JOC*Article*

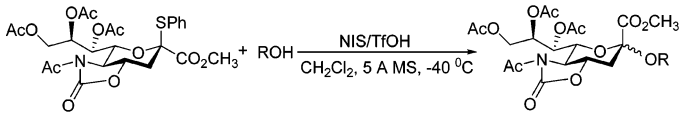
O-Sialylation with *N*-Acetyl-5-*N*,4-*O*-Carbonyl-Protected Thiosialoside Donors in Dichloromethane: Facile and Selective Cleavage of the Oxazolidinone Ring

David Crich* and Wenju Li

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061

dcrich@uic.edu

Received November 26, 2006



An *N*-acetyl-5-*N*,*4*-*O*-carbonyl-protected thiosialoside donor, the structure of which has been defined through X-ray crystallography, was prepared and tested in couplings to a wide range of acceptors. This donor gives excellent yields and α-selectivities in linking with various primary alkyl and carbohydrate acceptors under the *N*-iodosuccinimide and trifluoromethanesulfonic acid in situ activation method at −40 °C in dichloromethane. The favorable affect of the oxazolidinone substructure for α-sialylation is illustrated by a comparison study with a *N*,*N*-diacetylsialyl donor, which exhibited inferior yields and α-selectivities. The sialylation selectivity is independent of the anomeric configuration of the donor, but is highly related to the reaction temperature under the NIS/TfOH activation method. In contrast to the NIS/TfOH method, the Ph_2SO/Tf_2O promotion gives β-selective couplings in dichloromethane. The oxazolidinone of the *N*-acetyl-5-*N*,4-*O*-carbonyl protected sialosides, both α- and β-anomers, could be cleaved cleanly by treatment with sodium methoxide under mild conditions without removal of the acetamide.

Introduction

Sialic acids have been known for more than half a century as important residues incorporated in a wide spread of oligosaccharides and glycoconjugates with important functional roles in mammalian biology.[1] Among the more than 30 naturally occurring derivatives of sialic acids, *N*-acetylneuraminic acid (Neu5Ac) is the most common one and is present in a variety of glycosidic linkages, most typically α-(2,3) and α-(2,6) linkages to galactose (or lactose), as well as α-(2,8) or α-(2,9) linkages in polysialic acids. Over the years considerable efforts have been spent on the development of methodologies and strategies for efficient α-sialoside installation allowing for the chemical, enzymatic, or chemoenzymatic synthesis of complex sialoconjugates.[2] However, α-sialylation remains a formidable challenge owing to the inherent obstacles in sialic acid's unique structure: the hindered C-2-ketal carbon and the methylene C-3 ring carbon, prone to 2,3-elimination.

Progress in sialylation methodologies can be characterized into several categories: the application of various leaving groups, such as halides,[3] sulfides,[4] xanthates,[5] phosphates,[6] hydroxyl groups,[7] and *N*-phenytrifluoroacetimidates;[8] introduction of auxiliary participating groups at the C-3 position,

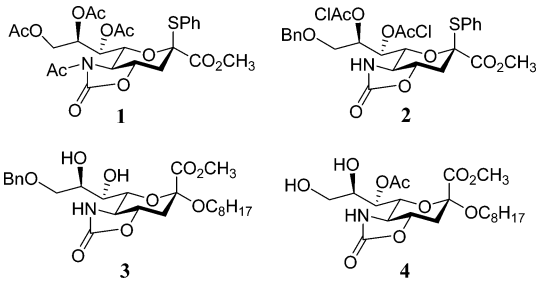
(1) (a) Schauer, R. *Sialic Acids*: *Chemistry*, *Metabolism and Function*; Springer-Verlag: New York, 1982; Vol. 10. (b) *Sialobiology and Other Novel Forms of Glycosylation*; Inoue, Y., Lee, Y. C., Troy, F. A., II, Eds.; Gakushin: Osaka, Japan, 1999. (c) *Biology of the Sialic Acids*; Rosenberg, A., Ed.; Plenum: New York, 1995. (d) Mammen, M.; Choi, S. K.; Whitesides, G. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2754−2794. (e) Simanek, E. E.; McGarvey, G. J.; Jablonwski, J. A.; Wong, C. H. *Chem. Rev.* **1998**, *98*, 833−862.

