Stereoselective α-Sialylation with Sialyl Xanthate and Phenylsulfenyl Triflate as a Promotor

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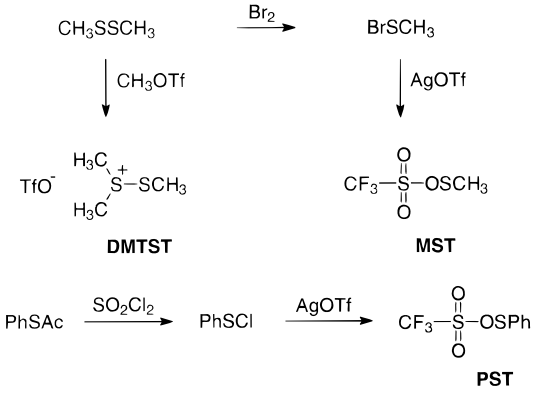
Reaction α- and β-xanthates **2** and **3** of sialic acid with glycosyl acceptors **5**−**8** in the presence phenylsulfenyl triflate (PST) as a promotor in a 2:1 mixture of CH_3CN/CH_2Cl_2 at low temperature affords α-sialosides in good yield and stereoselectivity. PST is prepared *in situ* by reacting benzenesulfenyl chloride with silver triflate. Less reactive acceptors **5** and **6** give a higher α/β ratio than more reactive allylic alcohol **7** and primary alcohol **8**; α-stereoselectivity is increased in a dilute solution. A possible mechanism of the reaction that involves intermediate α- and β-nitrilium cations **16** and **17** is discussed.

Introduction

Here we report an efficient α-stereoselective synthesis of sialyl glycosides using phenylsulfenyl triflate (PST) as a new promotor for sialyl xanthates **2** and **3** (Scheme 1). Sialic acid (Neu5Ac) frequently terminates the oligosaccharide chains of the 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 crucial in intercellular recognition.[4] Sialosides have been the subject of extensive research, and recent reviews describe synthetic approaches to their synthesis.[5]

Enzymatic synthesis has been used for multigram syntheses of sialosides.[6] It is, however, generally limited to natural products, or to close structural analogs of them, by the specificities of these enzymes. Practical and stereocontrolled chemical syntheses are of particular interest, especially for the preparation of analogs of sialosides. Recent reports have established the potential in oligosaccharide synthesis of thioglycosides and of sialic acid xanthate **3** when these compounds are activated with equimolar amounts of thiophilic reagents in nitrile solvents at low temperature.[7] Dimethyl(methylthio)-sulfonium triflate (DMTST)[8] and methylsulfenyl triflate (MST)[9] are the most effective activators; DMTST is prepared from dimethyl disufide and methyl triflate. MST is usually prepared *in situ* from methanesulfenyl bromide and silver triflate. Methanesulfenyl bromide in turn is synthesized from dimethyl disulfide and bromine and is unstable. Both DMTST and MST are unstable and



toxic, and some of the intermediates and reagents used in their preparation also are toxic, unstable, and expensive. Toxicity and a certain amount of O-alkylation limits their use to the small-scale reactions. Although the desired α-product is formed predominantly in nitrile solvents, as much as 30% of the undesired β-product has been reported in some cases.[10] A substantial amount of the sialic acid-derived donor undergoes elimination to sialyl glycal **4**; this side reaction decreases yields of the α-product to modest values.

In this paper we show that α-sialyl glycosides can be efficiently prepared from sialyl xanthates **2** and **3** using PST as a promotor. PST is, in fact, superior to both DMTST and MST. We demonstrate that this procedure can be used for a gram-scale synthesis of protected GM3 trisaccharide **10**. We discuss a possible mechanism of the reaction.

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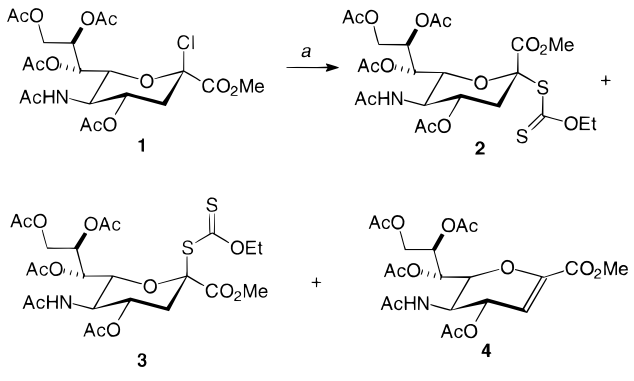
Table 1. Sialylation with Sialyl Xanthate 2

