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# Efficient Dehydrative Sialylation of C-4-Aminated Sialyl-Hemiketal Donors with $Ph_2SO/Tf_2O$

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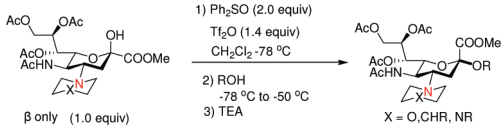


An efficient approach to the dehydrative sialylation of various substrates with C-4-aminated sialyl-hemiketal donors by using the reagent combination of diphenyl sulfoxide and triflic anhydride is reported. By using a C-4-hindered non-nucleophilic amine auxiliary, excellent yields and high α-stereoselectivities were obtained for coupling with a wide range of primary and secondary acceptors.

Sialic acid residues are incorporated in a wide range of oligosaccharides and glycoconjugates and are known to play important biological roles in higher animals and humans.[1] The lead member of the series, *N*-acetylneuraminic acid (Neu5Ac), is typically linked α-(2,3) or α-(2,6) to galactoside residues, or is polymerized in the form of α-(2,8) or α-(2,9) linkages. Over the years, a wide spectrum of sialylation methodologies for high stereoselectivity and high yielding synthesis of these complex sialoconjugates have been devised.[2] These methodologies can be characterized into several types: the introduction of various leaving groups at the C-2 position;[3] the incorporation of participating auxiliaries at the C-3 position;[4] the use of C-1 neighboring group participation;[5] the modification of the amino protective groups at the C-5 position;[2d,6] the formation of 1,5-lactam-Neu,[7] 5-*N*,4-*O*-carbonyl-Neu[8] or 5-*N*,7-*O*-oxazinanone;[9] and the development of new promoters. However, α-sialylation remains a formidable challenge in that the reaction often proceeds with low yields and poor α-stereoselectivity, and is characterized by undesirable 2,3-elimination due to an electron-withdrawing group at the anomeric center, the lack of a participating auxiliary substituent adjacent to the anomeric center, and a sterically hindered tertiary anomeric center.[2f,g]

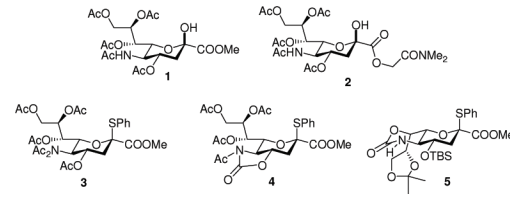


**FIGURE 1.** The structures of donors **1**−**5**.

Recently, Gin developed a new method for direct dehydrative sialylation with C2-hemiketal sialyl donors (**1**, **2**, Figure 1) using the activation system $Ar_2SO/Tf_2O$.[10] This was further extended by Crich to the sialylation of thioglycoside donors (**3**−**5**) in the presence of the hindered non-nucleophilic base 2,4,6-tri-*tert*-butylpyrimidine (TTBP).[11] It provides high yields and moderate α-stereoselectivities for donors **1**−**3**, and predominant *β*-stereoselectivities for donors **4** and **5**. With a view toward augmenting α-stereoselectivity, we are interested in developing rapid, low-temperature, α-stereoselective sialylations from C2-hemiketal sialyl donors, avoiding the use of the base TTBP that serves as a triflic acid scavenger for thioglycoside donors.

We report herein a series of C2-hemiketal sialyl donors in which the C-4 position is substituted with cyclic secondary amines as auxiliaries for the preparation of α-sialyl conjugates. In this context, cyclic secondary amines were employed because of their adaptations to the reaction of simultaneously stereoselective 2-*O*-deacetylation and 4-amination of peracetylated

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(4) (a) Okamoto, K.; Kondo, T.; Goto, T. *Tetrahedron* **1987**, *43*, 5909–5918. (b) Ito, Y.; Ogawa, T. *Tetrahedron* **1990**, *46*, 89–102. (c) Hossain, N.; Magnusson, G. *Tetrahedron Lett.* **1999**, *40*, 2217–2220.

(5) (a) Takahashi, T.; Tsukamoto, H.; Yamada, H. *Tetrahedron Lett.* **1997**, *38*, 8223–8226. (b) Haberman, J. M.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 1665–1668. (c) Ishiwata, A.; Ito, Y. *Synlett* **2003**, 1339–1343.

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(7) Ando, H.; Koike, Y.; Koizumi, S.; Ishida, H.; Kiso, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6759–6763.

