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α-Selective Sialylations at −78 °C in Nitrile Solvents with a 1-Adamantanyl Thiosialoside

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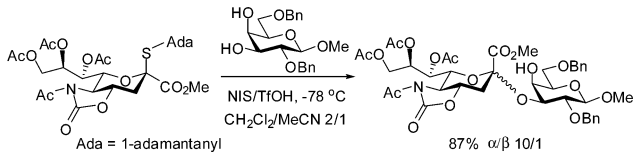
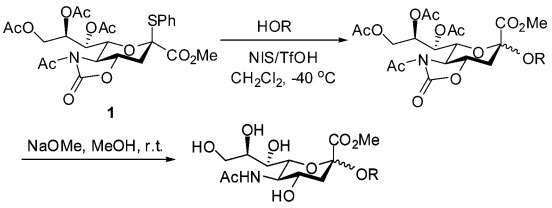


Novel 1-adamantanylthio sialosides were synthesized and coupled to acceptors under NIS/TfOH promotion conditions. These donors showed higher reactivity than the phenylthio sialosides and could be activated by NIS/TfOH in nitrile solvents at −78 °C to afford improved α-sialylations. With the *N*-acetyl-5-*N*,4-*O*-oxazolidinone-protected 1-adamantanylthio sialyl donor high α-selectivities could be achieved in the sialylations of both primary and sterically hindered secondary acceptors, including the important galactose 3-OH acceptors.

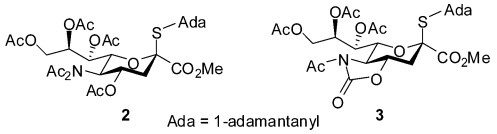
Oligosaccharides and glycoconjugates incorporating sialic acid residues are ubiquitous in high animals and human beings and play important roles in a wide variety of biological processes.[1] Over the years, considerable efforts have been spent on the development of sialoside donors bearing various leaving groups for efficient installation of α-sialyl linkages, among which 2-sulfide donors of Neu5Ac, including *S*-alkyl (methyl, ethyl) and *S*-aryl (phenyl and substituted phenyl) sialosides, have been widely applied.[2] In a previous report, we noted that an *N*-acetyl-5-*N*,4-*O*-oxazolidinone-protected 2-phenylthio sialoside donor **1** gave excellent yields and α-selectivities in linking to various primary alkyl and carbohydrate acceptors under the NIS/TfOH in situ activation conditions at −40 °C in dichloromethane (Scheme 1).[3] Importantly, following glycosylation, the oxazolidinone group was readily cleaved under mild conditions leaving the acetamide intact.[3] Similar investigations were also reported by the Takahashi and De Meo groups with *N*-desacetyl analogues of **1**, but harsher conditions were required for cleavage of the oxazolidinone moiety.[4]

SCHEME 1. Sialylations with Phenylthioglycoside 1



In an attempt to increase the α-selectivities of the sialylations of **1** with secondary sugar acceptors by means of the nitrile effect,[5] glycosylations promoted by NIS/TfOH were attempted in nitrile solvents at −40 °C. However, no reaction was observed. Noting the work of Oscarson and Lahmann on the reactivity order of various thioglycosides (glucose and galactose),[6−8] we turned our attention to the use of more reactive thiosialoside donors, which could possibly be activated in nitrile solvents at low temperature when improved α-selectivities could be anticipated.

Here we describe an investigation into the sialylations of 1-adamantanyl thiosialoside donors **2** and **3**. The 1-adamantanyl group was chosen because of its greater electron donating properties compared to Oscarson's preferred cyclohexyl group, and the solid (mp 99−106 °C) nonvolatile nature of 1-adamantanethiol, the precursor for the installation of 1-adamantanylthio leaving group, which reduces the odor problem common to most thiols.[9]



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(1) (a) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683. (b) Lis, H.; Sharon, N. *Chem. Rev.* **1998**, *98*, 637. (c) Mammen, M.; Choi, S.-K.; Whitesides, G. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2754. (d) Simanek, E. E.; McGarvey, G. J.; Jablonowski, J. A.; Wong, C.-H. *Chem. Rev.* **1998**, *98*, 833. (e) Ørntoft, T. F.; Vestergaard, E. M. *Electrophoresis* **1999**, *20*, 362.

