Highly Stereoselective α-Sialylation. Synthesis of GM_3-Saccharide and a Bis-Sialic Acid Unit

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The novel sialyl donor methyl [ethyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2-thio-3-(phenylthio)-2,3,5-trideoxy-D-*erythro*-α-L-*gluco*-2-nonulopyranosid]onate (**6**) was synthesized in six steps from *N*-acetylneuraminic acid in an overall yield of 47%. Donor **6** was shown to be superior to conventional sialyl donors in that the sialylation yields were higher, even with sterically hindered and unreactive sialyl acceptors, and the α/β-selectivity was virtually complete.

Introduction

In carbohydrate chemistry, sialylation is considered to be difficult and it is a reaction that often proceeds in relatively low yield.[1] However, with the use of thioglycoside sialyl donors[2] and sterically nonhindered acceptor saccharides, the yields approach those of normal glycosylations (60–80%). Still, the desired products are in many cases contaminated with a small amount of the undesired anomer, and removal of the latter by chromatography is often difficult. Low yields in sialylations are always accompanied by extensive 2,3-elimination of the donor, giving the corresponding sialic acid glycal when unreactive acceptors are used.[1]

Introduction of an elimination-suppressing and stereodirecting 3-S-substituent in the donor has made it possible to sialylate even unreactive acceptors in good yield with high stereoselectivity (these sialylations have been suggested to proceed via a reactive episulfonium intermediate).[3] However, such donors are more laborious to prepare, and removal of an auxiliary 3-S-substituent after the glycosylation step might be difficult. As a consequence, these elaborated donors should be reserved for cases where low yields and difficult separation of diastereomeric products are anticipated.

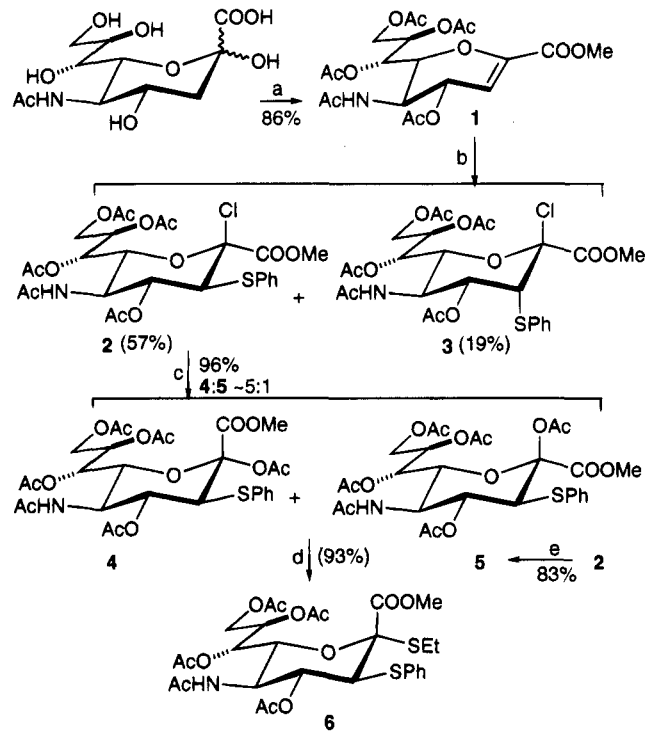
We now give a complete description of the synthesis of a novel sialyl donor (**6**) having several attractive features as stated in the preliminary report,[4] as well as its use for sialylation of some notoriously difficult acceptors, including a sialic acid acceptor (e.g. **10** and **11**).

Results and Discussion

1. Preparation of the Novel Sialyl Donor 6. Sialic acid was treated as described[5] with methanol and Dowex H^+-resin to give the corresponding sialic acid methyl ester, which in turn was acetylated to give the penta-*O*-acetate. Treatment of the latter with fresh trimethylsilyl trifluoromethanesulfonate (TMSOTf, 2 equiv; not 0.2[6]) gave the glycal **1** (92%; 86% from sialic acid, Scheme 1).[7] With lower grade TMSOTf, unwanted formation of a sialic acid 2,3-didehydro-4,5-oxazoline byproduct occurred to a significant extent.[8]

In a slight modification of the original procedure,[9] benzenesulfenyl chloride was added to **1** to give an easily separated mixture of the desired derivative **2** (57%), its

Scheme 1



[a] (a) MeOH, Dowex H^+, Ac_2O, pyridine, TMSOTf, MeCN, 0 °C, 6 h; (b) PhSCl, CH_2Cl_2, 20 °C, 7 d, Ar; (c) $Hg(OAc)_2$, AcOH/Ac_2O, 10:1, 40 °C, 18 h; (d) EtSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 20 °C, 18 h; (e) $HgBr_2$, $Hg(CN)_2$, $ClCH_2CH_2Cl/H_2O$, 100:1, reflux, 3.5 h, Ac_2O, pyridine, DMAP, 20 °C, 1 h.

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1995.

(1) (a) Okamoto, K.; Goto, T. *Tetrahedron* **1990**, *46*, 5835. (b) DeNinno, M. P. *Synthesis* **1991**, 583. (c) Kanie, O.; Hindsgaul, O. *Curr. Opin. Struct. Biol.* **1992**, *2*, 674.

(2) (a) Magnusson, G. *Adv. Drug Delivery Rev.* **1994**, *13*, 267. (b) Lönn, H.; Stenvall. K. *Tetrahedron Lett.* **1992**, *33*, 115.

(3) (a) Okamoto, K.; Kondo, T.; Goto, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 631. (b) Ito, Y.; Ogawa, T. *Tetrahedron* **1990**, *46*, 89.

(4) Ercégovic, T.; Magnusson, G. *J. Chem. Soc., Chem. Commun.* **1994**, 831.

(5) (a) Kuhn, R.; Lutz, P.; MacDonald, D. L. *Chem. Ber.* **1966**, *99*, 611. (b) Marra, A.; Sinay, P. *Carbohydr. Res.* **1989**, *190*, 317.

(6) Claesson, A.; Luthman, K. *Acta Chem. Scand., Ser. B* **1982**, *36*, 719.

(7) (a) Schmidt, W.; Christian, R.; Zbiral, E. *Tetrahedron Lett.* **1988**, *29*, 3643. (b) Nicolaou, K. C.; Hummel, C. W.; Iwabuchi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 3126, supplementary material.

(8) (a) Kumar, V.; Kessler, J.; Scott, M. E.; Patwardhan, B. H.; Tanenbaum, S. W.; Flashner, M. *Carbohydr. Res.* **1981**, *94*, 123. (b) Schreiner, E.; Zbiral, E.; Kleineidam, R. G.; Schauer, R. *Liebigs Ann. Chem.* **1991**, 129.

(9) Kondo, T.; Abe, H.; Goto, T. *Chem. Lett.* **1988**, 1657.

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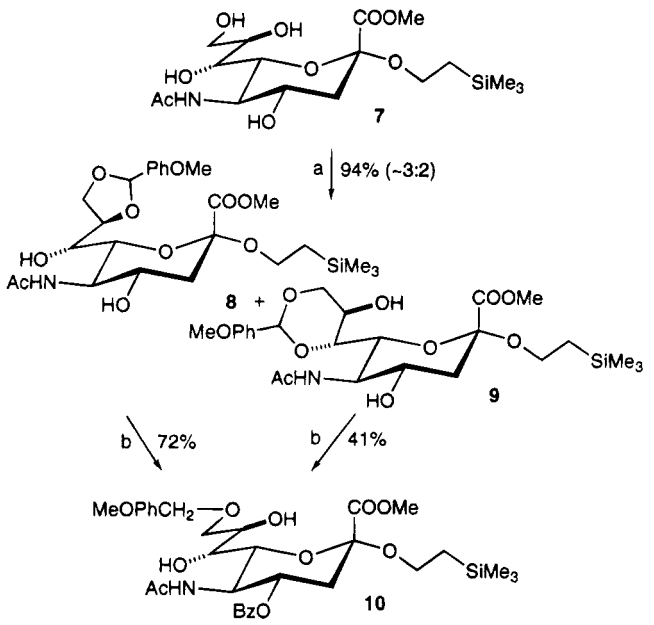
Scheme 2



[a] (a) $MeOPhCH(OMe)_2$, camphor–SO_3H, MeCN; (b) Et_3N, PhCOCl, −30 °C, CH_2Cl_2, BH_3Me_3N, $AlCl_3$, THF, 0 °C.

diastereomer **3** (19%), and unreacted **1** (10%). The somewhat higher **2**/**3** ratio claimed in the original procedure[9] was not realized in our study. The byproduct **3** might be a useful starting material for the preparation of a new sialic acid donor for β-sialylation.

