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Stereoselective Synthesis of a *C*-Linked Neuraminic Acid Disaccharide: Potential Building Block for the Synthesis of *C*-Analogues of Polysialic acids

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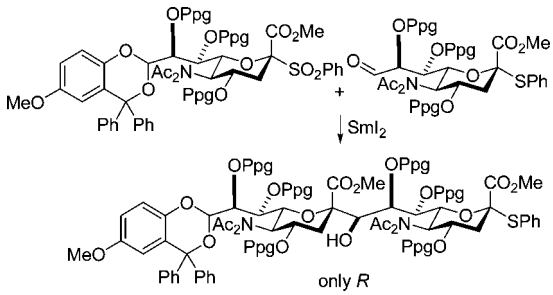

C-Linked neuraminic acid disaccharide was synthesized in a diastereoselective manner from a sulfone donor and aldehyde acceptor, which was protected as a propargyl ether, through a samarium-mediated coupling reaction. The resulting disaccharide has acetal and phenyl sulfide functional groups that can be easily converted into aldehyde and phenyl sulfone groups by photolysis and oxidation reactions to serve as disaccharide acceptor and donor, respectively.

Polysialic acid (PSA), a long linear α(2−8)-linked polymer of sialic acid, is widely distributed in nature, from bacteria to humans. PSA is expressed on the meningitis-causing bacteria *Neisseria meningitidis* B and the capsular polysaccharide of *Escherichia coli* K1.[1−3] It has also been found on the cell surface in a number of important cancers and is believed to be associated with metastasis and correlates with tumor progression.[4] PSA is most often found as an *N*-linked glycan on neural cell adhesion molecules (PSA-NCAM) and attenuates NCAM adhesion, facilitating neural cell migration and regeneration.[5] PSA is also found in embryonic tissues and participates in developmental biology.[6] In this respect, PSAs are important targets for biological studies, in the development of vaccines for protection against meningococcal infection, and for the treatment of various cancers including Wilms' tumor and small cell lung carcinoma.[7,8]

PSAs are known to exhibit both chemical and enzymatic hydrolytic instability.[9] The PSA glycosidic linkages are very labile and subject to self-cleavage under mildly acidic conditions. In contrast, *C*-glycosides, in which the interglycosidic oxygen atoms are replaced with carbon atoms, are resistant to chemical and enzymatic degradation.[10] The unusual lability of PSAs, their participation in developmental biology, and their reappearance in various tumors makes their *C*-glycosidic analogues ideal targets for a wide array of experimental, biological, and potential therapeutic applications.[11]

Over the past 10 years, samarium-mediated *C*-glycosylation reactions have been reported by our laboratory[12] and the Beau research group[13] for the synthesis of *C*-linked α-sialosides. Recently, we reported the first synthesis of a *C*-linked neuraminic acid disaccharide as a versatile precursor of *C*-analogues of oligosialic acids and gangliosides.[12f] However, this synthesis afforded a 1:1 ratio of *R*- and *S*-diastereoisomers at the bridge hydroxymethylene group, requiring additional steps to remove this hydroxyl group. The lack of stereoselectivity and the development of a more efficient strategy for *C*-oligosialic acids synthesis prompted us to investigate new protecting groups and a common donor−acceptor concept, widely used by others in oligosaccharide synthesis.[14] In this effort, we found that propargyl protecting group chemistry afforded a single diastereoisomer with a photolabile protecting group for sialic acid aldehyde protection. Furthermore, this protecting group was well suited for the development of a common donor−acceptor strategy owing to its easy introduction and removal under mild reaction conditions.

Herein, we report a diastereoselective synthesis of a *C*-linked neuraminic acid disaccharide that is useful as a donor−acceptor disaccharide for the further synthesis of *C*-linked α(2−8)