(2) (a) Boons, G.-J.; Demchenko, A. V. *Chem. Rev.* **2000**, *100*, 4539. (b) Ress, D. K.; Linhardt, R. J. *Curr. Org. Synth.* **2004**, *1*, 31. (c) Boons, G. J.; Demchenko, A. V. In *Carbohydrate-based Drug Discovery*; Wong, C. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 1, pp 55. (d) Kiso, M.; Ishida, H.; Ito, H. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 1, pp 345. (e) Halcomb, R. L.; Chappell, M. D. In *Glycochemistry*: *Principles, Synthesis, and Applications*; Wang, P. G., Bertozzi, C. R., Eds.; Dekker: New York, 2001; pp 177. (f) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503. (g) Hanashima, S.; Castagner, B.; Esposito, D.; Nokami, T.; Seeberger, P. H. *Org. Lett.* **2007**, *9*, 1777. (h) Roy, R. *Top. Curr. Chem.* **1997**, *187*, 241. (i) Hasegawa, A. In *Modern Methods in Carbohydrate Synthesis*; Khan, S. H., O'Niell, R. A., Eds.; Harwood: Amsterdam, The Netherlands, 1996; pp 277. (j) Hasegawa, A.; Kiso, M. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Dekker: New York, 1997; pp 357.

(3) Crich, D.; Li, W. *J. Org. Chem.* **2007**, *72*, 2387.

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(5) (a) Hasegawa, A.; Ohki, H.; Nagahama, T.; Ishida, H. *Carbohydr. Res.* **1991**, *212*, 277. (b) Schmidt, R. R.; Rücker, E. *Tetrahedron Lett.* **1980**, *21*, 1421. (c) Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694.

(6) Lahmann, M.; Oscarson, S. *Can. J. Chem.* **2002**, *80*, 889.

(7) It was found that the cyclohexylthio group was about three times as reactive as the ethylthio group, which in turn was twice as reactive as the methylthio group. The phenylthio donors were found to be even less reactive than the methylthio donors, whereas *p*-halophenylthio donors were inert under the DMTST promotion conditions, but could be activated by NIS/TfOH.[6]

(8) Roy, R.; Andersson, F. O.; Letellier, M. Use of electron-rich aryl thiosialosides. *Tetrahedron Lett.* **1992**, *33*, 6053.

(9) Li, Z.; Gildersleeve, J. C. Use of adamantanyl thioglycosides to suppress thioglycoside transfer. *J. Am. Chem. Soc.* **2006**, *128*, 11612.

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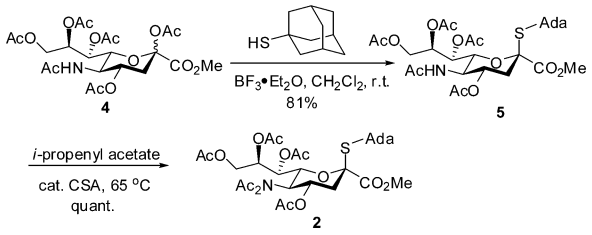
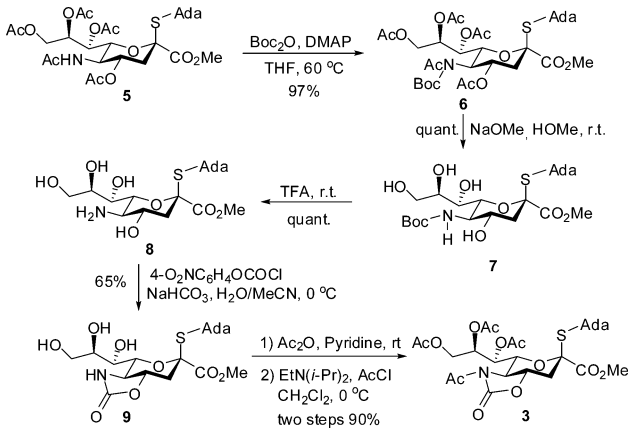
The penta-acetate derivative **4**[10] of neuraminic acid was reacted with 1-adamantanethiol in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at room temperature to afford 81% of the 1-adamantanyl thiosialoside **5** (Scheme 2).[11] Donor **2** then was derived from **5** in quantitative yield by treatment with isopropenyl acetate catalyzed by CSA at 65 °C (Scheme 2).

