of similarly reactive hydroxyls in carbohydrates. Two methodologies, regioselective silyl exchange technology (ReSET) and glycosyl iodide glycosylation have now been integrated to streamline the synthesis of the globo series trisaccharides (globotriaose and isoglobotriaose) and α-Lactosylceramide (α-LacCer). These glycoconjugates include tumor-associated carbohydrate antigens (TACAs) and immunostimulatory glycolipids that hold promise as immunotherapeutics. Beyond the utility of the step-economy syntheses afforded by this synthetic platform, the studies also reveal a unique electronic interplay between acetate and silyl ether protecting groups. Incorporation of acetates proximal to silyl ethers attenuates their reactivity while reducing undesirable side reactions. This phenomenon can be used to fine-tune the reactivity of silylated/acyetylated sugar building blocks.

INTRODUCTION

For the past five decades, cancer has been one of the top 10 causes of death in the United States, and the incidence rate is gradually increasing.1,2 Cancer treatments and therapeutics to eradicate the disease are being intensively investigated in an effort to improve quality of life for those who suffer. Carbohydrate-based vaccine development is one promising approach to this end.3−9 Cell membranes are decorated with carbohydrates in the form of glycolipids and glycoproteins with unique structures and aberrant glycosylation patterns that are correlated with tumor progression and metastases.10−14 Vaccines based on the carbohydrate epitopes of these glycoconjugates are promising therapeutic targets, as are the more recently discovered bacterial derived glycolipids that stimulate immune response. Limited access to sufficient quantities of these biomolecules is a discovery roadblock making practical synthesis of complex carbohydrates a top priority in a recent National Academy of Sciences publication on the future of glycoscience.15

One major class of mammalian glycosphingolipids (GSLs) is the globo series tumor-associated carbohydrate antigens (TACAs).3,4,10,14,16 Globotriaosyl ceramide (Gb3), isoglobotriaosyl ceramide (iGb3), Gb4, Gb5, and Globo H are the prominent members of this class (Figure 1). All of these biomolecules share a lactose core, which is diversified by galactosylation at either the 3′ or 4′ hydroxyls giving rise to iGb3 or Gb3, respectively. Gb3 in turn is the core structure shared by Globo H and Gb5. Given the centrality of the Gb3 core, its synthesis has been the focus of numerous investigations. Nicolaou and co-workers were the first to report the total synthesis of Gb3, and their approach remains one of the most efficient to date.17,18 A total of eleven steps from commercially available lactose were required to prepare a protected globotriaosyl that served as a donor for the ceramide aglycon. Seven of those steps were focused on orthogonally

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protecting lactose for \(4'-\)galactosylation. Similarly, all syntheses of globotriaosyl/iso- globotriaosyl that have engaged a lactosyl acceptor have required between 6 and 12 steps to prepare the disaccharide building block.\(^{16-29}\)

While \(\beta\)-linked ceramides are known TACAs, bacterial derived \(\alpha\)-linked analogues also stimulate an immune response and hold promise as vaccine adjuvants.\(^{30-33}\) Isolating these glycolipids from their natural environments is a challenging process that can lead to decomposition or even rearrangement of the molecules of interest.\(^{34}\) The lipid composition of the ceramide is also usually obtained as an inseparable and noncharacterizable mixture. For these reasons, chemical synthesis of \(\alpha\)-linked ceramides is the primary source of pure and homogeneous materials for immunological studies. To meet this need, our group developed one-pot syntheses of KRN7000, BbGL-II and \(\alpha\)-GalCer (Figure 2) and their glucosyl analogues,\(^{35,36}\) while the Wang\(^{37}\) and Savage\(^{24}\) groups have reported syntheses of \(\alpha\)-lactosylceramide, \(\alpha\)-Gb3 and \(\alpha\)-iGb3. These novel “sugar-capped” CD1d ligands for natural killer T (NKT) cells have been tested for their ability to stimulate cytokine release. The results established that the \(\alpha\)-linkage is required for immune response and that the oligosaccharide structures serve as immunomodulators. These findings and biological evaluations of TACAs clearly point to an emerging area of immunotherapeutic discovery based upon \(\alpha\) and \(\beta\)-linked ceramides, and access to sufficient quantities of these glycoconjugates is a critical need.

Recently, the concept of step-economy was introduced and has subsequently been advocated among synthetic chemists.\(^{38-41}\) Instead of the traditional linear synthesis or tour de force total synthesis, considerations of semisynthesis, diversity-oriented synthesis, function-oriented synthesis, and convergent synthesis can lead to high efficiencies in the production of drug leads. In applying this concept to glycoconjugate syntheses, eliminating the need for multiple protection/deprotection steps is an obvious starting point. Per-O-TMS protected monosaccharides have proven to be especially useful starting materials for step-economy protecting group manipulations.\(^{42-44}\) We have exploited these readily available compounds in a process coined regioselective silyl exchange technology (ReSET).\(^{45,46}\) In just two steps from free sugars, a wide range of partially acetylated/silylated carbohydrates can
be prepared and readily transformed to either the corresponding glycosyl donor or acceptor (Figure 3). The introduction of electron-withdrawing acetate groups to silyl sugars affords bifunctional modules that are more stable than their per-O-TMS counterparts, yet highly reactive in glycosylation reactions. The anomeric acetate can be converted into various leaving groups including halides, thioethers and acetimidates. Efforts reported herein have concentrated on integrating glycosyl iodide glycosylation with a tandem ReSET strategy to accomplish step-economy syntheses of globo series trisaccharides and α-lactosylceramide. The dual methodology platform expands the current organic synthesis toolbox and provides new insight into the electronic interplay of acetate and silyl ether functionalities and their influence upon chemical reactivity.

