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A New C(1)-Auxiliary for Anomeric Stereocontrol in the Synthesis of α-Sialyl Glycosides

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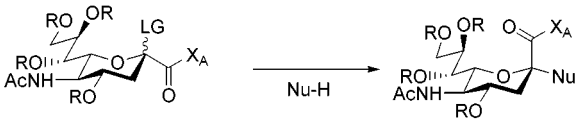
ABSTRACT

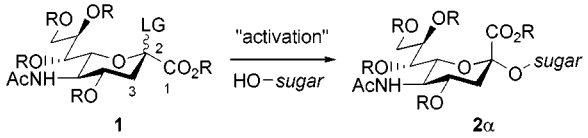


$X_A = OCH_2CONMe_2$

The installation of the novel *N*,*N*-dimethylglycolamide ester auxiliary onto the C(1)-position of protected neuraminic acid donors allows for the exploitation of C(1)-neighboring group participation to generate sialoside conjugates with good to excellent α-selectivity under a variety of sialylation protocols, including those that would otherwise lead to nonselective or *β*-selective sialoside products.

Oligosaccharides and glycoconjugates incorporating sialic acid residues play important roles in a host of biological processes, including, inter alia, immune response, cell proliferation, cell differentiation, and oncogenesis.[1] However, complex mammalian sialosides are typically isolated in exceedingly small quantities from natural sources; as a result, chemical[2] or enzymatic[3] syntheses have been instrumental in providing access to complex sialyl conjugates for use as biochemical probes and/or potential therapeutic agents. Most of the methods to synthesize sialic acid-containing oligosaccharides involve the use of glycosidic coupling strategies in which a C(2)-ketal bond is constructed in a coupling event (Scheme 1). Several glycosylation methods have been employed for the synthesis of sialosides employing sialyl donors **1** with specific anomeric latent leaving groups.[2] In this context, variable degrees of α/*β* selectivities are achieved and these selectivities are highly dependent on the nature of the substrates and reaction conditions. However, naturally occurring sialosides incorporate an α-C(2)-stereochemistry (equatorial), which is unfortunately not the thermodynamically favored epimer as a consequence of the anomeric effect. Thus, a critical and ongoing challenge in glycosylation employing sialyl donors is control over anomeric stereochemistry to generate α-linked sialyl conjugates with good anomeric selectivity.

Scheme 1



R = protective group LG = latent leaving group

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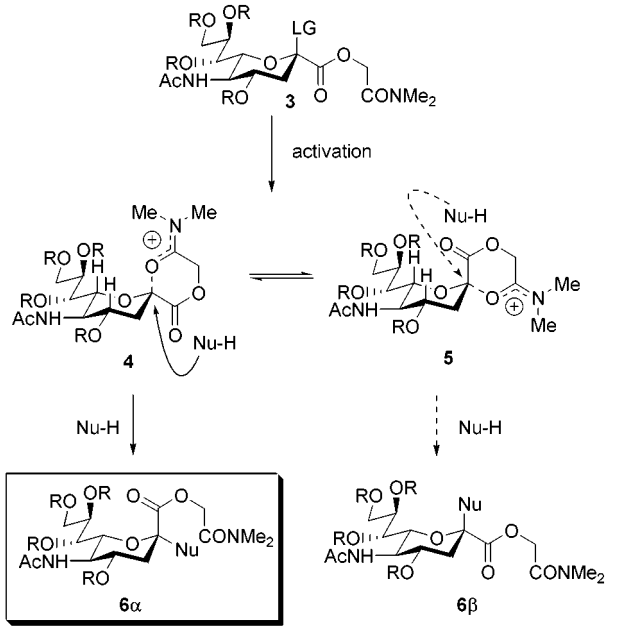
Increased α-selectivity has been achieved in several instances where sialosyl couplings have been performed in acetonitrile solvent, capitalizing on the generation of a putative sialyl β-nitrilium species as a reactive intermediate.[4] High[4c,5] to moderate[6] α-selectivities have been achieved, although yields are variable depending on the nature of the sialyl activating reagents and their compatibility with nitrile solvents. Neighboring group participation has also been extensively investigated as a means of influencing anomeric selectivity in the sialylation process. Traditionally, C(3)-neighboring group effects have been employed to control anomeric selectivity in sialosyl couplings; yet, this is not possible without elaborate derivatization of the sialyl donor. For example, protected neuraminic acid glycals (derived from protection and C(2)−C(3) elimination of neuraminic acid)[7] are typically oxidized to introduce a heteroatom substituent at the C(3) position (i.e., halogen,[8] sulfide,[7,9−13] selenide,[9] or oxygen substituents[12,14]). The resulting donor is then employed in the sialylation of the glycosyl acceptor followed by reductive removal of the C(3)-auxiliary to afford the desired fully protected sialyl conjugate. Although good α-selectivities can be obtained in many cases, the protracted multistep protocol in this approach severely detracts from the overall efficiency and broad utility of this strategy.