SCHEME 2. Synthesis of Donor 2



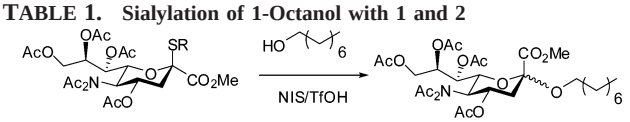
The preparation of donor **3** started with **5** (Scheme 3), to which a *N*-Boc group was introduced with Boc_2O in the presence of DMAP to give **6**. Deacetylation of **6** with NaOMe in MeOH at room temperature then gave **7**. The *N*-Boc group in **7** was cleanly cleaved by TFA to afford the intermediate **8**,[12] which was then transformed into the 5-*N*,4-*O*-carbonyl-protected derivative **9** by treatment with 4-nitrophenyl chloroformate and $NaHCO_3$ in H_2O/MeCN. The hydroxyl groups in **9** were acetylated with Ac_2O and pyridine at room temperature, and then the nitrogen in the oxazolidinone was acetylated with AcCl and $EtN(i\text{-}Pr)_2$ in a one pot procedure to afford the donor **3** in 90% yield.

SCHEME 3. Synthesis of Donor 3



The *N*,*N*-diacetyl protected adamantanyl thiosialoside donor **2** was first coupled to 1-octanol under NIS/TfOH promotion conditions in CH_2Cl_2 at −40 °C (Table 1, entry 1). In this glycosylation, donor **2** gave a higher glycosylation yield than its phenylthio counterpart **10** but still afforded the *β*-coupling product predominantly (Table 1, entries 1 and 2). It was then found that donor **2** could be activated at −78 °C in CH_2Cl_2 with NIS/TfOH, when it gave improved α-selectivity (Table 1, entry 3). When the solvent was changed to acetonitrile, the coupling reaction of **2** was achieved at −40 °C with the ratio being changed in favor of the α-anomeric product by the nitrile effect (Table 1, entry 4). Under the same conditions, activation of the phenyl thiosialoside **10** could not be achieved (Table 1, entry 5). The α-selectivity of the sialylation with **2** could be further improved when the reaction was performed at −78 °C using CH_2Cl_2/MeCN (1/1) or propionitrile as solvents (Table 1, entries 6 and 7). These results showed the 1-adamantanyl thiosialoside **2** to be a more reactive sialyl donor than the phenylthio derivative **10** in both CH_2Cl_2 and nitrile solvents at low temperatures. Moreover, use of the "nitrile effect" improved the α-selectivity, albeit to a limited extent.

TABLE 1. Sialylation of 1-Octanol with 1 and 2



10: R = Ph
2: R = 1-adamantanyl

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entry	donor	solvent	*T* (°C)	yield[a] (%)	α/*β*[b]
1	**2**	CH_2Cl_2	−40	89	1/8
2	**10**	CH_2Cl_2	−40	73	1/4
3	**2**	CH_2Cl_2	−78	92	1/2.5
4	**2**	MeCN	−40	89	1.6/1
5[c]	**10**	MeCN	−40		
6	**2**	CH_2Cl_2/MeCN(1/1)	−78	88	2/1
7	**2**	EtCN	−78	81	2.2/1

[a] Isolated yields. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] No activation observed.

Next, the *N*-acetyl-5-*N*,4-*O*-oxazolidinone-protected adamantanyl thiosialoside **3** was tested in couplings to a series of primary acceptors in CH_2Cl_2/MeCN (1/1) at −78 °C under NIS/TfOH promotion conditions (Table 2, entries 1−4).[13] The yields and selectivities of these reactions were excellent and comparable to those from the corresponding sialylations with *N*-acetyl-5-*N*,4-*O*-oxazolidinone-protected phenyl thiosialoside donor **1** promoted with NIS/TfOH in CH_2Cl_2 at −40 °C.[3]