(2) (a) Boons, G. J.; Demchenko, A. V. *Chem. Rev.* **2000**, *100*, 4539−4565. (b) Ress, D. K.; Linhardt, R. J. *Curr. Org. Synth.* **2004**, *1*, 31−46. (c) Boons, G. J.; Demchenko, A. V. In *Carbohydrate-based Drug Discovery*; Wong, C. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 1, pp 55−102. (d) Kiso, M.; Ishida, H.; Ito, H. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 1, pp 345−365. (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 177−220. (f) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531. (g) Boons, G. J. *Contemp. Org. Synth.* **1996**, *3*, 173−200. (h) Roy, R. *Top. Curr. Chem.* **1997**, *187*, 241−274. (i) Hasegawa, A. In *Modern Methods in Carbohydrate Synthesis*; Khan, S. H., O'Niell, R. A., Eds.; Harwood: Amsterdam, The Netherlands, 1996; pp 277−300. (j) Hasegawa, A.; Kiso, M. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Dekker: New York, 1997; pp 357−379.

(3) (a) Paulsen, H.; Tietz, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 927−928. (b) Paulsen, H.; Tietz, H. *Carbohydr. Res.* **1984**, *125*, 47−64.

10.1021/jo062431r CCC: $37.00
Published on Web 03/06/2007

including halogen,[9] sulfide,[10] selenide,[10b] or oxygen substituents;[10e,11] the use of C-1 neighboring group participations;[12] modification of the amino protective groups at the C-5 position;[13] and the development of new promotors, such as NIS/TfOH,[14] NIS/TMSOTf,[15] DMTST,[16] NBS/Bu_4NOTf,[17] and Ph_2SO/Tf_2O.[7,18]

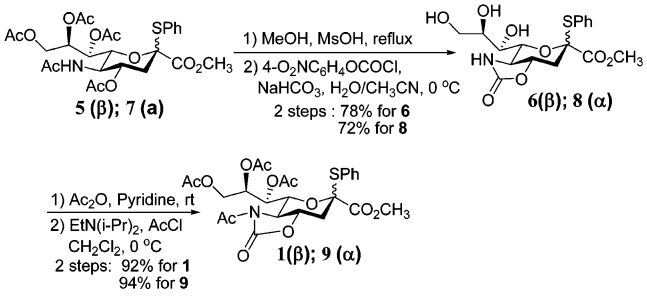


We directed our efforts in the α-sialylation field to the investigation of a new thiosialoside donor **1** featuring *N*-acetyl-5-*N*,4-*O*-carbonyl protection based on the knowledge that fused structures like 2-*N*,3-*O*-carbamates in glycosamine,[19] 2,3-*O*-carbonates in glucose,[20] and 3,4-*O*-carbonates in rhamnopyranose[21] can have dramatic affects on glycosylations, whether present in donors or acceptors. During the course of our investigation, Takahashi and co-workers described a related study on the use of 5-*N*,4-*O*-oxazolidinones as sialic acid donors (**2**) and acceptors (**3**,**4**), and achieved an elegant synthesis of α-(2→8)-oligosialosides by this means.[22] Our donor **1** differs from **2** by the presence of the *N*-acetamido group, which we included because of the known beneficial effects of double nitrogen protection,[13] and to facilitate deprotection.

Results and Discussion

Donor **1** was prepared from **5**[23] on a gram scale following the protocol employed for the introduction of *N*-acetyl-2-*N*,3-*O*-carbamates to the glusosamine series (Scheme 1).[19g,h] The anomer **9** was prepared analogously from **7**[23](Scheme 1). Both **1** and **9** are crystalline solids and showed excellent shelf-stability.

SCHEME 1. Preparation of Donors 1 and 9



First, the coupling of **1** with two alkyl alcohols, 1-octanol and 1-adamantanol, was surveyed under the diphenyl sulfoxide and triflic anhydride activation conditions in the presence of the hindered base 2,4,6-tri-*tert*-butylpyrimidine (TTBP) developed for other thiosialoside donors.[18] In both cases, β sialosides were obtained predominantly (Table 1, entries 1 and 2). Couplings to carbohydrate acceptors also showed unfavorable α-selectivities (Table 1, entries 3 and 4). The anomeric stereochemistry of all coupling products is assigned on the basis of the chemical shifts of the sialic acid *H*-3eq[24] and the $^3J_{C1,H-3ax}$ coupling constants.[25] The fused oxzolidinone structure does not affect the distinct difference of the $^3J_{C1,H-3ax}$ coupling constants between α- and β-anomers.

(4) (a) Zhang, Z.; Ollmann, I. R.; Ye, X.; Wischnat, R.; Baasov, T.; Wong, C. H. *J. Am. Chem. Soc.* **1999**, *121*, 734−753. (b) Nicolaou, K. C.; Ueno, H. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; pp 313−338. (c) Hasegawa, A. In *Modern Methods in Carbohydrate Synthesis*; Khan, S., O'Neill, R., Eds.; Harwood Academic Publishers: New York, 1996; pp 277−300.

