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5-*N*,4-*O*-Carbonyl-7,8,9-tri-*O*-chloroacetyl-Protected Sialyl Donor for the Stereoselective Synthesis of α-(2→9)-Tetrasialic Acid

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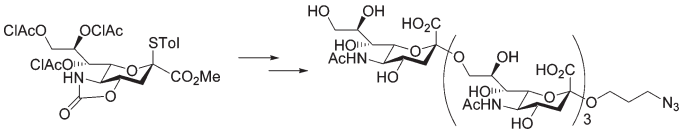

An efficient stereoselective synthesis of α-(2→9)-tetrasialic acid was achieved using tri-*O*-chloroacetyl-derivatized sialyl donor and a triol sialyl acceptor. Both the acceptor and the donor were also protected with a cyclic 5-*N*-4-*O*-carbonyl protecting group. The donor is highly reactive and enabled α-selective sialylation with various primary, secondary, and tertiary acceptors under in situ activation conditions (NIS/TfOH, −78 °C, acetonitrile/dichloromethane). The trans-fused oxazolidinone ring and *O*-chloroacetyl protecting groups were easily removed under mild reaction conditions to provide the fully deprotected α(2→9)-tetrasialic acid.

Introduction

Sialic acid is the generic term for *N*- or *O*-substituted derivatives of neuraminic acid, which is the most complex nine-carbon carboxylated monosaccharide. The sialic acids possess diverse substitution patterns and are typically found at the nonreducing terminus of *N*- and *O*-glycoproteins and glycosphingolipids.[1,2] Due to their domination at the termini of glycoproteins and glycolipids, sialic acids act either as masks or recognition sites for the ligand−receptor and cell−cell recognitions in many important biological events.[1−3] Recent studies in glycobiology revealed that linear homopolymers of sialic acids are linked either internally via contiguous α-(2→8) and α-(2→9) linkages, respectively, or via alternating α-(2→8) and α-(2→9) linkages. These polysialic acids were observed as capsular polysaccharides on the surface of bacteria such as *Escherichia coli* K1 and K92 and *Neisseria meningitides* Gps B and C. They function as virulence factors and have the potential to be used as antigens in antibacterial vaccines.[4,5] More than two decades ago, an α-linked (2→9)-disialic acid unit was found to be attached to lactosaminoglycan in human teratocarcinoma cells (PA1),[6] but only recently, the linear α-(2→9)-polysialic acids were found in C-1300 mouse neuroblastoma cells (NB41A3).[7] Additionally, a glycoprotein carrying α-(2→9)-polysialic acids has been identified in sea urchin sperm flagella.[8] The polysaccharides used in vaccines are typically isolated from their natural sources, and thus, they are sometimes heterogeneous and/or contaminated with other antigenic components. Therefore, a straightforward chemical synthesis for preparing pure oligosaccharides for carbohydrate-based vaccines would be of great value.

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One of the most difficult and challenging tasks in the synthesis of oligosialic acids is the formation of α-glycosidic bond during the coupling step with sialic acid. The presence of a destabilizing electron-withdrawing carboxyl group at the anomeric center and the lack of a participating auxiliary at the C-3 of sialyl donor often result in low to moderate yields of sialylation products with poor α-stereoselectivities. In addition, an undesirable *β*-elimination sometimes occurs, giving a glycal side product. Due to the interaction with the C5-NH group, the hydroxyl groups at the C8/C9 positions of the sialic acid have low reactivity toward sialylation, further impeding the synthesis of homo-oligosialic acids.[9] A variety of strategies have been developed to address these problems, and these strategies focus primarily on the anomeric leaving groups, the solvents, and the promoters.[10] The *N*-acetyl group at the C5 position of the sialyl donor has been replaced with *N*,*N*-diacetyl,[11a] 2,2,2-trichloroethoxycarbonyl (*N*-Troc),[11c,d] trifluoroacetyl (*N*-TFA),[11b] azido (N_3),[11e,f] *N*-Fmoc,[11g] *N*-phthalimide,[11h] and Boc[11i] groups, and these approaches have improved the reactivity and the α-selectivity of the sialylation reaction.[10e] Furthermore, 1,5-lactamized-sialyl acceptors have been developed as alternative strategies for enhancing the reactivity of the C8 hydroxyl groups toward glycosylation.[12]

Previously, we reported the development of C5 *N*-TFA-protected phosphite-based sialyl donors and demonstrated their α-selectivity in the sialylation reaction to achieve the synthesis of α-(2→9) pentasialic acid by iterative sialylation from the nonreducing end to the reducing end.[13] We also described a convergent [2 + 2] strategy for the construction of tetrasialoside by coupling a disialyl phosphite donor with a disialyl acceptor.[14] In the synthesis of oligosialic acids, these sialyl donors displayed higher reactivity compared to conventional donors and underwent an α-selective sialylation to form the glycosidic bond with improved yields. However, when the sugar chain is elongated, the α-selectivity in sialylation decreases. Thus, it remains a challenge in the synthesis of homo-oligosialic acid.

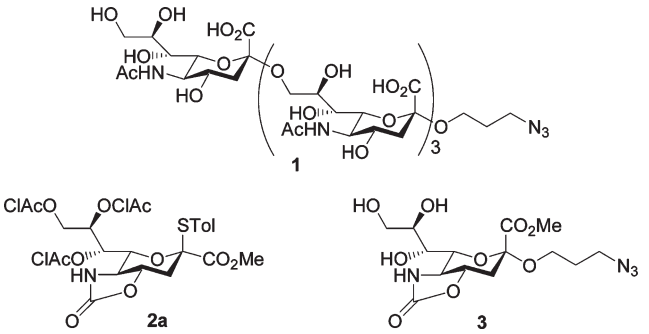

FIGURE 1. Structure of the α(2→9)-sialoside **1**, the 5-*N*,4-*O*-carbonyl-protected sialyl donor **2a**, and the acceptor **3**.

Another attractive approach involves the use of a nonparticipating oxazolidinone protecting group for thiosialosyl donors.[15−20] Reactions were performed in acetonitrile using NIS/TfOH as the promoter at −78 °C, and these donors showed improved reactivities and α-selectivities.[16b,17] Recently, Takahashi and co-workers used a 5-*N*,4-*O*-carbonyl-protected sialyl donor for the synthesis of α-(2→8)-[18] and α-(2→9)-tetrasialic[19] acids and obtained the sialylation products with exclusive α-selectivity, without the need for a participating solvent like acetonitrile. Similar results were also reported by Wong and co-workers in the synthesis of the protected α-(2→9)-tetrasialic[20] acids by using 5-*N*,4-*O*-carbonyl-protected phosphate-based sialyl donors. The influence of other protecting groups on the oxazolidinone-based sialyl donor, however, was not fully investigated. Herein, we describe the use of the 5-*N*,4-*O*-carbonyl-protected sialyl donor **2a** as an effective α-selective sialylation donor and its application on the stereoselective synthesis of α-(2→9)-tetrasialic acid **1** (Figure 1).

Results and Discussion

We envisaged that a 7,8,9-tri-*O*-chloroacetyl-derivatized sialyl donor **2a** and an acceptor **3** would be an ideal pair for improving the yield and the α-selectivity of the sialylation reaction. Both compounds are protected with a cyclic 5-*N*,4-*O*-carbonyl protection (Figure 1), and the strong electron-withdrawing nature of the chloroacetyl protecting groups is expected both to exert an influence upon the activation of the thioaryl leaving group and to enhance the solvent participation, forming the sialyl nitrilium intermediate.[21] Moreover, the reactivity of the primary hydroxyl group toward the sugar donor is higher than that of a secondary hydroxyl group. Thus, there is no need to protect the C7- and C8-OH during the glycosylation reaction between the C9-OH with the sugar donor.[13,14] In addition, the *O*-chloroacetyl groups can be introduced efficiently and can be removed selectively under mild reaction conditions (Et_3N in MeOH) in the presence of other acyl protecting groups.[22]

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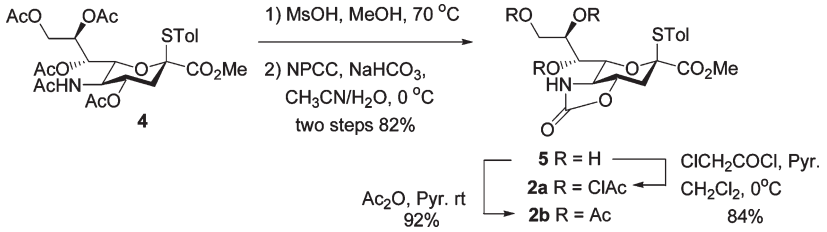
SCHEME 1. Preparation of the 5-*N*,4-*O*-Carbonyl-Protected Sialyl Donors 2a and 2b



