ORGANIC LETTERS

2003
Vol. 5, No. 14
2539−2541

Dehydrative Sialylation with C2-Hemiketal Sialyl Donors

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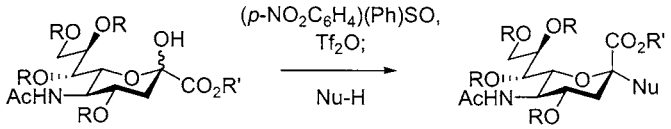
Received May 12, 2003

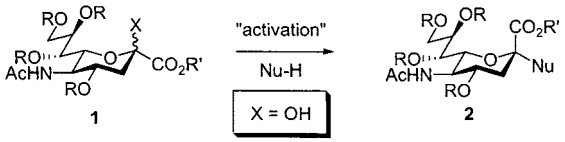
ABSTRACT



A new method for sialylation involving the dehydrative coupling of sialyl donors with the reagent combination of (*p*-nitrophenyl)(phenyl) sulfoxide and triflic anhydride is reported. This process establishes sialyl C2-hemiketals as viable sialyl donors for complex carbohydrate synthesis.

The development of new methods for the preparation of sialic acid conjugates is a major focus in carbohydrate synthesis owing to its prevalence in naturally occurring oligosaccharides. The most abundant sialic acid, *N*-acetylneuraminic acid (Scheme 1; **1**; R, R′ = H, X = OH), is a common substructure within glycolipids and glycoproteins and is implicated in a diverse array of biological functions such as immune response, oncogenesis, as well as cell recognition and adhesion.

Scheme 1



The preparation of sialyl conjugates by chemical methods usually involves the in situ activation of a latent C2-leaving group (X) within a selectively protected sialyl donor **1** (R, R′ = protective group), followed by substitution with a nucleophilic acceptor (Nu-H).[1] This transformation is particularly challenging in that: (1) anomeric bond formation occurs at the C2-ketal carbon of **1** as opposed to a less hindered anomeric acetal carbon in more common pyranosyl and furanosyl donors;[2] (2) 2,3-elimination of activated donors is often a competitive unproductive side reaction; and (3) naturally occurring sialosides incorporate the thermodynamically disfavored α-C2-stereochemistry (equatorial). Because of these challenges, only a handful of latent leaving groups (X) have been employed for sialylation, including halides, sulfides, xanthates, phosphites, and esters. However, direct dehydrative sialylations in which sialyl C2-hemiketals (**1**, X = OH) are employed as donors for the preparation of sialyl−carbohydrate conjugates have not been reported for complex carbohydrate synthesis.[3] We report herein the development of a method for dehydrative sialylation that establishes C2-sialyl hemiketals as viable carbohydrate donors for the preparation of sialyl conjugates.

We have recently demonstrated that dehydrative glycosylations with hemiacetal donors, employing the reagent combination of a diaryl sulfoxide (Ar_2SO) and triflic anhydride, is an effective method for anomeric bond

(1) (a) Okamoto, K.; Goto, T. *Tetrahedron* **1990**, *46*, 5835−5857. (b) DeNinno, M. P. *Synthesis* **1991**, 583−593. (c) Boons, G. J.; Demchenko, A. V. *Chem. Rev.* **2000**, *100*, 4539−4565. (d) Kiefel, M. J.; von Itzstein, M. *Chem. Rev.* **2002**, *102*, 471−490.

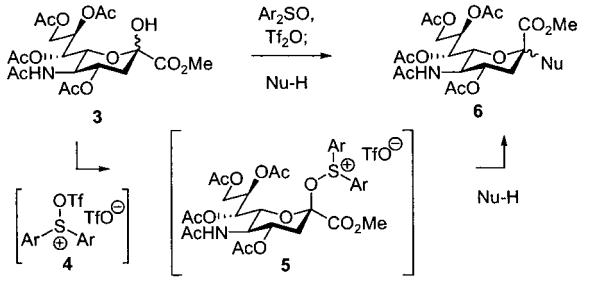
(2) (a) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531. (b) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21−123. (c) Davis, B. G. J. *Chem. Soc.*, Perkin Trans. 1 **2000**, 2137−2160.

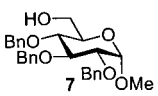
(3) A few early examples of Fischer glycosylations of simple alkyl alcohols with sialyl hemiketals have been reported in which the acceptor must also function as the reaction solvent. See: Meindl, P.; Tuppy, H. *Monatsh. Chem.* **1965**, *96*, 816−827.