Acetolysis of **2** with mercuric acetate in acetic acid/acetic anhydride, followed by chromatography of the crude reaction mixture, gave the α-acetate **4** and a mixture of **4** and the β-acetate **5** in a total yield of 96%. Hydrolysis of **2**, followed by acetylation of the intermediate hemiacetal, gave pure **5** (83%).

Treatment of the **4**/**5** mixture (α/β, ~5:1) with boron trifluoride etherate (BF_3·Et_2O) and ethanethiol in dichloromethane gave the novel sialyl donor **6** (93%) as a white powder. Compound **6** was a pure α-glycoside; no β-anomer was detected in the reaction mixture. Similar treatment of pure **5** gave **6** in 86% yield. Attempts to obtain crystalline **6** have so far been unsuccessful.

To summarize, the novel sialyl donor **6** was synthesized from the known glycal **1** in ~50% yield over three steps. This should be compared with the synthesis of its benzyl-protected (chlorosugar) counterpart, which requires about six steps.[3] Furthermore, the benzylation step caused us (and others[7b]) problems, and we abandoned the route after several unsuccessful attempts.

Compound **6** is stable and well-suited for use as a sialyl donor, especially when sterically hindered or otherwise unreactive acceptors are used (see below).

2. Preparation of the Sialic Acid Acceptor 10. Disialic acids normally have a 2 → 8 intersaccharidic linkage. The order of reactivity of the four hydroxyl groups in **7** (Scheme 2) was determined to be HO-9 ≫ HO-4 > HO-8 ≫ HO-7.[10] Therefore, it was considered reasonable to anticipate selective sialylation of HO-8 over HO-7 in an acceptor such as **10**.

(10) Ercégovic, T.; Magnusson, G. unpublished work.

The known[11] tetrol **7** was treated with *p*-methoxybenzaldehyde dimethyl acetal and camphor-10-sulfonic acid to furnish the *p*-methoxybenzylidene 8,9-acetal (**8**) (58%) and 7,9-acetal (**9**) (36%). Compound **8** was isolated as a 1:1 diastereomeric mixture, whereas **9** was a pure compound, which slowly epimerized during storage.

Benzoylation of HO-4 in **8**, followed by borane-induced reductive opening of the benzylidene protecting group, gave the desired acceptor **10** (72%). The major byproducts resulted from hydrolysis of the 2-(trimethylsilyl)-ethyl (TMSEt) and/or benzylidene groups. Using the same reaction conditions with compound **9** also gave **10** (41%), showing that the mixture of **8** and **9** can be used for the preparation of **10** without previous separation.

3. Comparison between 6 and Other Sialyl Donors. Sialylation of the sterically congested lactosyl acceptor **11**[12] was considered to be a critical test of the efficiency of various sialyl donors. The most convenient and high-yielding procedures to date are based on sialic acid thioglycoside donors, and therefore, only the xanthate **13**[13] and the methyl α/β-methylthio glycoside **16**[14] were used in the comparison with our novel donor **6** (Scheme 3).

As seen in Table 1, treatment of the acceptor **11** with the donor **6** gave the best result when the acceptor and promotor were used in excess. However, the unexpectedly high yield (54%) of 3-(phenylthio)-α-GM_3-saccharide (**12**) in the experiment where the donor/acceptor ratio was 1:1 is worth noting. A slight preference for the promotor combination of methanesulfenyl bromide/silver trifluoromethanesulfonate (MSB/AgOTf) as compared with *N*-iodosuccinimide/trifluoromethanesulfonic acid (NIS/TfOH) was found. Not only did the use of **6** give an unprecedented high yield with the hindered acceptor **11**, but also as a bonus, the α/β-stereoselectivity was virtually complete. This is in sharp contrast to the case with donors **13** and **16**, which gave mixtures of the α- and β-GM_3 saccharides **14** and **15**. Determination of the anomeric configuration of the sialic acid residue in the sialylation products shown in Scheme 3 was based on the J_{C1-H3a} value[17] as described in the comparative study in our preliminary communication.[4]

The less sterically hindered acceptors **17**, **20**, and **22** were sialylated with the donors **6** and **13**. The products (**18**, **19**, **21**, and **23**) were obtained in approximately the same yields (>70%), but again, the new donor **6** gave pure α-glycosides whereas the xanthate donor **13** gave α/β-mixtures.

The ultimate challenge in sialylation chemistry is the formation of bis-sialic acids, where the glycosidic linkage is present between the 2- and the 8-position of the two monosaccharide units. The donor **6** gave with the acceptor **10** the bis-sialic acid derivative **24** in 28% yield ($J_{C1'-H3'a}$ = 5.9 Hz), and ~40% of the acceptor **10** was recovered; the corresponding β-glycoside was not detected in the reaction mixture. A labile, unidentified bis-

(11) Hasegawa, A.; Ito, Y.; Morita, M.; Ishida, H.; Kiso, M. *J. Carbohydr. Chem.* **1989**, *8*, 125.
(12) Kameyama, A.; Ishida, H.; Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1989**, *193*, C1.
(13) Marra, A.; Sinaÿ, P. *Carbohydr. Res.* **1990**, *195*, 303.
(14) Hasegawa, A.; Ohki, H.; Nagahama, T.; Ishida, H.; Kiso, M. *Carbohydr. Res.* **1991**, *212*, 277.
(15) Wilstermann, M.; Magnusson, G. Unpublished work.
(16) Ray, A. K.; Nilsson, U.; Magnusson, G. *J. Am. Chem. Soc.* **1992**, *114*, 2256.
(17) Hori, H.; Nakajima, T.; Nishida, Y.; Ohrui, H.; Meguro, H. *Tetrahedron Lett.* **1988**, *29*, 6317.