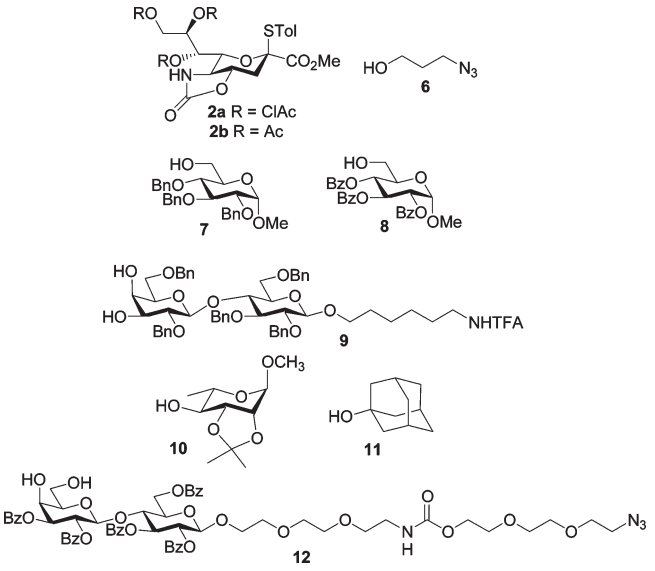
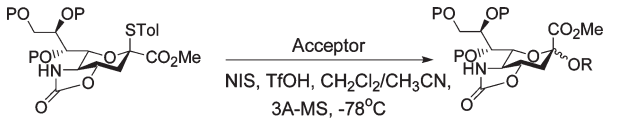


FIGURE 2. Structure of sialyl donors (**2a** and **2b**) and acceptors (**6**−**12**).

To probe the above-described assembly strategy, donor **2a** was prepared by a straightforward sequence starting from the known thioglycoside derivative **4**,[23] as shown in Scheme 1. The acetyl protecting groups in **4** were removed under acidic conditions (MsOH in MeOH), followed by selective protection of the C4-OH and the C5-NH_2 (4-nitrophenyl chloroformate (NPCC) and $NaHCO_3$ in CH_3CN/H_2O at 0 °C) to give the 5-*N*,4-*O*-carbonyl-protected derivative **5** in 82% yield over two steps. The remaining three hydroxyl groups on the exocyclic chain in **5** were *O*-acylated with $ClCH_2COCl$ to afford the fully protected donor **2a** in 84% yield. Its acetylated analogue **2b** was obtained from **5** by reaction with acetic anhydride in the presence of pyridine and was chosen as a reference compound for α-selectivity studies.

As shown in Figure 2, donors **2a** and **2b** were tested with regard to their α-selectivities in sialylation with various acceptors, ranging from simple alcohol to primary and secondary hydroxyl groups of sugar acceptors. The thiosialoside donors **2a** and **2b** were then coupled with 3-azido-1-propanol using NIS and a catalytic amount of TfOH as promoters (CH_2Cl_2/MeCN (2/1) at −78 °C)[16b] to give **13** and **14** in 85% and 83% yield with exclusive α-selectivity, respectively (Table 1, entries 1 and 2). Encouraged by these preliminary results, we then decided to study the influence of the protecting groups of the glycosyl acceptors. Thus, armed and disarmed acceptors

TABLE 1. Sialylations of Donors 2a and 2b with Acceptors 6−12[a]



entry	donor	acceptor	product	yield (%)	α/β
1	**2a**	**6**	**13**	85	α
2	**2b**	**6**	**14**	83	α
3	**2a**	**7**	**15**	93	α
4	**2a**	**8**	**16**	92	α
5	**2b**	**7**	**17**	95	α
6	**2b**	**8**	**18**	94	α
7	**2a**	**9**	**19**	75	10/1
8	**2b**	**9**	**20**	73	3/1
9	**2a**	**10**	**21**	80	1/1
10	**2a**	**11**	**22**	60	α
11	**2a**	**12**	**23**	75	α

[a]Tol = *p*-methylphenyl.

(compounds **7** and **8**) were examined under the above reaction conditions. Surprisingly, all the sialylations proceeded with high yields and stereoselectivities (entries 3−6). On the basis of the above observation, both donors provide similar yield and exclusive α-stereoselectivity when they are coupled with primary alcohols. To further evaluate the protecting group effect on glycosyl donor **2a** in the synthesis of α-(2→3) linkage, such as GM_3 antigen, acceptor **10** was prepared, and the α-selectivity of donor **2a** with **10** was significantly improved in comparison with the use of corresponding *O*-acetylated sialyl donor **2b** (entries 7 vs 8). Furthermore, when **2a** was coupled with secondary and tertiary hydroxyl groups (methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside **10** and 1-adamantanol **11**), the results also showed better α-selectivity (entries 9 and 10) than those using an acetyl protecting group of the *N*-acetyl- 5-*N*,7-*O*-oxazinanone sialyl donors.[16a,17] Sialylation of **2a** with lactosyl acceptor **12** afforded the trisaccharide **23** as a single α anomer (entry 11). It should be noted that the anomeric configurations of compounds **13**−**23** were assigned based on the chemical shifts of the H-3eq of sialic acid. The chemical shift of α-glycoside is more downfield than that of β-glycoside. The H-3eq chemical shifts of the synthesized α-anomers were located around δ 2.70−3.02 ppm, agreeing with the reported regions.[15,16] These model studies demonstrated that 7,8,9-tri-*O*-chloroacetyl-protected sialyl donor **2a** is a highly efficient and α-selective donor in sialylations.

The donor **2a** was then applied in the synthesis of oligosialic acid. We adopted a strategy in which the chain was elongated from the reducing end toward the nonreducing end. Removal of chloroacetyl protecting groups from **13** was accomplished with triethylamine (Et_3N) in MeOH and gave the triol acceptor **3** in 83% yield. With the triol acceptor **3** in

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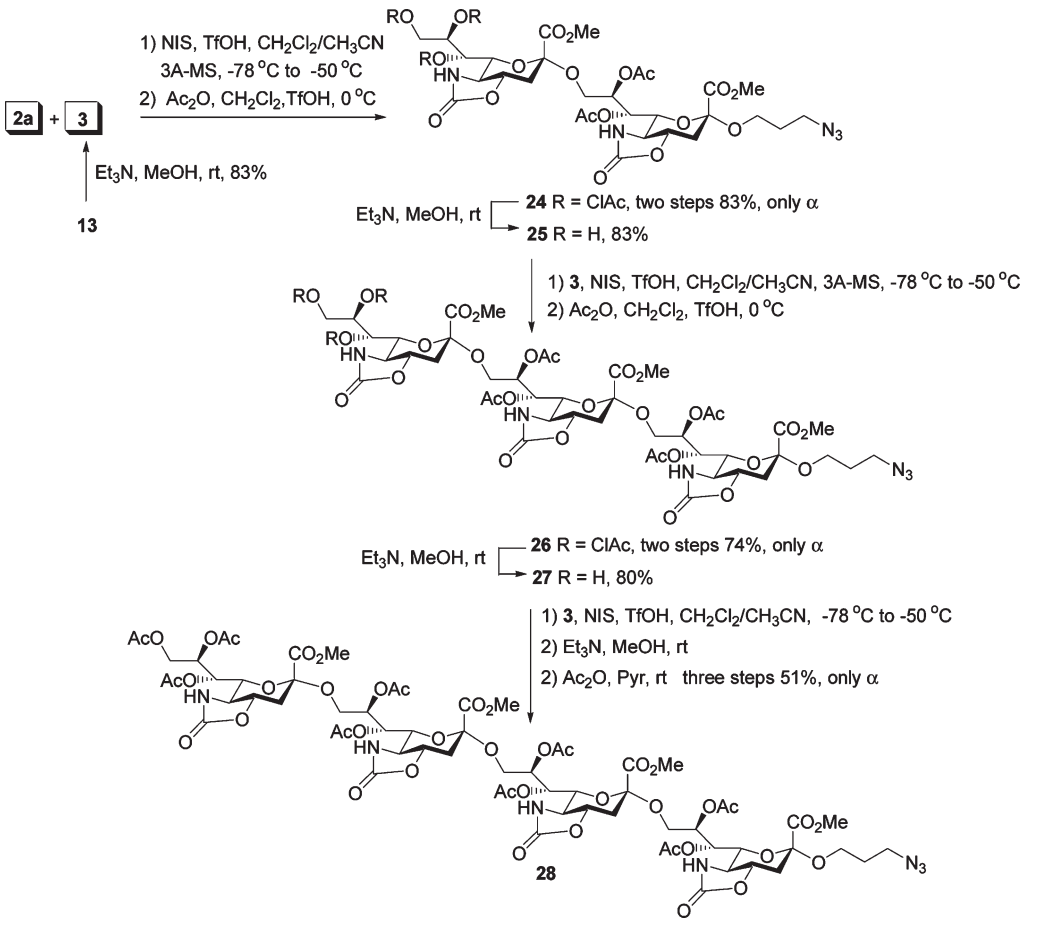
SCHEME 2. Synthesis of the Protected α-(2→9)-Linked Di-, Tri-, and Tetrasialic Acids 24, 26, and 28



