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A Practical Method for the Synthesis of Sialyl α-Glycosides

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Abstract: Addition of 2,4-dimethylbenzenesulfenyl chloride to sialic acid glycal gives *crystalline* 2-chloro-3-thiosialic acid **3** in 85% yield. Reaction of **3** with sodium thiomethoxide in acetonitrile at 0 °C affords the sialic acid donor α-2-(methylthio)-3-thiosialic acid **4** in quantitative yield. Sialylation of glycosyl acceptors **9** and **10** with **4** in the presence of phenylsulfenyl triflate (PST) as promotor in CH_3CN at −40 °C gives α-sialosides in good yield and excellent stereoselectivity. No β-sialosides are formed in either case. Removal of the auxiliary 3-(2,4-dimethylphenyl)-thio group is achieved in high yield using Ph_3SnH and AIBN in refluxing toluene. Protected GM_3 trisaccharide and 6-sial-2-yllactose were obtained on a gram scale.

Introduction

Stereoselective α-sialylation is one of the unsolved problems in carbohydrate chemistry. In this paper we describe a new 2-(methylthio)-3-thiosialic acid donor that is conveniently prepared in two steps from sialyl glycal. We show that when activated with phenylsulfenyl triflate (PST), this donor gives α-sialosides in excellent yield and stereospecificity.

Practical and stereocontrolled chemical syntheses of α-sialosides are important, because sialic acid (Neu5Ac) frequently terminates the oligosaccharide chains of glycoproteins and glycolipids that play a central role in cell surface recognition phenomena.[1] Cell surface sialosides serve as ligands for microbial toxins,[2] microbial adhesins that mediate attachment to host cells,[3] and lectins that mediate intercellular recognition.[4] Sialic acids are usually found in the terminal positions of oligosaccharides. The most abundant of these linkages include α2−3 to galactose, α2−6 to galactose or *N*-acetylgalactosamine, and α2−8 to Neu5Ac. Sialosides have been the subject of extensive research due to their potential as therapeutics, and recent reviews describe synthetic approaches to their synthesis.[5]

Sialic acid possesses a C-3 deoxy structure and exists solely as a 2α (equatorial) glycoside which is less favored in a stereoelectronic sense than a corresponding 2β (axial) glycoside. The C-2 carbon atom of sialic acid, to which sugar residues must be attached in glycosylation reactions, is quaternary and carries an electron-withdrawing carboxylate group; the formation of the carbocation is disfavored sterically and electronically. Classical methods in glycoside synthesis are, therefore, not successful. Donors based on the methyl ester of 2-halosialic acid give poor yield and stereoselectivity. Better stereoselectivity is obtained with the benzyl ester; the yield, however, remains low.[6] Stereoselectivity can also be increased with thioglycosides of sialic acid, when these compounds are activated with equimolar amounts of thiophilic reagents in nitrile

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1996.

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(2) Karlsson, K.-A. *Molecular Mechanisms of Microbial Adhesion*; Springer-Verlag: New York, 1988; pp 77−96.

(3) Sharon, N.; Lis, H. *Science* **1989**, *246*, 227−234. Paulson, J. C. *The Receptors*; Academic Press: New York, 1985; pp 131−219.

(4) Springer, T. A.; Lasky, L. A. *Nature* **1991**, *349*, 196−197. Paulson, J. C. *Adhesion: Its Role in Inflammatory Disease*; Stockton Press: New York, 1992; pp 19−42. Crocker, P. R.; Kelm, S.; Dubois, C.; Martin, B.; McWilliam, A. S.; Shotton, D. M.; Paulson, J. C.; Gordon, S. *EMBO J.* **1991**, *10*, 1661−1669.

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(6) Ratcliffe, M. R.; Venot, A. P.; Abbas, Z. S. Eur. Pat. Appl. EP 319,-253, 1990; *Chem. Abstr.* **1990**, *112*, 175281a.

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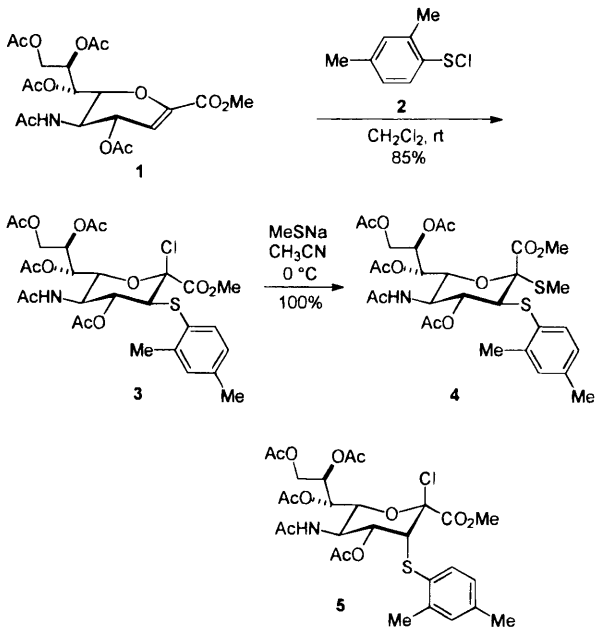
Scheme 1



solvents at low temperature.[7] A substantial amount of the sialic acid-derived donor undergoes elimination to sialyl glycal during glycosylation; this side reaction leads to modest yields. In practice, an excess of these donors (they are expensive and relatively difficult to prepare) is used in order to obtain reasonable yields.

Sialyl donors that have an auxiliary Br, OH, SPh, or SePh group have recently been introduced,[5b] in order to overcome the problem of poor stereoselectivity and glycal formation. These donors give exclusively α-sialosides and do not undergo undesired elimination to sialyl glycal. They, however, have not found wide use in carbohydrate chemistry due to the fact that multistep syntheses are required for their preparation.