(1) Finne, J. *J. Biol. Chem.* **1982**, *257*, 11966–11970.
(2) Swartley, J. S.; Marfin, A. A.; Edupuganti, S.; Liu, L.-J.; Cieslak, P.; Perkins, B.; Wenger, J. D.; Stephens, D. S. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 271–276.
(3) Robbins, J. B.; McCracken, G. H.; Gotschlich, E. C.; Ørskov, F.; Ørskov, I.; Hanson, L. A. *N. Engl. J. Med.* **1974**, *290*, 12216–12220.
(4) Theodosis, D. T.; Rougon, G.; Poulain, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 5494–5498.
(5) Hoffman, S.; Sorkin, B. C.; White, P. C.; Brackenbury, R.; Mailhammer, R.; Rutishauer, U.; Cunningham, B. A.; Edelman, G. M. *J. Biol. Chem.* **1982**, *257*, 7720–7729.
(6) Buttner, B.; Kannicht, C.; Reutter, W.; Horstkorte, R. *Biochem. Biophys. Res. Commun.* **2003**, *310*, 967–971.
(7) Rothbard, J. B.; Brackenbury, R.; Cunningham, B. A.; Edelman, G. M. *J. Biol. Chem.* **1982**, *257*, 11064–11069.
(8) Roth, J.; Zuber, C.; Wagner, P.; Taatjes, D. J.; Weisgerber, C.; Heitz, P. U.; Goridis, C.; Bitter-Suermann, D. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 2999–3003.
(9) Manzi, A. E.; Higa, H. H.; Diaz, S.; Varki, A. *J. Biol. Chem.* **1994**, *269*, 23617–23624.
(10) (a) Beau, J.-M.; Gallagher, T. *Top. Curr. Chem.* **1997**, *187*, 1–54. (b) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913–9959. (c) Liu, L.; McKee, M.; Postema, M. H. D. *Curr. Org. Chem.* **2001**, *5*, 1133–1167.
(11) Rutishauser, U. *Nature Rev. Neurosci.* **2008**, *9*, 26–35.
(12) (a) Vlahov, I. R.; Vlahova, P. I.; Linhardt, R. J. *J. Am. Chem. Soc.* **1997**, *119*, 1480–1481. (b) Du, Y.; Polat, T.; Linhardt, R. J. *Tetrahedron Lett.* **1998**, *39*, 5007–5010. (c) Bazin, H. G.; Du, Y.; Polat, T.; Linhardt, R. J. *J. Org. Chem.* **1999**, *64*, 7254–7259. (d) Kuberan, B.; Sikkander, S. A.; Tomiyama, H.; Linhardt, R. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2073–2075. (e) Dino, K. R.; Baytas, S. N.; Wang, Q.; Muñoz, E. M.; Tukuzoki, K.; Tomiyama, H.; Linhardt, R. J. *J. Org. Chem.* **2005**, *70*, 8197–8200. (f) Yuan, X.; Ress, D. K.; Linhardt, R. J. *J. Org. Chem.* **2007**, *72*, 3085–3088.
(13) (a) Abdallah, Z.; Doisneau, G.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5209–5212. (b) Malapelle, A.; Abdallah, Z.; Doisneau, G.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6016–6020. (c) Malapelle, A.; Coslovi, A.; Doisneau, G.; Beau, J.-M. *Eur. J. Org. Chem.* **2007**, *314*, 5–3157.
(14) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095.

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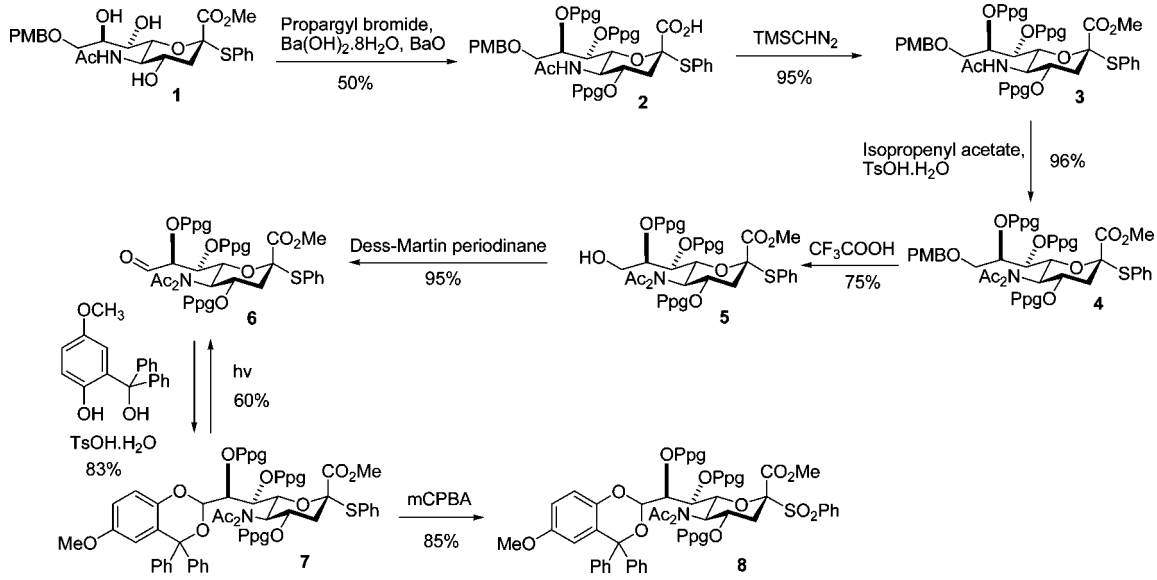
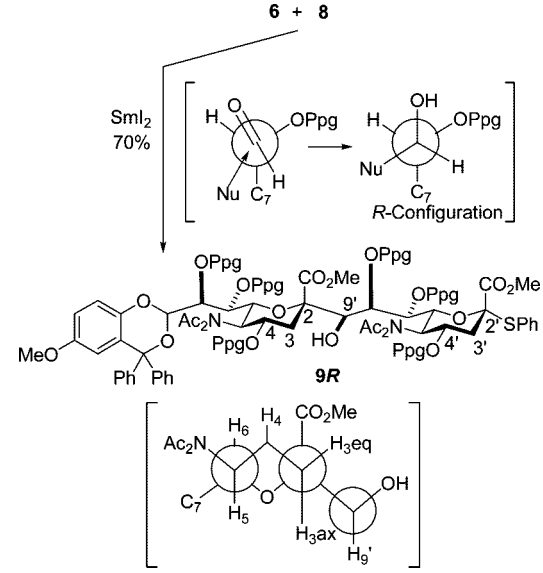
SCHEME 1