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(11) (a) Crich, D.; Li, W. *Org. Lett.* **2006**, *8*, 959–962. (b) Crich, D.; Li, W. *J. Org. Chem.* **2007**, *72*, 2387–2391. (c) Crich, D.; Wu, B. L. *Tetrahedron* **2008**, *64*, 2042–2047.

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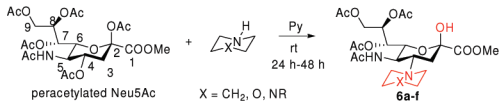
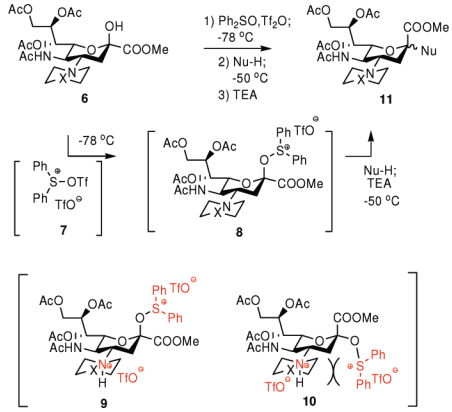
**SCHEME 1. Synthesis of Donors 6a−f**




**SCHEME 2. A Hypothetical Mechanism**

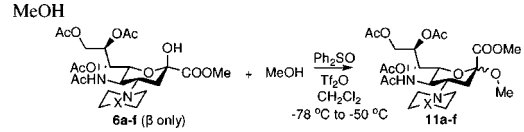



Neu5Ac (Scheme 1),[12] and their likelihoods to serve as triflic acid scavengers that promote direct dehydrative sialylation. It was reported that in situ generation of a diphenyl sulfoxide bi(triflate) intermediate **7** would lead to rapid activation of the C2-hemiketal within **6** to afford the C2-sialyloxosulfonium species **8**, which was subsequently converted to the sialyl conjugate **11** with an appropriate nucleophilic acceptor (Scheme 2).[10] We postulate that the sialyl donor **8**, which has a hindered non-nucleophilic tertiary amine, can subsequently trap the anionic byproduct of activation, triflate, to give two covalent double ion-pair intermediates **9** and **10**. Of these two putative reactive intermediates, the axial ($\beta$) orientation **9** is likely to predominate due to donor **6** being a $\beta$-anomer. More importantly, the repulsive interaction on the double ion-pair is also likely to make **9** adopt an axial ($\beta$) orientation, thus resulting in the preferred formation of the desired α-sialoside.

This hypothetical mechanism was initially exemplified by the coupling of a series of C-4-aminated sialyl-hemiketal donors with the model sialyl acceptor methanol by utilizing the $Ph_2SO$/$Tf_2O$ activation system. The resulting yields and anomeric selectivities of the sialylation reactions are summarized in Table 1. It is clear that using the standard protocol, the C-4 cyclic amine auxiliary exerts a dramatic effect in favoring the α-sialylation of the methanol acceptor.[13] For example, the coupling of a sialyl-hemiketal donor incorporating the C-4 morpholin-4-yl (Table 1, entry 1, **6a**) amine with methanol proceeded with excellent yield and high α-selectivity (98% yield, α:$\beta$ = 97:3) compared with the donors without the C-4 cyclic amine auxiliary (donors **1** and **3**) with a similar coupling protocol (Table 1, entry 7, **11g**; 98%, yield, 1:2, α:$\beta$;[10] entry 8, **11h**; 94% yield, 1.5:1, α:$\beta$[11a]). The structure of the α-sialoside **11a** was initially confirmed by COSY and HSQC NMR experiments, and the anomeric configuration was assigned on the basis of empirical $^1$H NMR rules.[14] Thus, the most useful characteristic parameters for a particular anomer are the chemical shifts of $H3_{eq}$ (α-anomer: $\delta$ = 2.40−2.60; $\beta$-anomer: $\delta$ = 2.10−2.30), H4 (α-anomer: $\delta$ = 2.30−2.60 ppm; $\beta$-anomer: $\delta$ = 2.80−3.10), and H9a (|α-anomer $\delta$ H9a − $\delta$ H9b| < |$\beta$-anomer $\delta$ H9a − $\delta$ H9b|; α-anomer: H9a, $\delta$ = 4.20−4.40 ppm; $\beta$-anomer: $\delta$ = 4.50−4.80).[5b,10c,11a,b,14a] The α-anomeric configuration of **11a** was further confirmed by X-ray crystallographic analysis (Figure 2[15]). More dramatic illustrations of the favorable stereochemical influence of the C-4 cyclic amine auxiliary arise in the sialylation examples shown in Table 1 (entries 2−6, sialosides **11b**−**f**; α predominant).