acceptor	donor/acceptor ratio	promotor	conditions[a]	product	yield[b] (%)	α:β
5	1:1.3	PhSCl/AgOTf	−70 °C → −40 °C/3 h	**9**	63	94:6
5	1:1.3	PhSCl/AgOTf/DTBP	−70 °C/3 h	**9**	74	95:5
6	1:1.5	PhSCl/AgOTf	−70 °C → −40 °C/3 h	**10**	61	96:4
6	1.5:1	PhSCl/AgOTf/DTBP	−70 °C/3 h	**10**	78[c]	96:4[d]
7	1:1.2	PhSCl/AgOTf/DTBP	−70 °C → −40 °C/3 h[e]	**11**	48	83:17
7	1.5:1	PhSCl/AgOTf/DTBP	−70 °C/15 min[e]	**11**	54	90:10
8	1:1.5	PhSCl/AgOTf	−70 °C → −40 °C/1 h	**12**	59	84:16
6	1:1.3	MeSBr/AgOTf[f]	−70 °C/1 h	**10**	31	86:14

[a] The concentration of **2** was ~0.05 mol/L; the ratio **2**:PhSCl:AgOTf:DTBP was 1:1.05:1.1:1.2. [b] The yield was determined by ^{1}H NMR and refers to a mixture of α- and β-anomers. [c] The isolated yield. [d] A ratio of >99:1 was obtained in a diluted solution, with the concentration of the donor **2** ≈ 0.01 mol/L, albeit in 52% yield. [e] The ratio **2**:PhSCl:AgOTf:DTBP was 1:1.05:1.1:2.5.

Scheme 1

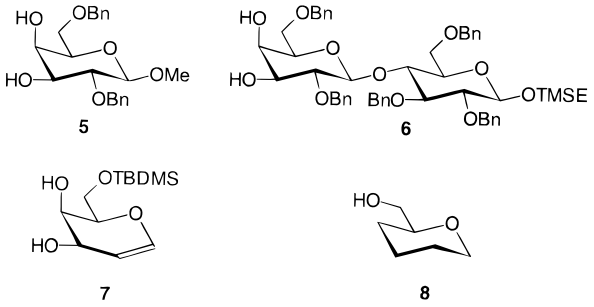


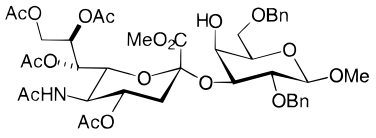
(a) KSC(S)OEt, acetone, rt

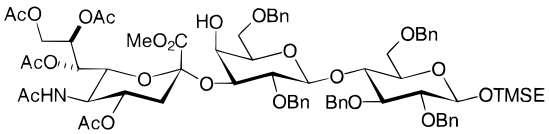
Results and Discussion

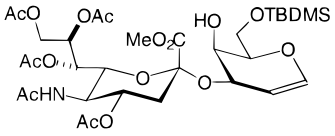
Preparation of Sialyl Xanthates. When sialyl chloride **1** was allowed to react with *O*-ethyl *S*-potassium dithiocarbonate in acetone at ambient temperature, a mixture of α- and β-sialyl xanthates **2** and **3** and glycal **4** was obtained (Scheme 1) in molar ratio 16:1:3, as determined by ^{1}H NMR. The proportion of glycal/product was increased when the reaction was carried out at 0 °C. α-Sialyl xanthate **2** was reported as the only a product when the reaction was carried out in EtOH.[11] We obtained the same product ratio in this solvent as in acetone. Chromatographic separation gave xanthates **2** and **3**, which were contaminated with sialyl glycal **4**, probably due to their partial decomposition on silica gel.

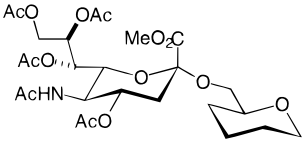
Sialylation. MST is less reactive than DMTST and, according to literature data, is more effective than DMTST for α-sialylation in terms of yield and stereoselectivity. We reasoned that PST, which is less reactive then MST, would be even better. PST was prepared *in situ* by reacting benzenesulfenyl chloride with silver triflate. Benzenesulfenyl chloride was synthesized by reacting phenyl thioacetate with SO_2Cl_2.[12] It also can be conveniently prepared by treatment of thiophenol or diphenyl disulfide with Cl_2 or SO_2Cl_2.[13] We found that unlike unstable methanesulfenyl bromide, benzenesulfenyl chloride was stable for at least 10 months at 4 °C under nitrogen. Sialylation of acceptors **5**−**8** with xanthate **2** was studied in a 2:1 mixture of acetonitrile/dichloromethane under conditions that are summarized in Table 1. Sialylation of acceptors **5**−**7** occurred at the more reactive 3-OH and gave rise to the predominantly α-products **9**−**11**. Racemic alcohol **8** was used as a model for NeuAc-2,6-Gal linkage that often occurs as an element in gangliosides. Compound **12** was obtained as a diastereomeric mixture.