10.1021/ol034815z CCC: $25.00
Published on Web 06/14/2003

construction.[4] When adapted to sialyl−hemiketal donors such as 4,7,8,9-tetra-*O*-acetyl-*N*-acetylneuraminic acid methyl ester (**3**, Scheme 2), this method provides a versatile approach

Scheme 2



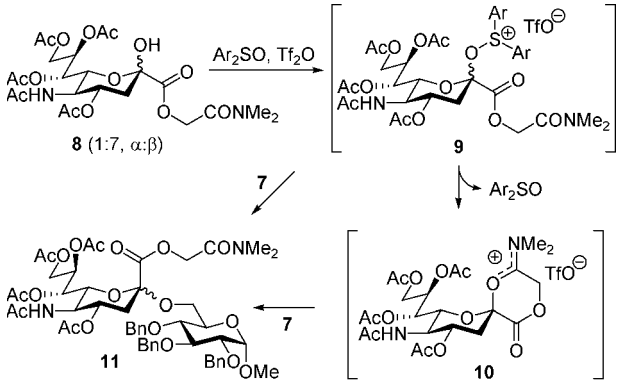
Entry	Ar_2SO	Nu-H	Solvent	Sialoside (**6**) Yield (α:β)
(1)	Ph_2SO		CH_2Cl_2	98% (1:2)
(2)	Ph_2SO		EtCN	89% (1:1)
(3)	Ph_2SO		CH_2Cl_2	72% (1:3)
(4)	$(m\text{-}CF_3C_6H_4)_2SO$		CH_2Cl_2	77% (1:2)
(5)	$(p\text{-}NO_2C_6H_4)(Ph)SO$		CH_2Cl_2	66% (2:1)

to dehydrative sialylation. In situ generation of a diaryl sulfoxide bis(triflate) intermediate **4** would lead to rapid activation of the C2-hemiketal within **3** to afford the C2-sialyloxosulfonium species **5**, an electrophile that represents a novel class of reactive sialyl donor. Subsequent anomeric bond formation with an appropriate nucleophilic acceptor (Nu-H) leads to the formation of the sialyl conjugate **6**. Initial investigations to assess the feasibility of direct dehydrative sialylation involved treatment of a solution of **3** and Ph_2SO in CH_2Cl_2 at −78 °C with Tf_2O, followed by the addition of 2-propanol as a model sialyl acceptor (3 equiv). Subsequent stirring of the reaction for 2 h at −50 °C led to the formation of sialoside **6** (Nu = $-OCHMe_2$, entry 1) in 98% yield (1:2 α/β). Similar results were also obtained when methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**7**) was employed as the sialyl acceptor to form the corresponding Neu5Ac(2→6)-Glu sialoside (72%, entry 3).

Although these early results establish the feasibility of dehydrative sialylation with C2-hemiketal sialyl donors, anomeric selectivity favors the non-natural β-glycosidic linkage, indicating that the predominant coupling pathway does not proceed through invertive displacement at C2 of a putative β-oxosulfonium intermediate **5** (Scheme 2). Dehydrative sialylation of 2-propanol was also investigated in propionitrile (entry 2) in the hopes that the formation of a reactive β-nitrilium intermediate (similar to that invoked in sialylations in acetonitrile solvent with C2-thio-sialoside donors)[5] would lead to improved α-selectivity. Although a comparable yield of the sialyl conjugate **6** was obtained (89%, entry 2), C2-α-selectivity was not significantly enhanced. Similar results were obtained when methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**7**) was employed as the acceptor (entries 4 and 5) using less nucleophilic diaryl sulfoxides such as bis(*m*-trifluoromethylphenyl) sulfoxide (entry 4, 77%; 1:2 α/β) and (*p*-nitrophenyl)(phenyl) sulfoxide (entry 5, 66%, 2:1 α/β).[6,7]

To augment α-selectivity in dehydrative sialylation, C1-neighboring group participation was explored employing the C1-*N*,*N*-dimethyl glycolamide protective group recently introduced by us.[8,9] This sialyl C1-protective group (i.e., **8**, Scheme 3) has been shown to enhance α-selectivity in

Scheme 3



Entry	Ar_2SO	Sialoside **11** (α:β)
(1)	Ph_2SO	72% (1:1)
(2)	$(m\text{-}CF_3C_6H_4)_2SO$	64% (1:1)
(3)	$(p\text{-}NO_2C_6H_4)(Ph)SO$	72% (3:1)

sialylation with a variety of coupling methods, presumably via generation and nucleophilic displacement of a β-sialyl-C2-imidate cation donor **10**, formed via dissociation of the putative anomeric C2-sulfoxide in **9**. This strategy is distinct from the more common approach of C3-neighboring group participation[10] in that multistep incorporation and removal of a transient C3-auxiliary is not necessary.

(4) (a) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597−7598. (b) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269−4279.

(5) (a) Hasegawa, A.; Ohki, H.; Nagahama, T.; Ishida, H.; Kiso, M. *Carbohydr. Res.* **1991**, *212*, 277−281. (b) Birberg, W.; Lönn, H. *Tetrahedron Lett.* **1991**, *32*, 7453, 7457.

(6) Use of electron-rich diarylsulfoxides such as bis(*p*-methoxyphenyl) sulfoxide led to incomplete activation of the C2-hemiketal, presumably a result of the attenuated electrophilicity of the sulfonium 4 (Ar = *p*-methoxyphenyl) relative to that of 4 (Ar = Ph).