Most importantly, donor **3** was found to be superior to **1** in couplings to sterically hindered acceptors. Thus, coupling of **3** and 1-adamantanol under NIS/TfOH promotion conditions in CH_2Cl_2/MeCN (1/1) at −78 °C gave the α-anomeric product in excellent yield, with only a trace amount of the *β*-anomer detected by ^1H NMR analysis of the crude reaction mixture (Table 2, entry 5). In the regioselective 3-OH sialylation of **16**, a much improved α-selectivity was obtained (Table 2, entry 6).[14,15] In the sialylation of a more sterically hindered 3-OH acceptor **17**, the α-Neu5Ac(2→3)Gal disaccharide was obtained as the major product (Table 2, entry 7). Presumably, the enhanced α-selectivities observed can be attributed to the nitrile effect as well as to the use of the reactive 1-adamantanylthio

(10) Marra, A.; Sinaÿ, P. *Carbohydr. Res.* **1989**, *190*, 317.

(11) The *β*/α ratio of adamantanyl thioglycosides in the crude reaction mixture was 6.6:1. As it had been previously demonstrated with **1** that stereoselectivity was independent of anomeric configuration in the donor,[3] no attempt was made to isolate the α-anomer of **5**.

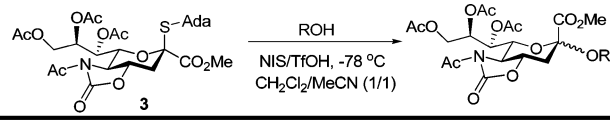
(12) The direct method for the removal of the *N*-acetyl group, heating with $MeSO_3H$ in MeOH, gave lower yields of **8** and was attended by the formation of the glycal resulting from elimination of the adamantanylthio group. For application of the $MeSO_3H$ method see ref 4a and: (a) Sugata, T.; Higuchi, R. *Tetrahedron Lett.* **1996**, *37*, 2613. (b) De Meo, C.; Demchenko, A. V.; Boons, G. J. *J. Org. Chem.* **2001**, *66*, 5490.

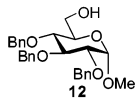
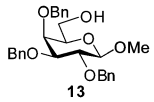
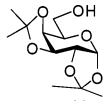
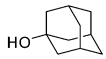
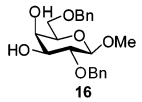
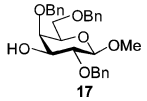
(13) Although the results from Table 1 indicated that the use of pure propionitrile gave better results than the 1/1 mixture of acetonitrile and dichloromethane, the latter system was selected for further investigation because of its generally better solubilizing properties, especially at −78 °C.

(14) The formation of the regioisomeric products arising from glycosylation at the 4-OH of acceptor **16** was not observed.

(15) The increased selectivity observed with **16** as compared to its 4-*O*-benzyl analogue **17** (see Table 2, entries 6 and 7 and Table 3, entry 4 and Table 4, entry 2) is noteworthy and presumably reflects the increased steric bulk of **17**.

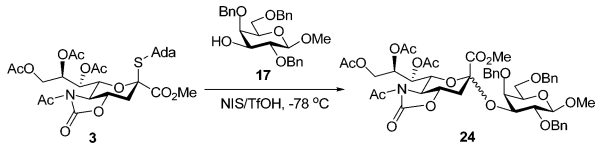
TABLE 2. Sialylation of Primary and Sterically Hindered Acceptors with 3



entry	acceptor	product: yield[a] (α/β)[b]
1		**18**: 95% only α
2		**19**: 91% only α
3		**20**: 89% only α
4		**21**: 90% only α
5		**22**: 92% (10/1)
6		**23**: 82% (8/1)[c]
7		**24**: 85% (3/1)

[a] Isolated yields. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Coupled to the 3-OH.