The yield and purity of the product increased when di-*tert*-butylpyridine (DTBP) was used as a proton scavenger. We note that less reactive alcohols **5** and **6** gave a higher α/β ratio than more reactive allylic alcohol **7** and primary alcohol **8**. This ratio is reversed relative to that which was observed with sialyl chloride **1** in in the presence of silver or mercury salts. Furthermore, we observed that α-stereoselectivity increased when the

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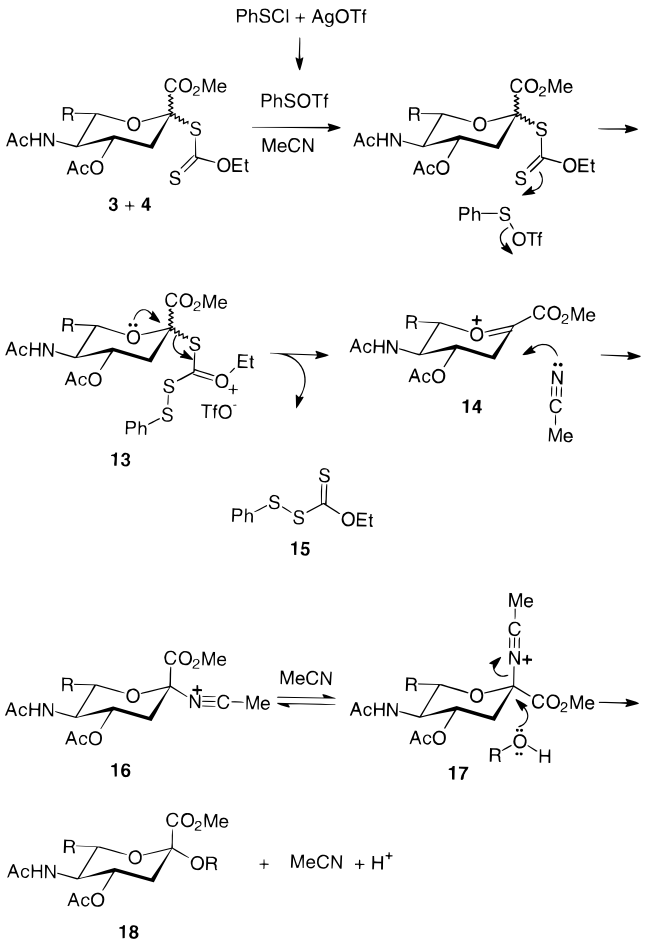
Scheme 2



reaction was conducted in a dilute solution, although the yield was lower. Only α-product **10** was detected by ^{1}H NMR with 1.5 equiv of donor **2** relative to acceptor **6** in a dilute solution. The yields of products **9**, **10**, and **12** were good; the yield of **11** was somewhat lower because PST can add to the double bond of the galactosyl glycal **7**. About 30% of the unreacted xanthate **2** was detected in this reaction. Sialyl glycal **4** was formed as a byproduct of the reaction.

We found that sialylation of lactosyl acceptor **6** with pure *β*-xanthate **3** gave the same α/*β* ratio of the product **10** as sialylation with α-xanthate **2**. For large-scale sialylations compounds **2**, **3**, and **4** were not separated. Using the crude reaction mixture of **2**, **3**, and **4** as sialyl donor, we prepared **10**—protected GM3 trisaccharide—on a gram scale.

The site of sialylation in the product **10** was determined by acetylation and observation of a downfield shift of the C-4′ proton. The stereochemistry of the new glycosidic linkage in products **9**−**12** was determined to be α on the basis of the occurrence of the NeuAc H-4 at ∼4.8 ppm as well as the $J_{\text{NeuAc7-8}} > 7.0$ Hz.[14] The stereochemistry of **10** was also confirmed by the measurement of the long-range coupling constant $J_{\text{C-1,H-3ax}} = 5.10$ Hz of the sialic acid residue.[15] In addition, the anomeric configuration of **2** and **3** was confirmed by the chemical shift difference between the two hydrogen atoms at position 9 [$\Delta\delta$(H(9) − H(9′))]: $\Delta\delta = 0.50$ ppm for α-**2**, $\Delta\delta = 0.14$ ppm for *β*-**3**.[14] The α/*β* ratios were determined by integration of $H(3)_{eq}$ signals in ^{1}H NMR spectra. Chemical shifts were smaller for *β*-glycosides (in the range 2.58−2.42 ppm for *β*-anomers of compounds **2**, **3**, **9**−**12**) than for α-glycosides (in the range 2.67−2.51 ppm for compounds **2**, **3**, **9**−**12**).[16]