Scheme 3

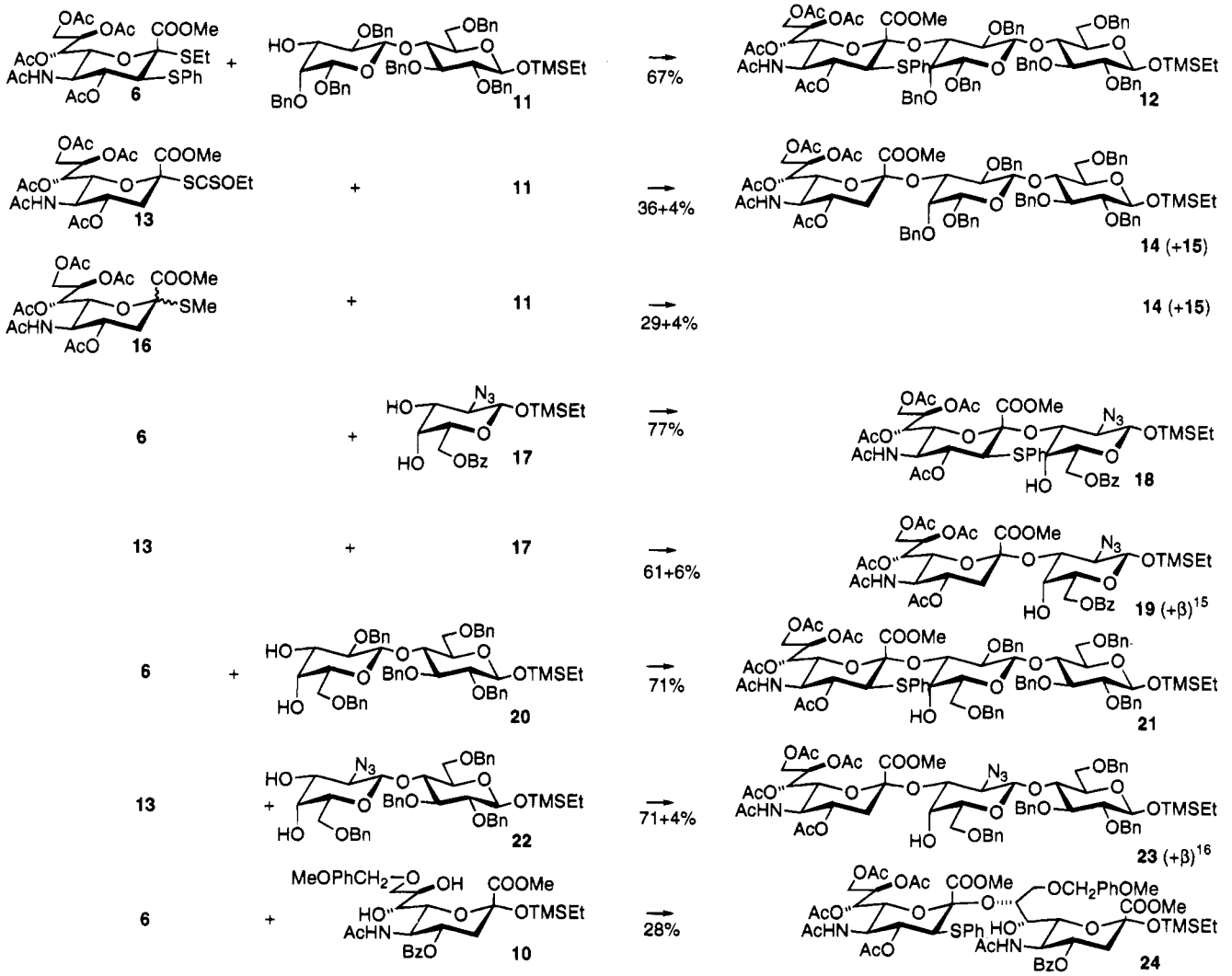


Table 1. Sialylation with the Sialic Acid Donors 6, 13, and 16

donor	acceptor	mole ratio[a]	P1/P2[a]	reaction conditions[b]	product	yield[c] (%)	α/β
6	**11**	1.0/1.0/1.1/1.1	MSB/AgOTf	MeCN/−40 °C	**12**	54	>99/1
6	**11**	1.0/1.5/1.6/1.6	MSB/AgOTf	MeCN/−40 °C	**12**	67	>99/1
6	**11**	1.0/1.5/1.7/0.5	NIS/TfOH	MeCN/−40 °C	**12**	57	>99/1
13	**11**	1.0/1.5/1.3/1.2	MSB/AgOTf	MeCN, CH_2Cl_2/−60 °C	**14** + **15**	36 + 4	90/10
16	**11**	1.0/1.5/1.5/0.7	NIS/TfOH	MeCN/−40 °C	**14** + **15**	29 + 4	88/12
6	**17**	1.0/1.0/1.3/1.3	MSB/AgOTf	MeCN/−40 °C	**18**	77	>99/1
13	**17**	1.0/0.7/1.0/1.0	MSB/AgOTf	MeCN, CH_2Cl_2/−78 °C	**19**[d]	61 + 6	90/10
6	**20**	1.0/1.5/1.4/1.4	MSB/AgOTf	MeCN/−40 °C	**21**	71	>99/1
13	**22**	1.0/0.5/1.0/1.0	MSB/AgOTf	MeCN, CH_2Cl_2/−78 °C	**23**[e]	71 + 4	95/5
6	**10**	1.0/0.6/1.4/1.4	MSB/AgOTf	MeCN/−40 °C	**24**	28	>99/1

[a] Donor/acceptor/promotor 1 (P1)/promotor 2 (P2). [b] The concentration of the acceptor **11** was ~0.10 M. [c] Based on the starting material (donor or acceptor) present in the smallest amount. [d] **19** was acetylated before isolation; this experiment was described in ref 15. [e] This experiment was described in ref 16.

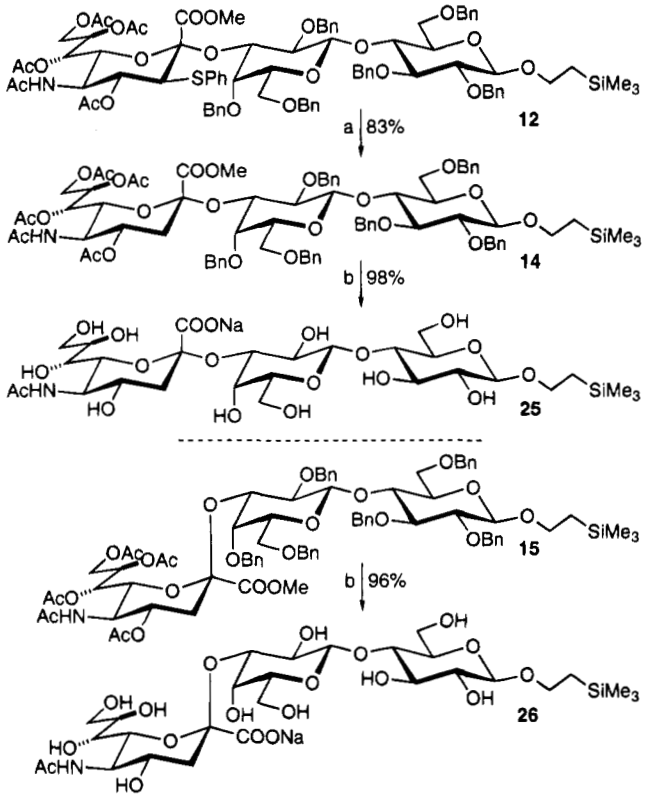
sialoside was also formed in an amount corresponding to the missing 20–30% of **10**. When the sialylation of **10** was attempted with **13** as the donor, the desired bis-sialic acid product was not formed; only elimination occurred to give the glycal **1** (85%). Such elimination reactions normally occur on attempted sialylation of highly hindered acceptors.[1a,b] Previous attempts to sialylate the 8-position in sialic acid acceptors either gave very low yields (~5%) or produced the β-anomer.[18,19]

4. Preparation of the GM_3-Trisaccharide. The auxiliary 3-phenylthio group in **12** was removed by treatment with triphenyltin hydride/azoisobutyronitrile in refluxing toluene, which gave the protected GM_3-trisaccharide **14** (83%) and recovered **12** (12%). When tributyltin hydride was used instead of triphenyltin hydride, the yield dropped to ~50%, with extensive formation of byproducts (Scheme 4).

The protecting groups of **14** were removed in a one-pot, three-step procedure consisting of hydrogenolysis of the benzyl groups, methanolysis of the acetate groups, and hydrolysis of the methyl ester. The GM_3-trisaccha-

(18) Kanie, O.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1988**, 7, 501.
(19) Tsvektov, Y. E.; Schmidt, R. R. *Tetrahedron Lett.* **1994**, 35, *8583*.

Scheme 4



[a] (a) AIBN, Ph_3SnH, toluene, 110 °C, Ar; (b) H_2, Pd/C, HOAc, rt, MeONa, MeOH, rt, Ar, NaOH, H_2O.

ride **25** was thus obtained as the sodium salt in 98% yield. Using the same reaction conditions with the β-anomer **15** gave the sodium salt of β-GM_3 (**26**) in 96% yield.

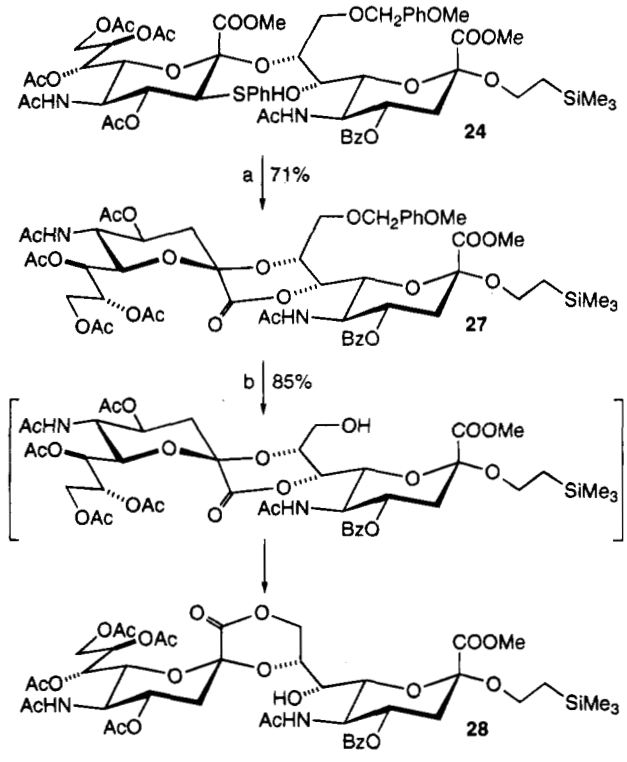
5. Lactonization of Bis-Sialic Acid Derivatives. The bis-sialic acid moiety present in gangliosides such as GD_3 and GQ_{1b} is known to undergo [8,9]-lactonization upon acid treatment.[20] We found that the bis-sialoside **24** formed the stable [8,7]-lactone **27** (71%) during the desulfurization reaction (Scheme 5). During hydrogenolysis of the 9-*O*-*p*-methoxybenzyl group of **27** in ethanol, the [8,7]-lactone isomerized to the more stable [8,9]-lactone **28** (85%), presumably via the corresponding unprotected [8,7]-lactone as indicated by TLC monitoring. Since ethanol was used as solvent, it might attack the lactone ring of the [8,7]-lactone; the intermediacy of an ethyl ester en route to **28** could therefore not be ruled out.