(5) (a) Marra, A.; Sinaÿ, P. *Carbohydr. Res.* **1989**, *187*, 35−42. (b) Whitesides, G. M.; Martichonok, V. *J. Org. Chem.* **1996**, *61*, 1702−1706.

(6) (a) Martin, T. J.; Schmidt, R. R. *Tetrahedron Lett.* **1992**, *33*, 6123−6126. (b) Kondo, H.; Ichikawa, Y.; Wong, C. H. *J. Am. Chem. Soc.* **1992**, *114*, 8748−8750.

(7) Haberman, J. M.; Gin, D. Y. *Org. Lett.* **2003**, *5*, 2539−2541.

(8) Cai, S.; Yu, B. *Org. Lett.* **2003**, *21*, 3827−3830.

(9) Okamoto, K.; Kondo, T.; Goto, T. *Tetrahedron* **1987**, *43*, 5909−5918.

(10) (a) Ercégovec, T.; Magnusson, G. *J. Org. Chem.* **1995**, *60*, 3378−3384. (b) Ito, Y.; Ogawa, T. *Tetrahedron* **1990**, *46*, 89−102. (c) Martichonok, V.; Whitesides, G. M. *J. Am. Chem. Soc.* **1996**, *118*, 8187−8191. (d) Ercégovec, T.; Magnusson, G. *J. Org. Chem.* **1996**, *61*, 179−184. (e) Castro-Palomino, J. C.; Tsvetkov, Y. E.; Schmidt, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 5434−5440. (f) Hossain, N.; Magnusson, G. *Tetrahedron Lett.* **1999**, *40*, 2217−2220.

(11) Okamoto, K.; Kondo, T.; Goto, T. *Tetrahedron* **1987**, *43*, 5919−5928.

(12) (a) Takahashi, T.; Tsukamoto, H.; Yamada, H. *Tetrahedron Lett.* **1997**, *38*, 8223−8226. (b) Danishefsky, S. J.; DeNinno, M. P.; Chen, S. *J. Am. Chem. Soc.* **1988**, *110*, 3929−3940. (c) Haberman, J. M.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 1665−1668. (d) Haberman, J. M.; Gin, D. Y. *Org. Lett.* **2003**, *5*, 2539−2541.

(13) (a) Demchenko, A. V.; Boons, G. J. *Chem. Eur. J.* **1999**, *5*, 1278−1283. (b) Pan, Y.; Chefalo, P.; Nagy, N.; Harding, C.; Guo, Z. *J. Med. Chem.* **2005**, *48*, 875−883. (c) Meijer, A.; Ellervik, U. *J. Org. Chem.* **2004**, *69*, 6249−6256. (d) De, Meo, C.; Demchenko, A. V.; Boons, G. J. *J. Org. Chem.* **2001**, *66*, 5490−5498. (e) Tanaka, H.; Adachi, M.; Takahashi, T. *Chem. Eur. J.* **2005**, *11*, 849−862. (f) Ando, H.; Koike, Y.; Ishida, H.; Kiso, M. *Tetrahedron Lett.* **2003**, *44*, 6883−6886. (g) Lu, K. C.; Tseng, S.-Y.; Lin, C. C. *Carbohydr. Res.* **2002**, *337*, 755−760. (h) Yu, C. S.; Niikura, K.; Lin, C. C.; Wong, C. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 2900−2903. (i) Scneider, R.; Freyhardt, C. C.; Schmidt, R. R. *Eur. J. Org. Chem.* **2001**, *9*, 1655−1661. (j) Tanaka, K.; Goi, T.; Fukase, K. *Synlett* **2005**, 2958−2962.

(14) Hasegawa, A.; Nagahama, T.; Ohki, H.; Hotta, K.; Ishida, H.; Kiso, M. *J. Carbohydr. Chem.* **1991**, *10*, 493−498.

(15) (a) Kiso, M.; Hasegawa, A. In *Neoglycoconjugates*; Lee, Y., Lee, R., Eds.; Academic Press: New York, 1994; Vol. 242, pp 173−183. (b) Terada, T.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1993**, *12*, 425−440. (c) Terada, T.; Ishida, H.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1995**, *14*, 751−768. (d) Terada, T.; Toyoda, T.; Ishida, H.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1995**, *14*, 769−790.

(16) Nagao, Y.; Nekado, T.; Ikeda, K.; Achiwa, K. *Chem. Pharm. Bull.* **1995**, *43*, 1536−1542.