hand, we then turned our attention to the synthesis of the α-(2→9) disialyl dimer (Scheme 2). Because the primary hydroxyl group is more reactive than the secondary hydroxyl group,[9,13,14] the (2→9) glycosidic bond was expected to be formed by the reaction between the donor **2a** and the acceptor **3**. Thus, coupling of the sialyl donor **2a** and the acceptor **3** using the in situ activation conditions (NIS/TfOH, CH_2Cl_2/MeCN (2/1), −78 °C followed by gradually warming to −50 °C) yielded the disialoside, which was acetylated to give the di-*O*-acetylated derivative **24** (83% yield over two steps). The long-range coupling constants of C1 with axial H3 ($^3J_{C\text{-}1,H\text{-}3ax}$) are 5.4 Hz ($\delta$ = 167.91 ppm) and 5.3 Hz (δ = 168.47 ppm), indicating that both anomeric centers of **24** are in the α-configuration.[14,24] These results further demonstrate that the donor **2a** exhibits good α-selectivity in the sialylation reaction with primary hydroxyl acceptors. To extend the sialic acid chain from the reducing end toward the nonreducing end, the *O*-chloroacetyl protecting groups of **24** were removed selectively with Et_3N to afford triol **25** (83%), which serves as an acceptor in the next sialylation reaction. Repeating the sialylation, acetylation, and dechloroacetylation reactions produced the higher order sialosides. This three-step sequence provided the tri- and tetrasialic acids in 74% and 51% yields, respectively. Because the chloroacetyl groups on the tetrasaccharide were unstable, these protecting groups were transformed to the more stable acetyl protecting groups. Extensive spectroscopic investigations were performed on the fully protected tetrasialoside **28** to identify the diagnostic α-linkages, which would thereby confirm the stereochemistry of the compound. The anomeric configurations of the resulting α-sialosides **26** and **28** were determined by analyzing the ^{1}H NMR spectra. The chemical shifts of the H-3eq (δ = 2.83−2.88) and H-4 (δ = 3.85−4.07) signals and the coupling constant $J_{7,8}$ (9.9−10.0 Hz) were in accordance with the empirical rules[24] for defining the anomeric configuration of 5-*N*,4-*O*-carbonyl-protected oligosialic acids. In addition, all of the H-3eq chemical shifts on fully protected derivatives **24**, **26**, and **28** and fully deprotected tetrasialic acid **1** are located at the position, 2.85 and 2.73 ppm, respectively. Interestingly, the chemical shifts of H-3eq on partially deprotected nonreducing end sialic acid of **3**, **25**, and **27** are more downfield (2.93 ppm) than those of fully protected sialic acids (2.85 ppm). Notably, the sialylation yield decreased gradually with increasing length of the sugar chain, but no β-anomeric product was obtained in any of the sialylation reactions.

Deprotection of the protected α-(2→9)-tetrasialoside **28** was then examined, as shown in Scheme 3. Upon exposure to

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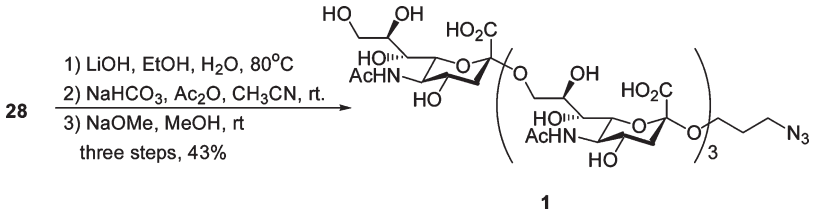
SCHEME 3. Synthesis of the Fully Deprotected α-(2→9)-Tetrasialic Acid 1



basic conditions (aqueous ethanolic lithium hydroxide) at 80 °C, both the 5-*N*,4-*O*-carbonyl-protecting groups and the ester groups were removed. The resulting amines were *N*-acetylated (Ac_2O, $NaHCO_3$), and then exposure to base under Zemplén conditions (NaOMe in MeOH) ensured complete removal of the partially regenerated *O*-acetyl groups. The fully deprotected α-(2→9)-tetrasialic acid **1** was obtained in 43% overall yield (three steps).

In conclusion, we have presented an efficient and highly α-selective method for the synthesis of α-(2→9)-tetrasialic acid using iterative dechloroacetylation, sialylation, and acetylation reactions. The 5-*N*,4-*O*-carbonyl-7,8,9-tri-*O*-chloroacetyl-protected sialyl donor **2a** was also demonstrated to be a highly reactive α-selective donor in sialylation reactions with various acceptors. Under in situ activation conditions (NIS/TfOH, −78 °C), the sialylation was complete within 1 h (based on TLC analysis).

Experimental Section

Methyl (4-Methylphenyl 5-amino-5-*N*,4-*O*-carbonyl-3,5-dideoxy-2-thio-D-*glycero*-β-D-*galacto*-non-2-ulopyranoside)onate (5). A stirred solution of compound **4** (8.5 g, 14.22 mmol) in MeOH (142 mL) was treated with methanesulfonic acid (2.43 mL, 42.67 mmol) at rt under N_2 and then was refluxed for 24 h. After being cooled to rt, the reaction mixture was quenched with an excess of Et_3N and then was concentrated under reduced pressure. The residue was dissolved in $MeCN/H_2O$ (1/2, 140 mL) in the presence of $NaHCO_3$ (5.97 g, 71.11 mmol), and the mixture was cooled to 0 °C. 4-Nitrophenyl chloroformate (7.17 g, 35.56 mmol) in MeCN (47.4 mL) was added to the vigorously stirred mixture over 20 min through an addition funnel, and the resulting solution was allowed to stir for an additional 3 h at 0 °C. After being warmed to rt, the reaction mixture was quenched with a 10% aqueous HCl solution, and the suspended solid was dissolved with EtOAc. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel flash column chromatography, eluting first with EtOAc and then changing to EtOAc/MeOH (10/1 to 5/1) to give compound **5** as white foam (4.81 g, 11.64 mmol, 82% over two steps): ^{1}H NMR (400 MHz, CD_3OD) δ 2.34 (s, 3H), 2.41 (dd, *J* = 12.6, 12.6 Hz, 1H), 2.87 (dd, *J* = 3.9, 12.6 Hz, 1H), 3.59 (dd, *J* = 1.8, 8.7 Hz, 1H), 3.59 (dd, *J* = 12.6, 9.9 Hz, 1H), 3.63 (s, 3H), 3.67−3.76 (m, 2H), 3.83 (dd, *J* = 2.4, 10.8 Hz, 1H), 4.63 (ddd, *J* = 3.9, 12.6, 12.6 Hz, 1H), 4.68 (dd, *J* = 1.8, 9.9 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 21.4, 38.4, 53.5, 59.6, 65.1, 71.4, 72.4, 75.9, 79.4, 91.1, 127.4, 130.9, 137.9, 141.7, 162.6, 170.8; HRMS (ESI) calcd for $C_{18}H_{23}NNaO_8S$ $(M + Na)^+$ 436.1042, found 436.1042.

Methyl (4-Methylphenyl 5-amino-5-*N*,4-*O*-carbonyl-7,8,9-tri-*O*-chloroacetyl-3,5-dideoxy-2-thio-D-*glycero*-β-D-*galacto*-non-2-ulopyranoside)onate (2a). To compound **5** (4.8 g, 11.62 mmol) dissolved in CH_2Cl_2 (58.1 mL, 0.2 M) was added pyridine (5.61 mL, 69.72 mmol) at rt under N_2, and the resulting solution was then cooled to 0 °C. Chloroacetyl chloride (3.22 mL, 40.67 mmol) in CH_2Cl_2 (19.4 mL) was added dropwise through an addition funnel to the vigorously stirred mixture. After being stirred at rt for 3 h, the reaction mixture was poured into a 10% aqueous HCl solution at 0 °C (50 mL). The aqueous layer was extracted three times with EtOAc. The combined extracts were washed with brine and were dried over $MgSO_4$. The solution was concentrated under reduced pressure and then was subjected to silica gel flash column chromatography (hexanes/EtOAc, from 4/1 to 2/1) to afford **2a** (6.27 g, 9.76 mmol, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (dd, *J* = 12.4, 12.4 Hz, 1H), 2.35 (s, 3H), 2.81 (dd, *J* = 3.8, 12.4 Hz, 1H), 3.21 (dd, *J* = 12.4, 12.4 Hz, 1H), 3.66 (s, 3H), 3.97 (AB quartet, *J* = 15.0 Hz, 2H), 4.07 (AB quartet, *J* = 15.0 Hz, 2H), 4.13 (AB quartet, *J* = 15.0 Hz, 2H), 4.33 (dd, *J* = 6.4, 12.5 Hz, 1H), 4.52 (dd, *J* = 2.4, 12.5 Hz, 1H), 4.59 (dd, *J* = 2.5, 12.4 Hz, 1H), 4.70 (ddd, *J* = 3.8, 12.4, 12.4 Hz, 1H), 5.26−5.29 (m, 2H), 5.54 (s, 1H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 36.4, 40.5, 40.7, 53.0, 58.3, 63.2, 72.0, 72.5, 73.1, 77.2, 88.8, 124.9, 130.2, 136.3, 140.9, 159.5, 166.8, 167.8; HRMS (FAB) calcd for $C_{24}H_{27}O_{11}C_{13}NS$ $(M + H)^+$ 642.0370, found 642.0362.