While the bulk of the advances to address this crucial problem of α-selective sialylation have involved multistep C(3)-derivatization, reports on the use of auxiliary functionalities at the C(1)-carboxylic acid position have been limited.[15] We report herein a new C(1)-auxiliary for neighboring group participation in glycosidic couplings with sialyl donors for the preparation of α-sialyl conjugates. In this context, a C(1)-*N*,*N*-dimethylglycolamide auxiliary (-OCH_2-$CONMe_2$) (i.e., **3**, Scheme 2) was employed because of its structural simplicity and its likelihood to participate favorably in the coupling event to enhance α-selectivity. It was anticipated that when a C(1)-derivatized sialyl donor such

Scheme 2



as **3** (Scheme 2) is activated under various glycosylation conditions, the resulting C(2)-oxocarbenium intermediate can be stabilized by the neighboring *N*,*N*-dimethylglycolamide carbonyl group from either an axial (β) orientation (i.e., **4**) or from an equatorial (α) orientation (i.e., **5**). Of these two putative reactive intermediates, **4** is likely to predominate due to the anomeric effect. More importantly, however, **4** is also likely to be more reactive toward the acceptor (Nu-H) since approach of Nu-H from the β-face (i.e., **5**) would be sterically disfavored relative to nucleophilic attack on the α-face (i.e., **4**), resulting in the preferred formation of the desired α-sialoside **6**α.

This hypothesis was verified by performing a series of comparative sialylations with 4,7,8,9-tetra-*O*-acetylneuraminic acid donors incorporating either the traditional methyl ester protective group at C(1) (**7**, Figure 1) or the *N*,*N*-dimethylglycolamide auxiliary at C(1) (**8**). The sialyl acceptors include simple alkyl alcohols such as cyclohexanol (**9**) and cholesterol (**10**), as well as carbohydrate-derived nucleophiles such as methyl 2,3,4-tetra-*O*-benzyl-α-D-glucopyranoside (**11**) and the diol acceptor methyl 2,6-di-*O*-benzyl-α-D-galactopyranose (**12**), a carbohydrate acceptor relevant to many naturally occurring gangliosides.

Three distinct methods for sialylation were employed to assess the generality of this neighboring group participation strategy. These include the use of sialyl chlorides, sulfides, and phosphites.[2,16] The resultant yields and anomeric selec-

(4) For the nitrile effect in *O*-glycosylation reactions, see: (a) Schmidt, R. R.; Rücker, E. *Tetrahedron Lett.* **1980**, *21*, 1421−1424. (b) Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694. For examples of the nitrile effect in sialylation, see: (c) Hasegawa, A.; Ohki, H.; Nagahama, T.; Ishida, H.; Kiso, M. *Carbohydr. Res.* **1991**, *212*, 277−281. (d) Birberg, W.; Lönn, H. *Tetrahedron Lett.* **1991**, *32*, 7457−7458. See also ref 2c.

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(15) For the use of alkylthioalkyl ester auxiliaries, see: (a) Takahashi, T.; Tsukamoto, H.; Yamada, H. *Tetrahedron Lett.* **1997**, *38*, 8223−8226. For the use of a 2-furanyl substituent as a masked C(1)-carboxylate functionality in glycosylations with C(5)-*epi*-sialic acid donors, see: (b) Danishefsky, S. J.; DeNinno, M. P.; Chen, S. *J. Am. Chem. Soc.* **1988**, *110*, 3929−3940.

(16) The sialyl donors **7** and **8** were prepared according to established protocols that proceed under thermodynamic control to provide selectivity for the β-anomers (see ref 2). The preparation of the chloride and diethyl phosphite donors of **7** afforded exclusively the β-anomers, while the preparation of the ethyl thioglycoside of **7** afforded a 6:1 mixture of β:α-anomers. The preparation of the corresponding donors of **8** all led to the formation of a single anomer whose spectral data are consistent with the C(2) β-configuration (see ref 2a and Supporting Information).