(17) Fukase, K.; Hasuoka, A.; Kusumoto, S. *Tetrahedron Lett.* **1993**, *34*, 2187−2190.

(18) Crich, D.; Li, W. *Org. Lett.* **2006**, *8*, 959−962.

(19) (a) Benakli, K.; Zha, C.; Kerns, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 9461−9462. (b) Kerns, R. J.; Zha, C.; Benakli, K.; Liang, Y. Z. *Tetrahedron Lett.* **2003**, *44*, 8069−8072. (c) Wei, P.; Kerns, R. J. *Tetrahedron Lett.* **2003**, *44*, 8069−8072. (d) Wei, P.; Kerns, R. J. *J. Org. Chem.* **2005**, *70*, 4195−4198. (e) Boysen, M.; Gemma, E.; Lahmann, M.; Oscarson, S. *Chem. Commun.* **2005**, 3044−3046. (f) Manabe, S.; Ishii, K.; Ito, Y. *J. Am. Chem. Soc.* **2006**, *128*, 10666−10667. (g) Crich, D.; Vinod, A. U. *Org. Lett.* **2003**, *5*, 1297−1300. (h) Crich, D.; Vinod, A. U. *J. Org. Chem.* **2005**, *70*, 1291−1296. (i) Mendlik, M. T.; Tao, P.; Hadad, C. M.; Coleman, R. S.; Lowary, T. L. *J. Org. Chem.* **2006**, *71*, 8059−8070.

(20) Crich, D.; Jayalath, P. *J. Org. Chem.* **2005**, *70*, 7252−7259.

(21) Crich, D.; Vinod, A. U.; Picione, J. *J. Org. Chem.* **2003**, *68*, 8453−8458.

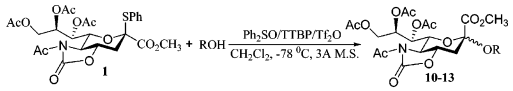
(22) Tanaka, H.; Nishiura, Y.; Takahashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 7124−7125.

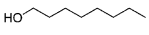
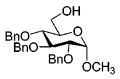
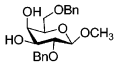
(23) Marra, A.; Sinaÿ, P. *Carbohydr. Res.* **1989**, *187*, 35−42.

(24) Dabrowski, U.; Friebolin, H.; Brossmer, R.; Supp, M. *Tetrahedron Lett.* **1979**, *20*, 4637−4640.

(25) (a) Hori, H.; Nakajima, T.; Nishida, Y.; Ohrui, H.; Meguro, H. *Tetrahedron Lett.* **1988**, *29*, 6317−6320. (b) Prytulla, S.; Lauterwein, J.; Klessinger, M.; Thiem, J. *Carbohydr. Res.* **1991**, *215*, 345−349.

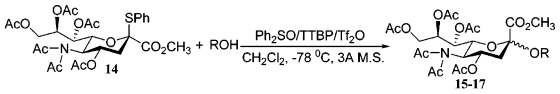
TABLE 1. Ph_2SO/Tf_2O-Promoted Couplings of 1

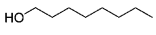
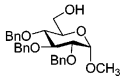


entry	acceptor	product: yield[a] (α:β)
1		**10**: 97% (1:2)[b]
2		**11**: 70% (1:3.7)[b]
3		**12**: 93% (1:1.5)[c]
4		**13**: 89% (<1:10)[b]

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

TABLE 2. Ph_2SO/Tf_2O-Promoted Couplings of 14



entry	acceptor	product: yield[a] (α:β)[b]
1		**15**: 93% (2:1)
2		**16**: 89% (3.8:1)
3		**17**: 91% (1.2:1)

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

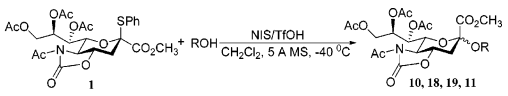
Under the same Ph_2SO/Tf_2O preactivation conditions, the *N*,*N*-diacetyl-protected sialoside donor **14** provided higher α-selectivities (Table 2, entries 1−3) than **1** in couplings to the same acceptors, indicating that the oxazolidinone group is detrimental to α-sialylation under the Ph_2SO/Tf_2O activation conditions.

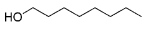
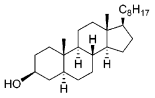
When the NIS/TfOH activation method was applied to sialylations with **1** in CH_2Cl_2 at −40 °C, we found that excellent yields and α-selectivities were obtained with 1-octanol (Table 3, entry 1), benzyl alcohol (Table 3, entry 2), and 3*β*-cholestanol (Table 3, entry 3). With the tertiary alcohol 1-adamantanol the α-selectivity dropped somewhat but the yield was still excellent (Table 3, entry 4).

