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Stereoselective Iterative One-Pot Synthesis of *N*-Glycolylneuraminic Acid-Containing Oligosaccharides

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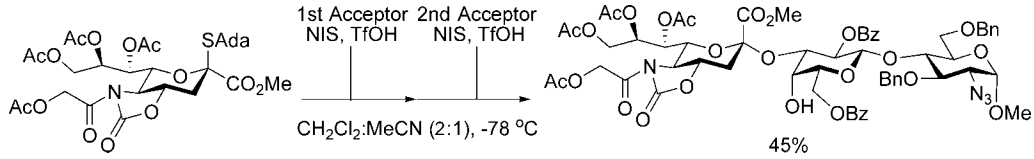
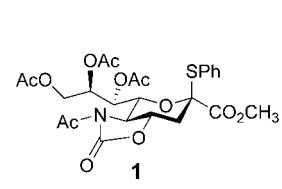
ABSTRACT



The use of an *N*-acyloxazolidinone-protected *S*-adamantanyl thiosialoside allows the highly stereoselective, one-pot multicomponent synthesis of α-sialoside-based oligosaccharides.

Along with the 2-deoxy-β-glycosides and the β-mannosides, the α-sialosides are considered to be one of the three most difficult classes of glycosidic bonds to assemble in a stereoselective manner.[1] Considerable progress has been made in recent years particularly through the use of sialyl donors carrying powerfully electron-withdrawing groups on N5[2] and with 5*N*,4*O*-oxazolidinone protected donors,[3] but the chemistry has not progressed to a level at which sialyl thioglycosides may be contemplated as components of one-pot iterative glycan syntheses of the type convincingly demonstrated by Huang and co-workers for numerous other classes of oligosaccharides.[4,5] We introduced the 5*N*-acetyl-5*N*,4*O*-oxazolidinone protected phenylthio sialoside **1** as a donor for α-selective sialylation from which the oxazolidinone group could subsequently be removed by a mild basic hydrolysis leading directly to the *N*-acetyl targets.[6] Unfortunately, donor **1** could not be activated in the requisite stereodirecting nitrile solvents ≤ −40 °C owing to its strongly disarmed nature. This led us to develop the adamantanyl thioglycoside analogue **2** which was cleanly activated in mixtures of acetonitrile and dichloromethane at −78 °C,



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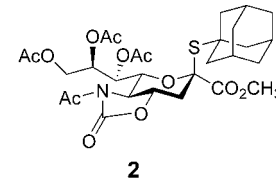

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leading to improved α-selectivities.[7] We report here that donors of type **2** are sufficiently armed to be used as the

(1) (a) Okamoto, K.; Goto, T. *Tetrahedron* **1990**, *46*, 5835–5857. (b) Hasegawa, A. In *Modern Methods in Carbohydrate Synthesis*; Khan, S. H., O'Niell, R. A., Eds.; Harwood Academic Publishers: Amsterdam, 1996, pp 277−300. (c) Hasegawa, A.; Kiso, M. *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; pp 357−379. (d) Kiso, M.; Ishida, H.; Ito, H. *Carbohydrates in Chemistry and Biology: Chemistry of Saccharides*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1, pp 345−365. (e) Boons, G.-J.; Demchenko, A. V. *Chem. Rev.* **2000**, *100*, 4539–4565. (f) Boons, G.-J.; Demchenko, A. V. *Carbohydrate-Based Drug Discovery*; Wong, C.-H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 1, pp 55−102. (g) Ress, D. K.; Linhardt, R. J. *Curr. Org. Synth.* **2004**, 31–46.

(2) (a) Tanaka, H.; Nishiura, Y.; Adachi, M.; Takahashi, T. *Heterocycles* **2006**, *67*, 107–112. (b) De Meo, C.; Priyadarshani, U. *Carbohydr. Res.* **2008**, *343*, 1540–1552.

(3) (a) Hossain, N.; Magnusson, G. *Tetrahedron Lett.* **1999**, *40*, 2217–2220. (b) Demchenko, A. V.; Boons, G.-J. *Chem.−Eur. J.* **1999**, *5*, 1278–1283. (c) Tanaka, K; Goi, T.; Fukase, K *Synlett* **2005**, *295*, 8–2962. (d) Tanaka, H.; Nishiura, Y.; Takahashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 7124–7125. (e) Farris, M. D.; De Meo, C *Tetrahedron Lett.* **2007**, *48*, 1225–1227.