### RESULTS AND DISCUSSION

#### Tandem ReSET to Prepare Bifunctional Lactose Modules

ReSET begins with per-O-silylated sugars, which undergo selective exchange of silyl ethers for acetate protecting groups. The reactions are typically run in pyridine with excess acetic anhydride, and exchange is mediated by the addition of acetic acid. Regiocontrol is correlated with acetic acid stoichiometry and microwave reaction time. Typically, the reactions afford a mixture of products, all of which are useful in making a library of different analogues. For example, treating per-O-silylated lactose with 3.0 equiv of AcOH for 1.25 h leads to production of the di- and triacetylated compounds (1 and 2, Scheme 1) in 20 and 53% yields, respectively, whereas increasing the amount of acetic acid to 7 equiv forces the production of compound 4 having only one silyl ether at the 4′ position and per-O-Ac lactose (5) after 3.75 h. Since the lactosyl 3′ and 4′ positions are the major glycosylation sites for globo series antigens, we attempted to establish conditions for preparing the disilyl ether analogue (3), but that compound could not be directly obtained in ReSET reactions of per-O-silylated lactose under any of the conditions evaluated. Previous studies in our lab indicated that proximal acetate groups facilitate silyl exchange; thus, we reasoned that greater regiocontrol might be achieved using compounds 1 and 2 in a tandem process. To our delight, the reaction proceeded nicely to afford the desired analogues, 3 and 4, in 31 and 25% yields, respectively. With these partially acetylated building blocks (1–4) in hand, focus shifted to employing them as either glycosyl donors or acceptors in oligosaccharide and glycoconjugate syntheses.

**ReSET Products as Glycosyl Donors: α-Lactosylceramide Synthesis.** Previous attempts to form and utilize per-O-TMS-lactosyl iodide led to complex reaction mixtures due to glycosidic bond cleavage and silyl exchange. We later discovered that C-6 acetates protect glycosidic linkages from TMSI degradation. Consistent with these findings, we were able to cleanly and quantitatively generate the lactosyl iodide from both 1 and 2 (Scheme 2A). Synthetic ceramide (7) was selected as the acceptor in the glycosylation studies due to its biological relevance. Iodide 6 was reconstituted in dry benzene and cannulated into a mixture of 7, tetrabutylammonium iodide (TBAI) and diisopropylethylamine (DIPEA). After heating the reaction to 65 °C in anhydrous benzene overnight, the reaction mixture was concentrated and subjected to acidic methanolysis prior to per-O-acetylation for characterization purposes (Scheme 2B). A mixture of the per-O-acetylated isomers was isolated in 89% yield, and the ratio of primary adduct (8) to secondary adduct (9) was 1.5 to 1.0, respectively, as determined by anomeric proton integration values obtained by 1H NMR.

The in situ anomerization process promoted by TBAI resulted in the exclusive formation of α-linked glycocolides;
The synthesis of α-lactosylceramide has several salient features: (1) the glycosyl donor (6) can be prepared in three steps and 72% overall from free lactose; (2) the lactosyl iodide is reactive enough to couple with unprotected or partially protected ceramides, yet the inter-residue glycosidic bond is stable enough to survive glycosylation; (3) only the desired α-linkage is obtained in good yield; (4) only TMS ether and acetate protecting groups are utilized, allowing mild deprotection steps that are compatible with alkene and amide functionality in the ceramide component. This methodology nicely complements reactions of per-O-acetylated lactose, which afford the β-anomer due to neighboring group participation of the C-2 acetate.\textsuperscript{52}

ReSET Products As Acceptors: Globo Series Trisaccharide Syntheses. Having demonstrated glycosylation...
efficiency with partially acetylated silyl donors, we set our sights on exploiting these substrates as glycosyl acceptors. Chemical syntheses of the Globo series TACAs involve the construction of the crucial $\alpha$-1,3 and $\alpha$-1,4 glycosidic linkages. Yet a simple first order disconnection of globotriaose and isoglobotriaose at these linkages leads to 4′-OH acceptor 12, 3′,4′-di-OH acceptor 13, or 3′-OH acceptor 14 (Figure 4), which are all readily available from the tandem ReSET products 2, 3, and 4.