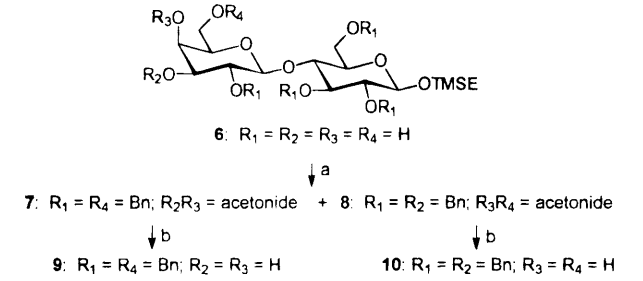
Enzymatic synthesis, on the other hand, can be used for multigram synthesis of sialosides. It is, however, generally limited to natural products and their analogs. In most cases sialosides that can be obtained using enzymes are susceptible to hydrolytic cleavage *in vivo* by sialidases. Chemical synthesis offers an advantage that analogs of sialosides can be prepared that are stable to sialidases.

Results and Discussion

We reacted sialyl glycal **1** with 2,4-dimethylbenzenesulfenyl chloride (10 equiv) in CH_2Cl_2 for two weeks at 0 °C under N_2 and obtained a *crystalline* chloride, **3**, in 85% yield.[8] The chloride **5** was formed as the only byproduct (4% yield) and remained in the mother liquor during crystallization (Scheme 1). The ratio of **3** to **5** did not change when the reaction was carried out at ambient temperature. The reaction of chloride **3** with sodium thiomethoxide (1.5 equiv) in acetonitrile at 0 °C afforded methyl thioglycoside **4** in quantitive yield. Compound **4** was indefinetely stable at 4 °C.

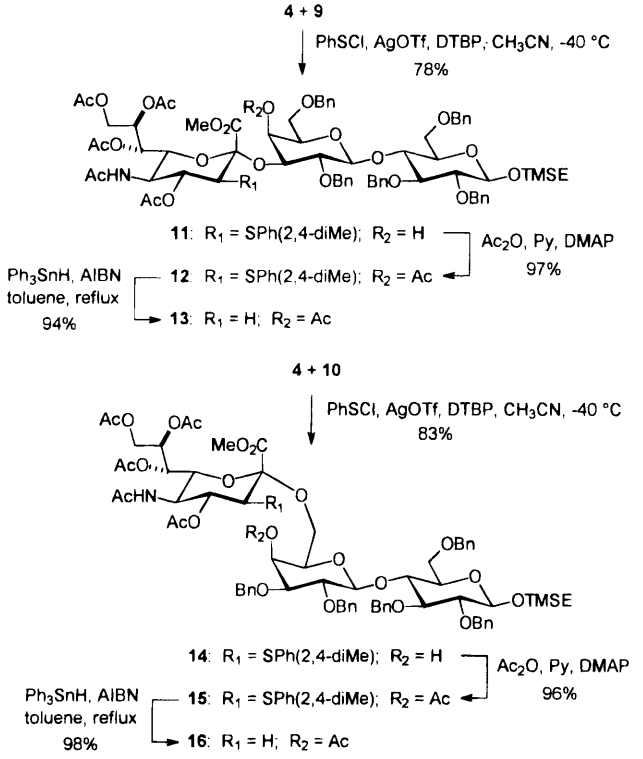
We prepared acceptors used for sialylation according to

Scheme 2[a]



[a] Reagents and conditions: (a) (i) $Me_2C(OMe)_2$, CSA catalyst, DMF, 25 °C, 1 h; (ii) NaH, BnBr, DMF; (b) aqueous AcOH, 80 °C, overall yield from **6**: **9**, 70%; **10**, 11%.

Scheme 3



Scheme 2. The (trimethylsilyl)ethyl-protected lactose **6**[9] was reacted with acetone dimethyl acetal and subsequently benzylated to give a mixture of acetonides **7** and **8** which were separated by silica gel chromatography. Removal of the acetonide group afforded acceptors **9** and **10** as crystalline materials.

Sialylation[10] of acceptors **9** and **10** with donor **4** was effectively achieved in CH_3CN at −40 °C using PST[11] as promotor and 2,6-di-*tert*-butylpyridine (DTBP) as proton scavenger (Scheme 3). Sialylation of acceptor **9** occurred selectively at the equatorial 3′-OH, rather than the axial 4′-OH, and generated the α-product **11** in 78% yield. Sialylation of **10** occurred at the primary 6′-OH, giving **14** in 83% yield. The only compounds in the product mixture were the unreacted acceptors (used in excess) and a small amount of the unreacted

(7) (a) Lönn, H.; Stenvall, K. *Tetrahedron Lett.* **1992**, *33*, 115−116. (b) Sabesan, S.; Neira, S.; Davidson, F.; Duus, J.; Bock, K. *J. Am. Chem. Soc.* **1994**, *116*, 1616−1634. (c) Martichonok, V.; Whitesides, G. M. *J. Org. Chem.* **1996**, *61*, 1702−1706.

(8) Addition of benzenesulfenyl chloride to sialic acid glycal gives a 2.3:1 mixture of diastereomeric chlorides. The desired major diastereomer was isolated by gradient column chromatography and converted to ethyl thioglycoside via a two-step procedure. See (a) Ercégovic, T.; Magnusson, G. *J. Chem. Soc., Chem. Commun.* **1994**, 831−832. (b) Ercégovic, T.; Magnusson, G. *J. Org. Chem.* **1995**, 3378−3384.

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(10) Sialylation can be performed with chloride **3** using AgOTf as promotor at −15 °C in THF for two days. The yield with acceptor **9**, however, is moderate (40−50%), the product is contaminated, and careful chromatography is required in order to obtain pure **11**.

(11) A similar procedure using methanesulfenyl triflate (MST) as promotor has been described by Magnusson.[8] MST, however, and some of the intermediates and reagents used in its preparation are toxic and unstable. Furthermore, a certain amount of O-alkylation products limit use of MST to the small-scale reactions.[7c]

donor **4**. No β-sialosides were detected in either case. Acetylation of **11**, and subsequent reductive removal of the auxiliary (2,4-dimethylphenyl)thio group using Ph_3SnH (10 equiv)/AIBN (1.2 equiv) in refluxing toluene, afforded **13**—protected GM_3 trisaccharide—in 91% yield after two steps. The same procedure for **14** afforded protected 6-sial-2-yllactose **16**—an element of many gangliosides—in 94% total yield. We applied this method for gram scale syntheses of **13** and **16** without any loss in yield and stereoselectivity.