Next, with **6a** as the model sialyl-hemiketal donor, a variety of alcohols (**12a**−**i**) were examined as acceptors under the same reaction conditions, and the results are summarized in Table 2. Sialylation of primary and secondary alcohols with donor **6a** proceeded smoothly with excellent yields and a high level of α-selectivities (Table 2, entries 1−4). For the hindered tertiary

**TABLE 1. Sialylation of C-4-Aminated Sialyl-Hemiketal Donors with MeOH**




| Entry | | Donor | Product: yield[a] (α:β) |
|---|---|---|---|
| 1 | | **6a** | **11a:** 98% (97:3[b]) |
| 2 | | **6b** | **11b:** 92% (92:8 [b]) |
| 3 | | **6c** | **11c:** 90% (93:7 [b]) |
| 4 | | **6d** | **11d:** 90% (91:9 [b]) |
| 5 | | **6e** | **11e:** 98% (95:5 [b]) |
| 6 | | **6f** | **11f:** 95% (98:2 [b]) |
| 7 | - | **1** | **11g:** 98% (1:2)[c] |
| 8 | - | **3** | **11h:** 94% (1.5:1)[d] |

[a] Isolated yields. [b] Determined by LC/MS. [c] Reported in ref 10c: sialylation of donor **1** with 2-propanol as acceptor. [d] Reported in ref 11a: sialylation of donor **2** with methanol as acceptor.

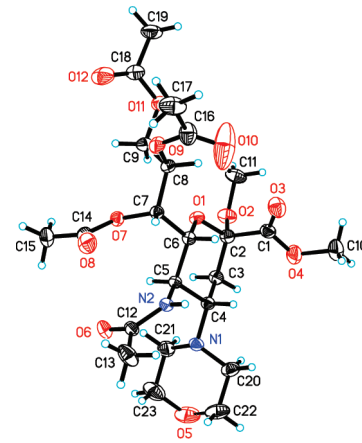



**FIGURE 2.** X-ray crystal structure of sialoside **11a**.

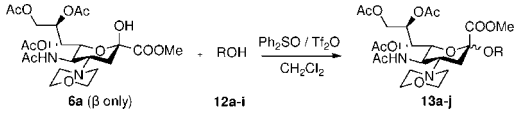
(12) (a) Ye, D. J.; Li, J.; Zhang, J.; Liu, H.; Jiang, H. L. *Tetrahedron Lett.* **2007**, *48*, 4023–4027. (b) Ye, D. J.; Deng, G. H.; Liu, W. F.; Feng, E. G.; Liu, H.; Jiang, H. L. *Tetrahedron* **2008**, *64*, 6544–6550.

(13) This protocol, employing 1.0 equiv of donor, 2.0 equiv of $Ph_2SO$, and 1.4 equiv of $Tf_2O$, is similar to that reported in ref 10c.

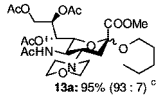
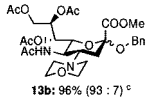
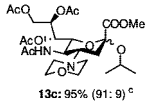
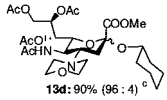
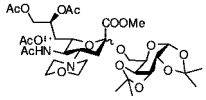
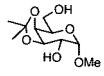
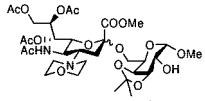
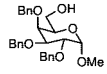
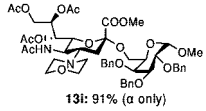
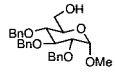
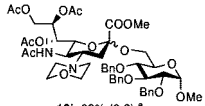
(14) The commonly used empirical $^1$H NMR rules are based on differences among H3, H4, and H9 chemical shifts, as well as coupling constants between H7 and H8, and, preferably, the sialic acid $^3J_{Cl,\ H3ax}$. For details, see: (a) Dabrowski, U.; Friebolin, H.; Brossmer, R.; Supp, M. *Tetrahedron Lett.* **1979**, *20*, 4637–4640. (b) Hori, H.; Nakajima, T.; Nishida, Y.; Ohrui, H.; Meguro, H. *Tetrahedron Lett.* **1988**, *29*, 6317–6320. (c) Atsufumi, N.; Tohru, T.; Nobuaki, M.; Kenji, M. *Org. Lett.* **2007**, *9*, 4742–4744.