The influence of temperature on the sialylation of **1** under the NIS/TfOH activation method in dichloromethane was studied with 1-adamantanol as the acceptor. The results show that higher α-selectivity could be achieved at lower temperature (Table 4, entries 1 and 2), but at the expense of reduced reaction rate. At −78 °C, no activation was observed over a period of several hours (Table 4, entry 3).

A series of carbohydrate acceptors were then coupled with **1** by the standard NIS/TfOH promotion method in dichloromethane at −40 °C. Sialylation of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside afforded the corresponding disaccharide **12** cleanly as a single α anomer (Table 5, entry 1). Excellent yields and α-selectivities were also obtained with methyl 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranoside and methyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (Table 5, entries 2 and 3) both affording important linkage types. With the secondary sugar acceptors, methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside and methyl 2,4,6-tri-*O*-benzyl-*β*-D-galactopyranoside, good

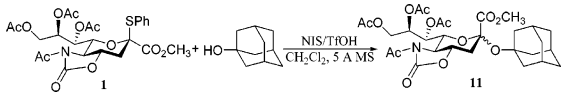
TABLE 3. NIS/TfOH-Promoted Couplings of 1 with Simple Alcohols



entry	acceptor	product: yield[a] (α:β)[b]
1		**10**: 96% (α only)
2		**18**: 95% (α only)
3		**19**: 89% (>10:1)
4		**11**: 91% (3.3:1)

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

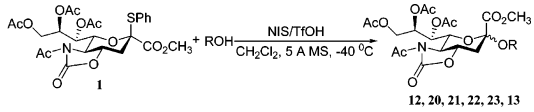
TABLE 4. The Effect of Temperature on the Sialylation of 1

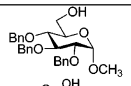
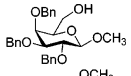
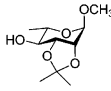
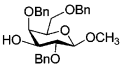
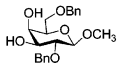


entry	reaction temp, °C	reaction time	yield,[a] % (α:*β*)[b]
1	−25	20 min	90 (1.6:1)
2	−40	2 h	91 (3.3:1)
3	−78		no activation

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

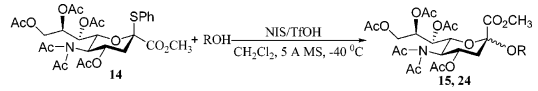
TABLE 5. NIS/TfOH-Promoted Couplings of 1 with Sugar Acceptors

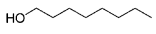


entry	acceptor	product: yield[a] (α:β)
1		**12**: 92% (α only)[b]
2		**20**: 90% (>10:1)[b]
3		**21**: 85% (>10:1)[b]
4		**22**: 87% (<1:10)[b]
5		**23**: 85% (1:8)[c]
6		**13**: 78% (1:1.3)[c, d]

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

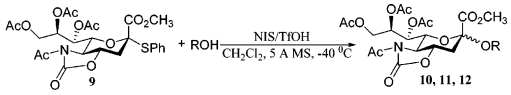
TABLE 6. NIS/TfOH-Promoted Couplings of 14

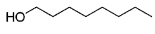
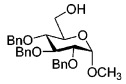


entry	acceptor	product: yield[a] (α:β)[b]
1		**15**: 73% (1:4)
2		**24**: 68% (1:1.9)

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

TABLE 7. NIS/TfOH-Promoted Couplings of 9



entry	acceptor	product: yield[a] (α:β)[b]
1		**10**: 95% (α only)
2		**11**: 92% (3.6:1)
3		**12**: 89% (α only)

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

yields were obtained but the reactions gave predominantly *β*-sialosides (Table 5, entries 4 and 5). In the regioselective 3-*O*-sialylation of methyl 2,6-di-*O*-benzyl-*β*-D-galactopyranoside, a greater population of α-anomer was obtained, but there still remains room for improvement (Table 5, entry 6).

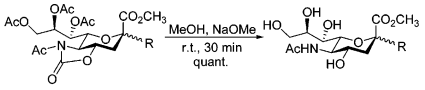
The favorable affects of the 5-*N*,4-*O*-carbonyl protecting system under the NIS/TfOH conditions are illustrated by comparison of Table 3, entry 1 and Table 5, entry 2 with corresponding couplings to the *N*,*N*-diacetyl-protected donor **14** presented in Table 6. It is also noteworthy that couplings with **1** generally proceed faster under the NIS/TfOH conditions than those to **14**, and typically afford higher yields owing to a reduced propensity for glycal formation.