We identified the site of sialylation in the products **11** and **14** on the basis of observation of a downfield shift of the C-4′ proton of their acetylation products. We determined the stereochemistry of the glycosidic linkage in compound **3** to be β and in compounds **4**, **11**, and **14** to be α by the measurement of the long-range $^{13}C-^{1}H$ coupling constants ($J_{^{13}C(C-1)-^{1}H(H-3,axial)}$) of the sialic acid residue using the method described by Hori.[12]

Conclusions

Addition of 2,4-dimethylbenzenesulfenyl chloride to sialyl glycal and subsequent substitution of chlorine with sodium thiomethoxide is an effective and economic method for the preparation of 2-(methylthio)-3-(phenylthio)sialic acid donor **4**. The reaction of this donor with glycosyl acceptors in the presence of PST in CH_3CN at low temperature affords α-sialosides in good yield, excellent stereoselectivity, and high purity. Donor **4** does not undergo the elimination to sialyl glycal during sialylation; good yields of α-sialosides are obtained using less than an equimolecular amount of it. Phenylsulfenyl triflate that is used as promotor for the sialylation is prepared *in situ* from silver triflate and stable benzenesulfenyl chloride. In comparison with other promotors used for thioglycosides, phenylsulfenyl triflate is nontoxic and does not give O-alkylated byproducts. Sialosides prepared using this method contain the 3-(2,4-dimethylphenyl)thio group, which is removed in high yield using Ph_3SnH.

The procedure described is superior in terms of stereospecificity, yield, simplicity, and reliability to any currently available chemical method for the preparation of sialyl α-glycosides. In terms of cost, in fact, it is superior to the enzymatic methods. It opens new avenues for the preparation of bioactive stable analogs of sialosides. We are currently studying the applications of this method for the synthesis of complex sialyl oligosaccharides.

Experimental Section

General Methods. Anhydrous reagents and solvents were prepared according to literature procedures.[13] Sialic acid was obtained from extraction of edible Chinese swiftlet's nest.[14] Sialic acid glycal was prepared according to a published procedure.[8b] 2,4-Dimethylthiophenol was obtained form Aldrich. Benzenesulfenyl chloride was synthesized by reacting phenyl thioacetate with SO_2Cl_2.[15] The proton chemical shifts for all compounds were assigned using ^{1}H homonuclear decoupling experiments.

2,4-Dimethylbenzenesulfenyl Chloride (2). To an ice-cooled suspension of *N*-chlorosuccinimide (4.61 g, 34.5 mmol) in CH_2Cl_2 (50 mL) was added dropwise within 15 min a solution of 2,4-dimethylthiophenol (4.75 g, 34.4 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at rt for 2 h, diluted with pentane (200 mL), and left overnight at 4 °C. The precipitate of succinimide was filtered, and the mother liquor was concentrated *in vacuo*. The residue was distilled *in vacuo* to give **2** (4.71 g, 75%), bp 58 °C, 0.5 mmHg (lit.[16] bp 87 °C, 2 mmHg).

Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-2-chloro-3-[(2,4-dimethylphenyl)thio]-2,3,5-trideoxy-D-*erythro*-β-L-*gluco*-2-nonulopyranosonate (3). To a solution of sialic acid glycal (3.76 g, 7.95 mmol) in CH_2Cl_2 (10 mL) cooled to −10 °C was added dropwise 2,4-dimethylbenzenesulfenyl chloride (5.43 g, 31.5 mmol), and the mixture was left under N_2 in the dark at 0 °C for 14 days. The reaction mixture was loaded on a short silica gel column and eluted with 10% ethyl acetate in $CHCl_3$ to give a mixture of chlorides **3** and **5** in a 95:1 ratio as determined by ^{1}H NMR. Compound **3** (4.38 g, 85% yield) was obtained in pure form by crystallization of the mixture from CH_2Cl_2/Et_2O/hexane: mp 95−105 °C; $[\alpha]^{23}_D$ = +2.3° (*c* 0.88, $CHCl_3$); IR (neat) 3504−3402 (br), 1753, 1749, 1665, 1372, 1221, 1035 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (s, 3 H), 1.86 (s, 3 H), 2.02 (s, 3 H), 2.07 (s, 3 H), 2.10 (s, 3 H), 2.25 (s, 3 H, *p*-CH_3 aromatic), 2.28 (s, 3 H, *o*-CH_3 aromatic), 3.68 (s, 3 H, CO_2CH_3), 3.97 (dd, *J* = 5.43, 12.58 Hz, 1 H, *H*-9), 3.98 (d, *J* = 10.71 Hz, 1 H, *H*-3), 4.24 (dd, *J* = 2.77, 12.58 Hz, 1 H, *H*-9), 4.34 (q, *J* = 9.97 Hz, 1 H, *H*-5), 4.38 (dd, *J* = 2.45, 10.89 Hz, 1 H, *H*-6), 5.08 (ddd, *J* = 2.70, 5.30, 8.11 Hz, 1 H, *H*-8), 5.33 (dd, *J* = 9.89, 10.60 Hz, 1 H, *H*-4), 5.41 (dd, *J* = 2.34, *J* = 8.15, 1 H, *H*-7), 5.45 (bd, *J* = 9.81 Hz, 1 H, N*H*COCH$_3$), 6.95 (s, 1 H, aromatic), 6.97 (d, *J* = 7.90 Hz, 1 H, aromatic), 7.41 (d, *J* = 7.90 Hz, 1 H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.49, 20.66, 20.70, 20.87, 22.98, 49.26, 53.99, 57.35, 62.04, 66.56, 69.16, 73.74, 103.18, 127.72, 129.69, 131.01, 132.22, 137.64, 139.20, 164.03 (C-1, $J_{C-1,H-3ax}$ < 1.00 Hz), 169.37, 169.86, 170.20, 170.47, 171.08; HRMS (FAB) calcd for $C_{28}H_{36}ClNO_{12}SNa$ (M + Na) 668.1544, found 668.1562. Compound **5** was obtained for analytical purposes by gradient chromatography (5% acetone in $CHCl_3$ → 10% acetone in $CHCl_3$) of the fraction of the mother liquor: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 3 H), 1.92 (s, 3 H), 2.04 (s, 3 H), 2.05 (s, 3 H), 2.19 (s, 3 H), 2.25 (s, 3 H), 2.41 (s, 3 H), 3.82 (s, 3 H, CO_2CH_3), 4.15 (dd, *J* = 5.86, 12.54 Hz, 1 H, *H*-9a), 4.19 (d, *J* = 3.84 Hz, 1 H, *H*-3), 4.39 (dd, *J* = 2.14, 10.83 Hz, 1 H, *H*-6), 4.47 (dd, *J* = 2.54, 12.50 Hz, 1 H, *H*-9b), 4.73 (q, *J* = 10.46 Hz, 1 H, *H*-5), 5.26 (ddd, *J* = 2.54, 5.86, 6.43 Hz, 1 H, *H*-8), 5.33 (bd, *J* = 9.71 Hz, 1 H, N*H*COCH$_3$), 5.41 (dd, *J* = 2.20, *J* = 6.71, 1 H, *H*-7), 5.77 (dd, *J* = 3.82, 10.66, 1 H, *H*-4), 6.94 (d, *J* = 7.90 Hz, 1 H), 6.95 (s, 1 H), 7.29 (d, *J* = 7.88 Hz, 1 H); MS (FAB) calcd for $C_{28}H_{36}ClNO_{12}SNa$ (M + Na) 668, found 668.

Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-2-chloro-3-[(2,4-dimethylphenyl)thio]-2,3,5-trideoxy-D-*erythro*-β-L-*gluco*-2-nonulopyranosonate (4). To a stirred suspension of MeSNa[17] (408 mg, 5.83 mmol) in dried MeCN (molecular sieves 4 Å) (50 mL) cooled to 0 °C was added chloride **3** (2.50 g, 3.87 mmol). The mixture was stirred at 0 °C for 3 h, after which the TLC (50% EtOAc in $CHCl_3$) indicated that the reaction was complete. The reaction mixture was diluted with a suspension of silica gel (10 g) in EtOAc (50 mL), filtered through a short silica gel column (2 × 10 cm), eluted with EtOAc, and concentrated *in vacuo* to give compound **4** (2.52 g, 100%) as a foam: $[\alpha]^{23}_D$ = +86.8° (*c* 1.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.84 (s, 3 H, SCH_3), 1.88 (s, 3 H), 2.01 (s, 3 H), 2.11 (s, 3 H), 2.12 (s, 3 H), 2.14 (s, 3 H), 2.26 (s, 3 H, *p*-CH_3 aromatic), 2.35 (s, 3 H, *o*-CH_3 aromatic), 3.46 (d, *J* = 11.09 Hz, 1 H, *H*-3), 3.79 (dd, *J* = 2.00, 10.94 Hz, 1 H, *H*-6), 3.88 (s, 3 H, CO_2CH_3), 4.07 (dd, *J* = 5.44, 12.51 Hz, 1 H, *H*-9a), 4.10 (q, *J* = 10.36 Hz, 1 H, *H*-5), 4.29 (dd, *J* = 2.68, 12.53 Hz, 1 H, *H*-9b), 5.22 (t, *J* = 10.69 Hz, 1 H, *H*-4), 5.26−5.34 (m, 3 H, *H*-7, *H*-8, N*H*), 6.94 (s, 1 H, aromatic), 6.99 (d, *J* = 8.02 Hz, 1 H, aromatic), 7.48 (d, *J* = 8.00 Hz, 1 H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.09, 20.64, 20.68, 20.73, 20.84, 21.05, 23.09, 50.46, 52.93, 58.34, 62.06, 67.42, 69.12, 73.67, 74.19, 87.22, 127.73, 130.87, 131.47, 132.96, 136.93, 138.61, 167.44, 169.97, 170.06, 170.10, 170.57, 170.91; HRMS (FAB) calcd for $C_{32}H_{43}NO_{14}SNa$ (M + Na) 720.2302, found 720.2276.

2-(Trimethylsilyl)ethyl [2,6-bis-*O*-(phenylmethyl)-β-D-galactopyranosyl]-(1,4)-2,3,6-tris-*O*-(phenylmethyl)-β-D-glucopyranoside (9) and 2-(trimethylsilyl)ethyl [2,3-bis-*O*-(phenylmethyl)-β-D-galactopyranosyl]-(1,4)-2,3,6-tris-*O*-(phenylmethyl)-β-D-glucopyranoside (10)

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(14) Roy, R.; Laferriere, C. A. *Can. J. Chem.* **1990**, *68*, 2045−2054.
(15) Thea, S.; Cevasco, G. *Tetrahedron Lett.* **1988**, *29*, 2865−2866.
(16) Almasi, L; Hanz, A. *Chem Ber.* **1961**, *94*, 725−728.
(17) It is important to weigh sodium thiomethoxide in a glovebox and to use dry CH_3CN.