oligosialic acids. The synthesis of *C*-glycosylation aldehyde acceptor **6** and sulfone donor **8** was straightforward from the known *C*-9 PMB protected compound **1**[12f] (Scheme 1). Propargylation of hydroxyl groups of **1** with propargyl bromide in the presence of barium hydroxide and barium oxide in DMF afforded the propargylated carboxylic acid derivative **2** in a modest 50% yield. Methylation of the carboxylic acid using $TMSCHN_2$ gave methyl ester **3** in 95% yield. Acetylation of the acetamido group in **3**, required to prevent intramolecular cyclization reaction at later stage in the synthesis, was performed by reaction with isopropenyl acetate in the presence of a catalytic amount of *p*-toluenesulfonic acid to afford **4** in 96% yield. The PMB protecting group on *C*-9 of compound **4** was chemoselectively removed using trifluoroacetic acid in DCM at −20 °C, affording **5** in 75% yield. Oxidation of the resulting C-9 hydroxyl group using the mild Dess−Martin periodinane oxidizing agent afforded the desired aldehyde acceptor **6** in 95% yield. The aldehyde group of **6** was protected with salicylic diol,[15] a photolabile carbonyl protecting group, to afford the fully protected acetal derivative **7** as a single diastereomer in 83% yield. The aldehyde derivative **6** could be recovered by photochemical deprotection of **7** in 60% yield using a 450 W medium-pressure mercury lamp fitted with a Pyrex filter sleeve to minimize undesired side reactions, demonstrating the utility of this photolabile aldehyde protecting group. The target sulfone donor **8** was obtained in 85% yield through the oxidation of compound **7** with 3-chloroperbenzoic acid.

Having the proper sulfone donor **8** and aldehyde acceptor **6** in hand, *C*-glycosylation was performed under the standard Barbier conditions.[16] As shown in Scheme 2, only one diastereoisomer **9*R*** was obtained in 70% yield, based on the consumed donor. Structural analysis of **9*R*** was performed using 1D and 2D NMR experiments including ^1H NMR, ^{13}C NMR, COSY, HSQC, TOCSY, and ROESY (see the Supporting Information). Initially, all protons and carbons were assigned. Next, their through-bond and through-spatial correlations were determined. The α-configuration of the newly formed *C*-glycoside was

SCHEME 2



confirmed by the presence of NOEs, in the 2D-ROESY spectrum, between H-4, H-6 and the methyl ester protons; such NOEs would only be observed in an α-sialoside adopting the $_5C^2$ conformation. The absolute configuration of the newly formed hydroxymethylene group was also identified in the same 2D-ROESY spectrum, which showed close spatial proximity between H-3ax and H-9′. The Felkin−Ahn model[17] can be used to predict the stereochemical outcome of a kinetically controlled addition of a nucleophile to a prochiral aldehyde. The bulkiest ligand α to the carbonyl group in **9*R***, the oxygen atom bearing propargyl group at *C*-8′, has a perpendicular relationship to the plane of the carbonyl group. The incoming nucleophile approaches to the carbonyl group through the Bürgi-Dunitz trajectory[18] *anticlinal* to the bulkiest oxygen atom at *C*-8′, resulting in *R*-configuration. Based on this analysis, shown in Scheme 2, and the presence of an NOE between H-3ax and H-9′, the *R*-configuration was confirmed.