When the hydrogenolysis was performed in *N*,*N*-dimethylformamide, the [8,7]-lactone seemed to be much less prone to rearrange into **28**. Furthermore, an equilibrium was found to exist (~2:1) between the [8,9]- and [8,7]-lactones in *N*,*N*-dimethylformamide-d_7 solution; pure **28** rearranged slowly into the corresponding [8,7]-lactone, as monitored by ^1H NMR over 2 weeks. These data indicate that the lactone rearrangements in bis-sialic acid residues can take place both via an intermediate ester and by direct nucleophilic attack of the hydroxyl group on the lactone carbonyl; an open form intermediate is therefore not required.

Conclusions

The novel sialyl donor **6** is a powerful sialylating agent even with sterically hindered and unreactive acceptors, such as **10** and **11**. With less hindered acceptors, such as **17**, **20**, and **22**, the donor **6** gives approximately the same glycosylation yields as conventional sialic acid thioglycoside donors (e.g. **13** and **16**) but the stereoselectivity is much higher. The high selectivity is especially useful when diastereomeric products of sialylation are difficult to separate, as is often the case with oligosaccharides consisting of more than two monosaccharide units.

Scheme 5



[a] (a) AIBN, Ph_3SnH, toluene, 110 °C, Ar; (b) H_2, Pd/C, EtOH, rt.

Experimental Section

General. NMR spectra were recorded with 500 and 300 MHz spectrometers. Assignment of ^1H NMR spectra was achieved using 2D-methods. Optical rotations were measured at 20 °C. Reactions were monitored by TLC using alumina plates coated with silica gel 60 F_{254} (Merck) and visualized either by using UV light or by charring with H_3PO_4 (aqueous 10% spray solution). Preparative chromatography was performed with Merck silica gel (35–70 μm, 60 Å). $CHCl_3$ used for preparative chromatography contained 1% of EtOH. CH_2Cl_2, toluene, and THF were distilled under N_2, over CaH_2 and sodium benzophenone ketyl, respectively. MeCN and NEt_3 were stored over 3 Å molecular sieves and filtered through a column of Al_2O_3 (activity I, Merck) immediately before use. Methanol was dried over 3 Å molecular sieves >3 days before use. Compounds obtained as white powders were precipitated with *n*-hexane from a chloroform/diethyl ether solution.

Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-2,3,5-trideoxy-D-*glycero*-D-*galacto*-non-2-enopyranosonate (1). To a stirred, ice-cooled solution of methyl 5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonate (4.97 g, 9.32 mmol) in MeCN (12.5 mL) was added trimethylsilyl trifluoromethanesulfonate (3.6 mL, 19 mmol) under Ar. The reaction mixture was kept at 2 °C for 6 h, and then pyridine (10 mL) was added slowly (ice-cooling),

(20) Ando, S.; Yu, R. K.; Scarsdale, J. N.; Kusunoki, S.; Prestegard, J. H. *J. Biol. Chem.* **1989**, *264*, 3478.

followed by toluene (25 mL). The mixture was concentrated, and the residue was chromatographed (toluene/acetone, 3:1 → 2:1, gradient) to give **1** (4.05 g, 92%) as a white foam. The ^{1}H NMR data were in agreement with those reported.[3a]

Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-2-chloro-3-(phenylthio)-2,3,5-trideoxy-D-*erythro*-β-L-*gluco*-2-nonulopyranosonate (2) and Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-2-chloro-3-(phenylthio)-2,3,5-trideoxy-D-*erythro*-β-L-*manno*-2-nonulopyranosonate (3). To a solution of **1** (4.05 g, 8.55 mmol) in CH_2Cl_2 (30 mL) was added benzenesulfenyl chloride (2.6 mL, 23 mmol) under Ar, and the mixture was left with protection from light at 20 °C. After 7 days, the mixture was concentrated and the residue was chromatographed ($CHCl_3$/acetone, 40:1 → 12:1 → 8:1 → 3:1) to give **2** (2.99 g, 57%), **3** (0.979 g, 19%), and unreacted **1** (0.405 g, 10%), all as white powders. The ^{1}H NMR data were in agreement with those reported.[9]

Methyl 5-Acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-3-(phenylthio)-D-*erythro*-α-L-*gluco*-2-nonulopyranosonate (4) and Methyl 5-Acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-3-(phenylthio)-D-*erythro*-β-L-*gluco*-2-nonulopyranosonate (5). To a stirred solution of **2** (358 mg, 0.579 mmol) in HOAc (2.5 mL) were added Ac_2O (0.26 mL) and mercuric acetate (227 mg, 0.712 mmol), and the mixture was kept at 40 °C for 18 h. Toluene (10 mL) was added, and the solution was concentrated. The residue was dissolved in $CHCl_3$/Et_2O (1:4, 20 mL) and washed with an aqueous 10% solution of KI (8 mL) and brine (4 mL). The organic phase was concentrated, and the residue was chromatographed (toluene/acetone, 4:1 → 3:1, gradient) to give **4** (124 mg) and a mixture of **4** and **5** (3.6:1, 234 mg) as white powders. The powders were combined to give a mixture of **4** and **5** (5.2:1, 358 mg, 96%). Compound **4**: $[\alpha]_D$ +17.3 (*c* 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.28 (m, 5 H), 5.47 (d, 1 H, *J* = 10.2 Hz), 5.36 (dd, 1 H, *J* = 2.3, 6.5 Hz), 5.18 (dd, 1 H, *J* = 11.0, 10.1 Hz), 5.11 (ddd, 1 H, *J* = 2.5, 5.8 Hz), 4.97 (dd, 1 H, *J* = 10.9 Hz), 4.34 (q, 1 H, *J* = 10.1 Hz), 4.34 (dd, 1 H, *J* = 12.5, 2.5 Hz), 4.02 (dd, 1 H, *J* = 5.8, 12.5 Hz), 3.84 (s, 3 H), 3.62 (d, 1 H, *J* = 11.0 Hz), 2.10, 2.07, 2.03, 2.01, 1.89, 1.86 (s, 3 H each); MS calcd for $C_{28}H_{36}NO_{14}S$ (M + H$^+$) 642.1857, found 642.1849. Compound **5**: $[\alpha]_D$ +6.7 (*c* 0.93, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.23 (m, 5 H), 5.51 (d, 1 H, *J* = 10.0 Hz), 5.37 (dd, 1 H, *J* = 2.3, 4.0 Hz), 5.28 (dd, 1 H, *J* = 11.0, 10.4 Hz), 4.97 (ddd, 1 H, *J* = 2.4, 6.8, 4.0 Hz), 4.51 (dd, 1 H, *J* = 12.4, 2.4 Hz), 4.28 (q, 1 H, *J* = 10.1 Hz), 4.13 (dd, 1 H, *J* = 6.8, 12.4 Hz), 4.00 (dd, 1 H, *J* = 10.7, 2.3 Hz), 3.67 (s, 3 H), 3.46 (d, 1 H, *J* = 11.0 Hz), 2.21, 2.14, 2.04, 2.03, 1.95, 1.88 (s, 3 H each); HRMS calcd for $C_{28}H_{36}NO_{14}S$ (M + H$^+$) 642.1857, found 642.1859.

Methyl [Ethyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2-thio-3-(phenylthio)-2,3,5-trideoxy-D-*erythro*-α-L-*gluco*-2-nonulopyranosid]onate (6). (a) To a stirred mixture of **4** and **5** (5.2:1, 337 mg, 0.525 mmol) in CH_2Cl_2 (2.5 mL) were added ethanethiol (0.078 mL, 1.05 mmol) and BF_3·Et_2O (0.34 mL, 2.7 mmol) under Ar, and the mixture was left at rt overnight. Pyridine/H_2O (4:1, 1 mL) was added under ice-cooling, stirring was continued for 10 min, and toluene (10 mL) was added. The mixture was concentrated, and the residue was chromatographed (toluene/acetone, 3:1) to give **6** (315 mg, 93%) as a white powder: $[\alpha]_D$ +61.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.25 (m, 5 H), 5.36 (d, 1 H, *J* = 10.1 Hz), 5.31 (m, 1 H), 5.28 (dd, 1 H, *J* = 1.9, 7.9 Hz), 5.17 (dd, 1 H, *J* = 11.2, 10.1 Hz), 4.31 (dd, 1 H, *J* = 2.4, 12.4 Hz), 4.10 (q, 1 H, *J* = 10.1 Hz), 4.10 (dd, 1 H, *J* = 4.6 Hz), 3.89 (s, 3 H), 3.81 (dd, 1 H, *J* = 10.9 Hz), 3.42 (d, 1 H, *J* = 11.2 Hz), 2.83 (dq, 1 H, *J* = 12.1, 7.5 Hz), 2,77 (dq, 1 H, *J* = 12.1, 7.5 Hz), 2.15, 2.12, 2.04, 1.94, 1.86 (s, 3 H each), 1.24 (t, 3H); HRMS calcd for $C_{28}H_{38}NO_{12}S_2$ (M + H$^+$) 644.1835, found 644.1824.