TABLE 3. Effect of Nitrile Concentration on Sialylation of 17 with 3



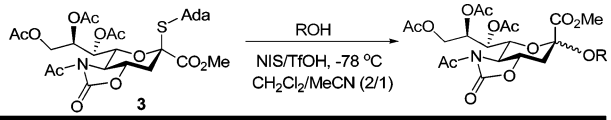
entry	solvent	solvent ratio	yield[a] (%) (α/β)[b]
1	CH_2Cl_2		83 (1/1.3)
2	MeCN/CH_2Cl_2	1/10	85 (2.6/1)
3	MeCN/CH_2Cl_2	1/5	87 (3.3/1)
4	MeCN/CH_2Cl_2	1/2	89 (4/1)
5	MeCN/CH_2Cl_2	1/1	85 (3/1)

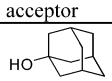
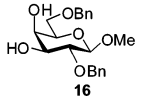
[a] Isolated yields. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture.

leaving group which permits activation at −78 °C. It is important to note that all the sialylation reactions of **3** with both primary and secondary acceptors were complete within 1 h and that the coupling products could be easily isolated from the clean reaction mixtures through simple chromatography on silica gel.

To probe the solvent effect further, a series of coupling reactions of donor **3** with the secondary acceptor **17** were conducted varying the proportions of MeCN and CH_2Cl_2 under NIS/TfOH promotion conditions at −78 °C (Table 3). It was found that a solvent mixture of 1/10 (V/V) MeCN and CH_2Cl_2, containing approximately 80 equiv of MeCN was sufficient to influence the selectivity (Table 3, entries 1 and 2). The best α-selectivity was achieved when the proportion of MeCN in the mixture was increased to 1/2 (v/v) (Table 3, entry 4). A further increase of the proportion of MeCN in the solvent to 1/1 led to a dropoff in α-selectivity, probably due to the increased solvent polarity and the associated increased ionic reaction character of the reaction (Table 3, entry 5).

TABLE 4. Sialylation of 15 and 16 with 3 under Optimized Conditions



entry	acceptor	product: yield[a] (α/β)[b]
1		**22**: 90% (only α)
2		**23**: 87% (10/1)[c]

[a] Isolated yields. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Coupled to the 3-OH.

When the MeCN/CH_2Cl_2 (1/2) solvent system was applied to the sialylations of 1-adamantanol and **16** with donor **3**, improved α-selectivities were observed (Table 4, entries 1 and 2) compared to those obtained from the corresponding sialylations performed in MeCN/CH_2Cl_2 (1/1) (Table 3, entries 1 and 2).[15]

In conclusion, the 1-adamantanyl thiosialosides are shown to have high reactivity under NIS/TfOH promotion conditions in nitrile solvents at −78 °C. With the *N*-acetyl-5-*N*,4-*O*-oxazolidinone-protected 1-adamantanylthio sialyl donor, both Neu5Ac α-(2→6) Gal and Neu5Ac α-(2→3) Gal glycosidic linkages can be installed efficiently with high yields and α-selectivities.

Experimental Section

Methyl (1-Adamantanyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-glycero-β-D-*galacto*-non-2-ulopyranoside)-onate (5). A mixture of **4**[10] (2.23 g, 4.2 mmol), anhydrous CH_2Cl_2 (25 mL), 1-adamantanethiol (0.819 g, 4.6 mmol), and $BF_3{\cdot}OEt_2$ (1.3 mL, 10 mmol) was stirred overnight at room temperature under N_2 and then diluted with CH_2Cl_2 (500 mL), washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was eluted from silica gel with EtOAc/hexanes/2-propanol (10/10/1) to give **5** (2.20 g, 3.4 mmol, 81%): $[\alpha]^{20}_D = -82$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHZ, $CDCl_3$) δ 5.46 (dd, $J = 2.0$, 3.0 Hz, 1H), 5.42 (d, $J = 10.5$ Hz, 1H), 5.30−5.24 (m, 1H), 5.15 (td, $J = 1.5$, 9.5 Hz, 1H), 5.01 (dd, $J = 2.0$, 12.5 Hz, 1H), 4.54 (dd, $J = 3.0$, 11.0 Hz, 1H), 4.20 (dd, $J = 9.0$, 13.0 Hz, 1H), 4.06 (q, $J = 10.0$ Hz, 1H), 3.82 (s, 3H), 2.53 (dd, $J = 5.0$, 14.0 Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.00−1.99 (m, broad, 9H), 1.97−1.93 (m, broad, 4H), 1.85−1.84 (m, broad, 6H), 1.68−1.62 (m, broad, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 170.9, 170.4, 170.2, 169.9 (C-1, $^3J_{C-1,\ H-3ax} = 2.5$ Hz), 86.2, 74.0, 72.8, 69.4, 69.0, 63.4, 52.9, 50.6, 49.6, 43.5, 40.0, 35.9, 29.8, 23.2, 21.2, 20.9, 20.8, 20.7; ESIHRMS calcd for $C_{30}H_{43}N_1O_{12}S_1Na$ ([M + Na]$^+$) 664.23985, found 664.23858.