(15) Wang, P.; Hu, H.; Wang, Y. *Org. Lett.* **2007**, *9*, 1533–1535.
(16) Excellent reviews on the application of SmI_2: Molander, G.; Harris, C. *Chem. Rev.* **1996**, *96*, 307–338.
(17) Anh, N.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61–70.
(18) Bürgi, H.; Dunitz, J.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065–5067.

Experimental Section

Methyl [Phenyl 5-acetamido-9-*O*-(*p*-methoxybenzyl)-3,5-dideoxy-4,7,8-tri-*O*-propargyl-2-thio-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid]onate (3). Propargyl bromide (18.7 mL, 168 mmol), $Ba(OH)_2 \cdot 8H_2O$ (13.2 g, 42 mmol), and BaO (12.9 g, 84 mmol) were added successively to a solution of compound **1** (4.5 g, 8.4 mmol) in anhydrous DMF (100 mL) at room temperature. After being stirred overnight, the reaction mixture was quenched by addition of $TsOH \cdot H_2O$ (15.9 g, 84 mmol) and then diluted with ethyl acetate (300 mL). After washing with saturated aqueous NH_4Cl (300 mL), the organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH, 20/1) to afford phenyl 5-acetamido-9-*O*-(*p*-methoxy)benzyl-3,5-dideoxy-4,7,8-tri-*O*-propargyl-2-thio-D-*glycero*-α-D-*galacto*-non-2-ulopyranosidic acid (**2**) (2.67 g, 50%): $R_f = 0.15$ (DCM/MeOH, 6/1). $TMSCHN_2$ (2 M in diethyl ether, 7.5 mL, 15 mmol) was added to a solution of **2** in methanol/diethyl ether (1/1, 100 mL) at room temperature. After being stirred for 3 h at the same temperature, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (33% ethyl acetate in hexane) to afford **3** (2.60 g, 95%): $R_f = 0.25$ (ethyl acetate/hexane, 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55−7.53 (m, 2H, aromatic), 7.37−7.28 (m, 5H, aromatic), 6.89−6.87 (m, 2H, aromatic), 5.48 (d, 1H, $J = 8.5$ Hz), 4.53 (s, 2H), 4.47 (dd, 1H, $J = 2.5$, 15.5 Hz), 4.26−4.19 (m, 2H), 4.15 (dd, 1H, $J = 2.5$, 15.5 Hz), 4.05 (dd, 1H, $J = 2.5$, 15.5 Hz), 3.97−3.93 (m, 2H), 3.89−3.86 (m, 2H), 3.80 (s, 3H), 3.74−3.68 (m, 3H), 3.62 (s, 3H), 3.61−3.59 (m, 1H), 2.94 (dd, 1H, $J = 4.5$, 12.5 Hz), 2.48 (t, 1H, $J = 2.5$ Hz), 2.44 (t, 1H, $J = 2.5$ Hz), 2.38 (t, 1H, $J = 2.5$ Hz), 1.95 (s, 3H), 1.79 (dd, 1H, $J = 11.5$, 12.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 169.1, 159.4, 137.1, 137.0, 130.5, 129.7, 129.6, 129.4, 128.9, 128.8, 113.9, 87.1, 81.1, 81.0, 80.2, 77.8, 76.5, 75.1, 74.9, 74.7, 74.5, 74.4, 74.2, 73.9, 73.2, 60.5, 58.2, 56.6, 55.6, 52.9, 50.7, 37.5, 24.0; HR MALDI-TOF MS *m*/*z* calcd for $C_{35}H_{39}NO_9S$ $[M + Na]^+$ 672.2238, found 672.2240.