Methyl (4-Methylphenyl 5-amino-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 (2b). To a solution of **5** (308 mg, 0.64 mmol) in pyridine (4 mL) was added acetic anhydride (2 mL) at 0 °C. The reaction was stirred for 12 h at room temperature and then concentrated in vacuo. The residue was diluted with EtOAc, and the resulting solution was washed with 10% HCl, saturated $NaHCO_3$, and saturated NaCl in sequence. The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/4) to afford **2b** (301 mg, 98%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.07 (s, 3H), 2.13 (s, 3H), 2.22 (dd, *J* = 12.5, 12.8 Hz, 1H), 2.33 (s, 3H), 2.78 (dd, *J* = 3.7, 12.8 Hz, 1H), 3.05 (dd, *J* = 9.7, 11.2 Hz, 1H), 3.60 (s, 3H), 4.22 (dd, *J* = 5.9, 12.5 Hz, 1H), 4.39 (dd, *J* = 2.0, 12.5 Hz, 1H), 4.56 (dd, *J* = 2.4, 9.7 Hz, 1H), 4.68 (ddd, *J* = 3.7, 11.2, 12.5 Hz, 1H), 5.14 (ddd, *J* = 2.0, 5.2, 5.9 Hz, 1H), 5.19 (dd, *J* = 2.4, 5.2 Hz, 1H), 5.40 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 20.8, 21.0, 21.4, 36.4, 52.8, 58.5, 61.9, 70.4, 70.9, 73.3, 76.9, 89.0, 125.3, 130.1, 136.2, 140.5, 159.3, 167.9, 170.2, 170.4, 171.4; HRMS (FAB) calcd for $C_{24}H_{30}NO_{11}S$ $(M + H)^+$ 540.1540, found 540.1550.

General Glycosylation Procedure. A solution of donor (0.16 mmol), acceptor (0.19 mmol), and freshly activated 3 Å powdered molecular sieves (0.5 g/mmol) in anhydrous CH_2Cl_2/MeCN (v/v = 2/1) was stirred for 1 h under N_2. The reaction solution was cooled to −78 °C, and then NIS (0.23 mmol) and TfOH (0.06 mmol) were added. The reaction mixture was stirred at this temperature for 10 min and then was stirred at −50 °C for 1 h. The reaction mixture was diluted with CH_2Cl_2 and was filtered through Celite. The filtered solution was washed with saturated aqueous $Na_2S_2O_3$ solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to give the target sialoside.

Methyl (3-azidopropyl-5-amino-5-*N*,4-*O*-carbonyl-7,8,9-tri-*O*-chloroacetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate (13): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (m, 2H), 2.05

(dd, J = 12.4, 12.4 Hz, 1H), 2.85 (dd, J = 3.5, 12.4 Hz, 1H), 3.09 (dd, J = 9.9, 9.9 Hz, 1H), 3.30 (dt, J = 6.2, 11.3 Hz, 1H), 3.37 (t, J = 6.2 Hz, 2H), 3.77−3.81 (m, 1H), 3.80 (s, 3H), 3.92 (ddd, J = 3.5, 9.9, 12.4 Hz, 1H), 4.06 (s, 2H), 4.17 (d, J = 15.3 Hz, 1H), 4.18 (s, 2H), 4.28 (dd, J = 1.7, 9.9 Hz, 1H), 4.32 (d, J = 15.3 Hz, 1H), 4.37 (dd, J = 3.8, 12.8 Hz, 1H), 4.52 (dd, J = 2.0, 12.8 Hz, 1H), 5.18 (dd, J = 1.7, 9.8 Hz, 1H), 5.35 (s, 1H), 5.64 (ddd, J = 2.0, 3.8, 9.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.0, 37.3, 40.5, 40.6, 41.1, 48.1, 53.3, 57.5, 62.3, 63.2, 68.2, 70.4, 73.5, 76.8, 100.2, 159.3, 166.4, 167.1, 168.2, 168.8; HRMS (FAB) calcd for $C_{20}H_{25}Cl_3N_4NaO_{12}$ $(M + Na)^+$ 641.0432, found 641.0436.

Methyl (3-azidopropyl 5-amino-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)-onate (14): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (m, 2H), 2.01 (dd, J = 10.8, 12.0 Hz, 1H), 2.03 (s, 3H), 2.14 (s, 3H), 2.15 (s, 3H), 2.84 (dd, J = 3.6, 12.0 Hz, 1H), 3.02 (dd, J = 9.8, 10.9 Hz, 1H), 3.29 (m, 1H), 3.35 (m, 2H), 3.77 (s, 3H), 3.8 (m, 1H), 3.92 (ddd, J = 3.6, 10.8, 10.9 Hz, 1H), 4.24 (dd, J = 1.9, 9.8 Hz, 1H), 4.26 (m, 2H), 5.09 (dd, J = 2.0, 9.8 Hz, 1H), 5.34 (s, 1H), 5.45 (ddd, J = 2.7, 2.9, 9.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 20.9, 21.2, 29.1, 37.6, 48.2, 53.1, 58.0, 61.9, 62.3, 67.1, 69.0, 73.7, 76.8, 100.2, 159.4, 168.6, 170.7, 171.7; HRMS (FAB) calcd for $C_{20}H_{28}O_{12}N_4Na$ $(M + Na)^+$ 539.1601, found 539.1600.

Methyl (5-amino-5,4-*N*,*O*-carbonyl-7,8,9-tri-*O*-chloroacetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate-(2→6)-(methyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside) (15): ^{1}H NMR (400 MHz, CD_3OD) δ 2.05−2.08 (m, 1H), 2.93−3.02 (m, 2H), 3.34−3.36 (m, 1H), 3.36 (s, 3H), 3.48 (dd, J = 3.5, 9.7 Hz, 1H), 3.56 (t, J = 9.8 Hz, 1H), 3.68−3.71 (m, 2H), 3.71−3.77 (m, 2H), 3.74 (s, 3H), 3.83−3.96 (m, 2H), 3.99 (br, 2H), 4.07−4.17 (m, 4H), 4.20 (dd, J = 1.8, 9.8 Hz, 1H), 4.33 (d, J = 15.5 Hz, 1H), 4.60 (d, J = 3.4 Hz, 1H), 4.64 (d, J = 12.3 Hz, 1H), 4.69 (d, J = 10.8 Hz, 1H), 4.76−4.82 (m, 3H), 4.90 (d, J = 10.8 Hz, 1H), 5.04 (dd, J = 1.8, 10.3 Hz, 1H), 5.23 (br, 1H), 5.42−5.46 (m, 1H), 7.27−7.34 (m, 15H); ^{13}C NMR (100 MHz, CD_3OD): δ 37.2, 39.8, 40.3, 40.9, 53.1, 55.2, 57.2, 62.4, 63.7, 67.4, 69.1, 69.6, 73.1, 73.2, 74.2, 75.7, 76.5, 79.2, 81.7, 98.1, 100.1, 127.2, 127.5, 127.6, 127.81, 127.87, 127.9, 128.2, 128.34, 128.36, 138.0, 138.5, 138.6, 158.9, 166.1, 167.8, 168.1; HRMS (FAB) calcd for $C_{45}H_{49}Cl_3NO_{17}$ $(M - H)^+$ 980.2066, found 980.2070.