Mechanism of the Reaction. We propose that in the first step sialyl xanthate reacts with PST to give the oxonium cation **14** via the formation of the intermediate **13** (Scheme 2). This conjecture is supported by the following facts: (i) the α/*β* ratio of the final product is independent of the stereochemistry of the starting xanthate; (ii) compound **15** was isolated in 86% as a major byproduct of the reaction. In the second step oxonium cation **14** is stabilized by reaction with acetonitrile to form nitrilium cations **16** and **17**. Nitrilium cations have been evoked to explain the stereoselectivities of glycosilation in acetonitrile solvents.[17] According to our semiempirical MO calculations (PM3[18] molecular model), **16** (R = Me) is 1.46 kcal/mol more stable than **17**. The nitrilium cation **16** is probably formed first due to kinetic and thermodynamic control. The attack of acetonitrile from the *re* side of **14** to form **17** is hindered by unfavorable steric interactions with protons at C-4 and C-6 of the sialic acid; both **16** and **17** are probably formed in this step. We assume that the nitrilium cations **16** and **17** are in equilibrium. In the third step acceptor ROH reacts with the cation **17** to give α-product **18**. Attack on cation **16** is very hindered due to protons at C-4 and C-6 and to the CO_2Me group. A small amount of the *β*-product is formed by reaction of the acceptor ROH with oxonium cation **14**. More reactive acceptors, such allylic alcohol **7** and primary alcohol **8**, are more likely to compete with acetonitrile for **14** and give a lower α/*β* ratio. The dilution of the reaction mixture with the solvent increases the ratio [CH_3CN]/[ROH] and, consequently, increases the α/*β* ratio for the product of the reaction.

Conclusion

PST is superior to MST in terms of both yield and stereoselectivity of sialylation. High stability of benzenesulfenyl chloride, combined with ease of its of preparation and its low toxicity, makes PST an effective reagent for stereoselective α-sialylation. Important deficiencies still remain in sialylation, however. Although PST is a useful reagent, it is not a panacea in synthesis of carbohydrates. Among these residual problems are the following: (i) overall yields are only moderate due to the formation of sialyl glycal during preparation of sialyl xanthates and during sialylation; (ii) some amount of the undesired *β*-product is always formed, especially with reactive alcohols; (iii) the product of the reaction is contaminated with traces of byproducts, separation of which requires careful chromatography.

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Experimental Section

General Methods. Anhydrous reagents and solvents were prepared according to literature procedures.[19] *N*-Acetylneuraminic acid was obtained from extraction of edible Chinese swiftlet's nest.[20] *O*-Ethyl *S*-potassium dithiocarbonate was recrystallized before use from EtOH. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. The proton chemical shifts for all compounds were assigned using ^{1}H homonuclear decoupling experiments.

