Published in final edited form as:

Org Lett. 2008 September 18; 10(18): 4033–4035. doi:10.1021/ol801548k.

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 potmulticomponent 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 bond 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 coworkers for numerous other classes of oligosaccharide.^{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, leading to improve α -selectivities.⁷ We report here that donors of type **2** are sufficiently armed to be used as the first component in Huang-type, thioglycoside-based iterative one pot oligosaccharide syntheses, and illustrate this principle through the synthesis of a number of *N*-glycolyl α -sialoside-based oligosaccharides of interest because of their potential as markers for human tumors.⁸

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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>.

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).

A series of glycosylations were then conducted by combining **4** with the acceptor in a 2:1 dichloromethane:acetonitrile mixture at $-78\text{ }^{\circ}\text{C}$ 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 donor 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}

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), thereby demonstrating viability of **4** in iterative one-pot oligosaccharide syntheses.¹¹

For selected examples, removal of the oxazolidinone group was achieved by heating to $70\text{ }^{\circ}\text{C}$ with aqueous ethanolic 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}

A series of four trisaccharides were then assembled by a one pot protocol in which a mixture of donor, the first acceptor (1:1.15) and molecular sieves were cooled to $-78\text{ }^{\circ}\text{C}$ 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 mins at $-78\text{ }^{\circ}\text{C}$ 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 allowed to come to $0\text{ }^{\circ}\text{C}$ and maintained at that temperature for 2 h before quenching (Scheme 3).^{12,13}

Without isolation the glycoyl group was reinstalled on the saponification product by treatment with chloroacetyl 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).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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

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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. 1961
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 supra-stoichiometric 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 Huang⁴ 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 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, begs the question as to the need for the acetyl glycolyl 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 **13** 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.

Scheme 1.
Donor Synthesis

Scheme 2.
Disaccharide Synthesis

Scheme 3.
Donor Synthesis

% yield

α : β ratio

δ_{C1}

$^3J_{C1-H3ax}$ (Hz)

$^3J_{\text{C1-H3ax}}$ (Hz) δ_{C1} $\alpha:\beta$ ratio

% yield

coupled product

5.2^a168.3^a

13:1

86

% yield

α : β ratio

δ_{C1}

$^3J_{C1-H3ax}$ (Hz)

coupled product

6.2^d

168.5^d

15:1

64

$^3J_{C1-H3ax}$ (Hz)

δ_{C1}

$\alpha:\beta$ ratio

% yield

coupled product

b

b

1:1

74

$^3J_{\text{C1-H3ax}}$ (Hz)	δ_{C1}	$\alpha:\beta$ ratio	% yield	coupled product
5.2 ^d	166.8 ^d	2:1	79

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(formation). After saponification the two anomers

Table 2

Deprotection of the Oxazolidinone Moiety

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;"> </div> <div style="text-align: center;"> <p>i) $\text{LiOH} \cdot \text{H}_2\text{O}$ EtOH/H_2O, 70 °C</p> <p>ii) acetoxyacetyl chloride $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, NaHCO_3</p> <p>iii) $\text{LiOH} \cdot \text{H}_2\text{O}$</p> </div> <div style="text-align: center;"> </div> </div>		
coupled product	deprotected product	% yield
5b	<p>12a</p>	81
5c	<p>12b</p>	83
5f	<p>12c</p>	80
8	<p>12d</p>	82
10	<p>12e</p>	75