Methyl (5-amino-5,4-*N*,*O*-carbonyl-7,8,9-tri-*O*-chloroacetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate-(2→6)-(methyl 2,3,4-tri-*O*-benzoyl-α-D-galactopyranoside) (16): ^{1}H NMR (400 MHz, CD_3OD): δ 2.14 (t, J = 12.5 Hz, 1H), 2.93 (dd, J = 3.4, 12.2 Hz, 1H), 3.01 (t, J = 10.7 Hz, 1H), 3.44−3.50 (m, 2H), 3.45 (s, 3H), 3.77 (s, 3H), 3.82−3.89 (m, 1H), 3.92 (dd, J = 1.9, 13.1 Hz, 1H), 3.98−4.04 (m, 4H), 4.08−4.16 (m, 3H), 4.21 (dd, J = 2.7, 10.1 Hz, 1H), 4.28 (d, J = 15.4 Hz, 1H), 5.00 (dd, J = 1.8, 10.2 Hz, 1H), 5.14 (dd, J = 2.5, 9.6 Hz, 1H), 5.22−5.28 (m, 3H), 5.63 (t, J = 9.8 Hz, 1H), 6.01 (t, J = 9.4 Hz, 1H), 7.29−7.54 (m, 9H), 7.86−7.95 (m, 6H); ^{13}C NMR (100 MHz, CD_3OD): δ 37.0, 40.1, 40.3, 40.9, 53.2, 55.7, 57.3, 62.2, 62.9, 67.5, 67.7, 68.5, 69.5, 70.9, 71.6, 73.2, 76.5, 97.0, 99.8, 128.1, 128.3, 128.5, 128.9, 129.2, 129.4, 129.5, 129.6, 129.8, 133.0, 133.3, 133.4, 158.9, 164.6, 165.7, 166.2, 166.8, 168.0; HRMS (FAB) calcd for $C_{45}H_{45}Cl_3NO_{20}$ $(M - H)^+$ 1024.1601, found 1024.1620.

Methyl (5-amino-7,8,9-tri-*O*-acetyl-5,4-*N*,*O*-carbonyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate-(2→6)-(methyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside) (17): ^{1}H NMR (400 MHz, CD_3OD): δ 1.84 (s, 3H), 1.99 (s, 3H), 2.04 (t, J = 6.0 Hz, 1H), 2.13 (s, 3H), 2.92−297 (m, 2H), 3.34 (s, 3H), 3.37 (dd, J = 1.8, 10.5 Hz, 1H), 3.48 (dd, J = 3.5, 9.7 Hz, 1H), 3.56 (t, J = 9.5 Hz, 1H), 3.71 (s, 3H), 3.71−3.72 (m, 1H), 3.77 (dd, J = 3.0, 12.8 Hz, 1H), 3.86−3.95 (m, 2H), 3.98 (dd, J = 1.9, 12.8 Hz, 1H), 4.17 (dd, J = 3.8, 10.4 Hz, 1H), 4.21 (dd, J = 1.9, 9.9 Hz, 1H), 4.59 (d, J = 3.5 Hz, 1H), 4.63 (d, J = 12.3 Hz, 1H), 4.71 (d, J = 10.9 Hz, 1H), 4.73 (d, J = 11.2 Hz, 1H), 4.77−4.79 (m, 2H), 7.24−7.34 (m, 15H); ^{13}C NMR (100 MHz, CD_3OD) δ 20.0, 20.2, 20.6, 37.1, 52.6, 54.8, 57.4, 61.1, 66.2, 69.1, 72.9, 73.1, 74.3, 75.4, 76.3, 76.6, 79.1, 81.5, 97.8, 99.8, 127.2, 127.4, 127.5, 127.6, 127.7, 127.9, 128.0, 128.1, 137.8, 138.2, 138.4, 167.7, 169.3, 170.0, 171.0, 177.7; HRMS (FAB) calcd for $C_{45}H_{53}NO_{17}Na$ $(M + Na)^+$ 902.3211, found 902.3201.

Methyl (5-amino-7,8,9-tri-*O*-acetyl-5,4-*N*,*O*-carbonyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate-(2→6)-(methyl 2,3,4-tri-*O*-benzoyl-α-D-galactopyranoside) (18): ^{1}H NMR (400 MHz, CD_3OD) δ 1.98 (s, 3H), 2.05 (s, 3H), 2.07 (s, 3H), 2.88 (dd, J = 3.0, 12.0 Hz, 1H), 2.96 (t, J = 11.0 Hz, 1H), 3.44 (s, 3H), 3.43−3.47 (m, 1H), 3.58 (dd, J = 2.9, 12.8 Hz, 1H), 3.74 (s, 3H), 3.79−3.90 (m, 2H), 4.05 (dd, J = 3.6, 10.8 Hz, 1H), 4.09−4.12 (m, 1H), 4.20 (dd, J = 3.1, 10.1 Hz, 1H), 4.95 (dd, J = 2.0, 10.1 Hz, 1H), 5.07 (td, J = 2.5, 10.1 Hz, 1H), 5.21−5.24 (m, 2H), 5.27 (br, 1H), 5.64 (t, J = 9.8 Hz, 1H), 6.00−6.05 (m, 2H), 7.27−7.54 (m, 9H), 7.85−7.95 (m, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 20.3, 20.3, 20.6, 36.7, 52.7, 55.3, 57.3, 60.9, 63.0, 66.3, 67.6, 67.9, 68.4, 70.6, 71.5, 73.2, 76.3, 96.7, 99.6, 127.9, 128.1, 128.7, 128.9, 129.1, 129.4, 129.4, 129.5, 132.8, 133.1, 159.0, 164.4, 165.50, 165.53, 167.6, 169.4, 170.1, 171.2, 177.7; HRMS (FAB) calcd for $C_{45}H_{47}NO_{20}Na$ $(M + Na)^+$ 944.2589, found 944.2589.

6-Trifluoroacetamidohexyl *O*-[methyl (5-amino-5-*N*,4-*O*-carbonyl-7,8,9-tri-*O*-chloroacetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate]-(2→3)-*O*-(2,6-di-*O*-benzyl-*β*-D-galactopyranosyl)-(1→ 4)-2,3,6-tri-*O*-benzyl-*β*-D-glucopyranoside (19): ^{1}H NMR (400 MHz, $CDCl_3$) for 19 α: δ 1.26−1.32 (m, 2H), 1.34−1.42 (m, 2H), 1.42−1.50 (m, 2H), 1.57−1.64 (m, 2H), 2.15 (dd, J = 12.3, 12.3 Hz, 1H), 2.55 (br, 1H), 2.84 (dd, J = 3.4, 12.3 Hz, 1H), 2.97 (dd, J = 10.8, 10.8 Hz, 1H), 3.20−3.27 (m, 2H), 3.33−3.44 (m, 3H), 3.43−3.56 (m, 4H), 3.57−3.7 (m, 4H), 3.73 (s, 3H), 3.85−3.95 (m, 4H), 3.98 (s, 2H), 4.08 (dd, J = 2.2, 12.7 Hz, 1H), 4.10 (d, J = 15.3 Hz, 1 H), 4.11 (d, J = 12.4 Hz, 1H), 4.12 (d, J = 12.4 Hz, 1H), 4.15(dd, J = 1.6, 10.8 Hz, 1H), 4.25 (d, J = 15.3 Hz, 1 H), 4.31 (d, J = 11.7 Hz, 1H), 4.32 (d, J = 7.8 Hz, 1 H), 4.34 (dd, J = 3.8, 12.7 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.46 (s, 2H), 4.61 (d, J = 7.8 Hz, 1H), 4.63 (d, J = 11.9 Hz, 1H), 4.69 (d, J = 11.1 Hz, 1H), 4.75 (d, J = 10.8 Hz, 1H), 4.78 (d, J = 11.9 Hz, 1H), 4.85 (d, J = 11.1 Hz, 1H), 4.92 (d, J = 10.8 Hz, 1H), 5.08 (dd, J = 1.6, 9.5 Hz, 1H), 5.20 (br, 1H), 5.61(ddd, J = 2.2, 3.8, 9.5 Hz, 1 H), 6.19 (br, 1H), 7.15−7.35 (m, 25H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 26.2, 28.6, 29.3, 35.6, 39.7, 39.8, 40.3, 40.9, 53.3, 57.2, 62.8, 67.7, 68.2, 68.2, 68.6, 69.5, 70.0, 71.9, 72.9, 73.2, 73.3, 74.7, 74.8, 74.9, 75.2, 76.5, 76.5, 77.0, 78.1, 81.7, 82.7, 99.6, 102.3, 103.4, 115.7, 127.1, 127.2, 127.2, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 128.0, 128.1, 128.20, 128.28, 138.0, 138.3, 138.5, 138.7, 138.9, 157.0, 159.0, 166.3, 166.9, 167.9, 168.3; HRMS (ESI) calcd for $C_{72}H_{82}N_2O_{23}F_3NaCl_3$ $(M + Na)^+$ 1527.4224, found 1527.4221.