To reduce the glycosylation strategy to practice, compound 4 was treated with Dowex acidic resin in MeOH to give the 4′-OH acceptor 12 in 90% yield (Scheme 3A). The long reaction time (10 h) was consistent with earlier results in our lab indicating that the rate of protodesilylation is attenuated with increasing numbers of acetate protecting groups. In an attempt to shorten the reaction time, we initially subjected 4 to TBAF/AcOH, but the reaction led to unresolved trans-acetylation products. However, a report from Ikawa and co-workers encouraged us to explore the deprotection of silyl ethers using Pd-catalyzed hydrogenolysis. Much to our delight, after 30 min under 1 atm H$_2$, 4 was transformed to 4′-OH acceptor 12 in 91% yield. In a similar manner, either acidic methanolysis or Pd-catalyzed hydrogenolysis was applied to 3, leading to 3′,4′-di-OH compound 13 in 92 and 91% yields, respectively (Scheme 3B). To confirm the deprotection was the result of hydrogenolysis and not acidic catalysis, a control experiment without the introduction of H$_2$ gas was conducted. No reaction was observed after 2 h, indicating that H$_2$ gas is required for the Pd-catalyzed deprotection.

In order to prepare 3′-OH acceptor 14, we looked to the work of Lin and co-workers, who published a one-pot procedure to selectively acetylate at the 4-position of galactose via 3,4-orthoester formation followed by selective acidic hydrolysis. The procedure showed excellent results when applied to monosaccharides but not oligosaccharides, presumably because of solubility issues. An adapted version of the methodology was applied to ReSET products 2 and 3 (Scheme 4). Compound 2 was first subjected to Pd-catalyzed hydrogenolysis and then concentrated to dryness. The resulting residue was reacted with trimethyl orthoacetate in the presence of catalytic camphor sulfonic acid (CSA) to form the cyclic orthoester at the 3′ and 4′ positions. After peracetylation, the orthoester was selectively hydrolyzed affording the 3′-OH acceptor 14 in almost quantitative yield. The four-step procedure was carried out in less than 3 h, and only one flash column chromatography purification was needed to obtain the target molecule. The consecutive hydrogenolysis–orthoester formation–acidic hydrolysis protocol was also applied to di-O-TMS compound 3, leading to the same 3′-OH acceptor 14 in almost quantitative yield (Scheme 4).

With all the acceptors (12–14) in hand, we next examined the glycosylation reactions to form the globo series trisaccharides (Table 1). Wishing to achieve efficient $\alpha$-galactosidation of the 4′-OH acceptor 12, we first tried using per-O-TMS galactosyl iodide promoted by TBAI in situ anomerization, but the major product obtained was silylated acceptor. We previously observed similar trans-silylation complications, especially in cases where the acceptor is hindered or unreactive. However, the per-O-benzyl galactosyl iodide derived from anomeric acetate 15 was reactive when activated with AgOTf, and the presence of benzyl protecting groups conveniently allowed UV monitoring of the reaction progress. Importantly, only the desired $\alpha$-1,4 linkage was obtained, which simplified the purification (Table 1, entry 1). The same reaction conditions with 1.5 and 2.5 equiv of...
iodide were applied to the glycosylation reaction with acceptor 13 to examine the relative reactivity of the two hydroxyl groups. When 1.5 equiv of iodide was used, the desired protected isoglobotraose (17) was obtained, albeit in a lower yield of 44% (Table 1, entry 2). When 2.5 equiv of iodide was added, not only was 17 obtained in 26% yield, but also the digalactosylated product (18) was obtained in 31% yield (Table 1, entry 3).

To avoid over-galactosylation, the 3′-OH acceptor 14 was introduced. In this case, the desired product (19) was obtained in 58% yield (Table 1, entry 4). Side reactions, which we attributed to acyl migration, were also observed on the TLC plate. To minimize this possibility, an acid scavenger (tetramethylurea, TMU)60 was added to the AgOTf-promoted glycosylation (Table 1, entry 5). The neutralized glycosylation procedure required higher temperature and longer time to complete; however, the target molecule (19) was obtained in 75% yield, indicating that the side reactions could be suppressed by the addition of weak base.

Debenzylation of compound 16 followed by reacetylation led to per-O-Ac globotriaose 20 in 95% yield (Scheme 5). Storing the trisaccharide in the peracetylated form was desired to increase stability. Moreover, the 1H NMR signals of compound 20 were better resolved than the benzylated counterpart (16), making compound characterization and quality control more reliable. Acetate protecting groups are also preferred when generating the glycosyl iodide of the trisaccharides. When compound 16 was treated with TMSI, the reaction became messy and glycosidic bond cleavage products were observed in crude MS analyses; another example of electron donating protecting groups rendering the glycosidic linkage susceptible to cleavage. In contrast, peracetylated 20 readily transformed to the corresponding iodide (22) in situ, and subsequent reaction leads to β-linked glycoconjugates.

Global deprotection of 16 continued with Pd-catalyzed hydrogenolysis followed by deacetylation yielding globotriaose (21) in nearly quantitative yield (Scheme 5). The total synthesis of globotriaose required only four steps from free lactose to form the globotriaose scaffold, and two more consecutive protecting group manipulations (total six steps) to the natural product globotriaose (21).

In 1988, Nicolaou and co-workers published the first synthesis of Gb3, which is arguably the most efficient synthesis until now.17 The approach required seven steps to prepare a selectively protected 4′-OH acceptor, which was glycosylated with per-O-Bn galactosyl fluoride under the activation of AgCl4 and SnCl2. During the process, seven protecting groups (OAc,..
OBn, OBz, OPiv, SPh, F, and benzylidene) were utilized. In contrast, the simplified RESET/glycosyl iodide synthetic platform involves only three steps to prepare the 4′-OH glycosyl acceptor and arrives at the globotriaose scaffold in four steps. Moreover, the glycosyl iodides react under neutral conditions avoiding toxic tin reagents as the promoter for α-1,4 glycosylation.