Methyl [Phenyl 5-(*N*-acetylacetamido)-9-*O*-(*p*-methoxybenzyl)-3,5-dideoxy-4,7,8-tri-*O*-propargyl-2-thio-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid]onate (4). A catalytic amount of $TsOH \cdot H_2O$ (190 mg, 1.0 mmol) was added to a solution of **3** (2.55 g, 3.92 mmol) in isopropenyl acetate (50 mL) at room temperature. The reaction mixture was heated to 60 °C and stirred for 5 h at the same temperature. After quenching by addition of NEt_3 (140 μL, 1.0 mmol), the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (25% ethyl acetate in hexane) to afford **4** (2.60 g, 96%): $R_f = 0.65$ (ethyl acetate/hexane, 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55−7.53 (m, 2H, aromatic), 7.35−7.24 (m, 5H, aromatic), 6.89−6.87 (m, 2H, aromatic), 4.67 (dd, 1H, $J = 2.5$, 15.5 Hz), 4.54 (d, 1H, $J = 11.5$ Hz), 4.47 (dd, 1H, $J = 2.5$, 15.5 Hz), 4.45 (d, 1H, $J = 11.5$ Hz), 4.67 (dt, 1H, $J = 5.0$, 10.5 Hz), 4.27−4.17 (m, 3H), 4.15 (dd, 1H, $J = 2.5$, 15.5 Hz), 4.10−4.06 (m, 2H), 4.03−4.00 (m, 1H), 3.92 (t, 1H, $J = 10.0$ Hz), 3.80 (s, 3H), 3.75 (t, 1H, $J = 3.0$ Hz), 3.69 (dd, 1H, $J = 7.0$, 11.0 Hz), 3.53 (s, 3H), 3.12 (dd, 1H, $J = 5.0$, 13.0 Hz), 2.45 (s, 3H), 2.44 (t, 1H, $J = 2.5$ Hz), 2.39−2.37 (m, 2H), 2.38 (s, 3H), 1.78 (dd, 1H, $J = 10.5$, 13.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 175.4, 168.5, 159.3, 136.9, 136.8, 130.9, 129.6, 129.4, 129.3, 129.0, 113.9, 88.5, 80.6, 79.5, 79.4, 79.3, 76.3, 75.7, 75.5, 75.4, 75.0, 74.7, 74.5, 73.2, 72.4, 59.9, 58.7, 58.0, 57.3, 55.6, 52.8, 40.0, 28.5, 26.0; HR MALDI-TOF MS *m*/*z* calcd for $C_{37}H_{41}NO_{10}S$ $[M + Na]^+$ 714.2343, found 714.2352.

Methyl [Phenyl 5-(*N*-acetylacetamido)-3,5-dideoxy-4,7,8-tri-*O*-propargyl-2-thio-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid]onate (5). Trifluoroacetic acid (7.0 mL) was added to a solution of **4** (2.60 g, 3.75 mmol) in DCM (50 mL) at −20 °C. After being stirred for 1 h at the same temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (100 mL). After separation, the organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (25% ethyl acetate in hexane) to afford **5** (1.59 g, 75%): $R_f = 0.27$ (ethyl acetate/hexane, 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56−7.54 (m, 2H, aromatic), 7.44−7.35 (m, 3H, aromatic), 4.57 (dd, 1H, $J = 2.0$, 9.5 Hz), 4.49 (dd, 1H, $J = 2.5$, 15.5 Hz), 4.32 (dt, 1H, $J = 5.0$, 10.5 Hz), 4.30 (dd, 1H, $J = 2.5$, 15.5 Hz), 4.19−4.06 (m, 5H), 3.92 (t, 1H, $J = 10.0$ Hz), 3.76−3.72 (m, 3H), 3.60 (s, 3H), 3.15 (dd, 1H, $J = 5.0$, 13.0 Hz), 2.47 (t, 1H, $J = 2.5$ Hz), 2.45 (s, 3H), 2.42 (t, 1H, $J = 2.5$ Hz), 2.40 (s, 3H), 2.39 (t, 1H, $J = 2.5$ Hz), 1.81 (dd, 1H, $J = 10.5$, 13.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 175.5, 168.6, 137.2, 130.5, 129.2, 129.0, 88.4, 82.5, 80.2, 79.4, 79.3, 75.9, 75.8, 75.7, 75.1, 75.0, 74.9, 72.1, 62.1, 59.9, 58.4, 58.3, 57.3, 52.9, 39.9, 28.6, 26.0; HR MALDI-TOF MS *m*/*z* calcd for $C_{29}H_{33}NO_9S$ $[M + Na]^+$ 594.1768, found 594.1765.