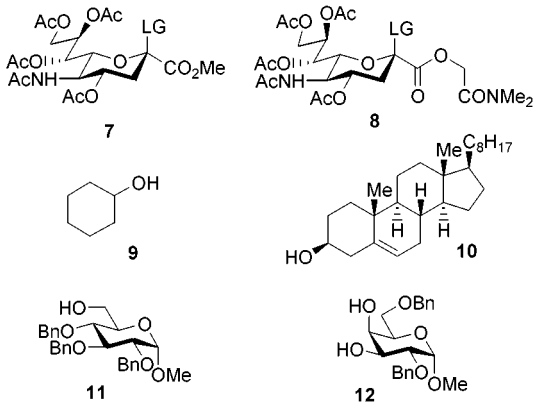


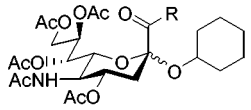
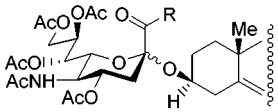
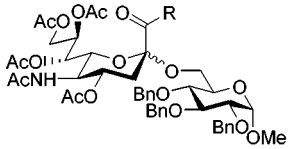
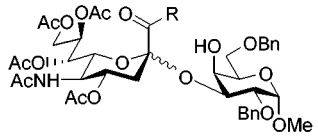
Figure 1. Carbohydrate coupling partners.

tivities of the sialylation reactions are summarized in Table 1. To assess the true extent of the influence of the new C(1)-auxiliary, the comparative glycosylation reactions were performed in the absence of acetonitrile to avoid possible perturbations in α-selectivity due to nitrile solvent effects. In these reactions, it is clear that the C(1)-*N*,*N*-dimethylglycolamide auxiliary (X_A) exerts a dramatic effect in favoring α-sialylation of nucleophilic acceptors under various glycosylation reaction conditions. For example, the coupling of cyclohexanol (**9**) with the sialyl chloride donor **7** incorporating the C(1)-methyl ester proceeded with good α-selectivity (entry 1, **13**; 5:1, α:*β*); yet, the incorporation of the C(1) auxiliary X_A on the sialyl donor (**8**) in the identical coupling protocol provided a significant enhancement in α-selectivity of the product sialoside (entry 1, **14**; 10:1, α:*β*).

More dramatic illustrations of the favorable stereochemical influence of X_A arise in the sialylation examples where no anomeric selectivity is obtained when a methyl ester functionality resides at C(1) of the donor (entries 3, 4, 6, and 7; sialosides **15**, **17**, **17**, and **19**, respectively). However, with the C(1)-X_A auxiliary present in the donor, high α-selectivities are achieved (entries 3, 4, 6, and 7; sialosides **16**, **18**, **18**, and **20**, respectively). Finally, striking examples of the positive influence of the C(1)-X_A auxiliary were also exhibited in entries 2, 5, 8, and 9, wherein the anomeric selectivities of the coupling reactions are reversed from being selective for the *β*-anomer in the absence of the C(1)-auxiliary to being selective for the α-anomer when X_A is incorporated in the sialyl donor. It is worth noting that the sialosyl coupling reactions with the C(1)-X_A derived sialosyl donors (**8**) proceeded with comparable if not better efficiencies (i.e., entry 7) when compared to their C(1)-methyl ester-derived counterparts (**7**).[17]

(17) For the low-yield preparation of **19** in entry 7, the corresponding C(2)−C(3) sialic acid glycal was also isolated with 22% recovery. In all of the other sialosyl coupling reactions, the formation of the byproduct corresponding to C(2)−C(3) elimination of the donor was minimal (0−10%). It is likely that the participatory nature of the C(1)-X_A auxiliary also helps to minimize the C(3) elimination pathway by providing added stabilization to the putative sialosyl C(2)-oxocarbenium intermediate.

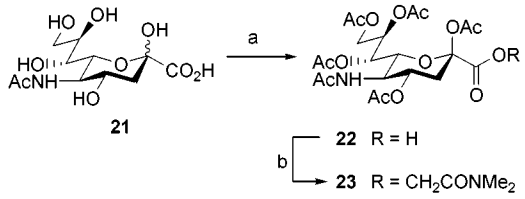
Table 1. Glycosidic Couplings

Entry	Donor [LG]	Acceptor	Reagents[a]	Product; Yield (α:β)	
					
1	**7** or **8** [-Cl]	**9**	A	**13**: R = OMe 74% (5:1)	**14**: R = X_A[b] 87% (10:1)
2	**7**[c] or **8** [-SEt]	**9**	B	**13**: R = OMe 90% (1:7)	**14**: R = X_A[b] 85% (3:1)
					
3	**7** or **8** [-Cl]	**10**	A	**15**: R = OMe 68% (1:1)	**16**: R = X_A[b] 64% (5:1)
					