Compounds 17 and 19 could be transformed to per-O-Ac isoglobotriaose (23) in 85% yield by hydrogenolysis and peracetylation (Scheme 6). In 2009, Castillon and co-workers published an efficient TBAI/AW-300 MS-promoted synthesis of iGb3 using per-O-Ac isoglobotriaose iodide and stannylceramide.61 The group purchased isoglobotriaose and peracetylated it prior to generating the iodide. In the total synthesis approach to iGb3 reported here, both 23 and the in situ generated iodide intercept the Castillon synthesis, providing a formal synthesis of iGb3.

Among the published syntheses of isoglobotriaose scaffold using 3′,4′-di-OH acceptors, galactosylation typically suffers from low yields and poor stereoselectivity. Moreover, the 3′,4′-di-OH acceptors require at least six or seven steps to prepare from free lactose. When using acetylated galactosyl bromide24 and trichloroacetimidate donors, the glycosylation yields ranged from 28 to 31% with inseparable α-1,3 and β-1,3 isomers. In order to eliminate side reactions and increase donor reactivity, both Ogawa25 and Schmidt27 have introduced O-benzyl-protected galactosyl thiomethyl and trichloroacetimidate donors. These reactive donors provided increased yields but did not prevent the formation of β-linked isomers. In contrast, O-benzyl protected galactosyl iodide (Table 1, entries 2 and 3) readily reacts with acceptors 12, 13, and 14 to afford the α-linked products exclusively and in yields ranging from 44 to 75%.

Selectively protected 3′-OH acceptors generally afford better yields than 3′,4′-di-OH acceptors, since there is no competition between the two hydroxyl groups. However, 6–8 steps were required in order to prepare the 3′-OH acceptors. The protecting group manipulations involved OAc, OBn, OPiv, OPMB, and SPh groups, and the preparation took days to complete.28,29 In comparison, the ReSET approach (Table 1, entry 4 and 5) required only three protecting groups (OBn, OAc, and OTMS) and 21 h to synthesize acceptor 14. The optimized glycosylation of compound 14 reached 75% yield when coupled with per-O-Bn galactosyl iodide.

**CONCLUSION**

The combined ReSET/glycosyl iodide glycosylation strategy provides a step-economy platform for glycoconjugate synthesis that centers on the conversion of per-O-TMS-lactose into selectively protected modules with differential reactivities.62 The orthogonally protected intermediates can be transformed into reactive glycosyl iodides in situ and coupled with...
unprotected or partially protected carbamides with high stereoselectivity in good yields. The marriage of these powerful platforms results in the exclusive formation of alpha-linked glycasures, which leads to increased efficiencies during the purification process. The bifunctional nature of these modules can be further exploited upon removal of the TMS groups yielding glycosyl acceptors ready for sugar chain elongation. When introduced into glycosylation reactions, the corresponding globo series tumor-associated carbohydrate antigens can be obtained in respectable yields. The TACA syntheses require only three protecting groups (OAc, OBn, and OTMS), which significantly reduces the number of protection/deprotection steps, not only in preparing the glycosyl acceptors, but also by direct activation of the anomeric acetyl or silyl ether to the glycosyl iodide. These combined features characterize a versatile synthetic platform for the rapid assembly of biologically relevant glycolipids.

Beyond the time and step efficiencies of these methodologies, a unique interplay between acetyl and silyl ether protecting groups is revealed. The acetyl protecting groups help suppress side reactions such as silyl migration and inter-residue glycosidic bond cleavage during TMSI-promoted iodide formation. Similarly, we find that proximal acetates significantly alter the reactivity of silyl ethers toward protodesilylation. This phenomenon is clearly evidenced in the acidic methanolysis of 4′-OTMS acetylated lactose (4), which took twice as long as analogue 3 having one less aceta, i.e., 3′,4-di-OTMS acetylated lactose. We attribute the reactivity attenuation to acetal electron withdrawing effects, which inductively reduce the basicity of the ether and acetal oxygen atoms. Exquisite control is afforded by acetate incorporation, as shown in the contrasting behavior of per-O-silylated lactose and 6,6′-di-O-Ac-per-O-silylactose (1) under the action of TMSI. Di- and trisaccharide substrates having no acetates undergo inter-residue glycosidic bond cleavage, whereas incorporation of only two acetate groups at the C-6 positions directs reactivity toward protodesilylation. These findings offer opportunities in systems removed from carbohydrate substrates where one could capitalize on the concept of attenuating ether reactivity by the inductive effects of proximal protecting groups.

**Experimental Section**

**Procedure for Tandem Regioselective Silyl Exchange (ReSET) of Per-O-TMS Lactose (Scheme 1).** In a 10 mL microwave reactor vessel with a dry stir bar, per-O-TMS lactose (500 mg, 0.54 mmol) was dissolved in anhydrous benzene (3 mL). The solvent was removed under rotary evaporation with argon backfilling. The azetropic distillation was repeated two additional times to dryness and 0.23 mmol: calculated on the basis of compound 2". The reaction was monitored by proton NMR until the corresponding glycosyl iodides. These combined features characterize a versatile synthetic platform for the rapid assembly of biologically relevant glycolipids.