Methyl [Phenyl 5-(*N*-acetylacetamido)-3,5-dideoxy-4,7,8-tri-*O*-propargyl-2-thio-D-*glycero*-α-D-*galacto*-non-2-(9-oxaulopyranosid)]onate (6). Dess−Martin periodinane solution (0.3 M in DCM, 36 mL, 10.7 mmol) was added slowly to a solution of **5** (1.53 g, 2.67 mmol) in DCM (100 mL) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was warmed to room temperature and then stirred for another 2 h. After quenching by adding of aqueous 0.1 M $Na_2S_2O_3$ solution (100 mL), the reaction mixture was separated. The organic phase was washed with saturated aqueous $NaHCO_3$ (100 mL), dried over anhydrous $MgSO_4$, and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford **6** (1.44 g, 95%): $R_f = 0.50$ (ethyl acetate/hexane, 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.50−7.35 (m, 5H, aromatic), 4.75 (dd, 1H, $J = 2.5$, 9.5 Hz), 4.48 (d, 1H, $J = 1.0$ Hz), 4.37 (dt, 1H, $J = 5.0$, 10.5 Hz), 4.33−4.29 (m, 3H), 3.94 (t, 1H, $J = 10.0$ Hz), 3.90 (dd, 1H, $J = 1.5$, 2.0 Hz), 3.66 (s, 3H), 3.16 (dd, 1H, $J = 5.0$, 13.0 Hz), 2.42 (s, 3H), 2.41 (s, 3H), 2.42−2.40 (m, 2H), 2.39 (t, 1H, $J = 2.5$ Hz), 1.84 (dd, 1H, $J = 11.0$, 13.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 175.7, 175.5, 168.7, 137.1, 130.6, 129.2, 129.0, 88.6, 84.9, 79.4, 78.8, 78.5, 77.1, 76.2, 76.0, 75.8, 75.1, 74.9, 72.2, 59.8, 58.2, 57.5, 57.3, 53.1, 40.0, 28.7, 26.0; HR MALDI-TOF MS *m*/*z* calcd for $C_{29}H_{31}NO_9S$ $[M + Na]^+$ 592.1612, found 592.1615.

Methyl [Phenyl 5-(*N*-acetylacetamido)-3,5-dideoxy-4,7,8-tri-*O*-propargyl-2-thio-D-*glycero*-α-D-*galacto*-non-2-(9-oxa-ulopyranosid)]onate 1′,1′-Diphenyl-5-methoxysalicylic Alcohol Acetal (7). A catalytic amount of $TsOH \cdot H_2O$ (57 mg, 0.3 mmol) was added to a solution of **6** (570 mg, 1.0 mmol) and 1′,1′-diphenyl-5-methoxysalicylic alcohol (920 mg, 3.0 mmol) in anhydrous benzene (20 mL) at room temperature. After being stirred for 1 day at the same temperature, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (15% ethyl acetate in hexane) to afford **7** (712 mg, 83%): $R_f = 0.45$ (ethyl acetate/hexane, 2/3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.22 (m, 13H, aromatic), 7.14−7.11 (m, 2H, aromatic), 6.97 (d, 1H, $J = 9.0$ Hz, aromatic), 6.77 (dd, 1H, $J = 3.0$, 9.0 Hz, aromatic), 6.40 (d, 1H, $J = 3.0$ Hz, aromatic), 5.51 (d, 1H, $J = 3.0$ Hz), 4.78 (dd, 1H, $J = 2.5$, 9.5 Hz), 4.49 (dd, 1H, $J = 2.5$, 15.5 Hz), 4.37 (dt, 1H, $J = 5.0$, 10.5 Hz), 4.33 (dd, 1H, $J = 2.5$, 15.5 Hz), 4.23 (d, 2H, $J = 2.0$ Hz), 4.15−4.07 (m, 3H), 3.99 (t, 1H, $J = 10.0$ Hz), 3.87 (dd, 1H, $J = 2.5$, 15.5 Hz), 3.62 (s, 3H), 3.31 (s, 3H), 3.10 (dd, 1H, $J = 5.0$, 12.5 Hz), 2.48 (s, 3H), 2.42 (t, 1H, $J = 2.5$ Hz), 2.40 (s, 3H), 2.38 (t, 1H, $J = 2.5$ Hz), 2.21 (t, 1H, $J = 2.5$ Hz), 1.73 (dd, 1H, $J = 11.0$, 12.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 175.2, 168.5, 153.3, 146.1, 146.0, 143.8, 136.8, 129.9, 129.6, 128.7, 128.4, 128.2, 128.1, 127.7, 126.0, 118.4, 114.9, 114.4, 95.3, 88.0, 84.6, 80.3, 79.8, 79.6, 77.7, 75.6, 75.0, 74.8, 74.6, 72.5, 59.6, 59.5, 57.3, 56.8, 55.8, 52.5, 39.8, 28.6, 25.9; HR MALDI-TOF MS *m*/*z* calcd for $C_{49}H_{47}NO_{11}S$ $[M + Na]^+$ 880.2762, found 880.2774.

Photochemical Reaction To Remove the Photolabile Aldehyde Protecting Group. A solution of acetal **7** (20 mg, 0.023 mmol) in acetonitrile (20 mL) was photolyzed at room temperature for 80 min. After photolysis, the reaction mixture was concentrated in

vacuo and then purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford aldehyde **6** (8.6 mg, 60%).