4	**7** or **8** [-Cl]	**11**	A	**17**: R = OMe 60% (1:1)	**18**: R = X_A[b] 61% (7:1)
5	**7**[c] or **8** [-SEt]	**11**	B	**17**: R = OMe 87% (1:10)	**18**: R = X_A[b] 80% (3:1)
6	**7** or **8** [-OP(OEt)$_2$]	**11**	C	**17**: R = OMe 77% (1:1)	**18**: R = X_A[b] 77% (6:1)
					
7	**7** or **8** [-Cl]	**12**	A	**19**: R = OMe 22% (1:1)	**20**: R = X_A[b] 56% (13:1)
8	**7**[c] or **8** [-SEt]	**12**	B	**19**: R = OMe 65% (1:4)	**20**: R = X_A[b] 80% (2:1)
9	**7** or **8** [-OP(OEt)$_2$]	**12**	C	**19**: R = OMe 78% (1:3)	**20**: R = X_A[b] 80% (3:1)

[a] Reagents: A = AgOTf (1.4 equiv), $PhCH_3$, −20 °C; B = NIS (3 equiv), TfOH (cat.), CH_2Cl_2, −50 °C; C = TMSOTf (cat.), −40 °C, CH_2Cl_2. [b] X_A = OCH_2CONMe_2. [c] A 6:1 *β*:α anomeric mixture of the ethyl thioglycoside of **7** was employed.

The utility of this C(1) participatory strategy relies also on the efficiency with which the auxiliary can be installed onto the sialyl donor and subsequently removed to liberate the free C(1)-carboxylic acid after the coupling event. Introduction of the *N*,*N*-dimethylglycolamide auxiliary onto penta-*O*-acetylneuraminic acid (**22**) is easily accomplished via a convenient protocol (Scheme 3). 2-Methanesulfonyloxy-*N*,*N*-dimethylacetamide (**24**), derived from the treatment of readily available 2-hydroxy-*N*,*N*-dimethylacetamide with

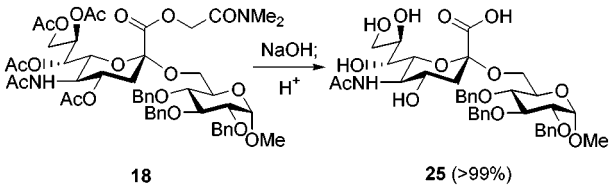
Scheme 3[a]



[a] Reagents and conditions: (a) Ac_2O, pyridine, 88%; (b) $MeSO_3CH_2CONMe_2$ (**24**), Cs_2CO_3, DMF, 88%.

methanesulfonyl chloride (Et_3N, CH_2Cl_2, 23 °C, 88%), is reacted with the cesium carboxylate of **22** to afford the X_A-derived neuraminic acid **23** in 88% yield. Conversion of **23** to the appropriate sialyl donors **8** can then be accomplished by well-established methods.[2] Following the coupling event, removal of the auxiliary X_A is equally simple and efficient (Scheme 4), requiring hydrolysis conditions that are typically

Scheme 4



used for saponification of C(1)-methyl ester-derived neuraminic acids. For example, when the sialosyl conjugate **18** is treated with a mixture of 1 N $NaOH_{(aq)}$ and MeOH (2:1 v/v), all of the neuraminic acid protective groups are cleanly removed, and the corresponding sialyl conjugate **25** is isolated in quantitative yield following LH-20 Sephadex chromatography.[18]

A new auxiliary for neighboring group participation in sialic acid couplings has been established via the installation of the *N*,*N*-dimethylacetamide ester auxiliary (X_A) onto the C(1)-position of protected neuraminic acids. This allows for the exploitation of C(1)-neighboring group participation to generate sialoside conjugates with good to excellent α-selectivity under a variety of sialylation protocols, including those that would otherwise lead to nonselective or *β*-selective sialoside products in the absence of the new C(1)-X_A auxiliary. Moreover, since the auxiliary X_A also functions as a convenient and inexpensive C(1)-protective group, this approach obviates the need for multistep derivatizations that are required for the traditional C(3)-neighboring group participation strategies. Efforts are currently underway to explore the use of these and other C(1)-auxiliary motifs and apply them to the synthesis of bioactive gangliosides.

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Supporting Information Available: Experimental details and spectral/analytical data for the glycoside products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The structures of the sialosides **13**−**20** were verified by base hydrolysis of all ester functionalities within the product sialyl conjugates and comparison of the products with literature structural data. For **13**−**14**, see ref 6. For **15**−**18**, see ref 8. For **19** and **20**, see: Thiem, J.; Sauerbrei, B. *Angew. Chem.* **1991**, *103*, 1521−1523.