(4) (a) Huang, X.; Huang, L.; Wang, H.; Ye, X.-S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5221–5224. (b) Wang, Y.; Huang, X.; Zhang, L.-H.; Ye, X.-S. *Org. Lett.* **2004**, *6*, 4415–4417. (c) Huang, L.; Huang, X. *Chem.−Eur. J.* **2007**, *13*, 529–540.

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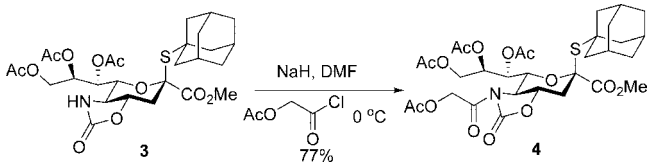
first component in Huang-type, thioglycoside-based iterative one-pot oligosaccharide syntheses and illustrate this principle through the synthesis of a number of *N*-glycoyl α-sialoside-based oligosaccharides of interest because of their potential as markers for human tumors.[8]

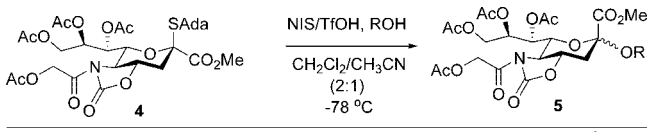
Adapting the synthesis developed earlier for the preparation of **2**,[7] oxazolidinone **3** was converted to the *N*-acetoxyacetimide derivative **4** in a straightforward manner (Scheme 1).

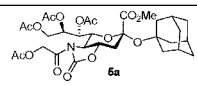
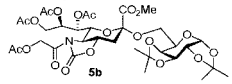
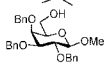
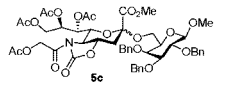
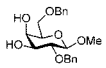
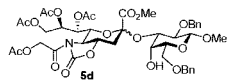
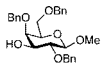
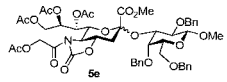
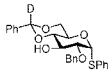
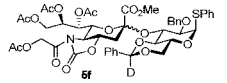
Scheme 1. Donor Synthesis



A series of glycosylations were then conducted by combining **4** with the acceptor in a 2:1 dichloromethane/acetontrile mixture at −78 °C before addition of *N*-iodosuccinimide and triflic acid, leading to the results presented in Table 1, from which it is apparent that donors **2** and **4** perform analogously under these conditions.[9] The dependence of coupling selectivity on the acceptor alcohol is noteworthy in the context of the current interest in the matching of acceptor/donor pairs.[10] The contrast between a 3,4-diol and a 4-*O*-benzyl 3-ol in the galactopyranose series is noteworthy but follows the established pattern in the literature.[6,7]

Table 1. Exploratory Coupling Reactions with Donor **4**

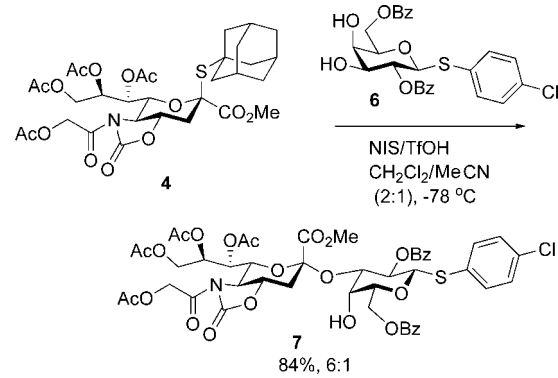


entry	acceptor	coupled product	% yield	α:β ratio	δ_{C1}	$^3J_{C1,H3ax}$ (Hz)
1		 **5a**	80	α only	171.5	5.2
2		 **5b**	91	α only	168.5	5.2
3		 **5c**	86	13:1	168.3[a]	5.2[a]
4		 **5d**	64	15:1	168.5[a]	6.2[a]
5		 **5e**	74	1:1	-[b]	-[b]
6		 **5f**	79	2:1	166.8[a]	5.2[a]

[a] Chemical shift and coupling constant reported for the major α-isomer. [b] Not determined. Benzylation of **5dα** gave **5eα** and enabled differentiation of the two isomers in this otherwise unseparable mixture (see Supporting Information). After saponification, the two anomers in this mixture could be separated and characterized (see Supporting Information).