(b) Compound **5** (60.3 mg, 0.094 mmol) was dissolved in CH_2Cl_2 (0.6 mL) and treated with ethanethiol (0.014 mL, 0.19 mmol) and BF_3·Et_2O (0.060 mL, 0.48 mmol) as described above. Workup and purification gave **6** (52 mg, 86%) as a white powder.

Methyl [2-(Trimethylsilyl)ethyl 5-acetamido-3,5-dideoxy-8,9-*O*-(*p*-methoxybenzylidene)-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (8) and Methyl [2-(Trimethylsilyl)ethyl 5-acetamido-3,5-dideoxy-7,9-*O*-(*p*-methoxybenzylidene)-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (9). To a stirred solution of **7**[11] (206 mg, 0.487 mmol) in MeCN (2.5 mL) were added anisaldehyde dimethyl acetal (0.2 mL, 1.2 mmol) and (±)-camphor-10-sulfonic acid (15 mg, 0.064 mmol) at rt. After 1 h, Et_3N (0.020 mL) was added. The mixture was concentrated, and the residue was chromatographed (CH_2Cl_2/MeOH, 40:1 → 25:1 → 12:1, gradient) to give **8** (154 mg, 58%) and **9** (95 mg, 36%) both as white powders. Compound **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (d, 1 H, *J* = 8.1 Hz), 5.90 (d, 1 H, *J* = 7.9 Hz), 5.89, 5.77 (s, 1 H each), 3.80, 3.80, 3.75, 3.73 (s, 3 H each), 2.72−2.62 (m, 1 H), 2.04, 2.00 (s, 3 H each), 1.84−1.73 (m, 1 H); HRMS calcd for $C_{25}H_{40}NO_{10}Si$ (M + H$^+$) 542.2373, found 542.2428. A sample of **8** was acetylated: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45 (dd, 1 H, *J* = 1.9, 4.1 Hz), 5.19, 5.10 (d, 1 H, *J* = 9.7 Hz), 5.01−4.87 (m, 1 H), 2.18, 2.10, 2.03, 2.03, 1.89, 1.86 (s, 3 H each). Compound **9**: $[\alpha]_D$ −56.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, 2 H, *J* = 8.8 Hz), 6.90 (d, 2 H), 5.75 (d, 1 H, *J* = 6.3 Hz), 5.42 (s, 1 H), 3.82, 3.80 (s, 3 H each), 3.41 (m, 1 H), 2.73 (dd, 1 H, *J* = 13.3, 4.7 Hz), 1.97 (s, 3 H), 0.88 (m, 2 H), 0.00 (s, 9 H); HRMS calcd for $C_{25}H_{40}NO_{10}Si$ (M + H$^+$) 542.2373, found 542.2413. A sample of **9** was acetylated: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.28 (ddd, 1 H, *J* = 5.2, 10.0 Hz), 4.91 (ddd, 1 H, *J* = 4.6, 12.3, 10.5 Hz), 2.14, 2.05, 1.96 (s, 3 H each).

Methyl [2-(Trimethylsilyl)ethyl 5-acetamido-4-*O*-benzoyl-3,5-dideoxy-9-*O*-(*p*-methoxybenzyl)-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (10). (a) To a stirred solution of **8** (191 mg, 0.353 mmol) in CH_2Cl_2 (3 mL) was added Et_3N (0.15 mL, 1.1 mmol) under Ar. The temperature was lowered to −50 °C, and benzoyl chloride (0.049 mL, 0.42 mmol) was added. The mixture was left at −30 °C for 16 h, and H_2O (0.012 mL) was added. The cooling bath was removed, and the mixture was stirred vigorously for 10 min and then applied directly onto a short column (2 cm) of silica gel. Elution with toluene/acetone (5:1, 150 mL), followed by concentration and drying in vacuo, gave a crude product which was dissolved in tetrahydrofuran (6 mL). After the mixture was cooled to 0 °C under Ar, BH_3Me_3N (119 mg, 1.63 mmol) and $AlCl_3$ (235 mg, 1.76 mmol) were added with vigorous stirring. After 10 min at 0 °C, the mixture was allowed to attain rt (5 min). Et_2O (8 mL) and ice−water (8 mL) were added, followed by CH_2Cl_2 (30 mL) and 0.1 M aqueous NaCl (30 mL). The organic phase was separated, and the aqueous phase was washed with CH_2Cl_2 (2 × 30 mL). The organic phases were combined, concentrated, and chromatographed (toluene/acetone, 4:1) to give **10** (165 mg, 72%) as a white foam: $[\alpha]_D$ −40.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05−6.83 (m, 9 H), 6.23 (d, 1 H, *J* = 8.0 Hz), 5.18 (ddd, 1 H, *J* = 4.9, 10.5, 12.0 Hz), 4.18−4.07 (m, 2 H), 3.95 (m, 1 H), 3.83 (dd, 1 H, *J* = 2.4, 9.9 Hz), 3.82, 3.79 (s, 3 H each), 3.62 (dd, 1 H, *J* = 6.0, 9.9 Hz), 3.61−3.55 (m, 2 H), 3.41 (m, 1 H), 2.72 (dd, 1 H, *J* = 12.9, 4.9 Hz), 2.15 (dd, 1 H, *J* = 12.0, 12.9 Hz), 1.91 (s, 3 H), 0.88 (m, 2 H), 0.00 (s, 9 H); HRMS calcd for $C_{32}H_{46}NO_{11}Si$ (M + H$^+$) 648.2840, found 648.2859.

(b) Treatment of **9** (84.2 mg, 0.156 mmol) as described above gave **10** (41.1 mg, 41%) as a white powder.

2-(Trimethylsilyl)ethyl 2,3,6-Tri-*O*-benzyl-4-*O*-{2,4,6-tri-*O*-benzyl-3-*O*-[methyl [5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-3-(phenylthio)-D-*erythro*-α-L-*gluco*-2-nonulopyranosyl]onate]-β-D-galactopyranosyl]-β-D-glucopyranoside (12). (a) To a mixture of the sialyl donor **6** (94.3 mg, 0.146 mmol), the lactoside acceptor **11**[12] (213 mg, 0.217 mmol), and activated 3 Å molecular sieves (210 mg) was added MeCN (1.9 mL), and the mixture was stirred at rt for 40 min. A solution of silver trifluoromethanesulfonate (62.5 mg, 0.243 mmol) in MeCN (0.3 mL) was added under Ar, and the temperature was lowered to −40 °C. A solution of methanesulfenyl bromide[21] in $ClCH_2CH_2Cl$ (0.085 mL, 0.24 mmol, 2.8 M) was added, and the mixture was stirred for 80 min at −40 °C. iPr_2NH (0.050 mL) was added, the stirring was continued for 5 min, and the mixture was allowed to reach

(21) Dasgupta, F.; Garegg, P. J. *Carbohydr. Res.* **1988**, *177*, C13.

rt. The mixture was filtered (Celite), washed (acetone), and concentrated, and the residue was chromatographed (toluene/acetone, 4:1) to give recovered **11** (113 mg) as a syrup and **12** (153.2 mg, 67%) as a white powder: $[\alpha]_D$ +2.2 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.10 (m, 35 H), 5.53 (ddd, 1 H, *J* = 2.5, 5.6, 8.1 Hz), 5.34 (dd, 1 H, *J* = 9.9, 11.3 Hz), 5.33 (dd, 1 H, *J* = 2.5, 8.1 Hz), 5.25 (d, 1 H, *J* = 10.1 Hz), 4.67 (d, 1 H, *J* = 7.6 Hz), 4.56 (dd, 1 H, *J* = 9.9, 2.7 Hz), 4.35 (d, 1 H, *J* = 7.8 Hz), 4.32 (dd, 1 H, *J* = 12.7, 2.5 Hz), 4.21 (q, 1 H, *J* = 10.0 Hz), 3.98 (dd, 1 H, *J* = 5.6, 12.7 Hz), 3.94 (dd, 1 H, *J* = 10.8, 2.5 Hz), 3.82 (s, 3 H), 3.72 (dd, 1 H, *J* = 7.6, 9.9 Hz), 3.52 (t, 1 H, *J* = 9.0 Hz), 3.40 (d, 1 H, *J* = 11.3 Hz), 2.08, 1.97, 1.92, 1.87, 1.84 (s, 3 H each), 1.04 (m, 2 H), 0.03 (s, 9 H); HRMS calcd for $C_{85}H_{102}NO_{23}SiS$ (M + H^+) 1564.6332, found 1564.6370.