were prepared according to a modified published procedure.[9] Reaction of TMSE-protected lactose **6** with acetone dimethyl acetal and subsequent benzylation afforded a mixture of acetonides **7** and **8**, not just **7** as reported.[9] This mixture was separated by column chromatography on silica gel eluting with 10% EtOAc in toluene. Treatment of **7** with 80% aqueous acetic acid gave known[7c] acceptor **9** in 70% overall yield. The same reaction of acetonide **8** afforded acceptor **10** in 11% overall yield. Compound **10** was crystallized from Et_2O/pentane: $R_f = 0.31$ (33% EtOAc in hexanes); mp 112−114 °C; $[\alpha]^{23}_D = +23.8°$ (*c* 1.33, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) −0.14 (s, 9 H, $Si(CH_3)_3$), 0.96−1.07 (m, 2 H, CH_2TMS), 2.20−2.38 (br s, 1 H, O*H*-6), 2.42 (d, $J = 9.16$ Hz, 1 H, O*H*-4), 3.03 (m, 1 H, *H*-5′), 3.15 (dd, $J = 3.27$, 9.29 Hz, 1 H, *H*-3′), 3.41 (br dd, $J = 2.51$, 9.84 Hz, 1 H, *H*-5), 3.55−3.66 (m, 4 H, OCH_2CH_2TMS, *H*-2, *H*-6a′, *H*-6b′), 3.71 (t, $J = 9.00$ Hz, 1 H, *H*-3), 3.74−3.84 (m, 3 H, H-2′, H-6a, H-4′), 3.96 (dd, $J = 4.06$, 10.94 Hz, 1 H, *H*-6b), 4.08−4.14 (m, 1 H, OCH_2CH_2-TMS), 4.24 (dt, $J = 2.11$, 9.38 Hz, 1 H, *H*-4), 4.36−4.41 (m, 3 H, 3 CH_2Ph), 4.43 (d, $J = 7.71$ Hz, 1 H, *H*-1), 4.52 (d, $J = 12.13$ Hz, 1 H), 4.58 (d, $J = 7.83$ Hz, 1 H, 1 H′), 4.78 (d, $J = 11.36$ Hz, 1 H), 4.86 (d, $J = 11.79$ Hz, 1 H), 4.89 (d, $J = 11.46$ Hz, 1 H), 4.94 (d, $J = 10.82$ Hz, 1 H), 5.08 (d, $J = 11.51$ Hz, 1 H), 5.26 (d, $J = 10.82$ Hz, 1 H), 7.05−7.32 (m, 19 H, aromatic), 7.39 (d, $J = 7.40$ Hz, 2 H, aromatic), 7.44 (d, $J = 7.60$ Hz, 2 H, aromatic), 7.62 (d, $J = 7.62$ Hz, 2 H, aromatic); HRMS (FAB) calcd for $C_{52}H_{64}O_{11}SiNa$ (M + Na) 915.4116, found 915.4110.

2-(Trimethylsilyl)ethyl 2,3,6-Tri-*O*-benzyl-4-*O*-{2,6-di-*O*-benzyl-3-*O*-[methyl [5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-3-[(2,4-dimethyphenyl)thio]-D-*erythro*-α-L-*gluco*-2-nonulopyranosid]onate]-β-D-galactopyranosyl}-β-D-glucopyranoside (11). Toluene (2 × 20 mL) was evaporated from the mixture of **4** (591 mg, 0.9 mmol) and **9** (981 mg, 1.1 mmol). The mixture was dissolved in CH_3CN (20 mL) and DTBP (337 μL, 1.5 mmol) and dried, and crushed molecular sieves 4 Å (3.0 g) were added. The mixture was stirred at rt for 0.5 h, then AgOTf (308 mg, 1.20 mmol) was added, and stirring was continued in the dark for an additional 1 h. After cooling to −40 °C, PhSCl (116 μL, 0.19 mmol) was added dropwise and the mixture was stirred at −40 °C for 1 h. Diisopropylamine (280 μL, 0.35 mmol) was added, and the mixture was stirred at −40 °C for 0.5 h. A suspension of silica gel (10 g) in EtOAc (75 mL) was added to the cold reaction mixture. After filtration through a fritt and concentration *in vacuo*, the reaction mixture was chromatographed, eluting with 10% acetone in $CHCl_3$ → 15% acetone in $CHCl_3$ to give trisaccharide **11** (1.05 g, 78%): $R_f = 0.48$ (20% acetone in $CHCl_3$); $[\alpha]^{23}_D = +13.7°$(*c* 0.99, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ −0.37 (s, 9 H, $CH_2Si(CH_3)_3$), 0.99 (m, 2 H, $CH_2Si(CH_3)_3$), 1.54 (s, 3 H), 1.69 (s, 3 H), 1.70 (s, 3 H), 1.83 (s, 3 H), 1.92 (s, 3 H), 2.01 (s, 3 H, CH_3 aromatic), 2.20 (s, 3 H, CH_3 arom), 3.03 (br s, 1 H, 4-O*H*), 3.40 (m, 1 H, *H*-5), 3.47 (s, 3 H, CO_2CH_3), 3.50 (d, $J = 11.37$ Hz, 1 H, *H*-3″), 3.58 (t, $J = 8.92$ Hz, 1 H, *H*-2), 3.61 (m, 1 H, $OCH_2CH_2Si(CH_3)_3$), 3.69 (dd, $J = 5.55$, 9.55 Hz, 1 H, *H*-6a′), 3.75 (t, $J = 9.10$ Hz, 2 H, *H*-3), 3.77 (t, $J = 9.53$ Hz, 1 H, *H*-2′), 3.88 (m, 1 H, *H*-5′), 3.89 (br s, 1 H, *H*-4′), 3.95 (dd, $J = 4.33$, 10.95 Hz, 1 H, *H*-6a), 3.99 (dd, $J = 7.20$, 9.55 Hz, 1 H, *H*-6b′), 4.10 (dt, $J = 7.00$, 9.50 Hz, 1 H, $OCH_2CH_2Si(CH_3)_3$), 4.16 (dd, $J = 6.37$, 12.52 Hz, 1 H, *H*-9a″), 4.22 (dd, $J = 2.31$, 10.85 Hz, 1 H, *H*-6″), 4.22−4.34 (m, 4 H, *H*-6b, *H*-4, N*H* C NNH_2Ph), 4.43 (d, $J = 7.55$ Hz, 1 H, *H*-1), 4.44 (d, $J = 11.98$ Hz, 1 H), 4.56 (d, $J = 11.89$ Hz, 1 H), 4.63 (d, $J = 11.25$ Hz, 1 H), 4.65 (m, 2 H, *H*-5″, *H*-9″), 4.69 (d, $J = 12.55$ Hz, 1 H), 4.73 (dd, $J = 3.24$, 9.44 Hz, 1 H, *H*-3′), 4.86 (d, $J = 11.57$ Hz, 1 H), 4.90 (d, $J = 12.58$ Hz, 1 H), 4.92 (d, $J = 7.89$ Hz, 1 H, *H*-1′), 4.96 (d, $J = 10.95$ Hz, 1 H), 5.07 (d, $J = 11.47$ Hz, 1 H), 5.30 (d, $J = 10.94$ Hz, 1 H), 5.42 (dd, $J = 2.30$, 7.69 Hz, 1 H, *H*-7″), 5.48 (t, $J = 10.77$ Hz, 1 H, *H*-4″), 5.69 (dt, $J = 2.50$, 7.80 Hz, 1 H, *H*-8″), 6.70 (s, 1 H), 6.74 (d, $J = 7.99$ Hz, 1 H), 7.05−7.68 (m, 26 H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.43, 18.46, 20.51, 20.61, 20.64, 20.80, 20.93, 23.15, 49.89, 52.83, 57.37, 62.14, 67.09, 67.13, 67.25, 68.59, 68.71, 72.44, 72.51, 72.54, 72.96, 73.18, 74.10, 74.88, 76.36, 76.68, 77.00, 77.32, 78.40, 82.01, 82.78, 100.44, 102.49, 103.01, 126.83, 127.13, 127.18, 127.29, 127.33, 127.40, 127.42, 127.47, 128.17, 128.22, 128.35, 130.13, 131.11, 134.28, 138.21, 138.46, 138.72, 138.83, 139.15, 139.24, 140.18, 168.56, 169.31, 169.95, 170.21, 170.45, 170.95; MS (FAB) calcd for $C_{80}H_{99}NO_{23}SSiNa$ (M + Na) 1524, found 1524.