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**General Procedure for α-Lactosylceramide Synthesis (Scheme 2).** In an oven-dried NMR tube, compound 2 (59 mg, 0.07 mmol) was added and dissolved in dry benzene-d4 (0.7 mL). After TMSI (12 μL, 0.08 mmol) was introduced to the reaction vessel, the reaction was kept and 0 °C and gradually warmed to rt over 4−5 h. The reaction was monitored by proton NMR until the corresponding iodide (6) formed in situ. Next, compound 6 was transferred to a 25 mL pear-shape bottle, azetroped with dry benzene (3 mL × 3) and dried under a high vacuum for 1 h to afford the iodide as a light yellow foam. Note: The iodide is highly reactive and moisture sensitive. Column chromatography or aqueous workup should be avoided.

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**Result:** The bifunctional nature of these modules significantly enhances during the reaction and purification conditions. The product consisted of inseparable α/β anomeric acetates and the major β-anomer is reported. TLC (EA/Hex = 40:60) Rf = 0.38; 1H NMR (800 MHz, CDCl3) δ 5.66 (d, J = 8.2 Hz, 1H, H-1), 5.21 (appt. t, J = 9.3 Hz, 1H, H-3), 5.06−5.00 (m, 2H, H-2, H-2′), 4.40 (dd, J = 12.0, 1.7 Hz, 1H, H-6a), 4.28 (d, J = 7.9 Hz, 1H, H-1′), 4.19−4.14 (m, 2H, H-6b, H-6′), 4.10 (dd, J = 11.0, 6.6 Hz, H-6′), 3.79 (appt. t, J = 9.3 Hz, 1H, H-4′), 3.77−3.72 (m, 2H, H-4′, H-5), 3.57 (appt. t, J = 6.6 Hz, 1H, H-5′), 3.53 (dd, J = 9.8, 2.7 Hz, 1H, H-3′), 2.11 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 0.12 (s, 9H), 0.11 (s, 9H); 13C NMR (200 MHz, CDCl3) δ 170.6, 170.5, 169.8, 169.7, 168.9, 168.9, 101.1, 91.6, 74.9, 73.6, 72.9, 72.6, 72.4, 71.6, 71.1, 70.5, 62.5, 62.1, 21.1, 20.84, 20.82, 20.7, 20.6, 0.4, 0.2; HRMS (ESI-ion trap) m/z calculated for [C29H41O12N2Si4 + NH4]+ 756.2925, found 756.2947.

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5.14 (dd, J = 10.4, 3.4 Hz, 1H, H-3''), 5.10 (dd, J = 9.5, 3.7 Hz, 1H, H- 2''), 5.05 (dd, J = 3.7 Hz, 1H, H-1'), 4.73 (dd, J = 10.4 Hz, 1H, H-6a, 4.63–4.58 (m, 1H, H-b''), 4.39 (dd, J = 7.8 Hz, 1H, H-1''), 4.22 (dd, J = 11.7, 6.4 Hz, 1H, H-b), 4.14 (dd, J = 11.1, 6.6 Hz, 1H, H-6'a), 4.11–4.05 (m, 2H, H-f, H-g), 3.77 (dd, J = 10.7, 5.2 Hz, 1H, H-a), 3.67 (appt. t, J = 9.5 Hz, 1H, H-f'), 3.50 (appt. t, J = 6.6 Hz, 1H, H-f'), 3.44 (dd, J = 8.0, 1.8 Hz, 1H, H-3a'), 2.02 (s, 3H, H-3b'), 2.00 (s, 3H, H-3c'), 1.95 (s, 3H), 1.87 (s, 3H), 1.74 (s, 3H), 1.69 (s, 3H), 1.66 (s, 3H), 1.55 (s, 3H), 1.35–1.26 (m, 52H, alkyl chain), 0.93–0.91 (m, 6H, terminal Me X & X'), 23C NMR (200 MHz, CDCl3) δ 172.3, 170.2, 170.1, 169.9, 169.8, 169.4, 169.2, 169.1, 137.3, 128.4, 128.3, 128.1, 128.1, 127.9, 126.1, 101.6, 96.7, 77.2, 73.1, 71.6, 71.5, 70.9, 70.7, 67.9, 67.4, 67.0, 62.6, 61.1, 51.3, 36.5, 32.8, 32.38, 32.37, 30.3, 30.28, 30.26, 30.25, 30.24, 30.19, 30.18, 30.0, 29.88, 29.87, 29.77, 29.72, 29.4, 26.1, 23.2, 20.9, 20.7, 20.6, 20.5, 20.4, 20.2, 20.1, 19.8, 14.4; HRMS (ESI-ion trap) m/z calculated for [C29H40NO12 + Na] + 1248.7228, found 1248.7277.