(b) To a mixture of **6** (204.8 mg, 0.318 mmol), **11** (472 mg, 0.48 mmol), and activated AW300 molecular sieves (450 mg) was added MeCN (4.0 mL), and the mixture was stirred at rt for 1.5 h. A solution of *N*-iodosuccinimide (118.7 mg, 0.528 mmol) in acetonitrile (0.8 mL) was added under Ar, and the temperature was lowered to −40 °C. Trifluoromethanesulfonic acid (0.013 mL, 0.15 mmol) was added, and the mixture was stirred for 70 min at −40 °C. iPr_2NH (0.2 mL) was added, and the stirring was continued for 5 min. The mixture was filtered (Celite), washed (acetone), and concentrated. The residue was dissolved in $CHCl_3/Et_2O$ (1:5, 60 mL) and washed with 0.1 M aqueous NaCl (60 mL). The organic phase was concentrated, and the residue was chromatographed (toluene/acetone, 6:1 → 4:1, gradient) to give **11** (244 mg) and **12** (284.6 mg, 57%).

2-(Trimethylsilyl)ethyl 2,3,6-Tri-*O*-benzyl-4-*O*-[2,4,6-tri-*O*-benzyl-3-*O*-[methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosyl)onate]-β-D-galactopyranosyl]-β-D-glucopyranoside (14) and 2-(Trimethylsilyl)ethyl 2,3,6-Tri-*O*-benzyl-4-*O*-[2,4,6-tri-*O*-benzyl-3-*O*-[methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-β-D-*galacto*-2-nonulopyranosyl)onate]-β-D-galactopyranosyl]-β-D-glucopyranoside (15). (a) To a mixture of the sialyl donor **13** (59.1 mg, 0.099 mmol), **11** (146 mg, 0.148 mmol), and activated 3 Å molecular sieves (160 mg) was added MeCN/CH_2Cl_2 (1:1, 1.2 mL), and the mixture was stirred at rt for 45 min. A solution of silver trifluoromethanesulfonate (31.3 mg, 0.122 mmol) in MeCN (0.3 mL) was added under Ar, and the temperature was lowered to −60 °C. Methanesulfenyl bromide[21] in $ClCH_2CH_2Cl$ (0.045 mL, 0.13 mmol, 2.8 M) was added dropwise over 5 min, and the mixture was stirred for 1 h at −60 °C. iPr_2NH (0.050 mL) was added, and the stirring was continued for 5 min. The mixture was allowed to attain rt, filtered (Celite), washed (acetone), and concentrated. The residue was chromatographed (toluene/acetone, 4:1) to give **11** (77 mg, 78 mmol) and **15** (5.0 mg, 3.5%) as syrups and **14** (52.0 mg, 36%) as a white powder. Compound **14**: $[\alpha]_D$ −11.0 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.10 (m, 30 H), 5.47 (ddd, 1 H, *J* = 8.4, 2.7, 5.5 Hz), 5.32 (dd, 1 H, *J* = 2.0, 8.4 Hz), 5.18 (d, 1 H, *J* = 10.1 Hz), 4.93 (m, 1 H), 4.59 (d, 1 H, *J* = 7.6 Hz), 4.38 (d, 1 H, *J* = 7.8 Hz), 4.33 (dd, 1 H, *J* = 12.4, 2.7 Hz), 4.08 (q, 1 H, *J* = 10.1 Hz), 4.07 (dd, 1 H, *J* = 3.2, 9.8 Hz), 3.99 (dd, 1 H, *J* = 5.5, 12.4 Hz), 3.91 (dd, 1 H, *J* = 10.7, 2.0 Hz), 3.72 (d, 1 H, *J* = 3.2 Hz), 3.71 (s, 3 H), 3.66 (dd, 1 H, *J* = 9.8, 7.6 Hz), 3.55 (t, 1 H, *J* = 9.0 Hz), 3.40 (dd, 1 H, *J* = 9.1, 7.8 Hz), 2.45 (dd, 1 H, *J* = 13.2, 4.8 Hz), 2.12 (1 H), 2.12, 2.02, 1.99, 1.91, 1.88 (s, 3H each), 1.05 (m, 2 H), 0.03 (s, 9 H); HRMS calcd for $C_{79}H_{98}NO_{23}Si$ (M + H^+) 1456.6299, found 1456.6296.

Compound **15**: $[\alpha]_D$ +1.5 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.08 (m, 30 H), 5.16–5.13 (m, 2 H), 5.05 (ddd, 1 H, *J* = 11.6, 4.6, 10.4 Hz), 4.99 (dd, 1 H, *J* = 2.2, 12.5 Hz), 4.54 (d, 1 H, *J* = 7.6 Hz), 4.37 (d, 1 H, *J* = 7.8 Hz), 3.97 (dd, 1 H, *J* = 10.0, 9.4 Hz), 3.86 (dd, 1 H, *J* = 11.1, 1.9 Hz), 3.78 (dd, 1 H, *J* = 10.0, 7.6 Hz), 3.69 (d, 1 H, *J* = 10.3 Hz), 3.52 (s, 3 H), 3.39 (dd, 1 H, *J* = 7.8, 9.4 Hz), 2.71 (dd, 1 H, *J* = 13.6, 4.6 Hz), 2.06, 2.02, 1.98, 1.92, 1.64 (s, 3 H each), 1.81 (dd, 1 H, *J* = 11.6, 13.6 Hz), 1.04 (m, 2 H), 0.03 (s, 9 H); HRMS calcd for $C_{79}H_{98}NO_{23}Si$ (M + H^+) 1456.6299, found 1456.6267.

(b) To a mixture of the sialyl donor **16** (109.6 mg, 0.210 mmol), **11** (312 mg, 0.317 mmol), and activated AW300 molecular sieves (360 mg) was added MeCN (2.6 mL), and the mixture was stirred at rt for 1.5 h. A solution of *N*-iodosuccinimide (69.2 mg, 0.308 mmol) in MeCN (0.65 mL) was added under Ar, and the temperature was lowered to −40 °C. Trifluoromethanesulfonic acid (0.012 mL, 0.137 mmol) was added, and the reaction mixture was stirred for 1.5 h at −40 °C. iPr_2NH (0.13 mL) was added, and the stirring was continued for 5 min, after which the reaction mixture was allowed to reach rt. The mixture was filtered (Celite), washed (acetone), and concentrated. The residue was dissolved in $CHCl_3/Et_2O$ (1:5, 42 mL) and washed with 0.1 M aqueous NaCl (40 mL). The organic phase was concentrated, and the residue was chromatographed (toluene/acetone, 6:1 → 4:1, gradient) to give **11** (225 mg), **15** (11.7 mg, 3.8%), and **14** (90.2 mg, 29%).

(c) To a stirred solution of **12** (184.1 mg, 118 mmol) and azoisobutyronitrile (15 mg, 0.092 mmol) in toluene (1.5 mL) was added a solution of triphenyltin hydride in toluene (0.70 mL, 1.2 mmol, 1.9 M) under Ar. After refluxing for 14 h, the mixture was cooled to rt and applied directly on a silica gel column. Elution (toluene/acetonitrile, 4:1 → 2:1, gradient) gave recovered **12** (21.7 mg, 12%) and **14** (141.7 mg, 83%), both as white powders.