6-Trifluoroacetamidohexyl *O*-[methyl (5-amino-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate]-(2→3)-*O*-(2,6-di-*O*-benzyl-*β*-D-galactopyranosyl)-(1→ 4)-2,3,6-tri-*O*-benzyl-*β*-D-glucopyranoside (20): ^{1}H NMR (400 MHz, $CDCl_3$) for 20α δ 1.26−1.33 (m, 2H), 1.34−1.41 (m, 2H), 1.41−1.50 (m, 2H), 1.56−1.64 (m, 2H), 2.00 (s, 3H), 2.02 (dd, J = 9.8, 12.2 Hz, 1H), 2.09 (s, 3H), 2.14 (s, 3H), 2.60 (br, 1H), 2.80 (dd, J = 3.5, 12.2 Hz, 1H), 2.94 (dd, J = 9.8, 10.9 Hz, 1H), 3.32−3.42 (m, 3H), 3.44−3.57 (m, 4H), 3.58−3.68 (m, 2H), 3.70−3.78 (m, 2H), 3.72 (s, 3H), 3.85−3.93 (m, 4H), 4.07 (dd, J = 3.9, 12.7 Hz, 1H), 4.13 (dd, J = 1.8, 9.7 Hz, 1H), 4.20 (dd, J = 2.0, 12.7 Hz, 1H), 4.31 (d, J = 7.8 Hz, 1H), 4.32 (d, J = 12.3 Hz, 1H), 4.40 (d, J = 11.8 Hz, 1H), 4.44 (d, J = 12.3 Hz, 1H), 4.56 (d, J = 7.8 Hz, 1H), 4.64 (d, J = 11.8 Hz, 1H), 4.70 (d, J = 11.1 Hz, 1H), 4.72 (d, J = 11.8 Hz, 1H), 4.73 (d, J = 11.8 Hz, 1H), 4.74 (d, J = 10.8 Hz, 1H), 4.84 (d, J = 11.1 Hz, 1H), 4.93 (d, J = 10.8 Hz, 1H), 5.04 (dd, J = 1.8, 9.3 Hz, 1H), 5.27 (s, 1H), 5.46 (ddd, J = 2.0, 3.9, 9.3 Hz, 1H), 6.19 (br, 1H), 7.16−7.36 (m, 25H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 20.6, 21.0, 25.6, 26.2, 28.7, 29.4, 35.7, 39.7, 53.1, 57.8, 61.7, 67.2, 67.8, 68.2, 68.6,

68.8, 69.6, 72.3, 72.9, 73.3, 73.7, 74.8, 75.0, 75.0, 75.3, 76.5, 76.6, 77.0, 78.1, 81.8, 82.8, 99.6, 102.4, 103.5, 116.1, 127.3, 127.52, 127.58, 127.8, 128.05, 128.08, 128.20, 128.21, 128.27, 128.3, 138.2, 138.4, 138.71, 138.73, 139.0, 157.1, 159.2, 168.2, 169.6, 170.5, 171.4; HRMS (ESI) calcd for $C_{72}H_{86}N_2O_{23}F_3$ $(M + H)^+$ 1403.5573, found 1403.5571.

Methyl (5-amido-5-*N*,4-*O*-carbonyl-7,8,9-tri-*O*-chloroacetyl-3,5-dideoxy-D-*glycero*-α/*β*-D-*galacto*-non-2-ulopyranoside)onate-(2→4)-methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (21): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.24 (m, 9H), 1.30 (s, 3H), 1.43 (s, 3H), 1.45 (s, 3H), 1.93−2.00 (m, 2H), 2.51 (t, J = 12.8 Hz, 1H), 2.79−2.85 (m, 2H), 3.00 (t, J = 10.5 Hz, 1H), 3.31 (broad s, 6H), 3.35−3.40 (m, 2H), 3.51 (dd, J = 5.8, 9.6 Hz, 1H) 3.58 (dd, J = 6.1, 9.6 Hz, 1H), 3.61−3.68 (m, 1H), 3.73 (s, 3H), 3.75 (s, 3H), 3.88−3.95 (m, 1H), 4.02 (s, 3H), 4.03 (s, 2H), 4.05−4.10 (m, 2H), 4.12 (br, 3H), 4.13 (s, 1H), 4.15−4.16 (m, 4H), 4.17−4.19 (m, 1H), 4.27 (d, J = 15.4 Hz, 1H), 4.31−4.41 (m, 2H), 4.48−4.55 (m, 2H), 4.66 (d, J = 12.8 Hz, 1H), 4.76−4.77 (m, 2H), 5.15 (dd, J = 1.3, 9.9 Hz, 1H), 5.24 (dd, J = 2.7, 5.8 Hz, 1H), 5.47 (br, 1H), 5.53 (dd, J = 2.1, 6.0 Hz, 1H), 5.64 (d, J = 9.8 Hz, 1H), 6.00 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1 (2 C), 25.7, 25.9, 27.5, 27.6, 36.9, 37.7, 40.1, 40.2, 40.3, 40.4, 40.5, 40.7, 52.7, 53.1, 54.7, 54.8, 57.6, 57.7, 62.5, 63.1, 63.7, 63.9, 68.7, 69.9, 71.0 (2 C), 72.4, 73.1, 75.7, 76.0, 76.2, 76.6, 76.9, 77.0, 77.1, 77.7, 98.0, 98.1, 98.9, 100.0, 109.0, 109.1, 159.3, 159.7, 165.9, 166.2, 166.8, 166.9, 167.0, 167.1, 167.8, 167.9; ESIHRMS calcd for $C_{27}H_{36}Cl_3NO_{16}$-Na $(M + Na)^+$ 758.0997, found 758.1025.

Methyl (1-adamantanyl-5-amino-5-*N*,4-*O*-carbonyl-7,8,9-tri-*O*-chloroacetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate (22): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 6H), 1.60 (s, 6H), 2.01−2.08 (m, 4H), 2.82 (dd J = 3.4, 12.1 Hz, 1H), 3.05 (t, J = 10.4 Hz, 1H), 3.74 (s, 3H), 3.77−3.86 (m, 1H), 4.05 (s, 2H), 4.16 (s, 2H), 4.20 (s, 1H), 4.33 (s, 1H), 4.37−4.41 (m, 2H), 4.56 (dd, J = 1.8, 12.8 Hz, 1H), 5.12 (br, 1H), 5.15 (dd, J = 1.3, 10.2 Hz, 1H), 5.32 (s, 1H), 5.51 (td, J = 2.8, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 30.9, 36.3, 40.2, 40.3, 40.4, 40.7, 43.2, 52.7, 57.6, 62.7, 68.8, 70.0, 73.5, 79.5, 99.2, 159.2, 166.3, 167.0, 167.9, 171.2; ESIHRMS calcd for $C_{27}H_{34}Cl_3NO_{12}$-Na $(M + Na)^+$ 692.1044, found 692.1053.

***O*-(8-Azido-3,6-dioxaoctyl)-*N*-3,6,9-trioxaoctylcarbamoyl *O*-[methyl (5-amino-5-*N*,4-*O*-carbonyl-7,8,9-tri-*O*-chloroacetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate]-(2→6)-*O*-(2,3-di-*O*-benzoyl-*β*-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzoyl-*β*-D-glucopyranoside (23):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (t, J = 12.8 Hz, 1H), 2.70 (dd, J = 3.4, 12.8 Hz, 1H), 3.20 (t, J = 10.4 Hz, 1H), 3.18−3.27 (m, 6H), 3.31−3.38 (m, 6H), 3.45−3.56 (m, 3H), 3.60−3.70 (m, 9H), 3.77 (s, 3H), 3.83−3.94 (m, 3H), 3.99 (s, 2H), 4.13−4.30 (m, 9H), 4.32 (dd, J = 4.4, 12.9 Hz, 1H), 4.44 (dd, J = 5.1, 11.9 Hz, 1H), 4.48 (dd, J = 2.3, 11.9 Hz, 1H), 4.60 (dd, J = 1.8, 11.9 Hz, 1H), 4.82 (d, J = 7.8 Hz, 1H), 4.86 (d, J = 7.8 Hz, 1H), 5.11 (dd, J = 3.1, 10.4 Hz, 1H), 5.18 (dd, J = 1.5, 9.1 Hz, 1H), 5.22 (t, J = 5.2 Hz, 1H), 5.33 (dd, J = 7.8, 9.3 Hz, 1H), 5.38 (br, 1H), 5.60 (ddd, J = 2.3, 3.8, 9.1 Hz, 1H), 5.66 (dd, J = 7.8, 10.4 Hz, 1H), 5.76 (t, J = 9.3 Hz, 1H), 7.12 (t, J = 7.8 Hz, 2H), 7.29−7.57 (m, 13H), 7.84 (d, J = 7.3 Hz, 2H), 7.81−7.99 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.2, 40.2, 40.3, 40.5, 40.8, 50.5, 53.3, 57.3, 62.1, 62.7, 63.1, 63.7, 65.8, 68.4, 69.1, 69.5, 69.6, 69.7, 69.9, 70.00, 70.06, 70.3, 70.40, 70.49, 72.0, 72.5, 72.9, 73.0, 73.7, 74.0, 76.30, 76.31, 77.2, 100.4, 100.5, 100.6, 128.2 (×4), 128.3 (×2), 128.6, 128.9, 129.2, 129.4, 129.5, 129.6 (×2), 129.6, 129.7, 132.9, 132.9, 133.1, 133.1, 133.3, 156.3, 158.9, 165.0, 165.1, 165.2, 165.7, 165.7, 166.3, 167.0, 167.9, 168.1; HRMS (ESI) calcd for $C_{77}H_{84}Cl_3N_5NaO_{33}$ $(M+Na)^+$ 1734.4012, found 1734.4022.