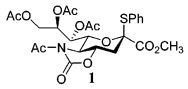
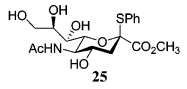
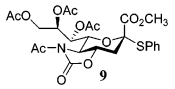
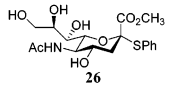
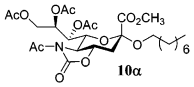
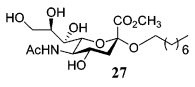
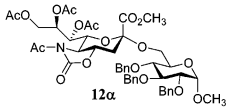
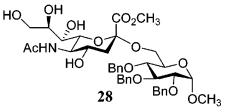
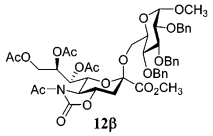
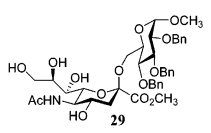
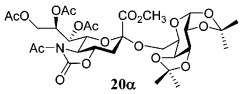
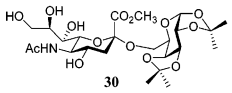
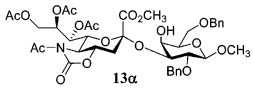
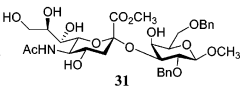
To probe the effect of anomeric configuration of the donor on sialylation, we tested the sialylations of α-anomeric isomer **9** under these NIS/TfOH promotion conditions in CH_2Cl_2. Comparable yields and selectivities were obtained in couplings with the same alcohols as for donor **1** (Table 7). Clearly these sialylaion reactions proceed through a common intermediate whose constitution is independent of the original anomeric configuration of the donors.

The hydrolysis of oxazolidinones typically requires harsh conditions often involving treatment with barium or lithium hydroxide in hot aqueous ethanol, which results in the concomitant removal of the acetamide group for *N*-acetyloxazolidinones.[26] Exceptions have been described but these appear to be limited to the *β*-series of glucosamine-based *N*-acetyloxazolidinones.[19c,e,h] We found that the oxazolidinone of the *N*-acetyl-5-*N*,4-*O*-carbonyl-protected sialosides could be removed selectively by treatment with sodium methoxide in methanol at room temperature, affording the desired *N*-acetamido products easily and cleanly (Table 8). This result parallels Oscarson's report on the deprotection of glycosides of *N*-acetyl-2-*N*,3-*O*-oxazolidinone-protected 4,6-di-*O*-benzyl-D-glucosamine, which gives the *N*-acetyl-glycosides directly.[19e] This deprotection method does not depend on the anomeric configuration of substrates, and renders application of the *N*-acetyl-5-*N*,4-*O*-carbonyl system especially attractive for the synthesis of complex sialoconjugates and oligosialosides by eliminating harsh conditions for oxazolidinone cleavage and the extra steps for reinstalling the acetamido group.

Further studies on the properties of *N*-acetyl-5-*N*,4-*O*-carbonyl-protected thiosialosides and their applications in the synthesis of various sialosides are underway in our laboratory.

TABLE 8. Selective Cleavage of the Oxazolidinones in Sialosides



entry	substrate	product
1		
2		
3		
4		
5		
6		
7		

Experimental Section

Methyl (Phenyl 5-amino-5-*N*,4-*O*-carbonyl-3,5-dideoxy-2-thio-D-glycero-*β*-D-galacto-non-2-ulopyranoside)onate (6). A stirred solution of methyl (phenyl 5-acetamideo-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-*β*-D-glycero-D-galacto-2-nonulopyranosid)onate (**5**)[23] (5.00 g, 8.57 mmol, 1.00 equiv) in methanol (80 mL) was treated with methanesulfonic acid (1.68 mL, 25.7 mmol, 3.0 equiv) at room temperature, and then refluxed under Ar for 24 h. After being cooled to room temperature, the reaction mixture was quenched with excess triethylamine, and then concentrated under reduced pressure. The concentrate and $NaHCO_3$ (3.60 g, 42.8 mmol, 5.0 equiv) were

(26) Kang, S. H.; Choi, H.; Kim, J. S.; Young, J. H. *Chem. Commun.* **2000**, 227−228.