Sialyl Xanthates 2 and 3. To a suspension of sialic acid methyl ester[21] (4.90 g, 15.2 mmol) in AcCl (250 mL) cooled to 0 °C was slowly added absolute MeOH (3.0 mL). The mixture was allowed to warm to rt, and stirring was continued for 3 days, during which time a clear solution was obtained. The end of the reaction was determined by NMR on a small sample (~0.5 mL) of the reaction mixture that was periodically taken, concentrated *in vacuo*, and redissolved in $CDCl_3$. The reaction mixture was concentrated *in vacuo*, and residual AcCl was coevaporated three times with $CHCl_3$. The obtained crude product was dissolved in AcOEt (20 mL) and run through a short silica gel column (4 × 10 cm), eluting with AcOEt. Concentration *in vacuo* afforded chloride **1** as a white foam (7.04 g, 91%). To a solution of chloride **1** (6.0 g, 11.8 mmol) in dry acetone (250 mL) was added solid *O*-ethyl *S*-potassium dithiocarbonate (2.14 g, 13.3 mmol) in small portions within 10 min. The mixture was stirred under N_2 in the dark at 0 °C for 12 h and then at rt for additional 12 h. The reaction mixture was diluted with pentane (150 mL), filtered, and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (150 mL) and washed with H_2O (2 × 50 mL), saturated $NaHCO_3$ (50 mL), and brine (30 mL). After drying ($MgSO_4$) and concentration *in vacuo*, the residue was run through a short silica gel column (4 × 10 cm), eluting with 25% acetone in $CHCl_3$. The eluents were concentrated to afford a mixture of **2** and **3** in molar ratio 16:1 contaminated with 19% w/w of sialyl glycal **4** (6.21 g, 72% of **2** + **3**, 21% of **4**). Column chromatography of 2.6 g of this mixture with 50% of EtOAc in $CHCl_3$ afforded xanthate **3**, R_f = 0.28, and known[10b] xanthate **2**, R_f = 0.22). ***O*-Ethyl *S*-(*N*-acetyl-4,7,8,9-tetra-*O*-acetyl-1-methyl-*β*-neuraminosyl)dithiocarbonate (3)** (98 mg) as a white foam: $[\alpha]^{23}_D$ = +79.2 (*c* 0.96, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.07, 3 H), 1.85 (s, 3 H), 1.94 (t, *J* = 12.63 Hz, 1 H, *H*-3ax), 2.00 (s, 3 H), 2.11 (s, 6 H, two C(O)CH_3), 2.13 (s, 3 H), 2.57 (dd, *J* = 4.64, 12.96 Hz, 1 H, *H*-3eq), 3.51 (dd, *J* = 7.99, 12.16 Hz, 1 H, *H*-9a), 3.79 (s, 3 H, CO_2CH_3), 4.01 (dd, *J* = 2.80, 12.11 Hz, 1 H, *H*-9b), 4.01 (q, *J* = 10.38 Hz, 1 H, *H*-5), 4.53 (m, 1 H), 4.63 (dd, *J* = 2.07, 10.73 Hz, 1 H, *H*-6), 4.77 (m, 1 H), 4.83 (dt, *J* = 4.60, 12.73 Hz, 1 H, *H*-4), 5.21 (ddd, *J* = 2.81, 4.13, 8.00 Hz, 1 H, *H*-8), 5.33 (dd, *J* = 2.13, 4.08 Hz, 1 H, *H*-7), 5.58 (bd, *J* = 10.10 Hz, 1 H, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.26, 20.68, 20.75, 20.83, 20.89, 23.08, 36.89, 42.58, 49.05, 53.37, 68.61, 70.89, 73.41, 86.41, 168.72, 170.03, 170.21, 170.77, 206.92; HRMS (FAB) calcd for $C_{23}H_{33}NO_{13}S_2Na$ (M + Na) 618.1291, found 618.1298. According to its ^{1}H NMR spectrum, compound **3** was contaminated with ~7% w/w of glycal **4**. ***O*-Ethyl *S*-(*N*-acetyl-4,7,8,9-tetra-*O*-acetyl-1-methyl-α-neuraminosyl)-dithiocarbonate (2)** (2.32 g) as a white foam, lit.[10b] mp 102−104 °C (benzene/hexane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.13, 3 H, OCH_2CH_3), 1.87 (s, 3 H), 1.99 (dd, *J* = 11.89, 12.73 Hz, 1 H, *H*-3ax), 2.00 (s, 3 H), 2.01 (s, 3 H), 2.10 (s, 3 H), 2.12 (s, 3 H), 2.61 (dd, *J* = 4.65 12.95 Hz, 1 H, *H*-3eq), 3.78 (s, 3 H, CO_2CH_3), 4.00 (q, *J* = 10.40 Hz, 1 H, *H*-5), 4.17 (dd, *J* = 5.22, 12.39 Hz, 1 H, *H*-9a), 4.31 (dd, *J* = 2.43, 12.46 Hz, 1 H, *H*-9b), 4.50−4.58 (m, 2 H, OCH_2CH_3, H-6), 4.79 (m, 1 H, OCH_2CH_3), 4.87 (ddd, *J* = 4.63, 10.36, 11.90 Hz, 1 H, *H*-4), 5.17 (d, *J* = 10.05 Hz, 1 H, N*H*), 5.26−5.32 (m, 2H, *H*-7, *H*-8). According to the ^{1}H NMR spectrum compound **2** was contaminated with ~15% w/w of glycal **4** which had the same R_f value as **2**. This mixture was used for the sialylations shown in Table 1.