Methyl 5-(*N*-Acetylacetamido)-3,5-dideoxy-4,7,8-tri-*O*-propargyl-2-phenylsulfonyl-D-*glycero*-α-D-*galacto*-non-2-(9-oxaulopyranosid)]onate 1′,1′-Diphenyl-5-methoxysalicylic Alcohol Acetal (8). 3-Chloroperbenzoic acid (233 mg, 60%, 0.94 mmol) was added to a solution of **7** (270 mg, 0.31 mmol) in DCM (15 mL) at 0 °C. After being stirred for 1 h at the same temperature, the reaction mixture was warmed to room temperature and then stirred for another 1 h to complete the reaction. Then, the reaction mixture was quenched by aqueous 0.1 M $Na_2S_2O_3$ solution (30 mL), separated, and washed with saturated aqueous $NaHCO_3$ (30 mL). The organic phase was dried over anhydrous $MgSO_4$ and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (15% ethyl acetate in hexane) to afford **8** (233 mg, 85%): $R_f = 0.35$ (ethyl acetate/hexane, 2/3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84−7.82 (m, 2H, aromatic), 7.64−7.61 (m, 1H, aromatic), 7.50−7.47 (m, 2H, aromatic), 7.37−7.25 (m, 10H, aromatic), 6.92 (d, 1H, $J = 9.0$ Hz, aromatic), 6.77 (dd, 1H, $J = 3.0$, 9.0 Hz, aromatic), 6.40 (d, 1H, $J = 3.0$ Hz, aromatic), 5.32 (d, 1H, $J = 2.5$ Hz, *H9*), 4.83 (dd, 1H, $J = 2.0$, 10.0 Hz, *H6*), 4.53 (dt, 1H, $J = 4.5$, 10.5 Hz, *H4*), 4.27 (dd, 1H, $J = 2.5$, 15.5 Hz, OCH_2CCH), 4.21 (dd, 1H, $J = 2.5$, 15.5 Hz, OCH_2CCH), 4.16 (dd, 1H, $J = 2.5$, 15.5 Hz, OCH_2CCH), 4.11 (dd, 1H, $J = 2.5$, 15.5 Hz, OCH_2CCH), 3.99 (t, 1H, $J = 10.0$ Hz, *H5*), 3.95 (dd, 1H, $J = 2.5$, 15.5 Hz, OCH_2CCH), 3.88 (dd, 1H, $J = 2.5$, 15.5 Hz, OCH_2CCH), 3.76 (s, 3H, COOCH_3), 3.74 (dd, 1H, $J = 2.0$, 8.5 Hz, *H7*), 3.65 (dd, 1H, $J = 2.0$, 8.5 Hz, *H8*), 3.63 (s, 3H, OCH_3), 3.25 (dd, 1H, $J = 4.5$, 12.5 Hz, *H3eq*), 2.47 (s, 3H, CH_3CO), 2.42 (t, 1H, $J = 2.5$ Hz, OCH$_2$CC*H*), 2.40 (t, 1H, $J = 2.5$ Hz, OCH$_2$CC*H*), 2.36 (s, 3H, CH_3CO), 2.09 (dd, 1H, $J = 11.0$, 12.5 Hz, *H3ax*), 2.01 (t, 1H, $J = 2.5$ Hz, OCH$_2$CC*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 175.0, 165.7, 153.5, 145.8, 145.7, 143.9, 134.8, 134.4, 131.2, 129.8, 129.0, 128.4, 128.3, 128.2, 127.8, 125.9, 118.4, 115.0, 114.4, 95.6, 94.7, 84.9, 80.2, 79.9, 79.2, 76.7, 75.6, 75.1, 75.0, 74.8, 73.8, 71.7, 59.6, 58.8, 57.1, 56.8, 55.8, 53.9, 32.6, 28.4, 25.; HR MALDI-TOF MS *m*/*z* calcd for $C_{49}H_{47}NO_{13}S$ $[M + Na]^+$ 912.2660, found 912.2676.