dissolved in CH_3CN (30 mL) and H_2O (60 mL) and cooled to 0 °C. To the vigorously stirred mixture was added 4-nitrophenyl chloroformate (4.32 g, 21.4 mmol, 2.5 equiv) in CH_3CN (30 mL) slowly through a dropping funnel, after which stirring was continued for 3 h at 0 °C. The resulting mixture was extracted with ethyl acetate (3 × 100 mL) 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 (**6**) as white foam (2.67 g, 6.68 mmol, 78% after two steps). $[\alpha]^{14}_D$ −186.0 (*c* 3.2, MeOH). ^{1}H NMR (500 MHZ, CD_3OD) δ 7.61−7.59 (m, 2H), 7.39−7.35 (m, 3H), 4.69 (dd, J = 1.5, 10.0 Hz, 1H), 4.62 (dt, J = 4.0, 12.5 Hz, 1H), 3.83 (dd, J = 2.5, 11.0 Hz, 1H), 3.75−3.69 (m, 2H), 3.60 (s, 3H), 3.62−3.57 (m, 2H), 2.88 (dd, J = 4.0, 13.0 Hz, 1H), 2.42 (dd, J = 13.5, 15.0 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.1, 161.1, 136.3, 129.6, 129.3, 128.7, 89.6, 77.8, 74.4, 70.7, 69.8, 63.5, 58.0, 52.1, 37.0. ESIHRMS calcd for $C_{17}H_{21}N_1O_8SNa$ ([M + Na]$^+$) 422.08804, found 422.08939.

Methyl (Phenyl 5-amino-5-*N*,4-*O*-carbonyl-3,5-dideoxy-2-thio-D-glycero-α-D-galacto-non-2-ulopyranoside)onate (8). 8 was prepared from **7**[23] following the same procedure as for **6**. $[\alpha]^{15}_D$ +23.1 (*c* 3.1, MeOH). ^{1}H NMR (500 MHZ, CD_3OD) δ 7.58−7.56 (m, 2H), 7.44−7.41 (m, 1H), 7.38−7.35 (m, 2H), 4.06−4.01 (m, 1H), 3.85−3.79 (m, 3H), 3.69−3.60 (m, 2H), 3.59 (s, 3H), 3.56 (dd, J = 2.0, 9.0 Hz, 1H), 3.12 (dd, J = 4.0, 12.0 Hz, 1H), 2.23 (t, J = 12.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.1, 160.9, 136.4, 130.0, 128.6, 87.9, 78.31, 78.28, 71.6, 70.0, 63.2, 57.0, 52.3, 36.7. ESIHRMS calcd for $C_{17}H_{21}N_1O_8SNa$ ([M + Na]$^+$) 422.08804, found 422.08929.

Methyl (Phenyl 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 (donor 1). A solution of compound **6** (2.67 g, 6.68 mmol) in pyridine (20 mL) was treated with Ac_2O (24 mL) and stirred at room temperature overnight, then concentrated under reduced pressure. The residue was dissolved in anhydrous CH_2Cl_2, treated with EtN(*i*-Pr)$_2$ (11.6 mL, 66.8 mmol, 10 equiv), and cooled to 0 °C before acetyl chloride (3.87 mL, 53.4 mmol, 8 equiv) was added dropwise, then the mixture stirred at 0 °C for 1 h. 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 column chromatography on silica gel eluting with EtOAc/Hex (1:1) to give donor **1** as a yellowish solid (3.49 g, 92%), which can be further purified by recrystalization from EtOAc/Et_2O/Hex to afford white needle crystals. Mp 152−153 °C (EtOAc/Et_2O/hexanes). $[\alpha]^{14}_D$ −117 (*c* 0.8, $CHCl_3$). ^{1}H NMR (500 MHZ, $CDCl_3$) δ 7.47−7.31 (m, 5H), 5.52 (t, J = 2.0 Hz, 1H), 4.96 (td, J = 1.5, 8.5 Hz, 1H), 4.86 (dd, J = 2.5, 9.0 Hz, 1H), 4.76 (dt, J = 4.0, 13.0 Hz, 1H), 4.34 (dd, J = 2.5, 12.0 Hz, 1H), 3.86 (dd, J = 8.0, 11.5 Hz, 1H), 3.73 (dd, J = 9.0, 11.5 Hz, 1H), 3.60 (s, 3H), 2.88 (dd, J = 3.5, 13.0 Hz, 1H), 2.49 (s, 3H), 2.32 (t, J = 12.5 Hz, 1H), 2.12 (s, 3H), 2.05 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 171.3, 170.4, 169.8, 167.8 (C-1, $^3J_{C-1,H-3ax}$ = 2.50 Hz), 153.6, 136.8, 130.2, 129.2, 128.2, 88.3, 75.7, 75.1, 73.9, 72.7, 62.9, 59.6, 52.8, 36.0, 24.8, 21.2, 20.85, 20.76. Anal. Calcd for $C_{25}H_{29}NO_{12}S$: C, 52.90; H, 5.15; N, 2.47. Found: C, 53.01; H, 5.15; N, 2.45.