Methyl (1-Adamantanyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-*N*-(1,1-dimethylethoxy)carbonyl-2-thio-D-glycero-β-D-*galacto*-non-2-ulopyranoside)onate (6). To a solution of **5** (2.36 g, 3.7 mmol) in anhydrous THF (15 mL) were added di-*tert*-butyl dicarbonate (8.04 g, 37 mmol) and DMAP (180 mg, 1.5 mmol) at room temperature. The mixture was stirred overnight at 60 °C under N_2 before it was cooled to room temperature and concentrated under reduced pressure. The residue was applied to

silica gel and eluted with hexanes/EtOAc (2/1) to give **6** (2.65 g, 3.6 mmol, 97%): $[\alpha]^{20}_D = -50$ (*c* 6.7, $CHCl_3$); ^1H NMR (500 MHZ, $CDCl_3$) δ 5.59 (dt, $J = 4.5$, 11.0 Hz, 1H), 5.31 (dd, $J = 2.0$, 10.5 Hz, 1H), 5.28 (s, broad, 1H), 5.08 (d, $J = 9.0$ Hz, 1H), 4.92 (d, $J = 12.5$ Hz, 1H), 4.70 (t, $J = 10.5$ Hz, 1H), 4.17 (dd, $J = 9.0$, 12.5 Hz, 1H), 3.78 (s, 3H), 2.57 (dd, $J = 5.0$, 13.5 Hz, 1H), 2.29 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.94 (s, 3H), 1.93 (s, broad, 6H), 1.87 (s, 3H), 1.83−1.80 (m, broad, 3H), 1.64 (s, broad, 9H), 1.60 (s, broad, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 170.8, 170.4, 170.3, 170.0, 169.7, 152.0, 86.2, 85.1, 74.0, 71.9, 69.3, 66.2, 63.2, 53.1, 52.7, 50.5, 43.5, 41.5, 35.9, 29.7, 28.2, 26.6, 21.0, 20.8, 20.65, 20.63; ESIHRMS calcd for $C_{35}H_{51}N_1O_{14}S_1Na$ ($[M + Na]^+$) 764.29228, found 764.29451.

Methyl (1-Adamantanyl 5-*N*,4-*O*-carbonyl-3,5-dideoxy-2-thio-D-glycero-β-D-*galacto*-non-2-ulopyranoside)onate (9). To a solution of **6** (2.65 g, 3.6 mmol) in methanol (10 mL) was added a catalytic amount of sodium methoxide. The solution was stirred for 1 h at room temperature and then quenched with Amberlyst 15 ion-exchange resin. The mixture was filtered through Celite and concentrated under reduced pressure to give **7**. The crude **7** was treated with trifluoroacetic acid (8.0 mL) for 1 h at room temperature, and then the mixture was concentrated under reduced pressure. The concentrate and $NaHCO_3$ (1.50 g, 17.8 mmol) were dissolved in MeCN (15 mL) and H_2O (30 mL) and cooled to 0 °C. To the vigorously stirred mixture was slowly added 4-nitrophenyl chloroformate (1.80 g, 8.9 mmol) in MeCN (15 mL) through a dropping funnel, after which stirring was continued for 3 h at 0 °C. The resulting mixture was extracted with EtOAc (100 mL × 3), and the combined extracts were washed with brine and then dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, eluting with EtOAc then EtOAc/MeOH from 10/1 to 5/1 to give the title compound **9** as white foam (1.06 g, 2.3 mmol, 65% after three steps): $[\alpha]^{20}_D = -162$ (*c* 2.2, MeOH); ^1H NMR (500 MHz, MeOD) δ 4.59−4.54 (m, 1H), 4.50 (dd, $J = 2.0$, 10.0 Hz, 1H), 3.84 (s, 3H), 3.83 (dd, $J = 2.5$, 7.0 Hz, 1H), 3.75−3.68 (m, 2H), 3.57−3.51 (m, 2H), 2.68 (dd, $J = 4.0$, 12.5 Hz, 1H), 2.26 (t, $J = 12.5$ Hz, 1H), 2.04−1.96 (m, broad, 9H), 1.70 (s, broad, 6H); ^{13}C NMR (125 MHz, MeOD) δ 172.0, 161.0, 86.1, 77.8, 73.8, 70.9, 70.2, 63.5, 58.4, 52.4, 50.2, 43.2, 39.1, 35.8, 30.0; ESIHRMS calcd for $C_{21}H_{31}N_1O_8S_1Na$ ($[M + Na]^+$) 480.16629, found 480.16637.