25S,3R,4E)-1-O-Acetyl-3-O-(α-L-octopyranosyl)-2-(N-octadecanoylamino)octadec-4-en-3,1-diol (10). Method A: To a 0.03 M solution of compound 3 (41 mg, 0.06 mmol) was added Dowex H+ resin (~80 mg) until the pH was 2–3. The suspension was allowed to stir at rt for 4.5 h until the starting material was completely consumed. Next, the Dowex acidic resin was removed via filtration, and the filtrate was concentrated to afford a viscous oil. The resulting residue was immediately purified by flash column chromatography (100% EA) to obtain compound 13 (34 mg, 18%) as a white foam.

To a 0.01 M solution of compound 3 (115 mg, 0.16 mmol) was added Pd(OH)2/C (20% Pd, 100 mg). The reaction mixture was allowed to stir under H2 gas (1 atm) for 0.5 h until the starting material was completely consumed. The Pd-catalyst was removed by a short plug of MeOH-packed Celite. The filtrate was concentrated to afford a viscous oil. The resulting residue was purified by flash column chromatography (100% EA) to obtain compound 13 (85 mg, 91%) as a white foam. The product consisted of inseparable α/β anomeric acetates, and the major β-anomer is reported: TLC (100% EA) Rf 0.36; 1H NMR (600 MHz, CDCl3) δ 5.67 (d, J = 8.8 Hz, 1H, H-1'), 5.23 (appt. t, J = 8.8 Hz, 1H, H-3'), 5.07 (appt. t, J = 8.8 Hz, 1H, H-2'), 4.81 (appt. t, J = 8.4 Hz, 1H, H-2'), 4.46 (d, J = 12.4 Hz, 1H, H-6a), 4.38–4.34 (m, 2H, H-1'–H-6b), 4.28–4.22 (m, 1H, H-6a), 4.22 (m, H, H-6b'), 3.84–3.77 (m, 3H, H-4, H-5, H-6'), 3.69–3.54 (m, 2H, H-3', H-5'), 2.13 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H), 2.06 (s, 2H), 2.03 (s, 2H); 13C NMR (150 MHz, CDCl3) δ 171.9, 171.0, 170.9, 169.8, 169.8, 169.6, 169.5, 106.9, 105.9, 105.8, 104.7, 75.6, 73.7, 72.9, 71.2, 70.4, 68.1, 62.1, 62.0, 59.8, 20.8, 20.7, 20.6; HRMS (ESI-ion trap) m/z calculated for [C14H23NO7 + NH3]+ 901.6314, found 901.6234.

25S,3R,4E)-3-O-Trimethylsilyl-2-(N-octadecanoylamino)octadec-4-en-1,3-diol (11). To a 0.01 M solution of compound 2 (70 mg, 0.08 mmol) was added Pd(OH)2/C (20% Pd, 50 mg). The reaction mixture was allowed to stir under H2 (1 atm) at rt for 0.5 h. Next, the reaction mixture was filtered through a MeOH-packed Celite pad to remove the Pd catalyst, and the filtrate was concentrated under reduced pressure. The resulting residue was then dissolved in dry acetonitrile (2 mL) and treated with trimethyl orthoacetate (32 µL, 0.25 mmol) and catalytic camphorsulfonic acid (~4 mg, 0.02 mmol). After 1 h, the reaction mixture was allowed to stand at rt for 1 h. Next, the reaction mixture was filtered through a MeOH-packed Celite pad to remove the Pd catalyst, and the filtrate was concentrated under reduced pressure. The resulting residue was then dissolved in dry acetonitrile (2 mL) and treated with Ac2O (50 µL, 0.50 mmol), NMe3 (105 µL, 0.75 mmol) and catalytic DMAP (~2 mg). After 0.5 h, the solvent was evaporated, and the dry residue was treated with 80% AcOH (at rt with vigorous stirring for another 0.5 h. The reaction mixture was then acetone and benzene to remove excess reagent. The resulting residue was purified using flash column chromatography (EA/Hex/MeOH = 3/1 to 4/1) to afford compound 14 (52 mg, 95%) as a white foam.