A thiogalactosyl acceptor **6** was then prepared by standard means (Supporting Information) and coupled to donor **4** under standard conditions resulting in the formation of disaccharide **7** in excellent yield and selectivity (Scheme 2),

Scheme 2. Disaccharide Synthesis



thereby demonstrating viability of **4** in iterative one-pot oligosaccharide syntheses.[11]

A series of four trisaccharides were then assembled by a one-pot protocol in which a mixture of donor and the first acceptor (1:1.15) and molecular sieves were cooled to −78 °C in a 2:1 dichloromethane/acetonitrile mixture before sequential addition of *N*-iodosuccinimide (1.0 equiv) and triflic acid (0.5 equiv). After stirring for 20 min at −78 °C, the second acceptor (1.5 equiv) was added, followed by further molecular sieves, NIS (2.0 equiv), and triflic acid (0.5 equiv), and the reaction mixture was allowed to come to 0 °C and maintained at that temperature for 2 h before quenching (Scheme 3).[12,13]

For selected examples, removal of the oxazolidinone group was achieved by heating to 70 °C with aqueous ethanolic

(5) Indeed, previous strategies directed toward the one-pot synthesis of sialylated oligosaccharides have necessitated the inclusion of the sialyl moiety as part of a disaccharide, thereby circumventing the issue of the low reactivity of sialic acid thioglycosides: Zhang, Z.; Niikura, K.; Huang, X.-F.; Wong, C.-H *Can. J. Chem.* **2002**, *80*, 1051–1054.

(6) Crich, D.; Li, W. *J. Org. Chem.* **2007**, *72*, 2387–2391.

(7) Crich, D.; Li, W. *J. Org. Chem.* **2007**, *72*, 7794–7797.

(8) (a) Blixt, O.; Paulson, J. C. *Adv. Synth. Catal.* **2006**, *345*, 687–690. (b) Malykh, Y. N.; Shaw, S. R. L. *Biochimie* **2001**, *83*, 623–634. (c) Varki, A. *Biochimie* **2001**, *63*, 615–622. (d) Angata, T.; Varki, A. *Chem. Rev.* **2002**, *102*, 439–469.

(9) Stereochemical assignments were made on the basis of the $^3J_{C1,H3ax}$ coupling constants: (a) Hori, H.; Nakajima, T.; Nishida, Y.; Ohrui, H.; Meguro, H. *Tetrahedron Lett.* **1988**, *29*, 6317–6320. (b) Haverkamp, J.; Spoormaker, T.; Dorland, L.; Vliegenthart, J. F. G.; Schauer, R. *J. Am. Chem. Soc.* **1979**, *101*, 4851–4853. (c) Prytulla, S.; Lauterwein, J.; Klessinger, M.; Thiem, J. *Carbohydr. Res.* **1991**, *215*, 345–349.

(10) (a) Spijker, N. M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed.* **1991**, *30*, 180–183. (b) Jayaprakash, K. N.; Chaudhuri, S. R.; Murty, C. V. S. R.; Fraser-Reid, B. *J. Org. Chem.* **2007**, *72*, 5534–5545. (c) Cid, M. B.; Alonso, I.; Alfonso, F.; Bonilla, J. B.; López-Prados, J.; Martín-Lomas, M. *Eur. J. Org. Chem.* **2006**, *394*, 7–3959.

(11) The use of the phenylthio glycoside corresponding to **6** resulted in lower yields and more complex reaction mixtures. For the relative reactivities of substituted arylthio glycosides, see: Huang, L.; Wang, Z.; Huang, X. *Chem. Commun.* **2004**, 1960–1961.