Preparation of Acceptors 5−7. Methyl(2,3)-*O*-2,6-bis-*O*-(phenylmethyl)-*β*-D-galactopyranoside (**5**) was prepared in 66% yield from methyl D-galactopyranoside following the procedure for synthesis of **6**. R_f = 0.49 (50% EtOAc in hexanes); mp 76−77 °C, $[\alpha]^{23}_D$ = +11.0 (*c* 1.68, $CHCl_3$); lit.[22] mp 80−81 °C, $[\alpha]^{25}_D$ = +10.0 (*c* 0.40, $CHCl_3$). 2-(Trimethylsilyl)ethyl 2,6-bis-*O*-(phenylmethyl)-*β*-D-galactopyranosyl-(1,4)-2,3,6-tris-*O*-(phenylmethyl)-*β*-D-glucopyranoside (**6**) was prepared in total 26% yield from lactose (six steps[23]). Compound **6** was crystallyzed from Et_2O/pentane: mp 88−89 °C, $[\alpha]^{23}_D$ = +15.9 (*c* 1.13, $CHCl_3$), lit.[20] mp 99.5−101 °C (after trituration); ^{1}H NMR (400 MHz, C_6D_6): δ −0.26 (s, 9 H, Si(CH_3)$_3$), 1.02 (m, 2 H, CH_2-TMS, 2.27 (d, *J* = 5.48 Hz, 1 H, *H*O-3), 2.47 (d, *J* = 2.73 Hz, 1 H, *H*O-4), 3.25 (t, *J* = 5.73 Hz, 1 H, *H*-5′), 3.34 (m, 1 H, *H*-3′), 3.39 (broad, dd, *J* = 2.30, 9.83 Hz, 1 H, *H*-5), 3.46 (dd, *J* = 5.30, 9.89 Hz, 1 H, *H*-6a′), 3.57 (dd, *J* = 7.85, 9.25 Hz, 1 H, *H*-2′), 3.59−3.67 (m, 3 H, *H*-2, *H*-6b′, OCH_2CH_2TMS), 3.71−3.77 (m, 3 H, *H*-3, *H*-6a, *H*-4′), 3.95 (dd, *J* = 3.92, 10.97 Hz, 1 H, *H*-6b), 4.12 (dt, *J* = 7.10, 9.54 Hz, 1 H, OCH_2CH_2TMS), 4.23 (d, *J* = 12.09 Hz, 1 H), 4.30 (t, *J* = 9.37 Hz, 1 H, *H*-4), 4.30 (d, *J* = 12.14 Hz, 1 H), 4.38 (d, *J* = 12.15 Hz, 1 H), 4.44 (d, *J* = 7.70 Hz, 1 H, *H*-1), 4.51 (d, *J* = 12.10 Hz, 1 H), 4.60 (d, *J* = 7.77 Hz, 1 H, *H*-1′), 4.69 (d, *J* = 11.60 Hz, 1 H), 4.86 (d, *J* = 10.64 Hz, 1 H), 4.89 (d, *J* = 11.03 Hz, 1 H), 4.97 (d, *J* = 11.13 Hz, 1 H), 5.08 (d, *J* = 11.51 Hz, 1 H), 5.27 (d, *J* = 11.12 Hz, 1 H), 7.04−7.61 (m, 25 H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.48, 18.37, 67.24, 68.29, 68.58, 68.68, 72.82, 73.05, 73.34, 73.44, 74.76, 75.02, 75.06, 76.61, 79.96, 81.82, 82.75, 102.51, 103.05, 127.11, 127.39, 127.44, 127.49, 127.54, 127.67, 127.76, 127.87, 127.93, 128.15, 128.19, 128.28, 128.37, 137.95, 138.21, 138.31, 138.66, 139.10; HRMS (FAB) calcd for $C_{34}H_{49}N_4O_8Na$ (M + Na) 335.3678, found 335.3678. 1,5-Anhydro-6-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-D-*lyxo*-hex-1-enopyranose (**7**) was prepared from D-galactal and *tert*-butyldimethylsilyl chloride according to Danishefsky et al.[24]

Benzenesulfenyl Chloride. To a solution of phenyl thioacetate (25 g, 164 mmol) in CCl_4 (10 mL) cooled to 0 °C was added SO_2Cl_2 (13.3 mL, 164 mmol) within 10 min. The mixture was stirred at rt for 30 min, concentrated *in vacuo*, and distilled using Kugelrohr. Distillation with a Vigreux column afforded benzenesulfenyl chloride as a red liquid (19.3 g, 81%), bp 51−53 °C/3 mmHg, *d* 1.25 g/cm^3 (lit.[25] bp 61.5 °C/5 mmHg).