(15) CCDC 687283 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**TABLE 2. Sialylation of C-4 Morpholin-4-yl Sialyl-Hemiketal Donor 6a with Acceptor Alchohols**[a]




**6a** (β only) **12a-i** **13a-j**

| Entry | Acceptor: ROH | t (h) | Product: yield[b](α:β) |
|---|---|---|---|
| 1 | **12a:** *n*-pentanol | 3 |  **13a:** 95% (93 : 7) [c] |
| 2 | **12b:** BnOH | 3 |  **13b:** 96% (93 : 7) [c] |
| 3 | **12c:**  | 3 |  **13c:** 95% (91: 9) [c] |
| 4 | **12d:**  | 3 |  **13d:** 90% (96 : 4) [c] |
| 5 | **12e:**  | 3 | [d] |
| 6 | **12f:**  | 3 | [d] |
| 7 | **12g:**  | 3 |  **13g:** 90% (93 : 7) [c] |
| 8 | **12h:**  | 3 |  **13h:** 90% (5:1) [e] |
| 9 | **12i:**  | 5 |  **13i:** 91% (α only) |
| 10 | **12j:**  | 5 |  **13j:** 89% (3:2) [e] |

[a] **6a** was chosen as the model donor. [b] Isolated yields. [c] Determined by LC/MS. [d] No coupling sialosides but only the 2,3-glycal derivative was detected. [e] Isolated ratios.

alcohols **12e** and **12f**, no coupling sialosides but only the undesired 2,3-glycal derivative[16] was detected. This may be due to the steric hindrance of a cyclic amine at the C-4 position that prevents the nucleophilic attack on the α-face of intermediate **9**. Optimal α-selectivities were obtained for the important galactose 6-OH derivatives (Table 2, entries 7−9). Interestingly, however, considerably lower selectivity was obtained with a glucose 6-OH derivative (Table 2, entry 10, 1.5:1, α:$\beta$). This substrate-dependent situation was also observed when sialylating with the sialyl donor **3**.[11a]

In summary, we have demonstrated that the challenging α-sialylation with C-4-aminated sialyl-hemiketal donors can be efficiently performed by using the $Ph_2SO/Tf_2O$ promotion system. The introduction of a hindered non-nucleophilic cyclic amine at the C-4 position is demonstrated to be important in these couplings and is anticipated to function in the formation of a double ion-pair intermediate by trapping the anionic triflate. Sialylation of a series of alcohol nucleophiles produced excellent yields and anomeric selectivities. With this new procedure, a series of 4-aminated Neu5Ac α-(2,6) Gal glycosidic linkages can be installed efficiently, which can be further explored to prepare a variety of biologically relevant sialyl-conjugated derivatives.

## Experiment Section

**General Experimental Procedure for the Sialylation Reactions.** To a solution of C-4-aminated sialyl-hemiketal donor **6** (0.10 mmol) and diphenyl sulfoxide ($Ph_2SO$, 0.20 mmol, 2.0 equiv) in anhydrous $CH_2Cl_2$ (2 mL) at −78 °C under positive argon pressure was added trifluoromethanesulfonic anhydride ($Tf_2O$, 23.2 $\mu$L, 0.14 mmol, 1.4 equiv). The reaction was stirred for 1 h, followed by the addition of a solution of acceptor **12** (0.25 mmol, 2.5 equiv) in anhydrous $CH_2Cl_2$ (0.5 mL) at −78 °C. The resulting solution was warmed to −50 °C and stirred for 2 h, then dry triethlamine (139.2 $\mu$L, 1.0 mmol, 10.0 equiv) was added. The resulting mixture was concentrated, and the residue was dissolved with EA (100 mL), then washed with water (2 × 20 mL) and brine. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The sialosides were isolated by flash column chromatography (see the Supporting Information for details).

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**Supporting Information Available:** Experimental details and characterization data for all compounds, and crystallographic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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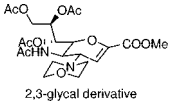
(16) Determined by LC-Ms and $^1$H NMR.




2,3-glycal derivative

$^1$H NMR (300 MHz, $CDCl_3$, ppm) $\delta$ 1.92 (s, 3H), 2.02 (s, 3H), 2.04 (s, 3H), 2.10 (s, 3H), 2.51−2.57 (br, 2H), 2.68−2.74 (br, 2H), 3.21 (m, 1H), 3.55−3.68 (br, m, 4H), 3.77 (s, 3H), 4.08−4.18 (m, 1H), 4.26−4.34 (m, 2H), 4.62 (dd, $J$ = 12.3, 3.3 Hz, 1H), 5.32−5.36 (m, 1H), 5.55 (t, $J$ = 4.2 Hz, 1H), 6.09 (d, $J$ = 2.7 Hz, 1H); LC-Ms $m/z$ 501 $[M + H]^+$ 100%.