2-(Trimethylsilyl)ethyl 2-Azido-6-*O*-benzoyl-2-deoxy-4-*O*-[methyl [5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-3-(phenylthio)-D-*erythro*-α-L-*gluco*-2-nonulopyranosyl]onate]-β-D-galactopyranoside (18). A solution of **6** (36.2 mg, 0.056 mmol) and **17** (23.5 mg, 0.057 mmol) in MeCN (0.55 mL) was stirred for 1 h at rt with 3 Å molecular sieves (0.16 g) under Ar. A solution of silver trifluoromethanesulfonate (18.2 mg, 0.071 mmol) in MeCN (0.25 mL) was added, and the temperature was lowered to −40 °C. A solution of methanesulfenyl bromide[21] in $ClCH_2CH_2Cl$ (0.025 mL, 0.070 mmol, ~2.8 M) was added in five portions during 10 min. After 3 h, Et_3N (0.2 mL) was added, the stirring was continued for 5 min at −40 °C, and toluene (5 mL) was added. The mixture was filtered (Celite), washed (toluene/acetone, 1:1), and concentrated. The residue was chromatographed (toluene/acetone, 3:1) to give **18** (42.9 mg, 77%) as a white powder: $[\alpha]_D$ +13 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.06–7.26 (m, 10 H), 5.49 (m, 1 H), 5.43 (ddd, *J* = 8.7, 2.8, 5.7 Hz), 5.38 (m, 1 H), 5.30 (m, 1 H), 4.58 (dd, 1 H, *J* = 5.2, 11.5 Hz), 4.55 (dd, 1 H, *J* = 7.5, 11.5 Hz), 4.30 (dd, 1 H, *J* = 10.0, 3.1 Hz), 4.28 (m, 2 H), 4.25 (dd, 1 H, *J* = 12.6, 2.8 Hz), 4.24 (d, 1 H, *J* = 8.2 Hz), 4.05 (bd, 1 H, *J* = 3.1 Hz), 4.02 (dd, 1 H, *J* = 5.7, 12.6 Hz), 3.98 (m, 1 H), 3.87 (s, 3 H), 3.78 (ddd, 1 H, *J* = 0.9, 5.2, 7.5 Hz), 3.61 (m, 1 H), 3.52 (d, 1 H, *J* = 11.3 Hz), 3.38 (dd, 1 H, *J* = 8.2, 10.0 Hz), 2.12, 2.05, 2.02, 2.01, 1.90 (s, 3 H each), 1.02 (m, 2 H), −0.01 (s, 9 H); $J_{C1'-H3'}$ = 5.9 Hz, cf. ref 17; HRMS calcd for $C_{44}H_{59}N_4O_{18}SSi$ (M + H^+) 991.3314, found 991.3321. A sample of **18** was acetylated: ^1H NMR (500 MHz, $CDCl_3$) δ 5.46 (bd, 1 H, *J* = 3.6 Hz), 4.86 (dd, 1 H, *J* = 10.0, 3.6 Hz), 4.41 (d, 1 H, *J* = 8.2 Hz), 3.66 (dd, 1 H, *J* = 8.2, 10.0 Hz), 3.36 (d, 1 H, *J* = 11.4 Hz), 2.10, 2.08, 2.05, 1.96, 1.93, 1.86 (s, 3H each).

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-(phenylthio)-D-*erythro*-α-L-*gluco*-2-nonulopyranosyl]onate]-β-D-galactopyranosyl]-β-D-glucopyranoside (21). A mixture of **6** (73.2 mg, 0.114 mmol), the lactoside acceptor **20**[22] (152.1 mg, 0.170 mmol), MeCN (1.4 mL), and 3 Å molecular sieves (0.25 g) was stirred for 30 min at rt under Ar. A solution of silver trifluoromethanesulfonate (41.8 mg, 0.163 mmol) in MeCN (0.3 mL) was added, and the temperature was lowered to −40 °C. A solution of methanesulfenyl bromide[21] in $ClCH_2CH_2Cl$ (0.057 mL, 0.16 mmol, ~2.8 M) was added in portions during 10 min. After 30 min, iPr_2NH (0.050 mL) was added, and the stirring was continued for 5 min at −40 °C. The reaction mixture was filtered through a short silica gel column (toluene/acetone, 2:1). The eluate was concentrated, and the residue was chromatographed (toluene/acetone, 6:1 → 4:1, gradient) to give recovered **20** (79.6 mg) as a syrup and **21** (118.2 mg, 71%) as a white powder: $[\alpha]_D$ +17.0 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.44–7.17 (m, 30

(22) Hasegawa, A.; Nagahama, T.; Ohki, H.; Kiso, M. *J. Carbohydr. Chem.* **1992**, *11*, 699.

H), 5.40 (ddd, 1 H, J = 7.9, 2.6, 5.8 Hz), 5.32 (dd, 1 H, J = 2.2, 7.9 Hz), 5.30 (d, 1 H, J = 9.6 Hz), 5.28 (dd, 1 H, J = 10.2, 11.2 Hz), 4.57 (d, 1 H, J = 7.8 Hz), 4.36 (d, 1 H, J = 7.8 Hz), 4.35 (dd, 1 H, J = 3.3, 9.3 Hz), 4.31 (dd, 1 H, J = 12.5, 2.6 Hz), 4.28 (q, 1 H, J = 10.1 Hz), 4.12 (dd, 1 H, J = 10.8, 2.2 Hz), 4.00 (m, 1 H), 3.97 (dd, 1 H, J = 5.8, 12.5 Hz), 3.93 (d, 1 H, J = 9.1 Hz), 3.89 (bs, 1 H), 3.84 (s, 3 H), 3.59 (m, 1 H), 3.55 (t, 1 H, J = 9.1 Hz), 3.44 (dd, 1 H, J = 9.3, 7.8 Hz), 3.38 (dd, 1 H, J = 7.8, 9.1 Hz), 3.34 (d, 1 H, J = 11.2 Hz), 2.65 (bs, 1 H), 2.05, 1.97, 1.96, 1.92, 1.89 (s, 3 H each), 1.03 (m, 2 H), 0.02 (s, 9 H); $J_{C1''-H3''}$ = 6.0 Hz, cf. ref 17; HRMS calcd for $C_{78}H_{96}NO_{23}SSi$ (M + H^+) 1474.5863, found 1474.5894. A sample of **21** was acetylated: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (d, 1 H, J = 3.3 Hz), 4.83 (dd, 1 H, J = 9.3, 3.3 Hz), 4.78 (d, 1 H, J = 7.7 Hz), 4.36 (d, 1 H, J = 7.8 Hz), 3.57 (t, 1 H, J = 9.0 Hz), 3.52 (dd, 1 H, J = 7.7, 9.3 Hz), 3.40 (dd, 1 H, J = 7.8, 9.0 Hz), 2.08, 1.96, 1.95, 1.87, 1.85, 1.80 (s, 3 H each).

Methyl [2-(Trimethylsilyl)ethyl 5-acetamido-4-*O*-benzoyl-3,5-dideoxy-9-*O*-(*p*-methoxybenzyl)-8-*O*-[methyl [5-acetamido-4,7,8,9-tetra-*O*-acetyl-3-(phenylthio)-3,5-dideoxy-D-*erythro*-α-L-*gluco*-2-nonulopyranosid]onate]-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (24). A mixture of **6** (201 mg, 0.312 mmol), the acceptor **10** (128.1 mg, 0.198 mmol), 3 Å molecular sieves (0.25 g), and MeCN (1.0 mL) was stirred for 30 min at rt under Ar. A solution of silver trifluoromethanesulfonate (111 mg, 0.432 mmol) in MeCN (0.25 mL) was added, and the temperature was lowered to −40 °C. A solution of methanesulfenyl bromide[21] in $ClCH_2CH_2Cl$ (0.16 mL, 0.44 mmol, ~2.8 M) was added in portions during 10 min. After 2 h, iPr_2NH (0.070 mL) was added, and the stirring was continued for 10 min at −40 °C. The reaction mixture was filtered (Celite, acetone) and concentrated. The residue was chromatographed (toluene/acetone, 4:1 → 2:1, gradient) to give recovered **10** (47 mg, 38%) as a syrup and **24** (69.1 mg, 28%) as a white powder: [α]$_D$ +11 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03−6.84 (m, 14 H), 6.12 (d, 1 H, J = 9.0 Hz), 5.41 (t, 1 H, J = 10.3 Hz), 5.39 (ddd, 1 H, J = 2.7, 7.4, 8.7 Hz), 5.30 (d, 1 H, J = 10.0 Hz), 5.26 (m, 1 H), 5.23 (dd, 1 H, J = 1.7, 8.7 Hz), 4.89 (dt, 1 H, J = 2.1, 7.4 Hz), 4.40 (d, 1 H, J = 11.4 Hz), 4.39 (dd, 1 H, J = 12.3, 2.7 Hz), 4.30 (q, 2 H, J = 10.0 Hz), 4.23 (d, 1 H, J = 11.4 Hz), 4.09 (dd, 1 H, J = 10.8, 1.7 Hz), 4.07 (dd, 1 H, J = 7.4, 12.3 Hz), 4.03−4.00 (m, 2 H), 3.90−3.81 (m, 2 H), 3.81, 3.81, 3.79 (s, 3 H each), 3.75 (m, 1 H), 3.67 (d, 1 H, J = 10.3 Hz), 3.39 (m, 1 H), 2.77 (dd, 1 H, J = 12.9, 5.1 Hz), 2.18, 2.09, 2.07, 1.91, 1.90, 1.88 (s, 3 H each), 0.79 (t, 2 H, J = 7.8 Hz), −0.04 (s, 9 H); $J_{C1'-H3'}$ = 5.9 Hz, cf. ref 17; HRMS calcd for $C_{58}H_{77}N_2O_{23}SSi$ (M + H^+) 1229.4407, found 1229.4384.