General Procedure for Sialylation. We demonstrate the general procedure on the synthesis of **10** using the mixture of xanthates **2** and **3** and glycal **4**. The same basic procedure was applied for all sialylations. A mixture of **2** and **3** and **4** (1.06 g, contained 1.44 mmol of **2** and **3**), **6** (0.86 g, 0.96 mmol), powdered molecular sieves (3.0 g, 4 Å), dry CH_3CN (20 mL), and dry CH_2Cl_2 (10 mL) was stirred under N_2 for 1 h. AgOTf (0.41 g, 1.58 mmol) and DTBP (381 μL, 1.70 mmol) were added, and the mixture was cooled to −70 °C and kept protected from light. PhSCl (180 μL, 1.55 mmol) in dry CH_2Cl_2 (1 mL) was added by running the solution down the cold wall of the reaction flask, and the stirring was continued for 2 h at −70 °C. The mixture was diluted with a suspension of silica gel (5 g) in EtOAc (30 mL), filtered (Celite), washed (saturated aqueous $NaHCO_3$ and water), dried (Na_2SO_4), and concentrated. The residue was chromatographed (10% acetone in $CHCl_3$ → 20% acetone in $CHCl_3$) to give **2-(trimethylsilyl)-ethyl (*N*-acetyl-4,7,8,9-tetra-*O*-acetyl-1-methyl-α-neuraminosyl)-(2,3)-2,6-bis-*O*-(phenylmethyl)-*β*-D-galactopyranosyl-(1,4)-2,3,6-tris-*O*-(phenylmethyl)-*β*-D-glucopyranoside (10)** as a foam (0.97 g, 0.71 mmol, 74%): $[\alpha]^{23}_D$ = +3.0 (*c* 0.98, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ −0.18 (s, 9H, Si(SH_3)$_3$), 1.01 (m, 2H, CH_2Si(SH_3)$_3$), 1.56 (s, 3H), 1.60 (s, 3H), 1.70 (s, 3H), 1.87 (s, 3H), 2.03 (s, 3H), 2.12 (t, *J* = 12.50

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Hz, 1 H, *H*-3ax″), 2.67 (dd, J = 4.57, 12.81 Hz, 1 H, *H*-3eq″), 2.86 (d, J = 3.06 Hz, 1 H, 4-O*H*′), 3.36 (s, 3 H, CO_2CH_3), 3.43 (broad dd, J = 2.62, 9.90 Hz, 1 H, *H*-5), 3.58−3.65 (m, 3 H, *H*-6a′, *H*-2, OCH_2CH_2TMS), 3.74 (t, J = 9.02 Hz, 1 H, *H*-3), 3.78 (bt, J = 6.50 Hz, 1 H, *H*-5′), 3.83 (dd, J = 7.87, 9.30 Hz, 1 H, *H*-2′), 3.84 (t, J = 9.30 Hz, 1 H, *H*-6a), 3.95 (m, 4 H, *H*-6b′, *H*-3′, *H*-6b, *H*-6″), 4.08−4.11 (m, 2 H, OCH_2CH_2TMS, *H*-4′), 4.20 (dd, J = 6.58, 12.41 Hz, 1 H, *H*-9a″), 4.29 (d, J = 12.04 Hz, 1 H), 4.32−4.40 (m, 3 H, *H*-4, N*H*, *H*-5″), 4.39 (d, J = 12.05 Hz, 1 H), 4.43 (d, J = 7.72 Hz, 1 H, *H*-1), 4.51 (d, J = 12.11 Hz, 1 H), 4.57 (d, J = 12.10 Hz, 1 H), 4.68 (dd, J = 2.57, 12.39 Hz, 1 H, *H*-9b″), 4.78 (dt, J = 4.50, 11.90 Hz, 1 H, *H*-4″), 4.70 (m, 3 H, three CH_2Ph), 4.90 (d, J = 7.74 Hz, 1 H, *H*-1), 4.97 (d, J = 10.86 Hz, 1 H), 5.08 (d, J = 11.58 Hz, 1 H), 5.30 (d, J = 10.86 Hz, 1 H), 5.42 (dd, J = 2.30, 7.61 Hz, 1 H, *H*-7″), 5.78 (dt, J = 2.56, 7.08 Hz, 1 H, *H*-8″), 7.05 −7.28 (m, 17 H, aromatic), 7.41 (d, J = 7.14 Hz, 2 H, aromatic), 7.45 (d, J = 7.34 Hz, 2 H, aromatic), 7.47 (d, J = 8.20 Hz, 2 H, aromatic), 7.67 (d, J = 7.18 Hz, 2 H, aromatic); β-anomer δ 2.58 (dd, J = 4.95, 12.96 Hz, 1 H, *H*-3eq′); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.49, 18.39, 20.42, 20.62, 20.73, 21.03, 23.04, 36.35, 49.10, 52.93, 62.20, 67.11, 67.20, 67.80, 68.33, 68.49, 68.84, 69.04, 72.36, 72.65, 72.93, 73.20, 74.79, 75.00, 75.25, 76.25, 76.56, 78.32, 81.91, 82.91, 98.34, 102.30, 102.98, 127.06, 127.19, 127.30, 127.38, 127.93, 127.99, 128.02, 128.10, 128.16, 138.31, 138.47, 138.72, 138.86, 139.09, 168.29 (C-1, $J_{C\text{-}1,H\text{-}3ax}$ = 5.10 Hz), 169.85, 169.95, 170.21, 170.50, 170.73; MS (FAB) calcd for $C_{72}H_{91}NO_{23}SiNa$ (M + Na) 1388, found 1388. Anal. Calcd for $C_{72}H_{91}NO_{23}Si$: C, 63.28; H, 6.71. Found: C, 62.97; H, 6.72. Additional chromatography of the front fraction (17% of $CHCl_3$ in hexanes) afforded ***O*-ethyl *SS*-phenyl carbonodithioperoxoate (15)** as a yellow liquid (285 mg, 86%), R_f = 0.48: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (t, J = 7.10 Hz, 3 H), 4.69 (q, J = 7.10 Hz, 2 H), 7.25−7.50 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.60, 71.48, 128.23, 129.12, 129.93, 135.86, 211.10; HRMS (EI) calcd for $C_9H_{10}OS_3$ 229.9894, found 229.9899.