Methyl 5-(*N*-Acetylacetamido)-3,5-dideoxy-2-*C*-{(9′*R*)-[methyl (phenyl 5′-(*N*-acetylacetamido)-3′,5′-dideoxy-4′,7′,8′-tri-*O*-propargyl-2′-thio-D-*glycero*-α-D-*galacto*-non-2′-ulopyranosid)]onate}-4,7,8-tri-*O*-propargyl-D-*glycero*-α-D-*galacto*-non-2-(9-oxaulopyranosid)]onate 1′,1′-Diphenyl-5-methoxysalicylic Alcohol Acetal (9*R*). SmI_2 solution (0.63 mL, 0.1 M in THF, 0.063 mmol) was added to a mixture of sulfone donor **8** (14 mg, 0.0157 mmol) and aldehyde acceptor **6** (12 mg, 0.021 mmol) and stirred for 5 min at room temperature. After quenching by aqueous 0.1 M $Na_2S_2O_3$ solution (2 mL), the reaction mixture was diluted with DCM (3 mL), separated, and washed with saturated aqueous $NaHCO_3$ (5 mL). The organic phase was dried over anhydrous $MgSO_4$ and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford **9*R*** {8 mg, 70%, calculated based on consumed donor **8** (8 mg)}: $R_f = 0.45$ (ethyl acetate/hexane, 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57−7.23 (m, 15H, aromatic), 6.92 (d, 1H, $J = 9.0$ Hz, aromatic), 6.77 (dd, 1H, $J = 3.0$, 9.0 Hz, aromatic), 6.42 (d, 1H, $J = 3.0$ Hz, aromatic), 5.53 (d, 1H, $J = 4.5$ Hz, *H9*), 5.23 (dd, 1H, $J = 2.0$, 10.0 Hz, *H6*), 4.75 (dd, 1H, $J = 2.5$, 10.0 Hz, *H6′*), 4.54−4.40 (m, 4H, 4 × OCH_2CCH), 4.35−4.29 (m, 3H, 2 × OCH_2CCH, *H4′*), 4.27−4.18 (m, 4H, OCH_2CCH, *H9′*, *H4*, *H8*), 4.10−4.02 (m, 4H, 3 × OCH_2CCH, *H8′*), 4.00 (dd, 1H, $J = 2.5$, 15.5 Hz, OCH_2CCH), 3.91 (d, 1H, $J = 2.5$ Hz, *H7′*), 3.87 (t, 1H, $J = 10.0$ Hz, *H5*), 3.85 (s, 3H, COOCH_3′), 3.82−3.75 (m, 3H, OCH_2CCH, *H5′*, *H7*), 3.64 (s, 3H, OCH_3), 3.54 (s, 3H, COOCH_3), 3.12 (dd, 1H, $J = 4.5$, 13.5 Hz, *H3eq*), 3.04 (d, 1H, $J = 10.5$ Hz, *OH*), 2.77 (dd, 1H, $J = 5.0$, 13.0 Hz, *H3′eq*), 2.50 (s, 3H, CH_3CO), 2.46 (t, 1H, $J = 2.5$ Hz, OCH$_2$CC*H*), 2.45 (s, 3H, CH_3CO), 2.41 (t, 1H, $J = 2.5$ Hz, OCH$_2$CC*H*), 2.40 (t, 1H, $J = 2.5$ Hz, OCH$_2$CC*H*), 2.38 (s, 6H, 2 × CH_3CO), 2.32 (t, 1H, $J = 2.5$ Hz, OCH$_2$CC*H*), 2.30 (t, 1H, $J = 2.5$ Hz, OCH$_2$CC*H*), 2.28 (t, 1H, $J = 2.5$ Hz, OCH$_2$CC*H*), 1.76 (dd, 1H, $J = 11.5$, 13.5 Hz, *H3ax*), 1.53 (dd, 1H, $J = 10.5$, 13.0 Hz, *H3′ax*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 175.9, 175.4, 174.8, 171.7, 169.5, 153.4, 146.1, 145.5, 143.7, 137.3, 130.4, 129.6, 129.3, 128.9, 128.5, 128.4, 128.2, 128.1, 127.7, 125.9, 118.4, 115.1, 114.5, 95.0, 87.8, 84.6, 84.3, 81.4, 80.4, 80.1, 79.7, 79.5, 79.4, 78.9, 78.1, 77.8, 76.2, 75.7, 75.3, 75.2, 75.1, 74.9, 74.7, 74.4 (2), 72.6 (2), 72.0, 60.5, 59.8, 59.6, 59.2, 58.7, 57.6, 57.3, 56.4, 55.8, 53.1, 52.4, 40.0, 37.3, 29.9, 28.6, 28.4, 25.9 (2); HR MALDI-TOF MS *m*/*z* calcd for $C_{72}H_{74}N_2O_{20}S$ $[M + Na]^+$ 1341.4448, found 1341.4452.

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Supporting Information Available: General procedures and ^{1}H and ^{13}C NMR spectra for all compounds **3**−**9*R*** and COSY, HSQC, TOCSY, ROESY, and HR ESI-MS spectra for disaccharide **9*R***. This material is available free of charge via the Internet at http://pubs.acs.org.

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