2-(Trimethylsilyl)ethyl 4-*O*-[3-*O*-[Sodium (5-acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosyl)-onate]-β-D-galactopyranosyl]-β-D-glucopyranoside (25). Compound **14** (67.6 mg, 0.0464 mmol) was dissolved in HOAc (6 mL), and the mixture was hydrogenated (H_2, 1 atm, Pd/C, 10%, 61 mg) overnight. The mixture was filtered (Celite, HOAc) and coconcentrated with MeOH/H_2O (2:1) and MeOH, and the residue was dried in vacuo. The dried residue was dissolved in dry MeOH (1 mL), and methanolic sodium methoxide (0.007 mL, ~2 M) was added at rt under Ar. After 2 h, Duolite C26 (H^+) resin was added. The mixture was filtered and concentrated, and the residue was dissolved in H_2O (0.5 mL) and treated with aqueous sodium hydroxide (0.024 mL, 0.048 mmol, 2.013 M) for 35 min at rt. The mixture was applied to a Sephadex G10 (Pharmacia) column. The material was eluted with water, and the fractions containing the product were first freeze-dried and then dried with a good oil pump to give **25** (34.5 mg, 98%) as a white foam: [α]$_D$ −6.3 (c 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 4.53 (d, 1 H, J = 7.9 Hz), 4.49 (d, 1 H, J = 8.0 Hz), 4.11 (dd, 1 H, J = 9.9, 3.1 Hz), 4.03 (ddd, 1 H, J = 5.2, 10.0, 12.6 Hz), 3.95 (d, 1 H, J = 3.1 Hz), 3.27 (t, 1 H, J = 8.6 Hz), 2.75 (dd, 1 H, J = 4.7, 12.5 Hz), 2.02 (s, 3 H), 1.80 (t, 1 H, J = 12.2 Hz), 1.07 (dt, 1 H, J = 5.5, 12.8 Hz), 0.97 (dt, 1 H, J = 5.3, 12.8 Hz), 0.02 (s, 9 H); HRMS calcd for $C_{28}H_{51}NO_{19}SiNa$ (M + H^+) 756.2722, found 756.2723.

2-(Trimethylsilyl)ethyl 4-*O*-[3-*O*-[Sodium (5-acetamido-3,5-dideoxy-D-*glycero*-β-D-*galacto*-2-nonulopyranosyl)-onate]-β-D-galactopyranosyl]-β-D-glucopyranoside (26). Compound **15** (22.2 mg, 0.015 mmol) was treated as above to give **26** (11.0 mg, 96%) as a white foam: [α]$_D$ −16 (c 0.85, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 4.48 (d, 1 H, J = 8.0 Hz), 4.47 (d, 1 H, J = 7.7 Hz), 4.24 (d, 1 H, J = 3.1 Hz), 4.17 (m, 1 H), 4.02 (ddd, 1 H, J = 5.3, 10.0, 12.5 Hz), 3.28 (dd, 1 H, J = 8.9, 8.0 Hz), 2.45 (dd, 1 H, J = 13.0, 4.7 Hz), 2.04 (s, 3 H), 1.68 (dd, 1 H, J = 11.8, 13.0 Hz), 1.06 (dt, 1 H, J = 5.5, 12.9 Hz), 0.97 (dt, 1 H, J = 5.2, 12.8 Hz), 0.02 (s, 9 H); HRMS calcd for $C_{28}H_{51}NO_{19}SiNa$ (M + H^+) 756.2722, found 756.2723.

Methyl [2-(Trimethylsilyl)ethyl 5-acetamido-4-*O*-benzoyl-3,5-dideoxy-9-*O*-(*p*-methoxybenzyl)-8-*O*-[5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*erythro*-α-L-*gluco*-2-nonulopyranosyloyl-1′ → 7-lactone]-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (27). To a stirred solution of **24** (111.8 mg, 0.090 mmol) and azoisobutyronitrile (14.7 mg, 0.895 mmol) in toluene (1.5 mL) was added a solution of triphenyltin hydride in toluene (0.5 mL, ~2 M, ~1 mmol) under Ar. After refluxing for 16 h, the mixture was allowed to reach rt and then applied directly to a silica gel column and chromatographed (toluene/acetone, 4:1 → 3:1, gradient) to give **27** as a white powder (70.2 mg, 71%): [α]$_D$ −56 (c 0.98, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01−6.92 (m, 9 H), 5.64 (ddd, 1 H, J = 5.6, 11.2, 10.3 Hz), 5.39−5.32 (m, 2 H), 5.27 (d, 1 H, J = 10.4 Hz), 5.04 (ddd, 1 H, J = 4.5, 12.2, 10.4 Hz), 4.97 (d, 1 H, J = 9.6 Hz), 4.94 (dt, 1 H, J = 4.7, 7.7 Hz), 4.59 (d, 1 H, J = 11.0 Hz), 4.49 (d, 1 H, J = 11.0 Hz), 4.49 (d, 1 H, J = 4.7 Hz), 4.40 (q, 1 H, J = 10.1 Hz), 4.23 (dd, 1 H, J = 2.4, 12.5 Hz), 4.21 (q, 1H, J = 10.1 Hz), 4.14 (d, 1 H, J = 10.6 Hz), 3.98 (dd, 1 H, J = 4.8, 12.5 Hz), 3.93 (dd, 1 H, J = 2.2, 10.7 Hz), 3.92 (d, 2 H, J = 7.9 Hz), 3.88 (s, 3 H), 3.82 (s, 3 H), 3.75 (m, 1 H), 3.39 (m, 1 H), 2.67 (dd, 1 H, J = 12.6, 4.5 Hz), 2.36 (dd, 1 H, J = 13.3, 5.6 Hz), 2.15, 2.11, 2.03, 1.99, 1.89, 1.66 (s, 3 H each), 2.06 (t, 1 H, J = 12.8 Hz), 1.79 (dd, 1 H, J = 11.2, 13.3 Hz), 0.81 (m, 2 H), −0.01 (s, 9 H); HRMS calcd for $C_{51}H_{69}N_2O_{22}Si$ (M + H^+) 1089.4111, found 1089.4100.

Methyl [2-(Trimethylsilyl)ethyl 5-acetamido-4-*O*-benzoyl-3,5-dideoxy-8-*O*-[5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*erythro*-α-L-*gluco*-2-nonulopyranosyloyl-1′ → 9-lactone]-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (28). A solution of **27** (14.8 mg, 0.0136 mmol) in EtOH (5 mL) was hydrogenated (H_2, 1 atm, Pd/C, 10%, 12.1 mg) for 12 h. The mixture was filtered (Celite, toluene/methanol, 1:1, 30 mL), the filtrate was concentrated, and the residue was chromatographed (toluene/acetone, 3:1 → 2:1, gradient) to give **28** (11.2 mg, 85%) as a colorless solid: [α]$_D$ −47 (c 0.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05−7.46 (m, 5 H), 6.22 (d, 1 H, J = 7.9 Hz), 5.51 (ddd, 1 H, J = 5.5, 11.5, 10.4 Hz), 5.35 (d, 1 H, J = 9.5 Hz), 5.35 (dd, 1 H, J = 2.3, 8.2 Hz), 5.30 (ddd, 1 H, J = 4.9, 11.8, 10.5 Hz), 5.16 (ddd, 1 H, J = 2.8, 5.5, 8.2 Hz), 4.77 (d, 1 H, J = 4.8 Hz), 4.65−4.58 (m, 2 H), 4.38 (ddd, 1 H, J = 8.2, 4.3, 9.3 Hz), 4.32 (dd, 1 H, J = 12.6, 2.8 Hz), 4.24 (q, 1 H, J = 10.1 Hz), 4.10 (dt, 1 H, J = 10.5, 7.9 Hz), 4.07 (dd, 1 H, J = 5.5, 12.6 Hz), 3.90 (m, 1 H), 3.86 (dd, 1 H, J = 10.6, 2.3 Hz), 3.84 (s, 3 H), 3.77 (dd, 1 H, J = 1.6, 10.5 Hz), 3.61 (ddd, 1 H, J = 1.6, 4.8, 8.2 Hz), 3.55 (m, 1 H), 2.78 (dd, 1 H, J = 12.7, 4.9 Hz), 2.50 (dd, 1 H, J = 13.5, 5.5 Hz), 2.15, 2.09, 2.05, 2.04, 1.98, 1.90 (s, 3 H each), 1.99 (dd, 1 H, J = 11.5, 13.5 Hz), 0.91 (m, 2 H), 0.02 (s, 9 H); HRMS calcd for $C_{43}H_{61}N_2O_{21}Si$ (M + H^+) 969.3536, found 969.3553.

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Supplementary Material Available: ^{1}H NMR spectra and ^{1}H NMR data with assigned signals for all title compounds described in the Experimental Section (22 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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