Applying the above procedure for sialylation, the compounds **9**, **11**, and **12** were prepared. Conditions, reagent ratios, and yields are given in Table 1. Compounds **9**, **11**, and **12** had R_f values (20% acetone in $CHCl_3$) close to the starting xanthate and glycal that was formed as a byproduct of the reaction. The fractions that contained xanthate, glycal, and the product were combined and concentrated *in vacuo*. Yields and product ratios were determined by ^{1}H NMR. Only selected NMR data are presented below.

Methyl (*N*-acetyl-4,7,8,9-tetra-*O*-acetyl-1-methyl-α-neuraminosyl)-(2,3)-*O*-2,6-bis-*O*-(phenylmethyl)-*β*-D-galactopyranoside (9): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.51 (dd, J = 4.67, 12.78 Hz, 1 H, *H*-3eq′), 3.54 (s, 3 H, OCH_3), 3.75 (s, 3 H, CO_2CH_3), 3.95 (dd, J = 5.80, 12.51 Hz, 1 H, *H*-9a′), 4.00 (dd, J = 2.21, 10.65 Hz, 1 H, *H*-6′), 4.29 (dd, J = 2.50, 12.50 Hz, 1 H, *H*-9b′), 4.83 (dt, J = 4.43, 11.88 Hz, 1 H, *H*-4′), 5.29 (dd, J = 2.10, 8.04 Hz, 1 H, *H*-7′); β-anomer δ 2.43 (dd, J = 4.91, 12.90 Hz, 1 H, *H*-3eq′); MS (FAB) calcd for $C_{41}H_{53}NO_{18}$-Na (M + Na) 870, found 870.

(*N*-Acetyl-4,7,8,9-tetra-*O*-acetyl-1-methyl-α-neuraminosyl)-(2,3)-*O*-1,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-D-*lyxo*-hex-1-enopyranose (11): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.62 (s, 6 H, $Si(CH_3)_2$), 0.87 (s, 9 H, Si-*t*-Bu), 2.62 (dd, J = 4.66, 12.91 Hz, 1 H, *H*-3eq′), 2.71 (d, J = 3.38 Hz, 1 H, 4-O*H*), 3.84 (s, 3 H, CO_2CH_3), 6.36 (d, J = 6.07 Hz, 1 H, *H*-1).); β-anomer δ 2.54 (dd, J = 4.96, 12.98 Hz, 1 H, *H*-3eq′); MS (FAB) calcd for $C_{32}H_{51}NO_{16}SiNa$ (M + Na) 756, found 756.

(1-Tetrahydropyranyl)methyl (*N*-acetyl-4,7,8,9-tetra-*O*-acetyl-1-methyl)-α-neuraminoside (12) was obtained as a mixture of two diastereomers. α-Diastereomers ^{1}H NMR (500 MHz, $CDCl_3$) 2.59 (dd, J = 4.66, 13.14 Hz, 1 H, *H*-3eq′), 2.61 (dd, J = 4.68, 13.28 Hz, 1 H, *H*-3eq′); ^{13}C NMR (100 MHz, $CDCl_3$) 98.60 and 98.82. β-Diastereomers: ^{1}H NMR 2.42 (dd, J = 5.05, 12.92 Hz, 1 H, *H*-3eq′), 2.47 (dd, J = 4.96, 12.98 Hz, 1 H, *H*-3eq′); ^{13}C NMR (100 MHz, $CDCl_3$) 98.14 and 98.28; HRMS (FAB) calcd for $C_{26}H_{39}NO_{14}Na$ (M + Na) 612.2268, found 612.2272.

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Supporting Information Available: ^{1}H NMR spectra for crude compounds **9**, **11**, and **12** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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