Methyl (Phenyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-2-thio-D-glycero-α-D-galacto-non-2-ulopyranoside)onate (donor 9). 9 was prepared from **8** following the same procedure as for **1**. Mp 148−149 °C (EtOAc/Et_2O/hexanes). $[\alpha]^{14}_D$ +13.4 (*c* 1.1, $CHCl_3$). ^{1}H NMR (500 MHZ, $CDCl_3$) δ 7.56−7.26 (m, 5H), 5.54 (dd, J = 1.5, 6.0 Hz, 1H), 5.34 (dt, J = 3.0, 7.0 Hz, 1H), 4.42 (dd, J = 3.0, 12.5 Hz, 1H), 4.34 (dd, J = 1.5, 9.5 Hz, 1H), 4.19 (dd, J = 7.0, 12.0 Hz, 1H), 3.98−3.92 (m, 1H), 3.59 (dd, J = 9.0, 11.0 Hz, 1H), 3.58 (s, 3H), 3.10 (dd, J = 3.5, 12.0 Hz, 1H), 2.45 (s, 3H), 2.16 (s, 3H), 2.11 (t, J = 13.0 Hz, 1H), 2.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 170.7, 170.2, 170.1, 168.1 (C-1, $^3J_{C-1,H-3ax}$ = 7.50 Hz), 153.4, 136.6, 130.2, 129.0, 128.3, 87.7, 75.7, 72.5, 70.5, 62.6, 59.1, 53.1, 36.7, 24.7, 21.1, 21.0, 20.9. Anal. Calcd for $C_{25}H_{29}NO_{12}S$: C, 52.90; H, 5.15; N, 2.47. Found: C, 53.13; H, 5.11; N, 2.47.

Coupling Protocol with Ph_2SO/Tf_2O/TTBP in Dichloromethane. A solution of donor **1** (0.11 mmol, 1 equiv), diphenyl sulfoxide (0.32 mmol, 3 equiv), TTBP (0.22 mmol, 2 equiv), and activated 4 Å powdered sieves in anhydrous dichloromethane (2 mL) was stirred for 1 h at room temperature under an argon atmosphere, and then cooled to −78 °C, followed by addition of Tf_2O (0.12 mmol, 1.1 equiv). After 10 min, a solution of the acceptor (0.22 mmol, 2 equiv) in dichloromethane (1 mL) was added. The reaction mixture was stirred for 1−6 h at −78 °C and then warmed to room temperature, diluted with dichloromethane, filtered through Celite, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The glycosides were isolated by column chromatography on silica gel eluting with THF/Hex systems to afford the sialosides.

Coupling Protocol with NIS/TfOH in Dichloromethane. A solution of donor **1** (61.3 mg, 0.11 mmol, 1.0 equiv), acceptor (0.16 mmol, 1.5 equiv), and activated 5 Å powdered molecular sieves (216 mg, 2.0 g/mmol) in anhydrous dichloromethane (2 mL) was stirred overnight under an argon atmosphere, and then cooled to −40 °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 for 20 min to 2 h until the disappearance of the donor on TLC, then quenched with triethylamine (22.6 μL, 0.16 mmol, 1.5 equiv) and warmed to room temperature. The mixture was diluted with dichloromethane, 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/Hex system to afford the sialosides.

Procedure for the Selective Cleavage of Oxazolidinones. To a solution of sialoside (0.1 mmol, 1.0 equiv) in methanol (2 mL) was added a few drops of sodium methoxide solution in methanol (∼70 μL, 0.3 mmol, 3.0 equiv) at room temperature. The mixture was stirred at room temperature for 30 min followed by treatment with Amberlyst 15 ion-exchange resin for 5 min. The mixture was diluted with methanol and filtered through a sintered funnel packed with Celite and silica gel. The filter pad was rinsed with methanol (3 × 5 mL) after filtration. The combined filtrates were concentrated under reduced pressure to afford the deprotected *N*-acetamido-sialosides in quantitative yield without further purification.

Acknowledgment. We thank Dr. D. J. Wink for X-ray crystallography of donor **1,** and the NIH (GM 62160) for financial support of this work.

Supporting Information Available: X-ray crystal structure of **1**, full characterization data, and copies of NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062431R