2-(Trimethylsilyl)ethyl 2,3,6-tri-*O*-benzyl-4-O-{2,3-di-*O*-benzyl-6-*O*-[methyl [5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-3-[(2,4-dimethyphenyl)thio]-D-*erythro*-α-L-*gluco*-2-nonulopyranosid]onate]-β-D-galactopyranosyl}-β-D-glucopyranoside (14) was prepared in 83% yield from **4** and **10** using the procedure for preparation of **11**: $R_f =$ 0.45 (20% acetone in $CHCl_3$); $[\alpha]^{23}_D = +17.2°$ (*c* 1.02, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ 0.00 (s, 9 H, $CH_2Si(CH_3)_3$), 1.00−1.10 (m, 2 H, $CH_2Si(CH_3)_3$), 1.60 (s, 3 H), 1.66 (s, 3 H), 1.85 (s, 3 H), 1.86 (s, 3 H), 1.98 (s, 3 H), 2.21 (s, 3 H, CH_3 aromatic), 2.35 (s, 3 H, CH_3 aromatic), 2.75 (dd, $J = 4.03$, 8.30, 1 H), 2.98 (d, $J = 3.06$, 1 H, 4′-O*H*), 2.36 (dd, $J = 3.99$, 9.58 Hz, 1 H, *H*-5′), 3.31 (dd, $J = 3.11$, 9.44 Hz, 1 H, *H*-3′), 3.36 (m, 1 H, *H*-5), 3.38 (d, $J = 10.86$ Hz, 1 H, *H*-3″), 3.52 (s, 3 H, CO_2CH_3), 3.61−3.66 (m, 2 H, *H*-2, $OCH_2CH_2Si(CH_3)_3$), 3.70 (t, $J = 8.85$ Hz, 1 H, *H*-3), 3.73 (t, $J = 9.46$ Hz, 1 H, *H*-4), 3.91 (dd, $J = 8.03$, 9.25 Hz, 1 H, *H*-2′), 3.99 (dd, $J = 4.06$, 9.88 Hz, 1 H, *H*-6a), 4.04 (t, $J = 9.33$, Hz, 1 H, *H*-6b), 4.12 (m, 1 H, $OCH_2CH_2Si(CH_3)_3$), 4.18 (dd, $J = 7.02$, 12.50 Hz, 1 H, *H*-9a″), 4.20 (dd, $J = 9.47$, 11.20 Hz, 1 H, *H*-6b′), 4.30 (t, $J = 2.73$ Hz, 1 H, *H*-4′), 4.42 (d, $J = 12.21$ Hz, 1 H), 4.44 (d, $J = 7.59$ Hz, 1 H, *H*-1), 4.48 (d, $J = 12.12$ Hz, 1 H), 4.50 (dd, $J = 2.24$, 10.67 Hz, 1 H, *H*-6″), 4.51 (d, $J = 7.77$ Hz, 1 H, *H*-1′), 4.56 (d, $J = 11.64$ Hz, 1 H), 4.62 (dd, $J = 2.73$, 12.36 Hz, 1 H, *H*-9b″), 4.69 (q, $J = 10.64$ Hz, 1 H, *H*-5″), 4.78−4.84 (m, 3 H), 4.92 (d, $J = 10.49$ Hz, 1 H), 5.04 (d, $J = 11.63$ Hz, 1 H), 5.18 (d, $J = 11.62$ Hz, 1 H), 5.24 (d, $J = 10.49$ Hz, 1 H), 5.45 (dd, $J = 2.21$, 7.51 Hz, 1 H, *H*-7″), 5.66 (dt, $J = 2.76$, 7.24 Hz, 1 H, *H*-8″), 5.77 (t, $J = 10.52$ Hz, 1 H, *H*-4″), 6.76 (s, 1 H), 6.79 (d, $J = 7.97$ Hz, 1 H), 7.06−7.68 (m, 26 H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.41, 18.46, 20.61, 20.66, 20.75, 20.81, 21.10, 23.12, 49.73, 52.51, 54.70, 60.33, 62.32, 64.35, 67.27, 68.29, 68.98, 71.13, 72.12, 72.25, 72.42, 73.10, 74.74, 74.78, 75.10, 75.20, 77.18, 79.32, 80.74, 81.74, 82.63, 101.29, 102.86, 103.10, 127.26, 127.38, 127.43, 127.47, 127.53, 127.57, 127.63, 127.77, 127.95, 128.00, 128.17, 128.22, 128.26, 128.29, 129.38, 130.96, 134.34, 138.36, 138.39, 138.42, 138.74, 139.30, 140.47, 167.83, 169.39, 170.00, 170.24, 170.62, 171.01; MS (FAB) calcd for $C_{80}H_{99}NO_{23}SSiNa$ (M + Na) 1524, found 1524.