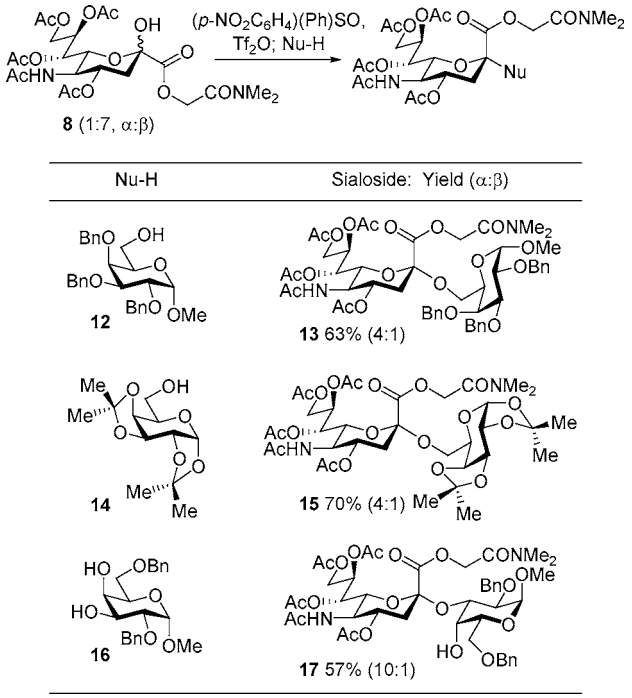
(7) No products arising from acceptor addition to the cationic imidate carbon were observed.

(8) Haberman, J. M.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 1665−1668.

(9) For another approach to the enhancement of α-selectivity in sialylations via C1-auxiliaries, see: Takahashi, T.; Tsukamoto, H.; Yamada, H. *Tetrahedron Lett.* **1997**, *38*, 8223−8226.

(10) (a) Ercégovic, T.; Magnusson, G. *J. Org. Chem.* **1995**, *60*, 3378−3384. (b) Okamoto, K.; Kondo, T.; Goto, T. *Tetrahedron* **1987**, *43*, 5909−5918. (c) Ito, Y.; Ogawa, T. *Tetrahedron* **1990**, *46*, 89−102. (d) Martichonok, V.; Whitesides, G. M. *J. Am. Chem. Soc.* **1996**, *118*, 8187−8191. (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.

Scheme 4



Thus, diphenyl sulfoxide mediated dehydrative sialylation of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**7**) with the C1-glycolamide-C2-hemiketal donor **8** (Scheme 3) provided a good yield of the corresponding (2→6)-sialyl conjugate **11** (entry 1). While the presence of the C1-glycolamide auxiliary increases the proportion of the α-sialoside product compared with that of the methyl ester sialyl donor **3** (i.e., entry 3, Scheme 2), this particular coupling was not stereoselective. It is likely that the presence of Ph_2SO in the reaction interferes with formation of the putative sialyl-C2-bicyclic imidate cation **10**, allowing for *β*-sialylation with the C2-oxosulfonium donor **9** to be a competitive pathway. As a result, other diaryl sulfoxides such as bis(*m*-trifluoromethylphenyl) sulfoxide and (*p*-nitrophenyl)(phenyl) sulfoxide, both incorporating electron-deficient aryl substituents, were also probed with the aim of minimizing the extent of sulfoxide participation following sialyl activation, thereby maximizing the influence of the C1-glycolamide auxiliary (Scheme 3, entries 2 and 3). Of these two sulfoxides, dehydrative sialylation with hemiketal **8** employing (*p*-nitrophenyl)(phenyl) sulfoxide provided a good coupling yield (72%; 3:1 α/*β*) with promising α-anomeric selectivity (entry 3).

Using this protocol with (*p*-nitrophenyl)(phenyl) sulfoxide, sialylations were performed on selectively protected galactopyranoside nucleophiles to afford neuraminic acid−galactoside conjugates that constitute key ganglioside disaccharide fragments (Scheme 4). For example, sialylation of methyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (**12**) and 1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranoside (**14**) afforded the corresponding Neu5Ac(2→6)Gal disaccharides **13** (63%) and **15** (70%), respectively, with good anomeric selectivity (4:1 α/*β*). Likewise, excellent α-selectivity was obtained when methyl 2,6-di-*O*-benzyl-α-D-galactopyranoside (**16**) underwent chemoselective 3-*O*-sialylation to provide the Neu5Ac-(2→3)Gal ganglioside subunit **17** (57%; 10:1 α/*β*).

In summary, a new method for sialylation involving the dehydrative coupling of C2-hemiketal sialyl donors with the reagent combination of (*p*-nitrophenyl)(phenyl) sulfoxide and triflic anhydride is reported. This process establishes a novel class of sialyl donor for carbohydrate synthesis and should prove useful for the preparation of a variety of biologically relevant sialyl conjugates.

Acknowledgment. This work was supported by the National Institutes of Health (NIGMS: GM58833).

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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