Scheme 3. Iterative Trisaccharide Syntheses

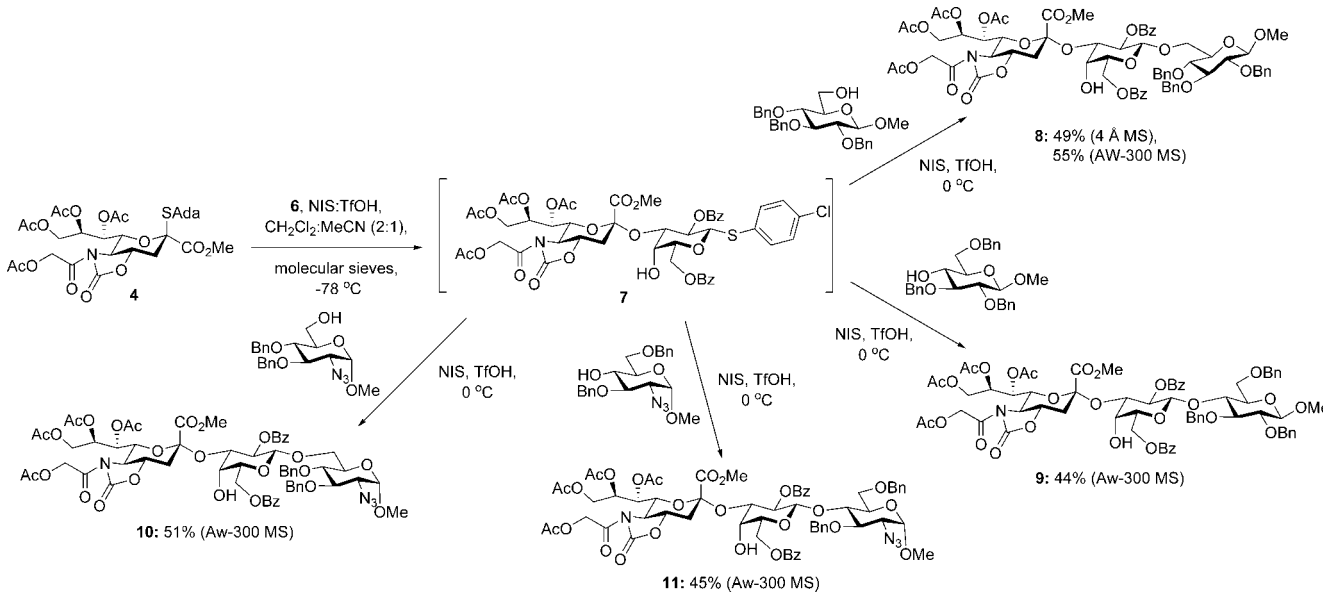
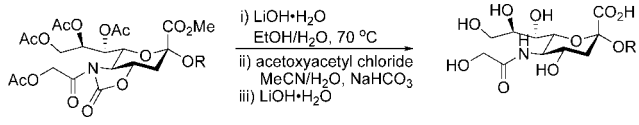
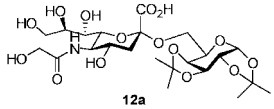
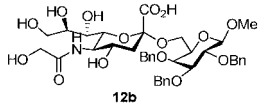
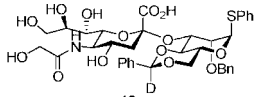
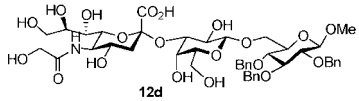
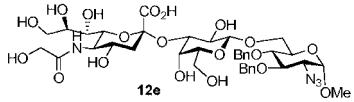


Table 2. Deprotection of the Oxazolidinone Moiety



coupled product	deprotected product	% yield
5b	 **12a**	81
5c	 **12b**	83
5f	 **12c**	80
8	 **12d**	82
10	 **12e**	75

lithium hydroxide. All attempts at selective removal of the oxazolidinone moiety without cleavage of glycoyl residue resulted in mixtures of products, necessitating the more vigorous conditions to ensure the complete removal of both nitrogen protecting groups.[14,15] Without isolation, the glycoyl group was reinstalled on the saponification product by treatment with acetoxyacetyl chloride and sodium bicarbonate, followed by exposure to lithium hydroxide. This protocol enabled the isolation of a series of *N*-glycolyl sialosides in excellent yield (Table 2).

Acknowledgment. We thank the NIH (GM62160) for support of this work.

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

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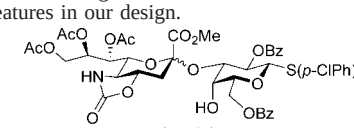
(12) The use of acid washed molecular sieves gives enhanced yields in this coupling process as compared to standard 4 Å molecular sieves. This appears to be because catalytic triflic acid can be employed in the case of the acid-washed sieves, as opposed to the suprastoichiometric amounts needed with the standard sieves which ultimately results in degradation of the glycosidic bond on warming.

(13) Although for the purposes of the present demonstration we have stopped at the trisaccharide level, it is clear from the work of Huang[4] that incorporation of the third sugar in the form of a hydroxyl thioglycoside would allow further chain extension.

(14) This observation differs from the *N*-acetyl series, when it is possible to cleave the oxazolidinone selectively leaving the acetamide in place, and bears witness to the enhanced reactivity of the glycolyl carbonyl group.

(15) Our inability to cleave the oxazolidinone selectively and the consequent need to resort to full saponification and subsequent re-introduction of the amide group beg the question as to the need for the acetylglycolyl group at the level of the glycosylation reaction, particularly in view of the work of Takahashi and DeMeo.[3c,d] In the event, however, glycosylation of donor **3** with acceptor **6** under the conditions employed in this study afforded the disaccharide **16** in 61% yield as a 1:1 mixture of anomers. This selectivity stands in evident contrast to that of Scheme 2 and highlights the advantage of the more electron-deficient *N*-acyl oxazolidinone that features in our design.



16 α/β = 1:1