2-(Trimethylsilyl)ethyl 2,3,6-Tri-*O*-benzyl-4-*O*-{2,6-di-*O*-benzyl-4-*O*-acetyl-3-*O*-[methyl [5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-3-[(2,4-dimethyphenyl)thio]-D-*erythro*-α-L-*gluco*-2-nonulopyranosid]onate]-β-D-galactopyranosyl}-β-D-glucopyranoside (12). Compound **11** (1.43 g, 0.95 mmol) was acetylated in a mixture of CH_2Cl_2 (10 mL), pyridine (5 mL), Ac_2O (2.5 mL), and a few crystals of DMAP to give **12** (1.42 g, 97%): $R_f = 0.51$ (33% CH_3CN in toluene); $[\alpha]^{23}_D = +18.6°$ (*c* 1.61, $CHCl_3$); a signal for *H*-4′ in ^1H NMR (500 MHz, C_6D_6) was detected at δ 5.84 (d, $J = 3.26$ Hz); MS (FAB) calcd for $C_{82}H_{101}NO_{24}SSiNa$ (M + Na) 1566, found 1566.

2-(Trimethylsilyl)ethyl 2,3,6-Tri-*O*-benzyl-4-*O*-{2,3-di-*O*-benzyl-4-*O*-acetyl-6-*O*-[methyl [5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-3-[(2,4-dimethyphenyl)thio]-D-*erythro*-α-L-*gluco*-2-nonulopyranosid]onate]-β-D-galactopyranosyl}-β-D-glucopyranoside (15). Compound **15** was prepared in 96% yield as described for **12**: $R_f =$ 0.52 (33% CH_3CN in toluene); $[\alpha]^{23}_D = +19.8°$ (*c* 1.22, $CHCl_3$); a signal for *H*-4′ in ^1H NMR (500 MHz, C_6D_6) was detected at δ 5.66 (d, $J = 3.59$); MS (FAB) calcd for $C_{82}H_{101}NO_{24}SSiNa$ (M + Na) 1566, found 1566.

2-(Trimethylsilyl)ethyl 2,3,6-Tri-*O*-benzyl-4-*O*-{4-*O*-acetyl-2,6-di-*O*-benzyl-3-*O*-[methyl [5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*erythro*-α-L-*gluco*-2-nonulopyranosid]onate]-β-D-galactopyranosyl}-β-D-glucopyranoside (13). AIBN (170 mg, 1.04 mmol) was added in small portions every 1 h over a period of 10 h to the mixture of **12** (1.26 g, 0.82 mmol) and Ph_3SnH (2.88 g, 0.82 mmol) in refluxing toluene (60 mL) under N_2. The reaction was then refluxed for an additional 5 h, cooled, and applied directly to a silica gel column. Elution (20% acetonitrile in toluene → 33% acetonitrile in toluene, gradient) gave the unreacted starting material **12** (49 mg, 4%) and the product **13** (1.08 g, 94%): $R_f = 0.38$ (33% CH_3CN in toluene), $[\alpha]^{23}_D = -7.2°$ (*c* 0.85, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ −0.29 (s, 9H, $Si(SH_3)_3$), 0.98 (m, 2H, $CH_2Si(SH_3)_3$), 1.59 (s, 3H), 1.60 (s, 3H), 1.74 (s, 3H), 1.76 (s, 3H), 1.81 (s, 3H), 2.00 (t, $J = 12.70$ Hz, 1 H, *H*-3ax″), 2.09 (s, 3H), 2.84 (dd, $J = 4.68$, 12.71 Hz, 1 H, *H*-3eq″), 3.38−3.47 (m, 3 H, *H*-5, *H*-5′, *H*-6a′), 3.57−3.63 (m, 3 H, *H*-2, *H*-6″, OCH_2CH_2-TMS), 3.74 (t, $J = 9.04$, 1 H, *H*-3), 3.79 (s, 3 H, CO_2CH_3), 3.83 (dd, $J = 7.88$, 9.46 Hz, 1 H, *H*-2′), 3.92 (d, $J = 10.45$, 1 H), 3.96 (dd, $J =$