To a 0.01 M solution of compound 3 (65 mg, 0.088 mmol) was added Pd(OH)2/C (20% Pd, 60 mg). The reaction mixture was allowed to stir at rt for 0.5 h. The reaction mixture was filtered through a MeOH-packed Celite pad to remove the Pd catalyst, and the filtrate was concentrated under reduced pressure. The resulting residue was then dissolved in dry acetonitrile (2 mL) and treated with Ac2O (50 µL, 0.50 mmol), NMe3 (105 µL, 0.75 mmol) and catalytic DMAP (~2 mg). After 0.5 h, the solvent was evaporated, and the dry residue was treated with 80% AcOH (at rt with vigorous stirring for another 0.5 h. The reaction mixture was then acetone and benzene to remove excess reagent. The resulting residue was purified using flash column chromatography (EA/Hex/MeOH = 3/1 to 4/1) to afford compound 14 (52 mg, 95%) as a white foam. The reaction mixture was then acetone and benzene to remove excess reagent. The resulting residue was purified using flash column chromatography (EA/Hex/MeOH = 3/1 to 4/1) to afford compound 14 (52 mg, 95%) as a white foam.
mixture was allowed to stir under H2 (1 atm) at rt for 0.5 h. Next, the reaction mixture was filtered through a MeOH-packed Celite pad to remove the Pd catalyst, and the filtrate was concentrated under reduced pressure. The resulting residue was then dissolved in dry ACN (2 mL) and treated with trimethyl orthoacetate (35 μL, 0.26 mmol) and catalytic CSA (∼4 mg, 0.02 mmol). After 1 h, NEt3 (~0.1 mL) was added to quench the reaction, and the reaction mixture was concentrated under reduced pressure. The residue was then treated with 80% AcOH/MeOH at rt with vigorous stirring for another 0.5 h. The reaction mixture was then azeotroped with benzene to remove the excess reagents, and the resulting residue was purified using flash column chromatography (EA/Hex = 3/1 to 4/1) to afford compound 14 (57 mg, 98%) as a white foam. The product consisted of inseparable α/β anomeric acetates, and the major β-anomer is reported: TLC (EA/Hex = 1/1) Rf 0.28; 1H NMR (600 MHz, CDCl3) δ 5.68 (d, J = 8.4 Hz, 1H, H-1), 5.30 (d, J = 2.9 Hz, 1H, H-4′), 5.24 (appt. t, J = 9.3 Hz, 1H, H-3), 5.06 (dd, J = 9.3, 8.4 Hz, 1H, H-2), 4.85 (dd, J = 10.0, 7.9 Hz, 1H, H-2′), 4.47 (dd, J = 12.1, 1.8 Hz, 1H, H-6a), 4.42 (d, J = 7.9 Hz, 1H, H-1′), 4.20 (dd, J = 12.1, 4.9 Hz, 1H, H-6b), 4.15–4.04 (m, 2H, H-6-ab), 3.86–3.73 (m, 4H, H-4′, H-3, H-5′), 2.46 (d, J = 6.3 Hz, 1H, OH), 2.18 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H); 13C NMR (150 MHz, CDCl3) δ 171.2, 170.7, 170.5, 170.4, 169.7, 169.5, 100.6, 91.6, 75.7, 73.6, 73.1, 72.5, 71.8, 71.0, 70.4, 69.1, 61.9, 61.4, 20.8, 20.81, 20.75, 20.73, 20.67, 20.5; HRMS (ESI-ion trap) m/z calculated for [C26H36O18 +N H4]′ 654.2240, found 654.2289.

General Procedure for Constructing Globotriaose and Isoglobotriaose (Table 1). To a 0 °C CH2Cl2 solution of compound 15 (conc. 0.1–0.2 M, 2.5 equiv) was added TMSI (2.8 equiv) under argon and cooled to −78 °C. Following workup, the reaction mixture was then purified by flash column chromatography (EA/Hex = 50:50) to obtain 18 (37 mg, 36%) as a white amorphous foam and compound 18 (63 mg, 31%) as a colorless oil (Table 1, entry 3). The product consisted of inseparable α/β anomeric acetates, and the major β-anomer is reported: TLC (EA/Hex = 1/1) Rf 0.33; 1H NMR (800 MHz, CDCl3) δ 7.41–7.54 (m, 5H, ArH), 7.58–7.60, 7.60–7.62, 7.62–7.64 (m, 5H, ArH), 7.64–7.66 (d, J = 8.3 Hz, 1H, H-1), 7.24 (m, 20H, ArH), 5.65 (d, J = 50:50) to obtain compound 17 (30 mg, 75%) as a white amorphous foam (Table 1, entry 4). Compound 17 was isolated using column chromatography (EA/Hex = 3/1 to 4/1) to afford compound 17 (183 mg, 0.32 mmol) and TMSI (50 μL, 0.36 mmol) were used for galactosyl iodide formation. The CH2Cl2 solution (1.5 mL) of iodide was then cannulated to the CH2Cl2 solution (1.5 mL) of 3′,4′-di-O-acetyl acceptor 13 (75 mg, 0.13 mmol) under the presence of AgOTf (103 mg, 0.42 mmol) at −78 °C to −30 °C for 4 h with the presence of activated 4 Å molecular sieves (300 mg). After workup, the reaction mixture was then purified by flash column chromatography (EA/Hex = 50:50) to obtain 17 (183 mg, 75%) as a white amorphous foam and compound 18 (63 mg, 31%) as a colorless oil. Following the general procedure for constructing the isoglobotriaose scaffold, compound 15 (183 mg, 0.32 mmol) and TMSI (50 μL, 0.36 mmol) were used for galactosyl iodide formation. The CH2Cl2 solution (1.5 mL) of iodide was then cannulated to the CH2Cl2 solution (1.5 mL) of 3′,4′-di-O-acetyl acceptor 13 (75 mg, 0.13 mmol) under the presence of AgOTf (103 mg, 0.42 mmol) at −78 °C to −30 °C for 4 h with the presence of activated 4 Å molecular sieves (300 mg). After workup, the reaction mixture was then purified by flash column chromatography (EA/Hex = 50:50) to obtain 17 (183 mg, 75%) as a white amorphous foam (Table 1, entry 4). Compound 17 was isolated using column chromatography (EA/Hex = 3/1 to 4/1) to afford compound 17 (183 mg, 75%) as a white amorphous foam.
mmol) and TMSI (20 μL, 0.15 mmol) were used for galactosyl iodide formation. The CH₂Cl₂ solution (1.5 mL) of the forming iodide was then cannulated to the CH₂Cl₂ solution (1.5 mL) of 4-′OH acceptor (34 mg, 0.05 mmol) under the activation of AgOTf (42 mg, 0.16 mmol) at −30 °C to rt for 24 h with the presence of activated 4 Å molecular sieves (300 mg) and tetramethylethylene (TMU, 20 μL, 0.16 mmol). After workup, the reaction mixture was then purified by flash column chromatography (EA/Hex = 50/50) to obtain 19 (45 mg, 75%) as a white amorphous foam (Table 1, entry 5). The product consisted of inseparable α/β anomer and acid, and the major β-anomer is reported: TLC (EA/Hex = 120 Rf 0.40; 1H NMR (600 MHz, CDCl₃) δ 6.73–7.23 (m, 20H, ArH), 5.66 (d, J = 8.2, H₂-1, H₂-2, 1.90 (d, J = 11.4 Hz, H₁, PhCH₂) 4.71–4.67 (m, 2H, PhCH₂ x 2), 4.69–4.17 (m, 2H, PhCH₂, H₂-6a), and 3.31 (d, J = 7.9 Hz, H₁-1), 4.10 (dd, J = 12.0, 5.1 Hz, H₁-3, H₂-6b), 4.07–4.01 (m, 2H, H₂-6a), 3.98 (dd, J = 10.0, 3.4 Hz, H₂-1, H₂-2), 3.87–3.71 (m, 6H, H-4, H₃-3, H₄-4, H₅-5), 3.66 (appt. t, J = 6.7 Hz, H₁-1, H₁-5), 3.55–3.45 (m, 2H, H₂-6b), 2.09 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 1.92 (s, 3H), 1.81 (s, 3H); 13C NMR (150 MHz, CDCl₃) δ 170.4, 170.3, 170.2, 169.6, 169.5, 168.8, 168.7, 138.7, 138.6, 138.1, 138.0, 138.2, 128.5, 128.3, 128.1, 128.15, 128.13, 127.9, 127.7, 127.6, 127.5, 127.4, 100.9, 95.1, 91.6, 78.4, 75.7, 75.2, 75.1, 74.8, 73.6, 73.3, 73.2, 73.0, 72.6, 71.1, 70.5, 69.9, 68.8, 68.4, 61.8, 20.8, 20.8, 20.7, 20.68, 20.66, 20.59, 20.44; HRMS (ESI–ion trap) m/z calc for [C₁₄H₁₂O₅Na₄]⁺ 625.1140 (detected 625.1140) and 627.1143 (detected 627.1147).