Methyl (3-Azidopropyl 5-amino-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate (3). A solution of compound **13** (600 mg, 0.97 mmol) in MeOH (24 mL) was treated with Et_3N (200 μL) and then was stirred at room temperature for 10 min. The mixture was then neutralized with a 10% aqueous HCl solution and was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexanes/EtOAc/MeOH, from 1/10/0, 1/1/0.12, 1/1/0.16 to 1/1/0.2) to afford **3** (315 mg, 83%): ^{1}H NMR (400 MHz, CD_3OD) δ 1.80 (m, 2H), 2.10 (dd, J = 11.8, 13.1 Hz, 1H), 2.93 (dd, J = 3.7, 11.8 Hz, 1H), 3.39 (t, J = 6.4 Hz, 2H), 3.46 (dt, J = 6.4, 12.4 Hz, 1H), 3.58 (dd, J = 1.8, 8.6 Hz, 1H), 3.61 (dd, J = 9.9, 11.1 Hz, 1H), 3.68 (dd, J = 5.5, 10.6 Hz, 1H), 3.79−3.86 (m, 2H), 3.86 (s, 3H), 3.89 (dt, J = 6.4, 12.4 Hz, 1H), 4.07 (ddd, J = 3.7, 11.1, 13.1 Hz, 1H), 4.12 (dd, J = 1.8, 8.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 30.1, 38.1, 49.3, 53.8, 58.6, 62.8, 64.7, 71.6, 72.4, 77.3, 79.1, 101.7, 162.7, 170.7; HRMS (ESI) calcd for $C_{14}H_{22}N_4NaO_9$ $(M + Na)^+$ 413.1284, found 413.1280.

Methyl (3-Azidopropyl 7,8-di-*O*-acetyl-5-amino-5-*N*,4-*O*-carbonyl-9-*O*-(methyl 5-amino-5-*N*,4-*O*-carbonyl-7,8,9-tri-*O*-chloroacetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate (24). A mixture of donor **2a** (206 mg, 0.32 mmol) and acceptor **3** (100 mg, 0.26 mmol) was dried azeotropically with toluene three times and then was dissolved in anhydrous CH_2Cl_2/MeCN (2/1, 4 mL) at rt under N_2. The resulting solution was transferred to a round-bottomed flask containing dry 3-Å MS (160 mg, 0.5 g/mmol) at rt under N_2. The reaction mixture was stirred for 10 min and then was cooled to −78 °C. NIS (90 mg, 0.4 mmol) and TfOH (17 μL, 0.13 mmol) were added to the reaction mixture. After being stirred at −50 °C for 1 h, the reaction mixture was warmed to 0 °C and then was quenched with a saturated aqueous $Na_2S_2O_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (4 mL), and then Ac_2O (121 μL, 1.28 mmol) was added at 0 °C under N_2, followed by TfOH (4.3 μL, 0.032 mmol). After being stirred for 15 min, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined extracts were dried over $MgSO_4$. After the solution was concentrated, the residue was purified by silica gel flash column chromatography (hexanes/EtOAc/MeOH, from 1/1/0 to 1/1/0.1) to afford **24** (211 mg, 83% over two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (m, 2H), 1.97−2.05 (br-dd, 2H), 2.16 (s, 3H), 2.21 (s, 3H), 2.82−2.87 (br-dd, 2H), 3.05 (dd, J = 10.8, 10.8 Hz, 1H), 3.13 (dd, J = 10.8, 10.8 Hz, 1H), 3.29 (dt, J = 6.4, 11.7 Hz, 1H), 3.35 (dd, J = 1.9, 12.7 Hz, 1H), 3.36 (t, J = 6.4 Hz, 2H), 3.78 (s, 6H), 3.78−3.93 (m, 4H), 4.05 (s, 2H), 4.16 (d, J = 15.3 Hz, 1H), 4.22 (s, 2H), 4.22−4.25 (br-dd, 2H), 4.28 (d, J = 15.3 Hz, 1H), 4.30 (dd, J = 4.2, 12.7 Hz, 1H), 4.52 (dd, J = 1.9, 12.7 Hz, 1H), 5.18 (dd, J = 1.8, 9.9 Hz, 1H), 5.22 (dd, J = 1.9, 9.9 Hz, 1H), 5.38 (br, 1H), 5.39 (s, 1H), 5.55 (ddd, J = 1.9, 4.2, 9.9 Hz, 1H), 5.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 21.1, 29.1, 37.2, 37.6, 40.5, 40.6, 41.0, 48.2, 53.1, 53.4, 57.2, 58.0, 62.2, 63.2, 63.6, 67.2, 67.9, 68.8, 70.3, 73.6, 73.7, 76.6, 76.9, 100.0, 100.1, 159.2, 159.7, 167.1, 168.3, 168.6, 169.8, 171.7, 177.8; HRMS (ESI) calcd for $C_{35}H_{44}Cl_3N_5NaO_{22}$ $(M + Na)^+$ 1014.1441, found 1014.1433.

Methyl (3-Azidopropyl-7,8-di-*O*-acetyl-5-amino-5-*N*,4-*O*-carbonyl-9-*O*-(methyl 5-amino-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate (25). The disialoside triol acceptor **25** (216 mg, 83%) was synthesized by the methods described in the synthesis of **3**: ^{1}H NMR (400 MHz, CD_3OD) δ 1.78 (m, 2H), 2.05 (dd, J = 11.8, 11.8 Hz, 1H), 2.08 (dd, J = 11.7, 11.7 Hz, 1H), 2.16 (s, 3H), 2.22 (s, 3H), 2.85 (dd, J = 3.6, 11.8 Hz, 1H), 2.93 (dd, J = 3.7, 11.7 Hz, 1H), 3.28 (dd, J = 10.1, 10.9 Hz, 1H), 3.35−3.39 (m, 1H), 3.40 (t, J = 6.2 Hz, 2H), 3.58 (dd, J = 10.1, 10.1 Hz, 1H), 3.59 (dd, J = 1.9, 8.5 Hz, 1H), 3.68 (dd, J = 2.6, 11.2 Hz, 1H), 3.69 (dd, J = 1.3, 11.4 Hz, 1H), 3.76−3.85 (m, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 4.00 (dd, J = 3.7, 11.2 Hz, 1H),

4.01−4.13 (m, 2H), 4.06 (dd, J = 1.9, 10.1 Hz 1H), 4.25 (dd, J = 1.7, 10.1 Hz, 1H), 5.29 (dd, J = 1.7, 9.3 Hz, 1H), 5.36 (ddd, J = 2.6, 3.7, 9.3 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 20.9, 21.2, 30.1, 37.9, 38.1, 49.2, 53.5, 53.6, 58.6, 58.7, 63.1, 63.8, 64.7, 69.5, 70.0, 71.4, 72.1, 75.0, 77.6, 78.4, 78.9, 101.1, 101.4, 162.0, 162.5, 169.9, 170.2, 171.8, 173.1; HRMS (ESI) calcd for $C_{29}H_{41}N_5NaO_{19}$ $(M + Na)^+$ 786.2293, found 786.2293.

Methyl (3-Azidopropyl-7,8-di-*O*-acetyl-5-amino-5-*N*,4-*O*-carbonyl-9-*O*-(methyl 7,8-di-*O*-acetyl-5-amino-5-*N*,4-*O*-carbonyl-9-*O*-(methyl 5-amino-5-*N*,4-*O*-carbonyl-7,8,9-tri-*O*-chloroacetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate (26). The trisialoside **26** (200 mg, 74%, two steps) was synthesized by the methods described in the synthesis of **24**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (m, 2H), 1.94−2.06 (m, 3H), 2.14 (s, 3H), 2.15 (s, 3H), 2.22 (s, 3H), 2.22 (s, 3H), 2.83−2.87 (m, 3H), 3.00−3.07 (br-dd, 2H), 3.14 (dd, J = 10.7, 10.7 Hz, 1H), 3.28 (dt, J = 6.7, 11.9 Hz, 1H), 3.31−3.37 (m, 2H), 3.37 (t, J = 7.7 Hz, 2H), 3.76 (s, 3H), 3.77 (s, 3H), 3.77 (s, 3H), 3.76−3.93 (m, 6H), 4.05 (s, 2H), 4.15 (d, J = 15.2 Hz, 1H), 4.17−4.27 (m, 6H), 4.28 (d, J = 15.2 Hz, 1H), 4.53 (dd, J = 1.9, 12.6 Hz, 1H), 5.17 (dd, J = 1.8, 9.9 Hz, 1H), 5.21−5.29 (m, 3H), 5.34−5.39 (m, 1H), 5.50−5.54 (m. 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 20.8, 21.1, 29.1, 37.1, 37.4, 37.6, 40.5, 40.6, 41.0, 48.2, 53.0, 53.1, 53.4, 57.2, 57.7, 58.0, 62.2, 63.3, 63.5, 67.0, 67.2, 67.8, 68.7, 68.8, 70.4, 73.6, 73.8, 73.5, 76.5, 76.6, 76.9, 99.8, 99.9, 100.1, 159.2, 159.5, 159.6, 166.4, 167.0, 168.0, 168.3, 168.6, 169.8, 169.91, 169.96, 171.5, 171.6; HRMS (ESI) calcd for $C_{50}H_{63}Cl_3N_6NaO_{32}$ $(M + Na)^+$ 1387.2450, found 1387.2456.