1.60, 10.94 Hz, 1 H, *H*-6a), 4.00 (dd, *J* = 4.24, 10.94 Hz, 1 H, *H*-6b), 4.06−4.12 (m, 2 H, OCH_2CH_2TMS, *H*-6b′), 4.28 (dd, *J* = 5.30, 12.55 Hz, 1 H, *H*-9a″), 4.36−4.43 (m, 4 H, CH_2Ph, *H*-5″, *H*-1, *H*-4), 4.60 (bd, *J* = 11.70 Hz, 2 H, CH_2Ph, *H*-9b″), 4.77 (d, *J* = 12.03 Hz, 1 H), 4.83 (d, *J* = 11.67 Hz, 1 H), 4.87 (d, *J* = 12.57 Hz, 1 H), 4.90 (dt, *J* = 4.53, 11.86 Hz, 1 H, *H*-4″), 4.94−4.98 (m, 2 H, *H*-3′), 5.06 (bd, *J* = 12.00 Hz, 1 H, two CH_2Ph), 5.17 (d, *J* = 7.60 Hz, 1 H, *H*-1′), 5.33 (d, *J* = 10.88 Hz, 1 H), 5.43 (dd, *J* = 2.64, 8.68 Hz, 1 H, *H*-7″), 5.48 (d, *J* = 3.28 Hz, 1 H, *H*-4′), 5.96 (ddd, *J* = 2.63, 5.20, 8.25 Hz, 1 H, *H*-8″), 7.00−7.65 (m, 25 H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.45, 18.43, 20.37, 20.69, 20.75, 21.21, 23.13, 37.52, 49.10, 53.02, 62.02, 66.99, 67.24, 67.53, 68.45, 68.60, 68.90, 69.48, 71.31, 72.13, 72.75, 73.09, 73.80, 74.82, 74.92, 74.95, 76.62, 76.69, 77.00, 77.32, 79.42, 81.98, 82.82, 97.26, 102.04, 102.92, 126.95, 127.04, 127.15, 127.27, 127.38, 127.43, 127.58, 127.70, 127.90, 127.99, 128.06, 128.14, 128.18, 138.13, 138.65, 138.72, 139.26, 139.36, 167.82, 169.84, 169.91, 170.27, 170.49, 170.75; MS (FAB) calcd for $C_{74}H_{93}NO_{24}SiNa$ (M + Na) 1430, found 1430.

2-(Trimethylsilyl)ethyl 2,3,6-tri-*O*-benzyl-4-*O*-{4-*O*-acetyl-2,3-di-*O*-benzyl-6-*O*-[methyl [5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*erythro*-α-L-*gluco*-2-nonulopyranosid]onate]-β-D-galactopyranosyl}-β-D-glucopyranoside (16) was prepared in 98% yield from **15** (730 mg, 0.47 mmol) utilizing the procedure for the preparation of **13**: R_f = 0.38 (33% CH_3CN in toluene); $[\alpha]^{23}_D = -1.9°$ (*c* 2.62, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ −0.27 (s, 9H, $Si(CH_3)_3$), 0.99 (m, 2H, $CH_2Si(CH_3)_3$), 1.57 (s, 3H), 1.58 (s, 3H), 1.81 (s, 3H), 1.84 (s, 3H), 1.95 (s, 3H), 2.05 (s, 3H), 2.12 (t, *J* = 12.73 Hz, 1 H, *H*-3ax″), 2.80 (dd, *J* = 4.65, 12.78 Hz, 1 H, *H*-3eq″), 3.42 (dd, *J* = 3.49, 9.70 Hz, 1 H, *H*-3′), 3.44 (s, 3 H, CO_2CH_3), 3.51 (ddd, *J* = 1.55, 4.85, 9.52 Hz, 1 H, *H*-5), 3.60 (dd, *J* = 7.76, 8.90 Hz, 1 H, *H*-2), 3.63 (m, 1 H, OCH_2CH_2TMS), 3.70 (m, 2 H, *H*-5′, *H*-6a′), 3.78 (t, *J* = 8.96 Hz, 1 H, *H*-2′), 3.80 (dd, *J* = 7.86, 9.50 Hz, 1 H, *H*-3), 3.91 (dd, *J* = 1.46, 10.85 Hz, 1 H, *H*-6a), 3.99 (dd, *J* = 4.94, 10.93 Hz, 1 H, *H*-6b), 4.10 (dd, *J* = 2.05, 10.23 Hz, 1 H, *H*-6″), 4.12 (m, 1 H, OCH_2CH_2TMS), 4.18 (m, 2 H, *H*-6b′, NH), 4.29 (dd, *J* = 6.56, 12.35 Hz, 1 H, *H*-9a″), 4.34 (t, *J* = 9.52 Hz, 1 H, *H*-4), 4.35 (d, *J* = 11.15 Hz, 1 H),4.40−4.47 (m, 3 H, CH_2Ph, *H*-5″, *H*-1), 4.56 (d, *J* = 12.27 Hz, 1 H), 4.69 (dd, *J* = 2.63, 12.31 Hz, 1 H, *H*-9b″), 4.79 (d, *J* = 11.10 Hz, 1 H), 4.82 (d, *J* = 12.43 Hz, 1 H), 4.83 (d, *J* = 11.69 Hz, 1 H), 4.84 (d, *J* = 7.80 Hz, 1 H, *H*-1′), 4.85 (d, *J* = 10.33 Hz, 1 H), 4.86 (dt, *J* = 4.65, 11.91 Hz, 1 H, *H*-4″), 5.02 (d, *J* = 11.18 Hz, 1 H), 5.06 (d, *J* = 11.62 Hz, 1 H), 5.34 (d, *J* = 11.15 Hz, 1 H), 5.47 (dd, *J* = 2.25, 7.31 Hz, 1 H, *H*-7″), 5.74 (d, *J* = 3.43 Hz, 1 H, *H*-4′), 5.78 (dt, *J* = 2.65, 6.87 Hz, 1 H, *H*-8″), 7.06 −7.44 (m, 23 H, aromatic), 7.68 (d, *J* = 7.36 Hz, 2 H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.43, 18.49, 20.69, 20.80, 20.82, 20.87, 20.99, 23.19, 37.75, 49.41, 52.87, 62.28, 62.69, 66.19, 67.30, 67.35, 68.49, 68.86, 68.90, 71.28, 71.98, 72.74, 73.05, 74.73, 75.18, 76.68, 77.00, 77.21, 77.32, 79.37, 80.09, 81.92, 82.83, 98.91, 102.12, 103.07, 127.16, 127.40, 127.45, 127.64, 127.67, 127.93, 128.03, 128.10, 128.20, 128.27, 128.28, 137.86, 138.45, 138.59, 138.74, 139.26, 167.81, 169.62, 170.00, 170.07, 170.19, 170.56, 170.95; MS (FAB) calcd for $C_{74}H_{93}NO_{24}SiNa$ (M + Na) 1430, found 1430.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for compounds **3**, **4**, **11**, **13**, **14**, and **16** and ^1H NMR for compound **10** (13 pages). See any current masthead page for ordering and Internet access instructions.

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