Methyl (1-Adamantanyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-2-thio-D-glycero-β-D-*galacto*-non-2-ulopyranoside)onate (3). A solution of **9** (1.06 g, 2.3 mmol) in pyridine (20 mL) was treated with Ac_2O (24 mL), stirred at room temperature overnight, and concentrated under reduced pressure. The residue was dissolved in anhydrous CH_2Cl_2, treated with EtN(*i*-Pr)$_2$ (4.0 mL, 23 mmol, 10 equiv), and then cooled to 0 °C before acetyl chloride (1.34 mL, 18.6 mmol, 8 equiv) was added. After warming to room temperature, the resulting solution was poured into saturated aqueous $NaHCO_3$ solution, the organic layer was separated, the aqueous layer was extracted twice with CH_2Cl_2, and the combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with EtOAc/hexanes (1/1) to give donor **3** (1.31 g, 90%): mp 144−145 °C (EtOAc/hexanes); $[\alpha]^{20}_D = -78$ (*c* 0.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.69 (t, $J = 2.5$ Hz, 1H), 5.29 (td, $J = 2.0$, 8.5 Hz, 1H), 4.77−4.66 (m, 3H), 4.14 (dd, $J = 8.0$, 12.0 Hz, 1H), 3.83 (s, 3H), 3.66 (dd, $J = 9.5$, 11.5 Hz, 1H), 2.79 (dd, $J = 3.5$, 13.0 Hz, 1H), 2.47 (s, 3H), 2.17 (t, $J = 13.0$ Hz, 1H), 2.12 (s, 3H), 2.10 (s, 3H), 2.01 (s, 3H), 2.03−1.97 (m, broad, 6H), 1.88−1.86 (m, broad, 3H), 1.65 (m, broad, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 171.0, 170.6, 169.7, 169.4, 153.7, 85.6, 75.1, 74.1, 73.4, 72.4, 63.3, 60.2, 53.0, 51.3, 43.6, 38.7, 35.9, 29.8, 24.8, 21.2. 20.8, 20.7; ESIHRMS calcd for $C_{29}H_{39}N_1O_{12}S_1Na$ ($[M + Na]^+$) 648.20855, found 648.20983.

General Coupling Protocol. A solution of donor (0.11 mmol, 1.0 equiv), acceptor (0.16 mmol, 1.5 equiv), and activated 4 Å powdered molecular sieves (216 mg, 2.0 g/mmol) in anhydrous CH_2Cl_2/MeCN (1/1, 2 mL) was stirred for 1 h under Ar, and then cooled to −40 °C (or −78 °C) followed by addition of NIS (58.3 mg, 0.26 mmol, 2.4 equiv) and TfOH (9.5 μL, 0.11 mmol, 1.0 equiv). The reaction mixture was stirred at −40 °C (or −78 °C) for 1 h and then quenched with triethylamine (22.6 μL, 0.16 mmol, 1.5 equiv). The mixture was diluted with CH_2Cl_2, filtered through Celite, washed with 20% aqueous $Na_2S_2O_3$ solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with THF/Hexanes system to afford coupling products, the spectra of which were identical to those of authentic samples.[3]

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Supporting Information Available: Full experimental details for the preparation of **2** and copies of NMR spectra for all new compounds and coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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