Methyl (3-Azidopropyl 7,8-di-*O*-acetyl-5-amino-5-*N*,4-*O*-carbonyl-9-*O*-(methyl 7,8-di-*O*-acetyl-5-amino-5-*N*,4-*O*-carbonyl-9-*O*-(methyl 5-amino-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-3,5-dideoxy D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate (27). The trisialoside triol acceptor **27** (133 mg, 80%) was synthesized by the methods described in the synthesis of **3**: ^{1}H NMR (400 MHz, CD_3OD) δ 1.79 (m, 2H), 1.99−2.08 (m, 3H), 2.16 (s, 3H), 2.17 (s, 3H), 2.23 (s, 3H), 2.25 (s, 3H), 2.84−2.88 (m, 2H), 2.92 (dd, J = 3.7, 11.6 Hz, 1H), 3.22−3.31 (m, 2H), 3.35−3.42 (m, 1H), 3.41 (t, J = 6.2 Hz, 2H), 3.50 (dd, J = 2.2, 11.2 Hz, 1H), 3.58 (dd, J = 10.5, 10.5 Hz, 1H), 3.59 (dd, J = 1.7, 8.5 Hz, 1H), 3.67 (dd, J = 2.7, 11.2 Hz, 1H), 3.68 (dd, J = 2.7, 11.2 Hz, 1H), 3.76−3.86 (m, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 3.93 (dd, J = 3.8, 11.2 Hz, 1H), 3.99 (dd, J = 3.4, 11.2 Hz, 1H), 4.01−4.13 (m, 4H), 4.21−4.25 (m, 2H), 5.25−5.40 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ 21.0, 21.2, 30.1, 37.9, 38.1, 53.5, 53.6, 53.7, 58.5, 58.7, 63.1, 63.9, 64.4, 64.8, 69.2, 69.4, 70.2, 71.5, 72.2, 75.0, 75.2, 77.6, 78.3, 78.4, 79.0, 101.2, 101.4, 161.9, 162.0, 162.5, 169.4, 170.0, 170.2, 171.7, 172.6, 172.8; HRMS (APCI) calcd for $C_{44}H_{60}N_6NaO_{29}$ $(M + Na)^+$ 1159.3302, found 1159.3308.

Methyl (3-Azidopropyl 7,8-di-*O*-acetyl-5-amino-5-*N*,4-*O*-carbonyl-9-*O*-(methyl 7,8-di-*O*-acetyl-5-amino-5-*N*,4-*O*-carbonyl-9-*O*-(methyl 7,8-di-*O*-acetyl-5-amino-5-*N*,4-*O*-carbonyl-9-*O*-(methyl 5-amino-5-*N*,4-*O*-carbonyl-7,8,9-tri-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2- ulopyranoside)onate (28). A mixture of the donor **2a** (61.1 mg, 0.095 mmol) and the acceptor **27** (90 mg, 0.079 mmol) was dried azeotropically with toluene three times and then was dissolved in CH_2Cl_2/MeCN (v/v = 2/1, 1 mL) at rt under N_2. The solution was transferred to a round-bottomed flask containing dry 3 Å molecular sieves at rt under N_2. The resulting reaction mixture was stirred for 10 min and then was cooled to −78 °C. NIS (32 mg, 0.143 mmol) and TfOH (5 μL, 0.038 mmol) were added sequentially. The reaction temperature was gradually increased to −50 °C, and then the mixture was stirred for 1 h. After completion of the reaction (as evidenced by TLC), the reaction mixture was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was washed with a saturated aqueous $Na_2S_2O_3$ solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in MeOH (1 mL), and then Et_3N (3 μL) was added at rt under N_2. After being stirred for 5 min, the reaction mixture was neutralized with a 10% aqueous HCl solution and then was concentrated. The residue was dissolved in pyridine (200 μL), and then Ac_2O (100 μL) was added at rt under N_2. After the reaction mixture was stirred for 12 h, the solvent was removed. The residue was dissolved in EtOAc and was washed with a 10% aqueous HCl solution, and then the aqueous layer was extracted with EtOAc. The combined extracts were dried over $MgSO_4$. The solution was concentrated, and the residue was purified by silica gel flash column chromatography (hexanes/EtOAc/MeOH, from 1/1/0 to 1/1/0.2) to afford tetrasialoside **28** (66 mg, 51% over three steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77−1.83 (m, 2H), 1.93−2.04 (m, 4H), 2.04 (s, 3H), 2.13 (s, 3H), 2.14 (s, 3H), 2.15 (s, 3H), 2.16 (s, 3H), 2.17 (s, 3H), 2.22 (s, 3H), 2.23 (s, 3H), 2.24 (s, 3H), 2.83−2.88 (m, 4H), 2.98−3.07 (m, 4H), 3.25−3.35 (m, 4H), 3.37 (t, J = 6.6 Hz, 2H), 3.75 (s, 3H), 3.75 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 3.76−3.95 (m, 8H), 4.15−4.23 (m, 4H), 4.21−4.23 (m, 2H), 5.11 (dd, J = 1.6, 10.0 Hz, 1H), 5.22−5.28 (m, 3H), 5.26−5.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 20.9, 21.2, 29.2, 37.4, 37.6, 37.7, 48.3, 53.1, 53.20, 53.26, 53.3, 57.8, 57.9, 58.0, 58.1, 61.8, 62.3, 63.3, 66.6, 66.8, 66.9, 67.2, 68.7, 69.0, 73.7, 73.8, 73.9, 76.7, 76.8, 99.9, 100.01, 100.05, 100.1, 159.2, 159.3, 159.4, 159.6, 167.9, 168.1, 168.7, 169.9, 170.0, 170.7, 171.2, 171.3, 171.5; HRMS (ESI) calcd for $C_{65}H_{85}N_7NaO_{42}$ $(M + Na)^+$ 1658.4628, found 1658.4631.

3-Azidopropyl 5-Acetamido-9-*O*-(5-acetamido-9-*O*-(5-acetamido-(5-acetamido-3,5-dideoxy-DD-*glycero*-α-D-*galacto*-non-2-ulopyranosylonic acid)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonic acid)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonic acid)-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonic Acid (1). To a solution of tetrasialoside **28** (40 mg, 0.024 mmol) in EtOH (2.5 mL) and H_2O (2.5 mL) was added LiOH (17.24 mg, 0.72 mmol) at rt under N_2. After being stirred at 80 °C for 16 h, the reaction mixture was neutralized with a 10% aqueous HCl solution and then was concentrated. The residue was dissolved in H_2O (1 mL), and then $NaHCO_3$ (28 mg) and Ac_2O (16 μL) were added at rt under N_2. After being stirred for an additional 3 h, the solvent was evaporated under reduced pressure. The residue was dissolved in MeOH (1 mL), and then NaOMe (30 mg) was added at rt under N_2. After being stirred for 16 h, the reaction mixture was neutralized with DOEWX 50WX8-200 resin, and the neutralized solution was concentrated. The residue was purified by P2 biogel column chromatography, eluting with H_2O, to give tetrasialic acid **1** (13 mg, 43% yield over three steps): ^{1}H NMR (600 MHz, D_2O) δ 1.60−1.70 (m, 4H), 1.83 (m, 2H), 2.03, 2.04 (s, 12H), 2.70−2.74 (m, 4H), 3.41 (t, J = 6.2 Hz, 2H), 3.52 (dt, J = 6.2, 10.0 Hz, 1H), 3.52−3.97 (m, 29H); ^{13}C NMR (100 MHz, D_2O, acetone-d_6) δ 22.4, 22.4, 28.8, 40.5, 40.7, 48.4, 52.2, 52.3, 62.1, 63.0, 65.2, 65.40, 65.48, 67.9, 68.4, 68.54, 68.57, 68.6, 68.75, 68.78, 68.8, 68.9, 70.5, 70.6 (× 2), 70.7, 72.0, 72.6, 72.7, 100.5, 100.9, 173.9, 175.2; HRMS (MALDI) calcd for $C_{47}H_{75}N_7NaO_{33}$ $(M + Na)^+$ 1288.4304, found 1288.4324.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.