To a MeOH solution of compound 16 (186 mg, 0.16 mmol) was added Pd(OH)₂/C (20% Pd, 63 mg) and molecular sieves (300 mg) and tetramethylurea (TMU, 20 mg) was added. The reaction mixture was stirred for 4 h. A white foam formed (Table 1, entry 6). The reaction mixture was then filtered through a plug of C18 reverse-phase silica gel and washed with acetone (0.1 mL) and lyophilized to a white foam (27 mg, 78%) as an amorphous foam (Table 1, entry 6). The product consisted of inseparable α/β anomer and acid, and the major β-anomer is reported: TLC (EA/Hex = 118 Rf 0.40; 1H NMR (600 MHz, CDCl₃) δ 6.29–7.23 (m, 20H, ArH), 5.49 (d, J = 11.0 Hz, H₁, PhCH₂), 4.90 (d, J = 11.4 Hz, H₁, PhCH₂) 4.71–4.67 (m, 2H, PhCH₂ x 2), 4.62–4.37 (m, 2H, PhCH₂, H₂-6a), and 3.41 (d, J = 7.9 Hz, H₁-1), 4.10 (dd, J = 12.0, 5.1 Hz, H₁-3, H₂-6b), 4.07–4.01 (m, 2H, H₂-6a), 3.98 (dd, J = 10.0, 3.4 Hz, H₂-1, H₂-2), 3.87–3.71 (m, 6H, H-4, H₃-3, H₄-4, H₅-5), 3.66 (appt. t, J = 6.7 Hz, H₁-1, H₁-5), 3.55–3.45 (m, 2H, H₂-6b), 2.09 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 1.92 (s, 3H), 1.81 (s, 3H); 13C NMR (150 MHz, CDCl₃) δ 170.4, 170.3, 170.2, 169.6, 169.5, 168.8, 168.7, 138.7, 138.6, 138.1, 138.0, 138.2, 128.5, 128.3, 128.1, 128.15, 128.13, 127.9, 127.7, 127.6, 127.5, 127.4, 100.9, 95.1, 91.6, 78.4, 75.7, 75.2, 75.1, 74.8, 73.6, 73.3, 73.2, 73.0, 72.6, 71.1, 70.5, 69.9, 68.8, 68.4, 61.8, 20.8, 20.8, 20.7, 20.68, 20.66, 20.59, 20.44; HRMS (ESI–ion trap) m/z calc for [C₁₄H₁₂O₅Na₄]⁺ 625.1140 (detected 625.1140) and 627.1143 (detected 627.1147).

Supporting Information General information and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.
The authors declare no competing financial interest.

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